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Malaysian Medical Association
4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
Website: www.mma.org.my

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42-1, Level 1, Plaza Sinar, Taman Sri Sinar, 51200 Kuala Lumpur. Tel: 03-6272 3767
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MJM

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Identify precisely all drugs and chemicals used, including generic name(s), dosage(s) and route(s) of administration. Do not use patients' names, initials or hospital numbers. Include numbers of observation and the statistical significance of the findings when appropriate.

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Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations, or both: emphasise or summarise only important observations in the text.

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Emphasise the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies.

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Acknowledgements:
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Authors are responsible for the accuracy of cited references and these should be checked before the manuscript is submitted.

The Journals names should be abbreviated according to the style used in the Index Medicus.

Articles published as abstracts only should not be used as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communication may be inserted (in parenthesis) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parenthesis). Information from manuscripts should be cited in the text as "unpublished observations" (in parenthesis).

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   NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017; 389(10064): 37-55.

Books and Other Monographs:
2. Personal Author(s)
   Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4th Edition. Cambridge University Press.
3. Chapter in Book
   McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.
4. Corporate Author
   World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.
   Institute for Public Health. National Health and Morbidity Survey (NHMS) 2017: Adolescent Health Survey 2017. Malaysia: Institute for Public Health, Ministry of Health Malaysia; 2017.
5. Agency Publication
   National Care for Health Statistics. Acute conditions: incidence and associated disability, United States, July1968 - June 1969. Rockville, Me: National Centre for Health Statistics, 1972. (Vital and health statistics). Series 10: data from the National Health Survey, No 69). (DHEW Publication No (HSM) 72 - 1036).

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   Kaos J. 40°C threshold for 'heatwave emergency' Kuala Lumpur: The Star Malaysia; [updated 18 March 2016, cited March 2016]. Available from: http://www.thestar.com.my/news/nation/2016/03/18/heatwave-emergency-threshold/.

Other Articles:
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All tables, illustrations and diagrams should be fully labelled so that each is comprehensible without reference to the text. All measurements should be reported using the metric system.

Each table should be typed on a separate sheet of paper, double-spaced and numbered consecutively. Omit the internal horizontal and vertical rules. The contents of all tables should be carefully checked to ensure that all totals and subtotals tally.

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CONTENTS Page

Original Articles

CONTENTS Page

CONTENTS Page

Writing Articles on Continuing Medical Education for Medical Journals

Sivalingam Nalliah, FRCOG[1], Lekhraj Rampal, DrPH[2]

[1]Faculty of Medicine, Clinical Sciences, International Medical University, Seremban, Malaysia, [2]Faculty of Medicine and Health Sciences, Universiti Putra Malaysia

ABSTRACT

Sharing of knowledge through Continuing Medical Education (CME) contribute immensely to professional development of skills in clinical medical practice. Thus, the writing of CME articles should adopt an approach that addresses the needs of the readers by attempting to fill gaps in their knowledge, skills, and ethics about clinical care. As such CME articles should be comprehensive and focused on specific areas. The specific learning outcomes should be well defined. In designing and development of such articles, pedagogic principles are to be borne in mind. In this article we outline a guide to writing a CME article, incorporating both the principles of instructional design and directed self-learning. The ideal CME articles will transit through multimedia-enhanced interactive online learning, with greater use of connectivity through the internet. Synchronous and asynchronous learning is in greater need, as distance and online learning are increasingly popular. Authors of CME articles will need to eventually design CME articles to be interactive, enriched with multimedia to engage their readers. Lesson plans employing instructional design principles should aim to promote both instructions for learning and formative assessment ensuring learning have taken place, and outcomes have been achieved. This article describes on how to write effective CME articles for medical journals.

KEYWORDS:
Writing, CME articles, learning outcomes, construct, instructional design, assessment

INTRODUCTION

The COVID-19 pandemic has seen the rapid proliferation of knowledge about the spread of this disease, its morbidity and mortality. The scientific community has been actively engaging in communicating advances in the prevention of this disease, its spread, identification of rapid diagnostic tests, therapeutic interventions in intensive care and informing policy makers and the public on all aspects of the viral infection. Due to the worldwide crisis precipitated by the COVID-19 pandemic, there has been an ever-increasing number of research studies on the causative virus and the disease. Vaccine for COVID-19 has been and is being developed and marketed globally at unprecedented scales and speed. Health care professionals, health providers, drug regulators and consumers, are in want of current information. The status of COVID-19 in Malaysia and Southeast Asian countries has been covered in previous issues of the Medical Journal of Malaysia.[1-4] Physical distancing, wearing a mask, avoiding crowds and washing our hands has become a major part of containing the viral infection as part of the Movement Control Order (MCO). This led to the disruption of normal transfer of accurate information and training of Registered Medical Practitioners (RMPs). This situation highlights the greater need for continuing medical education/continuing professional development (CME/CPD) through web seminars, video conferencing and existing medical journals Thus, this article focusses on how to write effective CME/CPD articles for medical journals. We also provide a guide for potential authors who wish to submit articles to medical journals. CME/CPD articles are a convenient means of communicating current information to health providers and other stakeholders. Systematic reviews indicate that CME articles improve individual competencies, resulting in quality patientcare by nurses and physicians. There is increasing evidence to show that CME articles have a positive impact on performance of physician leading to improved patient health outcomes.[5]

Editors of medical journals usually invite authors who are experts in a particular field, on specific topics of interest, to submit proposals on CMEs. The proposals should follow accepted, specific guidelines such as patient/population, intervention, comparison, outcomes (PICO) framework, apply systematic review strategies or specific instructions suggested by the editors, for comprehensive coverage and evidence-based outputs. In Malaysia, the accreditation body for CME/CPD is the Malaysian Medical Council (MMC). The guidelines on CPD for registered medical practitioners (RMP) has been established by MMC.[6] The RMP in Malaysia, must obtain a minimum of 20 CPD points per one CPD year as evidence of continuing professional development. Under the MMC CPD criteria, RMP will receive five CPD points for each CME article that the RMP has completed. The current CPD point collection is administered by the Ministry of Health's online myCPD, the Malaysian Medical Association (MMA) CPD mobile app and the Academy of Medicine of Malaysia (AMM)-CPD system.

GUIDE TO WRITING A CME ARTICLE: FORMAT

Table I can serve as a guide for authors to design and develop a good CME article. The essential components to justify its acceptability are indicated therein. The title of the article should be concise but informative. The expertise of the

Corresponding Author: Prof. Datuk Dr. Lekhraj Rampal
Email: lekhraj@upm.edu.my

author in the topic of CME topic and the recent articles published by the author related to that topic should be stated clearly in the proposal. The author must deliberate on the 'research question' and plan out the rationale for the CME article, and identify the differences between the information already available and the current situation for best practice. One of the prime reasons why a CME on the topic is chosen is due to the gaps in the knowledge available on that subject. Whilst writing CME articles, it is best to avoid a patronising approach. The contents should be evidence-based and be aligned to accepted 'standards of care' leading to good clinical practice. The latter is of particular importance when novel and/or therapeutic approaches are made. Journals should look into the possibility of moving to online CME with Blended Learning technology.

The subject material chosen must be suitable for the intended audiences. Authors should avoid either being too superficial or too detailed in the content. It is essential that CME should address the intended learning activities, focusing on the target audience to achieve the learning outcomes (LOs). The terms learning objectives and learning outcomes are often used interchangeably.

Disclosures of any conflict of interests is of particular importance, as the article should be free of any commercial interests. Industry-sponsored CME articles should be scrutinised for writing bias, and authors should clearly declare in case of such alliances. Ethical considerations should be included. The article should have no more than five LOs. This section should be followed by the instructions for the readers, the number of credit points and steps to earn the CME credit. Inclusion of self-checks, with some form of assessment that will reflect on the understanding of the subject matter by the participants, lending to competency and upskilling is recommended.

A short summary in the narrative form, not exceeding 250 words should be provided. The keywords at the beginning of the article, often creates interest in readers to further explore the contents. These should include the learning objectives/outcomes, ethical and professional issues that would arise, keywords, the main text, assessment with answers (e.g., MCQs), and references.

Learning outcomes

The learning outcomes should be 'intuitive and user-friendly', especially in medical education. Developing good LOs help in identifying specific knowledge and skills that would be learnt by the participants upon completing the CME. The LOs for a CME article should be specific, measurable, achievable, realistic, time bound (SMART), and should state how the LOs will be evaluated by a set of questions at the completion of CME. We recommend that the LOs should use action verbs using Bloom's Taxonomy[7] to achieve SMART outcomes. The scope of the article is well defined by stating the LOs clearly, e.g., 'At the end of this article, the learner should be able to be competent in …'. Learning outcomes are drawn from task analysis, each of which in turn, identifies each learning bite that is to be addressed.

Bloom B. et al., developed a hierarchy of educational objectives and published a framework for categorising educational goals in 1956, 'Taxonomy of Educational Objectives'. This framework consists of six major categories or levels within the cognitive domain, from the simplest to the most complex behaviour, which includes knowledge, comprehension, application, analysis, synthesis, and evaluation. To achieve SMART outcomes, it is recommended that action verbs employing Bloom's Taxonomy are used.[7] Anderson and Krathwohl (2001) revised this classical framework to help teachers understand and implement a standards-based curriculum.[7] Marrying cognitive domain to skills-learning by incorporating factual, conceptual, procedural, and meta-cognition domains, modifications of Bloom's original concepts can be applied to the design and development of CMEs. Cognitive processes of factual, conceptual and procedural domains are combined to meta-cognition as the learner (audience) needs to be aware of his own 'cognition'.[8]

Tips in writing learning outcomes

Bloom's taxonomy gives a list of measurable verbs to be used in writing the learning outcomes.[8] Usually, Bloom's taxonomy is used for development of curriculum. However, the types of assessments for CME for medical journals are usually limited to MCQs. Hence, the level of taxonomy may just be limited to Knowledge (Level I), Comprehension (Level II) and may be application (Level III), it cannot be used for higher order in the taxonomy. The latest update in the literatures for the preparation of a CME material could be retrieved using different search engines (OVID, PubMed, etc.), and using the Medical Subject Headings (MeSH) term, search criteria (Human study, date of publication, languages) with the utilisation of PICO in developing the search terms.

Learning outcomes should be simple, without compound words or adding two LOs with 'and'. The readers are looking for current and evidence-based information. As such, the content of CME must be above the basic knowledge of the reader, with sufficient educational information and knowledge to achieve higher order thinking. Verbs that are non-measurable should be avoided entirely, e.g., the learner should appreciate, understand, know, learn, be familiar with etc. Practitioners are naturally looking for CMEs that would supplement the current knowledge of the subject, so currency of information is vital.

Writing Measurable Learning outcome

Usual approaches to writing measurable learning outcomes are to have the 'end in mind'. Action verbs are essential in LOs, as we would like the learner to know what will be achieved at the end of the article. A spiral approach in writing measurable LOs, including assessment, is adopted as the sub-topics should be sequentially arranged. Authors should refer to Bloom's six levels of learning, which makes learning methodical and meaningful. The lowest level is 'remembering'. To apply the concept being introduced in the CME article, one needs to 'remember and understand' the concept. This learning activity is followed by 'evaluation and analysis'. The higher levels of learning are 'to create' and 'to evaluate'. The authors of CME need to be familiar with these levels and select the most appropriate level of learning that

Table I: Guide to Writing CME Articles

Title of Article
State your expertise in this topic and details of any recent article published on the subject
Provide a summary of the topic, written in either narrative or point form, not exceeding 250 words
Identify target audience and learner needs
Learning Outcomes (LOs) using measurable verbs, not exceeding five LOs
Describe practice gaps and new information or skills based on three domains: • Cognitive • Psychomotor skills • Affective / Practice
Provide reasons for existing practice gap if possible
State the specific competences that would be achieved at end of CME . These could focus on one or more of the following: • Medical knowledge and skills • Clinical practice, patient care, best practices, patient safety • Change in health system • Professionalism and bioethics
Read the 'Instructions to Authors' of the journal and ensure the following are closely followed : • All references are cited as instructed • Provide source of evidence to support your argument or statement regarding gaps in skills knowledge and practice • Include the source of all tables, graphics (unless they are original artwork) • Indicate permission has been obtained should figures and tables are not personally generated Assessment/ Evaluation

Table II: Modified Bloom's Taxonomy

Original Domain	**Change in Bloom's Taxonomy**	**New Domain**
Evaluation	→	Creating
Synthesis		Evaluating
Analysis	→	Analysing
Application	→	Applying
Comprehension	→	Understanding
Knowledge	→	Remembering

Table III: Incorporating Bloom's Taxonomy to Concepts

Facts	Specific information, data
Concepts	Concrete and abstract: common features, collated to provide a 'chunked' element
Procedure	Step-by step activities that leads to the final product in a sequential way
Processes	Workflow is shown in diagrammatic fashion
Principles	Governing terms, basic blocks that lend to development of guidelines

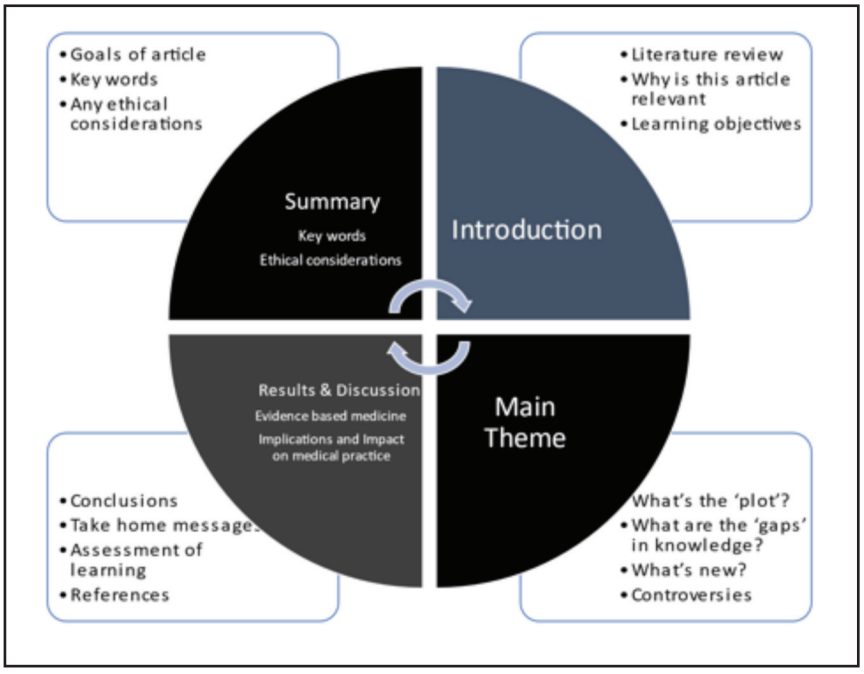

Fig. 1: Summary of Content of CME Article.

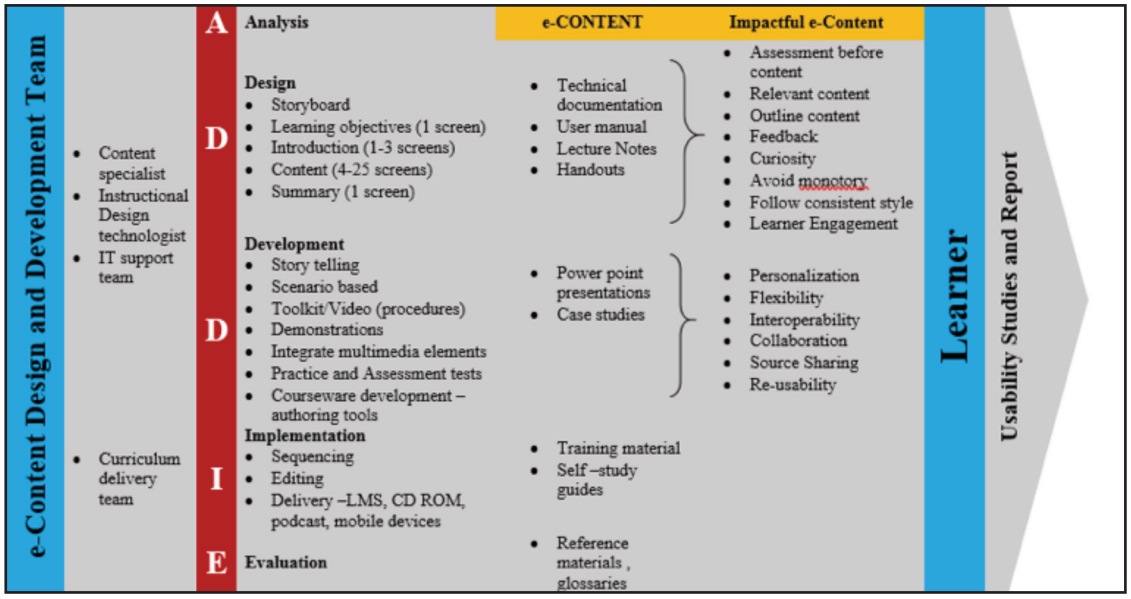

Fig. 2: Framework for Design and Development of e-Contents for CME.[18] (Sivalingam Nalliah, 2021, pp 76)

would be applicable to the reader. Selection of actions verbs according to the level of learning can be found in 'Revised Bloom's action-verbs.[9]

Main Text

A well planned and structured article should have a logical flow, e.g., PICO framework. Apart from identifying the LOs, it would be good to reflect on the content and determine if it meets the three domains of learning, i.e., cognitive, psychomotor, and affective components. These may not be of equal proportions. Images and diagrams are included as appropriate, to enhance learning. Table II shows the modified Bloom's taxonomy. Figure 1 summarises the essential contents for the main text reflected in Table II. In deciding the length of the article, authors should consider the acceptable time-duration for participants to read and complete tasks assigned for formative assessment.

Points to remember in the main text

In Instructional Design, especially for online learning, storylines are developed, and the lesson is designed and developed following principles of Instructional Design and Development like ADDIE, i.e., Analyse, Design, Develop, Implement, Evaluate.[10] Authors could employ such principles in writing their CME articles. This would become useful, as online journals also provide interactive learning approaches for upskilling and cognitive development. Details of pointers for writing online CME articles is shown in another section of this paper.

The following are some points to remember in designing the CME article:

- Logical, sequential, and well-organised concepts
- Repetition is to be avoided
- Headings and sub-headings are included to engage the reader
- Bullets points and boxes used appropriately
- Tables, figures, and diagrams are more useful than text alone, to explain complex information and concepts
- Flow charts and algorithms are useful for practice guidelines

In the 'introduction to the CME', the author should lay out the basic elements that the learner should be acquainted, to understand the concepts. In clinical CME articles, inter-relationships among the basic aspects of learning need to surface, to realise clinical reasoning skills. CME articles should avoid displaying facts, without exploring the understanding of the concepts. Suitable evidence should be presented to support a concept. Procedural knowledge can be learned, both through face-to-face approaches, and though text and online learning, which includes links to videos and animated diagrams, i.e., blended approach. Algorithms, flow-charts, and media-incorporated images, based on Instructional Technology principles are increasingly employed, in developing CME articles.

Reducing cognitive load is essential in any design of CME articles, by analysis of the learner's learning styles, needs, and scope of study. Current interactive CME courses often use the 'Lesson Plan' approach in engaging the learner. Gagne's 9-steps in instructional design of a lesson plan may be employed for active learning. Gagne's 9 steps are grouped into three phases. The pre-instructional phase could be directed self-learning and gaining attention, while the main CME article can focus on the main theme, i.e., instructional phase. The post-instructional phase can include self-assessment through reflective practice. Assessment and feedback assist in ensuring learning has taken place and lend to improved learning outcomes.[10,11] The main text should wind up the discussion with a 'conclusion'. This section, which should not be more than a paragraph, should

emphasize the salient points considered as take-home messages. Table III shows the incorporation of Bloom's taxonomy with the concepts generated by Anderson and Krathwohl.[8]

DEVELOPING SOCIALLY INTERACTIVE CME LEARNING MATERIALS

Digital technology has dramatically transformed conventional learning, leading to increased use of information and communication technology (ICT) and connectivity (internet) to facilitate online learning and massive open online courses (MOOC). Blended learning, with incorporation of eLearning is in vogue today. Current learning trends support the need for development of e-Contents, enabling synchronous or asynchronous distance learning.[12] Formal lessons and modular courses can be taken online remotely, and novel approaches are being adopted to engage the learner, using commercially available authoring tools like Articulate 360. Learning management systems have broad cloud- based or non-cloud-based platforms, for curriculum delivery, tracking progress of learning and assessing the learner.[13-15] Such self-paced learning, at the convenience of the learner, is becoming extensively used worldwide. Skills-learning based on units of learning can be delivered through 'microlearning and micro-credentialing'. There is evidence to support the increase in course completion when social and remote learning is introduced.

Multimedia is extensively used in developing interactive e-Contents. It can be made to be catchy and rich, apart from appealing to the audience. Multimedia used in learning, attracts individual learning styles focusing on visual, audio, and kinesthetic aspects. Graphic images, audio, video-creating, and editing are all employed to enrich the learning object.[14,15]

Authoring tools, which are software applications to create multimedia content for eLearning are extensively employed to develop interactive e-Contents, which would include illustrations, animations, gamification, audio podcasts and customised video productions.[15,16] There is huge scope for interactivity, navigation, editing, preview, and playback when authoring tools are employed. Three elements are necessary to engage learners, after creating awesome and appealing e-Contents. These are (i) personalisation, (ii) social learning (iii) gamification. The framework in Figure II portrays the big picture how the needs of the learner could be met in the designing and developing CME articles and learning materials for online learning adopting the ADDIE model. Instructional design and technology lend to dynamic learning products that can be easily updated and improved, based on feedback and assessment. It is of paramount importance to determine user experience and usability of online lessons for quality and currency of contents.[17,18,20]

Criteria for Quality e-Contents

The primary aim of e-Content in CME articles is to provide current and interactive lessons and online courses, appealing to 'digital native' learners of the 21st Century. Authors of lessons and CME materials for online learning should be mindful of the definition of e-contents. Online lessons and CME articles are not 'any form of digital data that is stored on a digital or analogue storage in specific format'. Apart from being evidence-based and scientifically correct, they should be well sequenced 'learning objects' arranged and aligned to meet the learning outcomes.[5,14] A good online CME article is adaptive, interactive, communicative, and collaborative (by providing a forum for feedback and evaluation). For higher level of LOs, it should promote reflective and explorative learning. It should be standardised, SCORM (shareable content objective model) and LMS (learning management system) compatible, without infringing copyright laws. An extensive discussion on design and development of e-Content for interactive learning is beyond the scope of this article and interested readers should refer to books on Instructional Design and Technology.[5,10,14]

Well-designed online CME articles will adopt similar approaches described above in identifying learning outcomes and presenting the subject matter in an organised and sequential manner. The aim is to understand the cognitive-psychomotor-affective needs of the audience. Online learning CME is designed for synchronous and asynchronous learning, employing the basic tenets of instructional design. Assessment of learning outcomes is an essential part of CME and should be standardised in its construct, apart from being contextually relevant.

The CME article should focus on how the salient learning outcomes will be achieved through assessments. The latter could be pre-test, post-test multiple choice items (OBA), which have a direct relationship with the CME outcomes, focussing on important and relevant content. Test items are based directly on the learning outcomes and relevant content. Controversial test items should be avoided, especially when the knowledge is incomplete, or the facts are debatable. Instructional design models are increasing employed in CMEs. When learning management systems and authoring tools are employed to develop CME articles, enriched content may be presented with self-check assessment tools as a package.[14,15,21]

ASSESSMENT AND EVALUATION OF CME ARTICLE

Assessment of learning outcomes is integral to CME. In clinical education, patient-care scenarios are preferred as they are more engaging and contextually relevant. Authors should only include information that would be required to answer the three to five most important "take-home" messages from your article. In constructing questions, clearly, relevant information provided in the stem should be derived from the key messages relayed in the article. Questions, that follow the stem should not be ambiguous. Common mode of assessment employed is multiple choice questions. Current pedagogic principles favour 'single best or one best answer (OBA)'. Distractors must be accurate and should not relate to regional information and expert opinions. Construct of OBA is better done by creating a brief clinical scenario which adds 'authenticity' to learning. Only information that is needed to answer the question should be included, and the correct answer should relate to the key findings in the article. Only 'positively' constructed questions should be posted, completely avoiding 'All of the following are correct EXCEPT

or All of the above and None of the Above. Care must be taken to ensure that all distractors are of the same category and as homogenous as possible. True/False and K-type questions are better avoided.

A tidy approach to constructing OBAs is to focus on 3-5 'take-home messages'. Develop a case scenario, if possible, and develop the stem for the question. Authors should keep the stem short and relevant to the objective of the assessment. Then, they should decide on the important point to write the correct answer, before penning the 'incorrect' plausible answers or distractors.

For CME articles, presented as online learning (e.g., MOOC), design assessment in a similar fashion. However, including multimedia and gamification have become a norm, as such technology-enhanced assessment modes are more engaging and motivating. Leaning management systems present innovations that facilitates provision of answers with immediate feedback. Tracking of the student's progress is electronically facilitated with access to self-generated completion badges and CME certificates. Most online courses would also provide a forum for peer-to-peer learning and promote social-cognitive learning. Evaluation of the whole online course is often welcome by the authors for further improvement of CME.

CONCLUSION

The concluding portion of a CME activity should highlight what learners should be able to do after completing the instructions or course. Recap of the importance of the topic and how practical application of the content will narrow the identified practice gap. It should focus on changes in outcome the author had planned to achieve.

Medicine is rapidly changing with application of new technology and therapeutics. Quality CME articles are written for specific purposes. CME/CPDs help practitioners to close the gap in knowledge and skills, which eventually leads to upskilling of health professionals and updating them with current standards of health care. Ultimately it will lead to improvement in patient care. CME activities also assist registered medical practitioners (RMP) to obtain CPD points for the renewal of your annual practicing certificate (APC).

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Smartphone electrocardiogram for QT interval monitoring in Coronavirus Disease 2019 (COVID-19) patients treated with Hydroxychloroquine

Andy Tze Yang Ko, MRCP[1], Lean Seng Chen, MRCP[2], Ing Xiang Pang, MRCP[2], Hwei Sung Ling, MRCP[2,3], Tze Cheng Wong, MBBS[1], Tonnii Loong Loong Sia, MRCP[1], Keng Tat Koh, MRCP[2]

[1]Department of Medicine, Sarawak General Hospital, Malaysia, [2]Department of Cardiology, Sarawak Heart Centre, Malaysia, [3]Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Malaysia

ABSTRACT

Introduction: The global pandemic of Corona Virus Disease 2019 (COVID-19) has led to the re-purposing of medications, such as hydroxychloroquine and lopinavir-ritonavir in the treatment of the earlier phase of COVID-19 before the recognized benefit of steroids and antiviral. We aim to explore the corrected QT (QTc) interval and 'torsadogenic' potential of hydroxychloroquine and lopinavir-ritonavir utilising a combination of smartphone electrocardiogram and 12-lead electrocardiogram monitoring.

Materials and Methods: Between 16-April-2020 to 30-April-2020, patients with suspected or confirmed for COVID-19 indicated for in-patient treatment with hydroxychloroquine with or without lopinavir-ritonavir to the Sarawak General Hospital were monitored with KardiaMobile smartphone electrocardiogram (AliveCor®, Mountain View, CA) or standard 12-lead electrocardiogram. The baseline and serial QTc intervals were monitored till the last dose of medications or until the normalization of the QTc interval.

Results: Thirty patients were treated with hydroxychloroquine, and 20 (66.7%) patients received a combination of hydroxychloroquine and lopinavir-ritonavir therapy. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs. 458.6±47.1msec, p=0.001). The maximum QTc interval (456.1±45.7msec vs. 464.6±45.2msec, p=0.635) and the delta QTc (32.6±38.5msec vs. 26.3±35.8msec, p=0.658) were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir. Five (16.7%) patients had QTc of 500msec or more. Four (13.3%) patients required discontinuation of hydroxychloroquine and 3 (10.0%) patients required discontinuation of lopinavir-ritonavir due to QTc prolongation. However, no torsade de pointes was observed.

Conclusions: QTc monitoring using smartphone electrocardiogram was feasible in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The usage of hydroxychloroquine and lopinavir-ritonavir resulted in QTc prolongation, but no torsade de pointes or arrhythmogenic death was observed.

KEYWORDS:
Coronavirus disease 2019, hydroxychloroquine, lopinavir-ritonavir, long QT, torsade de pointes, smartphone electrocardiogram

INTRODUCTION

The global pandemic of coronavirus disease 2019 (COVID-19) has led to the "off label" re-purposing of medications, such as chloroquine, hydroxychloroquine, azithromycin, and lopinavir-ritonavir for COVID-19.[1,2] The latest National Institute of Health (NIH) guidelines had recommended against the use of the abovementioned medications following studies that showed equivocal or non-beneficial results. However, they were commonly used during the initial phase of the outbreak.[3] These medications are potentially associated with drug-induced torsade de pointes (DI-TdP) and sudden cardiac death through prolongation of QT interval which necessitates close electrocardiography monitoring.[4]

The mechanism of QT prolongation is due to the inhibition of human-Ether-a-go-go Related Gene (hERG), which is a subunit of the I_{Kr} channel, or aggravating the late sodium channel (I_{NA-L}) during the early depolarisation phase, leading to prolong QT interval. Risk factors contributing to the increased risk of DI-Tdp have been validated by Tisdal et al.[5] Study on QT interval prolongation associated with the use of hydroxychloroquine with or without azithromycin has been reported by Mercuro and co-workers[6] and Bessière and co-workers.[7] However, the QT-prolonging potential of hydroxychloroquine and lopinavir-ritonavir in COVID-19 patients, whether as a single agent or in combination, has never been described before.

The SARS-CoV-2 virus has a high risk of transmission via respiratory secretions and to a lesser extent, contact. There had been reports of healthcare personal being infected with the virus in the line of service.[8] Thus, there was major concern regarding the safety and exposure of healthcare personal conducting regular 12-lead electrocardiogram monitoring for QT interval during the widespread use of QT-prolonging medications. KardiaMobile smartphone electrocardiogram (AliveCor®, Mountain View, CA) was suggested as an alternative to a 12-lead electrocardiogram in monitoring the QT intervals.[4] Although it seems to be a feasible recommendation, the utility of this method has never been

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Corresponding Author: Dr. Andy Ko Tze Yang
Email: andyko1989@gmail.com

described in any study on COVID-19 patients. We aimed to describe the use of a smartphone electrocardiogram in the monitoring of COVID-19 patients as well as the effect of the above mentioned medications on the QT interval.

MATERIALS AND METHODS

This was a single-centre, cross-section observational study evaluating patients with COVID-19 who were hospitalised at Sarawak General Hospital (SGH) in Sarawak, Malaysia. We included patients admitted between 16 of April to 30 of April 2020, who received hydroxychloroquine with or without lopinavir-ritonavir for COVID-19. Patients suspected to have COVID-19 and empirically started on hydroxychloroquine with or without lopinavir-ritonavir while waiting for nasopharyngeal polymerase chain reaction (PCR) test for COVID-19 were also included in the study. If the nasopharyngeal PCR tests for COVID-19 were repeatedly negative for two samples taken 24 hours apart, the treatment for COVID-19 was stopped. The standard regimen for hydroxychloroquine was 400mg twice daily on day-1, then 200mg twice daily for five days. The standard regimen for lopinavir-ritonavir was 400mg/100mg twice daily for 5 to 10 days.

Data on baseline demographic, routine blood investigations and clinical conditions were prospectively collected and updated daily. The first electrocardiogram (baseline) was taken before the initiation of hydroxychloroquine with or without lopinavir-ritonavir. The second electrocardiogram was taken 12 hours after the 1st dose of the medication(s). The electrocardiogram was recorded daily after that, until the last dose of the medication(s) for COVID-19 or until normalisation of the QTc interval (<470msec for male and <480msec for female).

The attending physician and nurses were given the options to monitor the QT intervals using a standard 12-lead electrocardiogram or the application of the KardiaMobile smartphone electrocardiogram. The utility of the KardiaMobile smartphone electrocardiogram in the isolation ward was described in Figure 1. Electrocardiogram was reviewed and manually evaluated by two cardiologists (L.H.S. and P.I.X.) to calculate the QTc intervals using the Bazett formula by electronic EP callipers. Both cardiologists performed an independent review of the electrocardiogram and were blinded to the baseline data of the patients. If there was a significant interobserver discrepancy in measurement, the final measurement was taken from the electrophysiologist (K.K.T.). QTc intervals of equal to or more than 500msec were immediately notified to the attending physician. The Tisdale score was applied retrospectively to evaluate QTc prolongation risk. Endpoints of interest were changes in QTc (delta QTc), maximum QTc interval, development of QTc interval of 500msec or more, interruption of hydroxychloroquine and/or lopinavir-ritonavir due to prolonged QTc, and event of torsade de pointes.

Patient information was de-identified and the study was carried out in accordance with the Helsinki Declaration 2013.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistic version 16 (IBM Corp., Armonk, NJ, USA). Descriptive statistics were reported as the number with percentage or mean with standard deviation, whichever appropriate. Categorical variables were analysed using the chi-square test or Fisher's exact test. Continuous variables were analysed using the student t-test. Receiver Operator Characteristic (ROC) curve was used to analyse the predictive value of Tisdale score to QTc interval of ≥500msec. The QTc prolongation risk (≥500msec) was evaluated in the univariate and multivariate logistic regression model.

RESULTS

Thirty patients were treated with hydroxychloroquine, and 20 (66.7%) patients received a combination of hydroxychloroquine and lopinavir-ritonavir therapy. The mean (SD) age of the patient was 46.0 (22.2) years, 20 (66.7%) were female, mean (SD) lowest potassium level was 3.98 (0.44) mmol/L, one (3.4%) patient with atrial fibrillation and heart failure (Table I). The majority (46.7%) of the patients had symptomatic pneumonia on presentation. Patients on hydroxychloroquine and lopinavir-ritonavir had a significantly higher incidence of pneumonia on presentation (2 (20.0%) vs. 18 (80%), p<0.001). Median (IQR) Tisdale score upon treatment initiation was 4.0 (2.0).

The mean (Standard Deviation, SD) baseline QTc interval was 434.6 (28.2)msec. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs 458.6±47.1msec, p=0.001) (Figure 2A). QTc interval of ≥500ms could happen from 12 hours to Day-5 after initiation of hydroxychloroquine with or without lopinavir-ritonavir (Figure 2B). The maximum QTc interval (456.1±45.7msec vs 464.6±45.2msec, p=0.635) and the delta QTc (32.6±38.5msec vs. 26.3±35.8msec, p=0.658) were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir. Five (16.7%) patients had QTc of 500msec or more, which was not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir (10% vs. 20%, p=0.640). Four (13.3%) patients required discontinuation of hydroxychloroquine and three (10.0%) patients required discontinuation of lopinavir-ritonavir due to QTc prolongation. However, no event of torsade de pointes or arrhythmia-related cardiac death was observed.

The mean (SD) PR interval was 178.6 (37.6) msec. The mean (SD) maximum PR interval was significantly prolonged compared to baseline (186.6 (35.0) vs. 178.6 (37.6), p<0.001). The maximum PR interval and delta PR interval were not significantly different between patients on hydroxychloroquine or a combination of hydroxychloroquine and lopinavir-ritonavir therapy. No patients developed significant bradycardia requiring temporary pacing, initiation of chronotropic agents, or interruption of medications due to prolonged PR interval.

Table I: Baseline characteristics of the patients

	Total (n=30)	HCQ (n=10)	HCQ+Kaletra (n=20)	p-value
Age (years), mean (SD)	46.0 (22.3)	43.6 (21.1)	47.2 (23.4)	0.685
Female, n (%)	20 (66.7)	7 (70.0)	13 (65.0)	0.784
Ethics, n (%)				
Malay	19 (63.3)	6 (60.0)	13 (65.0)	
Chinese	7 (23.3)	3 (30.0)	4 (20.0)	
Iban	3 (10.0)	1 (10.0)	2 (10.0)	
Indian	1 (3.3)	0 (0)	1 (5.0)	0.847
Atrial fibrillation, n (%)	1 (3.3)	1 (10.0)	0 (0)	0.333
Heart failure, n (%)	1 (3.4)	1 (10.0)	0 (0)	0.333
Serum creatinine (umol/L), median (IQR)	69.5 (20.0)	71.5 (49.0)	69.5 (12.0)	0.746
Serum potassium level (mmol/L), mean (SD)	3.98 (0.44)	3.92 (0.48)	4.01 (0.43)	0.593
Serum magnesium level (mmol/L), mean (SD)	0.91 (0.09)	0.91 (0.10)	0.91 (0.09)	0.984
Serum calcium level (mmol/L), mean (SD)	2.30 (0.08)	2.26 (0.06)	2.32 (0.10)	0.143
Clinical Stage, n (%)				
Asymptomatic	2 (6.7)	0 (0)	2 (10.0)	
Symptomatic no pneumonia	8 (26.7)	8 (80.0)	0 (0)	
Symptomatic pneumonia	14 (46.7)	0 (0)	14 (70.0)	
Symptomatic pneumonia requiring oxygen	6 (20.0)	2 (20.0)	4 (20.0	<0.001
Tisdale score at treatment initiation, median (IQR)	4.0 (2.0)	4.0 (4.0)	4.5 (2.0)	0.559
Baseline QTc (msec), mean (SD)	434.6 (28.2)	423.5 (34.6)	438.3 (24.7)	0.187
Maximum QTc (msec), mean (SD)	458.6 (47.1)	456.1 (45.8)	464.6 (45.2)	0.635
Delta QTc (msec), mean (SD)	20.4 (33.2)	32.6 (38.5)	26.3 (35.8)	0.658
Maximum QTc≥500msec, n (%)	5 (16.7)	1 (10.0)	4 (20.0)	0.640
Baseline PR (msec), mean, SD	180.6(38.6)	184.3 (44.3)	178.8 (36.5)	0.720
Maximum PR (msec), mean, SD	189.0 (41.3)	194.6 (48.4)	186.2 (38.3)	0.608
Delta PR (msec), mean, SD	6.2 (32.8)	10.3 (32.1)	7.4 (36.1)	0.831

Abbreviations: HCQ=hydroxychloroquine; Kaletra=Lopinavir/Ritonavir; QTc=corrected QT interval.

Table II: Univariate and Multivariate Logistic Regression Model for Predicting QTc > 500ms

	Odds Ratio	95%CI	P-value	Adjusted Odds Ratio	95% CI	p-value
Tisdale Score	1.74	1.06-2.86	0.028	NT		
Tisdale Score ≥8	11.00	1.27-95.17	0.029	20.11	1.10-367.61	0.043
Female	2.25	0.22-23.32	0.497	3.242	0.17-63.15	0.438
Age=>68	2.667	0.35-20.51	0.346	2.25	0.15-33.19	0.555
With Kaletra	2.25	0.22-23.32	0.497	11.97	0.18-812.95	0.249
Baseline QTc≥450	2.111	0.28-15.77	0.466	NT		
Creatinine Level	1.006	1.00-1.01	0.203	NT		
Lowest Serum Potassium Level <3.5mmol/L	2.875	0.21-39.68	0.43	1.84	0.36-95.95	0.761

Abbreviations: NT: not tested; QTc: corrected QT interval; Kaletra: Lopinavir/Ritonavir

The likelihood of prolonged QTc (≥500msec) was greater with a Tisdale score of ≥8 (odds ratio, OR 11.0; 95% Confidence Interval, 95%CI 1.27, 95.17, p=0.029) (Table II). Tisdale score of ≥8 appeared to be the only independent variable to predict QTc interval ≥500ms (adjusted OR 20.11; 95%CI 1.10, 367.61, p=0.043). The Receiver Operating Characteristic curve for Tisdale score to predict QTc≥500ms has an area under the curve of 0.81 (95%CI, 0.59, 1.00, p=0.032) (Figure 3). Tisdale score of ≥8 has the NPV of 91.7%; PPV of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500ms.

DISCUSSION

QTc interval in COVID-19 patients treated with hydroxychloroquine and lopinavir-ritonavir

Our study showed that hydroxychloroquine and lopinavir-ritonavir resulted in significant QTc prolongation in COVID-19 patients. This contradicted an earlier observational study which showed no QT prolongation issues with chronic hydroxychloroquine usage in systemic lupus erythematosus (SLE) patients.[9] However, there was a case report on life-threatening severe QTc prolongation associated with hydroxychloroquine in SLE patients.[10] Concordant with the studies done by Mercuro, et al[6] and Bessière, et al.,[7] which showed that 20% and 18% of COVID-19 patients treated with hydroxychloroquine with or without azithromycin had QTc prolongation of ≥500msec respectively, 16.7% of our patients had the maximum QTc interval≥500ms after treated with hydroxychloroquine and lopinavir-ritonavir. On the other hand, Saleh M, et al.,[11] reported a lower number of patients (8.96%) with QTc≥500msec after treated with hydroxychloroquine or chloroquine with or without azithromycin.

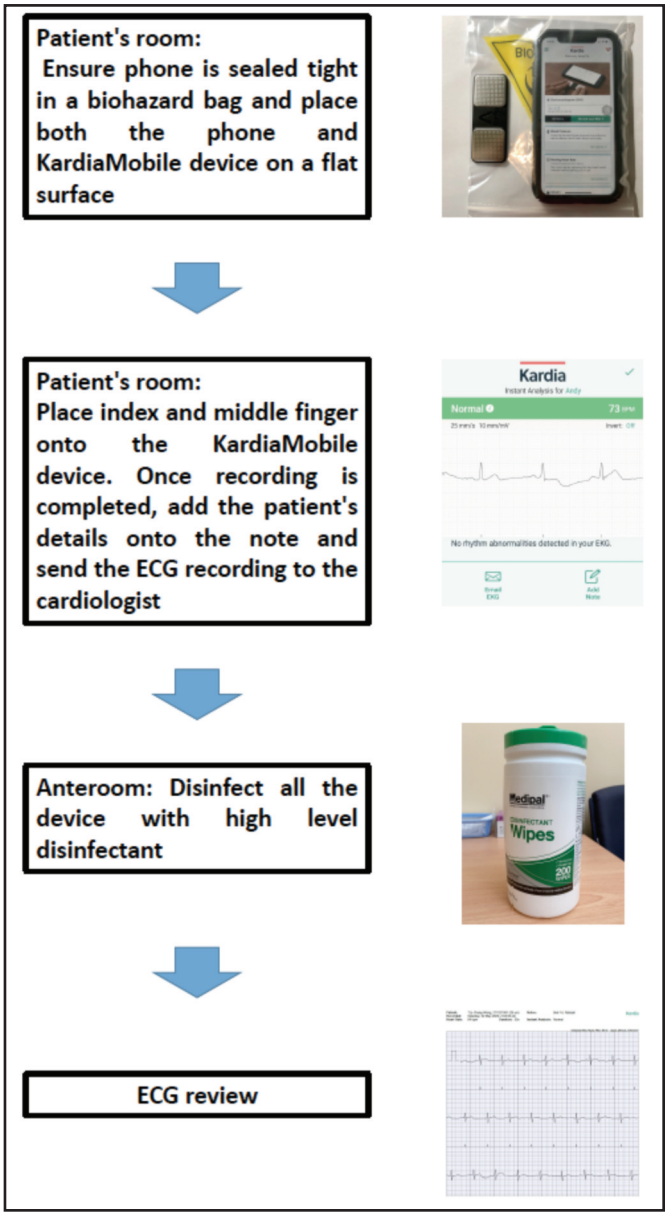

Fig. 1: Steps to use KardiaMobile device.

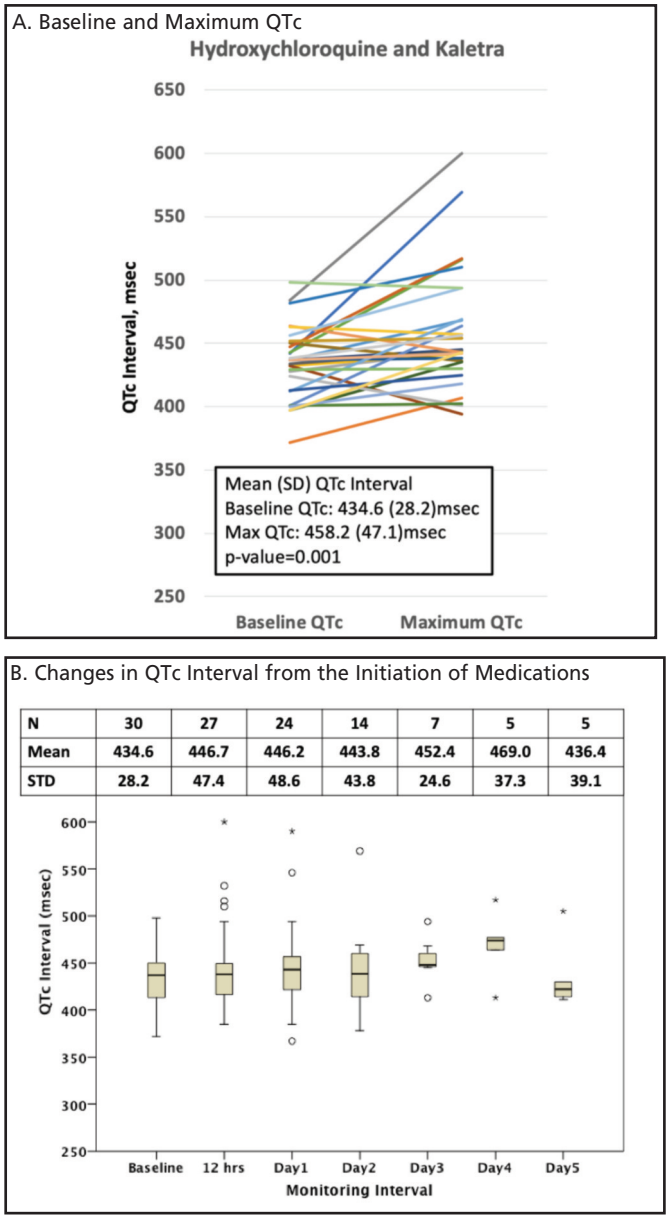

Fig. 2: (A) illustrates the changes in baseline QTc and maximum QT after hydroxychloroquine with or without lopinavir-ritonavir. The maximum QTc interval was significantly prolonged compared to baseline (434.6±28.2msec vs 458.6±47.1msec, p=0.001). (B) illustrates the serial monitoring of QTc interval after initiation of hydroxychloroquine with or without lopinavir-ritonavir. A prolonged QTc interval of ≥500ms could happen from 12 hours to Day 5 after initiation of hydroxychloroquine with or without lopinavir-ritonavir.

Our data showed that the combination of lopinavir-ritonavir did not significantly lead to a further increase in the QTc interval. This was contrary to azithromycin, which potentiated the prolongation property of hydroxychloroquine or chloroquine when used in combination.[6,7] Nevertheless, we observed a significant trend towards prolongation of PR interval in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The clinical implication of the PR prolongation was unknown because none of the patients developed haemodynamically significant bradycardia requiring temporary pacing or chronotropic support.

The increase in QTc could be seen as early as 12 hours after the first dose of medication, and as late as Day-5 after the initiation of medication. From our observation, the QTc interval usually normalized within 72 hours after stopping the medications. This finding was consistent with the description from the previous study.[11] The relationship between QTc interval and timing of medication is crucial in designing the recommendation for frequency and duration of QTc interval monitoring for future guidelines.

The Tisdale risk score[5] was the only independent variable associated with a QTc interval of ≥500msec. Tisdale risk score was validated to predict QT interval prolongation for

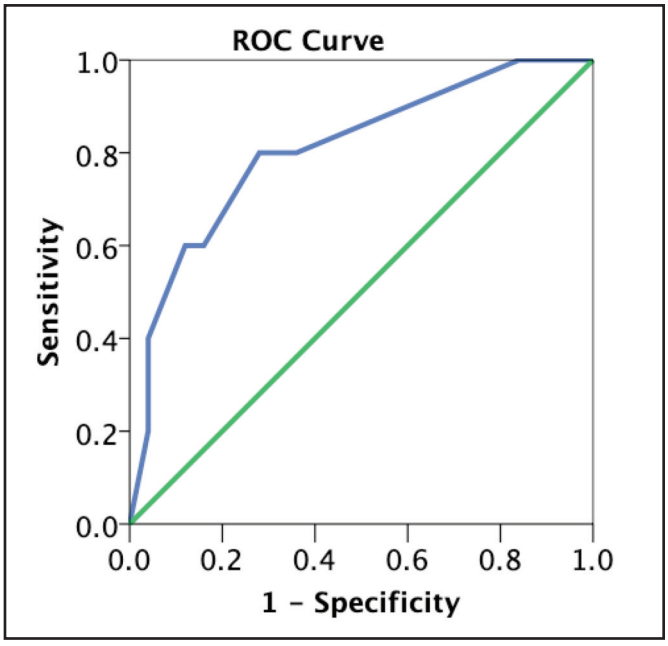

Fig. 3: Receiver Operating Characteristic Curve for Tisdale Score to QTc interval of ≥500msec. The area under the curve was 0.808 (95% confidence interval 0.59-1.00, p=0.032). Tisdale score of ≥8 has NPV of 91.7%; PPV of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500ms.

hospitalized patients. However, the utility of the Tisdale risk score was questionable in COVID-19 because there was only 2-3% of the study population was prescribed with 2 or more QT-prolonging medications. This situation is different in the COVID-19 pandemic in which COVID-19 patients were often put on two or more QT-prolonging medications.[4] The re-purposed medications for COVID-19 had put an unprecedented 'challenge test' for the QT interval. Nevertheless, our study showed that Tisdale risk score of ≥8 had a negative predictive value of 91.7%; positive predictive value of 50%, specificity of 88%; and sensitivity of 60% in predicting QTc≥500msec. In another words, the Tisdale risk score of <8 was a good predictor to predict QTc<500msec.

Monitoring of QTc interval

Our study demonstrated the utility of a smartphone electrocardiogram for monitoring QTc interval. Potential benefits include a lower risk of healthcare personal exposure, reduce the usage of resources (personal protective equipment and disinfectants), reduce manpower, and reduced electrocardiogram acquisition time. The limitations include loss of other valuable information on high-risk features of prolonging QT and its inapplicability in intensive care setting due to signal artifacts. In the context of managing patients with COVID-19, the fundamental component is that an intermittent single-lead electrocardiogram monitoring is better than no electrocardiogram monitoring.

Based on our study, QTc monitoring should include a baseline electrocardiogram done 12 hours after starting hydroxychloroquine and daily monitoring thereafter. The Tisdale score should also be calculated. We did not find added value on the calculation and monitoring of delta QTc. In the event of QTc≥500ms, drugs should be stopped. The monitoring should continue until the QTc normalized, which is usually seen within 72hrs. We did not identify any variable or score that can reliably exclude QTc monitoring. However, this approach requires further validation by future studies.

Risk of torsade de pointes and drug induced-sudden cardiac death

QTc prolongation is a surrogate for torsade de pointes and drug induced-sudden cardiac death. Interruption of hydroxychloroquine and lopinavir-ritonavir due to QTc prolongation of more than ≥500ms was seen in 10% of our patients. This was in concordance to the study done by Mercure et al (11%) and Bessière et al. (17%).[6,7] Saleh M et al., reported a lower incidence of discontinuation of medications (3.5%) due to QTc prolongation.[11]

No torsade de pointes was reported in our cohort of patients, similar to the majority of the previous studies.[7,11] This outcome may be due to our small sample size but may also be because QTc prolonging medications were stopped whenever the QTc was ≥500ms. However, Mercure et al reported a case of torsade de pointes three days after the combination of hydroxychloroquine and azithromycin was discontinued because of a QTc interval of 499 msec.[6] Nevertheless, our cohort of patients excluded severely ill patients requiring ICU care, which are more susceptible to malignant arrhythmias due to cytokine storms, myocarditis, or other factors.

LIMITATIONS

Our study population excluded COVID-19 patients requiring intensive care. Higher-risk groups may not have been represented. Hence the result may not be extrapolated to intensive care patients. Second, even though there was no outpatient treatment for COVID-19 in our study population due to local regulation, in which all patients diagnosed with COVID-19 by PCR are admitted, our study demonstrated the utility of smartphone electrocardiogram monitoring of QTc interval. This offers an alternative for monitoring the QT interval in countries practicing outpatient treatment for COVID-19. Lastly, our study had a small sample size. The result of our study may be hypothesis-generating, but these findings await validation from larger prospective studies.

CONCLUSION

QTc monitoring using Kardia smartphone electrocardiogram was feasible in COVID-19 patients treated with hydroxychloroquine with or without lopinavir-ritonavir. The use of hydroxychloroquine and lopinavir-ritonavir resulted in QTc prolongation, but no torsade de pointes or arrhythmogenic death was observed.

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DISCLOSURE

None

CONFLICTS OF INTEREST

None

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Chest radiographs in Coronavirus Disease 2019 (COVID-19)

Mohana Letchumanan, DRad[1], Adi Afiq Bin Md Anour, DRad[1], Shubash Shander Ganapathy, MPH[2], Syaman Harry, MRad[1], Nik Shah Hizan Binti Nik Lah, MMed[1], Norlimah Binti Arsad, MD[3], Nur Farhana Binti Ahmad Fisol, MBBS[4]

[1]Department of Radiology, Tawau General Hospital, Ministry of Health Malaysia, Sabah, Malaysia, [2]Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia, Selangor, Malaysia, [3]Director's Office, Ministry of Health Malaysia, Sabah, Malaysia, [4]Clinical Research Center, Tawau Hospital, Ministry of Health Malaysia, Sabah, Malaysia

ABSTRACT

Objectives: To recognize the radiographic patterns of coronavirus disease 2019 (COVID-19) in Malaysia.

Materials and Methods: Chest radiographs of patients confirmed with COVID-19 in Hospital Tawau, Sabah, Malaysia were retrospectively analyzed by two radiologists. The radiographic pattern, distribution among subgroups and evolution of the disease over time were determined.

Results: Among the 82 patients studied, 65 (79.3%) were males. Mean age of our cohorts was 37 ± 15 years. Baseline chest radiographs were abnormal in 37 patients (45.1%). Over half (52.9%) of the symptomatic patients had abnormal baseline radiograph. Among the children, patients with comorbidities, and patients 60 years of age and above, the abnormal radiographs were 14.3%, 71.4% and 69.3% respectively. Ground glass opacities were the commonest abnormal radiographic feature (35.4%), were peripherally located (35.4%) with predilection for the lower zones (29.3%). Most radiographic abnormalities were multifocal (20.7%) and frequently located in the left lung (19.5%). Radiographic recovery was observed in 15 of 18 patients (83%). Computed tomography (CT) scan demonstrated greater extent of the disease than observed in radiographs of the same patient.

Conclusions: COVID-19 pneumonia presented with a specific radiographic pattern in our cohort of patients, comprising of ground glass opacities in peripheral and basilar distribution, affecting a single lung field and was observed in both symptomatic and asymptomatic patients. Chest radiograph is a useful adjunct screening tool, and in combination with clinical and epidemiological assessment may facilitate in early diagnosis of COVID-19 pneumonia.

KEYWORDS:
COVID-19; Malaysia; chest radiograph; computed tomography

INTRODUCTION

Since it was declared as a global public health crisis in late January, the coronavirus disease 2019 (COVID-19) pandemic has expanded at an alarming rate, currently affecting over 2.8 million people globally and resulting in close 200 000 deaths (as of April 26,2020).[1] As we still strive to formulate an effective treatment and vaccine, the containment strategies are primarily focused on the rapid and accurate diagnosis of those infected, aiming to halt the further spread of this disease.

Although reverse transcriptase polymerase chain reaction (RT-PCR) assay remains a gold standard for diagnosing the infection, the emerging role of imaging as an adjunct in early detection of the infection has been emphasized in several reports.[2,3] As the disease primarily affects the respiratory system, computed tomography (CT) of chest had been used on a greater scale in China, the epicenter of the disease.[4] Characteristic patterns of lung changes of COVID-19 and its evolution over time has been laid out by many authors[5-8], hoping to accelerate the identification of the disease among the suspected individuals thus speeding the isolation process. Owing to inherent high sensitivity and fast turnover time, the radiological investigations have been focused on the use of CT.[2,9]

However, as the disease has spread outside China, the use of CT scan as a screening tool has been widely discouraged by most leading radiology organizations, mainly due to the risk of cross-infection.[10,11] Portable chest radiography has been suggested to be used as a triage tool instead of CT, to assess the severity of disease, for treatment planning and to monitor the progression of the disease.[10]

With only a handful of reports on radiographic patterns of COVID-19 infection across the literature,[12-14] we aim to familiarize radiologists and clinicians alike with the radiographic features of patients with COVID-19 infection in Malaysia. The main objectives of our study were to describe the radiographic characteristics of COVID-19 infection in general and among demographic subgroups in Tawau.

MATERIALS AND METHODS

The study was approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-20-698-54570). Informed consent was waived due to the retrospective nature of this study.

Study design and Participants

This was a cohort study carried out between 9th March and 13th April 2020 from secondary data of COVID-19 positive

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Corresponding Author: Mohana Letchumanan
Email: mohanaletchumanan@gmail.com

patients in Hospital Tawau (HT). All patients tested positive for COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) assay in HT, Sabah, Malaysia were enrolled. The demographic data, clinical findings and laboratory findings of patients were obtained from the hospital records and radiology imaging request forms. The chest radiographs (CXR) and CT images were retrieved from the electronic database and all information were keyed into a standard data collection form for the purpose of this study. Clinical outcomes were monitored up to April 18th 2020 the final date of follow-up.

Two radiologists (AA, general radiologist with two years of experience; SH, general radiologist with two years of experience) jointly reviewed all images to identify the key findings of the images. All findings were recorded based on the consensus of both radiologists. Should there be any discrepancy, disagreement or inability to reach a consensus, then a third independent radiologist (NSHNL, general radiologist with four years of experience) was consulted to determine the imaging findings.

Image Acquisition

Both baseline and follow up (CXR) were acquired in the posteroanterior projection (PA) using a portable chest radiograph device (Mobile X-ray Shimadzu, MobileArt Plus MUX-100H, Kyoto Japan). Volumetric (CT) studies were acquired without contrast medium using 16-multidetector CT scanner (Optima CT540, GE Healthcare Milwaukee, WI, USA) and reconstructed to 1.25mm thin slices in accordance to the local institutional protocol.

Image Analysis

Lung changes and lesions on CXR and CT images were reported based on the pattern of opacity, location and distribution following local guidelines by the Ministry of Health Malaysia Thoracic Special Interest Group, as adapted from the guideline by Radiological Society of North America (RSNA); Radiological Society of North America (RSNA) Consensus Statement on Reporting Chest CT Findings released in March 2020.15

Baseline and Follow up Radiographs

Pattern of lung opacities were classified into ground glass change, consolidation, interstitial (linear or reticular opacities) or nodular opacities. The distribution of the lung changes was categorized into (i) focal or (ii) multifocal; (i) peripheral, central or diffuse; (ii) right, left, or bilateral lung involvement; and (iii) upper zone, middle zone, lower zone or no zonal predominance. Peripheral and central demarcation was defined as halfway between lateral margin of the lung and hilum, while each lung is divided into three equal zones for the zonal distribution. Presence of pleural effusion, cavitation, pneumothorax, cardiomegaly and lymphadenopathy were also recorded. Overall, the radiographs were concluded as either normal, probable COVID-19, indeterminate or non COVID-19.

Radiographs were concluded as normal in the absence of any lung changes. Probable COVID-19 designated when lung changes were present at the periphery and in the lower lobes. The presence of lobar pneumonia, pulmonary edema or any other findings places the radiograph in non-COVID descriptor. An indeterminate appearance was assigned to the radiographs that do not fit into probable or non COVID-19 descriptors. Follow up CXR were assessed for the evolution of lung changes and classified as either resolution of findings, improvement or progression of findings when compared to the baseline or any available prior CXR from the same patient.

Computed Tomography Images

In HT, CT examination were performed for asymptomatic patients with suspicious baseline chest radiograph and those confirmed with COVID-19 infection demonstrating clinical deterioration. No CT examination was done for the purposes of the study, and only performed if requested by the treating physician. All CT were performed following local standard operating procedure and guideline.

Reporting guideline for CT scan followed local guideline adapted from the guideline by Radiological Society of North America (RSNA); Radiological Society of North America (RSNA) Consensus Statement on Reporting Chest CT Findings released in March 2020.[15]

The presence of typical CT appearances of COVID-19 infection (ground glass opacities, consolidation) and other features (reverse halo sign, perilobular densities and crazy paving pattern) as outlined by the local guideline were noted down, if present. The overall CT findings were categorized to typical, indeterminate, atypical appearance of COVID-19 infection and negative for pneumonia.

Statistical Analysis

Statistical analysis was performed with Microsoft Excel for Mac Version 16.18 and descriptive analysis was carried out where continuous variables were reported in mean and standard deviation and categorical variables reported in frequency and percentage.

RESULTS

A total of 82 COVID-19 patients were included in this study, most were males 65 (79.3%) and 15.9% of the total patients had co-morbidities. The average age was 37 ± 15 years (range 2 to 79 years). Seven patients (8.5%) were children, aged 18 years and below. There were also 7 patients aged 60 years of age and above in our study. On admission, 34 of 82 patients were symptomatic. Fever (38.2%) and cough (55.9%) were the most reported symptoms among the symptomatic patients. The most common co-morbidities were hypertension (8 of 82 patients) and diabetes mellitus (3 of 82 patients).

Two of three patients admitted to intensive care unit (ICU) were intubated; one succumbed to the infection (1 of 82, 1.2%); one recovered and one is still hospitalized as of the time of writing.

The demographic and clinical characteristics of the patients are summarized in Table I.

Table I: Demographics and clinical characteristics

CHARACTERISTIC	Mean ± SD / Frequency (%)
Age (years)	
Mean	37 ± 15
Range	2-79
Age Group (years)	
≤ 18 (Children)	7 (8.5)
19- 59 years	68 (82.9)
≥ 60 years	7 (8.5)
Sex	
Men	65 (79.3)
Women	17 (20.7)
Comorbidity	
No comorbid	69 (84.1)
With comorbid	13 (15.9)
Hypertension	8 (61.5)
Diabetes Mellitus	3 (23.1)
Chronic Obstructive Pulmonary Disease	1 (0.1)
Chronic kidney disease	1 (0.1)
Chronic liver disease	1 (0.1)
Others	4 (0.3)
Clinical Presentation	
Asymptomatic	48 (58.5)
Symptomatic	34 (41.5)
Fever	13 (38.2)
Cough	19 (55.9)
Runny nose	7 (20.6)
Sore throat	5 (14.7)
Loose stool	4 (11.8)

Note: Number in Parentheses are Percentages

Baseline Chest Radiograph Findings

Baseline CXRs were done between one to 19 days (average 7.8 days) after onset of symptoms. Of the 82 patients, 43 (52.4%) had normal baseline CXR, meanwhile 39 patients (47.6%) presented with abnormal CXR. Of the thirty-nine abnormal CXRs, 30 (76.9%) were concluded as probable and three (7.7%) as indeterminate. There were 6 (15.4%) abnormal CXRs reported as non-COVID with alternative diagnoses, which were consistent with pulmonary tuberculosis [5 of 6] and left hilar mass [1 of 6].

The predominant lung infiltrates were ground glass opacities (29 of 82, 35.4%) followed by consolidation (7 of 82, 8.5%). Consolidation in the CXRs generally occurred between five and eight days after onset of symptoms. Unilateral lung involvement was observed more than bilateral lung involvement (22 of 82, 26.8% vs 15 of 82, 18.3%) with a left lung predilection (19.5%). The distribution of the lung abnormalities showed a peripheral predominance (35.4%), affecting most commonly the lower zones (29.3%). Three patients showed both central involvements extending to and peripheral lung (Figure 1) and two patients had extensive lung abnormalities involving all zones of both lung fields. Pleural effusion was found in 3 (9.1%) patients. Pneumothorax and pneumomediastinum with surgical emphysema were observed in the post intubation radiographs of one patient in this study. Thoracic lymphadenopathy and cavitating lesions were not observed in our cohorts. The radiographic pattern of COVID-pneumonia summarized in Table II.

Subgroup Analysis by Sex, Symptomatic Status, Age and Comorbid

- Twenty five of 65 men (38.5%) and 8 of 17 (47.1%) women presented with abnormal radiographs that had COVID-19 radiographic features. Generally, both sexes had higher proportion of normal radiographs compared to abnormal radiographs.
- Symptomatic patients presented with greater proportion of abnormal CXRs in comparison to the asymptomatic patients (52.9% versus 32.7%).
- There were 7 patients 60 years of age and above in our study sample. Of the 7, three patients were symptomatic and 5 of 7 (71.4%) had probable findings in the baseline radiographs.
- Seven children (1-18 years) were tested positive for COVID-19 infection in our study sample and all were asymptomatic on admission. Baseline radiographs were normal in 6 patients. Bilateral perihilar interstitial lung opacities were observed in one patient (14.3%). This finding was thus concluded as indeterminate features. No follow up radiograph was performed for this patient.
- Among the 13 patients with comorbidities, 9 patients (69.2%) presented with lung abnormalities in the baseline radiograph on admission. We observed higher number of abnormal radiographs in patients with at least one comorbidity (69.2%) when compared to patients with no comorbidities (34.8%).

The distribution of COVID-19 related radiological findings among the subgroups shown in Figure 2.

Table II. Findings on Chest Radiograph and CT scan

Criteria	Findings	Frequency (%)
Baseline Chest Radiographs	Normal	45 (54.9)
	Abnormal	37 (45.1)
	Probable	30 (81.8)
	Indeterminate	3 (8.1)
	Non COVID-19	4 (10.8)
Lung Changes	Ground glass opacities	29 (35.4)
	Consolidation	7 (8.5)
	Interstitial opacities	4 (4.9)
	Nodular opacities	1 (1.2)
Distribution	Peripheral	29 (35.4)
	Central	2 (2.4)
	Diffuse	5 (6.1)
Lung Involvement	Right lung	6 (7.3)
	Left lung	16 (19.5)
	Bilateral lungs	15 (18.3)
Zonal Predominance	Upper zone	4 (4.9)
	Middle zone	3 (3.7)
	Lower zone	24 (29.3)
	No zonal predominance	6 (7.3)
Focality	Focal	17 (20.7)
	Multifocal	20 (24.4)
Other features	Pleural effusion	3 (3.7)
	Pneumothorax	1 (1.2)
	Pulmonary nodules	1 (1.2)
	Lymphadenopathy	0 (0.0)
	Other	3 (3.7)
Follow up Radiographs (n=38)	Normal baseline CXRs becoming abnormal	0 (0.0)
	Normal baseline CXRs becoming abnormal	0 (0.0)
	Complete resolution	6 (15.8)
	Improvement	9 (23.7)
	Progression	3 (7.9)
Computed Tomography (n=5)	Typical appearance of COVID-19	3 (60.0)
	Indeterminate	1 (20.0)
	Atypical	0 (0.0)
	Negative for pneumonia	1 (20.0)
	Lung Changes	
	Ground glass opacities	4 (80.0)
	Consolidation	1 (20.0)
	Special features	
	Crazy paving	1 (20.0)
	Perilobular density	1 (20.0)
	Reverse halo sign	0 (0.0)

Note: Number in Parentheses are Percentages

Follow-Up Chest Radiograph Findings

Thirty-eight patients had follow-up CXR performed with an interval of 4 to 6 days from the baseline radiographs, of which 18 were normal and 20 abnormal CXRs (16 concluded as probable, 2 as indeterminate and 2 were non-COVID) in the baseline radiograph. Only 2 intubated patients had radiographs either daily or at shorter intervals.

Of the 18 patients who had normal baseline radiographs, none developed abnormalities on follow-up radiographs. Among the 20 abnormal baseline CXRs, 2 exhibited chronic pulmonary tuberculosis changes and were designated as non-COVID, which remained unchanged during the follow up. While in the remaining 18 abnormal CXRs with probable or indeterminate COVID-19 pneumonia descriptors, radiological resolution was observed in 15 patients (83.0%) (Figure 3) on follow up CXR; 6 showed complete resolution and 9 with radiological improvement. Three patients showed progressive worsening of lung consolidation.

Chest Radiograph correlation with CT

Five asymptomatic patients in our study cohort with lung changes on baseline CXR underwent CT examination. CT scans revealed a greater extent of the lung involvement than what was depicted from the baseline radiograph. Typical imaging features of COVID-19 pneumonia of were observed in 4 patients who underwent CT examination, while one patient had no abnormality depicted on the CT examination. Bilateral peripheral ground glass opacity with a predilection for the lower lobes were observed in 3 patients. Intralobular reticulation were present in one of the patients, giving rise to the crazy paving appearance. Diffuse consolidation with atypical features (bilateral pleural effusion, pericardial thickening, pneumomediastinum and surgical emphysema) were depicted in one patient. CT findings of COVID-19 pneumonia summarized in Table II.

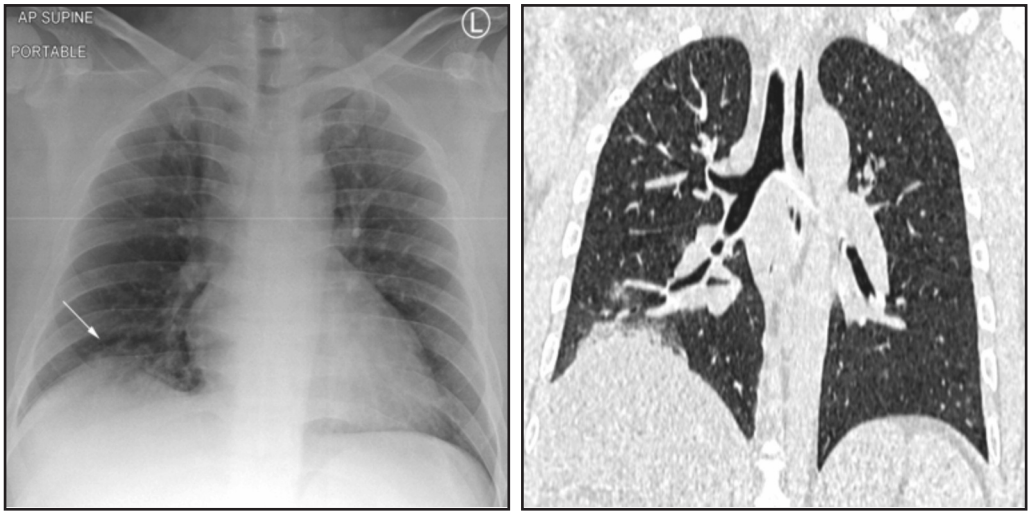

FIGURE 1A FIGURE 1A

Fig. 1: (A) Chest radiograph shows ground glass opacity at right lower zone. (B) Coronal CT image shows ground glass opacity at right lower zone corresponds to the finding on radiograph.

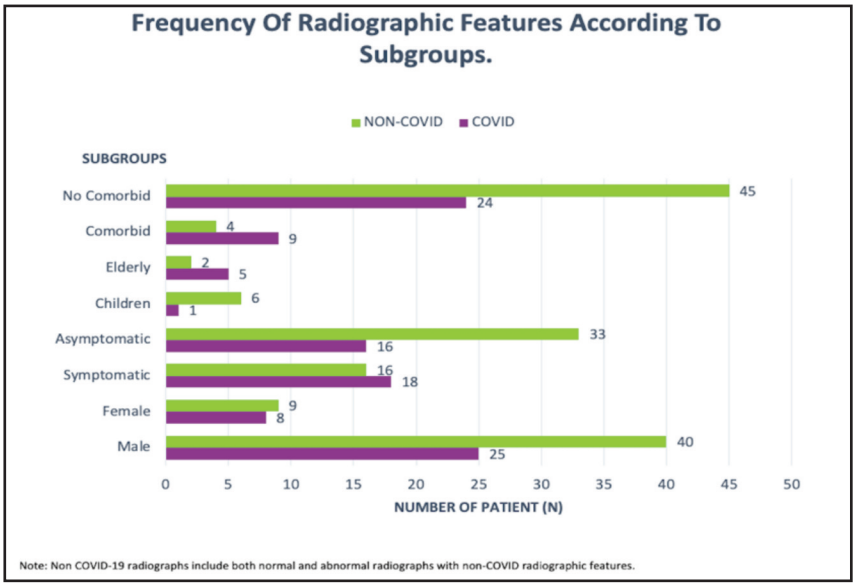

Fig. 2: Distribution of radiographs with COVID-19 and non-COVID-19 features among the various subgroups.

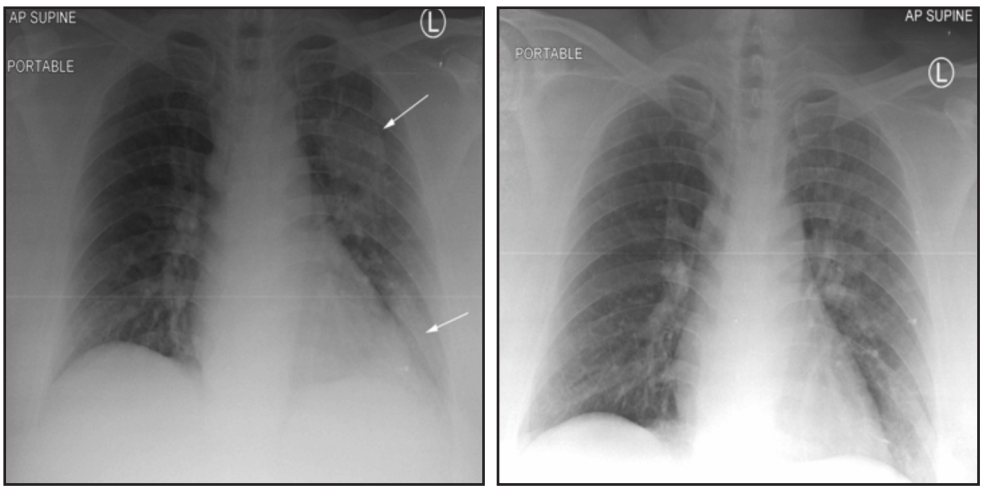

FIGURE 1A FIGURE 1B

Fig. 3: (A) Asymptomatic COVID-19 patient with consolidation at the left upper zone (arrow) and ground glass opacities at the left lower zone in the baseline radiograph. (B) Resolution of the lung abnormalities on day 5 of admission.

DISCUSSION

To the best of our knowledge, imaging profile of COVID-19 infection in Malaysia has not been published as yet. Patients of all ages were affected by the disease with predilection for males (79.3%). Greater proportion (54.9%) of the study sample presented with normal chest radiographs. Ground glass opacities (35.4%) and unilateral lung involvement (26.8%) were the predominant features in the abnormal radiographs, contrary to a few published studies which reported consolidation and bilateral lung involvement.[3,4] The lung changes were predominantly multifocal and peripheral in distribution more commonly affecting the lower zones, consistent with previous studies.[3-4,14,16,17] Patient who were sixty years of age and above, were symptomatic or had comorbidities were more common to have abnormal radiograph at admission, similar to the trend observed by other researchers.[14,18] Children aged 18 years and below, were all asymptomatic with 85.7% presented with no pneumonic changes in the radiograph. Radiological recovery observed in 83% of our study sample with one patient succumbing to the infection.

The mode of transmission suspected for the majority of our patients, more than 60% were directly linked to a religious event, thus explaining the young age and male predominance in our study sample. Females and children were predominantly the secondary contacts of these cases. Although we observed higher percentage (8.5%) of children contracting the disease than reported in the previous studies[19], all remained asymptomatic throughout the disease course. Milder form of the disease among children than their adult counterparts has been well reported in many studies.[19,20] More than half (48 of 82, 58.5%) of our patients were asymptomatic at presentation. This result is contrary to a large case series by the Chinese Center for Disease Control and Prevention which reported 1% of the study population were asymptomatic.[21] Patients presenting with pneumonic changes on radiograph at admission varies across the literature and were reported between as high as 60-80% in few earlier studies in China and Hong Kong.[3,4] Contrarily, we observed lower (45.1%) proportion of abnormal radiographs in our study group similar to the report from a case series in Korea and a study in ambulatory care setting in New York.[14,16] Among the abnormal CXRs, single lung involvement was more common (59.5%) and has been described lately, contrary to the more commonly reported bilateral lung involvement in earlier studies.[6,14,22] We attribute this finding to lower sensitivity of radiograph in detecting subtle lung changes in the early course of disease, in agreement with Wong et al.[3] Pleural effusion, notably were uncommon and observed only among patient above 40 years of age consistent with previous observations.[3,8,14,17-18] Although it has been described in only a few case reports, pneumothorax and pneumomediastinum with diffuse chest wall subcutaneous emphysema, are exceedingly rare findings, and were only present in our intubated patients, highly suggestive of complication of mechanical ventilation.[23,24] In HT, computed tomography was reserved only for asymptomatic patients with suspicious baseline chest radiograph and those confirmed COVID-19 demonstrating clinical deterioration. The predominant CT features as seen in the other previous studies were multilobar, bilateral lung ground glass opacities with peripheral distribution, and affection for the lower zones.[3,4,8] Consolidation was found in our patient admitted to ICU, consistent with a previous report by Huang et al.[6] As in previous reports, crazy paving was less frequent than ground glass opacities alone and consolidations, observed in a single patient with disease progression in our study.[25] In all these patients, the subtle abnormalities and single lung involvement on chest radiograph appeared more extensive on CT with bilateral lung involvement suggestive of the higher sensitivity of CT in detecting abnormalities.9 Follow up CXRs were used for clinical monitoring of COVID-19 infection during hospitalization in HT. We observed higher radiographic recovery in our study sample at 83%, as opposed to Ai et al., who observed 42% radiological recovery on CT prior to RT-PCR becoming negative.9 However, we should mention that we didn't obtain the virologic recovery data to make a valid comparison. Resolving lesions are subtle and may go unrecognized on CXR in comparison to CT.

Taking into account our study was a retrospective and observational study, there are several inherent limitations. Firstly, the study sample was small, as the study was limited to a single institution. The interval between RT-PCR result and baseline chest radiographs were not uniform (range of 1 to 20 days), largely due to the remote testing location of the COVID-19 designated laboratories, hence, baseline radiographs were obtained at various phases of illness, which may contribute to missed early COVID-19 pulmonary changes. Secondly, the radiologists interpreting the images were not blinded to the RT-PCR assay result and clinical manifestation of the patients, thus we cannot exclude some degree of reporting bias. Subtle radiographic features in the poor inspiratory supine radiographs may be also be under or overestimated. We had also described the pattern and frequency of lung findings among all COVID patients, rather than among patients with abnormal CXRs only, as to guide radiologists and clinicians on the most common findings and the frequency one would expect to find these changes when they review all COVID-19 patient CXRs.

CONCLUSION

Although a greater proportion of our patients presented with normal baseline radiographs, generally speaking, the abnormal group demonstrated specific patterns of COVID-19 complementing the radiographic and CT findings in the literature. Familiarization with the radiographic appearance of the disease may help in the early detection of the disease, especially this is pertinent in remote and economically challenged regions where access to reliable RT-PCR testing is limited or delayed and portable chest radiographs are more readily available instead. We may also reasonably conclude that chest radiograph is a useful adjunct screening tool for early isolation and mitigation of suspected patients specifically the symptomatic, 60 years of age and above and those with comorbidities while waiting for the RT-PCR result.

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ORIGINAL ARTICLE

Psychological symptoms among healthcare workers handling COVID-19 patients

Sim Sze Kiat, MS[1], Lau Bik Liang, MS[2], Siti Rosnaini Zaila Ramli, Sijil Matrikulasi KPM[1], Nur Hazira Abdul Muti, Sijil Asasi Sains Hayat Unimas[1], Nur Muzfirah Aniqah Abdul Rahman, Sijil Matrikulasi KPM[1], Jevitha Panicker Balachandran, Sijil Matrikulasi KPM[1], 'Alya Syafiqah Hamzah, Sijil Asasi Sains Hayat UM[1]

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, [2]Department of Neurosurgery, Sarawak General Hospital, Kuching, Sarawak

ABSTRACT

Introduction: Healthcare workers serve as the frontliners against the coronavirus 2019 disease (COVID-19) and this puts them most at risk of infection as they attend to numerous patients with unknown status. This study aimed to examine stress, anxiety, and depression among healthcare workers caring for COVID-19 patients in Sarawak General Hospital (SGH), Malaysia.

Materials and Methods: This cross-sectional observational study conducted in SGH during the pandemic with an online self-administered questionnaire composed of two parts, the socio-demographic characteristics, and the Depression Anxiety Stress Scale (DASS).

Results: A total of 105 healthcare workers responded to this study. A questionnaire in both Bahasa Melayu and English was used. The findings showed that all healthcare workers had mild anxiety, with the majority experiencing mild stress (57.1%), and almost half of the respondents experiencing mild depression (41%). Female subjects had a significant higher mean score in anxiety level and stress level compared to male subjects (10.0±3.20 vs. 8.6±2.93, $p<0.05$; 14.1±4.76 vs. 10.7±3.70, $p<0.05$, respectively). Staff who were transferred from other units to handle COVID-19 cases experienced more psychological symptoms. There were significant correlations between the depression, anxiety and stress levels among the healthcare workers and the number of children they had ($r=0.739$, $p=0.001$; $r=0.642$, $p=0.001$; $r=1$, $p=0.001$ respectively). However, the stress level among the healthcare workers was reversely correlated with their years of working experience ($r=-0.199$, $p=0.042$).

Conclusion: This study identified some socio-demographic factors associated with increased levels of stress, anxiety and depression among the healthcare workers during pandemic, which may lay ground for future interventions.

KEYWORDS:
Stress level, psychological symptoms, healthcare workers, COVID-19

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been declared as a pandemic by the World Health Organization (WHO) on 11th March 2020.[1] The WHO (2020) reported that no treatment has currently been shown to prevent or cure the disease, but there are coordinated efforts to develop vaccines and medicines for the prevention and treatment.[2] Many people have been directly or indirectly affected by the pandemic caused by the virus, and to the WHO it spreads through close contact via small droplets produced by coughing or sneezing, as well as by touching contaminated surfaces, according.[2] Doctors, nurses, and medical assistants play an important role as the frontliners in the fight against COVID-19, but they are also the most at risk of infection as they attend to numerous patients with unknown status. Bandyopadhyay et al. identified that a total of 152,888 infections and 1,413 deaths due to COVID-19 have been reported among healthcare workers in affected countries; 71.6% of those infected were women and 38.6% were nurses, while 70.8% of those who died were men, and 51.4% were doctors.[3] The total number of infections and deaths reported in healthcare workers was 3.9% and 0.5% of the total number of 3,912,156 patients with COVID-19 worldwide and 270, 426 COVID-19 deaths worldwide respectively.[3]

The mental status of healthcare workers, who may experience anxiety, depression, acute stress disorders, burnout, and post-traumatic stress disorders, should be of great concern to us all. Previous studies conducted during earlier world pandemic incidents reported that the prevalence of anxiety, depression, and stress commonly occur among healthcare workers during and after outbreaks. Further, these psychological symptoms can lead to long-lasting effects, and cause delayed urgent response, as well as jeopardised attention and decision-making during the current pandemic.[4] Based on previous studies, factors that contribute to stress in healthcare workers are their welfare of family members, closures of schools and daycares, and access to appropriate personal protective equipment (PPE).[5] Work experience plays an important role in helping healthcare workers deal with a pandemic. A study conducted in Canada during the outbreak of SARS reported that healthcare workers with fewer years of clinical experience are prone to experience prolonged psychological distress.[6]

Immense pressure and long working hours can be one of the causes of stress among healthcare workers, and this can

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Corresponding Author: Sim Sze Kiat
Email: sksim@unimas.my

further affect them mentally, physically, and emotionally. A study by Melchior et al., found that people who work in an environment with high workload and excessive pressure are more at risk of depression or anxiety compared to those who work under low physiological work demands.[7] This shows that healthcare the psychological wellbeing of workers should not be ignored, so they can provide the highest standards of care when treating patients while they work in high pressure environments. The aim of this study was to examine stress, anxiety, and depression among healthcare workers caring for patients with COVID-19 in Sarawak General Hospital (SGH), Malaysia.

MATERIALS AND METHODS

Study population

During the pandemic, we conducted a cross-sectional observational study to determine the stress, anxiety and depression levels of healthcare workers caring for patients with COVID-19. This study was conducted in Sarawak General Hospital (SGH), Malaysia, from June 2020 until July 2020. A convenient sampling method was used to select the participants. The sample size was determined using Raosoft, an online sample size calculator (http://www.raosoft.com/samplesize.html).[8] The estimated population of the study was around 150, confidence level was set to 95%, and the margin error was 5%. The estimation of the minimum possible sample size was 109. The inclusion criteria were healthcare workers who cared for COVID-19 patients. A self-administered questionnaire was used to identify the socio-demographic factors that might associate with the psychological symptoms among healthcare workers.

Measures and Variables

Psychological symptoms were assessed using the Depression Anxiety Stress Scale (DASS). The questionnaire was in both Bahasa Melayu and English to make it easier for the participants and minimise any misinterpretation. The questionnaire was comprised of two parts. Part A assessed the socio-demographic characteristics of patients, which included age, gender, family structure, profession, working experience, and educational level. Participants were not asked to provide any personal information on the questionnaire. Part B was the DASS test, which was divided into depression, anxiety, and stress subscales, with seven questions for each subscale. For each question, the lowest score was 0 and the highest was 3; the highest total score for each category was 21.9 For the total score, the sum of each subscale was multiplied by two, which shows the levels of stress, anxiety, and depression scored by the respondents where the range of each subscale was different.9 The categories for the stress level scores were: normal (0-10), mild (11-18), moderate (19-26), severe (27-34), and extremely severe (35-42). In terms of anxiety, the ranges were: normal (0-6), mild (7-9), moderate (10-14), severe (15-19), and extremely severe (20-42). Lastly, for the levels of depression, the score categories are as follows: normal (0-9), mild (10-12), moderate (13-20), severe (21-27), and extremely severe (28-42). All data were collected through an online questionnaire using Google Forms.

Procedure

An invitation email was sent to the heads of the departments at SGH via the coordinating staff that explained the objectives of the study, inclusion criteria for subject selection, which were attached to the patient information sheet (PIS), both in Bahasa Melayu and English, and the link to access the online questionnaire. The PIS and link to the questionnaire were disseminated to the healthcare workers through their respective heads of departments. Participants were able to decide whether they agreed or disagreed to participate in the study after reading the PIS. Implied consent was obtained through Google Forms (at the beginning of the questionnaire). Participants were not required to sign into any account to fill in the survey, which took approximately 10 to 15 minutes to complete. The final submission date for the questionnaire was listed as the 13th of July 2020, which was about 10 weeks after the distribution of the questionnaire. After such time, the link was disabled and no other personnel except the researchers was able to access it. The data were then retrieved from Google Forms and recorded in a separate offline Excel document, before being permanently deleted.

Ethics and confidentiality

Ethical approval was obtained from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-20-819-54744), and the University Malaysia Sarawak (UNIMAS) Faculty of Medicine & Health Sciences Research Ethics Committee (UNIMAS/NC-21.02/03-02 Jld.4 (91) prior to the start of any study-related activities. The researchers adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practise Guidelines. All the information recorded in the offline Excel document was kept confidential and permanently deleted from the computer system two months after the final report was completed. Personal information (name, identity card, passport number, staff number, phone number, or email address) was not required by the questionnaire. The subjects were coded by random numbers according to the time of submission. All information collected was used only for research purposes and were not disclosed to the participants' supervisors/employers. The participants were allowed to withdraw from the study at any time before the conclusion of data collection.

Statistical Analysis

The collected data were coded, entered, and analysed using Statistical Package for Social Sciences Program (SPSS) version 22.0. Descriptive analysis, median, mean and standard deviation were calculated. An independent t-test and analysis of variance (ANOVA) test were conducted to compare the DASS scores of healthcare workers according to their socio-demographic features. Pearson's correlation was used to evaluate the relationship between the DASS scores and years of working experience, number of children, number of working days per week, and number of working hours per day. Findings were considered statistically significant at the $p<0.05$ level.

RESULTS

Socio-demographic profile of the respondents

Table I summarises the socio-demographic profile of the respondents. The mean age of the respondents was 32.7 years. Among the 105 healthcare workers, 31.4% were males and 68.6% were females; 43.8% were doctors, 43.8% were nurses, 10.9% were medical assistants, and 1.9% were pharmacists and medical laboratory technicians. The mean years of service experience for the respondents was 8.5. Among all of the respondents 61.9% were married, while 38.1% were single. A majority of the respondents, 87.6%, were worried about spreading COVID-19 to family members.

DASS distribution of healthcare workers.

Table II shows the distribution of the respondents based on the classification of their stress, anxiety, and depression levels. Among the respondents, 42.9% experienced normal stress levels, while the others 57.1% experienced mild stress. In addition, all of the respondents experienced mild anxiety, while 59% showed normal depression levels and 41% showed mild depression levels.

DASS score of healthcare workers according to their socio-demographic profiles

Independent t-tests were conducted to compare the DASS scores of healthcare workers according to their socio-demographic data. As shown in Table III, there was a significant difference in the mean score of the stress levels between the male and female groups (10.7±3.70 vs. 14.1±4.76, $p<0.05$). There was also a significant difference in the mean score of the anxiety levels between both groups (8.6±2.93 vs. 10.0±3.20, $p<0.05$). However, no significant difference was found for the depression levels.

Significant differences were found between single and married groups for all three variables: stress, anxiety and depression. Significant differences for depression levels were only found between those who lived and did not live with their families (9.7±3.31 vs. 11.5±4.32, $p<0.05$). Moreover, no significant differences in the mean scores were found between participants who answered 'yes' and 'no' to the question of whether they were worried about spreading COVID-19 to family members. In terms of sleeping disturbances, significant differences were noted for stress, anxiety, and depression levels between the groups who did and did not experience sleeping disturbances since the MCO started. Finally, in terms of transferring from other units to handle COVID-19 patients as a frontliner, there was a significant difference in the mean score of the stress levels among the groups that did and did not transfer (16.1±3.52 vs. 12.8±4.74, $p<0.05$). There was also a significant difference between these groups in terms of both anxiety (11.7±3.24 vs. 9.3±3.11, $p<0.05$) and depression (13.4±4.19 vs. 10.1±3.67, $p<0.05$).

An ANOVA test was conducted to compare the DASS scores of healthcare workers with different educational levels and profession statuses. From Table IV, it can be seen that there were no significant differences noted in the mean scores of stress, and anxiety or depression levels across the different educational level groups. Similarly, no significant differences were found in the stress, anxiety, and depression levels of the healthcare workers across different professions.

Relationship between DASS score and years of working experience, number of children, working days per week, and working hours per day

Pearson's correlations were conducted to evaluate the relationship between the DASS scores and years of working experience, number of children, number of working days per week, and number of working hours per day. From Table V, it can be seen that there was a significant correlation between the stress level and years of working experience followed by the number of children the respondents had ($r=-0.199$, $p<0.05$ vs. $r=1$, $p<0.05$). The more years of working experience, the lower the stress level of the respondents. The higher the number of children of the respondents, the higher their stress levels with this factor being perfectly correlated. Furthermore, there was no significant correlation between the stress levels and number of working days per week or number of working hours per day. There was no significant correlation between anxiety levels and years of working experience ($r=-0.101$, $p>0.05$). In addition, there was no significant correlation between anxiety levels and the number of working days per week ($r=-0.049$, $p>0.05$), and between anxiety levels and the number of working hours per day ($r=-0.086$, $p>0.05$). As for depression levels, there was no significant correlation between depression levels and the years of working experience ($r=-0.150$, $p>0.05$), and between depression levels and the number of working days per week ($r=0.093$, $p>0.05$), or working hours per day ($r=-0.026$, $p>0.05$).

DISCUSSION

The COVID-19 virus that struck the world can have detrimental effects on the mental status of healthcare workers, such as their stress, anxiety, or depression levels. This study used the DASS to report the relationships between the levels of stress, anxiety, and depression and the socio-demographic factors of healthcare workers facing the COVID-19 outbreak in SGH. The overall findings of this study shows that all healthcare workers had mild levels of anxiety, with the majority of them experiencing mild stress, and almost half those sampled experienced mild depression. This is in agreement with a report stating that increased anxiety levels are the most prevalent among healthcare workers during and after an outbreak, followed by depression, and stress.[4] However, none of the respondents scored within the moderate range on any of the DASS subscales, showing that this pandemic is only mildly associated with stress, anxiety, and depression levels among healthcare workers.

Gender was found to be associated with stress and anxiety levels, with more females experiencing mild stress and anxiety compared to males. However, both males and females were more associated with stress than anxiety. According to a study by Jianbo et al., stress, depression, anxiety and insomnia symptoms were more severe in nurses (7.1%), women (5.8%) and frontline workers (1.7%) compared to physicians (4.9%), men (3.4%) and second-line workers (0.4%).[10]

Factors such as transfers to COVID-19 frontline units, sleep disturbances, having children at home, and respondents' marital status were also shown to be related to stress, anxiety, and depression levels of healthcare workers in the present

Table I: Socio-demographic profile of respondents (N=105)

	n	%	Mean (SD)
Age (year)			32.7 (±5.34)
Gender			
Male	33	31.4	
Female	72	68.6	
Profession			
Doctor	46	43.8	
Nurse	46	43.8	
Medical assistant	11	10.5	
Other (Pharmacist, medical laboratory technician)	2	1.9	
Educational level			
Diploma	48	45.7	
Undergraduate	27	25.7	
Postgraduate	19	18.1	
Doctorate	2	1.9	
Other (Post-basic diploma)	9	8.6	
Years of experience			8.5 (±5.61)
Work unit			
Accident and emergency department	31	29.5	
Intensive care unit	28	26.7	
Infectious disease unit	10	9.5	
Other (Medical ward, surgical ward, haemodialysis unit, obstetrics and gynaecology and biochemistry unit)	36	34.3	
Marital status			
Married	65	61.9	
Single	40	38.1	
Staff with children			
Yes	53	50.5	
No	52	49.5	
Living with family during the COVID-19 pandemic			
Yes	64	61	
No	41	39	
No. of working days per week			5.7 (±0.86)
No. of working hours per day			9.6 (±5.81)
Worried about spreading COVID-19 to family members			
Yes	92	87.6	
No	13	12.4	
Sleeping disturbances since Movement Control Order (MCO) started			
Yes	27	25.7	
No	78	74.3	
Transferred from other units to handle COVID-19 as frontliner			
Yes	9	8.6	
No	96	91.4	

Table II: DASS distribution of healthcare workers

	n	%
Stress		
Normal (0-10)	45	42.9
Mild (11-18)	60	57.1
Moderate (19-26)	0	0
Severe (27-34)	0	0
Extremely severe (35-42)	0	0
Anxiety		
Normal (0-6)	0	0
Mild (7-9)	105	100
Moderate (10-14)	0	0
Severe (15-19)	0	0
Extremely severe (20-42)	0	0
Depression		
Normal (0-9)	62	59
Mild (10-12)	43	41
Moderate (13-20)	0	0
Severe (21-27)	0	0
Extremely severe (28-42)	0	0

Table III: DASS score of healthcare workers according to socio-demographic variables

Associated Factors	Mean (±SD)		
	Stress	Anxiety	Depression
Gender			
Male	10.7 (3.70)	8.6 (2.93)	9.6 (3.70)
Female	14.1 (4.76)	10.0 (3.20)	10.7 (3.85)
p -Value	0.001	0.034	0.171
Marital status			
Married	12.2 (4.14)	9.0 (2.80)	9.5 (3.07)
Single	14.5 (5.30)	10.4 (3.63)	11.7 (9.5)
p -Value	0.021	0.036	0.010
Living with family during the COVID-19 pandemic			
Yes	12.4 (4.05)	9.2 (2.97)	9.7 (3.31)
No	14.1 (5.52)	10.1 (3.43)	11.5 (4.32)
p -Value	0.094	0.135	0.025
Worried about spreading COVID-19 to family members			
Yes	12.9 (4.71)	9.4 (3.13)	10.1 (3.57)
No	13.7 (5.01)	10.3 (3.52)	12.2 (5.05)
p -Value	0.596	0.356	0.180
Sleeping disturbances since Movement Control Order (MCO) started			
Yes	15.8 (4.39)	11.9 (3.71)	12.7 (3.99)
No	12.1 (4.49)	8.7 (2.51)	9.5 (3.41)
p -Value	0.001	0.001	0.001
Transferred from other units to handle COVID-19 as frontliner			
Yes	16.1 (3.52)	11.7 (3.24)	13.4 (4.19)
No	12.8 (4.74)	9.3 (3.11)	10.1 (3.67)
p-Value	0.041	0.035	0.011

*p value<0.05 indicated a significant difference.

Table IV: DASS score of healthcare workers according to education and profession

	Stress	Anxiety	Depression
Education			
Diploma	13.4 (3.99)	9.5 (3.12)	10.0 (3.29)
Undergraduate	12.3 (5.86)	9.2 (2.95)	10.4 (4.78)
Postgraduate	13.0 (5.27)	10.9 (3.98)	11.6 (4.34)
Doctorate	11.5 (6.36)	8.0 (1.41)	12.5 (0.71)
Other	13.8 (3.77)	8.1 (1.27)	9.0 (1.41)
P Value	0.870	0.172	0.406
F Value	0.311	1.630	1.010
Profession			
Doctor	12.5 (5.41)	9.7 (3.39)	11.1 (4.54)
Nurse	14.2 (3.82)	9.4 (2.83)	10.0 (3.17)
Medical Assistant	10.2 (2.27)	8.6 (3.23)	9.4 (2.73)
Other	16.5 (10.61)	13.0 (5.66)	7.5 (0.71)
P Value	0.137	0.329	0.236
F value	2.935	1.159	1.437

*p value<0.05 indicates a significant difference

Table V: Relationship between DASS score and years of working experience, number of children, working days per week, and working hours per day

	Depression		Anxiety		Stress	
	r value	p value	r value	p value	r value	p value
Years of working experience	-0.150	0.126	-0.101	0.306	-0.199	0.042
No. of children	0.739	0.001	0.642	0.001	1	0.001
No. of working days per week	0.093	0.345	-0.049	0.617	0.035	0.720
No. of working hours per day	-0.026	0.791	0.086	0.386	0.003	0.976

*p value<0.05 indicated a statistically significant correlation

study. It was observed that all these factors were associated with higher levels of mental stress among healthcare workers, followed by depression and anxiety. Specifically, healthcare workers who were transferred to COVID-19 frontline units were more stressed, anxious, and depressed compared to those who were not. This can be due to the differences in workload as COVID-19 frontline healthcare workers tend to work more compared to those in other departments. Furthermore, having to work in a new team with a new protocol and standard operating procedures may be an additional burden. In addition, knowing that working in the COVID-19 frontline unit is associated with a higher risk of becoming infected as exposure to high-risk patients increases, may be one of the reasons for the transfer contributing to stress, anxiety, and depression among healthcare workers.

In addition, the pandemic was also found to be associated with sleep disturbances among healthcare workers. Even though only 25.7% of healthcare workers reported sleep disturbances, the present study showed that they were more prevalent among those experiencing mild stress, anxiety, and depression. This is consistent with a previous study which stated that the levels of anxiety among healthcare workers in China significantly affected stress levels, leading to a reduction in self-efficacy and sleep quality.11 Moreover, the levels of stress, anxiety, and depression were associated with whether the staff has children; the higher the number of children, the higher their levels for these psychological symptoms.

Married workers not only needed to worry about their own protection, but also the safety of their family members, as they might be the source of infection to their loved ones. Mild stress, anxiety, and depression were found to be associated with single healthcare workers more than married ones, which could be explained by not having any support from partners. As shown in a study by Han et al., anxiety and stress levels in healthcare workers can be reduced by providing social support through family and friends, which helps improve their self-efficacy, resulting in better sleep quality.[11] Finally, it was also shown that the living environment is associated with depression levels; those who were not living with their families tended to have higher depression rates compared to those who had their family's support after they got off work.

The other aim of this study was to assess the relationship between years of working experience and the stress levels of healthcare workers. The longer the working experience, the lower their stress levels when confronting the COVID-19 pandemic. This is consistent with the findings of Paul and Teris, that showed that frontline nurses with clinical experience of less than 10 years were more prone to stress.[12] In another study conducted on nurses by Caputi and Humpel, it was shown that nurses with longer working experience were less associated with occupational stress than those with shorter working experience.[13] Another study conducted among public health nurses in Taiwan by Wang and Lee, reported that occupational stress was more prominent in younger public health nurses with shorter working experience.[14] Therefore, working experience is an important factor as it helps to provide a realistic understanding of emotional and physical aspects of working with patients. The results of our study suggest that supportive interventions can be provided to healthcare workers with shorter working experience as they are more likely to experience psychological distress.[15]

In general, healthcare workers caring for patients with COVID-19 in SGH experienced mild levels of stress, anxiety, and depression. Staff who were transferred from other units to handle COVID-19 cases experience more psychological symptoms. And healthcare workers with longer period of work experience have lower stress levels compared to others.

LIMITATIONS OF THE STUDY

This study has a few limitations. This was a single-centred study and conducted using an online self-administered questionnaire with convenience sampling method. The information gathered here may not represent other hospitals. The study could be improved by including multi-centres, applying probabilistic sampling (such as random sampling and stratified sampling), and using multivariate analysis in order to control for confounding factors.

CONCLUSION

The psychological symptoms among healthcare workers during pandemic should not be ignored, as these can affect their work performance in treating COVID patients, especially now that there is still no cure and frontliners are expected to continue in this fight against the disease for the unforeseeable future. Besides, these psychological symptoms may lead to long-lasting health effects as well. Mental health screening is important during pandemic to identify the healthcare workers at risks, and the DASS is a simple and useful screening tool for this. This study has identified some sociodemographic factors that were associated with the levels of stress, anxiety and depression among the healthcare workers, which may lay the grounds for future interventions, for example, early identification and psychological counselling for vulnerable groups (female staff, unmarried staff, staff with children, staff who stays away from family, and staffs being transfer to frontline from other units). The findings of this study may also be a useful reference for other frontliners such as police and army force.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Acceptance towards social network information system for earlier detection of Influenza outbreak

Muhammad Hafiz Bin Sulaiman, MScCommHealth, Azimatun Noor Aizuddin, PhD, Rozita Hod, PhD, Sharifa Ezat Wan Puteh, PhD

Department of Community Health, Faculty of Medicine, National University of Malaysia

ABSTRACT

Introduction: Influenza outbreak causes high economic burden to Malaysia and other countries in South East Asia. Scientists have found a relatively new way to detect influenza outbreaks early thus reducing the burden of disease by early intervention. This new technology is a social network information system which uses Facebook or Twitter data to detect potential influenza cases. Such system is good to be developed by the Malaysian government as it can detect influenza outbreaks three weeks earlier than the normal pathway. However, to implement this we require good evidence that the development will be accepted by potential users.

Objective: This study was looking at the acceptance towards using social network information system among public health workers.

Materials and Method: This study was done on 205 Malaysian One Health University Network (MyOHUN) members through email and physical survey.

Results: Results show that 62.4% public health workers accepted the use technology. The acceptance was shown to be associated with performance expectancy ($p<0.05$). However, unlike the very famous Unified Theory of Acceptance and Use of Technology (UTAUT) model, the acceptance of social network information system was not associated with effort expectancy, social factors, facilitating conditions and socio-demographic factors. Therefore, it is suggested that social network information system be developed by the authorities in Malaysia, and be developed in a way that the system could strongly increase performance in detection of outbreak earlier than the current normal pathways. As such the system to be accepted and used, it must be sensitive, specific and be able to detect influenza outbreak early

Conclusion: The development of social network information system is feasible as it is highly accepted and it's potential to improve early detection of influenza outbreak.

KEYWORDS:
Social network information system, early detection, Influenza outbreak

INTRODUCTION

Recently, computer scientists have found ways to use social network data to provide a much earlier warning of potential outbreaks of influenza to warn workers in diseases the field of surveillance. Computer scientists collect data from social network provider such as Twitter and Facebook and process those data to eventually produce information that can alert epidemiologists about potential outbreaks two to four weeks earlier than the formal surveillance system could offer.[1]

As the social network information is able to locate the potential outbreaks, the surveillance staff can be instructed to examine animals (including birds and pigs) in the location indicated by the social network information.[2] This earlier checking of animals in affected areas will allow for: the killing of birds and pigs at the affected area quickly; reduce the overall extent of influenza thus preventing potential pandemic events; and to plan for vaccination of human and animals early, thus reducing the influenza spread.[3,4]

The development of social network information system for the purpose of disease surveillance is actively ongoing in developed countries including the United States of America, Canada, the United Kingdom and Japan. Most of the research on social network application in influenza surveillance however is done in North American countries (The United States of America and Canada).[5]

Developing social network information system for disease surveillance by the Malaysian government should not be initiated without the input from the end users who will be finally using it on a day-to-day basis. This is to make sure that the government does not invest in the failing project if it turns out that the workers will not accept to use the social network information system.

Assessing acceptance is really important to decide whether developing the social network in Malaysia will be useful. Doing acceptance measurement in this case is similar to doing a market research prior to developing and introducing a new product.[6] Without an appropriate feedback from the potential users, a company might over-value their products just to know at the end that their products are not adopted by users.

Development of a new technology is expensive.[7] To develop a social network information system requires continuous recruitment (and payment of salary) of several professional computer scientists, expert statisticians, medical epidemiologists and other support staff are needed. Hardware includes servers that costs around MYR 30,000 and

This article was accepted: 14 January 2021
Corresponding Author: Azimatun Noor Aizuddin
Email: azimatunnoor@ppukm.ukm.edu.my

warehouse rent that costs around MYR 1500 per month. Before a large capital is invested into such development, an acceptance study such as this one should be done so that the probability of investment loss is reduced.

The aim is to determine the rate of public health workers who accepted to use social network information system for the purpose of influenza detection; to assess the association between (a) socio-demography and acceptance; (b) performance expectancy and acceptance; (c) effort expectancy and acceptance; (d) social factors and acceptance; (e) facilitating conditions and acceptance; (f) system-specific knowledge and acceptance; among public health workers.

MATERIALS AND METHODS

Unified Theory of Acceptance and Use of Technology (UTAUT) model is the guide of our study design (Venkatesh, 2003).[8] In the original UTAUT model, there are four main effects that affect acceptance: performance expectancy (PE), effort expectancy (EE), social factors (SF) and facilitating conditions (FC). The original UTAUT model also has four effect modifiers: gender, age, experience and voluntariness.

Figure 1 below is a modified UTAUT model. Main effects: it consists of five main effects which includes system-specific knowledge in addition to the other main effects in the original UTAUT model (PE, EE, SF and FC). Effect modifiers: instead of having separate variable for age and gender as effect modifiers in our model, we simplified them as socio-demographic factors. Socio-demographic factors consist of not only age and gender but also race, education, income and work experience. Unlike original UTAUT model, we excluded experience and voluntariness from our framework due to irrelevance.

We removed experience of use from our study: the experiment done by Venkatesh was involving measurement in three different time. Due to measuring three times, the experience measured are increasing from the first until the third measurement. This increase in experience are regressed together with other variables to see its effect on acceptance. However, our study only involves one time measurement, and for that reason, the experience is not able to be measured in our study.

Voluntariness of use is removed from the original UTAUT model in this study because this study only measures mandatory usage of technology (technology obligated by management in organization) and has nothing to do with individual oriented technology.

In our study, the dependent variable is acceptance (intention to use), while the actual usage (AU) - as in UTAUT model - is not included in our study as dependent variable because the actual use of such technology is still impossible. Due to the exclusion of AU dependent variable from our study, facilitating conditions (FC) becomes unfit for this study. This is because based on original UTAUT model, FC only has direct effect on AU and no effect on acceptance (intention to use). However, despite it being irrelevant, we still retain the FC variable to be to be regressed against acceptance (intention to use) because we like to see if it has effects on acceptance.

The study was done by sending questionnaires through email to Malaysia One Health University Network (MyOHUN) members across Malaysia (including East Malaysia). The study design used is cross sectional. The reason for MyOHUN as target population is that MyOHUN members are involved directly or indirectly in zoonotic disease prevention. Thus, the result of this study could at some extent be generalized to the general Ministry of Health CDC workers involved in preventing zoonotic diseases in Malaysia.

Currently, it is difficult to make CDC workers as target population because the information of CDC workers are more difficult to obtain and it is less likely to isolate those who work in preventing zoonotic disease from those who are not. As our outcome is to assess the acceptance to use social network technology in preventing influenza, it is less valid to include those who do not involve in zoonotic disease prevention in the study. Thus, to filter out those who do not involve in zoonotic disease prevention, we decided to use MyOHUN members as target group as it consists of only those involved in zoonotic disease prevention.

Sample size calculation was derived from prevalence sample size formula (Naing et al, 2006).[9] Among the 500 MyOHUN members, 300 public health workers was selected through simple random sampling method. The questionnaires were emailed to the selected prospective respondents. Respondents answered the questions at Google form and data is automatically registered to Google database. The respondents were reminded not to share the Google Form with other people to prevent duplicates and fake answers and abuse by non-respondents.

Data collection and strategy

Respondents were explained about the structure of the system, its processes, the input required and the outcome from the system. Information sheets were given to the respondents before they answered the questionnaire. Respondents were also given the chance to ask the surveyor team members in case they have any enquiry regarding the system. Answers were standardized as surveyors were briefed of the system during a workshop.

Survey duration lasted for 1 month. At the beginning of the survey, three surveyors were given all the materials (information sheets, survey tools and consent forms in digital). The three surveyors approached all the respondents either through emails, Whatsapp application or during face-to-face meeting. The survey materials were distributed and surveyors answered questions when asked for any further information. All answers were standardized.

Study tools and validation

Respondents were asked a question whether they will accept to use the proposed technology. The answer in form of 'yes' or 'no' (categorical, dichotomous) was given. Respondents' expectancy on improvement in performance, effort, social and facilitating conditions were measured by using UTAUT-based questionnaire which has been validated for use in Malaysia.

Knowledge assessment questions was developed and was intended to measure the knowledge of 'Social Network Information in Influenza Prevention' that consists of 10

Table I: Descriptive analysis of acceptance and demography among public health workers

Description	n	Percentage (%)
Acceptance		
No (Did not accept)	77	37.6
Yes (Accept)	127	62.0
Missing value	1	.5
Gender		
Female	102	49.8
Male	103	50.2
Age (years)		
<30	40	19.5
30-39.9	65	31.7
40-49.9	62	30.2
50-59.9	33	16.1
>60	5	2.4
Race		
Malay	160	78
Indian	1	0.5
Chinese	44	21.5
Education		
Diploma	1	0.5
Degree	101	49.3
Master	73	35.6
PhD/DrPH	30	14.6
Income (RM)		
<5,000	22	10.7
5,000-9,999	72	35.1
10,000-14,999	74	36.1
>15,000	31	15.1
Not reporting income level	6	2.9
Experience (years)		
<10	64	31.2
10-19.99	60	29.3
20-29.99	62	30.2
>30	19	9.3

Table II: Score for performance expectancy, effort expectancy, social factors and facilitating conditions

Domains and Items	n	Mean	Std. dev.
Performance expectancy (PE)			
I would find the system useful in my job. (PE1)	204	3.93	1.585
Using the system enables me to detect potential influenza outbreak more quickly. (PE2)	204	3.77	1.573
Using the system increases my productivity (PE3)	204	3.83	1.459
If I use the system, I will increase my chances of getting raise (PE4)	202	3.44	1.435
Effort expectancy (EE)			
My interaction with the system would be clear and understandable (EE1)	204	3.96	1.48
It would be easy for me to become skillful at using the system. (EE2)	204	4.29	1.65
I would find the system easy to use (EE3)	204	4.70	1.52
Learning to operate the system for earlier detection of influenza outbreak is easy for me. (EE4)	204	3.95	1.55
Social Factors (SF)			
People who influence my behavior think that I should use the system for earlier detection of influenza outbreak. (SF1)	201	3.55	1.52
People who are important to me think that I should use the system for earlier detection of influenza outbreak (SF2)	200	3.56	1.56
Facilitating Conditions(FC)			
I have the resources necessary to use social network information system for earlier detection of influenza outbreak.	203	3.27	1.51
A specific person (or group) is available for assistance with social network information system difficulties	203	3.31	1.56

questions. The assessment was tested on 30 people (mostly the medical doctors in HUKM) for its discrimination ratio and difficulty ratio. The difficulty ratio was 0.43 and the discrimination ratio was 0.84. Kuder-Richardson (for internal consistency) index was 0.7.

Those participants included in this study were anyone officially registered with MyOHUN, according to MyOHUN membership record and anyone not officially registered with MyOHUN but had followed MyOHUN activities or programs at least once. Those should be excluded are: (1) administrative staff; (2) non-Malaysians (3) members under 20 years old or more than 65 years old. The exclusion criteria are those who are not currently involved in prevention or education or research in zoonotic diseases.

Ethical approval was granted by Universiti Kebangsaan Malaysia to conduct research from 28th September 2017 - 27th March 2018 (UKM PPI/111/8/JEP-2017-618).

Table III: Association between sociodemographic factors, performance expectancy, effort expectancy, social factors, facilitating conditions and acceptance

Factors	Acceptance		Independent T-test / X^2	p value
	Yes (n% or mean)	No (n% or mean)		
Gender				
Female	32 (31.7%)	69 (68.3%)	3.19	0.08
Male	45 (43.7%)	58 (56.3%)		
Race				
Malay	59 (37.10%)	100 (62.90%)	0.13	0.72
Other races	18 (40%)	27 (60%)		
Education				
Degree/Diploma	38 (37.3%)	63 (62.7%)	0.92	0.63
Master	30 (41.1%)	43 (58.9%)		
PhD/DrPH	9 (31%)	20 (69%)		
Income[a]	9571+5025	10236+3924	0.99	0.33
Age[a]	38.59+10.99	40.47+10.08	1.22	0.22
Experience[a]	13.68+10.38	16.01+8.99	1.64	0.10
PET[a]**	17.08+4.59	11.32	-8.56	< 0.01
EET[a]**	18.45+4.56	14.34+4.85	-6.09	< 0.01
SFT[a]**	8+2.82	5.63+2.56	-5.95	< 0.01
FCT[a]**	7.49+2.69	5.08+2.32	-6.53	< 0.01
Total Marks**	6.81+1.73	5.95+1.97	-3.27	< 0.01

[a] Independent T-test
**Significant

Table IV: Multiple Logistic Regression using Enter method

Factors	Wald	p value.	OR (95% CI)
Gender(1)	.18	.67	0.85 (0.40 - 1.80)
Age	.29	.59	0.99 (0.96 - 1.03)
EET	.78	.38	1.05 (0.94 - 1.17)
SFT	1.00	.32	0.89 (0.71 - 1.12)
FCT	3.25	.07	1.22 (0.98 - 1.52)
TotalMarks	1.92	.17	1.15 (0.94 - 1.41)
PET [categorical]	17.88	.01	
PET [score 13-15]**	14.91	.01	7.94 (2.77 - 22.72)
PET [score 16-18]**	7.39	.01	4.99 (1.56 - 15.92)
PET [score > 19]**	10.88	.01	22.97 (3.57 - 147.91)
Constant	3.36	.07	0.08

*Significant factor at p value <0.05

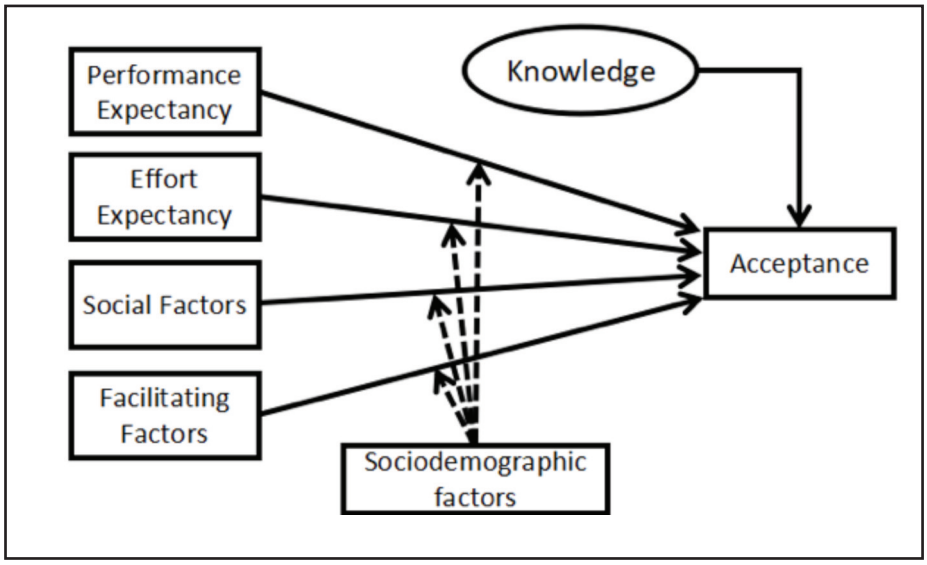

Fig. 1: Modified UTAUT model .

RESULTS

This cross sectional study was conducted among MyOHUN members nationwide. The data was obtained through Google Docs self-administered questionnaires. Response rate was 68.3% (205 out of 300 individuals responded to the research team's invitation).

At the onset of the study only about 180 individuals responded to the emails we sent to a list of 300 MyOHUN members (60% turnout ratio). To fulfil the minimum sample size of 196, we invited additional MyOHUN members who had attended seminar (Table Top Exercise) organized by MyOHUN to answer our survey form. We ended up with sample size of 205 respondents which satisfactoryily enough minimum sample size of 196 required for our study.[10]

This study shows that, 62.4% of public health workers accepted to use social network information system while a minority of 37.6% did not accept to use the technology. Among the respondents, one person did not answer the question which led to missing of 0.5% of data.

Among those who accepted to use the proposed technology, 78.8% were Malays, 20.5% Chinese and 0.8% Indians. Among them, 54.0% are female. Most of them (69.0%) works in Public Health while 8% of them are veterinary workers. Among those who accepted, 50.0% owns degree in any field, 34.0% has masters and 16.0% has PhD/DrPH. Most of those who accepted worked daily with influenza detection both in the office and field (58.0%) while 32.0% has not involved in both office and field work. Most of those who accepted to use the proposed technology is in the age group of 30 to 40 years old (37.8%) and had experience less than 10 years (37.8%).

For test of associations, gender, race and education level are in the form of categorical data. This combination with acceptance leads to a chi-square test. For test of associations for income, age and experience however, the data is in continuous form. This combination with acceptance leads to the use of independent Student's t test. From the tests done between gender, race, education, income, age and experience with acceptance, it was found out that they are all not significantly associated to acceptance with none of them have p value less than 0.05.

The table shows the significance of PET variable. Those with PET score of 13 to 15 is 7.93 more likely to accept the proposed technology compared to those with PET score of less than or equals to 12. Those with PET score of 16 to 18 is 4.99 more likely to accept compared to those with PET score of less or equals to 12. Those with PET score of more than 19 has the largest likelihood to accept the proposed technology (22.97 more likely to accept compared to those with PET score of less or equals to 12). Other variables were not significant with 95% confident interval crosses 1. The analysis also shows no interactions between variables.

DISCUSSION

The study shows that acceptance towards social network information system among MyOHUN members were more than 60%. Such percentage suggests that the majority of public health workers agreed to use the technology. Although not all of them agreed to use the technology, the percentage of acceptance can be made higher when the system is further structured according to the preference of users during its development.

The acceptance among MyOHUN public health workers were high enough when compared to the another study done recently on COVID 19. In a study by Anna Wnuk et al (2020),[11] when the respondents were asked to rate between 1 (strongly disagree) to 7 (strongly agree) whether they accept the implementation of social media surveillance for COVID 19. The average score resulted is 4.31 out of 7 (61.5%). The percentage of acceptance was similar to what we found in our study. However, we need to take precaution as both studies use different data form (continuous numerical versus categorical data)

Sociodemographic factors were found not to be associated with this acceptance. None of the factors (age, experience, income, gender, race and education) has p value less than 0.05 in the Student's T-test or Chi-square. Sociodemographic factors other than age and gender were not included in Multiple Logistic Regression to make analysis easier and they also were previously were found to be not significant by Venkatest in his UTAUT model. The two sociodemographic factors included in Multiple Logistic Regression (gender and age) were mentioned by UTAUT model to act as effect modifier or interactions.

However, after Multiple Logistic Regression was done, both gender and age was found to have no significant interactions with the main effects. This could possibly be due to the very specific target population (MyOHUN members) and very specific technology (social network information system) in this study. Unified Theory for Acceptance and the Use of Technology (UTAUT) model on the other hand was made based on general acceptance of any technology and used to predict acceptance in general population. Due to this fact, the UTAUT model predicted interaction between both gender and age to acceptance were not repeatable in this study.

Performance expectancy was found to be significant in simple logistic regression and multiple logistic regression. It was found out that performance expectancy is the only main effect that remained significant after running Multiple Linear Regression test. The importance of performance is so great due to the nature of job in the field of epidemiology and outbreak detection.

Public health workers consisted of health professionals who deal with influenza detection daily both in the office and in the field. Due to very demanding tasks, the professionals need to be very efficient in their jobs. As efficiency means producing greatest output with minimum input, their acceptance towards the technology also shaped in the way that only the technologies that increase their performance are accepted, while the technologies not effectively increasing performance are not accepted.

Our study also found that the higher the expectancy one has on the improvement of their performance after using social network information system, the more they are willing to accept it. This is explained by the value theory. As

performance increases, more output is produced by less input thus producing values through saving of costs. As saving of costs (in terms of money, time and labour) translates into profit, the willingness to pay for goods/service that enhances performance increases.[12] As willingness to pay is directly proportional to the probability of acceptance, the more the performance expectancy one has on social network information system, the more the likelihood of accepting it.

Effort expectancy, social factors, facilitating conditions and knowledge of social network information system was initially found to be significant using the Student's T-test and Simple Logistic Regression. However, as the variables were regressed together with other variables in Multiple Logistic Regression, the variables were found not to be significant. This suggested that the variables (effort, social factors, facilitating conditions and knowledge) are confounding factors.

This study was done on a specific population (MyOHUN members) for their acceptance of specific technology which has resulted in different model from a general UTAUT model. While UTAUT model provides a general guide for the acceptance of a technology, it does not specifically developed for the acceptance of social network information system for influenza detection and it does not target MyOHUN members.

This study has resulted in a specific model for the acceptance of social network information system among public health workers. The model is very simple with one independent variable (performance expectancy) and one dependent variable (acceptance). All other variables are excluded by multiple logistic regression due to no main effects and no interactions with acceptance. Acceptance among health professionals is seen as solely affected by performance expectancy. This is logical as these professionals are busy in every day job and would love something that increase their efficiency and performance.

Exclusion of most of UTAUT variables in multiple logistic regression and moderately strong pseudo-R^2 (0.42) means that the model is moderately predictive in determining the acceptance towards the proposed technology. This suggests that there are several other variables that are not explored and included in this study thus causing such pseudo-R2 value. This also means that UTAUT model that has been used to predict general technology acceptance is not the most suitable model to predict the acceptance of social network information system for early detection of influenza among public health workers. This could be due to very specific type of technology and very specific study population.

CONCLUSION

Based on this study the development of social network information system is feasible based on the percentage of people accepting to use the technology. The study also found that the acceptance towards such technology was affected by expectancy towards performance improvement after using the technology. Thus, in order to increase percentage of those accepting social network information system for earlier detection of influenza outbreak, the technology must be developed in a way that really improves performance and increase performance perception.

In order to develop a social network information system that really improves performance of surveillance units, research must be done to find the best filtering method for Twitter and Facebook posts so that the system is sensitive and specific (thus making it more effective). Developers also need to effectively communicate to each surveillance staff on how such technology could increase the performance of its users so that their perception will be good and they are more willing to accept and use the technology. This is because performance expectancy is the sole factor that influence the acceptance to use the technology and its influence is very huge.

It is suggested that the future studies be done by including more variables that are not covered in this study so that more associated variables will be discovered, greater pseudo-R^2 will be produced and more predictive model will be established.

CONFLICT OF INTEREST

All the authors declared no conflict of interest.

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Hepatocellular carcinoma: A local registry on risk factors, imaging patterns, treatment strategies and overall survival

Manju Tambe Raja, Dr.Rad[1], Nur Yazmin Yaacob, M.Rad[1], Wong Zhiqin, FRCP[2], Chik Ian, Dr.Surg[3]

[1]Department of Radiology, Faculty of Medicine, Hospital Canselor Tunku Mukhriz, [2]Department of Internal Medicine, Faculty of Medicine, Hospital Canselor Tunku Mukhriz, [3]Department of Surgery, Faculty of Medicine, Hospital Canselor Tunku Mukhriz

ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is among the common death-causing cancers worldwide. This liver malignancy is primarily diagnosed using radiological imaging techniques. Most of the patients in Malaysia present late and were diagnosed at an intermediate or advanced stage of Barcelona Clinic of Liver Cancer (BCLC). This causes a limitation on the treatment options for the patients.

Materials and Methods: We performed a retrospective cross-sectional study of HCC cases within a five-year period in our center with data collected from Hospital Canselor Tunku Mukhriz (HCTM). This study examines the HCC risk factors, the pattern of diagnosis, treatment options and overall survival.

Results: The findings from this study showed that viral hepatitis was the highest risk factor in which most of the patients were elderly males who presented with abdominal distension. In addition, given the high prevalence of metabolic diseases Malaysia, it is predicted that the number of non-alcoholic steatohepatosis (NASH)-related HCC cases might increase. Alpha-fetoprotein (AFP) proved to have no significant role in the detection of the disease. The number of patients detected at early BCLC was minimal, resulting in limited options of treatment. Overall survival of our HCC patients was poor at 17 months.

Conclusion: We conclude that HCC patients in HCTM mostly presented at late stage to hospital, hence limiting the treatment options and resulted in poor survival rate. Disease awareness should be implemented at primary care level to detect HCC at its early stage. Subsequently, a multidisciplinary hospital team is required to manage the disease at its different stages of presentation.

KEYWORDS:
Death-causing cancer, liver, prevalence, detection

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common death-causing cancers worldwide[1,2,3] with Hepatitis B virus (HBV) infection as the most prevalent cause.[4,5] Among the HCC patients in peninsular Malaysia in 2015, 57.6% had HBV while 2.4% had hepatitis C virus (HCV). The numbers of HCC cases have increased dramatically in proportion to the high prevalence of non-alcoholic steatohepatosis (NASH) in the population.[4,5]

An algorithm had been established by a local consensus on hepatobiliary imaging in 2015 to diagnose HCC based on Barcelona Clinic Liver Cancer (BCLC) algorithm (Figure 1).[6,7] Many cases were diagnosed late partially due to lack of technical and imaging expertise, such as in ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging (MRI) or liver biopsy facilities.[3,6] This subsequently restricted the choice of treatment options when the patients present at a later stage of HCC in our center.

According to an epidemiological study conducted in Malaysia in 2013 on BCLC, only 34.2% of stage A patients underwent surgery whereas more than half of the patients underwent radiofrequency ablation (RFA). In stage B and C patients, one-third underwent trans-arterial embolization (TAE) while others were offered supportive therapy.[5] In this article, for simplification, most locoregional therapy procedures will be addressed under a common term of TAE. This includes conventional trans-arterial chemoembolization (cTACE), TACE with drug eluting beads, as well as bland embolization. Another locoregional therapy is thermal ablation, which includes radiofrequency ablation (RFA) and microwave ablation. In Malaysia, these procedures were offered based on operator preference, which includes skill and funding.

This is a very timely study in view of the relatively high number of HCC cases with late presentation to hospital in Malaysia. The aim of this study is to improve understanding of the disease as it has a wide range of clinical presentations and diagnostic imaging findings. This study also aims to highlight the requirement of multidisciplinary team (surgery, hepatology, and radiology) in managing the disease.[8,9]

MATERIALS AND METHODS

The objective of the study was to assess for diagnostic imaging of HCC, the pattern of HCC imaging, the common risk factor, the primary team referrals, and treatment strategy for early HCC in the local setting.

This is a retrospective, cross-sectional prevalence descriptive study of HCC patients in HCTM presented over five years period starting from January 2011 until December 2015. A

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Corresponding Author: Manju Tambe Raja
Email: 697078@gmail.com

follow up were conducted until December 2019 for survival rate. OpenEpi online program (version 3) was used to calculate the correct sample size to compare the means. With a power of 80%, 95% confidence interval and a ratio of 1 between the groups of 180 and 200 patients, a total of 146 patients were calculated for the total sample size. The list of the patients was derived from a Case mix group in our hospital. The list of imaging modalities to diagnose HCC was obtained from Juke raid, Raid server, and RIS-PACS [Radiology Information System and Picture Archiving & Communications System]. The details of the patient were obtained from C-HETS [Caring Hospital Enterprise System]. Data were only collected for patients who fulfil the inclusion and exclusion criteria. The findings were recorded in SPSS [Statistical Package for the Social Sciences] version 22 based on the BCLC stages.

The patients with viral or non-viral hepatitis have had once in three months liver function test (LFT) surveillance. Patients with raised LFT were screened for USG and Alpha-fetoprotein (AFP) level in the blood. An elevation of AFP (cut off point of 200 úg/mol) and detection of a suspicious liver nodule on USG warranted a further CT scan for liver 4-phase assessment. Inconclusive CT scan on liver 4-phase findings required a further assessment by an MRI of the liver. Regular weekly multidisciplinary meetings were performed between the hepatologist, surgical team and radiologist to decide on mode of intervention as early HCC is considerably challenging to diagnose and treat. The final diagnosis of a typical pattern of HCC was confirmed by diagnostic imaging, whereas the atypical pattern of HCC was confirmed by histopathological diagnosis.

Inclusion criteria were all HCC patients who performed CT/MRI images at our centre and HCC patients referred from other hospitals with digitised CT/MRI images. Exclusion criteria involved patients diagnosed with HCC without CT/MRI images and as well as patients who are not diagnosed with HCC histopathologically.

Statistical analysis was performed using SPSS version 22.0. Descriptive statistics were used to obtain a percentage with a mean at a standard deviation of 95% confidence level. Cross-tabulation tests were used to estimate choice of CT or MRI in detecting HCC at early stage and to estimate ideal treatment option at early BCLC stage. One-way ANOVA test was used to assess the significant difference of AFP mean value in the BCLC stages. A p-value of less than 0.05 was used as a statistically significant. Kaplan-Meier method using a log-rank test was used to estimate the patients' median overall survival (OS) and to compare survival distribution between the stages of BCLC.

RESULTS

Details of 237 patients listed as HCC were derived from a Case mix. Out of the 237 patients, 66 patients were excluded from the study in which 18 patients were non-HCC at a final diagnosis while 48 patients had no digitized images. The details of the 171 patients were entered into the SPSS program.

The average age of the patients was between 50 to 72 years old with the median age of 61 years old. The minimum age was 19 years and the maximum age was 82 years old. Majority of the patients diagnosed with HCC were males with 80% while only 20% were females. About half of the patients (48.8%) were HBV carriers while 17.7% were HCV carriers and 1.8% of the patients were a combination of HBV and HCV carriers. 26.9% of viral hepatitis patients had overlapping steatohepatosis/ alcohol influence as well. NASH affected 36.5% of the patients while 10.0% experienced alcohol-induced hepatitis. 41.2% of the subjects have hypertension, 36.5% of them had diabetes mellitus (DM) and 29.8% had dyslipidemia. In conclusion, viral hepatitis is considered as the main risk factor of HCC in our center with HBV infection in the lead. No attempt was made to look at association between viral and non-viral hepatitis in this study.

Majority of the patients had abdominal pain (64.1%) as the common symptom while other symptoms include loss of appetite at 34.1%, fatigue at 32.9%, and jaundice at 24.7% [Table I].

Only 49 patients (29.7%) diagnosed with HCC in HCTM had been screened prior to disease manifestation. Twenty of these patients (40.8%) were diagnosed at an early stage of BCLC. Other than screening for HCC, we had 65 patients (39.4%) who presented upon onset of symptoms. Majority of these patients presented at an intermediate or advanced stage of the disease. Fifty-seven of our patients (30.9%) were referred from primary care and district hospitals with the majority of these patients presented with an advanced stage of HCC.

In this study, the AFP values in 104 patients were scored to look for correlation between AFP value and detecting suspicious liver lesion on USG. One-way ANOVA test was used for the mean difference. The result showed no significant correlation between high AFP value and positive USG findings, as p-value was 0.36 (>0.05). Hence, decision to perform USG liver should not be made solely based on AFP result.

USG images were available for 116 patients prior to HCC diagnosis and 71.6% of the patients showed the presence of liver nodule/ mass. The average tumor size found on CT and MRI were between 2.2 cm to 12.4 cm with a mean diameter of 7.3 cm. A portal vein thrombosis was noted in 52 patients (30.4%) while 3 patients had hepatic vein involvement and 7 patients had IVC involvement.

Hundred forty patients (82.4%) with HCC were diagnosed using CT scan images whereas 30 patients (17.6%) were diagnosed using MRI images. Only 11.8% of cases diagnosed using CT scan and 4.1% of cases diagnosed using MRI were detected at an early stage of BCLC.

The initial treatment options were tabulated for 171 patients as shown in Figure 3. 28 patients (19.8%) presented at an early BCLC stage of HCC (stage O and A). Ten (35.6%) of these patients had surgery, 15 patients (53.6%) had locoregional therapy, which includes TAE and thermal ablation, while 3 (10.8%) patients received systemic

Table I: Demographic data of the HCC patients

Demographic data	Mean ± Standard Deviation (SD)	n (%)
Age	61± 11 years	
Male: Female Ratio		4:1
Viral Hepatitis		
HBV		80 (48.8)
HCV		29 (17.7)
HBV+HCV Combination		3 (1.8)
Metabolic Disorder		
Hypertension		70 (41.2)
Diabetes		62 (36.5)
Dyslipidemia		51 (29.8)
Non-viral Hepatitis		
NASH (Non Alcoholic Steatohepatitis)		62 (36.5)
Alcohol- Induced		17 (10)
Common Symptoms		
Abdominal Distension/ Pain		109 (64.1)
Weight Loss/ Loss of Appetite		58 (34.1)
Fatigue		56 (32.9)
Jaundice		42 (24.7)

Table II: Correlation between high AFP levels and HCC in patients

Findings	Sum of Squares	Sig.
Between Groups	.702	.360
Within Groups	56.354	
Total	57.057	

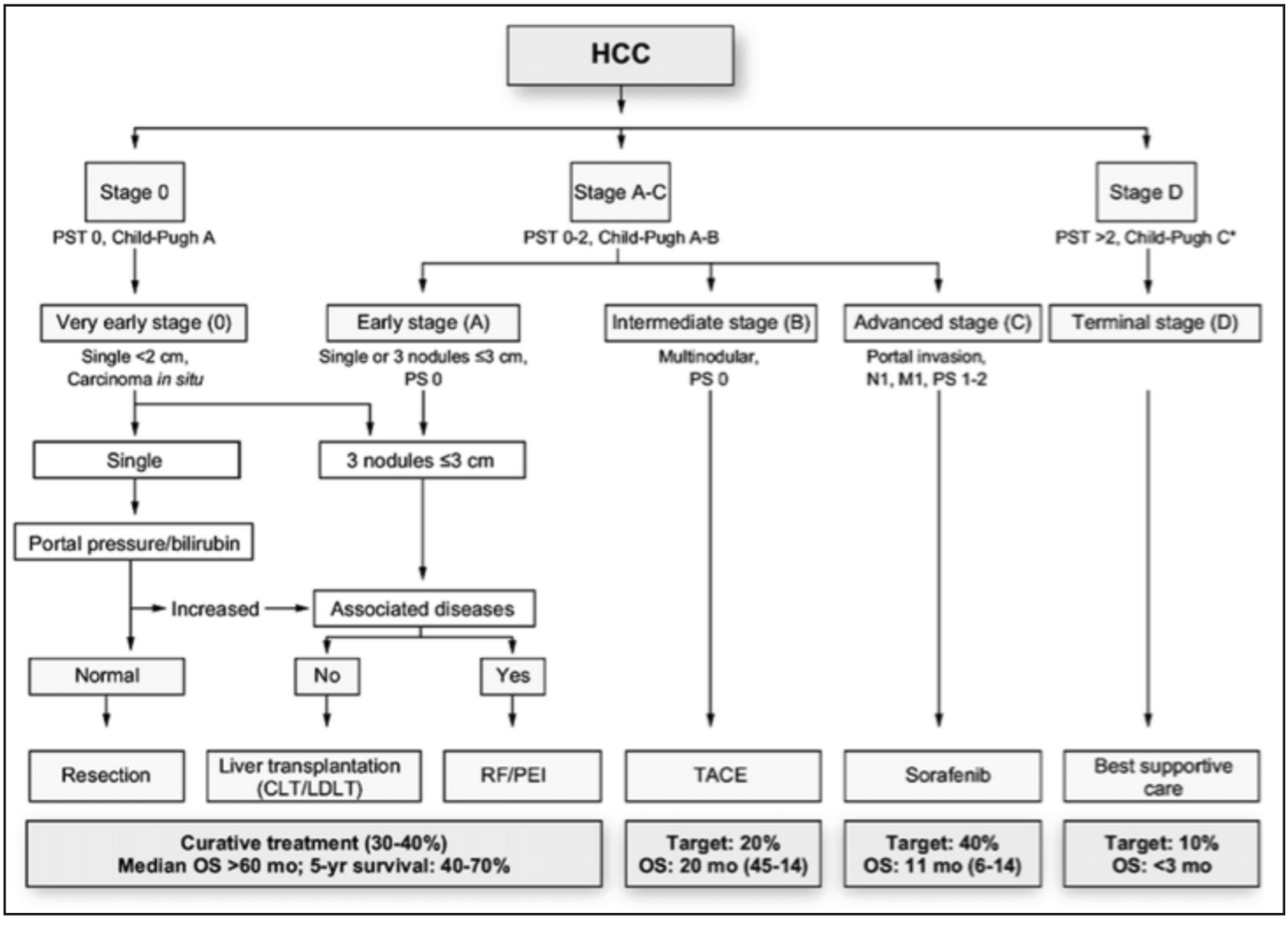

Fig. 1: Barcelona Clinic Liver Cancer Algorithm for Management of HCC[7]

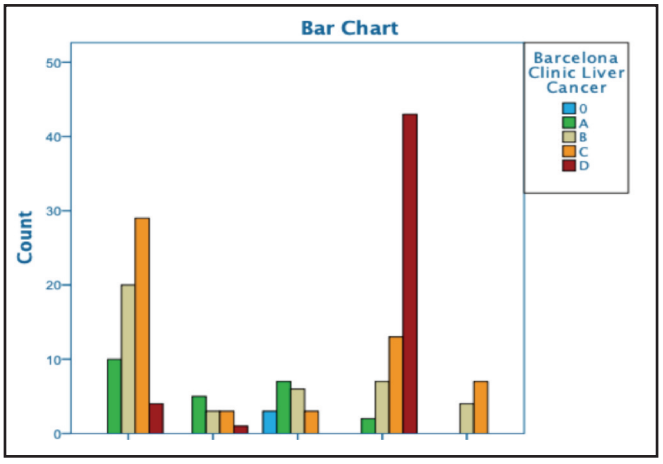

Fig. 2: Initial treatment given to HCC patients.

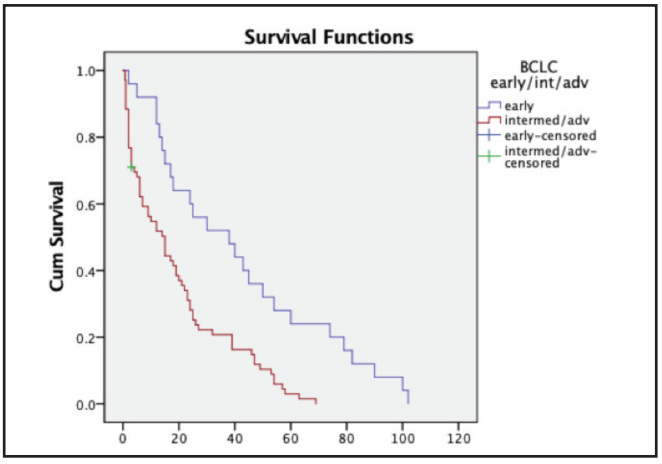

Fig. 3: Survival curve of HCC patients (in months).

treatment. Moreover, 143 patients (80.2%) presented at an intermediate (stage B) and advanced stage (stage C & D) with 9 (6.3%) patients had surgery, 61 patients (42.7%) had locoregional therapy, and 62 (43.3%) patients received systemic treatment. Eleven patients (7.7%) default treatment and lost to follow up.

Kaplan-Meier analysis showed the median overall survival estimation of 17 months (SD ±2.4) in 94 patients that were followed up until December 2019. Log-rank test in Figure 4 demonstrates a significantly longer survival rate in the early stage of BCLC compared to intermediate/advanced stages. Thirteen patients (20.3%) had a survival rate of 5 years and above after HCC diagnosis and treatment in our center, with majority of the patients diagnosed at an early stage of HCC (BCLC 0 and BCLC A). Twenty patients (21.3%) had a survival rate of 2 to 4 years with majority of them diagnosed at intermediate/advanced stages. Sixty-one patients (58.4%) had a survival rate of less than 2 years, which were diagnosed at intermediate/advanced stages. Only 1 patient belonging to the intermediate/advanced group was censored in view of unknown outcome. Overall findings indicate the importance of detecting the disease at an early stage to improve the survival rate of the patients.

DISCUSSION

This study identifies viral and non-viral hepatitis factors causing HCC as well as radiology diagnostic pattern that leads to detecting radiological diagnostic pattern that can detect HCC at its early stage. This will eventually enable us to administer promising treatment options and improving the OS of the patients.

In this study, the gender factor demonstrates 4:1 male to female ratio. This finding is similar as described in Asian Pacific Association for Study of Liver (APASL) 2017 Clinical Practice Guidelines (CPG) of HCC wherein male patients were more likely to be affected by disease, than female ranging from 2:1 to 4:1 ratio.[8,9] HBV infection is the leading risk factor of HCC in our study. This could be due to the lack of public awareness on HBV/HCV vaccination programme. Most of the patients in our study are elderly males with an underlying comorbid disease and a carrier of hepatitis B.[7-12] The CPG of Japan Society of Hepatology (CPG-JSH) of HCC highlights that patients requiring surveillance of HCC have been categorized as high-risk (cirrhosis type A, chronic HBV and HCV) and extreme high-risk patients (cirrhosis type B-involving portal hypertension and C-liver atrophy).[9] This emphasizes the need for active screening of viral hepatitis at a primary care level. Recently in August 2020, the Ministry of Health of Malaysia had launched a 1- week campaign for World Hepatitis Day. Rapid test kits for Hepatitis C had been distributed to various public health centers and about 1.9% of 11813 patients had been detected with the virus and referred to liver clinics.[10]

In our study, a high number of metabolic disorders were observed, raising risk of developing NASH-related HCC. According to recent studies, NASH-related HCC is becoming the major concern in developing countries as the viral hepatitis rates drop.[14] Hence it is necessary to raise awareness of controlling metabolic disorders as these can lead to HCC. This study demonstrated that most of the HCC patients presented to HCTM experienced abdominal pain. This is likely due to the lack of HCC screening in high-risk patients, thus most patients were in the late stage of HCC with mass-like symptoms.[15]

AFP results proved to be non-significant in determining the requirement of USG for HCC surveillance in this study. According to APASL, AFP is not a sensitive screening tool.[16,18] Therefore, since AFP is not significant in this study, patients with abdominal mass and a normal AFP level will still be warranted for imaging.

Among one-third of HCC patients who have been screened prior to diagnosis, only 40% were in the early stage of HCC. As per CPG-JSH for HCC, USG for extreme high-risk group patients is more frequently performed between 3 to 4 months.[8,9] We could follow this by increasing the frequency of USG surveillance from 6 months to 3 or 4 months for patients with underlying moderate to severe cirrhosis.

The mean tumor size detected on CT/MRI in our center was in the intermediate stage of BCLC and one-third of the patients

had portal vein thrombosis. As per CPG-JSH of HCC, 6 to 12 monthly CT/MRI surveillance is performed by option for patients in the extreme high-risk group.[8,9] In Malaysia, 4-monthly CT/MRI screening may not be practical due to limited resources and expertise in the hospital as well as burden of high cost for patients.[3,4]

In HCTM, CT scan and MRI of the liver is warranted for patients with high suspicion of HCC. Unfortunately, less than one-fifth of the HCC diagnosed patients were detected at an early stage of the disease. Few journals mention that there is no difference of efficacy in delayed phase (up to 1 hour) of contrast-enhanced MRI, in regards to detecting the disease at its early stage. Therefore, an image-guided biopsy is recommended for patients who had atypical CT/MRI findings, as histopathological tests are able to differentiate HCC from other liver malignancies.[19,22]

There is a wide variety of locoregional treatments offered based on the BCLC stages of HCC.[24,25] However, the cost for the treatment increases according to the severity of the disease.[23] Patients that defaulted treatment in this study were from the intermediate and advanced stage of the disease in which these patients rely highly on medical insurance or government subsidy.[4] Thus, early detection of the disease will reduce the burden of the cost for the treatment hence will improve compliance of the patients.

From the HCC survival curve, patients at the early stage of HCC have a longer survival rate compared to the advanced stage patients. This emphasizes the need for early detection and prompt treatment for HCC patients to improve the survival rate of HCC patients.

The limitation of this study is the sample size in which only HCC patients within the 5 years period were included since it is a retrospective analysis study. Only minimal data could be retrieved from patients referred from other hospitals as the case history was summarized in referral letters. 48 patients had to be excluded from this study due to the non-availability of their digitized CT or MRI images in our PACS system. Another 18 cases were excluded as histopathological test were confirmed to be non-HCC in origin.[11] Patients defaulted some treatments such as locoregional therapy due to financial constraint. Besides this, only initial procedure of treatment of patients was recorded in this study, thus we were not able to determine optimum treatment outcome.

CONCLUSION

The HCC patients in our center mostly presented at late stages, hence limiting the treatment options and resulting in poor survival rate. Disease awareness should be implemented at primary care level to detect HCC at its early stage. Subsequently, a multidisciplinary hospital team is required to manage the disease at its different stages of presentation.

ETHICAL APPROVAL

This study was approved by the Sekretariat Penyelidikan Perubatan dan Inovasi (SPPI) UKM (JEP2017-028).

DISCLOSURE STATEMENT

There is nothing to be disclosed by the authors.

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Hyperkalemia measurement between Blood Gas Analyser and Main Laboratory Biochemistry Analyser

Mohd Helmie Ismail, MBBS[1,2,3], Kamarul Aryffin Baharuddin, Mmed[1,2], Mohd Azmi Suliman, MBBS[4], Mohd Faiz Mohd Shukri, Mmed[1,2], Siti Natrah Che Has, MBBS[5], Zhen Zhen Lo, Mmed[1,6]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, [3]Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [4]Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [5]Klinik Kesihatan Wakaf Bharu, Wakaf Bharu, Kelantan, Malaysia, [6]Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

ABSTRACT

Introduction: Potassium level is measured for patients with high risk of hyperkalemia in the emergency department (ED) using both blood gas analyser (BGA) and biochemistry analyser (BCA). The study was conducted to evaluate the correlation and agreement of potassium measurement between BGA and BCA.

Materials and Methods: This is a prospective cross-sectional study on the data obtained from Hospital Universiti Sains Malaysia (Hospital USM) from Jun 2018 until May 2019. Blood samples were taken via a single prick from venous blood and sent separately using 1ml heparinised syringe and were analysed immediately in ED using BGA (Radiometer, ABL800 FLEX, Denmark) and another sample was sent to the central laboratory of Hospital USM and analysed by BCA (Architect, C8000, USA). Only patients who had potassium levels ≥5.0mmol/L on blood gas results were included. A total of 173 sample pairs were included. The correlation and agreement were evaluated using Passing and Bablok regression, Linear Regression and Bland-Altman test.

Result: Of the 173 sample pairs, the median of potassium level based on BGA and BCA were 5.50mmol/L (IQR: 1.00) and 5.90mmol/L (IQR: 0.95) respectively. There was significant correlation between two measurements (p<0.001, r: 0.36). The agreement between the two measurements showed within acceptable mean difference which was 0.27 mmol/L with 95% limit of agreement were 1.21mmol/L to 1.73mmol/L.

Conclusion: The result of blood gas can be used as a guide for initial treatment of hyperkalaemia in critical cases where time is of the essence. However, BCA result is still the definitive value.

KEYWORDS:
Hyperkalaemia, blood gas analyser, biochemistry analyser, point-of-care, agreement

INTRODUCTION

Hyperkalaemia is a life-threatening electrolyte disorder that may cause cardiac arrest if not treated early. It is commonly seen in patients who present with acute kidney injury and chronic kidney injury in the emergency department (ED).[1] The lethal toxicity of hyperkalaemia is known as it reduces myocardial conduction velocity and accelerates the repolarization phase, producing well described changes on surface electrocardiogram (ECG), including narrow, symmetrical T wave, prolonged PR interval, diminished P-wave amplitude, QRS widening and ultimately sinusoidal QRST that ends in asystole or ventricular fibrillation.[2]

Even though hyperkalemia may lead to a fatality, it is reversible if the condition is immediately diagnosed and treated by physicians. Therefore, immediate measurement of serum potassium becomes crucial as it may change the treatment approach in hyperkalemia patients, even during a cardiac arrest.[3] Blood gas analyser (BGA) is used not only to measure blood gas analysis but also electrolytes, especially potassium. This measurement helps in making a clinical decision while waiting for confirmatory results using biochemistry analyser (BCA).[3] BCA is usually located in the main laboratory and is considered as primary reference and accredited by the respective organisation.[4] However, BCA results are always delayed due to the distance from the ED. Therefore, they may compromise the treatment in critically ill patients and affecting their outcome.[1]

There are two methods used to measure the levels of potassium using electrolyte assay either direct or indirect which employing ion-sensing electrodes (ISE).[1,5] Direct ISE method does not require a diluent solution for samples to interact with the ISE membrane which applies to devices like BGA.[5] The indirect technique requires pre-analytical dilution with fixed volume diluent which takes about 20-30 minutes for the centrifuging which is used in BCA.[1] Comparison between these two methods, direct ISE method measures the actual electrolytes in plasma concentration without being affected by the concentration of solid components in plasma meanwhile indirect ISE method measures mean concentration of electrolytes after dilution in plasma and its measurement is affected by concentration of solid components such as protein or lipid in plasma.[6] Direct ISE method is preferred by clinical chemists as the method of choice as it is free from electrolyte exclusion effects, but the indirect method is still accurate as its widely used in

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Corresponding Author: Kamarul Aryffin Baharuddin
Email: amararyff@usm.my

laboratories and its automation process give advantage to measure a large number of samples at specific time.[7]

BGA is one of the bedside point-of-care test (POCT) that many physicians rely on to measure electrolytes and assist in making their clinical decision. It is becoming an important test in the EDs, intensive care units and operation theatres.[1,6,8-10] Hence, the reliability and validity of BGA should be comparable with the use of BCA that is known to be the gold standard for the measurement of potassium. According to the United States of Clinical Laboratory Improvement Act (USCLIA), the acceptance bias of serum measurement of potassium levels compared to BCA should not exceed ±0.5mmol/L.[11]

Many previous studies had been done to determine the correlation and agreement between BGA and BCA. Unfortunately, the results of the studies showed inconsistent outcomes. Generalisation of the results of previous studies with our current models in the laboratories may be dangerous as it's reliability is controversial.[12] The difference probably is due to different types of the analyser models.[13] Previous studies had compared a variety of BGA and BCA models such as Radiometer ABL505 versus Hitachi 717, Seimens Rapid Point 500 versus Abott C8000 Architect, GEM 3000 ABG analyser versus Olympus AU2700 discrete chemistry analyser, ABL825 FLEX analyser versus AU2700 Autoanalyzer, Bayer Rapidlab 865 versus Olympus AU640, Radiometer ABL800 versus AU640, Radiometer ABL90 FLEX versus Vy-5600 automatic biochemical analyser and other different types of analyser models.[8,14-20] In Malaysia, majority of laboratories are using the Radiometer models such as ABL800 FLEX, ABL90 FLEX and ABL80 FLEX. In the Universiti Sains Malaysia (USM), BGA model is Radiometer ABL800 in ED and BCA model is Architech C8000 in the main biochemistry laboratory.

The main reason of this study needs to be done because there was no previous study comparing the two types of analysers and the inconsistent outcome evaluating the correlation and agreement between BGA and BCA from the previous studies. Moreover, the outcome of this study may benefit for the centres that use the similar types of machines to evaluate the correlation and agreement between BGA and BCA. Hence, the objective of this study is to evaluate the correlation and agreement of potassium measurement between BGA and BCA.

MATERIALS AND METHODS

This was a comparative cross-sectional study was conducted from 1st June 2018 until 31st May 2019 at ED of USM, Kubang Kerian, Kelantan.

The sampled population were all patients with a potassium levels of 5.0mmol/L or more based on BGA. A total of 173 patients who fulfilled the inclusion and exclusion criteria were included. A single prick of venepuncture provided two blood samples in separate containers were obtained; one was the venous blood gas (VBG) for BGA test and the other one was for BCA test. Exclusion criteria were all patients whose blood samples sent for BGA and BCA tests were taken separately based on the documentation in the folder of the patients. Samples with faulty or machine error results were also excluded. The cut-off potassium level of 5.0mmol/l was chosen because it is the upper limit of the normal value. All data was recorded in ED Hospital USM Hyperkalaemia Checklist Form.

The sample size was calculated by using MedCalc v17.8 Software (Trial version) and a total of 173 blood samples were needed. Decision for potassium measurement by using BGA was exclusively depended on the managing team that consists of specialists, registrars, medical officers and house officers. However, it was also a standard practice that any blood sample that was sent for BGA test would also be sent for BCA test in the main laboratory. BGA test is conducted in the ED, within 10 metres radius and the result is immediately available. On the other hand, BCA test is conducted in the main laboratory and the distance was around 70 meter from the ED. The sample was transported by hospital attendants to the main laboratory. Results from BCA take about five hours to be ready through online system.[21]

All venous blood samples were collected in a sterile environment by trained staff, either by houseman or medical officers. Samples were collected in 1ml blood-gas syringes that were flushed with heparin (1:1000) beforehand and syringed out completely to prevent clotting and dilution that might affect the results. No bubbles inside the blood sample to minimise pre-analytical error. The blood samples were analysed immediately for BGA which was ABL800 FLEX Radiometer from Denmark.

In order to minimise bias or measurement error during sampling, short presentation on how to optimise on sampling of VBG was conducted during weekly department continuous medical education. Regular reminder was done during daily morning pass-over meeting. Since VBG is easier access, less pain and comparable to ABG (except in the partial oxygen pressure result), it has been widely used to measure electrolytes through BGA in the emergency settings for many clinical conditions.[22-24] VBG also has been shown to have good clinical positive correlation for sodium, potassium and creatinine.[25]

Another blood sample was sent to the main laboratory for BCA test using plain tubes and was analysed using Architect C8000 from the United States of America (USA) that was operated under the Pathology Department of Hospital USM. The procedure is considered as the gold standard of test for measurement of potassium levels and the laboratory was accredited by Malaysia Standards of International Organization for Standardization (MS ISO 15189:2007).[21] Quality control and assurance are done regularly to ascertain reliability of both test for measurement of potassium levels based on manufacturer recommendation and National Institute of Standards and Technology (NIST).

Statistical analyses were performed via IBM SPSS Statistics version 24 and RStudio software, version 1.2.5019, based on R Language, version 3.6.1. Wilcoxon Signed Rank Test was used to compare the medians of the results from two measurement methods (BGA and BCA). Linear Regression

Table I: Demographic Data and Common Cause of Hyperkalaemia (n=173)

Variables	n (%)
Gender	
Male	88 (50.9)
Female	85 (49.1)
Age (years)	
18-40	6 (3.5)
41-60	75 (43.4)
>60	92 (53.2)
Race	
Malay	166 (96.0)
Chinese	7 (4.0)
Initial triage	
Red	68 (39.3)
Yellow	100 (57.8)
Green	5 (2.9)
Causes of Hyperkalaemia	
Acute kidney injury	29 (16.8)
Chronic kidney disease	115 (66.5)
Drug-related	7 (4.0)
Hyperglycaemia emergencies	6 (3.5)
Others	16 (9.2)
Pattern of initial treatment	
VBG	93 (53.8)
Biochemistry Analyser	57 (32.9)
None	23 (13.3)
Prognosis	
Discharge	6 (3.5)
General ward	144 (83.2)
ICU/CCU/HDW	20 (11.6)
Death	3 (1.7)

Table II: Difference of Potassium reading between blood gas analyser (BGA) and biochemistry analyser (BCA) (n=173)

	Mean (SD) / n (%)	t-stat (df)	p-value
Potassium Reading			
BGA	5.77mmol/L (0.74)	4.65 (172)	<0.001[a]
BCA	6.05mmol/L (0.91)		
Differences			
Same Reading	12 (6.9%)		
Higher on BGA	28 (16.2%)		
Higher on BCA	133 (76.9%)		

[a]Paired T-test

Table III: Passing and Bablok Regression Statistic between the two methods (n=173)

Analyte	Linear Regression			Passing and Bablok Regression	
	β (95% CI)	r2	p-value	Intercept (95% CI)	Slope (95% CI)
Potassium	0.49 (0.39, 0.59)	0.36	<0.001	1.31 (1.17, 1.50)	-1.42 (-2.45, -0.58)

was used to calculate the correlation coefficient, while Passing and Bablok regression was used to compare slope and intercept between the two methods. Bland-Altman plot was used to assess the agreement between the two potassium measurement methods. A p value of <0.05 was accepted as significant.

RESULTS

Of the 173 paired blood samples that were analysed, 88 (50.9%) of the patients were males. The mean (Standard Deviation, SD) age of the patients were 61.0 (12.8) years, in which male patients mean (SD) age was 63.0 (13.4) years and the mean (SD) age of female patients was 58.9 (11.9) years. Majority of the patients (57.8%) were triaged to the yellow zone and 115 patients (66.5%) had background medical illness of chronic kidney disease (CKD). Only 6 hyperkalaemia patients with initial BGA results of ≥5.0mmol/l were eventually discharged, while others were admitted to the general ward, intensive care unit or died in the ED. The range of potassium levels based on BGA were from 5.0mmol/L to 9.2mmol/L. The median of potassium levels measured by BGA was 5.50mmol/L (IQR: 1.00 mmol/l), ranged from 5.00 to 9.20mmol/L. On the other hand, the median of serum potassium level measured by BCA was 5.90mmol/l (IQR: 0.95mmol/L), ranged from 3.80 to 10.00mmol/L.

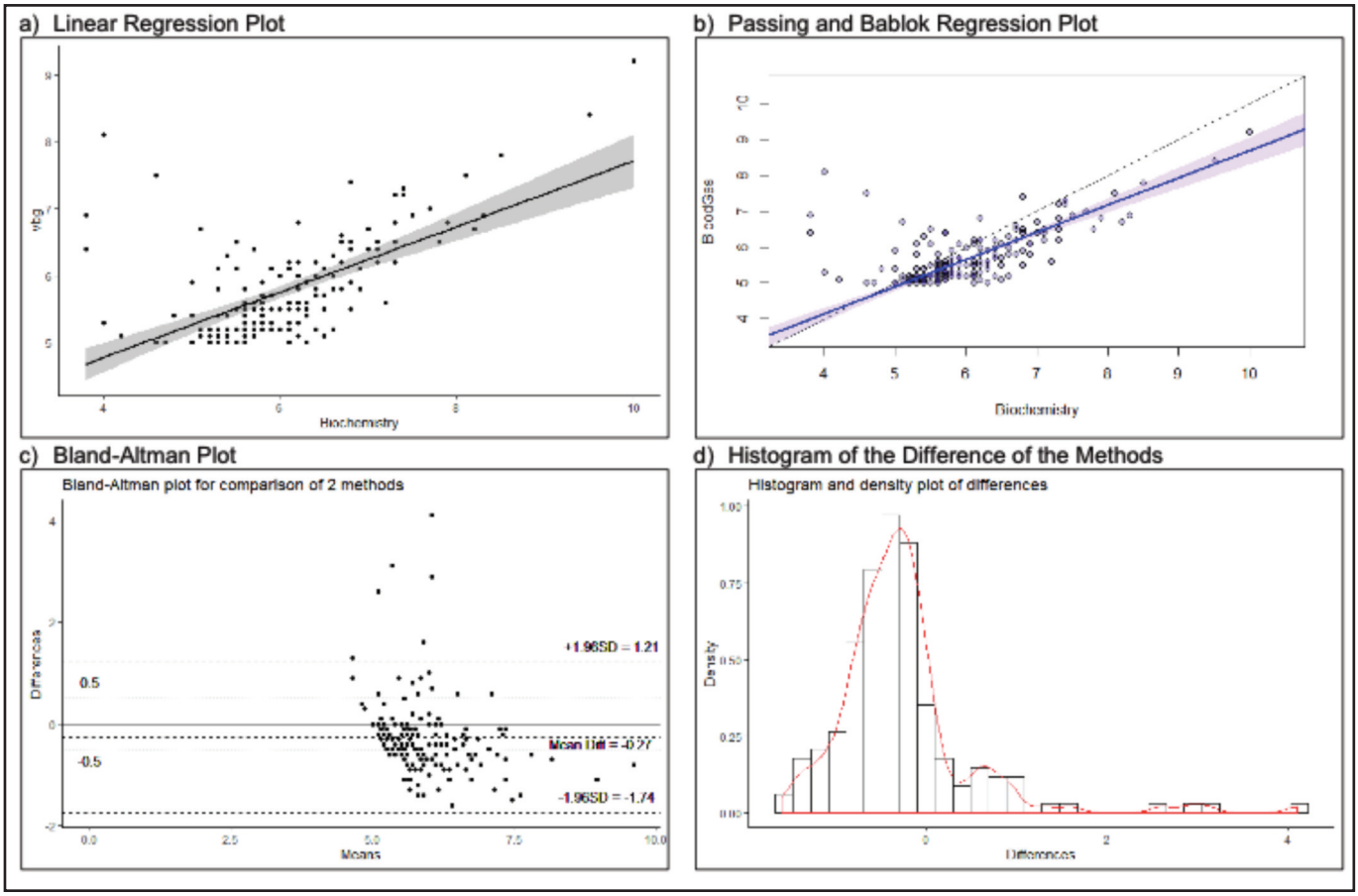

Fig. 1: Comparison between blood gas analyser (BGA) and biochemistry analyser (BCA). (a) Linear Regression Plot (b) Passing and Bablok Regression Plot (c) Bland-Altman plot with lower and upper agreement limits and (d) Histogram of the difference

While there was significant difference in the potassium reading in both methods, as summarised in Table II, there was positive correlation and accepted agreement between the two methods as shown in Table III and Figure 1. Linear regression shows positive correlation, while Passing and Bablok Regression shows that the slope was 1.31 and intercept at -1.42. The agreement between the two methods of potassium measurement with the mean of difference was 0.27±0.75mmol/L with 95% limit of agreement were 1.21mmol/L to 1.73mmol/L. The difference between the two analysers ranged from 0.48 to 1.02mmol/L. Out of 173 sample pairs, 96 blood samples (55.5%) had difference of ±0.5mmol/L or smaller and the rest 77 (49.5%) blood samples had difference of more than 0.5mmol/L between two methods of measurement.

DISCUSSION

POCT is a medical bedside diagnostic testing method, provides quicker results and allows for better immediate clinical decision-making of in-patient management.[26] The method includes blood gas analysis, electrolyte analysis, rapid cardiac markers diagnostics, rapid coagulation testing and others.[26] The reliability of BGA as one of the POCT for potassium measurement is important and lifesaving. Even general practitioners in European countries and the USA now use POCT for their clinical practices for managing non-emergency cases.[27] The BGA results have had the most impact for the care of patients compared to other investigations in POCT.[28]

Based on the Table I, the most common cause of hyperkalaemia was CKD that represented 66.5% of the patients. This is comparable with a study from Germany that found among the common cause of hyperkalaemia are kidney failure and hypoaldosteronism.[29] In addition to that, CKD is one of the important predictors for hyperkalaemia due to lower estimated glomerulus filtration rate (eGFR).[30-32] In fact, BGA is indicated in CKD patients to look for acidosis and hyperkalaemia in emergency settings.

In this study, most of the patients (57.8%) were initially triaged to yellow zone, followed by red zone (39.3%) and green zone (2.9%). Since yellow zone is considered semi-critical zone, most of hyperkalemia results were in the mild range between 5.0 and 6.0mmol/L. In fact, most of the hyperkalemia patients were asymptomatic. Symptoms like muscle weakness, ascending paralysis, heart palpitations and paraesthesia may develop at higher level above 6.5mmol/L.[33] Diagnostic uncertainty of hyperkalemia patients due to a variety of the complaints and unspecific electrocardiogram (ECG) could be the reason for patients to be triaged to yellow zone or green zone.[2] Patients who were triaged to the red zone had presented with acute life-threatening condition such as

altered mental state, hypotension or dyspnoea. However, these conditions do not necessarily correlate with the severity of hyperkalemia.[2] There were 93 hyperkalemia patients (53.8%) who were treated immediately based on the BGA results. We believe that the different approach of clinicians in initiating treatment of hyperkalemia patients depend on the clinical assessment, severity of the potassium levels, causes of hyperkalaemia and ECG findings. Clinicians are trained not to treat the hyperkalaemia as a stand-alone biomarker, but to manage the patients holistically.

Based on Table II, the median potassium value measured by BGA was 5.50mmol/L whereas the median of serum potassium measured by BCA was 5.90mmol/L. In general, the results of potassium from BGA tend to be lower than the levels measured by BCA. Only 12 (6.9%) blood samples had similar readings in the BGA and BCA methods. There were 133 (76.9%) blood samples that had higher reading and 28 blood samples (16.2%) that had lower reading on BCA compared to BGA. This finding is comparable with other studies that BGA has been shown to have lower readings compared to BCA up to 96.6% of the samples.[3,25,34] Measurement of potassium levels using BGA is underestimated due to pre-analytical bias by negatively charged heparin that binds to positively charged potassium in whole blood and it lowers the potassium measurement.34 However, in the case where the potassium level is much higher, the possible explanation is haemolysis of the whole blood in BGA that lead to the false elevation.[35]

Based on our results, there is a positive correlation between potassium levels measurement by BGA and BCA in hyperkaliaemic patients. Figure 1(a) shows that when the potassium spectrum measured by BGA increases, the difference measured by BCA increases. It may be more than 1.00mmol/L when potassium levels measured by BGA was more than 7.00mmol/L. This finding is comparable with a previous study based on the cohort with potassium level more than 6.00mmol/L3. The study found that the differences were up to 1.00mmol/L between two measurement methods for patients who had moderate to severe hyperkalemia.[3] Based on this finding, clinicians should be aware not to underestimated the value of potassium by BGA especially when the level is more than 7.00mmol/L. This could be the advantage of using BGA result as it could be safety measure to detect early hyperkalaemia as the potassium is possibly higher as expected. However, the clinicians should also be aware of pre-analytical bias as described above as safety issue and diagnosis of hyperkalaemia should be supported by other investigations such as ECG findings and risk factors of the patients.

Several studies assessed the correlation and agreement of BGA and BCA in different spectrum of potassium levels ranging from normal value to abnormal value.[36-40] However, most of the studies were based on wider range of potassium level from normal value to hyperkalaemia (abnormal value). Based on study done by LM Quin et al., measurement of potassium at physiological range showed good correlation and agreement between these two analysers but if potassium more than 5mmol/L whilst it had poor correlation and agreement and this may be due to the limitation of the machine to measure the potassium in critically ill patient.[37] Nanda et al., found positive correlation indicating agreement between BGA and BCA in managing of critically ill patients.[38] Mirzazadeh et al. and Uysal et al., found good agreement and strong correlation between BGA and BCA and can be accepted as a POCT for critically ill patients.[39,40] However, Budak et al., revealed that the result of BGA and BCA should not be used interchangeably in clinical practice even though the mean of bias was 0.25 mmol/L due to individual readings on BGA showing wide range of variability.[1] All these studies were based on wide range of potassium.

Contrary to other studies, Acikgoz et al., stated their study was the first time to evaluate the agreement between two potassium measurement methods in a cohort where the potassium more than 6mmol/L[3]. The result of study showed there was significant difference between these analysers with mean of bias 0.62mmol/L. Contrarily, our study shows the mean of bias is within an acceptable range of 0.27mmol/L based on Figure 1(c). The strength of our study is that the samples were collected prospectively from a single source (venous blood) whereas Acikgoz et al., compared retrospectively between venous and arterial blood.

There are some limitations to our study. The results of our study are limited to a single model of BCA and BGA. Even though this result cannot be generalised to other models, these findings are greatly helpful for centres that use similar models. On the other hand, to the best of our knowledge, there are no previous studies that showed that there was concordance between measurement of different types of BGA. Secondly, our practice is by using conventional syringes with pre-flushing heparin which is theoretically may affect the measurement of potassium by BGA.[32] We suggest the use of dried heparin syringes in order to optimize the accuracy of the measurement.

In future studies, financial implication may be of interest as the tests are run twice for the same sample. With more clinical data and resources, guidelines can be developed to delineate the clinical needs of BCA compared to BGA in ED. As of now, the focus is more towards immediate and lifesaving decision-making in hyperkalemia patients.

CONCLUSION

Among hyperkalemia patients, there is moderate correlation and acceptable agreement in the potassium level between BGA to BCA. However, the BGA results tend to be lower compared to BCA results. Therefore, clinicians should use the BGA results with caution in certain clinical situations where time is of the essence to initiate treatment of patients for hyperkalaemia. For a definitive value, BCA is still considered as a gold standard.

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ORIGINAL ARTICLE

Distribution of virulence genes and the molecular epidemiology of *Streptococcus pyogenes* clinical isolates by *emm* and multilocus sequence typing methods

Siti Nur Adila Hamzah, MSc[1], Mohd Nasir Mohd Desa, PhD[2], Azmiza Syawani Jasni, PhD[1], Niazlin Mohd Taib, Mpath[1], Siti Norbaya Masri, Mpath[1], Rukman Awang Hamat, Mpath[1]

[1]Department of Medical Microbiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [2]Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

ABSTRACT

Background: *Streptococcus pyogenes* has a variety of virulence factors and the predominant invasive strains differ according to specific *emm* types and geographical orientation. Although *emm* typing is commonly used as the gold standard method for the molecular characterisation, multilocus sequence typing (MLST) has become an important tool for comparing the genetic profiles globally. This study aimed to screen selected virulence genes from invasive and non-invasive clinical samples and to characterise the molecular epidemiology by *emm* typing and MLST methods.

Materials and Methods: A total of 42 *S. pyogenes* isolates from invasive and non-invasive samples collected from two different tertiary hospitals were investigated for the distribution of virulence factors and their molecular epidemiology by *emm* and multilocus sequence typing methods. Detection of five virulence genes (*speA, speB, speJ, ssa* and *sdaB*) was performed using multiplex polymerase chain reaction (PCR) using the standard primers and established protocol. Phylogenetic tree branches were constructed from sequence analysis utilised by neighbour joining method generated from seven housekeeping genes using MEGA X software.

Results: Multiplex PCR analysis revealed that *sdaB/speF* (78.6%) and *speB* (61.9%) were the predominant virulence genes. Regardless of the type of invasiveness, diverse distribution of *emm* types/subtypes was noted which comprised of 27 different *emm* types/subtypes. The predominant *emm* types/subtypes were *emm*63 and *emm*18 with each gene accounted for 11.8% whereas 12% for each gene was noted for *emm*28, *emm*97.4 and *emm*91. The MLST revealed that the main sequence type (ST) in invasive samples was ST402 (17.7%) while ST473 and ST318 (12% for each ST) were the major types in non-invasive samples. Out of 18 virulotypes, Virulotype A (five genes, 55.6%) and Virulotype B (two genes, 27.8%) were the major virulotypes found in this study. Phylogenetic analysis indicated the presence of seven different clusters of *S. pyogenes*. Interestingly, Cluster VI showed that selected *emm*/ST types such as *emm*71/ST318 (n=2), *emm*70.1/ST318 (n=1), *emm*44/ST31 (n=1) and *emm*18/ST442 (n=1) have clustered within a common group (Virulotype A) for both hospitals studied.

Conclusion: The present study showed that group A streptococccci (GAS) are genetically diverse and possess virulence genes regardless of their invasiveness. Majority of the GAS exhibited no restricted pattern of virulotypes except for a few distinct clusters. Therefore, it can be concluded that virulotyping is partially useful for characterising a heterogeneous population of GAS in hospitals.

KEYWORDS:
Emm type; Multilocus sequence typing; Streptococcus pyogenes; virulence genes

INTRODUCTION

Group *A Streptococcus* (GAS) or better known as *Streptococcus pyogenes* possesses various virulence factors that are involved in severe life-threatening infections. Invasive *S. pyogenes* infections have contributed to high lethality rates ranging from 10 to 30%, resulting in more than 600,000 deaths worldwide.[1] Virulence factors such as superantigens (SAgs), adhesins, proteases and leukocidins play a major role in the pathogenesis of *S. pyogenes* diseases.[2] For instance, adhesins are groups of proteins which are responsible for the initial attachment of *S. pyogenes* to epithelial cells.[3]

In the presence of other virulence factors such as M protein and streptokinase, *speB* gene can contribute to GAS pathogenicity.[4] Interestingly, specific serotypes of highly virulent *S. pyogenes* strains are recognised to express more than one fibronectin-binding proteins. The M1 and M49 serotypes were found to produce a cellular surface fibronectin-binding protein (FbaA), which has a pivotal role in *S. pyogenes* invasion into deeper tissues.[5] Superantigens such as streptococcal pyrogenic exotoxins (SpeA, SpeC and SpeG to SpeM) and the streptococcal superantigen (SSA) have been shown to mediate massive uncontrolled inflammatory reactions by overstimulating the host inflammatory cells mainly T-cell lymphocytes in severe invasive *S. pyogenes* infections.[6] Some of these toxin genes are exclusively

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Corresponding Author: Dr. Rukman Awang Hamat
Email: rukman@upm.edu.my

expressed in certain *S. pyogenes* serotypes. The M1 serotype that has a specific combination of *speA* and *smeZ* genes were found to increase the pathogenicity of this strain.[7]

To date, studies on the distribution of *S. pyogenes* serotypes and their virulence genes are limited in Malaysia.[8,9] Moreover, previous findings on *S. pyogenes* serotypes and virulence factors were characterised based on M-typing using specific antisera which is obsolete currently as the reagents are not widely available.[10] Besides, some of the *S. pyogenes* strains could not be typed by the antisera, thus limits the use of M-typing as the typing method of choice.[8,10] The *emm* typing method has now been accepted as the gold standard since M-protein is encoded by the 5′ end of the hypervariable region of *emm* gene, and this gene can be sequenced for the typing purposes.[11] Meanwhile, *S. pyogenes* genetic lineages can be characterised and globally compared using the multilocus sequence typing (MLST) method.[12] This method utilises seven highly conserved house-keeping genes and different nucleotide sequences can be determined to characterise different sequence types.[12] Previous data showed that certain *emm* types are associated with different types of *S. pyogenes* disease manifestations and invasiveness and the epidemiology of *emm* types is geographically oriented.[13,14] Therefore, to better understand the epidemiology of *S. pyogenes* infections in Malaysia, this pilot study aimed to characterise the selected virulence genes of *S. pyogenes* from various clinical specimens via *emm* typing and MLST methods.

MATERIALS AND METHODS

The present study was conducted in 2018 by utilising the previous collection of 42 *S. pyogenes* isolates which were obtained from two different tertiary hospitals from the year 2014 to 2015. The distance between these two hospitals is approximately 30km apart. The isolates were stored at -70°C and re-identification of the isolates was performed using the Gram staining method, bacitracin susceptibility (Oxoid, Basingstoke, United Kingdom), PYR test (Oxoid, Basingstoke, United Kingdom), latex agglutination (Oxoid, Basingstoke, United Kingdom), and species-specific polymer chain reaction (PCR) method.[15] The isolates were collected from blood (n=10), pus (n=22), tissue (n=7), wound (n=2) and throat (n=1). The sources for the isolates were categorised into invasive and non-invasive samples based on Creti et al.[16] The approval to conduct the study was obtained from the Ethics Committee for Research involving Human Subjects of Universiti Putra Malaysia with the reference number of UPM/TNCPI/RMC/1.4.18.2.

Multiplex polymerase chain reaction for the detection of selected virulence genes

Fresh bacterial colonies growing on Columbia agar enriched with 5% of sheep blood (Isolab Sdn. Bhd, Shah Alam, Selangor, Malaysia) were used for DNA extraction using the HiYield Genomic DNA kit (Real Biotech Corporation, Taipei, Taiwan) in accordance to the manufacturer's instructions. DNA extracts were stored at -30°C for further use.

Determination of five virulence genes (*speA, speB, speJ, sdaB,* and *ssa*) was carried out using a multiplex PCR kit (Qiagen, Germantown, USA) using few sets of primers (Table I) according to the multiplex PCR protocol described in a previous study.[17] An aliquot of DNA template (1μL) was transferred into an Eppendorf tube containing 12.5μL Qiagen® Muμtiplex PCR master mix with HotStarTaq DNA polymerase (Qiagen, Germantown, USA), 0.5μL of each virulence gene primer pair and 4.5μL multiplex PCR buffer. DNA amplification was performed using a Bio-Rad thermal cycler (Bio-Rad Laboratories Ltd., Watford, Hertfordshire, UK) with an initial denaturation process at 95°C for 3 min, followed by 35 cycles (30s at 94°C, 90 s at 57.4°C, 90s at 72°C) and the final extension process at 72°C for 10min. The PCR products were analysed with gel electrophoresis using 2% agarose gel containing 1× TBE buffer and 1μL of gel stain (Nanogene Solutions Sdn Bhd, Batu Caves, Selangor, Malaysia). The gel was then viewed using a gel documenting system Alpha image TM 2200 (Alpha Innotech Cooperation, San Liandro, USA). The multiplex PCR products of five virulence genes were sequenced and blasted with the GenBank sequences for the similarity index.

The emm typing of S. pyogenes

The *emm* typing was performed according to the recommended protocol by the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/ncidod/biotech/strep/protocols.htm). Bacterial DNA of all the isolates were prepared and PCR technique was used for DNA amplification using a Bio-Rad thermal cycler (Bio-Rad, California, UK). A set of forward and reverse primers were used as follows: 5′-TATT(CG)GCTTAGAAAATTAA-3′ and 5′-GCAAGTTCTTCAGCTTGTTT-3′, respectively. The PCR cycling conditions used were as follows: 94°C for 15 s, 46°C for 30 s, and 72°C for 75 s for the first 10 cycles, and then 94°C for 15 s, 46°C for 30 s and 72°C for 75 s (with a 10s increment for each of the subsequent 19 cycles). DNA purification and sequencing were performed by the 1st Base Laboratory Sdn. Bhd., Seri Kembangan, Malaysia. Received sequences were then edited using Bioedit software version 7.0 (https://bioedit.software.informer.com/7.0/) and compared with reference sequences using the BLAST algorithm.

Multilocus sequence typing (MLST) and phylogenetic study

The MLST was performed by sequencing seven housekeeping genes (*gki, gtr, murI, mutS, recP, xpt,* and *yqiL*) for all the isolates according to the established protocol with slight modifications.[18] A total of 4μL DNA template was mixed with 25μL of green master mix (Vivantis Technologies Sdn. Bhd., Subang Jaya, Selangor, Malaysia), 1.0μL of each housekeeping primer pair, and 19μL of PCR buffer. The PCR amplification was performed using a Bio-Rad thermal cycler (Bio-Rad, California, UK). An initial denaturation process was conducted at 95°C for 5 min, followed by 35 cycles (45 s at 55°C, 90 s at 72°C) and the final extension process at 72°C for 1 min. The sequencing analysis of DNA was conducted by MytacG Sdn. Bhd, Kajang, Selangor (Malaysia) and the data was submitted to the NCBI website for determination of gene similarity percentage using the BLAST analysis (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The sequence alignment was then analysed using a MEGA X software (https://www.megasoftware.net/home). In each locus, the different sequence was assigned by a distinct allele number, generating a seven-integer allelic profile for each isolate. Isolates with similar allelic profiles were assigned to the similar sequence type (ST). A complete database of alleles,

Table I: List of primer used for selected virulence genes in the present study

Virulence Gene	Forward primer (5'→3')	Reverse primer (3'→5')	Amplicon size (bp)
ssa	CGGAGGTGTTACTGAGCAC	GGTGCGGGCATCATATCGTA	274bp
speA	CCCCTCCGTAGATACATGCAC	ACACGACCAAGATTCAAGCCT	305bp
speJ	CTTTCATGGGTACGGAAGTGT	GCTCTCGACCTCAGAATCAACT	196bp
speB	AGACGGAAGAAGCCGTCAGA	TCAAAGCAGGTGCACGAAGC	952bp
sdaB	TATAGCGCATGCCGCCTTTT	TGATGGCGCAAGCAAGTACC	440bp

Table II: The distribution of five selected virulence genes according to the type of samples

Type of samples	*sdaB* n (%)	*speB* n (%)	*speJ* n (%)	*speA* n (%)	*ssa* n (%)
Invasive (n=17)	15 (45.5)	8 (30.8)	8 (36.4)	7 (35.0)	2 (11.1)
Non-invasive (n=25)	18 (54.5)	18 (69.2)	14 (63.6)	13 (65.0)	16 (88.9)
Total=42	33 (78.6)	26 (61.9)	22 (52.4)	20 (47.6)	18 (42.9)

Table III: Distribution of *emm* types, subtypes and sequence type (STs) according to the type of samples in this study

Type of samples	*emm* typing / subtyping (%)	Sequence type (%)
Invasive (n=17)	*emm63 (11.8), emm18 (11.8), emm1 (5.9), emm102.2 (5.9), emm76.5 (5.9), emm98.1 (5.9), emm12 (5.9), emm101 (5.9), emm81.8 (5.9), emm18.21 (5.9), emm15.1 (5.9), emm105 (5.9), emm86.2 (5.9), emm100.4 (5.9), emm89.28 (5.9)*	ST402 (17.7), ST28 (11.8), ST205(11.8), ST13 (5.9), ST60 (5.9), ST36 (5.9), ST25 (5.9), ST156 (5.9), ST442 (5.9), ST306 (5.9), ST147 (5.9), ST114 (5.9), ST549 (5.9), ST89 (5.9)
Non-invasive (n=25)	*emm28 (12), emm97.4 (12), emm91 (12), emm1 (8), emm71 (8), emm89 (8), emm102.2 (4), , emm76.5 (4), emm120 (4), emm63 (4), emm44 (4), emm6.1 (4), emm56 (4), emm70.1 (4), emm17.2 (4), emm57 (4)*	ST473 (12), ST318 (12), ST13 (8), ST313 (8), ST101 ST101 (8), ST55 (8), ST28 (4), ST60 (4), ST599 (4), ST168 (4), ST5 (4), ST426 (4), ST408 (4), ST31 (4), ST83 (4), ST300 (4)

allele sequences, and STs was obtained from the www.mlst.net website. Phylogenetic analysis was performed using the MEGA X software to produce distance-based dendrograms[19] and clustering of each isolate was performed using the MEGA X Sequence Alignment Editor to align the nucleotide sequences. Subsequently, phylogenetic tree branches were constructed using the aligned sequence obtained from the MUSCLE alignment in MEGA X software and information collected with the application of the neighbour-joining method using the MEGA X software.[20]

RESULTS

Among the 42 *S. pyogenes* isolates, the predominant virulence genes detected were as follows: *sdaB* (78.6%), *speB* (61.9%), *speJ* (52.4%), *speA* (47.6%) and *ssa* (42.9%). The distribution of five virulence genes in the invasive and non-invasive samples is shown in Table II. The gel electrophoresis patterns of multiplex PCR products are shown in Figure 1.

Table III shows the distribution of *S. pyogenes emm* types/subtypes according to the type of samples. In total, 27 different *emm* types/subtypes were detected in this study. No new *emm* types/subtypes were found. The predominant *emm* types/subtypes in invasive and non-invasive samples were *emm*63, *emm*18, *emm*28, *emm*97.4 and *emm*91 with 12% recorded for each gene. Meanwhile, application of MLST method indicated that the predominant sequence type (ST) in invasive samples was ST402 (17.7%) whereas ST473 and ST318 were the main ST in non-invasive samples with 12% recorded for each ST (Table III).

There were 18 different virulotypes detected, nevertheless, the main virulotypes were Virulotype A (five genes, 55.6%) and Virulotype B (two genes, 27.8%). This was followed by Virulotype C, D, E, F (16.7% for each); and Virulotype G, H, I (11.1% for each). Virulotype J to R represented 5.6% for each virulotype. The phylogenetic analysis revealed the prevalence of seven clusters of *S. pyogenes* in two different hospitals. Cluster V exhibited restricted patterns of two virulotypes which have three Virulotype A and two Virulotype L virulence genes. Meanwhile, a few *emm*/ST types shared only Virulotype A in Cluster VI. Figure 2 exhibits the phylogenetic tree of *S. pyogenes* strains inferred with the neighbour-joining method using concatenated sequences of seven housekeeping genes.

DISCUSSION

Streptococcus pyogenes is a human pathogen that is responsible for multiple infections globally. The pathogenic properties of *S. pyogene*s are often associated with the production of virulence factors such as superantigens, proteinases and adhesins. In particular, streptococcal erythrogenic exotoxins (SPEs) are involved in a massive inflammatory response and tissue destruction.[21] Thus, it is very important to determine the pathogenic potential of *S. pyogenes* strains and categorise them according to the MLST method for global comparison. Moreover, superantigen profiles of *S. pyogenes* strains are associated with specific *emm* types and their association differs across different countries.[22]

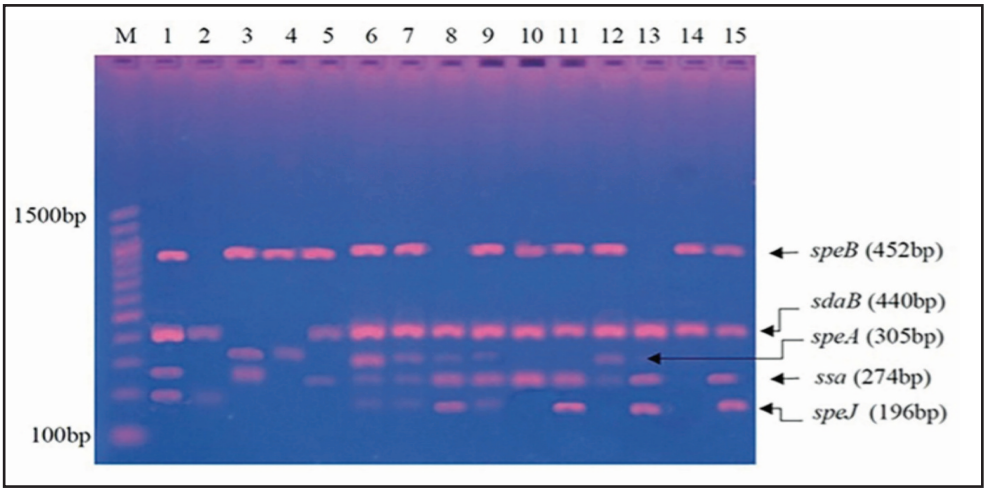

Fig. 1: Agarose gel electrophoresis patterns showing multiplex PCR amplification product for the *S. pyogenes* virulence genes. Lane M (Nanogene Solutions Sdn. Bhd., Batu Caves, Selangor, Malaysia): DNA molecular size marker (100bp). The specific virulence genes are labelled with arrows. Lane 1 to 10 represents isolates sampled from Hospital Serdang; Lane 11 to 15 represents isolates sampled from Hospital Kuala Lumpur.

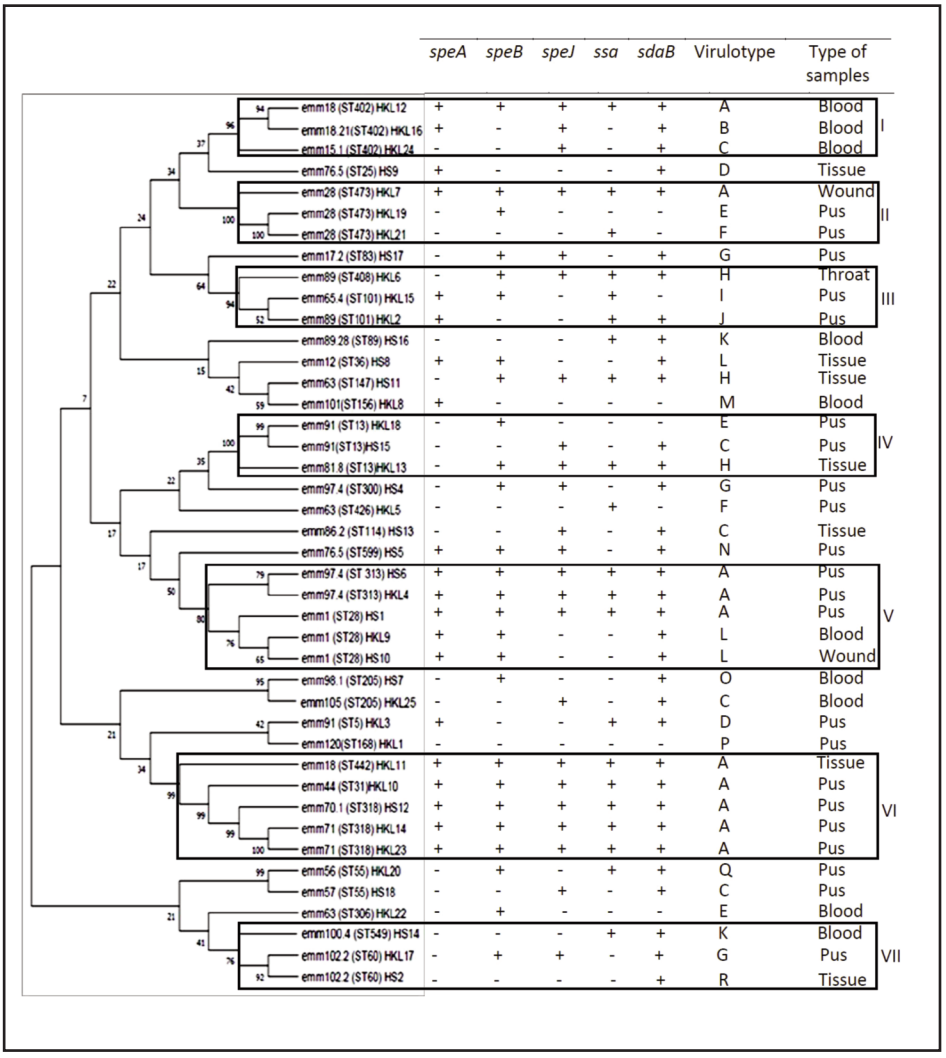

Fig. 2: Phylogenetic relationship among *S. pyogenes* strains inferred with the neighbor-joining method using concatenated sequences of seven housekeeping genes used for MLST. The taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. Cluster V and VI showed *S.pyogenes* strains with two restricted virulotypes (A and L) and only Virulotype A, respectively in two different hospitals. HS=Hospital Serdang; HKL= Hospital Kuala Lumpur. Virulotype A=five genes; Virulotype D and N=four genes; Virulotype E, F, H, J, L and Q=three genes; Virulotype B, I, K and O=two genes; Virulotype C, G, M and R (one gene); Virulotype P=no gene detected.

In the present study, all *S. pyogenes* isolates had at least one virulence gene regardless of their source. Comparatively, all five virulence genes (*sdaB, speB, speJ, speA* and *ssa*) were commonly detected in *S. pyogenes* isolates collected from non-invasive samples but not the invasive samples, which could be due to a slightly higher number of non-invasive samples in the present study (Table I). Nonetheless, high-frequency rates of similar virulence genes have also been reported among *S. pyogenes* strains from non-invasive samples in previous studies.[23,24] This is not surprising as the distribution of virulence genes varies due to the differences in the acquisition of the genes which can be chromosomally encoded or mediated by mobile genetic elements.[25] Both *streptococcal pyrogenic exotoxin A (speA)* (65.0%) and *streptococcal superantigen (ssa)* (88.9%) genes are highly transmissible via horizontal gene transfer through mobile genetic elements.[25] The emergence of phage-encoded exotoxins would create an unusual virulent clone among certain population due to selective pressures for bacterial fitness.[24] Moreover, the lack of specific immunity among the study population towards such strains may pose a substantial risk of a streptococcal outbreak in future. Similar findings have been reported where high frequency of *speA* gene was detected in non-invasive cases (pharyngitis) in Taiwan and Norway.[26,27] However, lower frequency rates have been reported in recent studies in Pakistan (38%) and India (25.1%).[24,28] The SpeA, SpeJ and SSA toxins have been commonly associated with severe *S. pyogenes* infections such as toxic shock-like syndrome, multiorgan failures and scarlet fever.[29] SpeB, a cysteine protease is a potent pro-inflammatory inducer and is commonly associated with necrotising fasciitis.[29] In the present study, a slightly low frequency of *speB* gene (61.9%) was noted from the analysis of *S. pyogenes* isolates. The *speB* gene was shown to be highly conserved in *S. pyogenes* isolates (100%) in some studies[28,30] while few studies have reported lower frequency rates ranging from 0 to 60%.[25,31] The differences in the prevalence rates of *speB* gene could possibly be explained by the different strains in certain geographical regions, the number and types of samples and the methods used for *speB* gene detection. Interestingly, streptococcal DNase B *(sdaB)* gene was frequently detected among non-invasive than invasive samples in this study (54.5% versus 45.5%) and only absence in isolates collected from HKL. This finding can be associated with the common observation in phylogenetic tree. The *sdaB* gene has been designated as a *streptococcal pyrogenic exotoxin F (speF)* gene that could directly damage pulmonary endothelial cells in a mouse model.[32] This chromosomally encoded gene causes increased permeability of lung blood vessels which is a risk factor for acute respiration distress syndrome (ARDS) cases.[32] The high-frequency rate of *sdaB/speF* gene (100%) among invasive strains was reported in a few studies.[24,30] Inversely, lower frequency rates of *sdaB/speF* gene were reported in recent studies.[28,33]

A diverse distribution of *emm* types/subtypes among *S. pyogenes* was observed, in which 27 *emm* types/subtypes were detected (Table III). No new *emm* types/subtypes were detected. The results obtained align with other findings which reported no dominancy of a single *emm* type/subtype.[34,35] Moreover, it has been documented that *S. pyogenes* strains in developing countries have diverse *emm* types compared to developed countries.[36] The *emm* types/subtypes were also widely distributed among invasive and non-invasive samples in the present study which is inconsistent with findings from other studies where certain *emm* types (*emm*1, 3, 6, 12 and 89) were specifically found in invasive strains.[1,37] In general, the frequencies of five virulence genes were higher in non-invasive than invasive isolates (Table 11) and serious attention is needed as phage-encoded superantigens in non-invasive *S. pyogenes* strains can easily be transferred to invasive *S. pyogenes* strains and other non-pathogenic streptococci via horizontal gene transfer.[28] Nevertheless, the findings from this study are in contrast with other previous findings where a higher percentage of virulence genes was noted in invasive than non-invasive samples.[7,28]

In the present study, few prominent clusters with restricted patterns of virulotypes were observed by phylogenetic analysis (Figure 2). The findings are in accordance with a study that demonstrated certain *emm* types shared the common toxin gene profiles.[24] Balaji and colleagues reported that different *emm* types had distinct toxin-gene profiles but a phylogenetic analysis was not investigated among their isolates.[24] The spe genes provide as marker for horizontal gene movements and encode the function of exotoxin in GAS pathogenesis. Surveillance that includes invasive (tissue sources) and non-invasive (pus) GAS isolates is important to distinguish between virulence properties and the prevalence of a particular GAS strain in the general population and to evaluate epidemiological changes in GAS diseases.[24]

Specific dominant virulotypes (A and L) were prevalent in both hospitals, and close monitoring via molecular typing methods is urgently required. Toxin gene profiling (virulotyping) has been proposed in many studies to support other molecular typing methods such as the MLST for genotypic determination of *S. pyogenes*.[7,32] Besides, it was reported that several *emm* types have specific toxin gene profiles which were reflected by the spread of specific invasive clones in European countries.[7,32] The *emm*1/ST28 isolates that exhibited virulotype A and L in this study could pose a risk of clonal transmission in both hospitals. Hypervirulent characteristic of *emm*1/ST28 strain is typically associated with high fatality rates among invasive streptococcal cases in some countries.[38,39] The different *emm*/ST types that exhibited virulotype A in this study could be explained by the restricted or lack of transfer of phage-encoded superantigen genes within this clone. It is still unknown whether a single virulotype detected in a clone could be due to the underlying biological factors or the selective advantage of *S. pyogenes* strains with certain *emm*/ST types. Nonetheless, different patterns of toxin gene profiling within multiple *emm* types are usually reflected by ongoing horizontal transfer of phage-encoded superantigen genes over time.[40] Thus, continuous molecular surveillance is needed to identify the emergence of novel lineages of *S. pyogenes* local strains.

This study has several limitations. The total sample was too small in the present study for the statistical analysis to be carried out resulting in findings from this study could not be generalised to other Malaysian hospitals. However, as this study in the first report on virulence characteristics of *S. pyogenes* in Malaysia, it is very important to investigate the current

molecular epidemiology of the local strains for controlling the potential clonal spread of *S. pyogenes* isolates in hospitals across the country.

CONCLUSION

S. pyogenes is genetically diversified, and apart from the emm typing and MLST methods, virulotyping is essential to characterise the heterogeneous nature of *S. pyogenes* strains. Future study with a larger sample number of *S. pyogenes* isolates from different sources is needed to support the findings from this study. Continuous monitoring of *S. pyogenes* via molecular methods is warranted in the future. Thus, potential nosocomial outbreaks of invasive clones can be controlled accordingly.

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Simulation study on quality of CPR between manual chest compression and mechanical chest compression devices performed in ambulance

Tuan Hairulnizam Tuan Kamauzaman, MMed (EM)[1], Johnny Ngu Tai Hock, MMed (EM)[2], Ariff Arithra, MMed (EM)[1], Abu Yazid Md Noh, MMed (EM)[1], Siti-Azrin Ab Hamid, MSc Medical Statistics (USM)[3], Junainah Nor, MMed (EM)[1]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia, [3]Biostatistic and Methodology Research Unit, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Background: Maintaining good quality CPR while transporting out-of-hospital cardiac arrest patients is very challenging. We aim to determine how different ambulance speed can affect the quality of chest compression performed either manually or mechanically.

Methods: This was an observational manikin-based study. A total of 96 participants as well as two types of mechanical compression devices: Lucas-2 and AutoPulse, performed one minute of continuous chest compression on BT-CPEA programmed manikin while the ambulance travelled at different speeds, i.e., idle state, 30km/hr and 60km/hr. Seven outcome variables of chest compression were measured. Performance data of different groups of compressor were compared and analysed using repeated measures analysis of variance (ANOVA).

Results: In manual chest compression, significant variation were noted among different speeds in term of average compression rate ($p<0.001$), average compression depth ($p=0.007$), fraction of adequate/insufficient compression depth and fraction of normal hands positioning with $p=0.018$, 0.022 and 0.034 respectively. Overall, AutoPulse and Lucas-2 were not affected by ambulance speed. Lucas-2 showed more consistent average compression rate, higher fraction of adequate compression depth and reduced fraction of insufficient compression depth as compared to manual compression with $p<0.001$, 0.001 and 0.043 respectively.

Conclusion: In this study we found that ambulance speed significantly affected certain aspects of manual chest compression most notably compression depth, rate and hand positioning. AutoPulse and Lucas-2 can improve these aspects by providing more consistent compression rate, depth and fraction of adequate compression depth during transport.

KEYWORDS:
Ambulance speed, chest compression, mechanical compression device, out-of-hospital cardiac arrest, prehospital care

INTRODUCTION

Incidence of out-of-hospital cardiac arrest (OHCA) is about 37 per 100,000 persons-years in Europe.[1] At the moment, the information regarding the incidence of OHCA in Malaysia and its outcome is still very limited and fragmented. Based on a study done at Hospital Kuala Lumpur in 2011, the survival rate for OHCA was only 16.8%.[2] There are various confounding factors, be it human or environmental, for the low survival rate of OHCA victims. For a primary responder to be able to transport the victims safely to the hospital while maintaining an effective cardiopulmonary resuscitation (CPR) in a mobile ambulance is indeed challenging.

A study showed that OHCA victims who had a shorter time to reach medical contact and received continuous good quality of life-support interventions during transportation had higher survival rates.[3] Emergency Medical Services usually face challenges to maintain a good quality CPR during transportation, especially when the ambulance encounters acceleration-deceleration, vehicle turning, ascending and descending slopes and uneven roads.[4] Another study showed increased CPR variabilities during ground ambulance transportation of patients in cardiac arrest when chest compressions were performed at the scene, in the ambulance and in the emergency department.[5]

Some centres advocate slow and constant ambulance speed during transportation of OHCA victim when CPR is in progress. However, a study indicates that even a constant speed of ambulance may directly affect the quality of CPR during patient transportation, factors such as increased rate and depth of chest compressions as well as no flow fraction.[6]

Mechanical compression device was first invented in the early 20's to overcome several issues encountered in CPR during ambulance transportation, including inconsistency of quality between different chest compressors, chest compressor fatigue that set in over time, and limited number of rescuers during CPR. Earliest manikin-based study done in 2007 comparing single rescuer CPR and active compression-decompression device showed that the latter was highly effective in delivering chest compressions and was not affected by the changes in a mobile environment.[7]

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Corresponding Author: Junainah Nor
Email: junainahnor@usm.my

However, there is still lack of evidence on patient outcome in OHCA after using different mechanical devices and manual compression in mobile environments especially when considering the speed of ambulances. Different devices have their pros and cons. AutoPulse has the advantage of giving circumferential compression for victims of different sizes based on chest circumferential diameter. Slight delay may occur in commencing chest compression due to the time taken by the machine to analyse and calculate the correct compression depth. Whereas Lucas-2 is set according to AHA BLS guideline for adult CPR. Some concerns arise regarding safety and efficiency in relatively small or big sized victims. Clear evidence showing improved patient outcome by using these mechanical compression devices in OHCA in term of survival and neurological function is still lacking.[8]

Emergency Medical Services in Malaysia has yet to recommend mechanical compression devices as the standard equipment in all prehospital respond teams. On the other hand, 2015 American Heart Association Guidelines for adult Basic Life Support (BLS) recommends that mechanical compression device may be a reasonable alternative to conventional CPR in specific settings in which the delivery of high quality CPR may be challenging or dangerous for the provider (e.g., limited rescuers available, prolonged CPR, CPR during hypothermic cardiac arrest, CPR in moving ambulance, CPR in the angiography suite, and CPR during preparation for Extracorporeal CPR).

Therefore, in this observational manikin-based study, we aimed to evaluate the effect of the speed of ambulance on the quality of chest compression performed by the two different types of mechanical devices and manual chest compression. We hope that the findings of the study will serve as a useful and an informative guide in making recommendations on how to improve our prehospital CPR.

MATERIALS AND METHODS

The study was performed with the approval of the Universiti Sains Malaysia (USM) Research Ethical Committee. The study was a prospective, manikin-based observational study conducted in Heath Campus, USM.

Participants in this study were selected from paramedics and doctors working in the Emergency Department (ED) as well as final year medical students from USM. A total of 96 participants were recruited for this study. The name list of the final year medical students were obtained, with prior permission, from the Dean of School of Medical Sciences, USM while those of the paramedics and doctors were obtained from the head of ED, Hospital USM. The participants were randomly selected from their group designation list (paramedic, doctor and student) by using Microsoft Excel RANDBetween function. The selected participants who did not consent or fulfil the criteria of this study were replaced by randomly selected names from the name list until the target sample size was achieved. Participants without a minimum BLS training, having injury or had difficulty in performing CPR, or unable to complete the task were excluded.

Study Protocol

All participants were told to perform one minute of continuous chest compression on a manikin according to 2015 American Heart Association (AHA) Guidelines for CPR: (1) compression rate 100-120/min, (2) depth of compression 5-6cm, (3) allow full chest recoil and (4) minimize compression interruption. Continuous chest compression was done in the rear compartment of an ambulance. The ambulance was operated with warning lights. Chest compression at a stationary state was performed with the engine of the ambulance kept on but the vehicle was in the idle state. Chest compression and data recording were started after the ambulance had achieved the targeted speed and each speed was maintained at ± 5km/hr range. GPS was used to monitor the ambulance speed. Participants did not support themselves with any structures in the ambulance while performing chest compression.

The trial started with 3 different groups of chest compressors, who were the medical students, paramedics and medical officers, followed by two mechanical compression devices namely AutoPulse and Lucas-2. One minute of manual chest compression was performed on the manikin right after the ambulance achieved each targeted velocity: idle state, 30km/hr and 60km/hr. To avoid the effect of compressor fatigue on the quality of CPR, participants were given 15 minutes of rest between trials. On the other hand, mechanical chest compression devices were applied correctly on the manikin based on the instruction manual. Continuous compression mode was selected and ran right after the ambulance achieved the targeted velocity. The ambulance run was repeated three times for each variable for each mechanical device. At the end of the trials, performance data was transferred from manikin to personal computer via blue-tooth and the results were summarized using a compatible software.

Research Tool

A programmed ACLS simulation manikin, CPR Evaluation Simulator BT-CPEA was used for the CPR performance evaluation. It is capable of measuring average compression rate, average compression depth, total hands-off time, fraction of adequate relaxation, and fraction of correct hands positioning. The manikin was strapped on a rigid spinal board that was secured on the ambulance stretcher. We used a van-based Mercedes-Benz Sprinter L2 H2 4x4 (Type B Ambulance) with a coil-spring-type suspension in this study. GPS was used to monitor ambulance speed to ensure that it travelled within ±5km/hr of the target speed.

Two mechanical compression devices commonly used in the prehospital care were used in this study, namely AutoPulse (2005) and Lucas-2 (2014). AutoPulse is an automated, portable, battery-powered compression device composed of a constricting band and half backboard that is intended to be used as an adjunct to CPR during advanced cardiac life support. It measures chest size and resistance before it delivers the unique combination of thoracic and cardiac chest compression. The compression depth and force varies per patient. The chest displacement equals a 20% reduction in the anterior-posterior chest depth. It runs in a 30:2, 15:2 or continuous compression mode, which is user-selectable, at a

rate of 80 compressions per minute. Whereas Lucas-2 is a chest compression system which includes a base unit with a back plate, carrying bag, patient straps, stabilization strap, suction cups, and one rechargeable lithium polymer battery. The operator can choose to deliver 30:2 compression-to-ventilation ratio or continuous CPR. Compression is delivered via piston with suction cup that allows chest recoil during decompression. Lucas-2 can deliver a compression rate of 102±2 per minute and a compression depth of 53±2mm which is strictly adhered to AHA adult BLS 2015 guideline.

Study Location
The study took place at an identified jogging track within the USM campus. The length of the identified road was approximately 1.8km long, straight and in good condition.

Outcome Variables
Average compression rate (compression/min), average compression depth (mm), fraction of adequate/insufficient/excessive compression depth (%), fraction of adequate chest relaxation (%) and fraction of normal hand positioning (%) were measured when manual chest compression and mechanical compression by two different types of devices were performed in the ambulance travelling at 0km/hr, 30km/hr and 60km/hr.

Statistical Analysis
Data was entered and analysed using IBM SPSS version 23.0. Numerical data were presented as mean (standard deviation) or median (interquartile range) based on normality of distribution. Categorical data were presented as frequency and percentage. Predefined outcome variables at an idle state, 30km/hr and 60km/hr were compared using repeated measure ANOVA. General linear model contrasts were tested for cases which did not show overt linearity. A p-value of less than 0.05 is considered to represent statistical significance at a 95% confidence interval.

RESULTS

Of the 96 participants, 32 were doctors, 32 paramedics and 32 medical students. The mean (SD) age of participants was 26.1±3.6 years old. Among the participants, 53.6% were males and 43.8% were females. All of them had received a minimum of BLS training while 28.1% of them had received advanced cardiac life support training. Forty-point six percent received their last training in the last 6 months, 18.8% within a year while 40.6% received training more than a year ago. Thirty-three-point three percent participants had no experience working in the ED and they were all medical students, 30.2% had worked less than 2 years, 27.1% had worked for 2 to 5 years while 9.4% had worked more than 5 years. Mean (SD) height of participants was 1.63m±0.09m while mean (SD) weight of participants was 61.11kg±13.36kg. Mean (SD) body mass index (BMI) for all participants was 22.96±4.10kgm^{-2}.

The mean of all outcome variables measured during manual and mechanical compression in the ambulance travelling at 0km/hr, 30km/hr and 60km/hr are summarized in Table I. Table II shows all the pairwise comparisons among different ambulance speed. We found a strong relationship between ambulance speed and the quality of manual chest compression. It showed a linear relationship between ambulance speed and average compression rate. As the speed of ambulance increased, the average compression rate also increased, and statistical significance was noted when the ambulance speed reached 60km/hr (p=0.001). Average compression depth decreased in a linear trend notably as soon as the speed of ambulance reached 30km/hr (p=0.007) and 60km/hr (p=0.016). The fraction of correct hands positioning during chest compression showed a significant decrease at 30km/hr (p=0.034). Other outcome variables such as hands-off time and the fraction of adequate relaxation did not show any statistical significance up till the speed of 60km/hr. Performance by Lucas-2 and AutoPulse did not show any statistically significant differences in all outcome variables.

Table III shows a pairwise comparison between the human group, AutoPulse and Lucas-2. Among those, three outcome variables showed a significant difference when the human group was compared with Lucas-2 and AutoPulse. These variables were average compression rate, fraction of adequate depth and fraction of insufficient compression depth. The effect of ambulance speed on average compression rate was more significant in the human group as compared to AutoPulse and Lucas-2 with p<0.001 and p=0.038, followed by the fraction of adequate compression depth with p=0.030 and p<0.001, and fraction of insufficient compression depth with p=0.028 and p=0.043. There were two outcome variables wherein only human group and AutoPulse had a significant difference. They were average compression depth and fraction of adequate chest relaxation with p=0.022 and 0.020.

In another sub-analysis to compare both the mechanical compression devices, we noticed that the AutoPulse and Lucas-2 showed significant statistical differences in three outcome variables. They were average compression depth, fraction of adequate compression depth and fraction of insufficient compression depth with p=0.019, p<0.001 and p<0.001 respectively. In term of fraction of excessive compression depth and fraction of normal hand positioning, we found no statistical significance among the three groups. Figure 1 further shows the estimated marginal means of average compression rate, average compression depth, and fraction of normal hand positioning among the three groups.

DISCUSSION

This is a follow-through study that evaluates the effects of ambulance speed on the quality of manual chest compression in a more detailed manner while comparing it with mechanical compression. Results of this study clearly showed that the speed of ambulance can affect many aspects of manual chest compression. We found a strong link between the speed of ambulance and manual compression rate which were both increased in a linear trend. The compression rate of 120/min generated the largest blood flow then it declined with a further increased rate.9 The increased compression rate could be associated with the adrenaline rush and therefore increased sympathetic response of the compressors. This was one of the features which was almost negligible in both mechanical compression devices.

Table I: Mean of all outcome variables

	Type of compressor	Speed of ambulance Mean (SD)		
		Idle	30km/hr	60km/hr
Average compression rate (/min)	Manual	122.23(16.2)	124.65(14.37)	127.79(14.36)
	Lucas-2	107(1)	104.67(2.08)	104.67(3.06)
	AutoPulse	94.67(1.53)	98(8.89)	82.67(1.53)
Average compression depth (mm)	Manual	49.41(7.26) 53(0)	47.68(8.12)	47.49(8.64)
	Lucas-2	53(0)	52.67(0.58)	53.33(0.58)
	AutoPulse	38.67(2.89)	36(1)	35.67(0.58)
Fraction of adequate compression depth (%)	Manual	47.4(33.01)	38.86(38.85)	37.21(32.57)
	Lucas-2	99.7(0.52)	98.47(1.19)	98.7(0.52)
	AutoPulse	0(0)	0(0)	0(0)
Fraction of insufficient compression depth (%)	Manual	42.92(38.08)	52.2(38.16)	51.47(40.12)
	Lucas-2	1.3(0.52)	0.3(0.52)	1.2(1.51)
	AutoPulse	100(0)	100(0)	100(0)
Fraction of excessive compression depth (%)	Manual	9.7(20.21)	8.94(21.09)	8.94(21.09)
	Lucas-2	0(0)	0(0)	0(0)
	AutoPulse	0(0)	0(0)	0(0)
Fraction of adequate chest relaxation (%)	Manual	97.32(13.65)	99.08(5.51)	99.17(2.85)
	Lucas-2	95.63(1.43)	97.73(1.10)	97.8(2.99)
	AutoPulse	84.87(1.40)	82.13(8.78)	97.4(2.71)
Fraction of normal hand positioning (%)	Manual	74.92(33.23)	67.17(35.26)	70.03(33.54)
	Lucas-2	93.77(1.10)	92.8(2.72)	90.43(3.49)
	AutoPulse	70.47(31.54)	20.33(12.48)	11.3(8.19)

Numerical values in table: mean (standard deviation)

Table II: Pairwise comparison among different speed of ambulance

	Velocity (km/hr)	Human		Lucas-2		AutoPulse	
		MD (95% CI)	p-value*	MD (95% CI)	p-value*	MD (95% CI)	p-value*
Average compression rate (/min)	0 vs. 30	-2.417	0.202	2.333	0.951	3.333	1
	0 vs. 60	-5.562	0.001	2.333	0.889	12	0.061
	30 vs. 60	-3.146	0.010	0.001	1	15.333	0. 221
Average compressiondepth (mm)	0 vs. 30	1.729	0.007	0.333	1	2.677	0.809
	0 vs. 60	1.917	0.016	-0.333	1	3	0.565
	30 vs. 60	0.188	1	0.333	1	-0.667	1
Fraction of adequate compression depth (%)	0 vs. 30	8.543	0.018	1.233	0.265	0	0
	0 vs. 60	10.191	0.011	1	0.583	0	0
	30 vs. 60	1.648	1	-0.233	1	0	0
Fraction of insufficient compression depth (%)	0 vs. 30	-9.273	0.022	-0.9	0.793	0	0
	0 vs. 60	-8.55	0.066	-1	0.583	0	0
	30 vs. 60	0.723	1	-0.1	1	0	0
Fraction of excessive compression depth (%)	0 vs. 30	0.758	1	0	0	0	0
	0 vs. 60	-1.366	1	0	0	0	0
	30 vs. 60	-2.124	0.945	0	0	0	0
Fraction of adequate chest relaxation (%)	0 vs. 30	-1.754	0.365	-2.1	0.791	2.733	1
	0 vs. 60	-1.848	0.443	-2.167	0.938	-12.533	0.099
	30 vs. 60	-0.094	1	-0.067	1	-15.267	0.020
Fraction of normal hand positioning (%)	0 vs. 30	7.743	0.034	0.967	1	50.133	0.477
	0 vs. 60	4.878	0.162	3.333	0.506	59.167	0.221
	30 vs. 60	-2.865	0.826	2.367	1	9.033	0.778

MD (95% CI): mean difference 95% confidence interval; vs.: versus.
*Repeated Measures ANOVA

Contrary to a previous study, our study demonstrated a linear decrease in average compression depth with the increasing speed of ambulance.[6] There was a significant decline of average compression depth at ambulance speed of 30 and 60km/hr. Inadequate compression depth is not favourable during CPR as it renders the CPR ineffective. The confined compartment in the ambulance and constant vibration during transportation are two strong factors associated with the instability on an ambulance.[10,11] Adequate compression depth is not only vital in achieving good venous return from compressed thoracic vessels but also improves coronary blood flow.[12] According to the findings of some studies, instability due to inertia during speed changes may negatively impact the quality of chest compressions performed during CPR in a moving environment. As such, the environment in a moving ambulance results in a lower percentage of chest compressions that achieve adequate depth, compared to chest compressions performed on an unmoving ground.[13,14]

Table III: Pairwise comparison among different group of compressors

	GROUP	Mean Difference (95% CI)	p-value*
Average compression rate (per minute)	Human vs. Autopulse	33.11	0.001
	Human vs. Lucas-2	19.44	0.038
	Lucas-2 vs. Autopulse	13.67	0.611
Average compression depth (mm)	Human vs. Autopulse	11.413	0.022
	Human vs. Lucas-2	-4.809	0.755
	Lucas-2 vs. Autopulse	16.222	0.019
Fraction of adequate compression depth (%)	Human vs. Autopulse	41.156	0.030
	Human vs. Lucas-2	-57.8	0.001
	Lucas-2 vs. Autopulse	98.956	0.001
Fraction of insufficient compression depth (%)	Human vs. Autopulse	-51.135	0.028
	Human vs. Lucas-2	47.932	0.043
	Lucas-2 vs. Autopulse	-99.06	0.001
Fraction of excessive compression depth (%)	Human vs. Autopulse	9.902	0.994
	Human vs. Lucas-2	9.902	0.994
	Lucas-2 vs. Autopulse	0	1
Fraction of adequate chest relaxation (%)	Human vs. Autopulse	10.388	0.020
	Human vs. Lucas-2	1.466	1
	Lucas-2 vs. Autopulse	8.922	0.273
Fraction of normal hand positioning (%)	Human vs. Autopulse	36.674	0.115
	Human vs. Lucas-2	-21.626	0.656
	Lucas-2 vs. Autopulse	58.3	0.055

CI: confidence interval; vs.: versus.
*Repeated Measures ANOVA

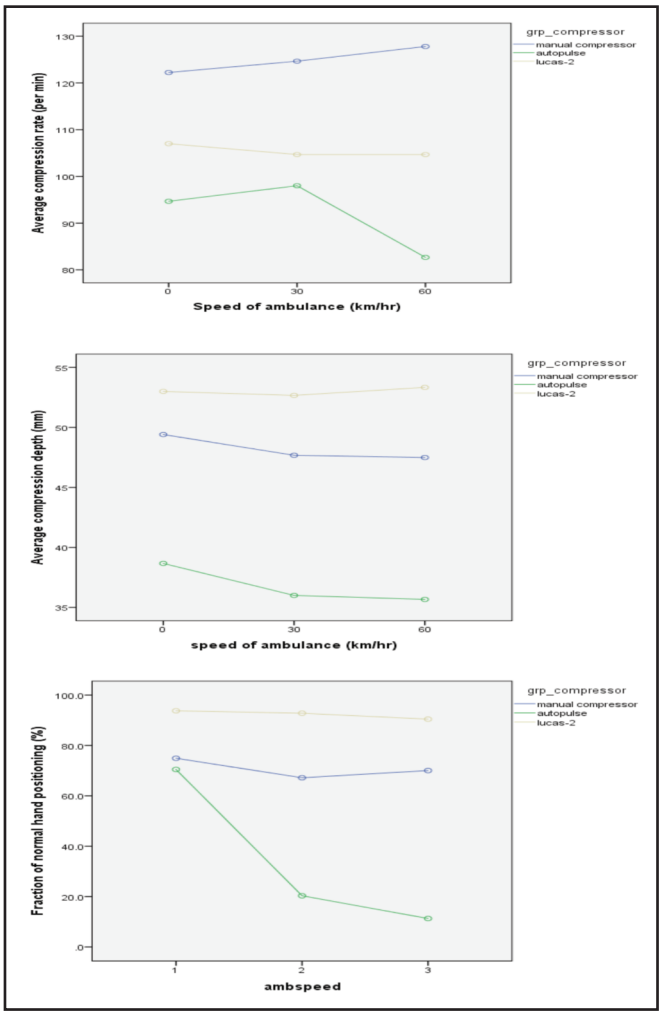

Fig. 1: Estimated marginal means of average compression rate (/min), average compression depth (mm), and fraction of normal hand positioning (%) at ambulance speed of 1) 0km/hr, 2) 30km/hr and 3) 60km/hr

Our fraction of normal hands positioning also showed a significant reduction in the human group when the speed of ambulance reached 30km/hr. Our results showed that even a slight increase in the speed of the ambulance can lead to an increased instability of chest compression. Abnormal hands positioning during chest compression renders not only ineffective CPR but also increases the risk of chest, cardiac and visceral organ injury.[15,16]

A similar test was repeated on AutoPulse and Lucas-2, however, both devices did not show any significant differences in their performance at three different speeds. When compared to both compression devices, we noted major disadvantages of manual chest compression were on the compression rate and compression depth. We noticed that there was a constant increase in the average compression rate in the human group as the speed of ambulance increased, while both mechanical compression devices were not affected. We also noticed that there was a constant decrease in the average compression depth in the human group which was not seen in both mechanical compression devices. While inconsistent performance of humans can be explained by the influence of various physical and physiological factors, both mechanical compression devices clearly have shown their superiority in giving continuous and consistent chest compression at all times regardless of the speed of ambulance. In this study, the fraction of normal hands positioning was of no difference when comparing both mechanical compression devices. We hypothesized that the clear effect of ambulance speed on hand positioning cannot be fully demonstrated due to the short duration of continuous chest compression in our study.

Sub analysis of both mechanical compression devices showed some variability mainly in term of compression depth. However, we need to bear in mind that both mechanical compression devices work in different ways and principles.

We think that we should exclude few variables namely fraction of adequate/inadequate/excessive compression depth for AutoPulse machine as it is designed in such a way that it generates circumferential compression based on chest circumference of the patients rather than a direct compression depth of 5-6 cm as proposed by AHA BLS adult.

A previous study showed that the quality of chest compression when performed on the ground is affected by gender and BMI.[17] Our study, however, was unable to demonstrate a clear association between various physiological factors, for instance, height, BMI, gender and age of the participants with the quality of chest compressions when performed on a moving ambulance. Similar negative results were also seen when looking into the associations between level of training, duration from the last training, and years of working experience in the prehospital care with the quality of chest compressions when performed on a moving ambulance.

CONCLUSION

Certain aspects of manual CPR can be affected by the speed of the ambulance. In this study, we demonstrated that the average compression rate, compression depth and fraction of normal hands positioning were affected by different ambulance speed. Whereas the quality of CPR of both mechanical compression devices were not affected by the speed of the ambulance. This condition, in which both mechanical compression devices were not affected by the speed of ambulance puts up a strong recommendation on utilizing mechanical compressions devices as mandatory equipment in OHCA, to ensure continuous high-quality CPR which can improve the patient survival.

LIMITATION OF STUDY

We intended to extend our study by increasing the speed of ambulance to 90km/hr but this was abandoned due to safety issues and unavailability of suitable study location. Another limitation of this study was the duration of chest compression performed. The reason we set only one minute of chest compression was to avoid other factors like compressor fatigue from affecting the quality of CPR. We hypothesized that if we prolonged the duration of chest compression, we may be able to demonstrate an adverse effect of ambulance speed on certain aspects like duty cycle and hand positioning. However, we feel that the primary goal of chest compression should be focused on generating adequate cardiac output, coronary and cerebral perfusion, and outcomes which are measurable by specially designed manikins.

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Granulocyte-Macrophage colony stimulating factor in asthmatic patients infected with respiratory syncytial virus

Shatha Farouk Abdullah, FIBMS

University of Baghdad Bab-al Moadhum Campus College of Medicine, Baghdad, Iraq

ABSTRACT

Introduction: It is estimated that at least 30 to 40% of asthma attacks in adults are related to respiratory infections with viruses. The majority of asthma-related viruses include respiratory syncytial virus (RSV), rhinovirus, and parainfluenza. Inflammatory cytokines are supposed to play a vital role in causing inflammation of the respiratory tract as regulators of proliferation, chemotaxis, and activation of inflammatory cells.

Objectives: The aim of this study is to assess the role of Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) in asthmatic airway hyper-responsiveness associated with RSV infections.

Materials and Methods: Forty five asthmatic cases and 45 healthy individuals were studied in a cross-sectional design. All asthmatics underwent symptom score assessment.GM-CSF concentrations in sputum and RSV-IgM/IgG in serum samples were measured for all participants by Enzyme Linked Immuno-Sorbent Assay (ELISA).

Results: The GM-CSF concentration level was significantly higher in asthmatics (270.27± 194.87pg/mL) especially among moderate and severe disease with mean concentration of 197.33±98.47 and 521.08± 310.04 respectively, compared to healthy controls (22.20±21.27 pg/mL) (p=0.0001). The sputum level of GM-CSF in asthmatics is highly significant associated with positive anti-RSV IgG sera which represents 35/45(77.8%) with mean GM-CSF concentration of (276.99± 86.42) compared with controls at about 31/45 (68.9%) with GM-CSF mean concentration of (22.84±23.47). On the other hand, positive anti-RSV IgM in asthma cases was 8 out of 45(17.8 %) with GM-CSF mean concentration of (307.25± 306.65). Furthermore, GM-CSF sputum level was significantly correlated with eosinophil count especially in moderate and severe asthma.

Conclusions: This study revealed that GM-CSF level is associated with eosinophilia and indicates asthma severity that might be evident during RSV infection .The distinctive GM-CSF features observed in the sputum from asthmatics with RSV may be useful as a diagnostic methods to help match patients with antibody therapy.

KEYWORDS:
Asthma, GM-CSF, eosinophil, cytokines, RSV, ELISA

INTRODUCTION

Asthma is known as an inflammatory disease in which a variety of cytokines are implicated. Thus, in episodes of asthma, numerous cytokines, consist of TNF, GM-CSF, IL1β, IL2, IL6, PG-D2 and Periostin are detectable in blood, sputum and in bronchio-alveolar lavage fluids.[1-3] Among these, granulocyte–macrophage colony-stimulating factor (GM-CSF) is recognized to have a vital role in eosinophil survival and in the activation of Antigen Presenting Cells (APC).[4]

GM-CSF is a glycoprotein of monomeric type produced by many cells including macrophages, T- cells, mast cells, endothelial cells and fibroblasts that were primarily regarded as (haematopoietic growth factor). It is stated at present that GM-CSF is a cytokine that responsible to activate, differentiate and plays a role in both adaptive and innate immune elements survival including cells of granulocytes, macrophages, dendrocytes and lymphocytes. Normal lung epithelium secrete small quantities of GM-CSF. However; it produced in greater amounts in asthmatics lung epithelial cells.[5] Epithelial cells have been shown to be the major source of GM-CSF in respiratory secretions of healthy people, while in patients with atopic diseases; eosinophils are the main and dominant source in respiratory tissues together with migrating lymphocytes and neighboring epithelial cells that are stimulated by external antigen.[6] GM-CSF supports the development, maturation and differentiation of myeloid cell, and dendritic cell, GM-CSF formation -signaling imbalance may perhaps lead to damaging inflammatory effects. Supporting evidences have revealed that GM-CSF plays an important role in a number of inflammatory and autoimmune diseases and in response to pulmonary infections. Of note GM-CSF along with IL-3 are the major cytokines of innate immune response whose vital role is determined for the expansion and succession of atopic asthma.[7]

Patients with asthma are prone to viral infection due to the already damaged respiratory epithelium which leads to further airflow obstruction. Furthermore, the cellular response to viral infections includes the disrupting tissue barrier and fixed inter-junctions, inhibiting apoptosis, increasing cell lysis , abnormal Th1 response and lowering the production of IFN-γ, as well as it facilitates viral receptors expression, viral shedding, but prevents viral clearance.[8] In addition, interleukins as well as many inflammatory mediators associated with allergic reactions or remodeling cytokines are induced in response to viral infections. Viruses

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Corresponding Author: Shatha Farouk Abdullah
Email: shthabdullah@yahoo.com

associated with the disease severity is influenced by the synergistic effects of allergic sensitization with the help of microbiome.[9]

The majority of asthma-related viruses are respiratory syncytial virus (RSV), rhinovirus, and parainfluenza. RSV is a frequent viral infection of upper respiratory tract during childhood and adulthood. Though occasionally, this infection might lead to more severe type of the lower respiratory disease. Early during the period of viral infection, local cells in the airway are triggered in an independent antigen pattern, provoking anti-viral reactions but besides stimulating and conscripting cells to the airflow that may possibly cause wheezing illnesses.[10] Specific orchestrated T and B cell responses against the virus may also have a worse impact in the existence of pre-inflamed respiratory airways. Lastly, virus -allergen interactions have synergistic effects that trigger bronchial inflammations.[11] It is likely that the increased definition of virus mechanisms to exhort inflammation will offer therapeutic goals for treating and possibly preventing atopic diseases and asthma.[12] Innate and adaptive immune system components contribute in controlling and get ridding of an infection with RSV, marked struggle against RSV re-infection that is conferred by previous infection seems to be attributed mainly through RSV-specific local secretory and serum antibodies.[13]

MATERIALS AND METHODS

Participants:

Forty five patients with asthma and 45 apparently healthy persons as controls were recruited in this study of a cross-sectional design; controls are of medical and paramedical healthy subjects without medical history, or any history of allergic diseases. This study was conducted at the Specialist Center for Allergy and Asthma Diseases in Baghdad, AL-Resafa and the Department of Microbiology/College of Medicine, University of Baghdad, Iraq, between July 2018 and June 2019. The protocol and methods were approved by the Scientific Ethics Committee of the Medical College Council, University of Baghdad, The approval number of ethics committee was 95 in 1 July 2018. We received verbal and written informed consent from all participants.

Patient groups were recruited randomly during their visits to seek medical care. Following respiratory infections and their impact on asthma and according to Global Initiative for Asthma (GINA) Guidelines[14], patients were divided prior to hospitalization (*i.e.* hospital admission as indicated for most of severe and some of moderate cases); therefore, according to their Pulmonary Function Test results that consider the force expiratory volume in one second (FEV_1) ≥ 80% as mild, from 60%-80% as moderate and ≤ 60% as severe asthma . Patients complained of typical symptoms of respiratory infection such as (rhinorrhoea, cough, dyspnoea, sputum, and fever) of about 4 days. However, all allergic investigations were negative for atopic diseases and those with influenza, metapneumovirus and rhinoviruses tested positive were excluded from the study.

The criteria for exclusion were chronic allergic rhinosinusitis and nasal polyps. Also, anyone who is smoker, on antibiotic treatment, on local or systemic antihistamines and/ or corticosteroids was excluded.

Sampling:

Sampling was done under strict sterile conditions taken by patients and researcher to ensure safety measures, using personal protective equipment (PPE) with the use a fit-tested N95 face mask. Sputum samples were spontaneously collected from clinically stable asthmatic patients who were pretreated with a short-acting beta 2 agonist (induced sputum not performed in order to overcome disease exacerbation). While an induced sputum samples in healthy controls were performed using nebulised hypertonic saline of (3%, 4% and 5%) concentrations for 5-7 min, as described by Saha et al.[15] The sputum was collected in a sterile container and then suspended using the 0.1% Mucolytic Dithio-Threitol (DTT) filtered and centrifuged at 3000rpm for 20 min. The sediment was stained by Wright's stain for differential cell counts, while the supernatants of about 2 ml were stored at –80°C as previously mentioned by Pavord et al. in 1997[16] for measuring the concentration level of GM-CSF using the commercial human ELISA kit (CUSABIO. China).

Five ml of blood samples were collected in EDTA tubes from all 90 subjects centrifuged at 2000x rpm for serum separation. We placed all serum samples in a two sets of 1.5 mL Eppendorf tubes each set of Eppendorf tube stored at -20°C until used. Both sets have been used for the detection of anti RSV-IgM/IgG using 2 kits of (Demeditec Diagnostics GmbH. Germany) following the manufacturer's instructions. GM-CSF assay utilized the quantitative sandwich enzyme immunoassay technique, and following the manufacturer's instructions. The undiluted standard was served as the high standard (1000ng/ml) while the sample diluent was served as the zero standards (0 ng/ml). In brief, 100ul of standards, control and patient samples were added to the microwell plates, which were then incubated for 2 hours at 37˚C. Next, the liquid of each microwells were removed without washing step. Then, 100ul of biotin-conjugated antibody specific for GM-CSF were added to each well, and the plates were incubated for an hour at 37˚C. Next, the contents of the microwells were discarded and washed three times with a wash solution. Then, 100 ul of avidin conjugated Horseradish Peroxidase (HRP) were added to each well, and the plates were incubated again for an hour at 37˚C, after that liquid was aspirated and the plate was washed 5 times. Then, the substrate solution was added and incubated for 15 minutes at 37˚C, the stop solution was added to each well, and the plates were incubated for five minutes at room temperature. Finally, at 450 nm the microwell plate was read within 5 minutes, and the results were calculated. According to producer's declaration, overall intra-assay and inter-assay precisions should be <8% and <10% respectively. The concentrations of GM-CSF were expressed in (pg/mL) with a range of 15.6 pg /mL - 1000 pg/mL. The minimum detectable dose of human GM-CSF was typically less than3.9 pg/ml. The sensitivity of this assay, or Lower Limit of Detection (LLD) was defined as the lowest protein concentration that could be differentiated from zero according to manufacturer's instructions.

The professional soft "Curve Expert 1.4" was used to make a standard curve, which was downloaded from Cusbio web. A standard curve was created by reducing the data using computer software capable of generating a four parameter logistic (4-PL) curve-fit. The data might be linearized by plotting the log of the GM-CSF concentrations versus the log of the O.D. and the best fit line can be determined by regression analysis.

Statistcal Analysis:
Data were expressed as Mean ± Standard Deviation (SD), the study groups were analyzed using the t-test to compare between the mean concentrations. The strength of the correlation between different parameters were explored using the Spearman's Rank Correlation Test. P values of ≤ 0.05 considered as statistical significant differences. We performed the analysis using the SPSS software (Statistical Package for the Social Sciences, version 20, IBM).

RESULTS

In this study, 45 asthmatics (22 men and 23 women, mean age 40.4 ± 12.97 years) and 45 healthy subjects (21 men and 24 women, mean age 40.01 ± 13.25 years) were included. The characteristics of the study groups shown in (Table I).

Table II shows that GM-CSF concentration level was significantly higher in asthmatics (270.27±94.87 pg/mL) especially among moderate and severe asthma with mean concentration of 197.33±198.47 and 521.08±310.04 respectively compared with control patients (22.20±21.27 pg/mL) (p=0.0001), high eosinophil count with significant differences were observed between asthmatics and control group (20.40±7.40 and 3.89±1.99) respectively with (P= 0.0001).Also illustrated in table II and III.

The mean concentrations of GM-CSF in sputum samples of asthmatic patients is highly significant associated with positive anti-RSV IgG in sera which represents 35 out of 45(77.8%) with mean GM-CSF concentration of (276.99± 288.42) compared with controls at about 31of 45(68.9%) with GM-CSF mean concentration of (22.84±23.47)(t = 4.8876; two tailed P -value < 0.0001). In this study, highly significant differences were found between the eosinophil counts in the patients with RSV-IgG (20.97±7.96) compared with controls (3.94±1.77) (t= 11.6499, p=0.0001). On the other hand, positive anti-RSV IgM in asthma cases was 8 out of 45(17.8 %) with GM-CSF mean concentration of (307.25± 306.65). Furthermore, anti-RSV IgM were positive in 8(17.8%) asthmatic cases. On the contrary, we were unable to detect anti-RSV IgM in samples of controls (Table IV).

Interestingly, the linear relationship between the GM-CSF concentration level in sputum and eosinophil counts were illustrated in (Figure 1); a positive significant correlation between two variables were found using Pearson correlation coefficient (r= 0.456306, r2 =0.2025) in asthmatics as an increase of one unit in GM-CSF sputum level will increase eosinophil count in about 20% accordingly. The two-tailed P-value equals 0.5437 and by conventional criteria, this difference is considered to be not statistically significant.

Table I: Characteristics of the study groups

Variable	Asthmatics No. =45	Controls No. =45
Age/yrs (Mean ± SD)	40.4 ± 12.97	40.01 ± 13.25
Men/Women(No.)	22/23	21/24
*FEV1: No. (%)		
Normal	0(0)	45(100)
Mild	12(26.7)	
Moderate	21(46.6)	
Severe	12(26.7)	

* FEV1: force expiratory volume in one second.

Table II: GM-CSF concentration among study groups

Study groups (No.)	GM-CSF Mean ±SD (pg/ml)	Eosinophil count Mean ±SD	p-Value
Asthmatics (45)	270.27± 194.87	20.40±7.40	0.0001
Controls (45)	22.20±21.27	3.89±1.99	

Table III : Mean concentration of GM-CSF in relation to asthma severity

Asthmatic patients	No.(%)	GM-CSF Mean ±SD (pg/ml) p-value	t- test
Mild	12 (26.7)	65.50±65.29	*0.03
Moderate	21 (46.6)	197.33±198.47	**0.0001
Severe	12 (26.7)	521.08±310.04	***0.0001

*mild vs moderate,
**moderate vs severe,
***mild vs severe.

Table IV: Mean GM-CSF concentrations and eosinophil counts in RSV infected study groups

Study groups No. (%)	GM-CSF Mean ±SD (pg/ml)	Eosinophil count Mean ±SD	p-Value
Asthmatics 45 (100)			
RSV-IgG 35(77.8)	276.99± 288.42	20.97±7.96	
RSV-IgM 8 (17.8)	307.25± 306.65	18.13±4.49	0.0001
Controls 45(100)			
RSV-IgG 31(68.9)	22.84±23.47	3.94±1.77	
RSV-IgM 0(0)	0	0	

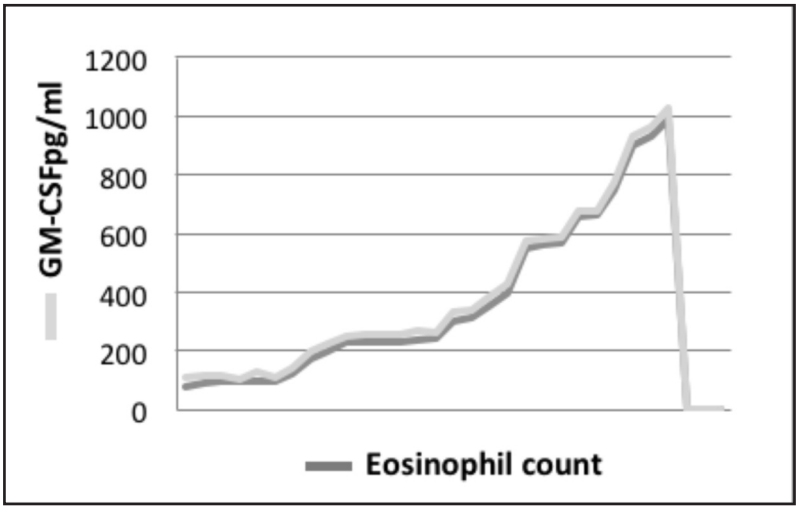

Fig. 1: Correlation of GM-CSF with eosinophil count among asthmatic patients.

DISCUSSION

In this study a noninvasive specimen using sputum for studying inflammatory cytokines, being rich enough with inflammatory cells and soluble mediators of inflammation and infection; it may be used to monitor disease severity and pathology.[17,18] Sputum sample collection is easily obtained from a well expectorated individuals, the problem arises in patient undergoing signs and symptoms of respiratory infection and therefore, an induced sputum collection from infected asthmatic patient might worsen his symptoms and end the patient with a crisis, so that a spontaneous expectorations from our patients were applied under close monitoring and relatively a small sputum volume were obtained. Whereas, for those healthy subjects induced sputum was used. In both groups, sputum sampling might associated with underestimation of biomarkers concentrations.[18]

The present results demonstrated that significantly higher sputum level of GM-CSF in cases with asthma than those of controls and the level were elevated among moderate and severe asthma. These readings support a possible role of GM-CSF in bronchial asthma and indicate that the expression of GM-CSF in excess in sputum is an essential element in disease crisis as severity is elicited by previous viral infections. Our findings are supported by Saha et al. who measured GM-CSF concentration level in the sputum and bronchial cells of asthmatics and chronic obstructive pulmonary disease(COPD) and they found that GM-CSF was raised in those with moderate (7/14) and severe (11/18) in those with asthma compared to control group, suggesting that GM-CSF over-expression both in sputum and the bronchial mucosa plays a particular role in severe disease.[15] Furthermore, Cates et al.[19] discovered that airway hyper-responsiveness in mice can be triggered upon sensitization with intranasal dust mites via a GM-CSF arbitrated mechanism. Previous study investigated IL-6, IL-8, and GM-CSF levels and sources in the nasal secretions in response to allergen sensitization using ELISA and immunohistochemistry suggesting that strong local immune reactivity of studied proinflammatory cytokines varied according to levels, sources, and mechanisms of release but were essential in the symptom of the allergic diseases6. While Sawada et al.[20] reported that GM-CSF production during an allergic crisis may be suppressed over a long period of time by IL-4, TGF-beta, or both in a way to help control the severe allergic response, and this suppression may increase the sensitivity of inflammation in the lung tissues after the attack by affecting the resident cells maturation20. Interestingly, preceding clinical studies have reported that anti- GM-CSF; blocking antibodies can be harmless and promising in many diseases of autoimmunity or inflammatory.[21]

In this study, previous RSV infection indicated by RSV-IgG detection was common among asthmatics compared to control group suggesting prior epithelial damage. It has been reported that viral respiratory infections are the main cause of severe asthma exacerbation in 80% of cases. At least 30%

- 40% of severe crisis in adult asthma are associated with respiratory viral infections and unfortunately the high-risk treatment failures are linked to these infections[22,23] of them is RSV which can provoke acute asthma exacerbation in adults, apart from Rhinoviruses, Human Metapneumovirus, Influenza, Parainfluenza, Adenovirus, Coronavirus, and Bocavirus were all confirmed in asthmatic attacks however at low frequencies.[24] Moreover, Johansson argued that the reasons behind this RSV induced asthma severity are not fully explained but may encounter to the immune system dysregulation towards the virus, leading to marked innate and adaptive immune elements recruitment and activation that can cause serious tissue injury.[13] Currently no effective anti-RSV drugs or related vaccines; so infection with the virus remains of a medical concern worldwide.

Current results showed that the level of GM-CSF and eosinophilic infiltration in sputum are higher in patients with RSV infected asthma (mainly of moderate and severe type) than in uninfected patients and in healthy controls. Also the local level of eosinophilic infiltration in the respiratory tract of asthmatic patients is almost higher in seven times than in the control patients and five times higher among RSV infected asthmatics than in the controls. Previous study by Ichinohe et al. 1999 indicated that several proinflammatory mediators as GM-CSF produced following RSV infection of epithelial airways seem to contribute to eosinophil infiltration.[25] On the other hand, Naessens et al. suggested that in post allergic attacks in the mice airways, there would be a defect in the maturation of alveolar macrophage cells residing in bronchial tree leading to a hypersensitivity of allergic lung cell to RSV infection, proposing that these immature post allergic cells might enhanced curative opportunity in controlling undesired RSV-infection with subsequent exacerbations in asthmatic patients26. Again, eosinophilia is established as one of the characteristics features of asthma as a therapeutic goal in order to validate corticosteroid treatment as well as for biotherapies with monoclonal anti-IL5 antibodies in patients with airway diseases.[17,27] It has been recommended to modify a variety of aspects of inflammatory processes in asthma, including mucus formation, hyperplasia of smooth muscle tissues, angiogenesis, and fibrosis and thus contributing to exacerbate asthma symptoms. In fact, many biological aspects of eosinophilia are controlled by GM-CSF, including a constant development and differentiation, chemokinesis, airway hyper-responsiveness and the endurance of eosinophil during the inflammatory lung illnesses. This recruitment seems to be an organ specific for inflamed lung. Thereby eosinophil regulation in organ specific can obtain in the context of GM-CSF signaling.[27]

Also in line with our result, other study disclosed that the sputum GM-CSF concentration was correlated with the sputum eosinophilia in subjects with asthma disease (rs= 0.28; p=0.007), all those with asthma (rs=0.3; p=0.04) and of moderate and severe disease[15], indicating that the most important source of the immune mediators in patients with asthma is the stimulated eosinophils thus ensuring the growth and activation of eosinophil that have been reported also in rhinosinusitis with nasal polyp by Shin et al.[28], therefore, a high abundance of eosinophils in the epithelial tissues of the patients can be explained. Thus, measuring local pro-inflammatory cytokines in sputum can be of interest to monitor the severity and to study the pathogenesis of allergic diseases.[29]

LIMITATION

Our study has some limitations. One of the main limitations is the small sample size of 45 patients and restricted to adult asthma where most of them had experienced RSV infections in their early lives. Another limitation is that we have not been able to prove a relationship between GM-CSF and as a result of differences in treatment especially with the use of steroids as expected that the expression of sputum GM-CSF in tissues is decreased by the use of corticosteroids; this is because most patients enrolled in this study were not adherent to their treatment. Further limitation is the use of sputum sample in this study to test GM-CSF instead of broncho-alveolar levage (BAL), although later is an invasive one but measuring cytokines in the sputum of the patients may not exactly reflect the level of GM-CSF related to severity of the disease. Further studies with larger numbers of patients including childhood asthma are necessary to ascertain our findings and to detect the comparative GM-CSF expression in bronchial tissue by various types of cells.

CONCLUSION

These results suggesting that GM- CSF may perhaps incriminated in asthma patho-physiology and considering this cytokine as a marker of asthma exacerbation. The distinctive GM-CSF features observed in the sputum from asthmatics with RSV may be useful as a diagnostic methods to help match patients with antibody therapy. However, further studies are needed with a higher number of patients to analyze the cytokines profile in sputum for controlling allergic diseases.

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CONFLICT OF INTEREST

None

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Alternate careers for medical graduates and house officers in Malaysia

Amaramalar Selvi Naicker, M.RehabMed[1], Vinoshini Devi A/P Kailaivasan, MBBS[2], Brenda Saria Yuliawiratman, M.RehabMed[1], Arvindran Alaga, MRCP[3], Kevin Ng Wei Shan, M.Anaes[4], Manimalar Selvi Naicker, M.Path[5], Ohnmar Htwe, M.Med.Sc. Rehab Med[1]

[1]Rehabilitation Medicine Unit, Department of Orthopedics & Traumatology, Faculty of Medicine, Universiti Kebangsaan Malaysia/ Hospital Canselor Tuanku Muhriz, [2]Hospital Teluk Intan, Perak, [3]Hospital Sultanah Bahiyah in Alor Setar, Kedah, [4]Department of Anaesthesiology, Faculty of Medicine, University of Malaya, [5]Department of Pathology, Faculty of Medicine, University of Malaya

ABSTRACT

Introduction: In recent years, many unresolved issues pertaining to house officers in Malaysia have led to a longer waiting time and a 'glut' of medical graduates with a surprising 20% dropout amongst those who join the housemanship programme. This appears to reflect the changing times, mindsets and work expectations of millennials who comprise this cohort reflecting a need to consider possibilities of career shifts especially so in these uncertain times. This study explores the perceptions, awareness and interest in alternative career options amongst recent graduates and house officers.

Materials and Methods: This was a study done between 2018 and 2019 using a questionnaire which was shared on various social platforms. Data analysis was done using Excel spreadsheet.

Results: A total of 450 house officers and 657 medical graduates responded. Expectedly 66.8% claimed lifelong passion whilst another 12.1% claimed family influence as their reason to do medicine. Most were aware of their career challenges and 40% of them were keen to consider career change and reskilling indicating a possible shift from traditional expectations of a medical career.

Conclusion: Whilst medicine is often considered a true calling, current challenges will require mental and emotional flexibility to explore other career opportunities. Thus, engagement programmes should be directed at medical graduates and house officers to identify and support those open to career transitions. This will help address current issues of internship bottleneck and rising dropout rates amongst internees. Early career change engagements will give them insight into their true career goals whilst opening up opportunities for those who wish to change.

KEYWORDS:
Alternative careers, medical graduates, house officers, career transition

INTRODUCTION

In recent years, the Ministry of Health (MOH) has highlighted some grim statistics regarding issues pertaining to housemanship training programme in Malaysia. Out of an average of 5,000 medical graduates (MG) qualifying annually (2000-3000 local graduates and 1500-2200 overseas graduates), only about 4000 are likely to be absorbed each year, leaving the remaining graduates jobless and waiting for up to eight months or more before job postings.[1-4] Furthermore, out of those who get into the housemanship programme, only 40-50% of them will be offered a permanent civil service position.[1,2] In the current cohort of housemen completing their training, almost all of them were offered contract medical officer (MO) positions in the UD41 category. This is unlike previous years where most MG were absorbed much sooner and every houseman was given a permanent position at the end of their training. Since the 'glut' of graduates in recent years, local news has highlighted their plight and their challenges in getting temporary employment. Many had to seek out jobs such as waiters or drivers while awaiting placement and some have even left the profession altogether.[5] Associations and medical graduates have urged the government to take measures so that they do not lose their skills during the long waiting period.[6,7] The government in turn has in the past few years taken several measures to address this situation. They have increased the number of training hospitals from 38 to 47, increased training positions from 10,835 to 11,706 through various hospitals in Malaysia, even changed the method of appointment from permanent to contract in which the trainees have the opportunity to undergo housemanship and obtain full registration as required under the Medical Act 1971, with the hope that many will leave for private practice. This they hoped would create vacancy to absorb more house officer (HO). They also extended the moratorium with the cooperation of the Education Ministry up to April 30, 2021 on new student intakes locally with the aim of imposing intake quota of medical graduates by universities in the country.[8]

Despite these measures there still remains an oversupply of MG waiting to be absorbed into service yearly and this figure is likely to snowball with increasing graduates from both local and overseas universities and limited internship positions. In the midst of these delays and uncertainties of their future as clinicians in the government service, an intriguing scenario is steadily being observed. There is a significant number of graduates who seem to drop out of the housemanship training program even before completion in

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Corresponding Author: Professor Dr Amaramalar Selvi Naicker
Email: asnaicker@yahoo.com

spite of all the challenges in getting into the training. Recent reports indicate a 20% yearly drop out.[9] Various studies in Malaysia highlight long working hours, stress at workplace leading to burnout, depression, harassment and discrimination,[10-12] post internship contract appointments with low salary (UD 41 position) and with little scope to further themselves in a local medical specialization program as reasons behind them for quitting early in their career.[10]

Dropping out of a medical career for similar reasons is increasingly being seen in other nations as well. In 2017, 57.4% of Foundation Year 2 doctors (FY1 and FY2 in NHS are similar to the 2-year housemanship programme in Malaysia) did not enter higher-training posts and 9000 doctors quit the NHS entirely in United Kingdom(UK).[13] Factors such as changes to junior doctors' salaries, hours-worked, inflexibility with schedules, lack of consistent teamwork, and an understaffed service have been some of the reasons for dropouts amongst the young professionals. Other issues driving the discontentment and dissatisfaction is a lack of feeling valued and supported as stated in studies from the UK and the Philipines.[13,14]

The above challenges faced in pursuing and completing the housemanship programme appears to be significant and concerning for all stake holders. However, it is also important to take note of a changing mindset, career expectations gaps, career opportunities and a desire to seek new challenges[15] or even the awakening to the fact that full-time patient care is not the best fit for some, may be additional factors that drive the young professionals to drop out and seek alternative careers. The traditional mould or expectation that medicine is a lifetime single career with no u-turns or alternative options is being increasingly challenged by millennials within the medical fraternity as well as in other professions around the world. It appears that millennials are more accepting to career changes and job hopping in search of what syncs with their values and expectations.[16] An article in the British Medical Journal (BMJ) stated that the main reason doctors look to transition is due to the rigidity in clinical training as well as lack of suitable opportunities.[17] Thus in UK, career transition search platforms for doctors such as Medic Footprints along with organisations like the British Medical Association (BMA) and the National Health service (NHS) have since aided transition for doctors who wished to seek out alternative career pathways.[18] However, in Malaysia, we are yet to recognise or embrace the possibilities of career transition amongst medical graduates and professionals. Hence, this study aims to explore the perceptions, awareness and interest in alternative career options amongst medical graduates and house officers to gain a better understanding on how these millennial professionals perceive their future in medicine and their willingness to make a career transition. As the reality of unemployment amongst medical graduates and practitioners looms, we hope this information will help the various stakeholders such as Ministry of Health, Education/Higher Education, Malaysian Medical Association and Malaysian Medical council to redesign engagement programs to not only guide those wishing to carry on with a medical career but also identify and support those looking for a career change.

MATERIALS AND METHODS

This is a questionnaire-based study undertaken between 2018 and 2019. Only HO and MG who are Malaysian citizens were included. The study instrument used was a Google form questionnaire with a total of 34 questions covering issues such as demographic details, academic/undergraduate qualification details, questions related to pre-housemanship temporary employment (where applicable) as well as questions related to alternate career options (this section questions amongst others skills possessed, awareness about non clinical alternative career options, keenness in pursuing an alternative career and willingness to undergo retraining if necessary).

The questionnaire was shared on various social platforms such as Facebook, Malaysian Medical Association (MMA), SCHOMOS, Doctors Only Bulletin Board System (DOBBS), Pre-housemanship Telegram groups and targeted WhatsApp groups. Data analysis was done using Excel spreadsheet (Pivot table).

RESULTS

Demographics

A total of 1,107 respondents,450 HO and 657 MG responded to this survey. More than half (51.7%) of the respondents were between the ages of 26-30 and the rest were between the ages 21-25 (who were mainly from the medical graduate category). There were more female respondents at 65.4%. The majority were Malays (47.8%) followed by Chinese (24.8%), Indians (21.7%) and the remaining 5.7% were from minority groups. Most were single whilst only about 188 of the respondents (17%) were married. In terms of income, the majority (66.4%) in the MG category were still financially supported by parents/ guardians with no other source of income, however the remaining 33.65 % of them claimed alternative incomes ranging from RM1000-5000 per month with a surprising 2% even earning between RM8000 to RM10,000/ month. On the other hand, most (75.1%) of the HO were earning RM3000-5000 although some of them (12.6%) claimed to have higher than average earnings of between RM5001 and RM10,000 (inclusive of side incomes). (Table I)

As for their academic background, nearly half (48.1%) of the respondents were recent graduates (2018) whilst the others were from the 2014 batch upwards. About a third of them (32.6%) graduated from Malaysian private colleges and 20.2% were from government universities. The rest were from overseas universities with only a small proportion of 1.2% of the total respondents were from unrecognized overseas institutions.

Medicine as a career

When exploring their reasons for doing medicine, an expected 66.8% claimed it to be their passion and lifelong ambition to be doctors. Interestingly however about 12.1% of the remaining admitted that they were in it due to family and peer influence, whilst less than 8% of them claimed that they took up medicine due to their good grades and rated the potential good income and job security as reasons to choose the course. (Figure 1)

Table I: Income of the participants

Personal Monthly Income	Number of doctors	Percentage of doctors
No of House officer -450 (40.7%)		
No income	23	5.1%
RM1,000	6	1.3%
RM 1,000 - RM 3,000	26	5.8%
RM 3,001- RM 5,000	338	75.1%
RM 5,001- RM 8,000	51	11.3%
RM8,001 - RM 10,000	2	0.4%
> RMIO,OOO	4	0.9%
Number of Medical Graduate-667(59.3%)		
No income	436	66.4%
RM 1,000	91	13.9%
RM 1,000 - RM 3,000	73	11.1%
RM 3,001- RM 5,000	25	3.8%
RM 5,001- RM 8,000	24	3.7%
RM8,001 - RM 10,000	5	0.8%
> RMIO,OOO	3	0.5%
Total number of participants	1107	100.00%

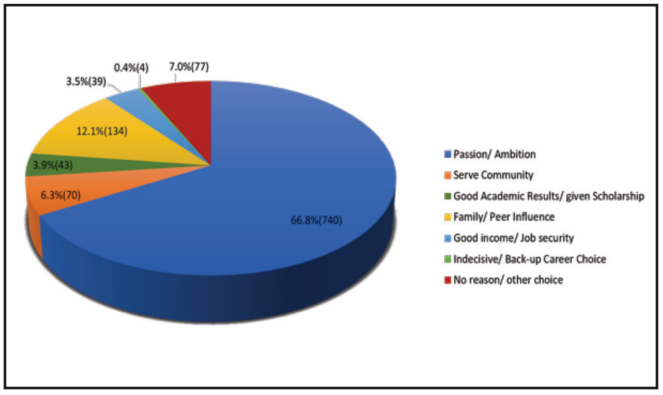

Fig. 1: Reasons for doing medicine.

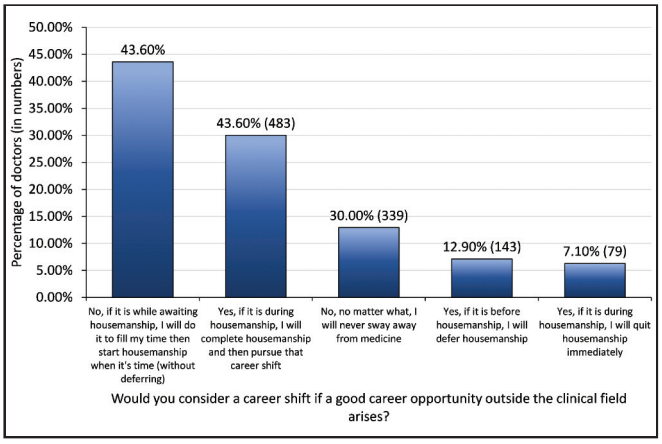

Fig. 2: If a good career opportunity outside the clinical field arises while awaiting housemanship or during housemanship, would you consider a career shift?

When asked about non-clinical career options, a large majority chose from industries such as teaching, Information Technology (IT) and engineering, business, whilst about 12% claimed to prefer health sciences related careers. Only 3% remained steadfast on the pursuit of medicine with no consideration for any other career.

Temporary employment- perceptions, challenges and job opportunities

When exploring their perceptions and issues pertaining to getting temporary jobs whilst waiting for their internship, about 45% of the participants preferred to seek out non-medical jobs whilst equal numbers preferred medically related jobs like clinic assistant/nurse, research/lab work and pharmacy assistant to keep in touch with medical knowledge. In terms of salary expectation 75% were expecting an entry monthly salary of between RM1000-2500 whilst 15% were willing to settle for a salary of less than RM1000 per month.

Most (85%) claimed that the challenges they faced in getting temporary jobs were due to limited availability of temporary employment, uncertainty of internship waiting period leading to lower motivation in performing the said jobs, their own fear of adaptation to jobs as they lack experience or skills outside their medical education, and that employers were often reluctant to engage them due to the possible expectation of a higher pay or them being overqualified for the job.

Amongst the current MG who were in temporary employment more than half of them (57%) were working full time. The main areas in which they were able to secure short term employment were in teaching, business, service industry and only 15% managed to get into preferred areas such as research, clinic/dental assistant jobs as well as pharmaceuticals. Surprisingly only half (53%) claimed to be satisfied with their temporary jobs.

Amongst reasons given by those who did not seek out temporary jobs were that they preferred to take a break, had family issues, temporary jobs were not medically related, studying for specialization exams as well as logistics as reasons whilst less than 10% claimed not to be in financial need.

Career Shift -awareness, interest and willingness

Although 97% of respondents were aware of recent challenges and uncertainties they face in pursuit of their career in medicine, surprisingly only 40% were aware of any alternative career options. So, expectedly most of them showed keenness to know more about alternative career options. More than half of them gave reasons such as burn out and loss of passion as possible drivers to look for alternative careers. The remaining cited poor career progression with job uncertainties, a higher income in nonmedical careers and concerns about work life balance as other possible reasons for the same. When enquired about additional knowledge, skills or experience that could potentially contribute towards an alternative career, most listed teaching, business, research, sports and fitness, media and even performing arts, nutrition, Information technology and finance.

However, when asked if they would seriously make a career shift if an opportunity arose, a little over half (56.5%) preferred to stay on with a medical career, whilst more than a third (37.1%) were keen to take up a career move either by deferring their housemanship if they had the option or upon completion of internship if they were already in the programme. About 6.3% were even willing to quit housemanship to take up an alternative career opportunity. (Figure 2) All those who were interested in a career change were also willing to undergo transition training/ reskilling for a new career of their choice.

When probed on their choice of program delivery for retraining in an alternative career most preferred to have an attachment and /or online learning. Acquiring a university degree was their least favourite choice. Half of them instead, preferred to acquire their new skills part time. When choosing an alternative career, not surprisingly more than 70% still preferred to be in non-clinical but health related fields. The favourite non-health industries were food and beverage, sports and fitness, IT, Media and performing arts.

Majority of those who were keen to explore alternative careers preferred to register with a job matching service that offered short term internship with participating organisations, transparent job matching method, training workshops and curricular vitae writing, meet and greet sessions with doctors who have made successful transitions.

Slightly over 40% of the respondents were keen to pursue a career change. In sub-analysing initial passion versus ultimate career decisions, it was not surprising that most (90%) who were interested in career change belonged to the group of respondents who claimed not to be 'passionate about medicine' at the out start and were willing to undergo training/ reskilling for an alternative career implying changing mindsets and possibly the need to accommodate to current challenges and employment expectation gaps.

DISCUSSION

Career expectations are jointly influenced by personal and environmental factors and the decision to be a physician is often made in the early stages of academic life sometimes even before attending high school as observed by a Finnish study, stating varying motivations including interest in people, prestigious professions, good salary and a smaller percentage indicating family influence.[19] In our study most of respondents claimed it to be their passion and lifelong ambition to be doctors whilst some others claimed pressures due to family and peer influence, good grades as well as potential good income and job security as reasons to choose the course. Interestingly another study also noted parental pressure as a reason to do medicine, especially if parents themselves were doctors.[20] So although the initial reasoning was passion, however unlike in other professions such as teaching or food industry where a student can gain some experience doing meaningful internships prior to completion, in medicine one cannot get to "experience" being a doctor without actually becoming one. Hence, it is likely a case of passion meeting reality.

Thus, it was not surprising that 40% of our study subjects were keen to make a career shift due to the current uncertainties surrounding their career progression. The trend of seeking alternative careers has been noticed in other countries as well with most of the reasons being work related.[21] A Philippine study found that job satisfaction was the primary reason for the career shift phenomenon among doctors.[14] Similarly a BMA study found that 3% of the cohort had quit medicine due to dissatisfaction, attractions of other careers, and working and pay conditions.[22] A report by a global analytics and advisory firm, on 'How millennials want to work and live' concluded that millennials (who made up the bulk of our respondents) have quite different approaches and expectations towards career. For millennials, a job is a lifestyle as well, which means their expectations will also require employers and organisations to move away from traditional organizational structures to ones that are inclusive of their values. They report that 21% of millennials claimed to have changed jobs within the past year, which is thrice more than that of non-millennials in the same period.[16] The fact we found a dropout rate of 20% amongst our Malaysian HO in training suggests that besides the need to address work related issues that contributes towards their decision to leave, one must also consider evolving work expectations and employee engagements. Current job insecurities that also limited specialist training opportunities are more reasons for many graduates and junior doctors to seek out opportunities elsewhere.

Several Malaysian studies noted stress and emotional burnout amongst house officers[23] and work-related anxiety pertaining to work performance, poor relationship with superiors and colleagues as well as work–family conflicts as reasons that together negatively affected their career aspirations.[24] This is further supported by Rubina et al., who highlighted the inverse relationship between job stress and job performance where she noted low job performance amongst the HO who had high job stress. Improved health and good inter-personal relationships among health care professionals was recommended and culture of openness and understanding, rather than of criticism, was also encouraged.[25] To help address the issues of work-related anxiety, job performance, lack of confidence and readiness to work, several organisations in Malaysia have undertaken to initiate and organise HO Preparatory courses, which are conducted for 6-15 months during the waiting period. The

course is a compilation of didactic learning and simulation, helping participants understand the scope of work and what is expected of them in the local setting. The study found that the HO Preparatory Course module was effective in increasing levels of confidence and readiness for medical graduates.[26]

The UK General Medical Council's approach is to have medical students shadow the outgoing new doctor whose post they will soon undertake. At the University of Nottingham, the two-week shadowing period was preceded by lectures/seminars on topics such as common medical/surgical emergencies, contracts, time managements, surviving the first two years of clinical practice, careers advice and so on which was found to be beneficial and highly valued by their graduates especially the experiential knowledge gained during shadowing.[27]
Although most studies highlighted dissatisfaction as a reason to quit housemanship, a Pakistan study by Rathore FA pointed out rising competition for specialty training positions and limited job placement as additional reasons for leaving the medical career.[28] Their findings correlated with our study that showed over 30% were concerned about the lack of directions for a definitive career pathway and the surmounting challenges in getting into speciality training programs.

The issue of oversupply of new MG is one faced by many countries. In Australia the number of medical graduates has increased,[29] and this trend is similarly seen here in Malaysia. Selection of candidates for entry into medical schools are not standardised in Malaysia with the Ministry of Education and the Malaysian Medical Council only setting basic academic requirements for entry into medical school.[30] The UK had implemented Biomedical Admissions Testing and Medical School Admission Testing since 2003 to further assess student aptitude and non-academic skills for medical school admissions. These screenings have been studied and validated extensively with the UK Clinical Aptitude Test (UKCAT) independently predictive of better medical school performance.[31] The introduction of these standardised selection/screening exams prior to medical school has been mooted by the Malaysian Medical Council and the Ministry of Education but yet to be implemented.

There have been suggestions to have graduate entry into medical schools which ensures a first degree in a related field that would allow for wider employment prospects and opportunities later. It also leads to more mature students who are able to handle better, the stress and responsibilities of medical studies.[32] The downside being longer study durations as well as added costs. Besides, the social aspects of mature medical students entering the strenuous path of medical training in their mid-twenties in the midst of greatest social change (e.g. marriage and starting a family) will need consideration.[33]

As an interim measure, the possibility of retraining those who wish to seek an alternative career to address the current issues of oversupply of medical graduates and inadequate placements needs to be explored in Malaysia. Our study results highlight that the majority of respondents were keen to explore this and were looking forward to guidance and opportunities. Thus, it is timely that the medical associations and universities consider discussions with the Ministry of Human Resources to open up the Human Resource Development Fund (HRDF) for medical graduate retraining.

Medical graduates and professionals quitting their careers is a reality that is increasingly being seen worldwide in the last decade or so. The increasing awareness and demand in seeking out alternative career pathways by medical professionals due to the universal constraints in medical training and employment opportunities has led many organisations such as Medic footprints, Doctopreneurs.com, NEJM careercenter.org and numerous online or career support groups to work together to assist doctors and medical graduates to make career transitions through provision of information, linkages with prospective employers, career events, counselling and career coaching activities.[34-36] Clearly, career shift by medical professionals should be seen as normal and doctors seeking to do so must be actively assisted.[36] Our study results indicating 40% of our respondents were keen for a career transition seems to correlate with MOH data that revealed more than 850 doctors (20%) have quit over the last 3 years during their housemanship programme, bearing in mind this does not include the total number of doctors who may have left clinical practice for non-medical careers beyond housemanship training which could potentially add to the seriousness of having comprehensive support systems and platforms to address this proposition.

A search on platforms for alternative career support for doctors in Malaysia revealed availability of several blogs and writings on this topic with suggestions on possible careers (both clinical and non-clinical but healthcare related) along with non-specific job portals for job seekers.[37,38] However, only one platform, Medic Footprints Malaysia seemed to be looking to specifically address the issues of alternative careers for medical professionals. They have held events to connect alternative career aspirants with medical professionals who have successfully transitioned.[39]

Our study reveals that there is keenness to explore alternative careers as well as willingness of MG and HOs to re-skill in the light of a very clear declaration of insufficient job availability and poor job security. This should be an impetus to moot dialogues amongst relevant authorities to embrace the everchanging landscape of medical practice by having coordinated programs involving career counselling, meeting with potential employers, on the job training, reskilling courses and certifications to assist medical professionals to successfully make career cross overs.

Most published materials in this theme in Malaysia have highlighted the many problems faced by the government and house officers in addressing the consequences of oversupply of medical graduates. Issues such as insufficient internship training positions, long waiting periods to get into training programme, vacancies created by interns dropping out midway through training and the lowered chances of speciality training due to the contract positions, however, remain unresolved till date.

The aim of our study on the other hand, was to understand their perceptions, awareness and interest in alternative careers which could then help stake holders to assist in coming with solutions to pave the way for successful career transitions.

Limitations of this study was primarily regarding the quality of information collected. As this was a questionnaire-based study and thus tried to keep the form concise and appealing whilst enabling objective evaluation of the responses. Most of our questions were with answers (as options) thus leaving little room for explanations which might have brought to light a broader perspective of issues pertaining to this study.

Recommendations and future directions

Embracing alternative careers by medical graduates and professionals will require a whole new mind set and willingness to look out of the box by the various persons and agencies involved. This may include:

Graduates (and possibly parents):

1. Hone talent and skills right from an early age.
2. Truly reflect on a career that you want and do due diligence before applying for medical school.
3. Work on other interests' part time/distance learning.

Medical schools

4. Comprehensive screening and more stringent entry qualifications and criteria.
5. Second skilling or concurrent certificate/ diploma options in industry relevant areas such as IT, business, law etc during and in conjunction with medical education as done in some countries.
6. Periodic counselling to assess ongoing desire and motivation to continue and appropriate career counselling to facilitate change if necessary.

Government

7. Better planning and foresight of wider needs in Malaysia which should be communicated to various medical schools which can then increase or decrease intake according to the needs.
8. Stricter regulations of medical schools and common qualification exam for all.
9. Proper expansions of services and posts according to population growth.
10. Redistribution of posts and resolve the maldistribution of workforce.
11. To set up a committee that will liaise, educate and create awareness amongst other corporations/ industries on the possibilities and advantages of employing medical graduates.

Community support groups & Corporations

12. Identify careers that can easily use the interchangeable skills that the medical degree offers (e.g., insurance, medico-legal, law, arbitration, pharmaceutical, biotechnology. bioinformatics etc).
13. Have short term internship programs/hands on courses that graduates can attend whilst still in med school.

These measures will not only open a wider net of career options but also allows for adaptiveness during periods of oversupply or career uncertainties.

Fortunately, we are going into times where doctors are increasingly being sought after into the corporate world in various roles for their abilities of critical thinking, dedication, conscientiousness and versatility in creating value.[40] Thus, making this an opportune time to introduce and counsel medical graduates and house officers who wish to make a career switch through a tripartite engagement involving relevant ministries, alternative career communities and support groups along with the corporates working together at several levels.

CONCLUSION

A career in medicine is usually a call of passion. However, changing times and needs will require mental flexibility and emotional readiness to use knowledge and experience that is gathered in other non-clinical careers that can be equally fulfilling. Pursuing alternative careers has been actively encouraged and practised in many developed nations and it is timely that Malaysian medical graduates embark in that direction too. In the longer term a well-supported system that embraces career transition is likely to address the issues of internship bottleneck and quitting by house officers and contract medical officers early in their careers, whilst working to identify intent for the best job fit.

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ORIGINAL ARTICLE

Visual outcomes after Phacoemulsification with Intraocular Implantation surgeries among patients with and without Diabetes Mellitus

Lim Jie Jie, MS[1], Mohamad Aziz Salowi, MS[2,3], Tassha Hilda Adnan, Bsc[4], Nor'aini Anuar, BSc[5], Nor Fariza Ngah, MS[6], May May Choo, FRCS[7]

[1]Department of Ophthalmology, Sultanah Bahiyah Hospital, Kedah, Malaysia, [2]Department of Ophthalmology, Selayang Hospital, Selangor, Malaysia, [3]Faculty of Medicine, Universiti Sultan Zainal Abidin, Terengganu, Malaysia, [4]Sector for Biostatistics & Data Repository, National Institutes of Health (NIH), Ministry of Health, Malaysia, [5]Department of Ophthalmology, Sultanah Aminah Hospital, Johor, Malaysia, [6]Department of Ophthalmology, Shah Alam Hospital, Selangor, Malaysia, [7]Department of Ophthalmology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: The aim of this study was to compare the visual outcomes of phacoemulsification with intraocular lens implantation (IOL) surgery in patients with and without diabetes mellitus (DM) in Malaysia over a 12-year period and to identify factors that may contribute to poor visual outcome.

Materials and Methods: Data was retrieved from the web-based Malaysian Cataract Surgery Registry (CSR). Peri-operative data for cataract surgery performed from 2007-2018 were analysed. Inclusion criteria were age ≥40 years, phacoemulsification and IOL and senile cataract. Combined surgeries, surgeries performed by trainees and ocular co-morbidities were excluded. Post-operative Best-Corrected Visual Acuity (BCVA) were compared. Factors affecting poor visual outcomes among those with DM were analysed using multivariate logistic regression to produce adjusted odds ratio (OR) for variables of interest.

Results: Total number of cases between 2007-2018 was 442,858, of whom 179,210 qualified for our analysis. DM group consisted of 72,087 cases (40.2%). There were 94.5% cases in DM group and 95.0% from non-DM group who achieved BCVA ≥6/12 (p<0.001). Among patients with DM, advanced age (70-79 years old, OR: 2.54, 95% Confidence Interva, 95%CI: 1.91, 3.40; 80-89 years old, OR: 5.50, 95%CI: 4.02, 7.51), ≥90 years, OR: 9.77, 95%CI: 4.18, 22.81), poor preoperative presenting visual acuity [<6/18–6/60] (OR: 2.40, 95%CI: 1.84, 3.14) and <6/60-3/60 (OR: 3.00, 95%CI: 2.24, 4.02), <3/60 (OR 3.63, 95%CI: 2.77, 4.74)], presence of intraoperative complication (OR 2.24, 95%CI: 1.86, 2.71) and presence of postoperative complication (OR 5.21, 95%CI: 2.97, 9.16) were significant factors for poor visual outcome.

Conclusions: Visual outcomes following phacoemulsification with IOL implantation surgery among cases with DM were poorer compared to cases without DM. Risk factors for poor visual outcomes among cases with DM were identified.

KEYWORDS:
Phacoemulsification, diabetes mellitus, visual outcome

INTRODUCTION

Diabetes mellitus (DM) is a non-communicable disease and its prevalence is on the rise in developing countries, including Malaysia. Malaysian National Health and Morbidity Survey (NHMS) in 2015 reported that there was an increase in the prevalence of diabetes in Malaysia from 15.2% in 2011 to 17.5% in 2015.[1] It is believed that population growth, age, urbanisation, sedentary lifestyle and obesity are among the contributing factors for an increasing number of patients with DM and the burden of disease.[2]

Klein et al., reported that cataracts occur at an earlier age and are 2-5 times more frequent in patients with DM.[3] Several theories such as the accumulation of sorbitol intracellularly, glycation of lens protein and impaired antioxidative mechanism of the lens proteins were proposed.[4,5] The Malaysian National Diabetes Registry (NDR) 2009-2012 reported the mean age of type-2 DM patients was 59.7 years, where the largest proportion was diagnosed at the age of 45 to 54 years, a major working population group.[6] Thus, visual loss occurring secondary due to DM may become an economic burden for the country.[7]

In general, the advancement of technology and techniques of cataract surgery, especially phacoemulsification had improved the visual outcomes of cataract surgery. However, in patients with DM, the outcomes may not be as predicted. Gupta reported in his study that there were non-significant results comparing mean post-surgical visual acuity in between the diabetic group and the control group. However, the diabetic group had a higher incidence of intraoperative and postoperative complications.[8]

This study aimed to compare the visual outcomes of phacoemulsification with IOL implantation surgery in patients with and without DM who presented for cataract

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Corresponding Author: Lim Jie Jie
Email: jie2lim@gmail.com

surgery at the Ministry of Health (MOH) facilities over the past 12 year period. The factors that may contribute to the poor visual outcome among patients with DM were also studied. The results of this study would potentially contribute to the prediction of factors affecting visual outcomes in DM group. Data from this will be useful for healthcare planners to improve on outcomes for this group of patients.

MATERIALS AND METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki. This was a retrospective registry analysis of data extracted from the Malaysian Cataract Surgery Registry (CSR) from 1st January 2007 to 31st December 2018 for patients who had undergone phacoemulsification with IOL implantation surgeries in all the MOH facilities. CSR is part of National Eye Database, a web-based password-protected surveillance system collecting data on eye diseases and clinical performance of the ophthalmology services in Malaysia. It consisted of systematic data entry according to predefined sets of preoperative, operative and outcome forms by designated paramedical staff. Details on the Malaysian CSR have been published elsewhere.[9,10]

Inclusion criteria were all patients aged 40 years old and above who have undergone phacoemulsification with IOL implantation surgery by qualified ophthalmologists. Patients were excluded if they had secondary cataract (non-senile), history of trauma, combined surgeries, previous non cataract surgeries, pre-existing ocular co-morbidities or had phacoemulsification surgery without IOL implantation. The two cohorts of cases were compared, based on the presence of DM at the time of surgery.

The demographic variables recorded included gender, age and ethnicity. Other variables included first or second eye surgery, any previous complication in the fellow eye, systemic illness such as hypertension, ischaemic heart disease, chronic renal disease, cerebrovascular accident, chronic lung disease or bronchial asthma, other associated systemic illness, presenting visual acuity (PVA), type of admission, type of anaesthesia given, laterality of the presenting eye, duration of surgery and presence of any intraoperative or postoperative complications.

Visual Impairment (VI) was classified according to the International Classification of Diseases 11 (2018); Mild – presenting visual acuity worse than 6/12, Moderate – presenting visual acuity worse than 6/18, Severe – presenting visual acuity worse than 6/60, Blindness – presenting visual acuity worse than 3/60.

Statistical analysis was performed using Statistical Package for Social Science, version 26.0 (SPSS, Inc., Chicago, III, USA) for Windows. Association of risk factors with visual outcomes were evaluated by logistic regression model. Adjusted Odds Ratio (OR) and its 95% CI were used to estimate a risk score for combinations of risk factors. A two-tailed p-value of <0.05 was considered as statistically significant.

RESULTS

The total number of cataract surgeries from 2007-2018 in the Malaysian MOH facilities was 442,858. After exclusion, the total number available for analysis was 179,210 cases. Among these, DM group consisted of 72,087 cases (40.2%), while non-DM group consisted of 107,123 cases (59.8%). (Figure 1)

The patients in the DM group were significantly younger and were more of females (percentage was also higher as compared to the non-DM group). (Figure 2) There were more cases in the DM group presenting with other systemic co-morbidities specifically hypertension, ischaemic heart disease, renal failure and cerebrovascular accident. (Figure 2) In both group, higher percentage of cases presented for the first eye surgery. Preoperatively, in terms of PVA, higher percentage of surgeries in the DM group were done at the level of severe visual impairment and blindness. There were significantly more cases done day-care in both groups although the percentage was lower in the DM group. There were higher percentage occurrence of posterior capsular rupture (PCR) and zonular dehiscence intraoperatively in the DM group. However, the difference in the percentage occurrence of infective endophthalmitis postoperatively was not significant. (Table I)

Postoperatively, in terms of BCVA, there was a significant difference in the percentage of eyes achieving BCVA≥6/12 between cases in DM group (81.0%) and cases in non-DM group (81.9%). In both groups, the percentage of postoperative PVA increased almost double folds upon correction (BCVA). (Table I)

DM was identified as one of the risk factors for BCVA<6/12 (poor VA). In the regression model, the percentage of cases achieving BCVA≥6/12 in patients with DM was significantly less than the percentage of patients with no DM (94.5% vs. 95.0%) likewise the percentage of cases achieving BCVA<6/12 in patients with DM was significantly higher than the percentage of patients with no DM (5.5% vs. 5.0%). (Table II) The percentages of BCVA≥6/12 in Table I and II were different; in Table I the denominators were the total number of each DM and non-DM group while the denominators in Table II were less due to missing data in the regression model.

Among patients with DM, advancing age, female gender, renal failure, cerebrovascular accident, first eye surgery, left eye, poor preoperative PVA (moderate visual impairment to blindness), duration of surgery, presence of intraoperative complication and presence of postoperative complication were the factors found contributing to the poor visual outcome. (Table III)

DISCUSSION

This study had a large sample size of information obtained from cataract surgery registry. Due to the online design and data collection processes, it was representative of the surgeries performed in all the MOH facilities throughout Malaysia.

Table I: The Profile of Cataract Surgery Population and The Association between Groups in Visual Outcomes (Malaysian Ministry of Health Facilities 2007 to 2018)

	DM group (n=72,087)		Non-DM group (n=107,123)		p-value[a]
	n	(%)	n	(%)	
Age (years):					
Mean (SD)	65.62 (8.21)	67.16 (8.83)	<0.001b		
Range	40, 100	40, 103			
Gender:					
Male	32,185	(44.6)	51,776	(48.3)	<0.001
Female	39,902	(55.4)	55,347	(51.7)	
Other systemic co-morbidity*:					
Hypertension	58,529	(81.2)	53,925	(50.3)	<0.001
Ischaemic Heart Disease	8,366	(11.6)	6,997	(6.5)	<0.001
Renal failure	2,231	(3.1)	1,168	(1.1)	<0.001
Cerebrovascular accident	1,126	(1.6)	1,104	(1.0)	<0.001
COAD/Bronchial asthma	2,270	(3.1)	5,093	(4.8)	<0.001
Other systemic illnesses	13,403	(18.6)	19,645	(18.3)	0.174
Surgery on:					
First eye	44,718	(62.0)	67,203	(62.7)	0.003
Second eye	27,320	(37.9)	39,842	(37.2)	
Laterality:					
Right eye	36,751	(51.0)	54,887	(51.2)	0.288
Left eye	35,336	(49.0)	52,236	(48.8)	
Pre-operative presenting visual acuity:					
VA ≥ 6/12 (Good vision)	4,273	(5.9)	6,451	(6.0)	<0.001
VA <6/12 – 6/18 (Mild VI)	6,948	(9.6)	10,431	(9.7)	
VA <6/18 – 6/60 (Moderate VI)	29,555	(41.0)	45,610	(42.6)	
VA < 6/60 – 3/60 (Severe VI)	5,977	(8.3)	8,078	(7.5)	
VA < 3/60 (Blindness)	24,178	(33.5)	34,562	(32.3)	
Type of admission:					
Day care	48,380	(67.1)	75,487	(70.5)	<0.001
Non-day care	22,753	(31.6)	30,163	(28.2)	
Intra-operative complications*:					
Posterior capsular rupture	1,053	(1.5)	1,392	(1.3)	0.004
Vitreous loss	450	(0.6)	593	(0.6)	0.054
Zonular dehiscence	334	(0.5)	392	(0.4)	0.001
Dropped nucleus	36	(0.0)	38	(0.0)	0.140
Suprachoroidal haemorrhage	1	(0.0)	3	(0.0)	0.535
Central corneal oedema	39	(0.1)	40	(0.0)	0.098
Others	468	(0.6)	631	(0.6)	0.110
Post-operative complications*:					
Infective endophthalmitis	21	(0.0)	49	(0.0)	0.084
Post-operative presenting visual acuity (PVA):**					
VA ≥ 6/12 (Good vision)	41,482	(57.5)	59,480	(55.5)	<0.001
VA <6/12 – 6/18 (Mild VI)	12,181	(16.9)	18,773	(17.5)	
VA <6/18 – 6/60 (Moderate VI)	10,879	(15.1)	18,103	(16.9)	
VA <6/60 (Severe VI)	391	(0.5)	611	(0.6)	
VA <3/60 (Blindness)	472	(0.7)	710	(0.7)	
Post-operative best corrected visual acuity (BCVA):**					
VA ≥ 6/12 (Good vision)	58357	(81.0)	87,769	(81.9)	<0.001
VA <6/12 – 6/18 (Mild VI)	1,621	(2.2)	2,142	(2.0)	
VA <6/18 – 6/60 (Moderate VI)	1,472	(2.0)	1,955	(1.8)	
VA <6/60 (Severe VI)	130	(0.2)	157	(0.1)	
VA <3/60 (Blindness)	195	(0.3)	319	(0.3)	

DM=Diabetes Mellitus; SD=Standard deviation; COAD=Chronic obstructive airway disease; VI=Visual impairment; IQR=Interquartile range, reported as 25th percentile–75th percentile.
Range was reported as minimum, maximum.
a Chi-square test.
b Independent t-test.
c Mann-Whitney U test.
* 1 patient can have more than 1 type of systemic co-morbidity, intra-operative complications and post-operative complications.
Result was reported based on available information; column percentage (%) was reported based on total number of each non-DM and DM group. The remaining unreported percentage is the missing value, adding up to 100%. All missing value is <10%, except for Sedation used (39.6% missing).
** A missing value of 9.0% PVA, and 14.0% on BCVA.

Table II: The Association between Diabetes Mellitus and other Risk Factors with Visual Outcomes (Malaysian Ministry of Health Facilities, 2007 to 2018)

	BCVA*					
	Good VA≥6/12 (n=146,126)		Poor VA<6/12 (n=7,991)		Adj. OR (95% CI)	p-value
	n	(%)	n	(%)		
Diabetes Mellitus:						
Yes	**58,357**	**(94.5)**	**3,418**	**(5.5)**	**1.25 (1.19, 1.33)**	**<0.001**
No	87,769	(95.0)	4,573	(5.0)	1.00	
Age group:						<0.001
40–49 years	4,860	(96.6)	170	(3.4)	1.00	
50–59 years	24,603	(96.7)	844	(3.3)	1.04 (0.86, 1.27)	0.667
60–69 years	62,357	(96.1)	2,497	(3.9)	1.39 (1.16, 1.67)	<0.001
70–79 years	47,312	(93.4)	3,364	(6.6)	2.66 (2.21, 3.19)	<0.001
80–89 years	6,822	(86.7)	1,042	(13.3)	5.84 (4.81, 7.08)	<0.001
≥90 years	172	(69.9)	74	(30.1)	13.82 (9.57, 19.98)	<0.001
Gender:						
Male	68,146	(95.3)	3,370	(4.7)	1.00	<0.001
Female	77,980	(94.4)	4,621	(5.6)	1.19 (1.13, 1.25)	
Hypertension:						
Yes	92,004	(94.7)	5,107	(5.3)	0.90 (0.85, 0.95)	<0.001
No	54,122	(94.9)	2,884	(5.1)	1.00	
Ischaemic Heart Disease:						
Yes	12,627	(94.7)	707	(5.3)	0.92 (0.84, 1.01)	0.077
No	133,499	(94.8)	7,284	(5.2)	1.00	
Renal failure:						
Yes	2,566	(91.4)	240	(8.6)	1.70 (1.46, 1.98)	<0.001
No	143,560	(94.9)	7,751	(5.1)	1.00	
Cerebrovascular accident:						
Yes	1743	(92.5)	142	(7.5)	1.31 (1.07, 1.60)	0.008
No	144,383	(94.8)	7,849	(5.2)	1.00	
COAD/Bronchial asthma:						
Yes	6,089	(95.9)	262	(4.1)	0.80 (0.69, 0.92)	0.002
No	140,037	(94.8)	7,729	(5.2)	1.00	
Surgery on:						
First eye	91,262	(94.4)	5,433	(5.6)	1.35 (1.27, 1.43)	<0.001
Second eye	54,767	(95.5)	2,554	(4.5)	1.00	
Previous intra-operative complication:						
Yes	1,344	(94.6)	76	(5.4)	1.16 (0.89, 1.50)	0.270
No	134,746	(94.8)	7,356	(5.2)	1.00	
Laterality:						
Right eye	74,850	(95.0)	3,948	(5.0)	1.00	<0.001
Left eye	71,276	(94.6)	4,043	(5.4)	1.12 (1.06, 1.18)	
Pre-operative PVA:						
VA≥6/12 (Good vision)	9,108	(98.1)	181	(1.9)	1.00	
VA<6/12–6/18 (Mild VI)	14,887	(97.3)	407	(2.7)	1.30 (1.06, 1.59)	0.012
VA<6/18–6/60 (Moderate VI)	62,104	(95.2)	3,149	(4.8)	2.41 (2.02, 2.88)	<0.001
VA<6/60 – 3/60 (Severe VI)	11,454	(94.4)	683	(5.6)	3.03 (2.50, 3.68)	<0.001
VA<3/60 (Blindness)	46,158	(93.1)	3,445	(6.9)	3.65 (3.06, 4.35)	<0.001
Type of admission:						
Day care	102,704	(95.1)	5,259	(4.9)	1.00	0.042
Non-day care	41,583	(94.1)	2,621	(5.9)	1.06 (1.00, 1.12)	
Anaesthetic type:						
General	4,693	(92.8)	364	(7.2)	1.22 (1.07, 1.40)	0.003
Local	140,878	(94.9)	7,591	(5.1)	1.00	
Duration of operation, minutes:						
Mean (SD)	23.70	(9.83)	26.82	(11.15)	1.021 (1.017, 1.02)	<0.001
Intra-operative complications:						
Yes	2,964	(83.5)	585	(16.5)	2.09 (1.84, 2.38)	<0.001
No	143,130	(95.1)	7,401	(4.9)	1.00	
Post-operative complications:						
Yes	184	(77.6)	53	(22.4)	4.10 (2.83, 5.94)	<0.001
No	142,363	(94.8)	7,779	(5.2)	1.00	

Adj. OR = Adjusted odds ratio; CI = Confidence interval; PVA = Presenting Visual Acuity; BCVA = Best Corrected Visual Acuity.
The outcome coded as 1 is "VA <6/12". Frequency (n) and row percentage (%) are reported based on available information, adding up to 100%.
* 132617 data included in the multiple logistic regression analysis (46593 data missing [26%]).
** 125573 data included in the multiple logistic regression analysis (53637 data missing [30%]).

Table III: The Association between Risk Factors with Visual Outcomes among Patients with Diabetes Mellitus (Malaysian Ministry of Health Facilities, 2007 to 2018)

	BCVA*					
	Good VA≥6/12 (n=58357)		Poor VA<6/12 (n=3418)		Adj. OR (95% CI)	p-value
	n	(%)	n	(%)		
Age group:						<0.001
40–49 years	1761	(96.1)	71	(3.9)	1.00	
50–59 years	11,314	(95.7)	504	(4.3)	1.25 (0.93, 1.68)	0.143
60–69 years	26,768	(95.5)	1,267	(4.5)	1.50 (1.13, 2.00)	0.005
70–79 years	16,516	(92.9)	1,254	(7.1)	2.54 (1.91, 3.40)	<0.001
80–89 years	1,969	(86.5)	308	(13.5)	5.50 (4.02, 7.51)	<0.001
≥90 years	29	(67.4)	14	(32.6)	9.77 (4.18, 22.81)	<0.001
Gender:						
Male	25,965	(95.1)	1,351	(4.9)	1.00	<0.001
Female	32,392	(94.0)	2,067	(6.0)	1.22 (1.12, 1.32)	
Hypertension:						
Yes	47,435	(94.4)	2,801	(5.6)	0.95 (0.86, 1.06)	0.356
No	10,922	(94.7)	617	(5.3)	1.00	
Ischaemic Heart Disease:						
Yes	6,789	(94.7)	380	(5.3)	0.88 (0.78, 1.00)	0.059
No	51,568	(94.4)	3,038	(5.6)	1.00	
Renal failure:						
Yes	1,628	(90.2)	177	(9.8)	1.89 (1.58, 2.26)	<0.001
No	56,729	(94.6)	3,241	(5.4)	1.00	
Cerebrovascular accident:						
Yes	877	(91.7)	79	(8.3)	1.32 (1.01, 1.73)	0.042
No	57,480	(94.5)	3,339	(5.5)	1.00	
COAD/Bronchial asthma:						
Yes	1,855	(95.7)	83	(4.3)	0.84 (0.65, 1.07)	0.157
No	56,502	(94.4)	3,335	(5.6)	1.00	
Surgery on:						
First eye	36,257	(94.0)	2,309	(6.0)	1.35 (1.24, 1.48)	<0.001
Second eye	22,060	(95.2)	1,108	(4.8)	1.00	
Previous intra-operative complication:						
Yes	581	(95.4)	28	(4.6)	0.96 (0.63, 1.45)	0.841
No	53,648	(94.5)	3,140	(5.5)	1.00	
Laterality:						
Right eye	29,784	(94.7)	1,680	(5.3)	1.00	0.004
Left eye	28,573	(94.3)	1,738	(5.7)	1.13 (1.04, 1.22)	
Pre-operative PVA:						<0.001
VA ≥ 6/12 (Good vision)	3,574	(97.8)	80	(2.2)	1.00	
VA < 6/12–6/18 (Mild VI)	5,907	(97.1)	174	(2.9)	1.33 (0.98, 1.82)	0.070
VA < 6/18–6/60 (Moderate VI)	24,259	(94.9)	1,314	(5.1)	2.40 (1.84, 3.14)	<0.001
VA < 6/60 – 3/60 (Severe VI)	4,828	(94.1)	304	(5.9)	3.00 (2.24, 4.02)	<0.001
VA < 3/60 (Blindness)	18,917	(92.7)	1,498	(7.3)	3.63 (2.77, 4.74)	<0.001
Type of admission:						
Day care	39,871	(94.7)	2,234	(5.3)	1.00	0.869
Non-day care	17,784	(94.0)	1,139	(6.0)	1.01 (0.92, 1.10)	
Anaesthetic type:						
General	1,755	(92.6)	140	(7.4)	1.17 (0.94, 1.45)	0.151
Local	56,380	(94.5)	3,263	(5.5)	1.00	
Duration of operation, minutes:						
Mean (SD)	23.75	(9.79)	26.83	(11.34)	1.02 (1.02, 1.02)	<0.001
Intra-operative complications:						
Yes	1,261	(81.7)	282	(18.3)	2.24 (1.86, 2.71)	<0.001
No	57,088	(94.8)	3,135	(5.2)	1.00	
Post-operative complications:						
Yes	63	(70.0)	27	(30.0)	5.21 (2.97, 9.16)	<0.001
No	56,875	(94.5)	3,330	(5.5)	1.00	

Adj. OR = Adjusted odds ratio; CI = Confidence interval; PVA = Presenting Visual Acuity; BCVA = Best Corrected Visual Acuity.
The outcome coded as 1 is "VA <6/12". Frequency (n) and row percentage (%) are reported based on available information, adding up to 100%.
* 53172 data included in the multiple logistic regression analysis (18915 data missing [26%]).
** 50333 data included in the multiple logistic regression analysis (21754 data missing [30%]).

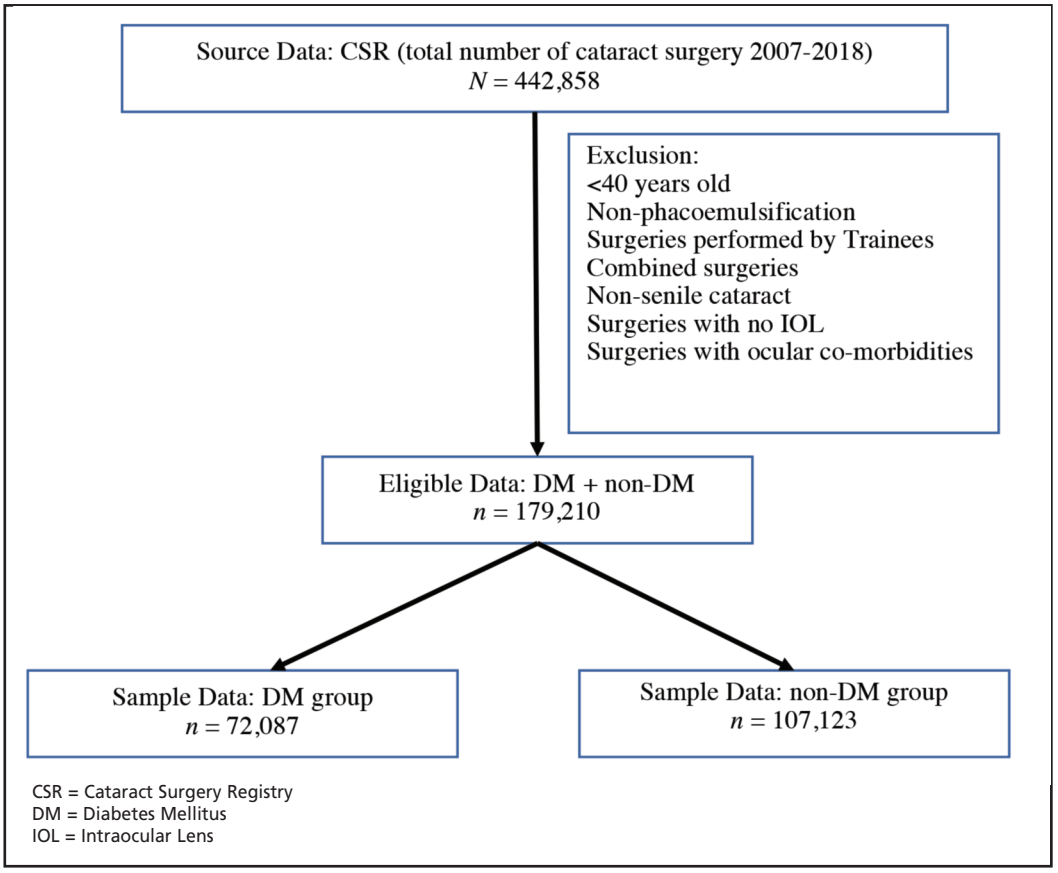

Fig. 1: Size of sample/cohort after exclusion.

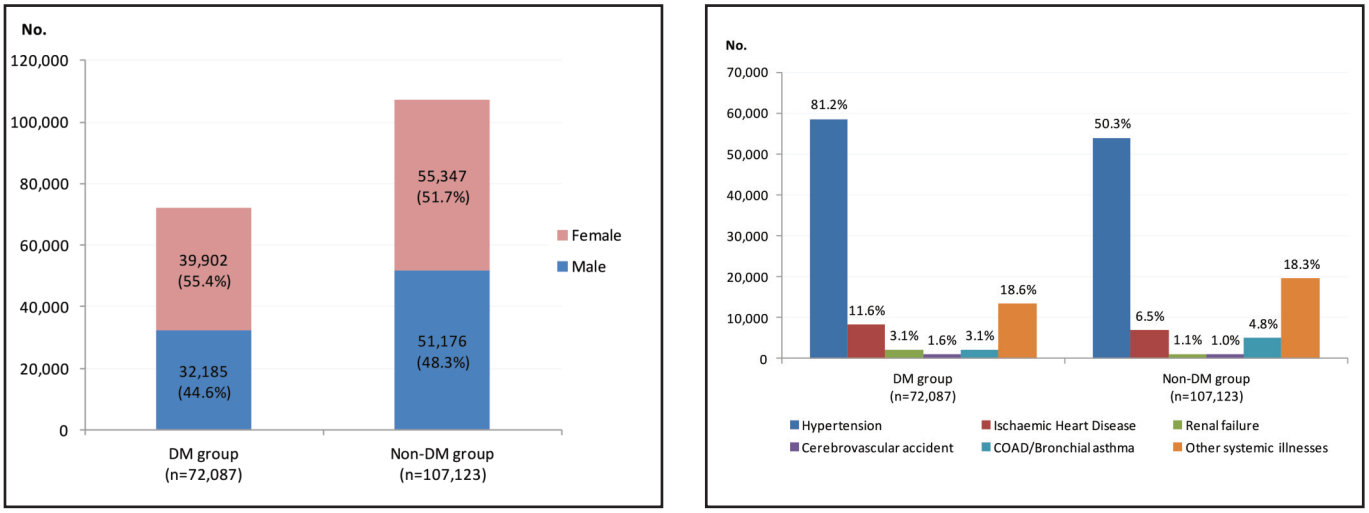

Fig. 2: Demographic profile and Concomitant Comorbidities of patients underwent phacoemulsification surgery, DM group and non-DM group patients (Malaysian Ministry of Health Facilities, 2007 to 2018).

As reported by Murkesh et al., patients with DM have relative risk of 1.1-2.9 of formation of various types of cataract, compared to patients without DM.[11] This was reflected in our data, where patients with DM who had undergone phacoemulsification surgery were younger. This finding also concurred with other studies.[3]

Hypertension, ischaemic heart disease, chronic renal disease and cerebrovascular accident were more frequently seen among our patients with DM. This could be contributed to the macrovascular and microvascular complications of DM. In our study, hypertension was present in 83.5% of patients with DM, higher as compared to what was reported by Squirrel et al, which was 58%.[12]

Majority of patients in DM group were females. In studies done in India, United Kingdom and a global study involving low-middle income countries, their findings showed similarity, i.e., more women had cataract than men.[13-15] It was assumed that the differences in albumin/total protein ratio and serum triglyceride level and postmenopausal oestrogen deficiency may be contributing factors for this finding.[16]

In both groups, one third of patients presented for the first eye surgery through all age groups. This was seen throughout the years in the registry since MOH commenced its data collection in 2002.[10] In general, this could be attributed to the lack of access to cataract surgical services within the population in particular those living in the remote areas. Nationwide strategies and efforts are underway to increase the cataract surgical rate and cataract surgical coverage by introducing cataract outreach programmes. This is being done by deploying screening and surgical teams to the targeted areas to capture patients with operable cataracts. A report in 2018 showed an increasing trend of patients presenting for second eye surgery.[10]

It was shown in this study that patients with DM had significantly worse presenting VA, with higher percentages of patients presenting in the category of severe visual impairment and blindness. Among the possible reasons for the late presentation among them were ignorance of symptoms, poor awareness regarding occurrence of eye complications, physical disabilities preventing them from seeking treatment or individual and cultural priorities where the other organ disabilities were given greater emphasis. Findings from the Malaysian National Diabetic Registry (NDR) also revealed that only 44.0% of patients with DM at the primary care level underwent scheduled funduscopic screening in the year 2012.[17] This low number may explain the failure of early reporting of symptom or early detection and referral of operable cataract, hence the late presentation. The percentage of cases which were done as day-care was lower in the DM group as compared to the non-DM group. This could be attributed to the admission to the ward for blood pressure and blood glucose optimisation preoperatively.

There were higher percentage occurrence of posterior capsular rupture (PCR) and zonular dehiscence intraoperatively in the DM group. Higher probability of eyes in patients with DM which had poor pupillary dilatation and more advanced or dense cataract resulting in more intraoperative manipulation and intraoperative complications such PCR and zonular dehiscence.[8,18] However, this could not be verified in this study due to the non-mandatory reporting of technical factors encountered intraoperatively (dense brown, white cataract, pseudoexfoliation and pupil problems).

The impaired immune status among the patients with DM may result in the increased risk of postoperative complications such as postoperative endophthalmitis.[19] In previous studies, about 14-21% of patients with endophthalmitis were diabetic.[20,21] However, the findings in this study did not show any difference in the percentage occurrence of infective endophthalmitis postoperatively between DM and non-DM group.

Analysis of data of postoperative visual outcomes revealed an increased percentage of eyes with VA≥6/12 (good vision) in both groups upon correction. For example, in the DM group, the postoperative PVA was 57.5%. Upon correction (BCVA), it increased to 81%. This could be due to the issues of biometric measurement. Similar to access for cataract surgery, it has been acknowledged that nationwide and efforts are underway to identify and rectify the issue. The results from this study also revealed that the percentages of BVCA≥6/12 among both groups were significantly different; eyes in DM group had lower percentage than eyes in the non-DM group (94.5% vs. 95.0%). This result differed with other studies, where their small-scale studies showed that non-diabetic group achieved better visual outcome, but the differences were insignificant.[22-24] Elsewhere in other studies it has been reported that causes of poor visual outcomes among diabetic group had been described as due to presence of macula oedema, posterior capsular opacity, cornea decompensation and higher incidence of postoperative endophthalmitis.[25-28] However, this study could not identify the causes (BCVA<6/12) due to the non-mandatory registry reporting for this specific data postoperatively. From the analysis of postoperative data with poor visual outcomes (BCVA<6/12 among eyes in DM group), it was shown that advancing age, female gender, presence of systemic illness such as chronic renal disease, cerebrovascular accidents, first eye surgery, poorer presenting visual acuity (<6/18–6/60 and <6/60), long duration of surgery, presence of intraoperative complications and postoperative endophthalmitis were the significant factors found to contribute to the poor visual outcome.

Older age, especially 70 years old and above has positive impact on poor visual outcomes among patients with DM. From a review article by TY Wong, it was shown that very elderly patients usually presented with multiple systemic illness and ocular comorbidities. They had higher risk of complications such as posterior capsule rupture, postoperative infection, raised intraocular pressure and cornea oedema. All these could be contributing factors for poor visual outcomes.[29]

Females were shown to have poorer visual outcomes among patients with DM, similar to other studies. Furthermore, they had higher incidence of posterior capsular opacities formation, probably due to their hormonal and biological differences.[30]

The presence of chronic renal disease and cerebrovascular accident were found to be contributing factors of poor visual outcomes. These findings correlated with Liu et al, showing that the presence of kidney disease had an adjusted OR of 1.04.[31] The presence of renal disease and cerebrovascular accidents could indicate the prolonged duration of DM and serve as a spectrum of vascular retinopathies in those patients. Patients with cerebrovascular accidents may have persistent visual field defect which persist after the cataract surgery and contributed to poor visual outcome.[32]

Patients undergoing cataract surgery for the first time might be more anxious compared to those who had cataract surgery done before. Hence, patients with first eye might be having high blood pressure, became uncooperative and had high vitreous pressure intraoperatively, leading to longer operating time and increased risk of complications.

Timing of when to perform cataract surgery in eyes of patients with DM has changed compared to what it was a decade ago. Recently, earlier cataract surgery among patients with DM had been advocated to allow better visualisation and timely management for proliferative diabetic retinopathy and macula oedema as both are the main cause of poor visual outcomes. In a study conducted by Wahab et al., they performed early cataract extraction on patients of older than 40 years with cataract grade I or II according to LOCS III (Lens opacification classification system III), to allow optimal visualisation of posterior segment. This allowed early detection of clinically significant macula oedema (CSME), monitoring and management of CSME.[33] However, to the best of our knowledge, there is no definite guideline available as yet for the indication and timing of cataract surgery among the patients with DM. In current practice, cataract surgery is recommended to patients if they are symptomatic or if the cataract obstructs the proper examination of fundus. In this study, eyes with poorer presenting visual acuity (possibly late presentation) was one of the risk factors for poor visual outcome after phacoemulsification surgery for eyes in the DM patients. We believe that scheduled screening in patients with DM is important to identify, therefore refer patients with operable cataract as it may potentially reduce the risk of poor visual outcomes. When these patients present to the hospital, earlier cataract surgery before fundus examination becomes difficult, preoperative optimisation and proper planning of cataract surgery to avoid intraoperative and postoperative complications should then be recommended to achieve better visual outcome post phacoemulsification surgery.

STUDY LIMITATIONS

This was a retrospective secondary data analysis study. Hence, there were some potential limitations. Firstly, some patients did not return for postoperative follow up, hence were excluded from the visual outcome analysis. It was possible that among these cases, which were not included in the study, may have been cases with poorer outcomes, which would have skewed out results to seem more favourable. Secondly, the study was limited by risk of reporting errors from the registry; however, this limitation was mitigated by inclusion of a very large patient sample size and regular monitoring of errors by NED officers appointed by the committee throughout the country. Thirdly, as this was a data analysis study, some data fields were not mandatory to allow for some degree of data collection compliance hence the missing data in some parts of the analysis. Nevertheless, the final sample data was sufficiently large to be analysed and used for the purpose of the study.

CONCLUSION

This study revealed poorer visual outcomes and higher percentage of intraoperative complication in phacoemulsification surgery with IOL implantation among eyes of patients with DM compared to those with no DM. Risk factors for poor visual outcome were identified. Scheduled screening, proper operative planning and anticipation of any intraoperative complications hence are mandatory to improve postoperative visual outcome for this group of patients.

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COMPETING INTERESTS

None

ETHICS APPROVAL

Ethical approval was obtained from the Medical Research and Ethics Committee of Malaysia Ministry of Health (Research ID NMRR-17-2103-37289).

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Barcelona Clinic Liver Cancer and Hong Kong Liver Cancer staging systems for prediction of survival among Hepatocellular Carcinoma patients

Sumitra Ropini Karuthan, MBBS[1], Peng Soon Koh, MSurg[2], Karuthan Chinna, PhD[3], Wah Kheong Chan, PhD[4]

[1]Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [2]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [3]School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, Malaysia, [4]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: We aimed to compare the Barcelona Clinic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) staging systems.

Materials and Methods: This is a retrospective study on patients with newly diagnosed hepatocellular carcinoma (HCC) at the University Malaya Medical Centre between 2011 and 2014. Survival times were analysed using the Kaplan-Meier procedure and comparison between groups was done using the log rank test.

Results: The data of 190 patients was analysed. Chronic hepatitis B was the most common aetiology for HCC (43.7%), but a large proportion was cryptogenic or non-alcoholic steatohepatitis-related (41.6%). Only 11.1% were diagnosed early (BCLC Stage 0-A) while majority were diagnosed at an intermediate stage (BCLC Stage B, 53.7%). The median survival rate was significantly different between the different groups when either of the staging systems was used ($p<0.05$ for all comparisons). However, the two staging systems lacked agreement (weighted kappa 0.519, 95%CI: 0.449, 0.589) with significant difference in median survival rates between BCLC Stage A and HKLC Stage 2, and between BCLC Stage C and HKLC Stage 4.

Conclusion: Both staging systems were able to stratify patients according to survival, but they only had moderate agreement with significant differences observed in two groups of the staging systems.

KEYWORDS:
Classification; liver cancer; survival analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide. A total of 841,000 new HCC cases were diagnosed with 782,000 deaths in 2018.[1] HCC has an average five-year survival of <15%.[2] Clinically, determining the cancer stage is important for predicting prognosis of individual patients and when considering treatment options. It also helps in the communication among healthcare providers.[3] Over the last three decades, several HCC staging systems have been proposed. However, few have been validated and there is no single system that has been accepted universally.[4] Studies comparing their discriminatory ability have had conflicting results, in part related to differences in the study populations between Asia and the United States or Europe.[5] Various parameters, including liver function, tumour burden and biology as well as patient factors have been included in the development of staging systems for HCC.

Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system, developed in 1999,[3] is widely used, especially in Europe and the United States of America as it has been validated externally and is endorsed by European Association for the Study of the Liver (EASL), European Organization for Research and Treatment of Cancer (EORTC) and American Association for the Study of Liver Diseases (AASLD).[6] BCLC includes tumour characteristics, liver function and overall physical status in prognostication of HCC patients. The BCLC has been shown to have lower ability for prognostication of advanced HCC.[7] The Hong Kong Liver Cancer (HKLC) staging system was developed in 2014 and was reported to have better prognostic value than the BCLC staging system.[8] Regarding the heterogeneity of the stages B and C in BCLC, HKLC is said to better stratify these patients and to result in better survival outcomes based on more aggressive treatment recommendations.[8,9]

In studies conducted in Korea,[10] Thailand[11] and India,[12] HKLC staging system was seen to predict overall survival (OS) better compared to the BCLC staging system. In a retrospective analysis of North American patients who underwent intra-arterial therapy for unresectable HCC, the HKLC staging system out-performed the BCLC system.[13] However, a study in Singapore showed that the BCLC staging system performed better in predicting OS compared to the HKLC staging system.[14] In this study, about 90% of the patients were of Chinese ethnicity. Furthermore, the capability of HKLC in European cohorts have been challenged.[15,16] In a recent study, the BCLC staging system was found to better predict OS for European patients than the HKLC staging system.[16]

In Malaysia, with a multi-ethnic Asian population, HCC is more prevalent among the Chinese compared to the Malays and Indians. Hepatitis B virus infection is the predominant

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Corresponding Author: Dr Chan Wah Kheong
Email: wahkheong2003@hotmail.com

aetiology among Malay and Chinese patients, while alcohol intake and cryptogenic causes, which are now recognized to be largely related to non-alcoholic steatohepatitis (NASH), are the most common among Indian patients.[17] Currently, the BCLC staging system is being used by clinicians in Malaysia. The suitability of the HKLC staging system is yet to be tested in Malaysia. The objectives of this study were to review the aetiology and presentation of HCC in recent years, to test the agreement between the BCLC and HKLC staging systems and to compare the survival times based on the BCLC and HKLC staging system in a cohort of patients with newly diagnosed HCC at a tertiary hospital in Malaysia.

MATERIALS AND METHODS

Patients and Methods

In this study, data of patients who were newly diagnosed with HCC at the University Malaya Medical Centre, Kuala Lumpur, Malaysia between 2011 and 2014 were retrospectively collected and analysed. Identification of patients was based on International Classification of Diseases (ICD) coding. Liver cancer was confirmed using the AASLD guidelines on a multiphasic computed tomography (CT) scan or a magnetic resonance imaging (MRI), where detected lesions had characteristic arterial hypervascularity and washout during the venous phase and raised α-fetoprotein (AFP) levels.[18] Demographic, clinical, laboratory, radiological, treatment, and survival information of each patient were collected. Survival time was defined as the time from the date of first diagnosis of HCC to the date of death or the date of data censoring (31 December 2016). The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the University of Malaya Medical Centre Medical Research Ethics Committee (MRECID No.: 201688-4126, Approval Date: 21 September 2016). Written informed consent was obtained from each participating subject.

Statistical Analysis

Data was analysed using IBM SPSS version 22. Continuous variables were presented as mean ± standard deviation or median (interquartile range) while categorical variables were presented as absolute number (percentage). Patients were grouped into the different stages according to the BCLC and HKLC staging systems. Weighted Kappa statistic was used to test the agreement between the two staging systems. Survival times were analysed using the Kaplan-Meier procedure while comparison between groups was done using the log rank test. Differences in the survival rates were compared using the log-rank test and p-value less than 0.05 was considered as statistically significant.

RESULTS

Patient characteristics

A total of 355 patients were diagnosed with HCC between January 2011 and December 2014. The medical records for all the patients were reviewed. Of these, 165 patients were excluded from the study (incomplete information, 98; liver metastases, 39; recurrent HCC, 20; other liver pathology, 8). The data for 190 patients were analysed. Patient characteristics are shown in Table I. The mean age of the study population was 61.7±12.3 years old and majority were males (73.2%). The study population was predominantly Chinese (64.2%) followed by Malays (23.2%) and Indians (12.1%). The most common aetiology for HCC was chronic hepatitis B virus (HBV) infection (43.7%) while chronic hepatitis C virus (HCV) infection, NASH and alcohol accounted for 8.4%, 7.4% and 6.3% of cases, respectively. Majority of patients (62.1%) had cirrhosis of liver. One third of patients had moderate or diuretic responsive ascites and 10.5% had severe or diuretic refractory ascites. Only 5.8% of patients had hepatic encephalopathy at the time of presentation. Majority of the patients were Child-Pugh A (43.7%) or B (41.1%) and were Eastern Cooperation Oncology Group (ECOG) 0 (55.3%) or 1 (29.5%). Majority of the patients (57.4%) had more than one tumour, and the median diameter of the largest tumour was 7.4 cm. Portal vein thrombosis was seen in 35.8%, while 28.9% had extrahepatic metastasis.

Median overall survival

At the time of data censor, 163 patients (85.8%) had died. The median overall survival was 4 months (95% Confidence Interval (95%CI): 2.8 months, 5.2 months). The number of patients in each stage according to the BCLC and HKLC staging systems are shown in Table II. The median overall survival rate based on BCLC staging is shown in Table III and the corresponding survival curves are presented in Figure 2a. There were no deaths among patients diagnosed as Stage 0. The median overall survival was significantly longer among patients diagnosed as Stage A compared with patients diagnosed as Stage B, among patients diagnosed as Stage B compared with patients diagnosed as Stage C, and among patients diagnosed as Stage C compared with patients diagnosed as Stage D ($p < 0.05$ for all comparisons). The median overall survival based on HKLC staging is shown in Table III and the corresponding survival curves are presented in Figure 2b. The median overall survival rate was significantly longer among patients diagnosed as Stage 2 compared with patients diagnosed as Stage 3, among patients diagnosed as Stage 3 compared with patients diagnosed as Stage 4, and among patients diagnosed as Stage 4 compared with patients diagnosed as Stage 5 ($p<0.05$ for all comparisons).

Comparison between the BCLC and HKLC staging systems

The comparison between staging based on BCLC and HKLC is shown in Table IV. There was moderate agreement between the two classifications with a weighted kappa value of 0.519 (95%CI: 0.449, 0.589). BCLC Stage 0 and HKLC Stage 1 could not be compared as there were no death in BCLC Stage 0. The median overall survival was not significantly different between BCLC Stage B and HKLC Stage 3, and between BCLC Stage D and HKLC Stage 5. However, the median overall survival was significantly longer among patients diagnosed as BCLC Stage A compared with patients diagnosed as HKLC Stage 2, and significantly shorter among patients diagnosed as BCLC Stage C compared with HKLC Stage 4 ($p<0.05$ for both comparisons).

DISCUSSION

In this study on 190 patients with newly diagnosed HCC at a tertiary hospital in Malaysia between 2011 and 2014, we found that most patients were Chinese and that chronic

Table I: Patients' characteristics

Overall population, n = 190	n (%)
Age (mean, SD)	61.7 ± 12.3
Gender	
Male	139 (73.2%)
Female	51 (26.8%)
Race	
Malay	44 (23.2%)
Chinese	122 (64.2%)
Indian	23 (12.1%)
Others	1 (0.5%)
Number of symptoms*	
Asymptomatic	46 (24.2%)
1	36 (18.9%)
2	37 (19.5%)
3	44 (23.2%)
4	20 (10.5%)
5	7 (3.7%)
Etiology	
Hepatitis B	83 (43.7%)
Hepatitis C	16 (8.4%)
Alcohol	12 (6.3%)
NASH-related	14 (7.4%)
Cryptogenic	65 (34.2%)
Cirrhosis	118 (62.1%)
Ascites	
No	106 (55.8%)
Moderate	64 (33.7%)
Severe	20 (10.5%)
Encephalopathy	
No	179 (94.2%)
Precipitant induced	10 (5.3%)
Chronic	1 (0.5%)
Site of metastasis (included multiple sites)	
Lung	29 (15.3%)
Lymph node	23 (12.1%)
Bone	12 (6.3%)
Adrenal	2 (1.1%)
Peritoneum	2 (1.1%)
Pancreases	1 (0.5%)
Cervix	1 (0.5%)
Stomach	1 (0.5%)
Full Blood Count	
Haemoglobin (g/dL)	12.2 (10.2 - 13.7)
White Blood Cells (×10^9/L)	7.9 (5.9 - 7.8)
Platelet (×10^9/L)	192 (132 - 268)
Liver Function Test	
Albumin (g/L)	32 (25 - 37)
Bilirubin (umol/L)	19 (12 - 37)
ALP (U/L)	163 (101 - 263)
ALT (U/L)	56 (34 - 82)
AST (U/L)	83 (39 - 163)
GGT (U/L)	220 (105 - 362)
Others	
INR	1.2 (1.1 - 1.4)
AFP (IU/ml)	130 (9 - 4329)
Creatinine (µmol/L)	79 (62 - 105)
ECOG	
0	105 (55.3%)
1	56 (29.5%)
2	25 (13.2%)
3	3 (1.6%)
4	1 (0.5%)
Number of tumours	
1	81 (42.6%)
2	23 (12.1%)
3	11 (5.8%)
Multiple	75 (39.5%)

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Child-Pugh Grade	
A	83 (43.7%)
B	78 (41.1%)
C	29 (15.3%)
Size of the largest tumour	7.4 (4.2 – 11.4)
Portal Vein Thrombosis	68 (35.8%)
Extrahepatic Metastasis	55 (28.9%)

*The symptoms asked included: Abdominal pain, Loss of weight, Loss of appetite, Jaundice, Abdominal distention, Variceal bleeding

Table II: The number of patients in each stage according to the BCLC and HKLC staging systems

BCLC staging system	HKLC staging system					Total
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	
Stage 0	5	0	0	0	0	5
Stage A	16	0	0	0	0	16
Stage B	9	35	28	23	7	102
Stage C	0	1	9	14	10	34
Stage D	0	0	0	0	33	33
Total	30	36	37	37	50	190

Table III: Median overall survival in months by BCLC and HKLC staging systems

	n	Estimate	95% Confidence Interval	
			Lower Bound	Upper Bound
BCLC staging system				
Stage 0	5	37	-	-
Stage A	16	30	7.5	52.5
Stage B	102	5	2.5	7.5
Stage C	34	2	0.7	3.3
Stage D	33	1	0.5	1.6
Overall	190	4	2.8	5.2
HKLC staging system				
Stage 1	30	42	16.2	67.8
Stage 2	36	10	5.3	14.7
Stage 3	37	4	2.1	6.0
Stage 4	37	3	2.1	3.9
Stage 5	50	1	0.4	1.6
Overall	190	4	2.8	5.2

Table IV: Summary of pairwise comparisons between BCLC and HKLC survival times

	Compared Pairs	No.	Median	95% CI	p-value	Conclusion
Comparison 1	BCLC Stage 0	5	37	-	-	
	HKLC Stage 1	30	42	-		
Comparison 2	BCLC Stage A	16	30	7.5, 52.5	<0.05	Not similar
	HKLC Stage 2	36	10	5.3, 14.7		
Comparison 3	BCLC Stage B	102	5	2.5, 7.5	>0.05	Similar
	HKLC Stage 3	37	4	2.1, 6.0		
Comparison 4	BCLC Stage C	34	2	0.7, 3.3	< 0.05	Not similar
	HKLC Stage 4	37	3	2.1, 3.9		
Comparison 5	BCLC Stage D	33	1	0.5, 1.6	>0.05	Similar
	HKLC Stage 5	50	1	0.4, 1.6		

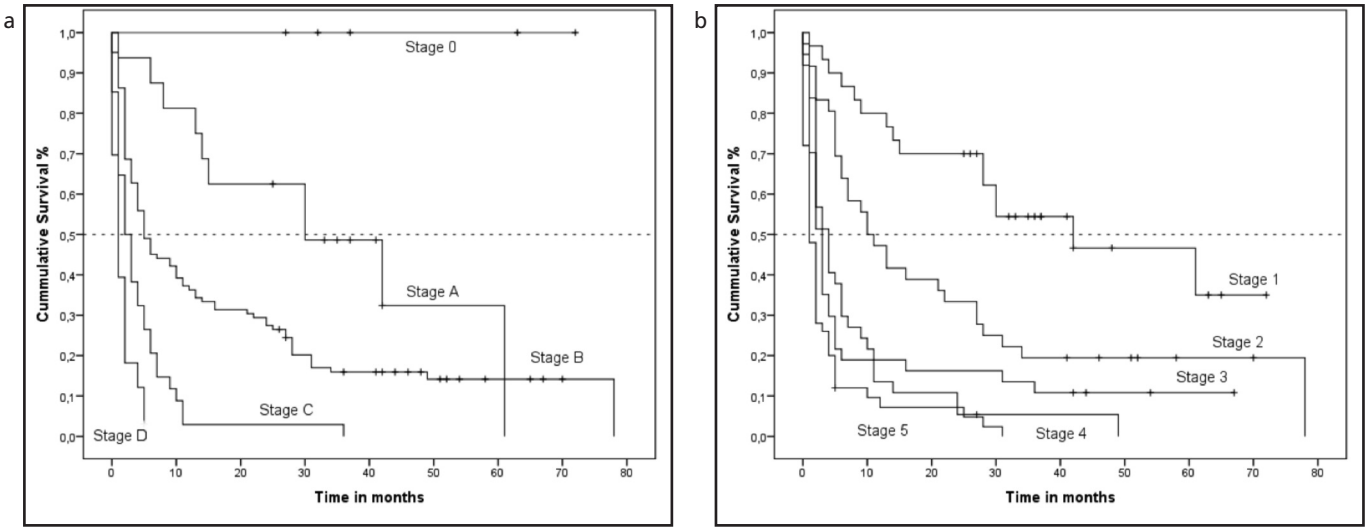

Fig. 1: Survival curves according to (a) BCLC, and (b) HKLC staging systems.

hepatitis B infection remained the leading aetiology, similar to an earlier study conducted at the same centre between 2006 and 2009.[17] This is consistent with the higher prevalence of chronic hepatitis B infection among the Chinese (4-7%) compared with the Malays (2-4%) and Indians (<1%) in the multi-ethnic population in Malaysia.[19] However, there was an over two-fold increase in the proportion of HCC patients with cryptogenic cause, from 16.4% in the earlier study to 34.2% in the current study. This is not including the 7.4% of patients who had a diagnosis of NASH prior to the diagnosis of HCC in the current study. Overall, this is reflective of the changing epidemiology of HCC, where NAFLD-related HCC is expected to increase in Asia, parallel to the increasing prevalence of NALFD in recent years.[20] The current study also found a larger proportion of patients presenting at BCLC Stage B compared with the previous study (53.7% vs. 21.6%). This is largely contributed by a decrease in the proportion of patients presenting at an earlier stage (11.0% in the current study compared with 34.5% in the previous study), which may be accounted for by the marked increase in proportion of HCC in patients with cryptogenic cause or NASH. The later presentation of NAFLD-related HCC may be due to lack of HCC screening because of previously undiagnosed cirrhosis, limitation of ultrasound to detect small tumours because of associated obesity or even the development of HCC in noncirrhotic NAFLD patients.[20]

BCLC and HKLC are the most commonly used staging systems to determine the prognosis and the best treatment modality for HCC patients. However, controversies exist as to which is a better staging system. The BCLC staging system was developed based on a cohort consisting of mainly HCV-infected patients, and most patients had more advanced liver disease.[3,10] In the cohort that the HKLC staging system was derived, the most common aetiology was HBV infection, and majority of patients had preserved liver function. These factors may partly explain the differences observed in the two staging systems.[8] To the best of our knowledge, this is the first study comparing the BCLC and HKLC staging systems in Malaysia. We found that both staging systems were able to stratify patients into distinct groups with significantly different overall survival rates that decreased with increasingly advanced stages. However, there was only a moderate level of agreement between the two staging systems, as indicated by a weighted kappa value of 0.519. Pairwise comparisons between the 5 stages of BCLC and HKLC staging systems showed significant dissimilarities in overall survival between BCLC Stage A and HKLC Stage 2, and between BCLC Stage C and HKLC Stage 4. These can be explained by inherent differences in the two staging systems. HKLC Stage 2 includes intermediate tumours defined as (1) ≤5 cm, either >3 tumour nodules or with intrahepatic venous invasion, or (2) >5 cm, ≤3 tumour nodules and no intrahepatic venous invasion, which are considered as Stage B in the BCLC staging system.[8,21] While the HKLC staging system considers patients with intermediate tumours for potentially curative treatments such as resection, ablation or transplantation, the BCLC staging system offers palliative chemoembolization. Although the HKLC staging system offers a more aggressive treatment approach that may lead to a better outcome in some patients, the inclusion of patients with intermediate tumours as Stage 2 in the HKLC staging system largely explains the significantly shorter overall survival compared with Stage A in the BCLC staging system. Moreover, treatment options were largely guided by the BCLC staging system during the study period.

One of the limitations of our study is that we could not look into the treatment choice based on the two different staging systems and the effect on the overall survival. As aforementioned, treatment options were largely guided by the BCLC staging system during the study period. Moreover, the choice of treatment also depended on the availability of local expertise and resources. Ideally, the performance of the two staging systems in guiding the treatment of HCC should be compared in a randomized study, but this may not be feasible due to the complexity of the disease (both the tumour and underlying liver disease), individual patient factors and expertise of the attending multi-disciplinary team. Second, the study was retrospective and there were missing data that

would not allow us to properly stage some of the patients. Another limitation is that this is a single centre study and may not be generalized to the entire Malaysian population. Nevertheless, we believe our report provides some insight into the demography, aetiology, clinical features and classifications of this disease in Malaysia.

CONCLUSION

In conclusion, while chronic hepatitis B infection is still the leading aetiology for HCC in a multi-ethnic population in Malaysia, a marked increase in cryptogenic and NASH-related HCC has been observed. Both the BCLC and HKLC staging systems were able to stratify patients according to overall survival but the two staging systems only had moderate agreement with marked differences in overall survival observed especially between BCLC Stage A and HKLC Stage 2. Further studies are needed to determine which staging system would perform better in guiding treatment option for HCC patients.

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ETHICAL APPROVAL

This study was approved by the University of Malaya Medical Centre Medical Research Ethics Committee (MRECID No.: 201688-4126, Approval Date: 21 September 2016). Written informed consent was obtained from each participating subject.

CONFLICTS OF INTEREST DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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Development of hearing impairment inventory for religious duties of Muslim adult

Sarah Rahmat, PhD[1], Shahirah A Rahman, B.Aud[1], Nur Hanisah Tukiran, MSc[1], Ramli Musa, MMed[2], Nur Ain Othman, MSc[1], Ahmad Aidil Arafat Dzulkarnain, PhD[1]

[1]Department of Audiology and Speech Language Pathology, Kuliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Kuantan, Pahang, Malaysia, [2]Department of Psychiatry, Kulliyyah of Medicine, International Islamic University Malaysia, Jalan Hospital, Kuantan, Pahang, Malaysia

ABSTRACT

Objective: This study is a preliminary work to develop a Malay version questionnaire named '*Inventori Persepsi bagi Muslim yang Memiliki Masalah Pendengaran* (IPM3P)' to assess the perception on Islamic understanding and practice among Muslim adults with hearing impairment.

Methods: The scale development involved three phases: i) generation of domains based on the literature, ii) generation of sub-domains based on literature review and Islamic panel survey, and iii) generation of items.

Results: Preliminary version of IPM3P consists of 59 items was produced, representing three domains: Obligation (18 items), Practice (21 items), and Difficulty (20 items), and seven sub-domains (*'Ibadah', 'Aqidah', 'Muamalat', 'Tasawwuf', 'Akhlak','Da'wah', and 'Sirah'*).

Conclusion: The preliminary version of IPM3P needs to be psychometrically tested. This pioneering study may become an impetus towards more research pertaining to understanding the effect of hearing loss towards religious life in the future in Malaysia.

KEYWORDS:
Muslim adults with hearing impairment, Malay questionnaire, Islamic understanding and practice, hearing loss and religious life

INTRODUCTION

Religion and spirituality is perceived to significantly contribute towards good quality of life.[1] Adherence to religion and spirituality elements has been determined to be a key factor in developing a good coping mechanism among cancer patients.[2] The importance of the religious element is further substantiated by meta-analysis studies showing that the religious belief and practice have a significant effect on the avoidance of criminal behaviour and can significantly improve the values and behaviours of the offenders.[3,4] In addition, parents who have children with disability have found that the reliance on God has given them patience and inner peace to overcome misfortunes in life.[5] All of the findings are in line with the core teachings of Islam which emphasise on the role of Islam in ensuring a good life in this world and in the hereafter (The Quran: 16: 97).[6] Based on the above mentioned facts, we recognised the importance of imparting the religious elements, specifically imparting the Islamic values to our hearing impaired-Muslim patients in order to assist them in coping with their hearing disability. Hence, there is a need to design a scale that could serve as a tool to measure the perception of Muslims with hearing impairment related to the performance of their religious duties. This scale can later be used to assist the clinician to design a rehabilitation strategy which imparts the Islamic values among the Muslim patients with hearing impairment. The development of such scale would be the main focus of this study.

Albeit the importance of religion in life, the acquisition of religious input and knowledge, and religious or Islamic practice may be hindered in people who have hearing impairment. A few studies have shown that hearing impaired Muslim children faced difficulty in reading and reciting the Quran which is the central religious text of Islam.[7,8] In addition, previous studies that have been conducted on students showed that Muslim students with hearing impairment had difficulty in reciting basic recitation during payers, mainly due to poor ability to memorisise.[7,9] These studies have shown that Muslim students with hearing impairment faced difficulty in understanding religious teaching that involved abstract thinking.[7] All these findings showed that the hearing impaired population (specifically teenagers and children) may be lagging behind in terms of Islamic practice as compared to their peers with normal hearing.[8,9] This could be due to improper delivery of Islamic input that caters to the learning needs of children with hearing impairment.[7,10]

There are few studies looking at the aspect of understanding difficulties that are faced by the Muslims with hearing impairment in performing Islamic practices. The available few studies mainly focused on the recitation of the Quranic and Arabic prayers, but not on other religious aspects such as attending religious ceremony, acquiring Islamic knowledge, playing leadership roles in the Islamic community and performing *'Da'wah'* (see definition in table I).[8,9] To our knowledge previous studies have also focused on understanding the difficulties that are faced by those with hearing impairment in religious practice and understanding among the students and children, but no studies have been conducted to understand the scenario in adults.[7–10] Since lifestyle and needs may differ between different age groups,

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Corresponding Author: Sarah Rahmat
Email: sarahrahmat@iium.edu.my

the effects of hearing impairment towards understanding and practicing Islam among the Muslim adults warrant further investigation. To our knowledge, no related studies have been conducted to understand the impact of hearing loss on religious life among adults, partly due to the absence of tools to investigate the perception of Muslim adults with hearing impairment on their Islamic understanding and practice. Thus, the aim of this study is to develop a Malay version of hearing impairment inventory for religious duties for Muslim adults: *'Inventori Persepsi bagi Muslim yang Memiliki Masalah Pendengaran'* (IPM3P), to assess the Islamic understanding and practice among hearing impaired adults.

Overview of Theoretical framework of IPM3P Development

The objective of the IPM3P development was to investigate the perception of Muslim adults with hearing impairment towards their Islamic understanding and practice. To achieve this objective, the IPM3P was designed to investigate the perception of Muslims with hearing impairment in understanding their obligations as Muslims, and how they perceived their practice as a Muslims. Three main components; domain, sub-domain and items; were generated to produce the first preliminary version of IPM3P. The generation of three IPM3P sub-domains which has been based on the Theory of Planned Behaviour which links one's belief and behaviour.[11] The basis of referring to the Theory of Planned Behaviour in developing the domain of IPM3P is further elaborated in phase one in the Methodology section. Under each domain, the sub-domains that were related to the basic areas of Islamic understanding and practice were generated. The generation of the sub-domains has been conducted through a thematic analysis of the literature review and an Islamic panel survey, is discussed in Phase Two. The generation of the sub-domains which was thought to be necessary in order to include a wide area of Islamic understanding and practice under each domain. Items for each sub-domain under its respective domain were developed based on findings of literature review as well as the responses from the Islamic panel survey. The overview of the theoretical framework of IPM3P development is illustrated in Figure 1. A total of 59 items were derived for the initial development of IPM3P (preliminary version of IPM3P) but was later modified and shortened to become 36 items (12 items for each 'obligation', 'difficulty' and 'practice' domain) following the series of psychometric evaluations. This paper will mainly focus on the development of the preliminary version of IPM3P (59 items), while the psychometric evaluation and the finalisation of IPM3P will be discussed in a separate publication.

MATERIALS AND METHODS

There were three (3) phases involved in development of the IPM3P; i) generation of domain, ii) generation of sub-domain, and iii) generation of items. The section below explains the methodological approach of each phases.

Phase One: Generation of domain and the theoretical framework

The IPM3P was formulated based on the Theory of Planned Behaviour. According to the theory, one's intention to perform (or not to perform) a behaviour is the key factor that influences that action.[11] Accordingly, the tendency of Muslims with hearing impairment to perform the Islamic practice and obligation strongly depends on their intention to perform (or not to perform) the practice and obligation. According to the theory, the three factors that have been shown to influence intention are; i) attitude, ii) subjective norm, and iii) perceived behavioural control.[12] Attitude is referred to as a favourable or unfavourable evaluation to do the actions. Subjective norm is referred to the person's beliefs that specific individuals or groups think whether he/she should or should not perform the behaviour. Meanwhile perceived behavioural control is the feeling of ease or difficulty in performing a behaviour. The derivation of domain of IPM3P was based on the aforementioned factors that influence intention and behaviour.

The three domains of IPM3P are as follows: i) *'Persepsi Terhadap Tanggungjawab'* ('Perception towards obligation', denoted as 'obligation' in this paper), ii) *'Perlaksanaan'* (Practice), and iii) *'Kesukaran'* (difficulty). The derivation of each domain has its own specific justification in relation to the theory of planned behaviour. Figure 1 illustrates how the Theory of Planned Behaviour influences the development of domain in IPM3P, and the relation to the question that is intended to be answered in IPM3P. While it is difficult to measure one's intention to practice and understand Islam, the attitudes towards Islamic practice and understanding can be measured by measuring the perception of obligation towards Islamic understanding and practice. According to the Theory of Planned Behaviour, attitudes towards an action or behaviour is determined by dominant beliefs about that action or behaviour. For example, if a Muslim believes that prayer is obligatory for a Muslim and is required by God, he or she will at best find a way to perform the prayer regardless of any circumstances (time constraint, disability, e.g. hearing or physical impairment) that he or she may face. In other words, one's perception towards an obligation of Islamic understanding and practice hypothetically will determine the attitudes towards the Islamic practice, which subsequently influences the intention, and hence his or her Islamic practice and behaviour. This is the basis of deriving the first domain for IPM3P, which is the *'Persepsi Terhadap Tanggungjawab'* (Perception towards obligation, denoted by 'Obligation'), and the second domain which is 'Perlaksanaan' (Practice).

In other words, the questionnaire is designed to investigate "How Muslims with hearing impairment perceive their obligation towards understanding and performing Islamic practice (obligation domain)?" and "Do Muslims with hearing impairment understand and practice Islamic teaching (Practice domain)?". The third domain in the IPM3P is *'Kesukaran'* (difficulty) which has been derived based on two basis, which are: i) to investigate the level of difficulty that is faced by the Muslims with hearing impairment in different basic areas of Islamic understanding and practice; ii) to investigate whether perceive behavioural control (feeling of ease or difficulty in performing Islamic practice) could be another factor that influences intention towards a behaviour and subsequently determines that behaviour. Thus the 'difficulty' domain has been designed to answer, "What is the level of difficulty that is faced by Muslims with hearing impairment in gaining an understanding of Islamic teaching and in performing Islamic practice?"

Phase Two: Generation of sub-domain
As explained earlier, sub-domains were derived in order to cover a wide area of basic principles of Muslim religiosity, and to further specify basic components that should be understood and practiced as Muslims. These basic principles and components were intended to be assessed in Muslims with hearing impairment. To generate the sub-domain, two sources were referred: i) the literature review, and ii) input from the survey on Islamic panel.

Participants
A total of 12 individuals were identified as the Islamic panel (two university lecturers who hold PhD in Islamic studies, three secondary school religious teachers who hold Bachelor degree in Islamic studies, three workers and four students who are actively involved in Islamic society activities or holding any position in Islamic society), aged between 24 to 55 years old participated in this survey. The selection of panellists from different backgrounds was to ensure that the opinions collected through the survey were from panellist who were involved in various Islamic background. The involvement of different adult age groups among the panellists was to resemble different age group of the real hearing impaired Muslim adults. All participants needed to be able to communicate, read and write in Bahasa Melayu as the survey was conducted in Bahasa Melayu.

Procedure
a) Literature review
Literature review concerning the Islamic worldview and Muslim religiosity were identified.[13,14] The main components forming the Islamic worldview and Muslim religiosity model were identified from the review. These main components is compared and merged later to the ones from the survey on Islamic panels, to form the sub-domain of IPM3P.

b) Survey
A simple Bahasa Melayu written open ended survey was given to the panellists. The panellists were asked to list down the basic Islamic components that a Muslim should understand and practice in order to be good Muslims. The written survey was physically distributed to ten members of the panellists as they were reachable, while the other two panellists were contacted via email. A standardised instruction was given to all panellist to ensure that they had the same understanding regarding the survey. All the responses were recorded and were analysed using thematic analysis to derive the domain for the questionnaire. The final sub-domains were produced upon agreement during a review by an expert committee.

Data analysis
A thematic analysis following the steps proposed by Braun and Clarke (2006) was conducted to analyse the responses from the survey as well as the literature findings, which eventually generated the sub-domains of IPM3P.[15] Firstly, the responses that were given by the Islamic panels were familiarised and repeatedly read in an active way. After that, features of responses that appear more obvious were coded into 'unit analysis'. All unit analysis that shared a common theme were classified under a proposed potential sub-domain. All potential sub-domains were reviewed by an expert committee (consisting of authors and one independent Islamic expert) to ensure that all the coded unit analysis were mapped into the potential sub-domain. Some of the proposed potential sub-domains changed after the review and the final reviewed sub-domains were identified based on the consensus of the expert committee. The categorisation of the survey responses and literature review findings into seven specific sub-domains were based on the definition listed in Table I.

Phase Three: Generation of items
Generation of items was done based on the findings from a rapid review of literature search and responses from the survey (described in Phase Two). Items were generated for each sub-domain under each respective domain.

Procedure
Rapid review method was carried out to investigate the perception on obligation, practice and difficulties in understanding and practicing Islam among the hearing impaired population that were reported in the previous literature. The literature search was conducted using several free online databases such as PubMed, Google scholar, Science direct, IIUM Database, freefullpdf, Web of Science, Medline, ProQuest and google book, using "effects of hearing loss to religion", "hearing impaired adult and religious life", "hearing loss and religion", "hearing loss and religious life" as key phrases. Findings from the review were categorised into the predetermined domains and sub-domains. These findings were used in generating the items under the relevant domain and sub-domains.

Apart from finding of the rapid literature review, individual responses from the Islamic panel survey (derived from Phase Two) were also used to generate items under the respective sub-domain and domain. The items were generated with a consensus from the research team. Table III specify the example of generation of an item in IPM3P, specifically item no.1 under 'Obligation' domain and *'Ibadah'* sub-domain. The item was generated based on findings from the rapid literature review and Islamic panel survey. Five Likert's Scale was used for the scoring method.

RESULTS

Phase One: Generation of domain
The derivation of domain for IPM3P was based on the Theory of Planned Behaviour. Three domains were generated: i) Obligation, ii) Practice, and iii) Difficulty. The theoretical framework for domain derivation can be referred in the earlier section.

Phase Two: Generation of sub-domain
From the literature review, Kraus and Hamzah (2010) have suggested a comprehensive model for measuring Muslim religiosity that is mainly based on the Islamic worldview and *tawhidic* paradigm which mainly covers the concept of *'Aqidah'*- believe in oneness of God.[13] This Islamic worldview should be manifested in religious personality, in the act of worship *('Ibadah')*, Islamic character *('Akhlak')* and interaction with other human beings *('Muamalat')*. Thus from the literature review four basic components of Muslim religiosity were identified: i) *'Aqidah'*, ii) *'Akhlak'*, iii) 'Ibadah', and iv) *'Muamalat'*.

Table I: Final reviewed sub-domain and its definition

Sub-domain	Definition
'Aqidah'	Article of faith, belief or creed. Something that one has a firm belief in and in this context, it refers to Islamic belief.[21]
'Ibadah'	Submission or worship, including speech and actions with the purpose of seeking Allah's pleasure.[21]
'Akhlak'	Practice of virtue and moral values.[21]
'Muamalat'	Transactions or dealings involves human beings and other creation.[21]
'Tasawwuf'	Tasawuf teaches one to purify one`s inner side of the life, improve one`s moral character, and build up one's inner and outer life in order to attain perpetual pleasure of Allah, resulting in a state of perpetual bless. Its subject matter is the purification of the soul, and its end or aim is the attainment of eternal satisfaction and blessedness.[22]
'Da'wah'	The call to Islam (to invite people to Allah or to Islam).[21]
'Sirah'	The biography or scholarship of the life of Prophet Muhammad.[21]

Table II: Relevant literature search findings

No	Study	Findings	Domain	Sub-domain
1	Ghadim et al.[17]	Perception of family members which believe that hearing impaired child does not necessary to receive the same level of education as normal children do particularly Islamic education and reciting the Quran.	Obligation	*Ibadah*
		Schools are not familiar with the methods of teaching the Quran to the deaf and there are not many teachers who are expert in this area.	Difficulty	*Ibadah*
2	Abdullah & Ali[16]	The mastery of prayer among hearing- impaired- student is at a weak level due to cognitive disability, weak language proficiency and the limitation of communication of hearing-impaired students to the study of religion.	Difficulty	*Ibadah*
3	Awang et al.[7]	Students could not read Al-Quran and the teaching of component in recitation Al-Quran cannot be conducted due to their difficulty in communication.	Difficulty	*Ibadah*
		Hearing impaired students could not understand the content of the *Fardhu Ain* class	Difficulty	*Ibadah*
		The students may easily forget what they have learned due to poor memorising ability.	Difficulty	*Ibadah*
		Hearing impaired students do not want to go to Fardhu Ain class as they perceive the class is not interesting	Practice	*Ibadah*
		Hearing impaired students faced difficulties to understand abstract information and the terms in Islam. Abstract thinking includes matter related to faith *('Aqidah')* and *'Sam'iyyat'*	Difficulty	*Aqidah*
4	Harun[9]	100% of respondents in Politeknik agree that they are easily forget the basic recitation in prayers	Difficulty	*Aqidah*
		100% of respondents in Politeknik performed their prayers with physical movement only, not including recitation	Practice	*Ibadah*
5	Saari, Umat and Mat[8]	Hearing impaired children poorly recognize the basic Al-Quran phonemes.	Difficulty	*Ibadah*
		Hearing impaired children admitted their difficulties in producing Al-Quran phonemes.	Difficulty	*Ibadah*

Table III: Example of items generation based on findings from literature search and Islamic panel survey for sub-domain Ibadah under 'perception on obligation' domain

DOMAIN: PERCEPTION TOWARDS OBLIGATION						
Sub-domain	**Item number**	**Findings**	**Analysis unit**	**Source (Reference) Version'**	**Generated Items** *'Bahasa Melayu*	**Statement (+/-)**
Ibadah	1	Perception of family members which believe that hearing impaired child does not necessary to receive the same level of education as normal children do particularly Islamic education and reciting the Quran.	Gaining knowledge	Literature review (Ghadim et al).[16]	***I must learn Islamic knowledge as other Muslims do*** *'Saya perlu mempelajari ilmu agama Islam seperti orang lain'*	+
		Gaining knowledge about Fadhu Ain and Fardhu Kifayah and understand its importance	Gaining knowledge on Fardhu Ain and Fardhu Kifayah	Survey (Panellist A2)		
		Attending class on various discipline	Attending class	Survey (Panellist A8)		

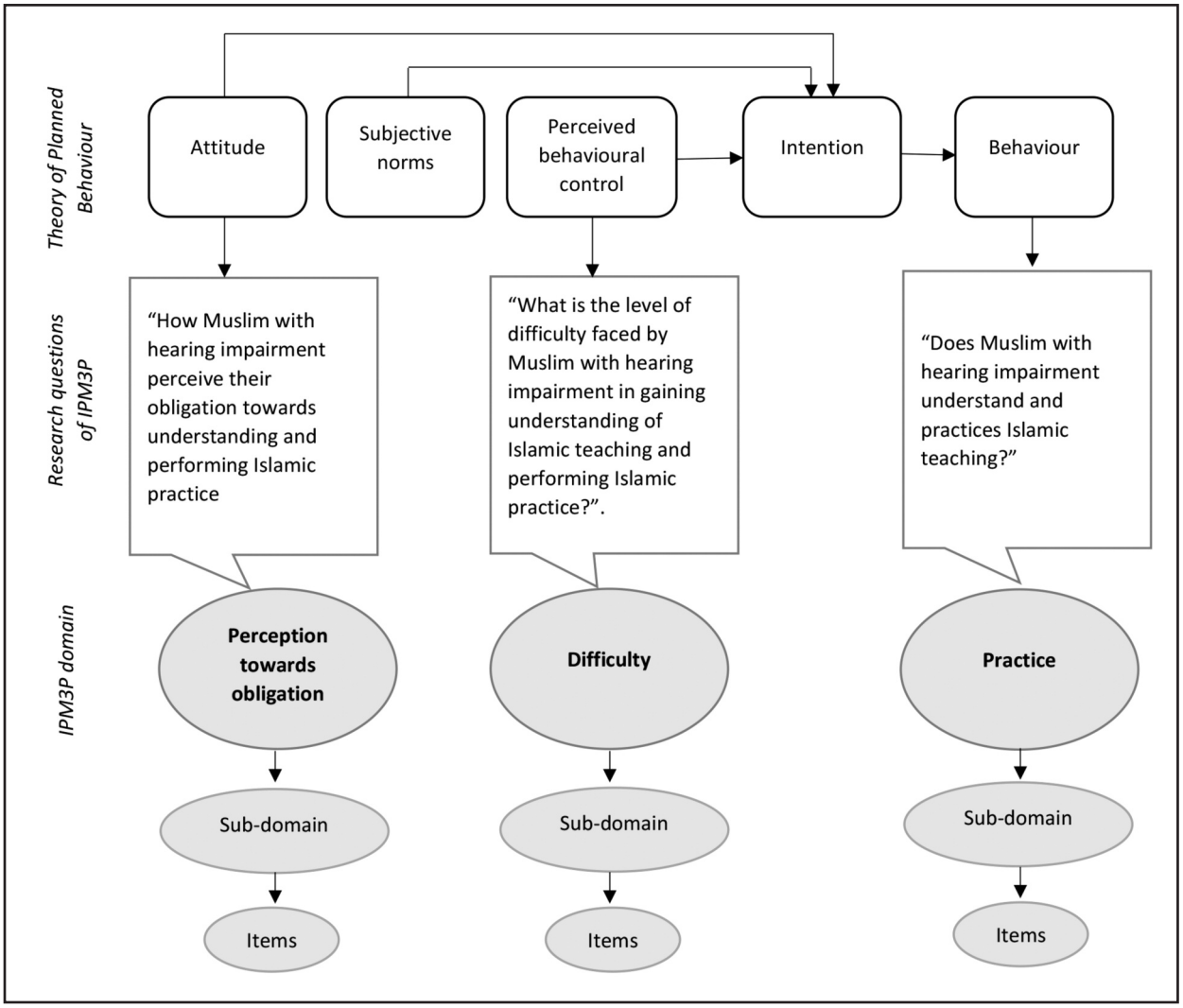

Fig. 1: Theoretical framework of IPM3P development.

A total of 182 responses were gathered from an Islamic panel survey (*'Aqidah'*: 39, *'Ibadah'*: 77, *'Muamalat'*: 25, *'Da'wah'*: 4, *'Akhlak'*:16, *'Tasawwuf'*:19, *'Sirah'*: 2). A thematic analysis of the survey responses shows partly similar basic components that should be mastered as a Muslim to that from the literature review, with six basic components (*'Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf'*) that should be practiced, and seven basic components *('Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf', 'Sirah'*) that should be understood by a Muslim. Thus taking into account the findings from the literature review and the survey, six sub-domains (*'Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf'*) were used to generate the items under the 'practice' domain, and seven sub-domains *('Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf', 'Sirah')* were used to generate the items under the 'obligation' and 'difficulty' domain during the initial stage of IPM3P development. Details on the generation of items will be discussed in the following section.

Phase Three: Generation of items

Five relevant studies were identified from the rapid literature review.[7–9,16,17] The findings from the rapid review were mapped into the pre-determined domain ('Obligation', 'Practice' and 'Difficulty'), and sub-domain (*'Aqidah', 'Ibadah', 'Muamalat', 'Da'wah', 'Akhlak', 'Tasawwuf', 'Sirah'*). Findings on perception of obligation showed that parents perceived that the hearing impaired children were less obliged to learn Islam.[17] While findings for domain practice showed that Muslim students with hearing impairment did not practice *'Ibadah'* completely (missing *'Fardhu ain'* class and performing prayers with physical movement only, not including recitation).[7,9] Most of the study showed that the hearing-impaired population had difficulties in the sub-domain *'Ibadah'* such as in performing prayers, reciting Al-Quran and attending *'Fardhu ain'* classes.[7–9,16,17]

A total of 59 close-ended items were derived for the first preliminary draft of IPM3P; 18 items for perception towards obligation domain, 20 items for practice domain, and 21 items for difficulty domain. These items were made from a

total of 36 positive and 23 negative statements. For domain 'perception towards obligation' and 'difficulty', the response is rated as (1) *'sangat tidak setuju'* (totally disagree), (2) *'tidak setuju'* (disagree), (3) *'tidak pasti'* (not sure), (4) *'setuju'* (agree), to (5) *'sangat setuju'* (totally agree). For domain 'practice', the response is rated as (1) *'sangat tidak kerap'* (very rarely), (2) *'tidak kerap'* (rarely), (3) *'tidak pasti'* (not sure), (4) *'kerap'* (frequent), to (5) *'sangat kerap'* (very frequent). The first preliminary draft of IPM3P (59 items) underwent further psychometric evaluation, which will be described in our next publication.

DISCUSSION

The aim of this study was to develop a tool (IPM3P) to measure the perception of Muslim adults with hearing impairment towards their Islamic understanding and practice. The focus of an adult group was merely due to the absence of study in understanding the process in the adult population, as compared to the few studies that had been conducted among Muslim children with hearing impairment.[8,10] To understand the behaviour or the action of Muslims with hearing impairment regarding Islamic understanding and practice, the theoretical framework of the development of IPM3P is based on the Theory of Planned Behaviour which suggests a few factors affecting the behaviour of an individual.[11] The translation of the Theory of Planned Behaviour into the theoretical framework of IPM3P is illustrated in Figure 1. To confirm the theoretical framework of IPM3P, further study is needed to understand: i) the relationship between perception of obligation and practice as a Muslim among adults with hearing impairment, ii) the relationship between the level of Islamic practice and the level of difficulty in understanding Islamic teaching and performing Islamic practice among Muslim adults with hearing impairment.

The inclusion of the sub-domain that was gathered from the response of an Islamic panel survey and the literature during the development stage was mainly intended to generate items that were comprehensive in assessing a wide area of Islamic understanding and practice. The assessment of a wide area of Islamic understanding and practice was intended to address the gap of previous research in this area where the findings had mainly focused on the aspect of *'Ibadah'*.[7–9] Apart from *'Ibadah'*, there are other components which are considered important for a Muslim, from the perspective of an Islamic world view. The main components of Islamic and *'tawhidic'* (Oneness of God) worldview is *'Aqidah'*, which can be manifested through the act of worship (*'Ibadah'*), good Islamic character *('Akhlak Islamiyah')* as well as relationship with other human beings *('Mua'malat')*.[13,14] Apart from that, the purpose of Islam is to purify the inner life of man through having a good concept of *'Tasawwuf'*, and thus may be considered as important components of Muslim's religiosity. These components, in addition to *'Sirah'* and *'Da'wah'* (which are also considered important as a Muslim from the view of Islamic panel), form the basis of generating the sub-domain of IPM3P. During the thematic analysis for sub-domain generation, recurring sub-domain was identified from the literature and survey findings showing that the data had reached a saturation point.[18] This data saturation indicates that the identified sub-domains appear very important in moulding a good Muslim character and practice. The inclusion of all the sub-domains is hoped to enable a holistic assessment on the effects of hearing loss towards Islamic understanding and practice.

During the initial stage of the development of IPM3P item, the initial version of IPM3P consisted of quite a large number of items representing each domain and sub-domains (59 items), in order to prepare for any item deletion following the later stage of psychometric analysis.[19] Unlike other sub-domains which consist of quite a large number of items, the preliminary version of IPM3P only includes two items under the sub-domain *'Sirah'*. This was because the item under the sub-domain *'Sirah'* was slightly more difficult to be generated to suit each domain. In addition, only two responses concerning *'Sirah'* were gathered out of 182 responses during an Islamic panel survey, as compared to other sub-domains which yielded a higher number of responses. Thus less weight of item generation was given for the sub-domain *'Sirah'*.

CONCLUSION

In conclusion, this study offers an early information on how measurement can be developed to assess the perception of Muslim adults with hearing impairment towards their Islamic understanding and practice. Preliminary version of IPM3P consists of 59 items that has been produced, representing three domains: 'Obligation' (18 items), 'Practice' (21 items), and 'Difficulty' (20 items), and seven sub-domains *('Ibadah', 'Aqidah', 'Muamalat', 'Tasawwuf', 'Akhlak', 'Da'wah', and 'Sirah')*. The preliminary development of IPM3P served as a preliminary step to further understand the religious need and religious difficulty among Muslim adults with hearing impairment.

RECOMMENDATIONS

The preliminary version of IPM3P needs to undergo a series of psychometric evaluation including content, face and construct validity, as well as reliability assessment, before it can be used on a wider Muslim population with hearing impairment.

ACKNOWLEDGEMENT

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ORIGINAL ARTICLE

Knowledge, attitude, practice and perception on sunscreen and skin cancer among doctors and pharmacists

Qin Jian Low, MRCP(UK)[1], Kuo Zhau Teo, MBBS[1], Tzyy Huei Lim, MRCP(UK)[1], Seng Wee Cheo, MRCP(UK)[2], Wen Yee Evelyn Yap, MRCP(UK)[3]

[1]Department of Internal Medicine, Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia, [2]Department of Internal Medicine, Hospital Lahad Datu, Lahad Datu, Sabah, Malaysia, [3]Department of Dermatology, Hospital Pakar Sultanah Fatimah Muar, Muar, Johor, Malaysia

ABSTRACT

Introduction: Excessive ultraviolet light (UV) can cause premature skin aging and potentially skin cancer. Currently there is a lack of awareness among health care professionals and the public on sun protection. The objectives of this study were to determine knowledge on sunscreen and skin cancer among health care professionals, to evaluate the knowledge, attitude, practice and perception of doctors and pharmacists toward the usage of sunscreen as protection against UV radiation.

Materials And Methods: This is a cross-sectional study conducted among doctors and pharmacists in Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia. Questionnaires were used in this study.

Results: A total of 384 participants completed the questionnaires. The participants consisted of 323 doctors (84.1%) and 61 pharmacists (15.9%). The age group of the participants ranged between 25 till 55 years old. Ninety doctors (27.9%) and thirty-one pharmacists (51.0%) reported used sunscreen daily (p<0.001). This finding showed that there was a deficit in the practice of sun protection. Pharmacists scored a higher knowledge score of median 12 (IQR=3.0) while the doctors scored 11 (IQR=2.0). This study showed a significant association between ethnicity and skin cancer knowledge (p<0.05).

Conclusion: This study demonstrated a lack of knowledge of sunscreen and skin cancer prevention among health care practitioners. This finding supports better medical education program on this topic.

KEYWORDS:
Sunscreen, skin cancer, knowledge, practice, perception

INTRODUCTION

Exposure to sunlight is required for vitamin D synthesis. Ultraviolet (UV) radiation (290 to 400 nm) is responsible for sunburn, photoaging and skin malignancy. Ultraviolet B (UVB) radiation (280-320nm) represent five percent of UV radiation reaching the surface of the earth which causes sun burn, pigmentation, inflammation and can induce melanoma and skin cancer. Ninety five percent of UV radiation arriving at the earth surface is ultraviolet A (UVA) (320 to 400 nm).[1,2] UVA consists of UVA1 (340 to 400 nm) and UVA2 (320 to 340 nm). UVA1 is less potent than UVA2 in inducing erythema.[3] Ultraviolet A is responsible for skin pigmentation and photoaging.[3,4] Measures such as avoiding peak hours of sun, sun protective clothing and sunscreen applications are crucial to reduce the potential harm due to UV exposure.[5]

Sunscreen lotions are topical preparations which contain filters that reflect or absorb radiation in the UV wavelength. They can be categorized into organic or inorganic filters.[2] Organic filters such as cinnamates and salicylates are aromatic compounds that absorb UV radiation and convert it to a negligible amount of heat.[2] Inorganic filters such as zinc oxide and titanium dioxide reflect and scatter UV light over a wide range of wavelengths.[2,6] A broad-spectrum sunscreen combines filters of different ultraviolet absorption spectra and is able to absorb both UVA and UVB radiation. The sun protection factor (SPF) is a measurement used to measure a sunscreen ability to protect one from sunburn which is primarily caused by UVB.[7,8]

Geographically, Malaysia is located on the equatorial and experiences hot and humid weather throughout the year. Malaysians are exposed to sunlight daily and it is imperative for health care professionals to be competent and comfortable to advice their patients correctly about sun protection. There is limited published data of knowledge of sun protection among health care professionals locally. Ammar Ihsan Awadh et al. reported that final year pharmacists displayed better sunscreen knowledge and perception on sunscreen usage than final year medical students from the International Islamic University Malaysia.[9] Internationally, there are reported population-based study on sunscreen use and perception.[12]

The objectives of this study were to explore knowledge on sunscreen and skin cancer, attitude, practice and perception among health care professionals on sunscreen and skin cancer.

MATERIALS AND METHODS

Study Design and Setting

This is a cross sectional questionnaire-based study among doctors and pharmacists conducted by a team of doctors from the internal medicine department of Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia between 1st July to 31st November 2019. Exclusion criteria included doctors and pharmacists who were unable or refused to provide consent.

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Corresponding Author: Low Qin Jian
Email: lowqinjian@moh.gov.my

A content and face validity method were conducted by the investigators.

The questionnaire was developed according to earlier studies and approved by our Clinical Research Committee of Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia.[9] The content of the questionnaire was reviewed and approved by our expert dermatologist. The design of the questionnaire contained practices of sunscreen use, attitude and knowledge on sunscreen and skin cancer. The first section of the questionnaire consisted of demographic profile of the doctors and pharmacists. As the medical education of both medicine and pharmacy undergraduate programs are conducted in the English language in Malaysia, the English version of the questionnaire was distributed without the need for translation. The study protocol was approved by the Ministry of Health Research Ethics Committee (MREC) and the National Medical Research Registry with the registration number NMRR-19-1470- 48459.

Sample and Setting

The prevalence of any response (items from KAP) may be low, moderate or high. The sample size calculation was based on a formula to determine prevalence in a targeted population where prevalence of 50.0% will always yield the largest sample size based on fixed margin of error. Therefore, the sample size calculation is based on to determine a prevalence of 50.0% with margin of error of 5.0% for any response of the KAP items. Thus, the minimum required sample size for 95% confidence interval is 384 respondents. Sample size was calculated using epiinfo software version 7.2.0.1. Doctors and pharmacists were recruited from each of the department. The participants filled up the questionnaires individually after receiving the written instructions.

Content validity was conducted among two senior medical doctors and one dermatologist to ensure all the questions are valid and relevant to the patients. No amendments were made at this stage. Next, face validity was conducted among ten respondents consisting of pharmacists and medical doctors. No amendment was made also at this stage. No pilot study was conducted since the earlier researchers concluded the questionnaire is appropriate, reliable and valid since previously the study using the same questionnaire was published elsewhere.[9] Basis of validity was determined based on content and face validity only.

Data Collection and analysis

The questionnaires were distributed to the participants. A brief description of the study and an invitation to participate was provided in writing. After completing the questionnaires, the participants were asked to return the questionnaire. Participants were asked to convey any problems they face to the investigator so that immediate changes can be made to facilitate data collection. Responses to the questionnaire items and questions were entered into IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. for analysis of descriptive statistics.

RESULTS

Out of the total of 473 doctors and 80 pharmacists, 323 (68.3%) doctors and 61 (76.3%) pharmacists returned the completed questionnaires. Five questionnaires were rejected because they were incomplete. Thus, a total of 384 completed questionnaires were collected. This study sample consisted of 175 male and 209 female participants. The age of our participants ranged from 20 to 60 years old. Table I and II describe the demographic data of participants. Table III summarizes the attitude, practice and perception of participants among doctors and pharmacists towards sunscreen use. Table IV and V describe the knowledge on sunscreen questionnaires.

The total number of returned questionnaires were from 323 (68.3%) doctors and 61 (76.0%) pharmacists. Among the 323 doctors who completed the questionnaires, 142 (44.0%) were house officers, 149 (46.1%) were medical officers and 32 (9.9%) were specialists. Sixty-one pharmacists which consists of 20 (33.0%) provisionally registered pharmacists and 41 (67.0%) fully registered pharmacists returned the completed questionnaires. The majority of the doctors and pharmacists were of the female gender and were from the 20 to 30 years age group. Two hundred and eighteen (67.5%) doctors and 44 (72%) pharmacists had Fitzpatrick skin type IV and V.

We interviewed all our participants about their practice of daily sunscreen use. Seventy-eight doctors (74.0%) and 23 (38.0%) pharmacists do not have the practice of daily sunscreen usage. Twenty-six (68.0%) male and 75.0 (59.0%) female participants did not have the practice of daily sunscreen usage. Majority of doctors (70.0, 66.0%) and pharmacists (37.0, 61.0%) answered correctly about the timing of sunscreen application before sunlight exposure. In the doctor's cohort, media (33.0, 32.0%) was the top influencer for daily sunscreen use while in the pharmacist's cohort, family (18.0, 30.0%) was the top influencer. Mass media exposure with sun-protection information positively influenced the perception and sunscreen use among the doctor's cohort.

DISCUSSION

Our findings showed that 51.0% pharmacists and 28.0% doctors reported to have the practice of daily use of sunscreen. Ammar Ihsan Awadh et al. reported a similar finding where final year pharmacy students (47.5%) use more sunscreen than final year medical students (36.6%).[9] This was possibly related to the fact that pharmacists are more familiar with sunscreen products. The majority of pharmacist respondents were females (92.0%) and they were generally more aware of the importance of sun protection. In our cohort, the practice of sunscreen use showed no significant differences between both genders as the majority of male (67.5%) and females (57.9%) do not have the practice of daily sunscreen use.

The assessment of knowledge about the use of sunscreen showed that female respondents scored a higher percentage of correct answer than the male respondents with a statistically significant association (p=0.011). This is possibly due to the fact that females are more concerned on sun protection and sunscreen use. There is a famous Asian belief that 'a fair skin can hide three facial flaws'.[10] Asian females have long considered being fair as a desirable trait.[10] Therefore, they are more compliant to sun protection

Table I: Socio-demographic background of participants (N=384)

	Doctors (n=323)	Pharmacists (n=61)
Position– no. (%)	House officers 142 (44.0) Medical officers 149 (46.1) Specialist: 32 (9.9)	†PRP: 20 (33.0) ‡FRP: 41 (67.0)
Age– no. (%)		
20 till 30 years old	206 (63.8)	44 (72.0)
31 till 40 years old	109 (33.7)	15 (25.0)
41 till 50 yeas old	7 (2.2)	2 (3.0)
51 till 60 years old	1 (0.3)	0 (0)
Gender – no. (%)		
Male	170 (52.6)	5 (8.0)
Female	153 (47.4)	56 (92.0)
Ethnicity – no. (%)		
Malay	172 (53.3)	24 (39.0)
Chinese	131 (40.5)	34 (56.0)
Indian	16 (5.0)	3 (5.0)
Biracial/Others	4 (1.2)	0 (0)
Status – no. (%)		
Single	127 (39.3)	50 (82.0)
Married	138 (42.7)	11 (18.0)
In a relationship	58 (18.0)	0 (0)
Fitzpatrick Type – no. (%)		
Type II & III	105 (32.5)	17 (28.0)
Type IV & V	218 (67.5)	44 (72.0)

Data are presented as number (%) of participants.
†PRP = Provisionally registered pharmacists; ‡FRP = Fully registered pharmacists.

Table II: Socio-demographic background of participants who completed the questionnaire (N=384)

Occupation – no. (%)	
Doctor	323 (84.1)
Pharmacist	61 (15.9)
Doctors – no. (%)	
House officers	142 (44.0)
Medical Officers	149 (46.1)
Specialist	32 (9.9)
Pharmacist – no. (%)	
†PRP	20 (32.8)
‡FRP	41 (67.2)
Age – no. (%)	
20 till 30 years old	250 (65.1)
31 till 40 years old	124 (32.3)
41 till 50 yeas old	9 (2.3)
51 till 60 years old	1 (0.3)
Gender – no. (%)	
Male	175 (45.6)
Female	209 (54.4)
Ethnicity – no. (%)	
Malay	196 (51.0)
Chinese	165 (43.0)
Indian	19 (4.9)
Others	4 (1.1)
Status – no. (%)	
Single	177 (46.0)
Married	149 (38.9)
In a relationship	58 (15.1)
Fitzpatrick Type – no. (%)	
Type II & III	122 (31.8)
Type IV & V	262 (68.2)

Data are presented as number (%) of participants.
†PRP = Provisionally registered pharmacists; ‡FRP = Fully registered pharmacists.

Table III: Practice of sunscreen usage among doctors and pharmacists (N=384)

Questionnaires	Doctors (n=323)	Pharmacists (n=61)	p values
Do you use sunscreen? – no. (%)			
Yes	90 (27.9)	31 (51.0)	<0.001
No	209 (64.7)	23 (38.0)	
Occasionally	24 (7.4)	7 (11.0)	
How frequently do you apply your sunscreen? – no. (%)			
Occasionally	103 (31.9)	20 (33.0)	<0.001
Every morning or evening	33 (10.2)	10 (16.0)	
Once a day	122 (37.8)	25 (41.0)	
Every 4 hours	65 (20.1)	6 (10.0)	
When do you apply your sunscreen before sunlight exposure? – no. (%)			
Immediately before	55 (17.0)	14 (23.0)	<0.001
30 minutes before	210 (65.0)	37 (61.0)	
60 minutes before	58 (18.0)	10 (16.0)	
Influence to use sunscreen– no. (%)			
Media	128 (39.6)	16 (26.0)	<0.001
Family	50 (15.5)	18 (30.0)	
Friends	87 (27.0)	6 (10.0)	
Health care professionals	41 (12.7)	12 (20.0)	
Others	17 (5.2)	9 (14.0)	
Will you recommend the usage of sunscreen to others? – no. (%)			
Yes	209 (64.7)	42 (69.0)	<0.001
No	76 (23.5)	4 (7.0)	
Unsure	38 (11.8)	15 (24.0)	

Data are presented as number (%) of participants.
p values are calculated based on Pearson Chi-square test.

Table IV: Attitude of sunscreen use among doctors and pharmacists (N=384)

Questionnaire	Doctors (n=323)	Pharmacists (n=61)	p values
Will you encourage parents to apply sunscreen to their < 6 months old baby? – no. (%)			
Yes	131 (40.6)	6 (10.0)	<0.001
No	173 (53.5)	55 (90.0)	
Unsure	19 (5.9)	0 (0)	
Sunscreen is effective at preventing sunburn. – no. (%)			
Agree	256 (79.3)	58 (95.0)	0.012
Disagree	56 (17.3)	3 (5.0)	
Unsure	11 (3.4)	0 (0)	
Sunscreen is effective in preventing skin cancer. – no. (%)			
Agree	302 (93.5)	58 (95.0)	0.008
Disagree	7 (2.2)	3 (5.0)	
Unsure	14 (4.3)	0 (0)	
Sunscreen is effective at preventing skin aging. – no. (%)			
Agree	302 (93.5)	54 (89.0)	0.126
Disagree	7 (2.2)	7 (11.0)	
Unsure	14 (4.3)	0 (0)	
Sunscreen is required on a cloudy or rainy day. – no. (%)			
Agree	227 (70.3)	44 (72.0)	0.035
Disagree	67 (20.7)	17 (28.0)	
Unsure	29 (9.0)	0 (0)	
Sunscreen should be applied when going for outdoor activities during a cloudy day. – no. (%)			
Agree	287 (88.9)	49 (80.0)	<0.001
Disagree	19 (5.8)	12 (20.0)	
Unsure	17 (5.3)	0 (0)	
Sunscreen should be applied when going for outdoor activities during a sunny day. – no. (%)			
Agree	318 (98.5)	61 (100.0)	0.620
Disagree	1 (0.3)	0 (0)	
Unsure	4 (1.2)	0 (0)	

cont..... pg 216

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Sunscreen should be applied when going swimming at the pool, beach or waterfall. – no. (%)			
Agree	315 (97.5)	61 (100.0)	0.462
Disagree	1 (0.3)	0 (0)	
Unsure	7 (2.2)	0 (0)	
Sunscreen should be applied when attending lectures, working in hospital or any indoor activities. – no. (%)			
Agree	230 (71.2)	45 (74.0)	0.003
Disagree	62 (19.2)	16 (26.0)	
Unsure	31 (9.6)	0 (0)	
Sunscreen should be applied when attending any occasions at night. – no. (%)			
Agree	114 (35.3)	21 (34.0)	0.142
Disagree	178 (55.1)	40 (66.0)	
Unsure	31 (9.6)	0 (0)	
What does SPF stand for? – no. (%)			
Correct	217 (67.2)	40 (66.0)	0.806
Incorrect	106 (32.8)	21 (34.0)	
Which of the following has higher risk of skin cancer? – no. (%)			
UVA	182 (56.3)	35 (57.0)	0.018
UVB	106 (32.8)	26 (43.0)	
Unsure	35 (10.9)	0 (0)	
If one is working in-door (e.g. Office job), one does not need to wear sunscreen. – no. (%)			
Agree	167 (51.7)	45 (74.0)	<0.001
Disagree	128 (39.6)	16 (26.0)	
Unsure	28 (8.7)	0 (0)	
Melanoma is a form of skin cancer. – no. (%)			
Agree	315 (97.5)	58 (95.0)	0.294
Disagree	8 (2.5)	3 (5.0)	
Unsure	0 (0)	0 (0)	
Wearing sunscreen can cause vitamin D deficiency– no. (%)			
Agree	26 (8.1)	8 (13.0)	0.019
Disagree	264 (81.7)	53 (87.0)	
Unsure	33 (10.2)	0 (0)	

p values are calculated based on Pearson Chi-square test.

Table V: Sunscreen and skin cancer knowledge scores among different sub-group

Scores	Sunscreen knowledge scores Median (IQR)	P values
Occupation– no. (%)		
Doctors	11.0 (2.0)	0.008
Pharmacists	12.0 (3.0)	
Gender– no. (%)		
Male	11.0 (2.0)	0.011
Female	12.0 (3.0)	
Age– no. (%)		
20 till 30 years old	11.0 (3.0)	0.993
31 till 40 years old	11.0 (2.0)	
41 till 50 yeas old	12.0 (3.0)	
51 till 60 years old	13.0 §	
Ethnicity– no. (%)		
Malay	11.0 (3.0)	<0.001
Chinese	11.0 (3.0)	
Indian	9.0 (3.0)	
Others	7.5 (4.0)	
Status– no. (%)		
Single	12.0 (3.0)	0.668
Married	11.0 (2.0)	
In a relationship	11.0 (3.0)	
Fitzpatrick Type– no. (%)		
Type II & III	11.5 (4.0)	0.007
Type IV & V	11.0 (2.0)	

p values are calculated based on Pearson Chi-square test.
We applied non parametric test since normality assumptions is not assumed.
§There is only one respondent in the 51 till 60 years old category.

measures and sunscreen use. This finding was also reported by Ammar Ihsan Awadh et. al where females in their cohort are more concerned about the usage of sunscreen use and tend to use it more regularly than male respondents.[9] On the other hand, pharmacists reported a higher percentage of correct answer than doctors although this did not reach statistical significance (p=0.008).

Majority of the doctors (65.0%) and pharmacists (61.0%) were aware of the correct timing to apply sunscreen before sunlight exposure and the need to apply sunscreen even when working indoors. The correct time required to apply sunscreen before going out is 30 minutes. The majority of the respondents in our cohort were well aware with the fact that sunscreen is effective in preventing sunburn, skin cancer and skin aging. The benefits of sunscreen usage include prevention of sunburn, skin cancer, wrinkling, ageing, pigmentary disorder and photo-dermatoses.[6,11]

Majority of the respondents (56.3% doctors and 57.0% pharmacists) were unaware of that UVB is responsible for more skin cancers than UVA. SQ Wang, et al. reported that majority of the participants in New Jersey did not understand the subtle but crucial differences between UVA claim for a product and the sun protection factor (SPF) value listed on the product.[13] Compared to UVA, UVB have a shorter wavelength but higher energy which could damage the outermost skin layers and directly lead to skin cancer.[14] Sun protection factor (SPF) is a measure of effectiveness of sunscreen in preventing UVB in reaching the skin. The majority of respondents (67.2% doctors and 66.0% pharmacists) were aware of the meaning of SPF and choose a sunscreen based on its SPF value.

The majority of doctors (81.7%) and pharmacists (87%) were well aware that wearing sunscreen does not cause vitamin D deficiency. R. E. Neale et al. in the effect of sunscreen on vitamin D: a review reported that there is little evidence that sunscreen decreases 25(OH)D concentration and suggested that skin cancer prevention advice should not be neglected.[15]

STUDY LIMITATION

This is a single centre among doctors and pharmacists who had participated voluntarily. This data does not reflect the entire cohort of doctors and pharmacists working in this centre. Thus, results are not representative of all the hospital in Johor or in Malaysia as a whole.

CONCLUSION

This study demonstrated that there is a lack of knowledge on sunscreen and skin cancer among health care providers in this study. We propose a more structured continuous education programme to improve the sunscreen and skin cancer knowledge among health care providers. With adequate sun protection and skin cancer knowledge, we can disseminate the information to patients and together reduce the detrimental effects of sunlight on human skin.

ETHICAL APPROVAL

This study was approved by the Ministry of Health Research Ethics Committee (MREC) and the National Medical Research Registry with the registration number of NMRR-19-1470-48459. All respondents gave their informed consent prior to their participation in this study.

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CONFLICT OF INTEREST

The authors hereby certify that the work which was reported herein had not received any financial support from any pharmaceutical company or other commercial source and neither the authors nor any first degree relatives have any special financial interest in the subject matter discussed in our manuscript.

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ORIGINAL ARTICLE

Healthcare utilisation among elderly in Malaysia: The mediating role of health literacy

Noor'ain Mohamad Yunus, PhD[1], Noor Hazilah Abd Manaf, PhD[2], Azura Omar, PhD[2], Nurita Juhdi, PhD[2]

[1]Faculty of Business and Management, UiTM Puncak Alam Campus, [2]Kulliyyah of Economics and Management Sciences, International Islamic University Malaysia

ABSTRACT

Background: The relationship between the socio-demographic characteristics of the older persons and healthcare utilisation is well established. However, the process underlying this relationship is poorly understood particularly in the Malaysian context.

Materials and Methods: A cross-sectional study was conducted from February to April in 2016 to examine the mediating effect of health literacy on the relationship between age and healthcare utilisation. A total of 452 older persons were recruited from 14 public hospitals in Malaysia.

Results: The average age of the respondents was 66.69 years old, with an age range between 60 to 105 years. The findings reveal that the relationship between age and healthcare utilisation was mediated by health literacy.

Conclusion: The results help to improve the understanding of healthcare utilisation among the older persons in Malaysia, which is beneficial to the healthcare provider and policymakers.

KEYWORDS:
healthcare utilisation; health literacy; older persons

INTRODUCTION

The world population is ageing rapidly. In Malaysia, older persons are defined as those who are 60 years old and above, the cut-off age adopted by the United Nations (UN). The older persons account for 2.83 million (9.13 per cent) of Malaysia's total population of 31 million.[1] Malaysia will become an ageing nation in 2030, where 15 per cent of its population will consist of older persons.[2] The increasing number of older persons is contributed by lower fertility rate, longer life expectancy, and excellent public healthcare. This phenomenon brings a major impact on the social and economic health of Malaysia. Ageing is a matter of great challenge for the health sector as the ageing population will lead to the increase in demand for healthcare and social support, which may consume a large portion of fund allocation for healthcare services.[3] This issue will subsequently be a significant challenge for the Malaysian healthcare system.[4] The average outpatient visit by older persons is 5.92 visits per-year compared to only 4.1 visits per year for the rest. Moreover, older persons have more hospital admissions (157 admissions per 1000 compared to 86 admissions per 1000 for the average population), and a longer length of stay than any other age groups.[5,6] It is projected that about 40 per cent of the total healthcare expenditure is utilised by older persons, which amounts up to 9.32 billion a year.[7] This led to an increase in complexity in the health services, as well as the increment of expenditure.

The significance of healthcare utilisation among older persons leads to the realisation of the importance of understanding the nature of healthcare utilisation. As population ageing is inevitable, study on the healthcare utilisation needs to be emphasised. However, healthcare utilisation among the older persons has not been sufficiently examined and adequately understood in Malaysia to grant justified explanation for healthcare providers and policymakers to plan appropriate strategies in overcoming issues related to the utilisation of healthcare resources. Although the study of healthcare utilisation has been of interest over the past decades, most researchers have paid a substantial amount of attention towards understanding the determinants of healthcare utilisation from individual's characteristics namely predisposing, enabling and need for care. Thus, there is a lack of empirical evidence in this area of study, and there is the need to close this gap by conducting further research in this subject. Apart from that, a growing body of literature linking health literacy to healthcare utilisation is available.

Health literacy is a recent concept that refers to how individuals with limited health literacy may find it challenging to utilise health services. This concept was explicitly mentioned as an area that has to take prioritised action for World Health Organization (WHO), European Commission's Health Strategy 2008-2013, and Ministry of Health Malaysia (Country Health Plan 2011-2015). For example, the enhancement of health literacy among Malaysian has become one of the focus of National Key Result Area (NKRA) in the health sector, which include the promotion of health literacy programmes for the population.[8] Health literacy can be defined as personal, cognitive and social skills which determine the ability of individuals to gain access, to understand and use the information to promote and maintain good health.[9] It emphasises on individual skills that are necessary to obtain, process, and understand health information and services in assisting individuals to make appropriate health decisions. Given the notion that health

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Corresponding Author: Noor'ain Mohamad Yunus
Email: noorainyunus@uitm.edu.my

literacy may influence the utilisation of healthcare services this argument needs to be further validated.[10] The effects of health literacy on health status and utilisation are suggested to be indirect, which possibly happen through conditions such as knowledge of diseases.[11,12] Thus, it is expected that health literacy may demonstrate significant determinants of healthcare utilisation.

With 2030 looming closer, this phenomenon is not being given enough attention where the rapid increase is not in tandem with the resources required to cater to the care needs and services for older persons. Thus, a timely need for comprehensive research to be conducted. This study intends to fill the gaps in preceding healthcare utilisation studies. Based on the synthesis of available literature, the mediating variable of health literacy on the relationship between age and healthcare utilisation was examined.

MATERIALS AND METHODS

Design, Sample and Setting

A positivist approach was used to explore the relationship between variables. The study was primarily conducted via a survey among the older outpatients who were 60 years old and above in 14 public hospitals in Peninsular Malaysia. Upon approval from the Malaysia Research Ethics Committee (MREC) and the hospital directors, questionnaires were distributed to 500 respondents from 14 public hospitals in Johor, Negeri Sembilan, Kuala Lumpur, Selangor, Perak, Pahang, and Kelantan. One state hospital, one district hospital, one minor specialist hospital and one non-specialist hospital were randomly selected from each region. Nine out of 14 hospitals provide outpatient facilities within the hospital compound under the administration of the hospitals. However, five hospitals, specifically major specialist hospitals, did not have outpatient facilities as the patient must go to the health clinic, which is under the authority of the health state department for their medical treatment. The researcher was instructed by Clinical Research Centre (CRC) of the hospitals to conduct the research in outpatient specialist clinics such as general medicine department, general surgery department or respiratory medicine department in their hospitals. Purposive sampling was used in selecting the respondents. This process is based on the availability and agreement of respondents to participate in the survey without the need to choose the respondents systematically.

Data Collection Procedure

A few screening questions were asked to ensure that the respondents fulfilled the inclusion criteria. The following screening questions were asked before the respondents were given the questionnaires: 1) How old are you? 2) Do you live at home or in a care home/institution? Once the respondents satisfied all the above-mentioned criteria, only then the enumerators started the interview process. The whole structure of the study was explained to the respondents by providing an information leaflet with an invitation to participate in the study. They were further informed that their participation in this study is voluntary, and they can withdraw at any time. Other than that, they were also assured of the confidentiality, and that the findings will be presented anonymously. Those who agreed to participate were asked to sign a consent form and complete the questionnaire. The administered survey which took 10 to 15 minutes was carried out in the waiting area while the patients waited to be called for consultation with their doctors. A total of 500 questionnaires were distributed to the respondents, and there were only 477 questionnaires that were returned to the researcher, which yielded 95.4% of the response rate. Out of 477 responses, the researcher had to discard 25 questionnaires. As a result, this study only used 452 responses in generating the profile summary and data reduction procedure.

Development of Instrument

The development of the research instrument for this study was based on the extensive review of literature by combining the existing validated measurement. The questionnaire, which consisted of three sections measuring demographic data, health literacy, as well as healthcare utilisation, was used to collect data. The participants were requested to complete the questions relating to their demographic backgrounds, such as age, gender, ethnicity, education level, income level, and accessibility to healthcare facilities. Health Literacy Management Scale (HeLMS) developed by Jordan and colleagues was used to operationalise health literacy.[13] The HeLMS was designed to assess individuals' abilities as well as their broader social and environmental contexts to determine the overall capacity to seek, understand, and utilise health information within the healthcare settings. The study adopted five dimensions of health literacy, namely the knowledge to gain access to health information (I know where the doctor can be contacted, and I know how to get doctor's appointment), verbal communication (I ask the doctor questions to help me understand health information and I get the information I need when seeing a doctor), the need to be proactive (I change to a different doctor to get better care, and I get a second opinion about my health from a health professional) literacy skills (I read written information, e.g., leaflets given to me by a doctor, I read health information brochures found in hospitals or at a doctor's clinic), and skills to manage health (I use health information from doctor to make decisions about my health, and I follow instructions that a doctor gives me). The instrument consisted of 10 items with a five-point-Likert scale response ranging from 1 (strongly disagree) to 5 (strongly agree). The Cronbach's alpha was calculated to examine the measurement reliability with the result of Cronbach's alpha is 0.82, suggesting that the measures were highly reliable.

In measuring healthcare utilisation, the respondents were required to recall the frequency of their healthcare utilisation in the earlier three months. One open-ended question which was "In total, how many times did you receive healthcare or consultation in the last three months?" was constructed by the researcher as it was stated that an open-ended scale that collects counts is the most flexible and allows for the count data model.[14] The questionnaire was translated to the Malay language using a guideline for a cross-cultural adaptation and translation of a questionnaire.[15]

A pilot test was conducted among 30 older persons to test all the variables of the study after completing the instrument to ensure the individuals in the sample can understand the questions and capable of meeting the survey. The results and

Table I: Demographic profile of the respondents

	Frequency	Percentage	Mean	SD
Age				
60-74 years old (Younger Old)	400	89.5	66.69	6.078
75 years old and above (Older-old)	47	10.5		
Gender				
Male	210	47.0		
Female	237	53.0		
Ethnicity				
Malay	332	74.3		
Chinese	57	12.8		
Indian	58	13.0		
Education level				
No formal education	104	23.3		
Primary school	149	33.3		
Secondary school	152	34.0		
College/University	42	9.4		
Personal Income per month				
Less than RM1000	257	58.4		
RM 1001- RM2000	115	26.1		
RM 2001 and above	68	15.5		
Distance from the closest health facility				
Less than 10km	254	56.8		
11 to 20km	106	23.7		
More than 20km	87	19.5		
Healthcare Utilisation in the Last Three Month			1.96	1.41

Table II: Descriptive analysis of Health Literacy

	Mean	SD
Health Literacy	3.49	0.71
Knowledge where to access health	3.62	0.76
Application to manage health	3.38	0.79

Table III: t-Test results for association between Age group and Health Literacy

	Mean (SD)	t	p- value
60-74 years old (Younger old)	3.51 (0.72)	2.15	0.03
75 years old and above (Older-old)	3.28 (0.61)		

Table IV: Summary of mediating role of Health Literacy on the relationship between Age and Healthcare Utilisation

	Without Mediator	With Mediator	Conclusion
Age	-0.13**	-0.12*	Partial Mediator
Health Literacy		-0.14**	
R	0.13	0.19	
Adjusted R	0.02	0.04	
R square change	0.018	0.019	
F change	7.78	8.44	
Sig. F change	0.00	0.00	
Durbin Watson		1.75	

** Significant at the 0.01 level, * Significant at the 0.05 level

modification based on the pre-test and pilot test were used to generate the final version of the instrument for this study. Several concerns related to administration (time to complete the survey), organisation of the survey (the flow and order of the questions), and content of the questions (redundancy of item, confusing item, technical language, and jargon) managed to be identified during the pilot study.

RESULTS

Data were analysed using SPSS version 22.0. The hierarchical regression analysis was conducted to examine the mediating effects of health literacy on the relationship between age and healthcare utilisation. Table I presents the demographic profile of the respondents. Based on the findings, the average age of the respondents was 66.69 years old (Standard Deviation, SD 6.08). With regards to the healthcare utilisation, the results revealed that older outpatients have an average of 1.96 visits to their healthcare providers in the last three months.

The factors measured by this scale are knowledge to access health and application to manage health. The HeLMS was computed, and the findings in this study revealed that the

respondents have a high level of health literacy. All items, when collapsed to form a single variable for health literacy, have a mean score of (Mena 3.49, SD 0.71). This indicates that the respondents have a high level of health literacy. As depicted in the table, knowledge to access health domain (Mean 3.62, SD 0.76) had a higher score compared to the application to manage health (Mean 3.38, SD 0.79). Table II presents the descriptive analysis of health literacy.

An independent sample t-test was computed to compare health literacy scores for respondents aged between two groups. The result of t-test as shown in Table III indicates that there was a significant difference in scores for the older persons age from 60-74 years old (mean 3.51, SD 0.72) and more than 75 years old group (mean 3.28, SD 0.61); t (444) = 2.15, p=0.03 which indicates that younger older persons experienced a higher degree of health literacy than the older group. The magnitude of the difference in the means (mean difference 0.235, 95% confidence interval 95%CI: 0.06, 0.19) was large (eta squared = 0.10).

Finally, Hierarchical Regression analysis was carried out to look into the mediating effects of health literacy on the relationship between age and healthcare utilisation.16 The first step indicates that age is a significant predictor of healthcare utilisation (β= (-0.13), p<0.01). In Model one, the model was significant when age and healthcare utilisation were entered F [(1,436) = 7.78, p<0.01], which explained 1.8% variance in healthcare utilisation scores.

Next, after entering health literacy at step 2, the total variance explained by the model was 3.2% F [(1,435) = 8.44, p<0.01] and the introduction of health literacy explained an additional 1.4% variance in healthcare utilisation. The inclusion of health literacy as the mediator variable revealed that it was a partial mediator between age and health care utilisation (β = (-0.132), p<0.01) where the beta value of age was reduced but still significant. Therefore, it is summarised that health literacy partially mediates the relationship between age and healthcare utilisation. Table IV exhibits the result of regression analysis.

DISCUSSION

This study aimed to identify the mediating effect of health literacy on the relationship between age and healthcare utilisation. Health literacy is a significant lever to help individuals assume responsibility for their health. The findings indicated that health literacy mediated the relationship between age and healthcare utilisation. The result showed that the older persons score higher on knowledge to access health compared to the application to manage health. This signifies that the older persons know how to access healthcare services. Even though they know how to access healthcare, they are nevertheless less likely to apply the knowledge in managing their health. In relation to age, the finding reveals that younger older persons experienced a higher degree of health literacy compared to the older-old group. This finding is supported by results from previous studies on health literacy.[17-20] This may be explained by the fact that older adults had fewer opportunities for education in the past. However, this trend has improved dramatically over the years. Nowadays, younger older persons are better educated and more likely to possess different knowledge and ideas about old age than their predecessors.

In understanding the role of health literacy in healthcare utilisation, this study examined the relationship between health literacy and healthcare with those of previous studies, which found that health literacy is correlated with healthcare utilisation.[21-23] A previous study found that health literacy associates with outpatient visits and hospitalisation. The low level of health literacy increases difficulties in taking medications and interpreting medication labels and health information, which may reflect in higher hospitalisations.24-26 Besides, people with low health literacy are more likely to have more inferior health status and higher mortality rates which lead to greater use of healthcare services such as consultations, outpatient visits, and hospitalisation.[24,27-29] Moreover, individuals with low health literacy are less likely to participate in preventive services as well as poorer medication adherence.[28,30]

The mediating role of health literacy was evidenced between age and healthcare utilisation. Consistent with the published reports on the association between age and healthcare utilisation.[31-34] The result of this study confirms that age is a predictor of healthcare utilisation. Also, in accordance with the literature the present study confirms that age is associated with health literacy.[35-37] This study also finds that health literacy is associated with healthcare utilisation, which is in line with past research.[38] The mediation analysis reveals that health literacy partially mediates the relationship between age and healthcare utilisation.

CONCLUSIONS

The escalation of healthcare costs due to an ageing population is becoming a major concern. However, few research on healthcare utilisation among older persons in Malaysia. In response to this scenario, the present study has investigated the determinants of healthcare utilisation among older persons in Malaysia. Drawing on the context of health literacy, the findings of this study shed further light on the importance of psychological aspects that predicts healthcare utilisation. Moreover, this study has confirmed that health literacy is a predictor to healthcare utilisation among older persons.

This study has limitations in several aspects. The generalizability of the results focuses only on the older persons in peninsular Malaysia without considering the older persons in the states of Sabah and Sarawak. Therefore, future study should bridge the gap of this limitation. The research approach was deductive, which begins with a theory, developing hypotheses from that theory, followed by collecting and analysing the data to test the hypotheses. This approach restricted the researcher to understand what is going on, or what is perceived to be going on, in the health care setting.

The findings of this study can assist healthcare providers in planning strategies and programmes to encourage older persons to utilise healthcare services. Besides, the results will help the health planner to establish the provision of specific facilities to ensure the care and protection of older persons.

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Incidence of Retrocaecal Acute Appendicitis at the Hospital Sultanah Nora Ismail (HSNI) Batu Pahat

Nur Bazlaah Bahari, MBBS, Khairuzi Salekan, MS(Gen Surg), Fadya Nabiha Ahmad Shariffuddin, MBBS, Mohd Nadzri Misni, MRad, Nur Bazilah Bahari, BET(MedElectronics), Hirdayu Abu Bakar, MBBS, Fazlin Farhana Mohd Isam, MBBS

Department of Surgery, Hospital Sultanah Nora Ismail (HSNI) Batu Pahat, Ministry of Health Malaysia

ABSTRACT

Background: A surgical audit study among Batu Pahat population was conducted in determining the commonest position of appendix in post appendectomy.

Methodology: This is a retrospective study. A total of 204 cases of patients underwent an appendectomy admitted to the surgical ward from January 2017 until January 2018 at Hospital Sultanah Nora Ismail (HSNI) were audited retrospectively.

Results: This findings showed different figures of ascendancy in gender among patients who underwent an appendectomy with females 58.8% and males 41.2%. The perforation rate was 40.7% and delay in diagnosis was found to be 19.1%. The perforated appendix had a significantly higher incidence in males with a correlation of p-value 0.04. Retrocaecal appendix (RA) remained the commonest position for patients who underwent an appendectomy with 26.9%. RA is associated with an increased incidence of perforation (p-value 0.01).

Conclusion: The position of appendix in our patients who underwent an appendectomy is parallel to the reports available globally in that it is retrocaecal followed by retroileal as the commonest position among residence of Batu Pahat.

KEYWORDS:
Appendix position, perforated appendix, negative appendicectomy

INTRODUCTION

Batu Pahat is the second largest city after Johor Bahru in the state of Johor with a population of more than 400,000 people. The district hospital, also known as Hospital Sultanah Nora Ismail (HSNI), has a busy surgical unit with about 6,000 admissions a year with a total of 1200 emergency surgeries. About 1/6 of emergency cases are related to appendicitis.

The appendix is a worm-like structure located at the base of the caecum whose function is unknown but thought to play a role in immune reaction. Based on Bollinger et al. (2007), it may be a "safe house" or "storage tank" for commensal bacteria. However, its removal leaves no apparent functional deficit.[1] In the early 1900s, Gladstone and Wakely made the first comprehensive study of the position of an appendix in which the study was done on 3,000 anatomic dissections where they described the post-caecal and retrocolic position as the commonest in their study.[2]

Global literature states that more than 65% of the anatomical positions of the appendix is retrocaecal position, followed by paracaecal and the other positions of the appendix in different percentages. The variation of incidences has been reported regarding the positions of the appendix due to variations in ethnicity, sex, age, obesity, and seasons of the year. Based on the ambiguous idea that appendicitis is an irreversible progressive disease that may lead to complications such as perforation, consequently the removal of the appendix is the gold standard of treatment.[3-7]

Various studies were done in African countries, the Middle East, and European countries, shows different patterns of the position of the appendix. A previous study in Africa showed a wide variance in the positions of the appendix in autopsies. One of the first reports of appendix position in 125 Nigerian autopsies from West Africa reported retrocaecal and pelvic positions of 38.4% and 31.2% respectively.[8] Apart from that, 103 Zambian cadavers from East Africa studied in 1979 showed that pelvic position was ahead of retrocaecal position in which the data showed 43.6% and 20.3% respectively.[9] Nevertheless, another study in Serbia region of Balkan in which is a part of Southeast Europe, carried out in 2008 by Dejanlic et al. who evaluated 65 patients who underwent an open appendectomy reported that pelvic is the commonest position with about 57% while paracaecal as the slightest position with 3.07%.[10] A study in Iranian Cadavers, a part of Middle East countries, showed the anatomical positions were pelvic, subcaecal, retroileal, retrocaecal, ectopic, and preileal by 55.8%, 19%, 12.5%, 7%, 4.2%, and 1.5% respectively.[11]

This variance of anatomy may face a challenge during appendectomy because it may require the extension of a transverse incision or additional muscle splitting during surgery. These may cause difficultly during surgery in which prolongs the operating time and may affect the cosmetic outcome. Therefore, the perception of these variations is important for preoperative planning. To the best of our knowledge, there is no study from South East Asian countries concerning the positions of the appendix. Thus, the purpose of the study is to identify the common appendix positions in Batu Pahat population.

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Corresponding Author: Nur bazlaah Bahari
Email: bazlaah_90@yahoo.com

METHODOLOGY

This surgical audit study was carried out at the surgical ward of the HSNI from January 2017 to January 2018. The data was collected retrospectively in May 2020 from post-operative notes of the study subjects that underwent the appendectomies. Pre-operative diagnosis of an acute or perforated appendix was made by the hands of surgical Medical Officers (SMO) with, on average, 6 month very intensive experience and surgeons. The appendectomies for this study subjects was performed by SMO at HSNI.

All patients who underwent an open appendectomy from January 2017 to January 2018 in the department of general surgery HSNI were included with a total number of 204 cases of patients. A central hospital database, which tracked all appendectomy performed for the indication of acute appendicitis or perforated appendicitis, was used to identify the cohorts of patients. The data collected included demographic data, types of operation performed, pre- and post-operative diagnosis, and the positions of the appendix. Histopathological findings were included in the sample collection. The diagnostic error was calculated based on the number of appendices removed without evidence of inflammation in histology findings. The detection rate of missed diagnosis was calculated based on patients diagnosed preoperatively with acute appendicitis then changed to perforated appendix post-operatively. The relationship between retrocaecal appendix and inflamed appendicitis at intraoperative findings was compared using a chi-square on computer software which is SPSS version 22.0.

RESULTS

Out of the 204 patients underwent the appendectomy, there were 84 (41.2%) male and 120 (58.8%) female patients. Age and gender distribution of the patients are summarized in Table I. The male to female ratio was 1:1.4. The age ranged between 5-73 years. The majority of patients were between 11 - 20 years (32.8%). The mean age of presentation was 26.3 years, the standard deviation of ± 13.4 years, and the median age was 22 years. The racial distribution of patients underwent an appendectomy at HSNI comprised of Malays being 160 patients (78.9%), Chinese 14 patients (6.9%), Indians 3 patients (1.5%), and others including non-Malaysians being 27 patients (12.7%). Patients with perforated appendix was found to have a higher incidence in the Malay population i.e. 66 patients, compared to other races including Chinese 5 patients, and non-Malaysians being 12 patients.

Pre-operatively, out of 204 patients, 71.6% (146 patients) were diagnosed with acute appendicitis whereas 27.4% (56 patients) were diagnosed with a perforated appendicitis.

Post-operative diagnosis

The post-operative diagnosis was sub-categorized into Acute Appendicitis (AA) being 115 (56.4%), Perforated Appendix (PA) as 83 (40.7%), and Non-Inflamed Appendices (NIA) as 6 (2.9%). In 115 patients with AA, 6 cases were found with other pathologies such as Right Twisted Ovarian Cyst (1 case), Carcinoid tumour (2 cases), Appendicular mass (1 case), Volvulus of Meckel's Diverticulum (1 case), and Perforated Prepyloric Ulcer (1 case). In 83 patients with a PA, 45 cases were found as suppurative appendicitis. For NIA, most of the post-operative diagnosis related to gynaecological causes such as pelvic inflammatory disease (1 case), right ovarian teratoma (1 case), and white appendix found in 6 cases. A higher incidence of perforation was found in male patients with a p-value of 0.04. The detection rate of missed diagnosis in patients diagnosed preoperatively as AA then changed to PA post-operatively were 39 patients (19.1%).

Diagnosis accuracy based on histopathologic finding

Overall, a total of 13 patients had NIA removed, giving a diagnostic error rate of 6.4%. This diagnosis rate calculation is based on Lee et al. (1993), a study which was done in Hospital Kuala Lumpur.[12] The details of the pathological findings in these patients are presented in Tables II. Of the 204 patients, 13 NIA confirmed histopathologically, 6 patients were diagnosed with AA postoperatively with other pathological conditions stated in Table II, another 7 patients were diagnosed with acute appendicitis post-operatively. White appendices were mostly presented in female patients which accounted for 11 cases and the other 2 cases were male patients. Retrocaecal remained the highest incidence of negative appendectomy (5 cases).

Position appendices and its relation

The commonest position was the retro-caecal position in 55 patients (26.9%), followed by the retro-ileal position in 53 patients (26%). Other positions were less common: pelvic in 42 patients (20.6%), subcaecal in 30 patients (14.7%), preileal in 15 patients (7.4%), paracaecal in 8 patients (3.9%), and subileal in 1 patient (0.5%). The commonest anatomical location for females was retrocaecal position by 36 cases (17.6%) and for males was retroileal by 24 cases (11.8%). However, no anatomical position of the subileal was observed in males. Table 4 shows the distribution of the positions of appendicitis and ages. The commonest position in our study was retrocaecal that presented a range of age 21 - 30 years old with 24 cases (11.8%), followed by the retro-ileal position with a range of age 11 - 20 years old by 22 cases (10.8%).

As for the relation between the position of appendices and histological findings, it was observed that most of the PA were in pelvic position by 11 cases (5.4%), followed by retroileal by 9 cases (4.4%), retrocaecal by 7 cases (3.4%), subcaecal by 6 cases (2.9%), paracaecal by 3 cases (1.5%), and preileal by 2 cases (1%). Most of the RA were presented with acute appendicitis with a value of 43 cases (21.1%). As shown in Table V, there is a significant relationship between the position of appendices and histological findings of a perforated appendix (p-value 0.007 i.e. < 0.05). Using the same value of Pearson's Chi-square towards gender and race, it also shows a significant p-value < 0.05. However, there is no relationship between position and age group with a p-value of 0.219.

DISCUSSION

Acute appendicitis is the commonest acute abdominal emergency in Malaysia. At the HSNI, it accounts for 17% of the total of 1200 emergency operations in the department of General Surgery. As reported in most publications, appendicitis is most frequently seen in young people. Persons

Table I: Distribution of age and gender of patients underwent appendectomy

Age (Years)	Gender		Total Count (%)
	Female	Male	
1-10	9	6	15 (7.4%)
11-20	43	24	67 (32.8%)
21-30	37	26	63 (30.9%)
31-40	13	11	24 (11.8%)
41-50	11	10	21 (10.3%)
51-60	6	6	12 (5.9%)
61-70	1	-	1 (0.5%)
71-80	-	1	1 (0.5%)
Grand Total	120	84	204 (100.0%)

Table II: Pathological characteristics of 204 patients who underwent the appendectomy for presumptive diagnosis of acute appendicitis

Distribution of patients according to histopathologic findings	n (%)
Positive appendectomy	191 (93.6%)
Acute appendicitis	102 (50%)
Acute appendicitis with impacted faecolith	11 (5.4%)
Acute suppurative appendicitis	36 (17.6%)
Acute suppurative appendicitis with perforation	38 (18.6%)
Unusual histopathological findings	4 (2%)
Carcinoid Tumour	1
Partial atresia	1
Fibrous obliteration	1
Villous adenoma	1
Negative appendectomy	
Other pathological condition without appendicitis	13 (6.4%)
Right twisted fallopian tube cyst	4 (2%)
Meckel diverticulitis	1
Pelvic inflammatory disease	1
Right ovarian teratoma	1
Distribution of patients with negative appendectomy according to age range	
12 - 20 y	3 (1.5%)
21 - 30 y	7 (3.4%)
31 - 40 y	3 (1.5%)

Table III: Results of preoperative clinical findings of the perforated appendix with HPE confirmed and sensitivity and specificity for the diagnosis of the perforated appendix

RESULT	Perforated appendix (HPE confirmed)	Non-Perforated appendix (HPE confirmed)
Pre-operative clinical diagnosis		
Perforated appendix	24	32
Non-Perforated appendix	14	134

* Sensitivity: 24/38 (63.2%), Specificity: 134/166 (80.7%), Positive predictive value: 24/56 (43%), Negative predictive value: 134/148 (90.5%)

Table IV: Association between positions of appendix and age

Age (Years)	Position							Total Count of Subject
	Paracaecal	Pelvic	Preileal	Retrocaecal	Retroileal	Subcaecal	Subileal	
1-10	1	3	-	6	3	2	-	15
11-20	2	16	5	11	22	11	-	67
21-30	2	11	4	24	16	6	-	63
31-40	2	5	-	9	4	3	1	24
41-50	1	3	2	3	6	6	-	21
51-60	-	3	4	1	2	2	-	12
61-70	-	-	-	1	-	-	-	1
71-80	-	1	-	-	-	-	-	1
Grand Total	**8**	**42**	**15**	**55**	**53**	**30**	**1**	**204**

Table V: Distribution of the cases based on the position of the appendix

Histological findings	Position							Total Count of Subject
	Paracaecal	Pelvic	Preileal	Retrocaecal	Retroileal	Subcaecal	Subileal	
Acute Appendicitis	5	28	13	43	41	22	1	117
Perforated Appendix	3	11	2	7	9	6	-	74
Non-Inflammed Appendicitis	0	3	0	5	3	2	-	13
Grand Total	8	42	15	55	53	30	1	204

of any age may be affected, with the highest incidence occurring during the second and third decades of life. In our study, the mean age of patients was 26.3 yrs. In this study, appendicitis occurred more frequently in females than in males, with a female-to-male ratio of 1.4:1 (58.8% females and 41.2% males), peaked in the 11-20-year age group (n:67, 32.8%). Unlike other studies, our study showed a difference in terms of gender dominance. Primatesta et al. (1994) showed a similarity with our findings concerning the greater number in female cases.[13]

A total of 104 cases (51%) out of the 204 total cases for pre-operative diagnosis matched with the post-operative for acute appendicitis and perforated appendix as 44 cases (21.6%). In contrast, 39 perforations were not diagnosed until after the operation, giving a detection rate of only 19.1%. This study showed that the sensitivity and specificity were 63.2% and 80.7% respectively. Based on a study done in Turkey by Cüneyt Kırkıl et al. (2013) and Konan et al. (2011), sensitivity and specificity values should be higher than 80%.[14,15] We calculated the sensitivity and specificity value based on histologically proved cases shown in Table III. The results showed that sensitivity was lower than 80% and thus, it does not have enough sensitivity. The results showed that the specificities of acute appendicitis were 80.7%. In addition, the results showed that if the patients were not diagnosed with perforated appendix, the perforated appendices will be negative in a larger number of patients. The positive predictive value was 42.9% whereas the negative predictive value was 90.5%.

As for our study, emergency appendectomy with normal appendix was more common in females and the average age of 26-year-old, as 11 (5.4%) out of 13 (6.4%) patients in this study were young females, similar to the findings of Primatesta and Moeed Iqbal et al. (1994 and 2000).[13,16] As reported in most studies, females contribute to most of the negative appendectomies due to the female anatomical and physiological differences that result in many differentials diagnosing of acute abdomen.[17,18] In our opinion, this group of young female patients of whom the diagnosis of acute appendicitis was not clear, should be admitted, monitored by serial examination, imaging, and diagnostic laparoscopy if available. This approach will lead to a decline in negative appendectomies. Zeilke et al. (1998)[19] has expressed similar views. Commonly encountered pathologies include ovarian torsion, haemorrhagic ovarian cyst, pelvic inflammatory disease, and ectopic pregnancy.

The groups that have difficulties in the diagnosis of acute appendicitis are children, young females, elderly of both genders, and pregnant ladies.[20] Apart from clinical assessments, imaging such as ultrasound or CT scan may be a benefit for these groups to reduce the rate of negative appendectomy and unnecessary exposure of surgical complications in atypical presentation for elderly in which appendicular mass or malignancy is suspected. However, in Malaysia, especially in the district hospitals, imaging is not recommended as a routine investigation to diagnose acute appendicitis where the clinical assessment is suggestive of acute appendicitis. If a patient is clinically diagnosed with acute appendicitis, they do not need to proceed with further investigations. Patients with acute appendicitis are still being managed without imaging with acceptable rates of negative appendicectomies and perforations.[21] However, based on Seetahal et al. and Marudanayagam et al. (2011 and 2006), the reported rates of histology-proven negative cases following appendectomy have ranged between 9.2% and 35%. Besides, the rates of negative cases are particularly high for women in the childbearing years.[22,23] The rate of negative appendectomy found in this current study (6.4%) is low compared to that in the published reports. This eventually shows our good clinical skills to diagnose an acute abdomen condition is proven by our low negative appendectomy rate. We hope in the future, careful decisions with the help of advanced technology should be made especially in patients where difficulties occur in diagnosing in order to create a harmonious health care environment.

In our study, the commonest type of appendix position was the retro-caecal position which was found in 55 patients (26.9%), followed by a retro-ileal position, in 53 patients (26%) and the lowest was subileal position in 0.5% of the total 204 cases. This finding was similar to the classic work of Wakeley (1933), which reported that the retrocaecal is the commonest position. Various studies taken from outside of Malaysia including the African countries, Middle East, European countries, and Hong Kong showed a different pattern of the position of the appendix. A study that is similar to our study is a study from West Africa done by Varshney et al. (1996) contrasting with other studies wherein the majority of appendices were located anteriorly or in pelvic positions. A study in Iranian Cadavers, apart from Middle East countries by Tofighi et al. (2013) stated that these differences may be due to many factors which include genetics, race, or ethnicity and lifestyle factors like nutritional regimens in determining the position of the appendix.[24] Nevertheless, retrocaecal appendices remain the most common position in females (n:36, 17.65%) and in males, while the commonest position was retro-ileal (n:24, 11.76%). As stated above, appendicitis is usually presented in the 21-30-year age group whereby the commonest appendix position was retrocaecal position (n:24, 11.76%), followed by retro-ileal position (n:22, 10.78%) at 11 - 20 years age group. This is shown in Table IV based on the association between the position of appendix and age among the studied people.

In the patients presented with acute appendicitis, most of the intraoperative findings were documented as retrocaecal as a

position of appendices (n:43, 21.08%). However, in the patients presented with a perforated appendicitis, the pelvic position remained the most position documented in the intraoperative notes. Clinically, in retrocaecal appendicitis, it is difficult to elicit tenderness on palpation in the right iliac region and even deep pressure may fail to elicit tenderness because the caecum, distended with gas, prevents the pressure exerted by the palpating hand from reaching the inflamed appendix, so it has been termed "silent appendicitis".[25] Retrocecal appendix has also been postulated to have high chances of gangrenous complications because their blood supply is more prone to kinking and more liable to inflammation when fixed retrocaecally.[26]

There are several limitations to this study. Our retrospective analysis of the suspected appendicitis who underwent appendectomy did not include the history and clinical examination to value the diagnosis that was made. This particular analysis can, therefore, not be compared to the published reports, and we are limited to the establishment of the diagnosis. To overcome this, a prospective rather than retrospective study, following up patients with suspected appendicitis who appendectomy may be required. For the purpose of statistical analysis, we classified each diagnosis into an acute or perforated group by evaluating the context and the wording of the report. Another limitation is the time-lapse from the diagnosis to the operation. However, it was rather disappointing to find that perforated appendix was not operated on earlier when compared to non-perforated cases. Delayed surgery could be due to the long operation theatre list. Limited operation time in theatres occur in district hospitals as surgeons are sharing one slot with other three departments including orthopaedics, obstetrics, and gynaecology. Furthermore, the diagnosis and surgeries were carried out by medical officers and there might be some errors in documentation of the position and initial diagnosis. Thus, we hope that this study will be as our future reference undertakings that would ameliorate the general surgery services in HSNI.

The initial approach of this audit focusing on the position of appendices as to the best of our knowledge, in Malaysia, we hardly found a study of position appendices in the Malaysian population. However, this audit was a single-centred and did not include the general population in Malaysia. We hope that this study will be a fore-runner for other studies.

CONCLUSION

The position of appendices in our study of 204 patients who underwent the appendectomy reflects the global reports that shows retrocaecal, retroileal followed by pelvic, as the commonest position among Batu Pahat population. The diagnosis of acute appendicitis was clinical. In equivocal cases, diagnostic error rate could be reduced if repeated examinations were performed and added imaging might be beneficial until more definitive signs were obtained before proceeding to do the operation. The audit began with an aim and this study also revealed some demographic features of acute appendicitis in our locality as well as highlighted the factors that could be useful in auditing clinical judgments. We agree that there is a need to improve the collection of clinical data, which will consequently improve the quality of care and management of the operated patients.

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Patient and procedure selection for bariatric and metabolic surgery in Malaysia- The Malaysian Consensus

Abdul Gafoor Abdul Mubarak, M. Med. Surgery (USM)[1], Reynu Rajan, MS. General Surgery (UKM)[2], Kirubakaran Malapan, M. Med. Surgery (USM)[3], Vimal Kumar Vasudeavan, MS. General Surgery (UKM)[3], Nik Ritza Kosai Nik Mahmood, FRCS[2], Tikfu Gee, MS. Surgery (Malaya)[4], Haron Ahmad, MS. General Surgery (UKM)[5]

[1]Island Hospital Penang , Penang, [2]Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, [3]Gleneagles Hospital, Penang, [4]Sunway Medical Centre, Selangor, [5]KPJ Damansara Specialist Hospital. Selangor

ABSTRACT

The rise in obesity has fuelled the current debate of its classification as a disease. Contrary to just being a medical condition or a risk factor for other diseases, obesity is a complex disease with multifaceted aetiology as well as its own disabling capacities, pathophysiology, and comorbidities. The problem of obesity in Malaysia is serious and calls for active intervention by all stakeholders ranging from government agencies to insurers and healthcare providers. To aid efforts to curb obesity, this consensus statement for bariatric surgery provides a basis for inclusion and exclusion criteria as well as the types of procedures accepted as the norm in Malaysia. This consensus statement was initiated by the Society of Endoscopic and Laparoscopic Surgeons of Malaysia and was collaborated with representatives from the Ministry of Health Malaysia.

KEYWORDS:
Bariatric surgery, bariatric policy, obesity, malaysia weight loss

INTRODUCTION

Obesity is fast becoming a global pandemic with over one million affected individuals.[1] Malaysia is not an exception. Approximately 45.3 percent of Malaysians have been identified as either overweight or obese.[1] The fast food culture, the ubiquitous popularity of fast food, increasingly sedentary lifestyles, and the mechanisation of transportation modalities are among the many factors that have led to this health dilemma.[2] The burgeoning growth of the middle-class has further resulted in higher income that feeds such sedentary lifestyles and access to fatty fast food.[2]

The growing prevalence of obesity in Malaysia goes hand in hand with the rise in Type 2 Diabetes Mellitus (T2DM), which was found to affect 3.5 million (17.5%) individuals in 2015.[1] Malaysians are from three predominant races, namely Malays, Chinese, and Indians and differences in BMI and medical conditions are observed. For instance, the occurrence of obesity and T2DM has been reported to be higher in Malaysians of Indian women compared with men and Malaysians of other ethnicity.[3] Specifically, the Indians have a higher preponderance of central obesity; the Malays have a genetic tendency for both diabetes and obesity; whilst the Chinese have a lower limit for obesity.[4] Based on this, a lower BMI standard is recommended for the Malaysian population.[4]

Worldwide obesity as an obvious concern and a major public health challenge and the associated co-morbidities can dampen the productivity of the working class and threaten future economic development in addition to compounding healthcare costs.[5] In 2010 alone, global expenditure on diabetes was estimated at approximately USD$376 billion, forcing member states of the World Health Organisation (WHO) to take immediate notice and introduce plans to combat the rise of obesity and diabetes by 2025.[6]

Malaysia has a dual healthcare system, i.e. public and private. The public system, which is heavily subsidised the Malaysian government, consists of hospitals under the Ministry of Health, Malaysia (MOH), the Ministry of Higher Education, and the Ministry of Defence. The private sector, comprises hospitals under private or equity ownership either by a single conglomerate or a group of conglomerates. This dual system makes it challenging to implement standards for adoption across the board. Another unique aspect of Malaysia's healthcare is its dependence on insured clients rather than out-of-pocket payees in the private sector.[5]

The members of the Society of Endoscopic and Laparoscopic Surgeons of Malaysia (SESLMA) and the Malaysian Bariatric Society (MyMBS) consist of approximately 62 surgeons who perform open and laparoscopic surgery. Currently, the stance of Malaysian insurance players is that bariatric surgery is a cosmetic procedure. This paper aims to rebut this stance by explaining the importance of bariatric surgery as a necessary metabolic procedure with benefits far beyond cosmetic gains. Advocating that such surgery should be covered by the existing and new policies, this consensus statement advocates the cooperation of the two aforementioned societies to produce a guideline that hopes to serve both the public and private sectors.

Trends in bariatric/metabolic surgery have changed considerably in the last decade, leading to an influx of new findings. While the Malaysian guidelines acknowledges these new developments and have adopted from them, there remains a need to review the newer findings and propose an updated country-specific consensus for bariatric/metabolic

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Corresponding Author: Abdul Gafoor Abdul Mubarak
Email: gafoormubarak@yahoo.com

surgery. Therefore, the consensus statement recommended in this paper are drawn from previously published guidelines, such as those by National Institute of Health (NIH), Japanese Society of Surgery for Obesity and Metabolic Disorders (JSSO), Asia Pacific Metabolic and Bariatric Surgery Society (APMBSS), Obesity Surgical Society of Australia and New Zealand (OSSANZ), Asian Consensus Meeting on Metabolic Surgery (ACMOMS), Asian Diabetic Surgery Summit (ADSS), Diabetes Surgery Summit (DSS), and the IFSO-APC. The aim of this document is to enlist the guidelines developed by a consensus committee comprising bariatric surgeons, endocrinologists, dieticians, pharmacists, intensivists and anaesthetists and is essentially a guide for surgeons and centres that perform Bariatric Surgery as one of their services. Though the initial focus was to provide a guide for Ministry of Health facilities exclusively, the scope was then expanded to encompass the entire health framework of Malaysia.

MATERIALS AND METHODS

The consensus statement were drafted in several meetings held at various points of time beginning in 2014. The meeting committee was initially termed the Bariatric Metabolic Working Committee and eventually evolved to become the Bariatric and Metabolic Framework Committee. The role of this committee was to draft the framework of this policy so that a standard guideline can be adopted by its members.

Meetings were normally conducted as smaller groups with specific assignments. The assignments included discussing the following:

1. Reviewing existing policies and tailoring them for the Malaysian context;
2. Including training protocols and training centres; and
3. Discussing goals and targets to be achieved through this policy.

At the end of the meetings, a drafting committee was elected to write the agreed consensus and subsequently present the report to the MOHM for approval. The drafting committee completed a final meeting in Putrajaya, the administrative capital of Malaysia, on 14th May 2019. To further validate the consensus, the committee also invited several key international surgeons in the field of bariatric and metabolic surgery. The members of the committee were assigned roles and were accepted as voting members. A vote was held to adopt or reject the said policy. The consensus process was done by circulating the document to all members of the committee for recommendations and subsequent approval or corrections. The elected members then act as representatives in their respective fields. These guidelines were finalized after complete agreement from all voting members.

RESULTS

The consensus statements adopted from the meetings are as follows.

Part 1. Indications for Bariatric Surgery

The following patients are indicated for bariatric surgery:

1) Morbid obesity without any comorbidities:

i. Bariatric surgery should be considered for the treatment of obesity in suitable patients with BMI ≥ 37.5 kg/m^2 who fulfil the selection criteria.

2) Morbid obesity with metabolic syndrome:

i. The surgical approach may be considered as a non-primary alternative to treat obesity in suitable patients with BMI ≥ 32.5kg/m2 with metabolic syndrome or cardiovascular risk following inadequate weight loss by virtue of medical therapy and lifestyle modifications.

3) Low BMI with or without comorbidities:

i. Any surgery for metabolic syndrome or obesity related comorbidity in patients with a BMI ≤ 32.5kg/m2 should not be a routine clinical practice and should be strictly performed only under clinical study protocol with informed consent from the patient and prior approval from an ethics committee.

4) Age restriction:

i. Bariatric surgery is generally recommended for patients between the ages of 18 and 65 years.

5) Special circumstances:

i. Upon consultation with a physician, paediatrician, orthopaedic surgeon, clinical psychologist, or a surgeon, bariatric surgery may be performed in morbidly obese adolescent patients provided they have attained the physiological bone maturity consistent with Tanner stage four.

Part 2. Selection Criteria for Bariatric Surgery

Patients who fulfil the indications in Part 1 should satisfy the criteria below:

1) Weight loss history:

i. Previous nonsurgical attempts at weight reduction for at least six months.

2) Patient commitment:
Patients are required to comply with the prescribed programme1, which includes:

i. Follow-up visits with healthcare teams, voluntary participation in support groups, and other recommendations made by healthcare teams.
ii. Recommended medical management, including the use of dietary supplements and exercise routine.
iii. Compliance with instructions regarding any recommended procedures or tests.
iv. Smoking cessation for a minimum of four weeks prior to surgery.

Part 3. Types of Bariatric Procedures

The committee also deliberated on several established studies comparing the effectiveness of various treatments, in particular sleeve gastrectomy and the gastric band7,8. The consensus recommends the four procedures listed below, in line with recommendations from international guidelines for bariatric surgery:

Restrictive

1) Gastric band
2) Sleeve gastrectomy (Refer to Figure 1)

Malabsorption

3) Biliopancreatic diversion / Duodenal switch (BPD/DS)
4) Roux-en-Y gastric bypass (Refer to Figure 2)

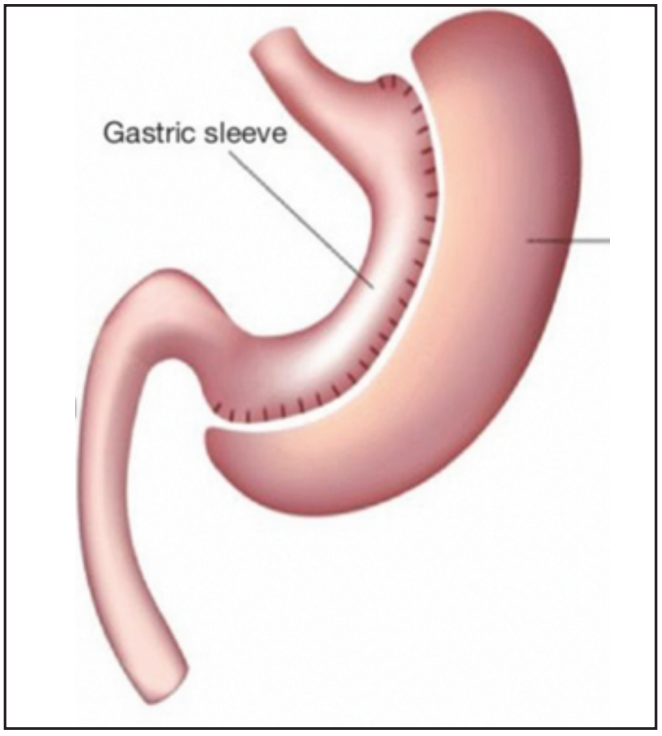

Fig. 1: Sleeve Gastrectomy.

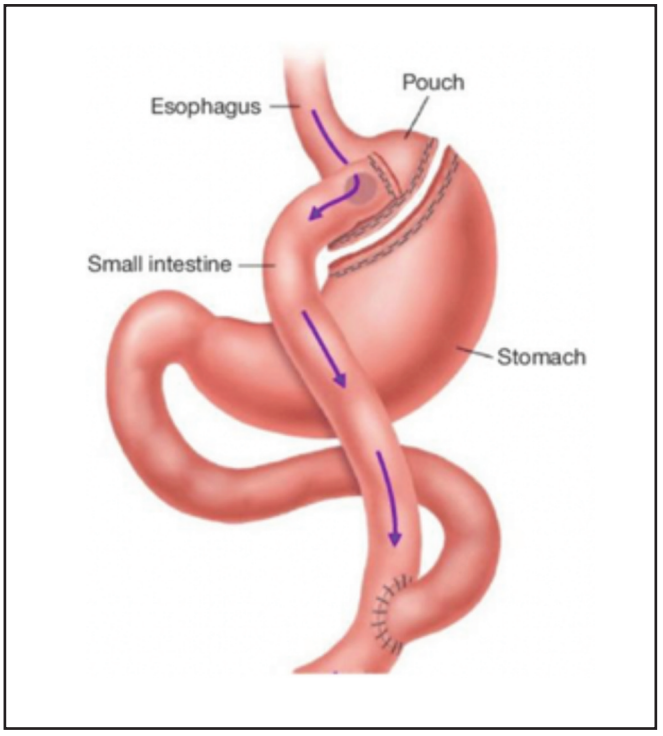

Fig. 2: Roux-en- Y Gastric Bypass (RYGB).

Although novel bariatric surgical procedures (outside the scope of the four mentioned) have shown promising results for Asians, such procedures should only be carried out by surgeons with experience. Examples of these new procedures include the One Anastomoses Gastric Bypass (OAGB) and the Single Anastomoses Duodenal Ileal Bypass with Sleeve Gastrectomy (SADI-S).[9]

Part 4. Contraindications to Bariatric Surgery

It was agreed upon that the following patients are contraindicated for this procedure:

1. Pregnant patients.
2. Patients who are unable to comply to continuous medical follow-ups as required.
3. Patients with non-stabilised psychotic disorders, severe depression, or personality and eating disorders, unless specifically advised by a psychiatrist/psychologist.
4. Patients with reversible endocrine disorders that can cause obesity.
5. Patients with alcohol abuse and/or drug dependencies.
6. Patients with diseases threatening their life in the short term (ASA-4).
7. Patients who are unable to care for themselves and have no long-term family or social support to provide such care.

Part 5. Audit and Governance

All bariatric surgery procedures must be documented using a standard notification document. All forms of patient data should be kept by the bariatric nurse or case manager and dispatched for audit on a yearly basis upon request. Mortality from bariatric surgery should be reported with adequately filled and submitted Post Operative Mortality Report forms.

DISCUSSION AND CONCLUSION

Bariatric and metabolic surgery continues to gain acceptance around to world due to its popularity of the technique and outcome. In Malaysia, the introduction of bariatric and metabolic surgery remains at a moderate level with several hospitals offering surgical services and establishing dedicated weight loss units.[3] Existing information suggests that the sleeve gastrectomy remains the popular procedure of choice in Malaysia. In a study conducted at the Taiping Hospital, Malaysia and published in 2019, the sleeve gastrectomy was performed on more than half of the patients while the other patients underwent bypasses. A survey among surgeons also showed the same outcome reflecting their preference for the sleeve gastrectomy.[3]

Facts on obesity stipulates that Malaysia has the highest number of overweight and obese patients among Asians at 64 percent of males and 65 percent of females.[4] Reports also reveal that the prevalence of diabetes among adults aged 18 and above increased from 11.6 percent to 17.5 percent over the nine-year period from 2006 to 2015.[2] The presence of hypertension remains high as well at around 30 percent.[2] Notably, more than half of cases of diabetes or hypertension are undiagnosed.[10] Throughout the world, newer and more amended policies have been developed to combat diabetes, which include algorithms for the treatment of diabetes with bariatric surgery.[10] The worrying figures mentioned above warrant a review of the current strategies, particularly in relation to combating this problem in Malaysia. Better policies are required not just to guide practising surgeons and physicians on referral policies but also to streamline and standardise the existing practices of bariatric and metabolic surgery in Malaysia.

In Malaysia, two issues need to be addressed pertaining the progression of bariatric and metabolic surgery. First, there is a lack of policies and training programmes for surgeons and this may be resolved through this consensus statement, as well as through efficient top-down direction from the MOHM. The second issue is the lack of support and coverage from insurance providers for this procedure, and consequently cost needs to be borne by patients to undergo the procedure in public facilities. Though the operative fees and hospital administrative charges are minimal, patients still have to pay for consumables such as staplers, energy devices, and trocars. In Malaysia, patients can fund their bariatric and metabolic surgery via withdrawals from their Employers Provident Fund, reimbursement from the Federal Government (JPA), or a soft loan from a local financial P2P portal with low interest and flexible payment schemes.[11]

The existing evidence points towards a dire need for a standardised policy to allow all stakeholders to be on the same page. The field of bariatric science evolves continuously and as such it is essential that this change is effectively embraced to offer the best service to patients. Hence, the rapid changes in this field demands that policy be revisited every three years to adapt to latest developments. It is also hoped that better research goes into the phenotyping and genotyping of the Malaysian population to determine the cause of growing obesity rates. While this consensus paper serves as a guide for surgeons undertaking bariatric surgery, it should be noted that it does not constitute a strict guideline that restricts further changes in the future.

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Development of the rural Palliative Care Services by the Kuala Lipis District Hospital

Carol Lai Cheng Kim, MMED (UKM)[1], Tay Khek Tjian, MRCP(UK)[1], Rafidah Abdullah, MRCP(UK)[2]

[1]Department of Internal Medicine (Palliative Care Subspecialty), Hospital Kuala Lipis, Pahang, [2]Department of Medicine Hospital Putrajaya

SUMMARY

In recognising the palliative care (PC) needs globally and in Malaysia, services were developed to serve the rural area of Kuala Lipis, Pahang. This communication describes the initial a Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis, stages of development towards achieving a successful implementation. PC services were led by Kuala Lipis district hospital include inpatient referrals, outpatient and community care through home visits. These services involve multi-disciplinary team inclusive of representatives from health clinics and allied health. Referrals and opioid usage have demonstrated an increasing trend since its implementation in October 2018. Implementation of rural PC services is feasible; however, long-term sustainability needs to addressed.

KEYWORDS:
Palliative care, community, opioid usage, Kuala Lipis

INTRODUCTION

The definition of Palliative Care (PC) is comprehensively defined by the World Health Organization (WHO) 2002.[1] Worldwide, 25.5 million deaths were reported to experience serious health related issues in 2015; 81% from residents from low and middle-income countries.[2] This number is expected to increase to 48 million by the year 2060; with ageing populations and the rise of non-communicable and other chronic diseases worldwide.[3] WHO estimates that worldwide only 14% of people who needs PC are currently receiving it.[4] Amongst the 234 countries, 42% of these countries do not have access to PC and 32% only had access to isolated services.[5]

In Malaysia, the estimated of patients requiring PC was more than 56,000 annually; of which only 8.3% of the needs were met.[6] This number is projected to increase to more than 240,000 by the year 2030; an increase by 240% when compared to 2014.[7] It has been suggested that PC should be a universal human right of all humans but yet these services are not widely available.[8,9] The WHO public health initiatives described four important aspects in establishing PC and service sustainability - policy, drug availability, education and implementation.[10] In Malaysia, the first three important aspects has been addressed at the level of PC and recognised as amongst the forefront in Southeast Asia region.[5] National policy and national strategic plans have been incorporated into the PC services. Financial support has been allocated annually for on-going training and education. Opioids are available to be prescribed by physicians. The main challenges lie is the fourth aspect - in the on-the-ground implementations especially in the rural and district regions.

In recognising the need to deliver PC, a dedicated team of healthcare professional and volunteers have initiated services to the community of a rural area. Prior to its development, there was no access to PC or hospice services for patients within the rural district of Kuala Lipis; with the nearest availability is in Kuala Lumpur, the capital city (approximately distance of 60 km). Kuala Lipis is located at the north east region of the state of Pahang, in the middle of the Peninsular Malaysia and has a total of 10 *Mukims* (sub-districts), covers an area of 5,168 km^2 which is 14.6% of the Pahang state area with a population of 106,814. The main industries in Kuala Lipis are agriculture and gold mining. The healthcare facilities consist of 1 district hospital with minor specialists as the referral centre; and eight *Klinik Kesihatan* (Health Centre) and 23 *Klinik Desa* (Rural Community Clinics). The hospital has basic clinical specialties (without sub-specialities). The primary care services are led by a District Health Officer and assisted by a team of doctors led by one family medicine specialist. Rural clinics are run by staff nurses and community nurses. The service was supported by PC unit from the Hospital Selayang, in Selangor (near Kuala Lumpur).

The main objective of initiating PC in a district hospital was to provide basic PC to patients with incurable diseases and terminally ill in the community. This initiative adopted the PC approach, one of the three different options outlined by Worldwide Hospice and Palliative Care Alliance.[11] PC approach is "adopted by all the healthcare professionals, provided they are educated and skilled through appropriate training".[11] This study describes the development of PC services in the community led by general internal medicine physicians by a rural district hospital.

Prior to implementation, a Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis of the pre-existing services was performed as outlined in table I.

As PC awareness grew among the healthcare workers and community, the number of patients referred increased. Services commenced with in-patients; which was expanded to out-patients and community home visits.

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Corresponding Author: Carol Lai Cheng Kim
Email: carolck138@gmail.com

Table I: Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis of the pre-existing services

Strengths	Weakness
Support from the Hospital Administrative team and other healthcare personnel Identified local champions and volunteers Opportunity Many patients with chronic medical illnesses with frequent admissions, poorly controlled symptoms for exacerbation of their medical illnesses.	In a district hospital, resources were limited - staff and limited - staff and limited PC based drugs Limited availability of opioids Lack of manpower and PC trained staff No dedicated staff; hence multi-tasking Lack of knowledge amongst patients and healthcare workers Lackadaisical attitude and skepticisms from colleagues Stigmatization of the use of opioids. New prescribed medications are not available out of office hours. Threats Lack of sustainability Burnout Difficulties in transportation (logistics)

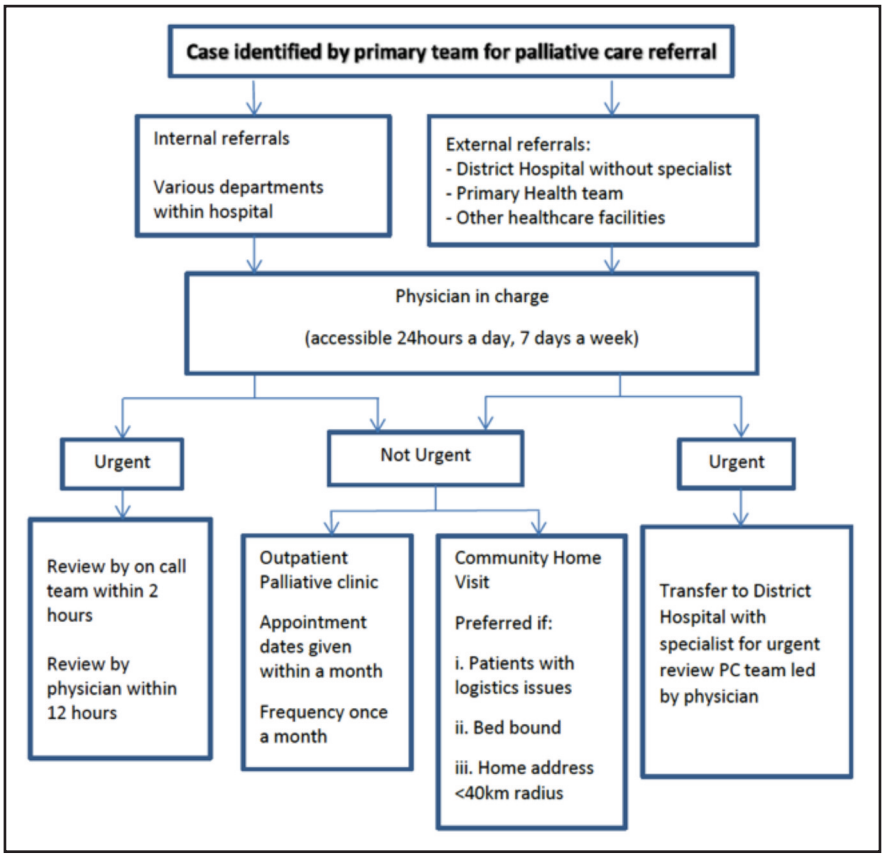

Fig. 1: Referral flowchart for PC in Hospital Kuala Lipis.

Structure of PC team

PC team consisted of members from different units to facilitate a more holistic approach at the hospital and primary care level. A flowchart of the workflow is shown in Figure 1. Referrals are directed to physicians with special interest in PC (Department of Internal Medicine), who were accessible 24 hours a day, 7 days a week.

Inpatient services

Upon referral, the PC team will review health problems of these patients in the respective wards and draw up a holistic management plan. In-patient care are given by physicians, supported by a team of allied health staff made up of nurses, pharmacists, occupational therapists, physiotherapists and dietitians. Patients who are terminally are seen within 24 hours to provide end of life care. Subsequent care plans were given as appropriate outpatient appointments or home visit.

Outpatient services

Outpatient PC Clinic is scheduled monthly at a dedicated clinic facility within the hospital. A dedicated staff nurse is responsible for record keeping and follows up on the appointments of patients. Each clinic is attended by a physician, staff nurse, dedicated pharmacist, and a physiotherapist. Each clinic review will include review of symptoms, medications and defining goals of care. Patients and caretakers are referred to the hospital counsellor for counselling if required. A pharmacist reviews medication for compliance of patients, efficacy and adverse effects. Physiotherapist plans appropriate exercise regimes, with concurrent treatment delivered in order to reduce the burden of multiple appointments. The other PC teams will be present upon availability.

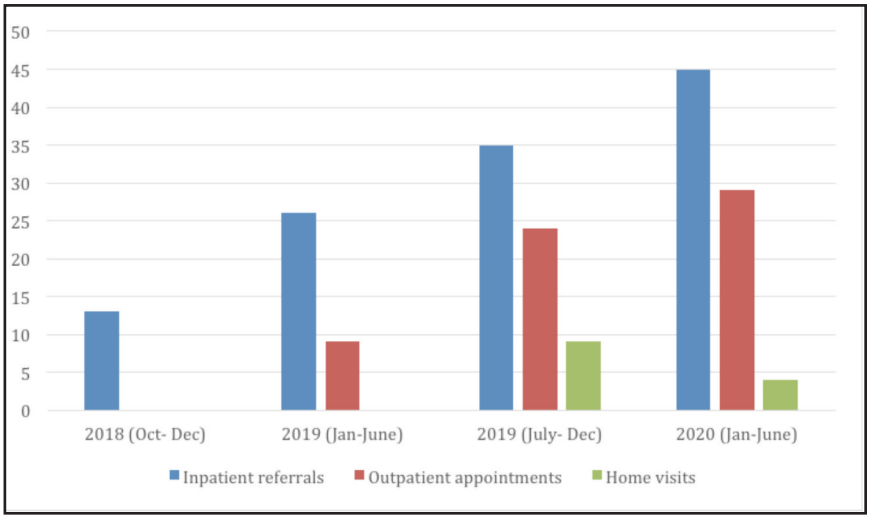

Fig. 2: Statistics of PC services.

Community PC

Community home is done within working hours and the coverage area is within a 40km radius from Kuala Lipis. For terminally ill patients, home visits are arranged 1 or 2 days after their discharge from the hospital. Community PC team consists of a physician, medical officer, and pharmacist. Occupational therapist and volunteer nurses will join the visit based on availability. During each visit, the doctor will review of condition and symptoms of patients, offer counselling and support to the patients and family members. The pharmacist will carry a medication box containing basic PC medications; with prescription and dispensation of medication done during the home visit to reduce burden of caretakers visiting healthcare facility of for prescriptions. The occupational therapists would assess the Activity of Daily Living index of patients and home accessibility. Occasionally, primary care team will join the home visit as their locality would enable more frequent follow ups. Continuation of care is ensured via networking with primary care team.

Opioid usage

Although opioids are accessible in Kuala Lipis hospital, their use was very limited and generally not for PC services. Since the introduction of PC services in 2018, opioid usage in Hospital Kuala Lipis has increased significantly; 2018: 9880ml/year, 2019: 11,010ml/year, and 2020: 30,658ml/year. This increment of usage of morphine reflects the increased awareness, knowledge, confidence in prescribing opioids and acceptance of usage of opioids by patients and their family members.

To sustain delivery of PC services in the community, volunteers, community appointed champions, and leaders will need to be empowered. An integrative network between the community and the healthcare systems should be planned; drawing the success in Kerala, India.[12]

CONCLUSION

Palliative care services can be implemented in rural areas; led by internal medicine physicians in a district hospital. This will increase access for patients and families at the end of life and this scheme should be considered nationwide.

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CASE SERIES

Outcomes of Subliminal Transscleral Cyclophotocoagulation treatment in glaucoma

Jun Yong Chow, MD[1,2], Wan Norliza Wan Muda, M.MED[2], Mae-Lynn Catherine Bastion, MS[1]

[1]Department of Ophthalmology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, [2]Department of Ophthalmology, Hospital Tengku Ampuan Afzan, Kuantan, Jalan Tanah Putih, 25100 Kuantan, Pahang, Malaysia

SUMMARY

Background: Subliminal transscleral cyclophotocoagulation (SL-TSCPC) is a new alternative therapy to reduce intraocular pressure (IOP) safely and effectively. However, there are few studies regarding SL-TSCPC by Supra 810 laser machine and limited data regarding its effectiveness in moderate severity glaucoma that still has good preservation of vision. This study was conducted to evaluate the outcome of SL-TSPCPC in various types of glaucoma including patients with good vision.

Methods: A retrospective, non-comparative, analytical case series of all patients who received SL-TSCPC treatment from October 2018 to April 2019 at Hospital Tengku Ampuan Afzan, Pahang, Malaysia. Data was collected during the second week, sixth week, third month and sixth month follow-up. The primary outcome measure gave success rate at six months post-treatment. Secondary measures were changes in visual acuity, mean IOP reduction, mean number of IOP lowering medications reduced and ocular side effects noted during follow-up.

Results: The success rate was 43.8% (seven eyes out of sixteen eyes) at six months post-treatment. The mean IOP reduced from 43.0mmHg±14.8mmHg pre-treatment to 24.7mmHg±12.0mmHg at two weeks post treatment with 42.6% reduction. Subsequently, mean IOP at sixth week, third month and sixth month were 33.8mmHg±16.9mmHg, 35.2mmHg±14.9mmHg, and 29.0mmHg±16.2mmHg respectively. Vision maintained in 13 patients, two patients had improvement in vision however, five patients had deterioration in vision. No serious ocular side effects were noted.

Conclusion: Subliminal TSCPC is a safe and alternative method of lowering IOP in moderate to advanced glaucoma over 6 months duration of follow-up. As it has good safety profile and repeatability, it is a good treatment option for patients with uncontrolled glaucoma.

KEYWORDS:
Glaucoma, intraocular pressure, subliminal diode laser, transscleral cyclophotocoagulation

INTRODUCTION

Glaucoma is a progressive optic nerve disease characterized by damage of optic disc with associated visual field defects.[1] It is the most common cause of irreversible blindness in the world.[2] Medications, lasers, or surgery are options to treat glaucoma by lowering the intraocular pressure (IOP).[3] Conventional transscleral cyclophotocoagulation (TSCPC) is commonly used to reduce IOP in painful blind eyes or eyes with poor visual potential, failed multiple filtering surgeries, and poor surgical candidates. The mechanism of TSCPC is by destruction of the ciliary body by continuous diode laser delivery, thereby decreasing aqueous production with subsequent IOP reduction. However, complications associated with TSCPC include pain, persistent inflammation, vision loss, hypotony, phthisis bulbi, scleral thinning, macular oedema, intraocular haemorrhage, retinal detachment, aqueous misdirection syndrome and rarely, sympathetic ophthalmia. Occurrence of severe complications is thought to be due to collateral damage to surrounding tissues.[4]

Micropulse TSCPC (MP-TSCPC) or subliminal TSCPC (SL-TSCPC) offers a variety of traditional TSCPC to treat glaucoma. Subliminal TSCPC has a similar mode of action in laser delivery as micropulse TSCPC, where diode laser is delivered in ultrashort and repetitive pulses (on and off time). The major difference between SL-TSCPC and MP-TSCPC are different machine used. SL-TSCPC is delivered by Supra 810 laser machine, Quantel Medical while MP-TSCPC is delivered by IRIDEX laser machine. With this system, short bursts of energy deliver pulses to photocoagulate the targeted tissue (pigmented epithelium of the ciliary body) during the "on-cycle" while surrounding tissue is allowed to cool and remain below the photocoagulation threshold during the "off-cycles". So, it is theoretically able to prevent damage to the surrounding tissue.[5] Some studies have demonstrated that MP-TSCPC is an effective and safe alternative to traditional TSCPC at lowering IOP, with possible decreased rates of complications.[6,7] Subliminal TSCPC shows a good profile that able to reduce IOP safely and effectively.[8] However, more studies are needed to evaluate their safety profile and efficacy. Thus, the aim of this study is to determine the effectiveness and side effects of SL-TSCPC for various types of glaucoma, including glaucoma in patients with good vision.

MATERIALS AND METHODS

This study is a retrospective, non-comparable, analytical medical record reviews of all subjects with various types of glaucoma that received SL-TSCPC treatment from October 2018 to April 2019 at Hospital Tengku Ampuan Afzan,

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Corresponding Author: Chow Jun Yong
Email: derrick-chow@hotmail.com

Pahang, Malaysia as the SL-TSCPC machine was only available during this period of time. All patients who received SL-TSCPC treatment during this period were recruited and no patients excluded. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institute. Informed written consent was obtained from all patients prior to their enrolment in this study. Data were collected and analysed each post SL-TSCPC visit. The background characteristics of patients, best corrected visual acuity (BCVA), type of glaucoma, staging of glaucoma, IOP, number of glaucoma medications, ocular history were recorded for each patient. Visual acuity was measured using Snellen chart. Good vision is defined as visual acuity of 6/12 and better. IOP was measured by goldmann applanation tonometry. The SL-TSCPC procedure was performed in an outpatient setting. Subtenon anesthesia with three to four milliliter of 2% lignocaine hydrochloride was given before the procedure. After laser therapy, patients were reviewed at second week, sixth week, third month and sixth month. One to two-week duration of topical steroid and antibiotic were prescribed after the procedure and then tapered accordingly. Each patient had their vision, IOP, number of medications required, and presence of any complications recorded during subsequent follow-up. Outcome measures were the number of patients who achieved surgical success, changes of visual acuity, mean IOP reduction, mean reduction of IOP lowering medications, and documentation of ocular side effects.

The supra 810 laser machine, Quantel Medical was used. It emits infrared diode laser with a wavelength of 810 nm. It delivered 2000mW energy in fast repetitive on and off phase (micropulse mode) for 160s for all patients. The probe was moved in a "to and fro" motion over three mm behind the limbus of upper and lower conjunctiva sparing the three and nine o'clock positions. The duration of treatment for each hemisphere was 80 seconds (s), therefore the total duration of the treatment was 160s. The treatment settings were adjusted individually based on the patient's condition and manufacturer recommendation.[8] There are two treatment settings which are duty cycle of 31.3% (time on 0.5s, time off 1.1s) for patients with no previous history of active ocular inflammation or keratitis, while the duty cycle of 25% (time on 0.62s, time off 1.9s) for patients with active ocular inflammation, good best corrected visual acuity or moderate visual field defects. There was no standard technique for the sweeping motion during application (fast vs. slow).

Surgical success in this study was determined by multiple patient outcomes. Surgical success was defined as an IOP of 6–21 mmHg or a reduction of IOP by 20% from the baseline with antiglaucoma medications.9 Failure was defined as: (1) IOP < six mmHg with hypotony maculopathy, (2) loss of ≥ three Snellen lines, and (3) require further glaucomatous surgical intervention to control the IOP.10 The primary outcome measure was success rate at 6-month post-treatment. Secondary outcome measures were changes of visual acuity, IOP reduction, and ocular side effects noted during each visit.

RESULTS

A total of 20 eyes of 18 patients were treated with subliminal TSCPC in this study. The mean age of treated patients was 58 years old with the range from 12 to 75 years old. There were nine male patients (50.0%) and nine female patients (50.0%). Most patients were Malays (n=13, 72.2%), followed by Chinese (n=4, 22.2%) and Indians (n=1, 5.6%). Twelve patients had treatment in the right eye (66.7%), four patients had treatment in the left eye (22.2%) and two patients had treatment in both eyes (11.1%). There were five eyes (25%) with good vision (6/12 and better) which underwent SL-TSCPC with duty cycle 25% while another 15 eyes (75%) underwent SL-TSCPC with duty cycle 31.3%. All patients were on medical glaucoma therapy prior to treatment and six patients (33.3%) had undergone prior incisional glaucoma surgery [Table I]. Neovascular glaucoma was the predominant diagnosis (n=10, 50%), followed by primary open angle glaucoma, steroid-induced glaucoma, and others [Table II]. The average duration of follow-up post-treatment was 5.7 ± 2.7 months. Percentage of follow-up was initially 19 (95%) eyes at second week visit; 15 (75%) eyes at sixth weeks; 18 (90%) eyes at third month; and 16 (80%) eyes at sixth month. The reason attributing to dropout was defaults on clinic appointments and missing documents on patients follow up.

The success rate was 43.8% (seven eyes out of sixteen eyes) at sixth month post-treatment in this study [Figure 1]. Four eyes were excluded as they defaulted follow up at sixth month post-treatment. Half of the neovascular glaucoma patients were in the failure group (six out of twelve eyes). The reasons of treatment failure are shown in Table III.

In this study, the mean IOP was reduced from 43.0mmHg ± 14.8mmHg pre-treatment to 24.7mmHg ± 12.0mmHg at second week post-treatment, a 42.6% reduction. Subsequently, mean IOP at six weeks, three months, and six months post-treatment were 33.8mmHg ± 16.9mmHg, 35.2mmHg ± 14.9mmHg, and 28.7mmHg ± 16.7mmHg respectively. The IOP reduction from baseline was 21.4% at six weeks, 18.1% at three months and 33.2% at six months. Meanwhile, the mean number of topical antiglaucoma eyedrops maintained the same from 3.5 pre-treatment to 3.5 at second week but further reduced to 2.8 at six weeks, 2.6 at three months, and 3 at six months post-treatment. Besides, the mean number of systemic IOP lowering agents were 0.4, 0.1, 0.2, 0.1, and 0 at pre-treatment, second week, six weeks, three months, and six months post-treatment respectively. Percentage of patients on systemic medication were 35% pre-treatment, 26% at second week, 20% at six weeks, 11% at three months and none of patients were on systemic IOP lowering medications after six months post-treatment. Table IV summarizes the mean IOP, IOP reduction, the mean number of medication and percentage of patient on systemic medication at each follow-up for all patients.

Vision changes after SL-TSCPC were common. Visual acuity changes at six months post-treatment were 5% (n=1) of eyes gained three Snellen lines of vision and 5% (n=1) improved two Snellen lines. Vision maintained unchanged for majority of the patients (65%, n=13). However, 15% (n=3) of eyes dropped one Snellen line, and 5% (n=1) of eyes decreased two

Table I: Demographic data

Demographic Data	n
No. of eye (No. of patients)	20 (18)
Mean age ± SD (years)	58 ± 16
Male : Female	9 : 9
Ethnicity, N (%)	
• Malay	13 (72.2%)
• Chinese	4 (22.2%)
• Indian	1 (5.6%)
Laterality of the eye	
• Right eye	12 (66.7%)
• Left eye	4 (22.2%)
• Both eyes	2 (11.1%)
Prior history of ocular glaucoma procedure	6 (33.3%)
• Trabeculectomy+ mitomycin C	3 (15%)
• Conventional TSCPC	3 (15%)
Visual acuity	
• 6/12 and better	5 (25%)
• <6/12 - 6/18 (early visual impairment)	0 (0%)
• <6/18 – 6/60 (moderate visual impairment)	1 (5%)
• <6/60 – 3/60 (severe visual impairment)	1 (5%)
• <3/60 (blind)	13 (65%)
Staging of glaucoma based on standard automated perimetry	
• Stage 1: early defect , mean deviation (MD) <-6 dB	3 (15%)
• Stage 2: moderate defect, MD -6 to -12 dB	1 (5%)
• Stage 3: advanced defect, MD -12 to -20 dB	0 (0%)
• Stage 4: severe defect, MD > -20 dB	2 (10%)
• Stage 5: end-stage defect	14 (70%)

Table II: Distribution of types of glaucoma

Types of glaucoma	n (%)
Neovascular glaucoma secondary to	10 (50%)
• Proliferative diabetic retinopathy	7 (35%)
• Retinal vein occlusion	2 (10%)
• Ocular ischemic syndrome	1 (5%)
Primary open angle glaucoma	4 (20%)
Steroid-induced glaucoma	2 (10%)
Juvenile open angle glaucoma	1 (5%)
Primary angle closure glaucoma	1 (5%)
Phacomorphic glaucoma	1 (5%)
Plateau iris syndrome	1 (5%)
Total	20 (100%)

Table III: Reasons of eye with treatment failure

Reasons	Number of eyes, n (%)
Glaucoma drainage device implantation	3 (18.8%)
Intraocular pressure	
• Static	3 (18.8%)
• Increased	1 (6.2%)
• Less than 20% reduction	1 (6.2%)
Three snellen lines vision loss and more	1 (6.2%)
Total	9 (56.2%)

Table IV: Comparison of mean IOP, IOP reduction, mean number of medications and percentage of patient on systemic medication among pretreatment (Tx), post Tx during each follow up at second week, sixth week, third month and sixth month

Duration post / treatment	0	2 weeks (W) ± 1W	6 weeks ± 3W	3 months (M) ± 6W	6 months ± 6W
Number of eyes	20	19	15	18	16
Mean IOP ± SD	43.0 ± 14.8	24.7 ± 12.0	33.8 ± 16.9	35.2 ± 14.9	29.0 ± 16.2
IOP reduction	0	18.3(42.6%)	9.2(21.4%)	7.8(18.1%)	14.0(32.6%)
Mean number of medication	topical 3.5 systemic 0.4	topical 3.5 systemic 0.1	topical 2.8 systemic 0.2	topical 2.6 systemic 0.1	topical 2.8 systemic 0
Patient on systemic medication (%)	35	26	20	11	0

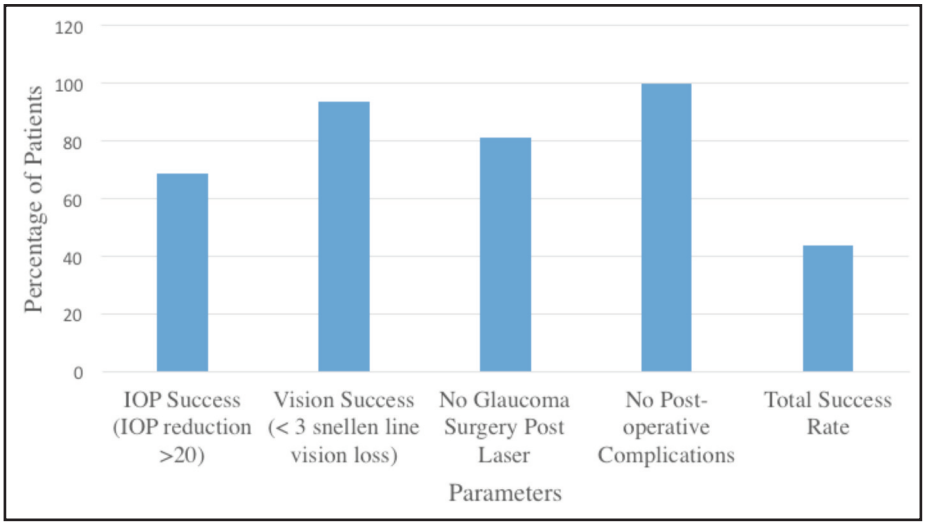

Fig. 1: Percentage of patients with intraocular pressure (IOP) success, vision success, no post laser surgery, no post-operative complications and total success rate.

Snellen lines. There was one eye (5%) with plateau iris syndrome that had visual deterioration by more than three lines from 6/12 to hand movement. Thirteen eyes (65%) pre-treatment vision was blind (range from hand movement to non-perception of light), two eyes had severe visual impairment and five eyes vision were 6/12 and better.

Out of the 20 eyes treated with SL-TSCPC, six eyes (30%) required further laser or surgical intervention for adequate IOP control; three eyes underwent glaucoma drainage device (Ahmed tube) implantation, with surgery proceeded for one eye two weeks post SL-TSCPC, while two eyes had surgery done three months post SL-TSCPC. Two eyes required re-treatment with subliminal TSCPC at four months post first laser treatment. Needling procedure was performed in one eye with advanced primary angle closure glaucoma after five months.

All patients developed slight conjunctival injection and anterior chamber inflammation post treatment. This resolved by the second week post-treatment in all patients following treatment with topical steroids. There was no serious ocular side effects documented during any of follow-up visits such as hyphaema, hypotony, scleral thinning, scleral perforation, sympathetic ophthalmia, and phthisis bulbi.

DISCUSSION

In this study, the success rate was 43.8% at six months follow-up. This success rate is lower compared to other studies such as Alice et al. who found that the success rate of micropulse TSCPC treatment was 66% at six months.9 Higher rates of treatment success were observed by Tan et al. and Aquino et al. who found that the success rate in MP-TSCPC treated eyes at 18 months was 80% and 52% respectively.[5,7] The lower success rate in our study population is attributed to a higher proportion of neovascular glaucoma among all our patients (50%) compared to other studies. Besides, different laser machine was used, all the above studies were using IRIDEX laser machine whereas Supra 810 laser machine was used in our study. Furthermore, five eyes underwent laser treatment with duty cycle of 25% as their vision was good or had a history of uveitis. Out of these five eyes, three eyes were in the treatment failure group which may be due to the lower delivered energy compared to that used in the above studies. Keilani et. al. study stated that SL-TSCPC at 31.3% duty cycle (83.5% success rate) is more effective than the 25% duty cycle SS-TSCPC (65% success rate).[11] One patient with phacomorphic glaucoma contributed to the failure rate as her refusal of cataract extraction left her IOP uncontrolled, due to unresolved pathology of the intumescent cataract. Our mean IOP reduction at six months post-treatment was 17.6mmHg which is similar to Lutic et al.'s study.8 Our study has shown that the subliminal TSCPC can maintain the IOP lowering effect for at least six months. This procedure can be repeated as it is not cyclodestructive and has limited collateral damage. The result of 43.8% success rate has shown to be similar to traditional TSCPC in Matthias et al. study which reported a 42% success rate (IOP 4-18 mm Hg, 20% IOP reduction, and no major complications) at a six month period.[12]

In this study, a drastic drop in IOP was seen in early visits followed by slight increment of IOP until the third month, where it then decreased to around 33% IOP reduction at six months post-treatment. The reduction in IOP seen is due to enhanced uveoscleral aqueous outflow as well as reduced aqueous humor production. Two studies have shown increased uveoscleral outflow post transscleral photocoagulation therapy over the pars plana area.[13,14] After that, the IOP increment during sixth weeks and third months post-treatment are due to the withdrawal of systemic and topical IOP lowering agents. In view of repeated procedures (additional SL-TSCPC laser and surgical interventions) were mostly performed three months post initial SL-TSCPC, the mean IOP at six months of follow-up is lower than mean IOP at six weeks and three months post initial treatment.

In the six months of follow-up post-treatment, the vision of majority of patients remained stable in this study. Only one eye (5%) had a decrease of more than three Snellen lines and one eye (5%) reduced two Snellen lines. Emanuel et al. study

reported 8.2% of patients experienced more than three Snellen lines loss at third month following MP-TSCPC treatment15 while 20% of eyes worsened by two or more lines in another study.[16] Our patient with plateau iris glaucoma that lost more than three Snellen lines of vision had significant cataract, development of central retinal vein occlusion with neovascular glaucoma secondary to uncontrolled IOP which further contributed to vision loss.

There was no serious side effect noted during follow-up such as prolonged inflammation, hypotony, scleral perforation, and phthisis bulbi. These results showed SL-TSCPC had a better safety profile compared to the traditional TSCPC. Thus, subliminal transscleral cyclophotocoagulation may provide an alternative option of bridging the gap between medical therapy and surgical options such as minimally invasive glaucoma surgery (MIGS), and traditional glaucoma-filtering surgery.

The limitations of this study include the small sample size and incomplete data collection as several patients defaulted on follow-up clinic visits. Patients with uneventful events after SL-TSCPC treatment are more likely to default clinic follow-up because of the logistic issues and waiting time in the clinic. As a result, bias may be introduced to the data leading to lower success rates and higher complication rates. Therefore, this study should be repeated with as a multicentre trial with larger sample size and longer study duration to determine the effectiveness, duration of the SL-TSCPC effect and detect late complications.

CONCLUSION

Subliminal TSCPC is a safe method to reduce the IOP in moderate to advanced glaucoma patients during this study's 6 month monitoring. Since it is a repeatable procedure, it can prolong the time for invasive glaucoma surgery in patients who refuse or not fit for surgery. It is an option for glaucoma patients that are refractory to medication and with good vision. With a good safety, efficacy profile and superior patient comfort during application, subliminal TSCPC can be offered as an alternative for patients with uncontrolled glaucoma who have difficulty in compliance to eye drops, or are unable to afford MIGS devices. However, patients should be well informed regarding possible complications that may occur.

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CONFLICT OF INTEREST STATEMENT

There is no any potential financial and non-financial conflicts of interest that could have appeared to influence the work reported in this paper.

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The Cobblestone Heart

Tan Wang Jie, MRCP, Suzila Che Sayuti, MMed, Azza Omar, MMed, Mat Zuki, MMed

Department of Medicine,Hospital Raja Perempuan Zainab II ,15200 Kota Bharu, Malaysia

SUMMARY

Sarcoidosis is a chronic, multisystem disorder. A 38 years old lady presented at Hospital Raja Perempuan Zainab II, Kota Bharu ,Malaysia with cough and breathless for 2 months and constitutional symptoms of weight loss and loss of appetite. She was initially treated as smear negative pulmonary tuberculosis for 5 months. However, her clinical condition deteriorated with worsening New York Heart Association (NYHA) class 1 to class 3. Subsequently, workout of computed tomography(CT) thorax showed multiple perilymphatic distribution of nodules and multiple mediastinal lymphadenopathy coupled with pleura biopsy showed non caseating granuloma and cardiac magnetic resonance imaging (MRI) with positive late gadolinium enhancement revised the diagnosis of pulmonary sarcoidosis with cardiac involvement. Patient's functional status and cough improved with immunosuppresant was given in tapering dose fashion

INTRODUCTION

Sarcoidosis is a chronic, multisystem disorder. Although clinical evidence of myocardial involvement is present in only 5% of patients with sarcoidosis, subclinical cardiac involvement as proven by autopsy is present in 20 to 30% of cases.[1] Myocardial involvement of sarcoidosis has been proven to occur much more commonly in patients presenting with cardiac symptoms compared with those who do not have cardiac symptomatology (84 vs 4%) with morbidity up to 90 % and mortality of 30%.[2]

CASE REPORT

We describe here a case of 38 years old lady who presented at the Hospital Raja Perempuan Zainab II .with breathlessness and cough for 2 months, no loss of appetite and weight and denied any failure symptoms. Chest radiograph revealed multiple nodular opacity over right upper and middle lobe of lungs. She was empirically treated as smear negative pulmonary tuberculosis with negative sputum acid fast bacilli (AFB) initially and subsequent sputum mycobacterium (MTB) culture yielded no growth. Persistent symptoms of cough and weight loss with non-improving serial chest radiograph were observed during follow up day 14, 1 month of anti tuberculous medication. We noticed the patient had new onset of heart failure symptoms i.e. orthopnoea and bilateral leg swelling after 2 months of treatment with chest radiograph with worsening consolidation of right upper and middle lobe and right pleural effusion. Urgent computed tomograph (CT) thorax showed multiple mediastinum matted lymph node enlargement with multiple peribronchovascular distribution of nodular opacity with coalesce consolidation over the right middle lobe and right pleural effusion. She underwent pleuroscopy after the new onset of exudative right pleural effusion revealed multiple well form coalescing non granulomatous inflammation over parietal pleura. Blood was unremarkable with normal calcium level, angiotensin converting enzyme level and normal erythrocyte sediment rate (ESR) of 20mm/hr. With the new onset of cardiac symptoms reduced effort tolerance and worsening NYHA status and abnormal electrocardiogram (ECG) of multiple premature ventricular ectopics (PVCs), right bundle branch block and poor R wave progression over precordial leads, we ordered urgent echocardiogram (ECHO) which showed dilated cardiomyopathy with global hypokinesia and with reduced left ventricular ejection fraction (LVEF) of 33%. With highly suspicions of cardiac sarcoidosis, as recommended in the American Thoracic Society (ATS) guidelines 2020, we proceeded with cardiac MRI showed extensive and variable pattern of myocardial inflammation and fibrosis with positive late gadolinium enhancement predominant at basal left ventricle (LV) segment. the patient fulfilled >2 major criteria -3 major (1, basal interventricular septal thinning, gadolinium enhanced MRI of myocardium, depressed LVEF <50% and 1 minor criteria of multifocal arrhythmia-premature ventricular contraction in 2017 Japanese Ministry of Health and Welfare Criteria for diagnosis of cardiac sarcoidosis. Eventually, 0.5mg/kg corticosteroid with weekly incremental dosage of methotrexate from 7.5mg /week up to 20mg/week planned for 6 months were initiated. Besides, anti-heart failure medication T perindropil 8mg and bisoprolol 2.5mg OD and spironolactone 25mg OD were given under cardiology care. Her repeated computed tomograph thorax after 3 months of treatment showed significant improvement of resolving nodules and consolidations (arrow) and reducing sizes of mediastinum lymphadenopathy (arrowhead). However, there was residual right pleural effusion which we attributed it to pleural sarcoidosis and heart failure in combination. Repeated ECHO after 3 months of treatment revealed static ejection fraction of 30 % with dilated cardiomyopathy. Otherwise, she clinically remained well with no reported failure symptom with low dose 10mg steroid daily and 20mg /week methotrexate. We planned to follow up every 3monthly with close monitoring of her heart and lung function by doing chest radiograph, cardiac positron emission tomography PET scan imaging to assess the cardiac disease activity and blood investigations to monitor for methotrexate MTX toxicity.

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Corresponding Author: Wang Jie Tan
Email: tanwangjie@gmail.com

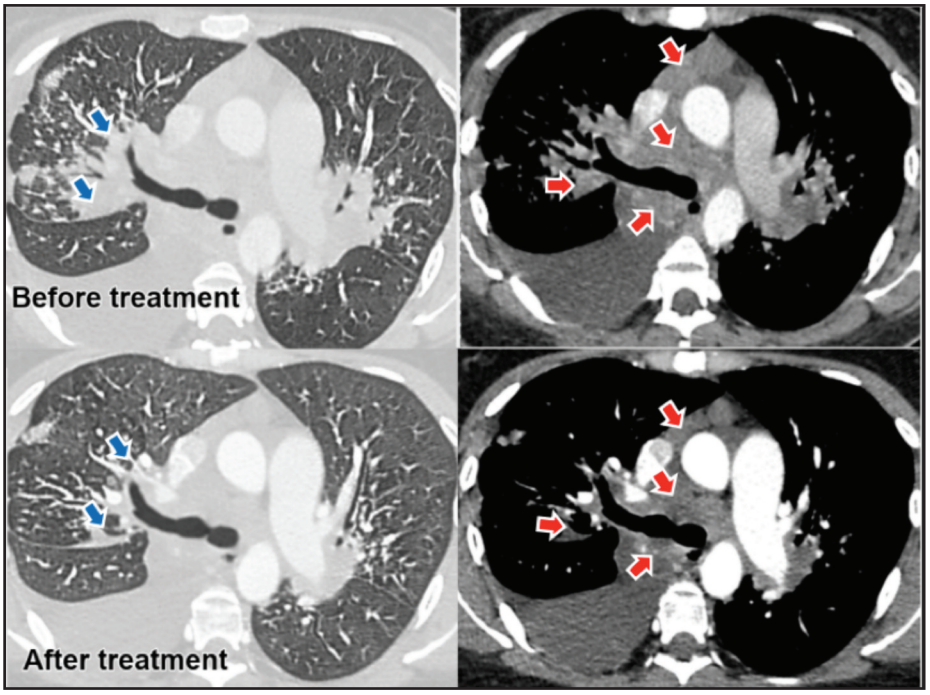

Fig. 1: Pre and post treatment CT thorax image showing resolving peribronchovascular nodules and consolidation (blue arrow) and reducing sizes of station 3A, 4L ,4R ,7 and 10R and mediastinum lymph nodes (red arrow).

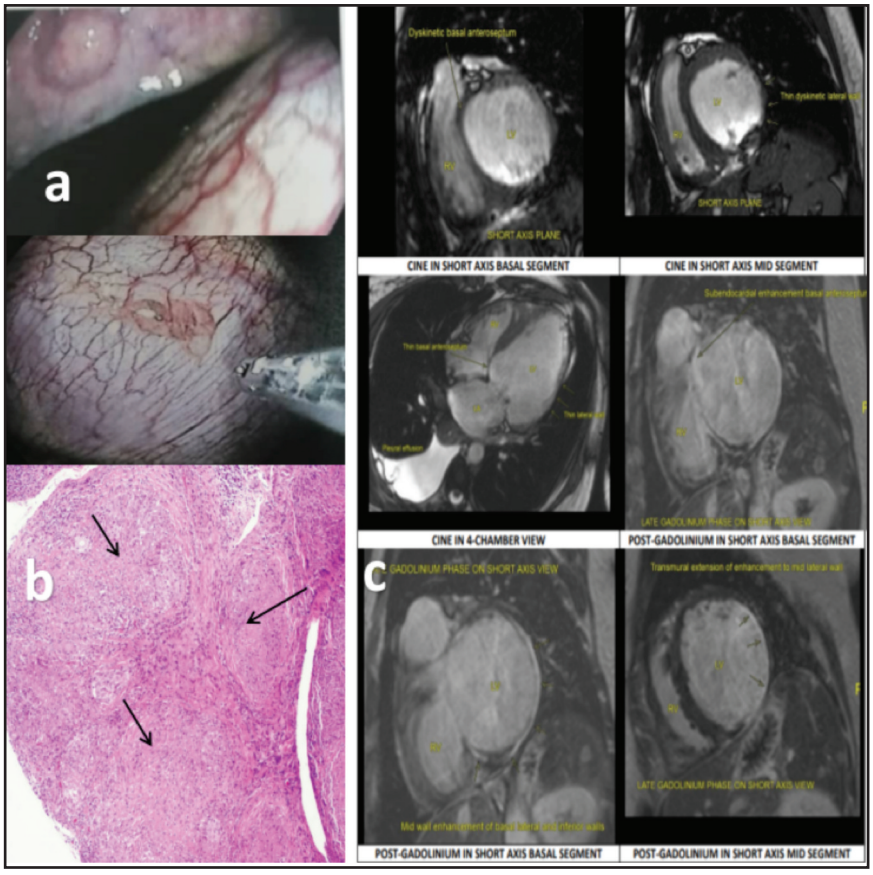

Fig. 2: (a):Pleuroscopy revealed parietal pleura nodule.
(b):Pleural biopsy histology showed multiple coalescing granuloma (arrow).
(c):Cardiac MRI showed late gadolinium enhancement at basal left ventricular segment.

DISCUSSION

Sarcoidosis is a disease with multiorgan inflammatory disorder and no definite criteria to diagnose. The cause is usually idiopathic, and clinical presentation and prognosis is variable. The diagnosis of sarcoidosis is not standardized, but is based on three major criteria: a compatible clinical presentation, the finding of non-necrotizing granulomatous inflammation in one or more tissue samples (not always required, as discussed subsequently below), and the exclusion of alternative causes of granulomatous disease.[1] Sarcoidosis exhibits myriads of spectrum of manifestations ranging from asymptomatic to progressive and relapsing disease. This disease is now much more prevalent than previously estimated and mortality is higher than reported earlier. Certain clinical features are pathognomic for the condition which include Lofgren's syndrome, Lupus Pernio and Heerfordt's syndrome.[5] With nonspecific clinical features of sarcoidosis, histological evaluation of detecting tissue granulomas is imperative in establishing the final diagnosis. Typical histological features are sarcoidosis granuloma include well-formed concentrically arranged layers of immune cells with most prominent central core of macrophage aggregates and multinucleated giant cells.[5] Sarcoidosis granulomas are most often non-necrotic. However, some variants of mixture necrotic and nonnecrotic granulomas can be present in particularly nodular pulmonary sarcoidosis. Differential diagnoses and alternative condition must be excluded in the evaluation of sarcoidosis. CT thorax of the patient revealed mutiple nodular opacity with peribronchovascular distribution and multiple mediastinal lymphadenopathy (Figure 1). As tuberculosis is endemic in Malaysia ,both tuberculosis and atypical mycobacterial infections have to be excluded . In relation to our case, sputum and pleural tissue for mycobacterium culture were both negative and patient did not respond to standard antitubercular medications, which was an important clinical vignettes to find alternative diagnosis to tuberculosis .Patient denied of occupational history and environmental exposure to birds or metals to exclude hypersensitive pneumonitis and chronic beryllium disease which might mimic sarcoidosis.[5]

Cardiac sarcoidosis has been described only in less than 5 % of patients with systemic involvement.[3] Diagnosis of cardiac sarcoidosis is often challenging and there is no definite guidelines of the treatment and disease monitoring. Cardiac sarcoidosis diagnosis usually is inferred when there is diagnosis of histology proven extracardiac sarcoidosis with deteriorating heart function.[2] We did pleuroscopy for our patient and found nodules in parietal pleura in which the histology and cardiac MRI as shown in Figure 2. Histopathological examination revealed multiple non-caseating coalescing granulomatous inflammation and negative for mycobacterium culture. The cardiac MRI showed-severely dilated left ventricle with reduced ejection fraction, LVEF 30%, myocardial inflammation of basal septum and basal inferior LV and RV walls. Extensive mid wall fibrosis of basal lateral, inferior and inferoseptal walls with transmural extension into the mid to apical lateral walls, mid inferior wall and the apex of the LV, Subendocardial fbrosis/infarction of basal anteroseptal LV wall and subepicardial fibrosis of part of basal inferior right ventricle wall. With regards to diagnosis of cardiac sarcoidosis based on the Japanese Ministry of Health and Welfare Criteria, most of the cases fall into the category of clinically diagnosis group in view of endomyocardial biopsy rarely been performed.[2] Major criteria include 1)Advanced atrioventricular block 2) Interventricular septum basal thinning 3)Positive Gallium -67 uptake in heart 4)Depressed left ventricular ejection fraction<50%. Minor criteria include 1)Abnormal ECG findings: Ventricular arrhythmia, axis deviation,complete right bundle branch block or abnormal Q wave 2)Abnormal ECHO: wall motion abnormality 3)Perfusion defect in nuclear imaging 4)Delayed gadolinium enhancement on cardiac MRI 5)Interstitial fibrosis or monocyte infiltration on cardiac biopsy.Clinical diagnosis of cardiac sarcoidosis fulfilled when 2 or more major criteria or 1 major and 2 or more minor criteria are satisfied. Glucocorticoids are a therapeutic choice when it comes to sarcoidosis.

However, there is scarcity of data in regards to their implication in the treatment of cardiac sarcoidosis with no randomised controlled trial (RCT) data. Based on recommendations of the American College of Cardiology (ACC), American Heart Association, and the Heart Rhythm Society, steroid sparing therapy such as methotrexate in our case is important to control the inflammation over the myocardial tissue while optimization of heart failure medication are the cornerstone in treating cardiac sarcoidosis.[2] Other suggested steroid sparing agents in ACC recommendation in low level evidence level depicted in case reports are infliximab, azathioprine, cyclosporine.[2] There are no guidelines available on follow ups for cardiac sarcoidosis. Edward et al suggested that for serial PET cardiac scan 3- 6 months to assess the cardiac activity and monitor treatment response. However, further randomized clinical trial are needed in this in this new field.[2]

Anecdotal data from an observational survey based on a study of 104 cases demonstrated increased survival. Another retrospective observational study from Japan by Yazaki et al. demonstrated a 75% survival at five years in the glucocorticoid arm versus 10% in non-steroid treated patients.[3] The optimal dose of prednisolone and duration of therapy has not been established. Yazaki et al. suggested that an initial dose as low as 30 mg per day may be effective, followed by a slow tapering over 6-12 months once symptomatic improvement has been achieved.[4] Other reports suggested that treatment with prednisolone is effective in preventing progressive pump failure, scar formation and sudden death.[4,5]

Currently, the role of glucocorticoids in the management and treatment of patients with cardiac sarcoidosis remains unclear. Cardiac sarcoidosis usually present in the form of supraventricular and more commonly ventricular arrhythmia, conduction abnormalities such as first-degree heart block progressing to complete heart block, valvular dysfunction such as mitral incompetence, cor pulmonale with advanced fibrotic pulmonary sarcoidosis, pericarditis, or heart failure.[5] Progressive heart failure has accounted for about 25 to 75% deaths in sarcoidosis. The prognosis of symptomatic cardiac sarcoidosis is not well defined. A

previous autopsy series of 113 patients concluded that survival in most patients are limited to approximately 2 years after development of cardiac symptoms.[5]

Sudden cardiac death due to ventricular tachyarrhythmia or conduction block accounts for 30 to 65% of the deaths. Implantable cardiac defibrillator ,ICD implantation should be strongly considered in patients with known cardiac sarcoidosis, LVEF less than 35%, NYHA class III-IV or those with history of spontaneous sustained ventricular tachycardia or ventricular fibrillation. For those patients who progressed, heart transplant remains the last resort for the treatment of refractory cardiac sarcoidosis.[5]

CONCLUSION

One of the main challenges in the assessment of patients with systemic sarcoidosis is determining when and how to evaluate cardiac involvement. Cardiac sarcoidosis should be suspected by all clinicians when an otherwise healthy young or middle-aged patient develops cardiac symptoms or in a patient with known sarcoidosis who develops arrhythmia. Unfortunately, there is no randomized clinical trial for the treatment of cardiac sarcoidosis, further research is necessary for cardiac sarcoidosis to fully understand the impact this treatment regimen will have on patients with cardiac sarcoidosis.

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CONSENT

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

CONFLICT OF INTEREST

The authors declare that there was no potential conflict of interest relevant to this article was reported.

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Concurrent Influenza A and Pulmonary Melioidosis in pregnancy

Wen Foong Tan, MRCP, Heng Gee Lee, MRCP

Department of Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia

SUMMARY

Melioidosis is endemic in Sabah. It causes significant morbidity and mortality if diagnosis and treatment is delayed. Important risk factors include diabetes, chronic kidney diseases, chronic lung diseases, thalassaemia, immunosuppressive therapy, and hazardous alcohol consumption. Influenza A is usually a self-limiting disease but is associated with high morbidity and mortality in high-risk populations especially during pregnancy. Both melioidosis and influenza A commonly present in patients with pneumonia. Secondary bacterial pneumonia is a known complication in approximately one third of patients with severe pneumonia due to influenza A, resulting in intensive care unit admissions. However, melioidosis is not commonly recognized as an aetiology in secondary bacterial pneumonia complicating influenza A infection. This is important as empirical antibiotics that are used to treat secondary bacterial pneumonia due to influenza A often do not cover melioidosis. Here we report a rare case of concurrent pulmonary melioidosis and influenza A in a 30-year-old primigravida at 27 weeks of pregnancy in the Queen Elizabeth Hospital, Sabah, Malaysia to highlight the challenge in the recognition and management of both infections in a melioidosis endemic area.

INTRODUCTION

Influenza A and melioidosis are common community acquired infections with pulmonary involvement, both with significant morbidity and mortality in pregnant patients if the treatment is delayed. A review by the World Health Organization (WHO) working group reported that the incidence of symptomatic laboratory confirmed influenza infection ranged from 0.1 per 10,000 pregnancies to 486 per 10,000 pregnancies with the incidence of ICU admission ranging from 0.01 per 10,000 pregnancies to 6.8 per 10,000 pregnancies.[1] With regard to melioidosis in Sabah, the incidence rate was 2.57 per 100,000 population in 2013.[2] Herein, we report the first case of concurrent Influenza A with pulmonary melioidosis in a pregnant lady in Sabah, Malaysia.

CASE REPORT

A 30-year-old primigravida at 27 weeks of pregnancy presented with two days history of fever, productive cough, coryza and myalgia. She had no difficulty in breathing and also denied any history of contact with patients with respiratory illness or animals. There was no recent history of travel. Her past medical history included hypertension and papillary thyroid carcinoma for which she had a total thyroidectomy, lymph node excision and radioiodine therapy three years prior to the current presentation. She was a housewife.

On examination, she was febrile (38°C), tachypnoeic with a respiratory rate of 28 breaths/minute with oxygen saturation of 98% on nasal oxygen 3L/min, blood pressure was 124/85mmHg and pulse rate was 90 beats/minute. Examination of the lungs revealed bilateral coarse crepitations. The rest of the physical examination was unremarkable. Blood investigations revealed WBC $9.2x10^9$/L (predominantly neutrophils), haemoglobin of 11.9g/dL, platelet $252x10^9$/L, and CRP was 28 mg/L. Renal and liver function tests were normal. Arterial blood gas on ambient air showed type 1 respiratory failure – pH 7.4, pO_2 77mmHg, pCO_2 28mmHg, and HCO_3 18.6mmol/L. HIV test was negative. Admission electrocardiogram showed sinus rhythm and chest radiograph showed bilateral basal pulmonary infiltrates. Bedside echocardiography was normal. She was treated for severe influenza with superimposed bacterial pneumonia with intravenous ceftriaxone, azithromycin and oseltamivir.

Over the next three days, her fever persisted with increasing oxygen requirement and a repeat chest radiograph (Figure 1) showed worsening pulmonary infiltrates. Antibiotics were escalated to piperacillin/tazobactam on the same day for treatment of superimposed nosocomial pneumonia. Initial sputum cultures and blood cultures were sterile. Sputum for H1N1 PCR was positive for influenza A. However, her condition continued to deteriorate, and she required mechanical ventilation on day-7 of illness. Both the chest radiograph and arterial blood gases were consistent with acute respiratory distress syndrome, and therefore a decision was made to further escalate the antibiotics to intravenous meropenem the following day. A computed tomography (CT) of the chest on day 11 of illness (Figure 2) showed ground glass opacities of both lung fields consistent with pneumonitis.

Subsequently, her fever subsided after three days of intravenous meropenem, and she was extubated on day 14 of illness. Sputum culture on day 16 of illness grew *Burkholderia pseudomallei* which was sensitive to ceftazidime, meropenem and imipenem. Sputum was inoculated on blood

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Corresponding Author: Heng Gee Lee
Email: henggee77@gmail.com

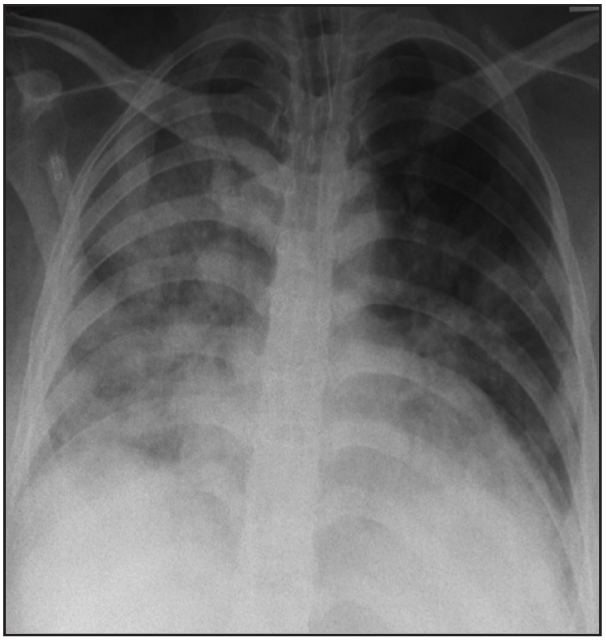

Fig. 1: Chest radiograph on day 3 of illness showed worsening opacities over bilateral lung fields.

Fig. 2: Computed tomography of the chest on day 11 of illness showed ground glass opacities involving both lungs, but worse on the right.

agar and MacConkey agar. Identification of *B. pseudomallei* was done with VITEK 2 compact system (BioMerieux, Lyon, France) and antibiotic sensitivity test was performed with Etest. Repeated blood culture was sterile and melioidosis serology (IgM ELISA) was negative. Antibiotics was de-escalated to intravenous ceftazidime in view of clinical improvement on day 20 of illness. Following this, she had an emergency lower segment caesarean section for foetal distress and delivered a preterm baby on day 32 of illness. She completed two weeks of intravenous ceftazidime and was discharged well after five weeks of hospital stay with oral trimethoprim/sulphamethoxazole for another three months. Both mother and child remained well in 2019, two years after discharged.

DISCUSSION

Influenza in pregnancy is known to cause significant morbidity and mortality. Immunological and physiological adaptations that occur in pregnancy make them particularly vulnerable to the complications. Pregnancy-associated complications include hyperthermia, low birthweight, preterm delivery, and perinatal mortality. Hyperthermia in early pregnancy is associated with neural tube defects and other congenital anomalies; and in late pregnancy is associated with neonatal seizures, neonatal encephalopathy, cerebral palsy and death.[3] Case series reported that about half of the influenza cases in pregnant women were complicated by bacterial pneumonia, with a quarter of them resulting in death, especially in the third trimester. Initiation of neuraminidase inhibitors within 48 hours of onset of symptoms confers a lower risk of severe disease and complications. Therefore, influenza vaccination is advocated to prevent as well as minimise the severity of the infection in pregnant women, thus improving both maternal and foetal outcomes.[3]

Melioidosis is a disease caused by *B. pseudomallei* and is endemic in Malaysia. Clinical manifestations range from asymptomatic carriage, chronic infection to acute disseminated bacteraemia and septicaemic shock.[2,4] The mode of infection include inhalation and contact via cutaneous wounds. The most common presentation is pneumonia which accounts for approximately half the number of the total cases. Impaired host defence in conditions such as diabetes mellitus, chronic kidney disease, chronic lung disease, thalassaemia, and malignancy have been implicated as risk factors for contracting melioidosis.[4]

Our patient had severe H1N1 influenza A complicated by pulmonary melioidosis. There are two possibilities to explain this concurrent infection. The first is that our patient had acquired both influenza A and *B. pseudomallei* at about the same time. Initial cultures were negative on admission as the melioidosis infection was probably in the incubation phase of the disease. Melioidosis serology (IgM) was likely to be a false negative result. Furthermore, it is not a routine practice to send serology for *B. pseudomallei* in Malaysia and serology is not a reliable method of diagnosis. An article by Shirley et al., reported that the sensitivity of in-house IgM ELISA was only 76.14% and IgG ELISA was a better diagnostic test. Culture remains the gold standard of diagnosis.[5] Another consideration would be reactivation of melioidosis from a latent focus. In the Darwin study, it was reported that about 4% (19) of 540 cases had reactivation of disease.[4] Latency of up to 29 years from exposure to *B. pseudomallei* to development of clinical disease, had been reported. The most common clinical presentation of reactivation was pulmonary melioidosis.[4] In our patient, her risk factor for acquiring melioidosis was due to environmental exposure to *B. pseudomallei* in the soil during gardening. A similar case of reactivation of melioidosis in a Vietnam veteran with acute influenza had been described. Pregnancy is not a known risk factor for melioidosis infection.

CONCLUSION

Influenza is frequently complicated by bacterial pneumonia, thus there should be a high index of suspicion of melioidosis as a cause of concurrent bacterial pneumonia in endemic areas as earlier empirical treatment of melioidosis will lead to better outcome.

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CASE REPORT

Fatal outcome of catheter-related bloodstream infection caused by Multidrug-Resistant Mycobacterium mucogenicum

Faridah Sulung, MD[1,3], Siti Asma' Hassan, MPath[1,3], Zeti Norfidiyati Salmuna, MPath[1,3], Tuan Noorkorina Tuan Kub, PHD[1,3], Intan Baiduri Badri, MSc[2,3], Azura Hussin, MPath[4]

[1]Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, [2]School of Health Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, [3]Hospital Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, [4]Department Pathology, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

SUMMARY

***Mycobacteria mucogenicum (M. mucogenicum)* is a rarely isolated pathogen. It has emerged as a significant pathogen in immunocompromised patients including those with cancer, organ transplant, or patients on immunosuppressive medication. Chemotherapy may reduce the ability of the bone marrow of these to respond to infection, and patients will be at risk for neutropenic sepsis, which leads to fatal complications. Here, we report a case of an 18-year-old boy was seen at Hospital Raja Perempuan Zainab II, Kelantan with acute lymphoblastic leukaemia (ALL) who presented with catheter-related bloodstream infection (CRBSI) caused by *M. mucogenicum*. He succumbed due to neutropenic sepsis with multiorgan failure.**

INTRODUCTION

Non-tuberculous mycobacteria (NTM) are the unusual cause of human infections, but the cases are higher in immunocompromised patients.[1] The infection has been found widespread in the environment, including water, soil, and bioaerosols. The most common disorders caused by NTM is bacteraemia, followed by catheter-related, nosocomial, and soft tissue infections. NTM is divided into slow-growing mycobacteria and rapidly growing mycobacteria (RGM). The organisms that grew in less than seven days are called RGM. Slow growing NTM are more commonly isolated compared to RGM. RGM is frequently associated with nosocomial infections resulting from a contaminated water sources and hospital equipment.[3] Identification of NTM using traditional methods is time-consuming, requires well-trained staff, and does not accurately identify the organism to the species level. However, the present advanced and modern technology able to identify the rare species of RGM more frequently and precisely within a short period. The objectives of this case report is to share the rare cause of catheter-related bloodstream infection (CRBSI) due M. mucogenecum for clinical management and hopefully improve patient outcome.

CASE REPORT

An 18-year-old boy with an underlying ß-thalassemia trait was diagnosed with B-cell acute lymphoblastic leukaemia (ALL) two years earlier was seen at Hospital Raja Perempuan Zainab II. A chemoport was inserted before the initiation of the first chemotherapy. During the admission he was on the consolidation phase of chemotherapy, on week 66, with modified German ALL protocol. He has never had a chemoport-related infection and was relatively well in between the admission.

For the current admission, he was electively admitted for the continuation of chemotherapy. On day-3 of admission, he developed a spike in temperature (38.5°C). It was associated with chills and rigors.

He was normotensive and tachycardic. Chemoport site was clean, no purulent discharge, non-tender, and not erythematous. His white blood cell (WBC) was 8.22 $x10^9$/L, haemoglobin of 12.6g/L, platelet of 144 $x10^9$/L and absolute neutrophil count (ANC) was 7.96x109/L with raised in C-reactive protein (CRP) (147mg/L; Lung auscultation and his chest x-ray were normal. Blood was taken for culture before the initiation of antibiotics. Intravenous (IV) cefepime 1gm 12 hourly was given empirically for the sepsis. However, the source of infection was still unknown.

The sample from the patient grew small, whitish colonies on blood sheep agar (Figure 1). It appears as gram-positive bacilli on gram staining. Acid-fast bacilli stain was also positive. Identification of the organism was performed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonik, Bremen, Germany), and *M.mucogenicum* was identified with a score of 1.98 using the MALDI Biotyper reference library. The sample was sent to the national referral laboratory (Makmal Kesihatan Awam, Sungai Buloh, Selangor, Malaysia), confirmed that the organism was *M.mucogenicum*, and proceeded with sensitivity testing. However, in HRPZ IIsetting, the sensitivity testing took about two weeks for the result to be available.

Antibiotic was changed to IV ciprofloxacin 400mg 12 hourly and IV amikacin 800mg once a day as the preferred treatment of choice for NTM. The second blood culture was taken from his chemoport (central sample) and peripheral site. *M.mucogenicum* was isolated from both samples. The central sample grew 2 hours earlier than the peripheral sample, which fulfilled the criteria of catheter-related bloodstream infection (CRBSI) based on IDSA guidelines.[2]

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Corresponding Author: Dr Siti Asma' Hassan
Email: sitiasmakb@usm.my

Fig. 1: Mucoid whitish small colonies of M.mucogenicum on blood sheep agar.

After a few days of treatment, his condition showed no sign of improvement. He developed neutropenic sepsis with acute liver injury possible secondary to drug-induced. Full blood count showed; WBC $0.99x10^9$/L, ANC of $0.56x10^9$/L and single-digit platelet. There was derangement in the liver enzymes; aspartate transferase was 263U/L (normal value: <50 U/L), alanine transferase of 304U/L (normal value: <50UL), and alkaline phosphatase of 74U/L (normal value: 52-171U/L). IV ciprofloxacin was discontinued as it may contribute to acute liver injury. He was started on subcutaneous Neupogen, IV methylprednisolone, and IV imipenem 1gm 6 hourly.

Despite appropriate therapy given to him, his condition further deteriorated. He developed type 1 respiratory failure secondary to nosocomial pneumonia. His ANC remained below $0.5x10^9$/L with worsening of aspartate transferase and alanine transferase more than 2000U/L. He succumbed on day 14 of admission. The cause of death was severe neutropenic sepsis secondary to pneumonia. The anti-tuberculosis sensitivity testing result from the referral laboratory showed resistance to ciprofloxacin, doxycycline, clarithromycin, and tobramycin.

DISCUSSION

M.mucogenicum belongs to a rapidly growing RGM group of non-tuberculous mycobacteria (NTM). It is an unusual cause of human infections, but the cases are higher among immunocompromised patients. Infection caused by M.mucogenicum results in various spectrum of disease, either pulmonary or extrapulmonary disease like skin and soft tissue infection (SSTI), bacteremia, CRBSI, meningitis, and peritonitis.[1] The prevalence of pulmonary NTM infection was reported to be 8.6 episodes per 100,000 people in the United States of America (USA).[3] However, the prevalence in Southeast Asia countries, including Singapore and Malaysia, is limited. The incidence rate for pulmonary NTM in Japan and Taiwan was higher than the USA, 14.7 and 46.0 cases per 100, 000 population, respectively.[3] The earliest outbreak of *M.mucogenicum* was discovered in 1976 from intermittent peritoneal dialysis, which developed peritonitis. The investigation of the outbreak reported that it was caused by ineffective disinfection and colonisation of the machine by M.mucogenicum.[4] Implanted central venous port devices or chemoport are used in oncologic patients for chemotherapy access, delivery of parenteral nutrition, or blood transfusions. Infections are the most common complication of chemoport compared to catheter thrombosis, vessel stenosis, or catheter fracture with embolisation of catheter materials. Port-related infections are commonly seen in haematological malignancies, probably due to prolonged neutropenia, and intensive chemotherapy compared to solid tumors.[5] The incidence rate for port-associated infection was 2.5%.[6] In Malaysia, a 4 year-study showed that out of 102 chemoport insertions, 5 (4.9%) had port-related infection.[7] In our patient, his chemoport was inserted two years earlier. He had never experienced any complication relating to his central line until this episode where he developed CRBSI caused by M.mucogenicum. Several studies reported that water from taps may be contaminated with this organism or suboptimal water chlorination was the source of *M.mucogenicum* infection.[1,4] During showering, the catheter was exposed to tap water, resulting in contamination of the catheter. Given this information, the source of infection in this patient is still unestablished. There was no additional environmental sampling done for this case to confirm the source of infection. Our patient had an episode of neutropenic fever with chills and rigors, high in CRP, no signs of infection at the chemoport site, and *M.mucogenicum* was isolated from paired blood culture. CRBSI is diagnosed in patients with signs and symptoms of exit-site infection like pain and tenderness at the catheter site, erythematous skin, and purulent discharge.[4] Fever with or without rigors in 30-60 minutes of commenting infusion is a typical symptom of CRBSI.[8] It can be misdiagnosed when patients have atypical presentations like non-specific malaise, hyperbilirubinemia, hypoalbuminemia and raised in inflammatory markers like CRP, erythrocyte sedimentation rate, and procalcitonin.[8] *M.mucogenicum* CRBSI are seen more likely in long term intravenous catheters.[1] A case report of the external ventricular drain (EVD)-associated with *M.mucogenicum* meningitis was reported recently. The patient developed meningitis after day 5 of EVD placement.[4]

Our isolate was a rapid grower (grew on blood agar within seven days) NTM, which was identified as M.mucogenicum by MALDI-TOF. Mycobacterium organisms need to be identified up to species level as it helps to predict in vitro susceptibility and gives a guide for antibiotic therapy. Today, molecular methods like PCR sequencing (16s RNA gene sequencing) and PCR hybridisation are the new gold standard in the identification of mycobacterium.4 The standard conventional tests that we used previously were laborious, time-consuming, and gave a significant challenge in identifying the Mycobacteria species. However, DNA sequencing test is only available in some of the laboratories. MALDI-TOF mass spectrometry is another method that can be used to identify Mycobacteria species accurately. It is cost-effective, has a short turn-around time, and easily implemented in a routine laboratory.

M. mucogenicum was reported as the most susceptible organism among RGM species.[9] They are susceptible to aminoglycoside, fluoroquinolones, tetracyclines, macrolides, carbapenem, cefoxitin, and trimethoprim-sulfamethoxazole.[2] Non-tuberculous MDR is defined when the isolates are resistant to at least four different classes of antimicrobials.[9] Non-tuberculous multidrug-resistance (MDR) is rarely reported due to the limited number of isolates. Our isolate was *M.mucogenicum* MDR with susceptibility to trimethoprim/sulfamethoxazole, amikacin, moxifloxacin, linezolid, and imipenem, intermediate to cefoxitin but appears resistant to four different classes of antibiotics, which were ciprofloxacin, doxycycline, clarithromycin, and tobramycin (fluoroquinolone, tetracycline, macrolide, and aminoglycoside). Other than multiorgan involvement, the possibility of fatality in this patient was due to treatment failure. It is learned that he developed acute liver injury induced by ciprofloxacin, despite treatment escalation using imipenem was in place. His chemoport was kept *in-situ* since his first insertion about 66 weeks earlier. It was only 2 weeks later that when the final sensitivity revealed resistance to fluoroquinolone. The initiation of appropriate antibiotics and removal of the catheter may have increased the likelihood of recovery.[1] On the other hand, catheter salvage may result in treatment failure.[9,10] There is no specific guideline regarding the ideal duration of treatment for RGM CRBSI. Intravenous antimicrobial may be given at least 2 weeks, followed by oral therapy for another two weeks.,[9] Total antimicrobial treatment varies from 4 to 24 weeks.10 CDC guidelines recommend covering the catheters during bathing to prevent M.mucogenicum catheter-related bloodstream infection.[9]

CONCLUSION

Delayed diagnosis and treatment of MDR NTM may lead to the fatality of a patient. A modern microbiological machine-like MALDI-TOF can identify NTM within hours compared to the culture method. The timely and reliable result is important to aid the clinician in treating patients, hence reducing the mortality rate.

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Disseminated Melioidosis with Spinal Intraosseous Abscess

Kar Chuan Soo, MBBS[1], Kok Soon Lee, MRCP[1], Shangyan Ooi, MBBS[1], Ani Darwina, MMed[2], Sumithra Sannasey, MMed[2], Heng Gee Lee, MRCP[1]

[1]Infectious Disease Unit, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, [2]Radiology Department, Queen Elizabeth Hospital, Kota Kinabalu, Sabah

SUMMARY

Melioidosis is endemic in the State of Sabah, Malaysia. We report a case of a 34-year-old man with one-week history of fever and cough, three days history of diarrhoea and vomiting, which was associated with a loss of appetite and loss of weight for one-month. Clinically, he had hepatosplenomegaly and crepitation over his right lower zone of lung. Chest radiograph showed right lower lobe consolidation. Ultrasound abdomen showed liver and splenic abscesses. Ultrasound guided drainage of splenic abscess yielded Burkholderia pseudomallei. Magnetic resonance imaging (MRI) lumbosacral confirmed right sacral intraosseous abscess after he developed back pain a week later. He received 6 weeks of intravenous antibiotics and oral co-trimoxazole, followed by 6 months oral co-trimoxazole and had full recovery.

INTRODUCTION

Melioidosis is an infection caused by the gram negative bacterium *Burkholderia pseudomallei*. It is endemic in Sabah, Malaysia. The important risk factors associated with melioidosis are diabetes mellitus (DE), chronic kidney disease, chronic lung disease, underlying immunosuppression, thalassaemia, and underlying malignancy. Melioidosis is usually acquired via percutaneous inoculation with contaminated soil or water, inhalation, aspiration, and ingestion. Here, we report a case of a male with underlying diabetes who had disseminated melioidosis involving the spine, lungs, multiple liver abscesses and splenic abscesses.

CASE REPORT

A 34-year-old man with underlying diabetes mellitus, presented at the Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia with one-week history of fever and productive cough, three days history of diarrhoea and vomiting, and one-month history of loss of appetite and loss of weight. He worked as a security guard and did not engage in recreational activity involving soil or contaminated water. On examination, he was febrile with temperature 38.7 ^{0}C and was haemodynamically stable. He had hepatosplenomegaly and crepitations over his right lower zone of lung. Other clinical examinations were unremarkable. Results of relevant blood investigations are shown in Table I. His blood results showed hypochromic microcytic anaemia along with leucocytosis, hyponatremia and raised C-reactive protein. His random blood sugar was 16.7 mmol/L. Chest X-ray showed right lower lobe consolidation. Ultrasound abdomen showed a 10 cm x 9 cm heterogenous collection over the posterior pole of spleen and a heterogenous collection seen within segment III, VII, and VIII of the liver, with a largest 2.8 cm x 3.8 cm abscess seen at segment III of the liver.

He was treated empirically with intravenous Ceftazidime 2g every 8-hourly for melioidosis in view of underlying DE and because melioidosis is endemic in Sabah. His first blood culture was sterile. Ultrasound guided drainage of splenic abscess was done, and 30 ml of blood-stained pus was aspirated. Pus culture from splenic abscess grew *B.pseudomallei*, which was sensitive to Ceftazidime and Meropenem. His antibiotic was escalated to intravenous Meropenem 1g every 8-hourly in view of persistent fever and bacteraemia despite abscess drainage from the spleen. Contrasted CT thorax and abdomen showed multiple hypodense liver lesions of varying sizes (largest at segment IVa measuring 3.2 cm x 2.8 cm x 2.4 cm), multiple scattered heterogeneously enhancing hypodense splenic lesions (largest measuring 4.6 cm x 4.6 cm x 4.6 cm) and multiple lung nodules at apical segment of right upper lobe.

During the second week of admission, he developed lower back pain which was aggravated by walking and was tender on palpation. There was no neurological deficit. MRI lumbosacral showed right sacral intraosseous abscess (2.3 cm x 1.4 cm x 2.2 cm) with inflammation of the adjacent right sacral nerve root. A smaller intraosseous abscess was also seen in the superior endplate of S1 sacral body measuring 1.5 cm x 2.2 cm x 0.8 cm (Figure 1). Patient completed 6 weeks of intravenous Meropenem which was later de-escalated to intravenous Ceftazidime together with oral co-trimoxazole, followed by another 6 months of eradication phase with oral co-trimoxazole. Reassessment scan with MRI lumbosacral after intensive phase treatment showed resolving right sacral intraosseous abscess (1.4 cm x 0.6 cm x 0.8 cm) and sacral body of S1 abscess (1.3 cm x 1.0 cm x 0.5 cm)(Figure 2). He made full recovery and was well in 2020, two years after discharge.

DISCUSSION

Melioidosis is endemic in Southeast Asia and northern Australia.[1] In Sabah, the incidence rate of melioidosis is 2.7

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Corresponding Author: Heng Gee Lee
Email: henggee77@gmail.com

Table I: Blood Investigations

Investigation	Day 1 of admission	After complete treatment	Normal range
Haemoglobin (g/dl)	11.4	16.8	13 -17
White cell count (10 ^3/uL)	11.9	6.9	4 -10
Neutrophil (10^3/uL)	10.6	4.3	2 -7
Platelet (10^3/uL)	276	185	150 – 410
CRP (mg/L)	184.4	1.1	< 5
Na (mmol/L)	112	134	136 -145
K (mmol/L)	3.6	4.2	3.5 – 5.1
Cl (mmol/L)	74	101	98 – 107
Urea (mmol/L)	2.6	5.4	3.2 – 7.4
Creatinine (umol/L)	73.4	109.7	63.6 – 110.5
Total protein (g/L)	68	85	
Total bilirubin (umol/L)	39.6	9.4	3.4 – 20.5
Albumin (g/L)	25	46	35 – 50
Globulin (g/L)	43	39	
ALP (U/L)	1085	108	40 – 150
ALT (U/L)	82	60	0 -55
AST (U/L)	154	45	5 – 34

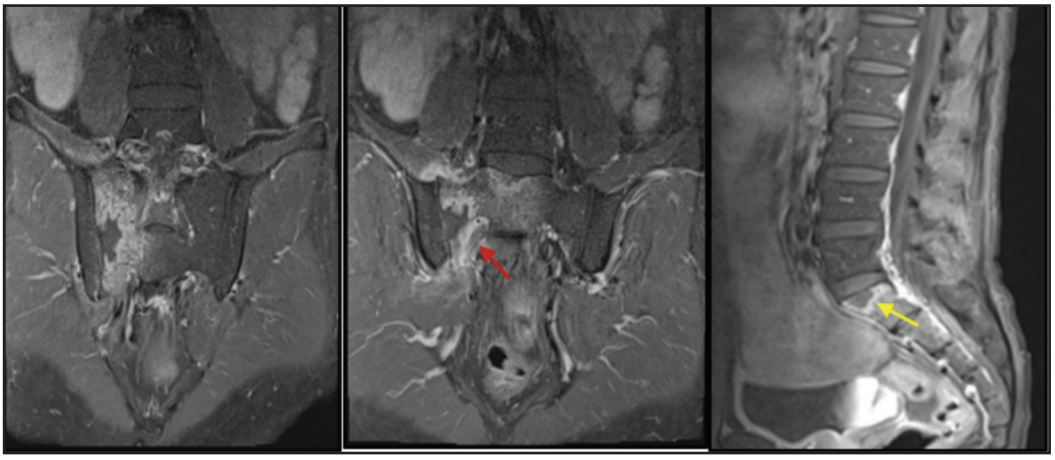

Fig. 1: Coronal T1WFS post contrast image shows a thick-walled abscess in the right sacral ala with minimal enhancement of the adjacent right sacral nerve (red arrow). Another smaller intraosseous collection noted in the superior end plate of S1 sacral body (yellow arrow).

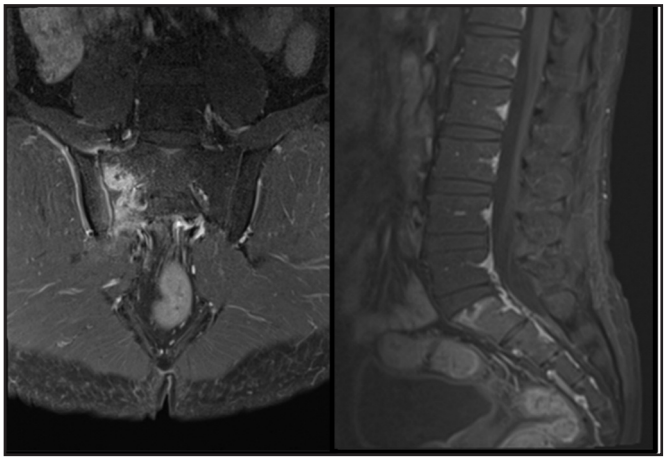

Fig. 2: Coronal T1WFS post contrast image at 1 month follow up shows marked reduction in size of the abscess in both right sacral ala and superior end plate of S1 sacral body.

per 100,000 population.[2] Melioidosis can be acquired via percutaneous inoculation with contaminated soil or water, inhalation, aspiration, and ingestion.[3] Patients with risk factors such as DE, chronic kidney disease, chronic lung disease, thalassemia, malignancy, immunosuppression, hazardous alcohol intake and advanced age are at risk of melioidosis infection. Occupational or recreational exposure involving contaminated soil and water are commonly associated as the infecting event.

Melioidosis can present with various clinical manifestations involving any sites, hence making this disease a great mimicker. Pneumonia is the most common clinical presentation.[4] Musculoskeletal involvement is a well-recognised manifestation of melioidosis. However, B.pseudomallei is a relatively rare causative organism in musculoskeletal infections.[5] Our patient had multiple organs involvement including liver, spleen, lungs, and sacral intraosseous abscesses. He had risk factor of DE, but no infecting event was identified. Development of spinal abscess could be secondary to haematogenous spread from another region, but sacral region involvement is rare.

Detailed history taking and risk factors assessment are important to make timely provisional diagnosis and to start empirical treatment. This is because few intravenous

antibiotics are effective to treat melioidosis during the intensive phase. These include intravenous Ceftazidime, Meropenem or Imipenem which are not usually used as first line antibiotics in community acquired pneumonia or sepsis. Culture isolation from patient bodily fluids remains the gold standard for diagnosis and is important to guide antimicrobial de-escalation therapy later. Delayed treatment of spinal abscess can lead to a permanent neurological deficit and even fatality. Thus, detailed clinical assessment, followed by prompt utilisation of MRI scan is necessary to avoid diagnostic delay in patient who presents with musculoskeletal symptoms and signs. Large deep-seated spinal abscess needs to be drained for good source control.

Antibiotics treatment of melioidosis consists of two phases of therapy, which are the induction phase and the eradication phase. During the initial intensive phase, either intravenous Ceftazidime or Meropenem or Imipenem is used. Oral co-trimoxazole is combined early with intravenous antibiotics in skin and soft tissue infection, septic arthritis, osteomyelitis, prostatic infection, and central nervous system infection in view of good tissue penetration. After successful intensive phase treatment, oral co-trimoxazole is continued as the eradication phase therapy. The duration of both the intensive phase and eradication phase therapy depends on the anatomical organ involvement of the disease and the severity of infections.

CONCLUSION

Melioidosis is a serious neglected tropical disease and is endemic in Sabah, Malaysia. Early recognition and source identification are particularly important for successful treatment of patient. Surgical intervention is often useful in large deep-seated abscess to achieve good source control. Good source control together with appropriate antibiotics and adequate duration of antibiotics are required to achieve successful patient outcome.

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CASE REPORT

Emergency Laparotomy in a COVID-19 patient with acute abdomen

Razeen Hassan, MB BCh BAO (NUI)[1], Johari Mustafa, M Med Surg (UKM)[1], Jasjit Singh Nijhar, MRCS (Ire), M Med Surg (UKM)[1], Sharifah Baizura Syed Alwi, MRCPI[2], Low Lee Lee, MRCP (UK)[2], Nil Amri Mohamed Kamil, M Med Surg (UKM)[1]

[1]Department of Surgery, Hospital Sultanah Bahiyah, Alor Setar, Kedah, [2]Infectious Disease Unit, Department of Medicine, Hospital Sultanah Bahiyah, Alor Setar, Kedah

SUMMARY

We describe here the first laparotomy involving a COVID-19 patient in Malaysia. A 60-year-old man screened positive for SARS-CoV-2 in March 2020 and developed acute abdomen in the ward in Hospital Sultanah Bahiyah, Kedah. He underwent laparotomy and cholecystectomy for gangrenous cholecystitis. All personnel adhered to infectious control precautions, donning full personal protective equipment (PPE) throughout the surgery. Post-operatively, due to raised septic parameters, he was carefully diagnosed with and treated empirically for superimposed bacterial sepsis instead of cytokine release syndrome, with confirmed blood culture of *Klebsiella pneumoniae*. Patient was discharged well later. None of the staff involved in his care developed COVID-19 infection.

INTRODUCTION

COVID-19 disease was declared a pandemic on 11th March 2020 by the World Health Organisation (WHO) and the first case in Malaysia was reported on 25th January 2020. Subsequently, a new COVID-19 cluster was identified on 27th February, involving 4,942 attendees of *Tabligh* (religious) gathering at Sri Petaling, Malaysia.

Hospital Sultanah Bahiyah (HSB) is a 923-bedded referral centre of COVID-19 cases in the state of Kedah. The Department of Surgery has designated a separate team within the department who will scrub in for all COVID-19 surgical cases. Surgeries were carried out according to principles outlined in the Ministry of Health (MOH) guidelines on Management of Coronavirus Disease 2019 in Surgery, which included minimal staffing, adherence to infectious control precautions, donning of personal protective equipment (PPE) (N95 mask, goggles, disposable gowns, double gloves), pre-operative intubation and post-operative extubation in a negative pressure room at the intensive care unit (ICU). There is a reserved operation theatre (OT) with stand-alone air-conditioning system and modified air handling unit (AHU) to prevent return of air ventilating the theatre, which was located next to the emergency department (entry point of HSB) used for all COVID-19 surgeries in the hospital.

COVID-19 positive patients may be asymptomatic, pre-symptomatic (not yet develop signs and symptoms of pneumonia upon positive swab) or symptomatic upon swab detection. Symptomatic COVID-19 patients develop lower respiratory tract infection which may progress to acute respiratory distress syndrome (ARDS) with severe hypoxaemia. A subgroup of COVID-19 patients may develop cytokine-release syndrome (CRS) which is the unregulated release of characteristic cytokines (interleukin (IL) 6), persistent fever, with organ and tissue damage, conferring high mortality rate to the host.

We describe here the multidisciplinary management of a 60 year-old, pre-symptomatic COVID-19 positive male who developed acute abdomen in ward requiring laparotomy, complicated with COVID-19 pneumonia, bacterial sepsis and multi-organ impairment post-op.

CASE REPORT

A 60-year-old Indian national man attended a religious gathering at Sri Petaling, Malaysia in March 2020. Following the outbreak of COVID-19 at that gathering, he tested positive (real-time reverse-transcriptase polymerase chain reaction (RT-PCR)) for SARS-CoV-2 in Kedah yet remained asymptomatic. Patient was subsequently admitted to the COVID-19 isolation ward at HSB. He has type II diabetes mellitus and hypertension. Five days after admission, he had persistent right hypochondriac pain, fever and vomiting. As abdominal pain could be the presenting symptoms of COVID-19 infection, oral Hydroxychloroquine was initiated. Two days later, he developed generalised peritonitis and was planned for laparotomy. Pre-operative chest X-ray (CXR) showed bilateral peripheral, ground-glass heterogenous opacities thus suspension Lopinavir-Ritonavir (Kaletra®) was started prior to transfer to ICU.

Patient was transferred from the COVID-19 isolation ward to ICU for pre-operative intubation. He was then sent to the operation theatre (OT) dedicated for COVID-19 cases for surgery. The surgical team consisted of a consultant general surgeon, a general surgeon, a medical officer, two nurses and one consultant hepatopancreatobiliary surgeon (who was later called in to assess the necrotic-appearing cystic duct). All OT personnel donned and doffed full PPE, supervised by the infectious control team. The anaesthesiology team, consisting of a consultant anaesthetist and a medical officer, both wore powered air-purifying respirator (PAPR) suits, while the

This article was accepted: 20 January 2021
Corresponding Author: Razeen M. Hassan
Email: mohdrazeen@live.com

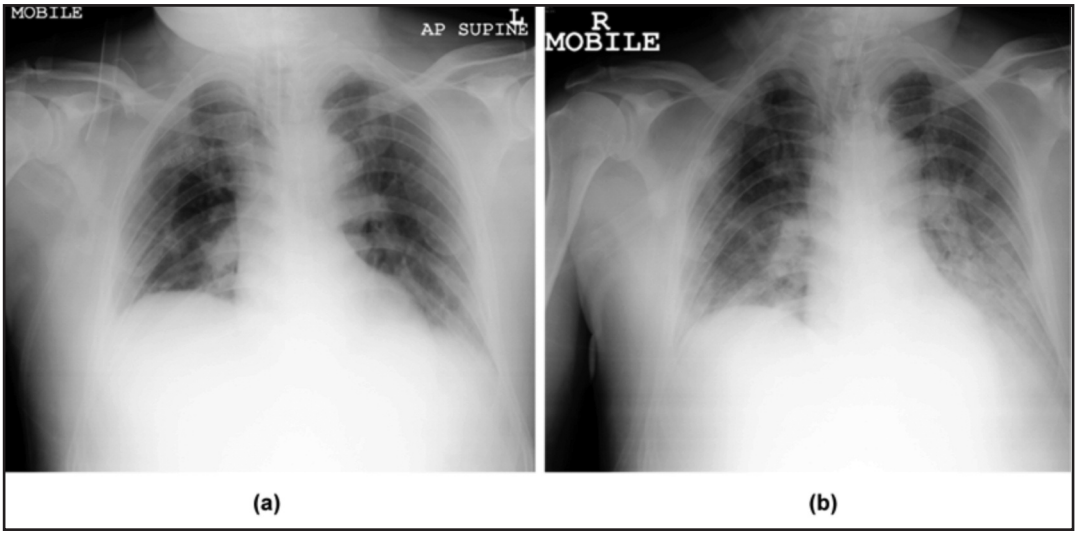

Fig. 1: (a) Chest X-ray (CXR) POD1, (b) CXR POD4.

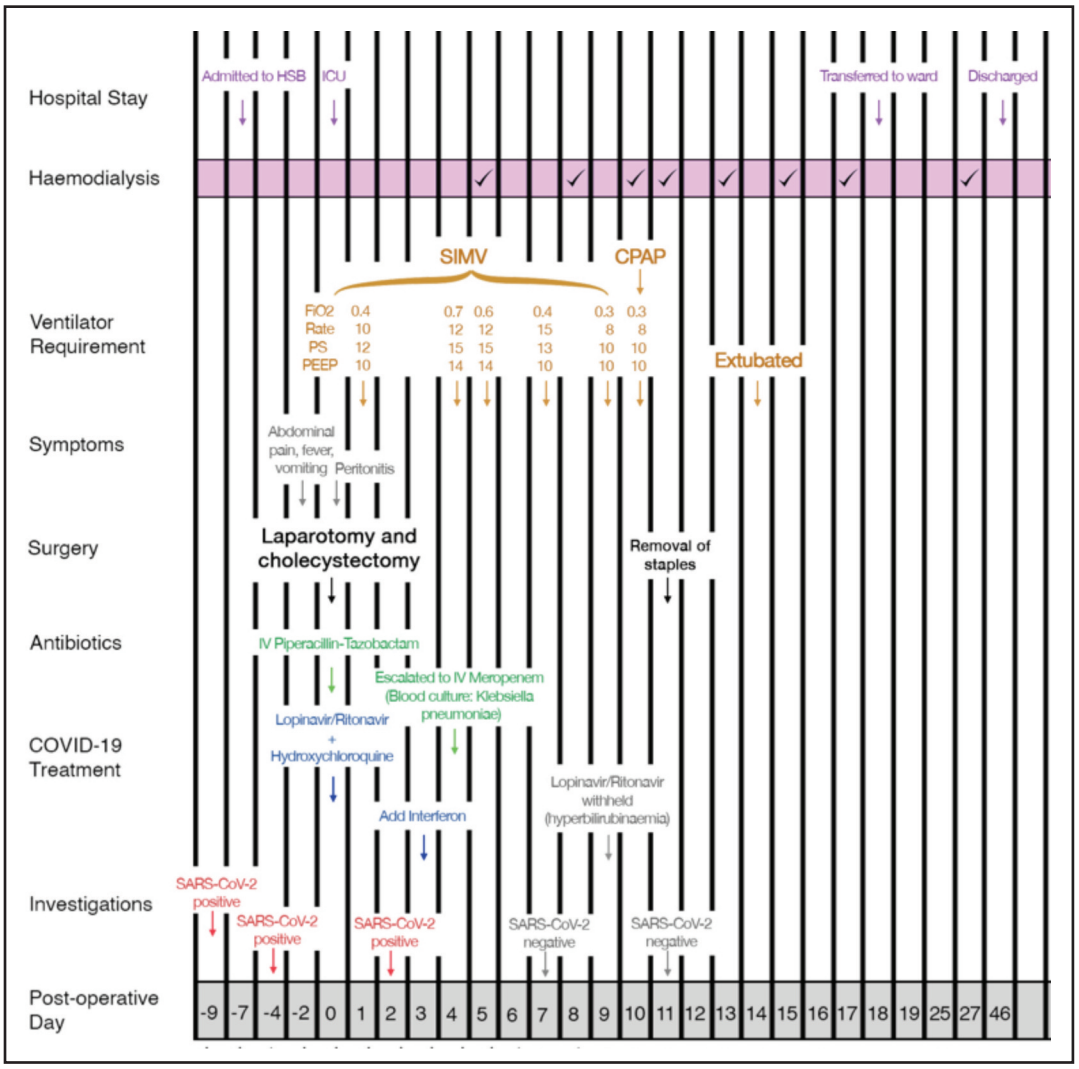

Fig. 2: Timeline of patient care.

anaesthesiology medical assistant donned full PPE. Disposable drapes and gowns were used for surgery. Laparotomy was undertaken, revealing a gangrenous gallbladder with a viable cystic duct, thus cholecystectomy was done. There was also a localised collection of 100ml bilious peritoneal fluid at the right upper quadrant with 40ml of dirty bile spillage during mobilisation of gallbladder, albeit no interloop collection was seen. Duration of the surgery was two hours.

Post-operatively, the patient was transferred to ICU. He required single inotropic support (IVI Noradrenaline 2ml/hr, 8mg/ml) and was started on IV Piperacillin-Tazobactam. Post-operative CXR revealed worsening bilateral ground-glass opacities at the periphery of lower zones (Fig. 1). On post-op day (POD) 3, patient was considered as critically-ill with multi-organ involvement and was started on subcutaneous injections of Interferon beta-1b 44mcg EOD for four doses.

On POD4, bile culture grew *Weisella (Lacto.) confusa* (gram positive bacilli) and tracheal aspirate culture grew *Klebsiella pneumoniae* (Extended spectrum beta-lactamase producing organism (ESBL)). Patient was febrile (Temperature: 39.7°C) with double inotropic support and leucocytosis (WCC 5.9 → 23.3 x10^9/L). As the sepsis worsened, patient developed acute kidney injury (AKI) and underwent haemodialysis (HD) on POD5. In view of persistently high C-reactive protein (CRP) levels (>154mg/L), rising ferritin levels (1474 → 2849 → 3894ng/mL) and rising procalcitonin levels (3.53 → 4.76 → 79.37µg/L), he was treated for bacterial sepsis instead of CRS with IV Meropenem 1g TDS and IV Ampicillin-Sulbactam 9g TDS. Two days later, blood culture returned as *Klebsiella pneumoniae* (ESBL). His response to treatment is reflected in reducing levels of procalcitonin level (8.3µg/L on POD8) and CRP (36.07mg/L on POD12).

On POD9, patient's bilirubin and alanine transaminase (ALT) levels rose (Bilirubin: 20 → 59 →129µmol/L, ALT 46 → 61 → 77U/L). Bedside abdominal ultrasound revealed no biliary tree obstruction. Patient was treated as drug-induced hyperbilirubinaemia and suspension Lopinavir/Ritonavir was withheld, following which bilirubin and ALT levels normalised.

Patient's wound healed well and the gallbladder histopathological examination (HPE) revealed acute on chronic cholecystitis. Throughout ICU admission, patient required 8 sessions of dialysis. His SARS-CoV-2 swab samples were negative from 4th sample onwards. He was extubated on POD13 and transferred to COVID-19 isolation ward on POD17 for rehabilitation and renal recovery. He was discharged well on POD46. None of the staff involved in his care developed COVID-19 infection.

DISCUSSION

In comparison with the single-centre, 8-patient COVID-19 positive cohort requiring abdominal surgery in Wuhan,[1] our patient was the first critically-ill COVID-19 patient who was discharged well post-emergency laparotomy.

The benefit of abdominal computed tomography (CT) scan in a COVID-19 patient with acute abdomen has to be weighed with risks of viral transmission to patients and staff at the Radiology department. As with regular patients, COVID-19 patients with generalised secondary peritonitis are indicated for laparotomy regardless of imaging[2,3]. Similarly, all COVID-19 patients with acute abdomen - without secondary peritonitis - should not have the appropriate imaging study delayed if indicated, regardless of COVID-19 status. An elderly man from China[4] underwent laparotomy for iatrogenic peptic ulcer perforation upon discovering pneumoperitoneum on CXR - which is an indication for surgery - thus he underwent early emergency surgery with minimal exposure of radiation required to treat his disease. Our patient was clinically diagnosed with secondary peritonitis, which was an indication for laparotomy, thus CT scan was not done before surgery. Similarly, DA Soesolo et al.[5] subjected their patient for laparotomy upon discovering peritonism, although their patient died after surgery due to complications of bowel necrosis. Our patient was a good candidate for surgery as he was haemodynamically stable with no comorbidity prior to laparotomy.

Pre-operative imaging should be considered in patients who are haemodynamically stable with localised peritonitis[2] to assess the extent of containment of perforation for consideration of non-operative, percutaneous drainage of abscesses if present (i.e., percutaneous transhepatic cholecystostomy for gallbladder empyema or percutaneous pigtail drainage of localised diverticular abscess). Patients with peritonitis may have significant interloop collection which requires peritoneal washout with large amount of normal saline, thus we regard laparotomy as the more time-efficient procedure than laparoscopy to explore and definitively eliminate the surgical source of sepsis in COVID-19 patients.

Post-operatively, we monitored the progression and response to treatment of pneumonia using portable chest X-rays with machines reserved for COVID-19 patients in the ICU. Therefore, the pre- and post-operative CT Thorax changes of ground-glass appearance and pleural effusion seen in the Wuhan[1] cohort were not ascertained in our patient.

Culture from pus obtained intra-operatively grew *W.confusa*, a gram positive bacilli which is intrinsically resistant to Vancomycin. This organism is commonly found in fermented food and raw milk, which our patient consumes.

Our patient developed COVID-19 pneumonia with superimposed ESBL *K.pneumoniae* bacteraemia, complicated with multi-organ involvement. Surgical patients with COVID-19 who develop persistent temperature and worsening septic parameters must be carefully diagnosed with either CRS, bacterial sepsis or new-onset sepsis, as the treatment differs for each diagnosis; CRS is treated with tocilizumab (interleukin-6 receptor antagonist) and steroids as well as discontinuation of interferon, while sepsis is treated with antibiotics.

CONCLUSION

Emergency surgery for acute abdomen in COVID-19 patients should not be delayed by pre-operative CT scan if the indication for surgery is met. Post-operative COVID-19 patients with persistent fever and rising septic parameters should be promptly diagnosed and treated for either new-onset sepsis or CRS as treatment differs for each diagnosis. All surgical patients with COVID-19 pneumonia require close monitoring and early multidisciplinary team management where indicated.

ACKNOWLEDGEMENT

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CASE REPORT

Haemorrhagic transformation: A serious complication of massive ischemic stroke

Mohd Ridzuan Mohd Said, MMed, Mohd Al-Baqlish Mohd Firdaus, MMed

Department of Medicine, International Islamic University of Malaysia, Pahang, Malaysia

SUMMARY

Acute ischaemic stroke is a debilitating disease and may lead to haemorrhagic transformation associated with few factors such as high National Institute of Health Stroke Scale (NIHSS), low Modified Rankin Score (MRS), cardio-embolic clot and others.[1] We report herein a 61 years old man whom presented with left sided weakness and diagnosed with acute right middle cerebral artery (MCA) infarction. Thrombolytic therapy was not offered due to low Alberta Stroke Program Early CT (ASPECT) score and hence managed conservatively. However, within 24 hours, his Glasgow Coma Scale (GCS) reduced by 4 points and urgent Computed Tomography (CT) brain confirmed haemorrhagic transformation with midline shift. He underwent emergency surgical decompression and subsequently had prolonged hospital stay complicated by ventilated acquired pneumonia. He recovered after a course of antibiotic and discharged to a nursing home with MRS of 5.

INTRODUCTION

Haemorrhagic transformation (HT) is a devastating complication of acute ischaemic stroke and the mechanism is related to migration of emboli and abnormal permeability of blood-brain barrier.[2] We report herein a case of acute right middle cerebral artery (MCA) infarction and later transformed into haemorrhagic infarction.

CASE REPORT

A 61 years old man, right handed with underlying hypertension, Type 2 Diabetes Mellitus, dyslipidaemia and Ischaemic Heart Disease (IHD) presented with sudden onset of left sided hemiparesis. The symptom started at 5.30 am when he was performing prayer and was associated with abrupt onset of aphasia and loss of sensation on left limbs. Otherwise, he denied any fall or syncopal attack prior to the current presenting complaints. In addition, he was prescribed with Clopidogrel when diagnosed with IHD previously in 2012 but confessed to non-compliance with the antiplatelet.

Clinically, his blood pressure (BP) was elevated to 189/102 mmHg with heart rate of 97 beats per minutes (bpm). He was afebrile and nil additional heart sound is auscultated. Neurological examination revealed left sided hemiparesis with power of 0/5, hypotonic and hyperreflexia. Plantar was up-going with intact proprioception. In addition, cranial nerve examination demonstrated left cranial nerve 7 palsy, dysphasia and homonymous hemianopia suggestive of a total anterior circulation stroke with NIHSS of 25. Otherwise, no carotid bruit was heard on neck auscultation.

Electrocardiogram revealed a sinus rhythm with ST depression at lateral leads (Lead 1, AVL, V5 and V6). Bloods investigations revealed mild thrombocytopenia of 134 x 109/L with normal counts of haemoglobin, 16.1 g/dL and total white cell counts of 5.5 x 10^9/L. Creatinine was elevated to 116.6 umol/L but other electrolytes including urea, potassium were within normal limit. In addition, INR was 1.23 ratio with random blood sugar of 7 mmol/L.

He arrived in Emergency department, at 8.15 am, stroke call activated and underwent urgent CT brain. CT angiography revealed loss of grey white matter junction and effacement of the sulci within the right MCA territory (Figure 1A). Right M1 thrombus was present with total ASPECT score of 3. Hence, he was classified as Total Anterior Circulation Infarction (TACI) based on Oxfordshire Community Stroke Project (OCSP). However, thrombolysis therapy not administered due to low ASPECT score.

He was admitted to Stroke Care Unit at 9.15 am, immediately commenced on Clopidogrel with regular stroke care. However, his GCS reduced from 15/15 to 11/15 at 4.00 pm and vital sign showed BP of 180/99 with heart rate of 50 bpm. Urgent CT brain was performed and revealed hyperdense lesion within right MCA territory infarct with mass effect on the frontal and temporal horns of right lateral ventricle (Figure 1B).

He was referred to a neurosurgeon and underwent emergency decompression craniotomy. Post operatively, he was managed under ICU care with cerebral protection. Unfortunately, his recovery was complicated by seizures which resolved after commencement of phenytoin. He also acquired Ventilated Associated Pneumonia (VAP) and completed antibiotics. Upon discharge he was observed with similar degree of right hemiparesis and MRS of 5/6.

DISCUSSION

Acute ischaemic stroke is a debilitating disease and is associated with significant disability and mortality. High fatality rate has been reported during the initial 30 days of acute presentation due to cardiovascular event, infection and its consequence.[3] In addition, HT is frequently observed post-acute ischaemic stroke and worsened the prognosis with mortality rate of 50%.[3]

HT occurred when blood products extravasated into an area of infarction and Alvarez-Sabin et al. has outlined on several mechanisms for these physiological changes. During an

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Corresponding Author: Brian Mohd Ridzuan Mohd Said
Email: ridzuan.said85@gmail.com

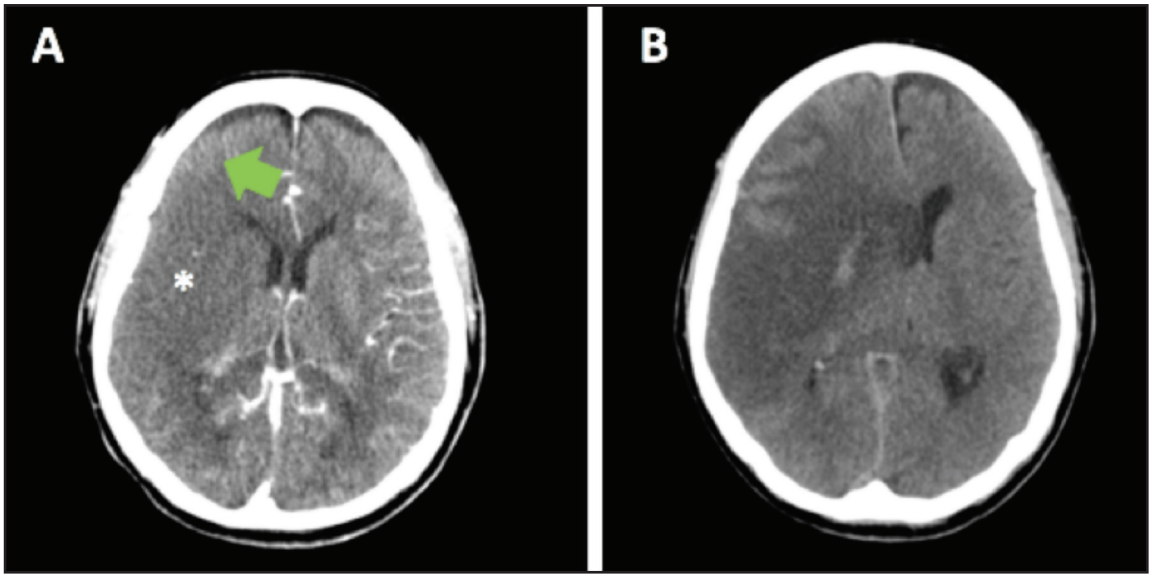

Fig. 1: CT imaging of brain. (A) Showed acute right MCA infarct with effacement of sulci (Green arrow) and loss of grey white matter differentiation (*). (B) Showed haemorrhagic transformation with mass effect on previous right MCA infarct territory.

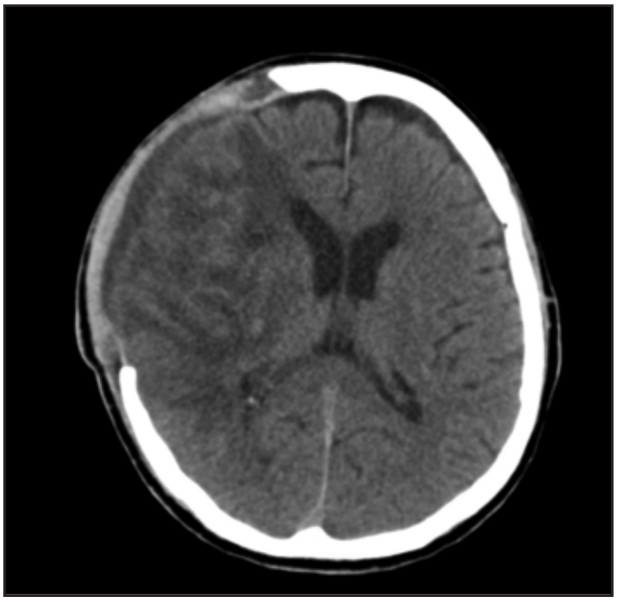

Fig. 2: Repeated CT Brain post right parito-temporal craniotomy. Previously seen right MCA infarct with haemorrhagic transformation showed involution changes with less perilesional oedema.

acute ischaemic event, cytokines are released and together with leucocyte migration impaired the blood - brain barrier and thus triggering extravasation of blood products.[2]

In addition, migration of emboli distally also contributes to HT.[2] Collateral circulation to the ischaemic tissue is promoted once the emboli migrate and augmented by hypertensive episode lead to HT.[2] Another mechanism is related to thrombolytic agents such as Alteplase with 6% risk of developing HT.[3] As the thrombolytic agent is dissolving the clot and restoring the perfusion to ischaemic tissue, the process is linked with endothelial cell damage and disrupts the blood-brain barrier permeability.[3]

In term of risk factors, Kablau et al. had demonstrated on few predictor factors for HT including NIHSS score.[1] NIHSS score of more or equal than 9 and MRS scores of 3 or above on admissio were associated with higher risk of developing HT as well as territorial infarctions when compared to lacunar stroke.[1] Moreover, it was postulated that higher incidence of HT is observed with cardio-embolic stroke due to higher chance for reperfusion when the clots resolved spontaneously or migrated distally.[1]

Furthermore, hyperglycaemia or uncontrolled Diabetes Mellitus during admission is also a crucial predictor factor as 42.4% of patients with HT were observed with blood glucose more than 11 mmol/L.[4] Moreover, non-favourable outcomes were observed in these patients with 29.2% being disabled and 11.5% dead.[4] In addition, impaired kidney function is observed with greater risk of developing HT especially when Glomerular Filtration Rate is less than 30.[4]

Classification of stroke syndrome based on OCSP offers an essential prognostication value but it was unfortunate for our patient who presented with high NIHSS and TACI which was associated with worst prognosis.

Antithrombotic therapy is the mainstay of treatment of acute ischaemic stroke, but the question remains on the safety of the therapy post HT events. Concern for worsening of HT might lead to hesitancy among physicians on commencing the medication promptly.[5] However, Kim et al found no significant association between the use of antithrombotic and neurological deterioration or aggravation of HT, thus suggested for adjustment of practice among physicians.[5]

Apart from surgical intervention for HT, Lapchak et al. had postulated on several potential pharmacological approaches

such as free radical- spin trap compound, membrane metalloproteinase inhibitor and platelet inhibitors.[3] Free radical - spin trap agent such as α- phenyl-N-t-butylnitrone (PBN) reduces HT by scavenging free radical at the blood-endothelial cell interface and thus lead to normalization of blood-brain barrier.[3] The inhibition of membrane metalloproteinase (MMP) reduces brain oedema or haemorrhage as MMP activation contribute to activation of TNF - α and thus damaged brain tissue and its micro vessels.[3]

CONCLUSION

The care for acute ischaemic stroke especially with haemorrhagic transformation requires multi - disciplinary approach including a physician, surgeon, physiotherapist, dietitian and nursing staff as the condition is associated with poor prognosis with devastating disability.

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Dengue Encephalitis associated with symptomatic hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion

Ng Wei Wei, MRCP, Brian Cheong Mun Keong, FRCP

Department of Medicine, Hospital Teluk Intan, Perak, Malaysia

SUMMARY

A previously well 21-year-old girl presented to Hospital Teluk Intan, Perak, Malaysia with a short history of fever, vomiting and altered sensorium. She was diagnosed with dengue encephalitis as her dengue NS-1 antigen was positive and her cerebrospinal fluid (CSF) dengue polymerase chain reaction (PCR) was positive with serotype DENV-2. She also had severe hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) which caused an episode of seizure. She recovered well with supportive management. SIADH and dengue encephalitis should be considered as one of the differential diagnosis in patients presenting with fever and altered sensorium especially in dengue endemic countries like Malaysia.

INTRODUCTION

The clinical spectrum of dengue fever ranges from undifferentiated mild febrile illness to severe disease with plasma leakage, organ impairment and shock. Neurological complications of dengue are uncommon and can manifest as encephalitis, encephalopathy, myelitis or Guillain-Barre Syndrome. According to Soares et al, dengue virus accounts for 75% of encephalitis with normal CSF cellularity in dengue endemic regions, followed by Herpes Simplex Virus 1 (HSV1).[1] Hyponatremia is a common observation in severe dengue and is believed to be a marker of disease severity.[2] We describe a case of dengue encephalitis with severe symptomatic hyponatremia.

CASE REPORT

A 21-year-old lady who was previously well, presented with one day history of high-grade fever and multiple episodes of vomiting to Hospital Teluk Intan, Perak, Malaysia. Clinical examination on admission revealed temperature of 38.8°C, blood pressure 130/72 mmHg and pulse rate 108 bpm. She was restless and confused but still able to obey simple commands.

Initial investigations revealed haemoglobin of 12.4 g/dl, white cell count 9.1 x 10^3/ul (neutrophil 90%, lymphocyte 3%), haematocrit 35.2% and platelet 190 x 10^3/ul. She also had hyponatremia with sodium level of 120 mmol/l. Her aspartate transaminase (AST) was slightly elevated at 59 u/l while her alanine transaminase (ALT) was normal. Dengue was suspected as her father and brother were also warded for dengue fever. Her dengue virus NS-1 antigen was positive while dengue IgM and IgG were negative. She had contrasted CT brain done and the finding was normal with no meningeal enhancement. She was diagnosed with dengue encephalitis and admitted.

Nine hours after admission, she developed one episode of generalized tonic clonic seizure which lasted for 40 seconds. Repeated serum sodium was 117 mmol/l with a calculated serum osmolality of 242 mOsm/kg. This was despite her not having any more episodes of vomiting and was on 1.2 mls/kg/hr of normal saline infusion since admission. Post fitting her Glasgow Coma Score (GCS) reduced to E4V2M5 (total 11/15). Patient was not hypovolemic and perfusion was good. She was given hypertonic saline (3%) correction followed by Sterofundin (balanced isotonic elctrolyte solution) as maintenance drip. Her sodium level improved gradually to 128 mmol/l. Urine sodium and urine osmolality were not taken prior to correction. Post correction her urine sodium was 170 mmol/l and urine osmolality was 124 mOsm/kg.

The conscious level of the patient did not improve despite correction of her serum sodium. Lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed no cells, no growth on culture, normal CSF protein (0.43 g/l) and CSF glucose 3.6 mmol/l (random blood sugar was 6.0 mmol/l). CSF for dengue PCR was tested positive and DEN-2 serotype was identified.

She was given symptomatic treatment and closely observed in the intensive care unit. There was no further episode of seizure. Her conscious level returned to normal on day 3 of admission. Her platelet count decreased progressively in trend but there was no evidence of hemoconcentration. She started to develop transaminitis on day 4 of admission with highest AST level reaching 1237 u/l and ALT l280 u/l but remained asymptomatic. Her bilirubin and alkaline phosphatase remained normal throughout admission. Her fever only began to settle on day 6 of illness with concurrent improvement of her transaminases.

During this time, her creatine kinase was also found to be markedly elevated at 37,490 U/l. She did not have any muscle aches or myoglobinuria and her renal profile was normal with good urine output. Echocardiography was not done as she was improving clinically with no chest pain,

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Corresponding Author: Brian Cheong Mun Keong
Email: keabcmk@hotmail.com

Table I: Investigation chart of the patient

Day of Admission	1	2	3	4	5	6	7	8	9	10
TWC (x10^9/l)	9.1	5.7	3.5	2.0	2.0	1.9	2.4	1.8	2.4	2.1
Hb (g/l)	12.4	12.0	13.8	13.5	13.4	13.1	12.2	11.1	11.1	10.1
Hct (%)	35.2	32.9	37.5	37.1	38.1	35.7	33.4	31.7	36.5	36.5
Plt (x10^9/l)	190	174	135	104	63	60	55	87	87	221
Urea (mmol/l)	1.9	1.3	1.6	2.2	2.8	2.8	2.4	1.6	1.8	1.4
Na (mmol/l)	120	117	129	127	125	127	133	137	136	139
K (mmol/l)	2.8	3.4	3.5	4.2	3.9	3.8	3.4	3.8	3.5	3.9
Creatinine (mmol/l)	47	40	41	40	44	43	49	50	42	35
Calculated serum osmolality (mmol/kg)		242								
Urine Na (mmol/l) post correction		170								
Urine Osmolarity (mmol/kg) post correction		124								

tachycardia or failure symptoms. The creatine kinase gradually improved. She was discharged well after nine days in the ward. Upon discharge, her WCC was 4.35 x 10^3/ul, platelet count 488 x 103/ul, AST 51 U/l, ALT 70 U/l and creatine kinase 195 U/l.

DISCUSSION

The main symptoms of dengue encephalitis are headache, altered sensorium and seizures. As in our patient, dengue encephalitis can present as early as day one of illness. The criteria for dengue encephalitis are: i) fever; ii) acute signs of cerebral involvement; iii) presence of anti-dengue IgM antibodies or dengue genomic material in the serum and/or cerebrospinal fluid; iv) exclusion of other causes of viral encephalitis and encephalopathy.[3] Dengue virus has four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). The serotypes most frequently implicated in causing neurological complications are DEN2 and DEN3.[4] Although MRI brain is the imaging modality of choice in encephalitis, it is not specific nor essential as a plain CT scan can rule out other life-threatening complications like intra-cerebral bleeding. A MRI brain was not done for our patient as our centre does not have this facility.

Hyponatremia is a common electrolyte disturbance and may play an important role in the prognosis of dengue fever and associated complications. The incidence of CNS and bleeding complications have been reported to be higher with severe hyponatremia.[2] Our patient had severe hyponatremia which caused seizure and altered sensorium. The degree of hyponatremia appeared to be disproportionate to her vomiting which had already stopped upon admission and normal saline drip commenced. The cause of hyponatremia could have been due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) as her serum osmolality was less than 280 mOsm/kg. Although urine osmolality and urine sodium was not done before correction, the diagnosis of SIADH was suspected as her serum sodium dropped further following hydration. In SIADH restriction of fluid is the recommended treatment. Urine sodium post correction was elevated likely due to the sodium load from the 3% saline infusion. Her urine osmolality was still above 100 mOsm which in the context of serum hypo-osmolality suggests arginine vasopressin (AVP) excess.

The occurrence of SIADH with encephalitis is a known association. Other mechanisms of hyponatremia postulated in association with dengue fever are excess water from increased metabolism, decreased renal excretion, or the influx of sodium into the cells as a result of dysfunction of sodium potassium pump.[5]

The patient's conscious level was slow to respond to the correction of hyponatremia. Recovery from neuropsychiatric effects of hyponatremia may be delayed. Therefore, it is possible that acute hyponatremia was the cause of the neurological manifestation of the patient instead of dengue encephalitis.

Another interesting finding in our patient was the markedly elevated creatine kinase of above 30,000 U/l in the absence of symptoms as well as other laboratory evidence of rhabdomyolysis like hyperkalemia. Dengue fever, although commonly causes muscle aches and joint pains, rarely causes creatine kinase to be raised to this degree. Seizures can also cause elevation of creatine kinase. However, very raised levels are usually seen after a violent status epilepticus. Our patient's fit only lasted for 40 seconds. Other causes of markedly elevated creatine kinase are rhabdomyolysis, myositis and myocarditis, all of which have been reported before in complicated dengue fever. As the patient was clinically well, it was decided that she did not warrant further investigations like an echocardiography or muscle biopsy.

The management of dengue fever and its complications remain mainly supportive. Careful monitoring of symptoms and a high index of suspicion for its myriad complications is important. The outcome of dengue encephalitis is variable with many studies showing good recovery.

CONCLUSION

Dengue encephalitis is increasingly being recognized as a complication of dengue fever. It should be suspected in all patients with fever and altered sensorium in dengue endemic areas. It can be confirmed by CSF dengue PCR and treatment is supportive. Dengue fever can also be associated with SIADH leading to symptomatic hyponatremia which can present with seizures and altered conscious levels.

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CASE REPORT

Septic arthritis of temporomandibular joint

Nursofia Diana Azmi, MD[1], Nasibah Mohamad, MMed[2], Nor Adibah Razali, MMed[3], Ahmad Kamal Tarmizi Zamli@Zamdi, Master of Clinical Dentistry[4], Nur Asma Sapiai, MMed[2]

[1]Department of Radiology, Institut Kanser Negara, Wilayah Persekutuan Putrajaya, Malaysia, [2]Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, [3]Department of Radiology, Hospital Kuala Lipis, Kuala Lipis, Pahang, Malaysia, [4]Department of Maxillofacial Surgery, Hospital Tengku Ampuan Afzan, Pahang

SUMMARY

Septic arthritis (SA) occurrence for temporomandibular joint (TMJ) is rare. Pain, fever, swelling or loss of TMJ function are the typical presentation. The more common diagnosis for these presentations is internal derangement, osteoarthritis and rheumatoid arthritis. Therefore, TMJ septic arthritis is a challenging diagnosis and at risk of delayed diagnosis. We present a case of TMJ septic arthritis in a 46 year old Malay female with underlying hypertension and hypercholestrolemia, which was diagnosed as internal derangement in the initial presentation. The initial radiograph was normal. Arthrocentesis procedure had temporarily relieved the symptoms before progressive facial swelling developed after a week. Contrast enhanced computed tomography (CECT) brain revealed left TMJ abscess formation with left condylar erosion. Patient subsequently improved after wound debridement, left condylectomy and antimicrobial therapy.

INTRODUCTION

Septic arthritis (SA) occurrence for temporomandibular joint (TMJ) is rare.[1] Patient usually presents with pain, fever, swelling or loss of TMJ function. The established aetiology is haematogenous dissemination or local spread. They are mostly caused by *Staphylococcus aureus, Streptococcus* and *Pseudomonas aeruginosa*.[1] Typically, patient comes with risk factors either trauma, systemic or autoimmune diseases, for example rheumatoid arthritis, diabetes, systemic lupus erythematosus or hypogammaglobulinemia.[2]

SA in the joints has a mortality rate of 12%. 75% of survivors have significantly reduced function of the affected joint. SA of the TMJ is known to result in significant morbidity if the diagnosis is delayed.[3] We want to highlight the importance of prompt TMJ septic arthritis diagnosis to avoid the complications.

CASE REPORT

A 46 year old Malay female with underlying hypertension and hypercholesterolemia presented with limited mouth opening for one month associated with pain and facial swelling. Patient had no fever or history of trauma. White blood count (WBC) was not elevated: 8.0x10^3/uL. Orthopantomogram showed subtle left TMJ joint widening only notice retrospectively (Figure 1). Symptoms persisted despite taking analgesia for two weeks. Arthrocentesis of left TMJ was done for closed lock of left TMJ (internal derangement) with the improvement of interincisal distance from 21mm (preoperative) to 36 mm (post-operative). The patient was well for 8 days before experiencing the same symptoms for one week. Progressive swelling noted from left TMJ region to left infraorbital region. It was warm, tender and firm. Yellowish discharge oozed from the inner part of the cheek. Mouth opening was 15mm. She was afebrile, WBC 10.1x10^3/uL and C-reactive protein (CRP):119 mg/L. Initial diagnosis was left parotid abscess. Contrast-enhanced computed tomography (CECT) brain noted collection around the left condylar process associated with erosion and left condylar process subluxation (Figure 2). Intraoperatively, there was pus discharge with inflamed capsule and left condylar head erosion. Wound debridement and condylectomy of left mandibular condyle were done (Figure 2). Histopathology examination (HPE) report was consistent with inflammation. Pus and tissue culture showed no growth. Patient was on IV ceftazidime 1g TDS for 16 days and IV metronidazole 500 mg TDS for ten days. Upon discharge, Tablet ciprofloxacin 500mg BD was given for 14 days. Patient was symptoms free after the procedure. No recurrence reported after six month follow up.

DISCUSSION

SA is a medical emergency due to its irreversible complication. TMJ septic arthritis leads to joint destruction and subsequent bony ankyloses and fibrosis.[3] In our patient, the most likely cause of delayed TMJ septic arthritis diagnosis is subclinical infection. Patient has no risk factor or fever, and serial white blood count was normal, despite having symptoms for one-month duration. On top of that, the initial radiograph showed a normal joint space, except for subtle widening at the left lateral aspect. The occult infection worsened after the arthrocentesis, which could be due to local spread to neighbouring soft tissue resulting from the capsular breach.

The established aetiology of TMJ septic arthritis is haematogenous or local spread. The haematogenous spread from the distant primary is more common.[3] The elderly and children less than three years old are most commonly involved.[2] The common risk factors in an adult include older age group, diabetes mellitus, rheumatoid arthritis, immunosuppression, skin infection, penetrating trauma and

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Corresponding Author: Nasibah Mohamad
Email: nasibahmohamad@yahoo.com

Fig. 1: Orthopantomogram done during admission shows no obvious findings except for subtle widening of left TMJ at lateral aspect (black arrow) notice retrospectively. No bony erosion.

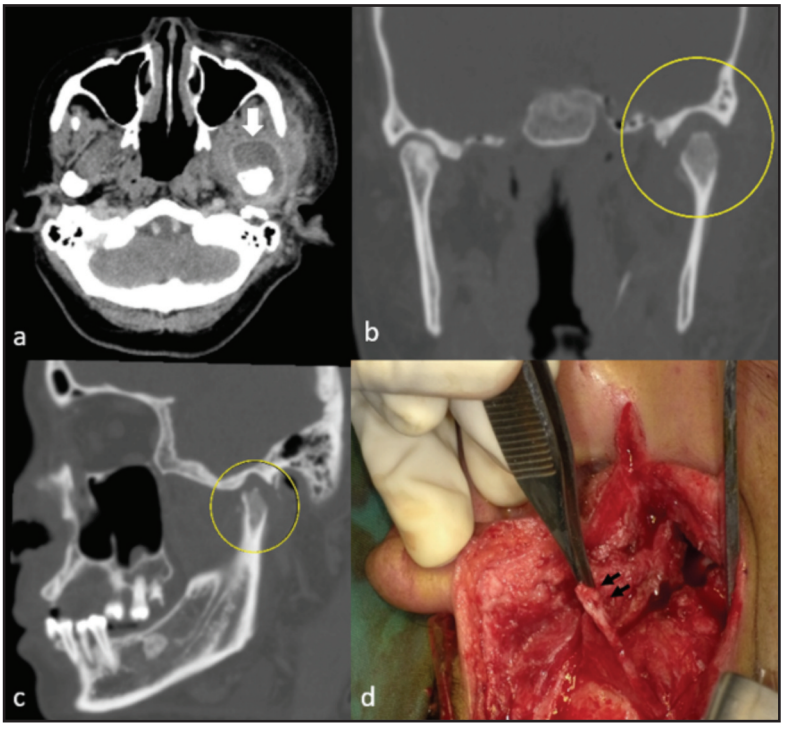

Fig. 2: Contrast enhanced CT brain: a. axial soft tissue setting showed rim enhancing collection at the left condylar process (white arrow); b. coronal reconstruction and c. sagittal reconstruction in bone setting showed left condylar erosion, joint widening and subluxation (yellow circle); d. Intraoperatively, left condylar erosion identified (black arrow).

arthroscopy procedure.[2] Few publications have reported local spread to TMJ after the molar tooth extraction, intra-articular injection, facial burns and otitis externa. The TMJ capsular breach due to blunt trauma has facilitated haematogenous spread of infection.[4]

The common presenting complains of SA TMJ are warm, erythematous pre-auricular swelling associated with pain, limited mouth opening and malocclusion. Differentials include infection; dental abscess, pharyngitis, retropharyngeal abscess, peritonsillar abscess, mastoiditis, parotitis, sialadenitis and lymphadenitis.[4] However, in the absence of inflammation, neoplastic process arising from mandibular condyle, parotid tumour, as well as other systemic diseases, namely rheumatoid arthritis, gout and pseudogout are diagnoses of choice.[3,4] Early diagnosis of TMJ septic arthritis is not easy as not all cases exhibit signs of inflammation. Therefore imaging plays an important role in suspected SA. The earliest sign of septic arthritis is joint effusion as a result of pus and inflammatory exudates accumulation in a joint space. Both MRI and CT imaging can detect joint effusion in the early stage.[5] However CT imaging is an excellent tool in demonstrating bony anatomy of TMJ, temporal bone and skull base. It can detect bony erosion and evaluation of potential extension to the contiguous soft tissue. MRI is superior in demonstrating the soft tissue anatomy surrounding the TMJ.[5] MRI was not done in this patient due to non-availability in the district hospital.

Elevated white blood count above the 12,000/mm^3 is one of four parameters used for clinical prediction of SA.[2] The serum erythrocyte sedimentation rate (ESR) and C-reactive protein are systemic acute phase reactants that can be elevated in SA. These three markers are non-specific and can be elevated in a non-infectious inflammatory condition. The procalcitonin level is a serum marker that can rise rapidly due to bacterial infection. Unlike ESR and CRP, serum procalcitonin remain low in systemic inflammatory disorders.[2] Nevertheless, these four markers are not predictive for SA. Therefore, correlation with the clinical history, physical examination and culture findings are mandatory.

There is no clear consensus on the management of TMJ septic arthritis and a few methods have been proposed including needle aspiration, arthroscopy and arthrotomy.[4] However, if the abscess formation is established, exploration and surgical drainage must be performed immediately. If bony erosion and cartilage erosion are identified intraoperatively, the condylectomy is required.[4] A paediatric patient diagnosed with TMJ septic arthritis is treated by aspiration alone and washout in acute setting. Immediate empirical antibiotic therapy is mandatory when diagnosed and later should be tailored to culture and sensitivity. Duration of antibiotic treatment should be at least 30 days.[4]

CONCLUSION

SA requires rapid and aggressive treatment as infection can lead to quick, permanent destruction. The pitfall in diagnosis is due to the rarity of the case and overlapping clinical findings with other inflammatory diseases coupled with lack of specific laboratory findings. Thus, high clinical suspicion and timely diagnosis are crucial in minimising the risk of ankylosis, impaired joint mobility and function, bone deformity and fibrosis.

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Isolated hypotension after the induction of general anesthesia refractory to fluids and vasopressors: An indicator of anaphylaxis

Chuang Shin Mok, M. Anesthesiology, Vanessa Lee, MBBS

Department of Anaesthesiology & Critical Care, Hospital Bintulu, Bintulu, Sarawak, Malaysia

SUMMARY

Differentiating between anaphylaxis and hypotension during general anaesthesia is difficult, especially when patients present with only hypotension and without any of the other classical features of anaphylaxis. We report the successful management of an anaphylactic reaction to rocuronium that presented as isolated hypotension in a 45-year-old Indonesian man presented with lacerations on the scalp and right pinna caused by an assault to the head after the induction of general anaesthesia, refractory to fluids and high doses of vasopressors. This case highlights that a possible indicator of anaphylaxis can be the presence of isolated hypotension during general anaesthesia, refractory to vasopressor agents.

INTRODUCTION

Intraoperative hypotension during general anaesthesia is a more common problem than perioperative anaphylaxis, whose incidence is estimated to be 1:10000.[1,2] Failure to differentiate between the two can lead to a delay in definitive treatment, which is a risk factor for mortality. Our case highlights the importance of identifying isolated refractory hypotension after the induction of general anaesthesia, as this may be the only indicator of anaphylaxis. We report a case of isolated hypotension during general anaesthesia who are refractory to fluids and repeated doses of vasopressors, anaphylaxis should be suspected, and a test dose of intravenous adrenaline can be administered earlier for better clinical outcome.

CASE REPORT

A 45-year-old Indonesian man presented with lacerations on the scalp and right pinna caused by an assault to the head. He was scheduled for emergency wound debridement, toilet, and suturing of the scalp. A computed tomography (CT) brain scan revealed no intracranial bleeding. Multiple facial bone fractures were observed and conservative management of these was recommended.

The patient had no history of diabetes mellitus, hypertension, myocardial infarction, heart failure or any other medical problem. He had no known history of any surgery. He did not smoke cigarettes and had no known allergies. His functional status was good. His peripheries were warm, his vital signs were normal with blood pressure of 134/75 mmHg and there were no signs of active bleeding, anaemia or electrolyte imbalance. He was mildly dehydrated, with a coated tongue, and capillary refill time of 2 seconds. Pain was tolerable with pain score of 3.

Electrocardiography showed a sinus tachycardia of 120 beats per minute. Chest radiography was normal, with no signs of pneumothorax. Other preoperative assessments were within normal range. Renal profile revealed a urea of 5.1 mmol/L and creatinine of 85 micromole/L. Six hours prior to the operation, an intravenous dose of ceftriaxone (50 mg/kg) was administered in the emergency department.

General anaesthesia was induced with the intravenous administration of fentanyl (2 mcg/kg), propofol (2 mg/kg), and rocuronium (1 mg/kg). The patient was intubated, and general anaesthesia was maintained with 2.5% sevoflurane in an oxygen/air mixture. He was ventilated on pressure control ventilation, inspiratory pressure of 14, rate 12, Fio2: 0.4, Peep 6.

After 5 minutes of general anaesthesia, the patient developed hypotension (65–80/40–50) based on the first reading from non-invasive blood pressure monitoring. The operation had not yet started and skin preparation with chlorhexidine was not applied on the patient. Differential diagnoses such as pneumothorax, sepsis, and myocardial infarction were ruled out. The patient displayed a tachycardia of 105 beats per minute, a decrease, compared to the rate measured prior to the induction of general anaesthesia. No obvious ischemic changes were observed in the electrocardiographic readings. A carotid pulse was present. Peak pressure from the ventilator was 20 cm H_20 with similar initial ventilator setting and the end tidal carbon dioxide measurement was 25 mmHg. There was no decrease in oxygen saturation or signs of fever, flushing, urticaria, or bronchospasm. A measurement of venous blood gases 30 minutes into anaesthesia indicated a state of metabolic acidosis with pH 7.15, bicarbonate level 15.5 mmol/L, potassium level 4.0 mmol/L, and haemoglobin level 10.8 g/dL.

The patient did not respond to the usual boluses of vasopressors such as phenylephrine (total dose 2 mg) and ephedrine (total dose 30 mg). A total of 30 mL/kg of Ringers lactate was administered as fluid resuscitation; noradrenaline infusion was started up from an initial dose of $0.1_{mcg/kg/min}$, titrated up to $0.8_{mcg/kg/min}$ as shown in Figure 1. Despite these measures, a mean arterial pressure of 65 mmHg could not be achieved. Anaphylaxis was suspected and the

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Corresponding Author: Chuang Shin Mok
Email: shinf22@gmail.com

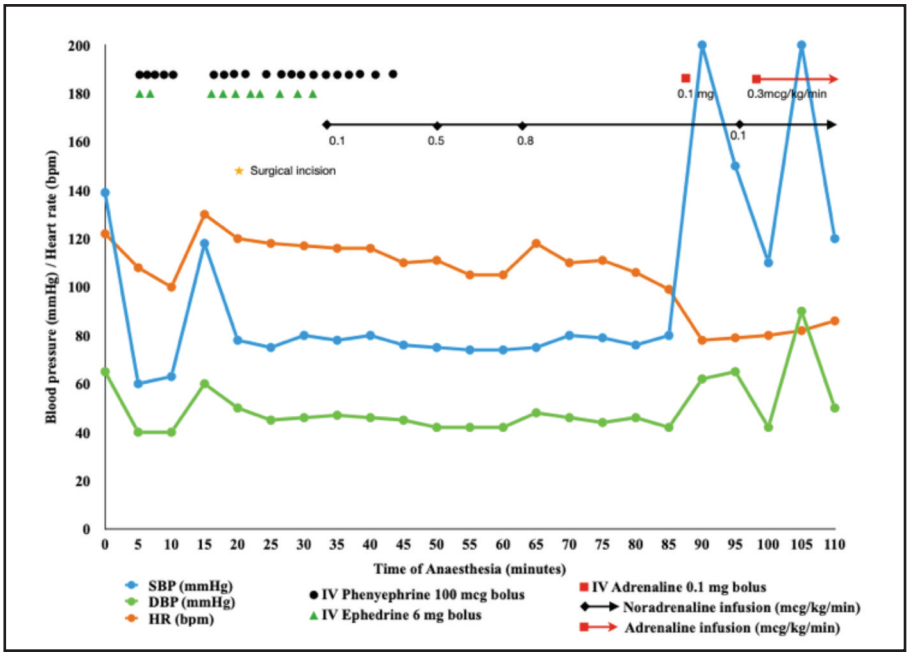

Fig. 1: Intraoperative vital signs and drug administration over time during anaesthesia.
Hypotension refractory to vasopressors commenced 5 minutes into anaesthesia. An improvement in blood pressure was noted after a single bolus dose of intravenous adrenaline. [SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate]

patient was given a single bolus dose of adrenaline 100 mcg (1:10000). The blood pressure responded to this bolus dose, with a surge in blood pressure up to 200/70 mmHg. Intravenous adrenaline was then initiated up to an infusion rate of 0.28mcg/kg/min through a newly inserted femoral central venous line. The patient's blood pressure was maintained at a range of 140–200/60–90 mmHg. Intravenous hydrocortisone (200 mg) and chlorpheniramine (10 mg) were administered intraoperatively as part of the anaphylaxis treatment.

The surgery commenced 15 minutes post induction as patient was initially treated as usual post general anaesthesia hypotension. Estimated blood loss was minimal and a total fluid of 3 litres were given intraoperatively (2500 ml of Ringer lactate plus 500 ml of Albumin 5%). The patient was admitted to the intensive care unit (ICU) postoperatively, where he was placed on a ventilator for 1 day. He was also supported haemodynamically with Noradrenaline 0.1mcg/kg/min and Adrenaline of 0.4mcg/kg/min. Measurement of his blood gases on entry into the ICU indicated a more severe metabolic acidosis with pH of 7.0 and bicarbonate of 7.0 mmol/L. With no evidence of diabetic ketoacidosis, the metabolic acidosis was managed according to standard treatment guidelines. His postoperative haemoglobin level was 10.5 g/dL while his kidney function showed a deterioration with creatinine level 111 micromole/L and urea level 5.3 mmol/L. Clinically, he was not dehydrated with the initial inferior venous cava scan of 1.6 cm. Transthoracic echocardiography indicated the absence of valve and regional wall motion abnormalities. All the cardiac chambers were of normal size with good right and left ventricular function. Ejection fraction was more than 60%.

On day 2 of ICU admission, the patient showed significant clinical improvement; he was fully conscious and on low setting pressure support ventilation. He was weaned off from inotropic support with resolved tachycardia. His blood gases and kidney functions returned to normal, with good urine output. He was extubated and discharged after 2 days and given an allergy card, indicating his possible rocuronium allergy. The patient refused to undergo any allergy skin testing after receiving advice regarding its risks and benefits.

DISCUSSION

Anaphylaxis has always posed a diagnostic challenge. One study reported that up to 40% of all patients who died because of anaphylaxis, did not receive any adrenaline.[3] Our diagnosis of anaphylaxis was based on clinical observations. These include the responsiveness of the patient's hemodynamic to a single bolus dose of adrenaline, the resistance to vasopressors, and the relatively short recovery time in the ICU.

Only 5.6% of patients with anaphylaxis present with isolated cardiovascular features.[1] Hypotension after induction of general anaesthesia is more common, especially when propofol is used for induction. Except for tachycardia, which our patient had prior to the operation, there was no evidence of the other classical features of anaphylaxis. The anomalous presentation of the anaphylaxis resulted in a delay in the implementation of treatment plan.

The first limitation of this study was our inability to obtain the patient's serum tryptase levels. However, since not all anaphylactic situations produce an elevation of tryptase level, a normal tryptase level does not exclude the diagnosis.[4]

The second limitation was our inability to persuade the patient to undergo allergy skin tests, mainly due to his cost constraints. Thus, the aetiology of anaphylaxis in this case remains unknown. The administration of antibiotics 6 hours prior to the operation was uneventful. The use of propofol and fentanyl was less likely to be the cause.[1] The 6th National Audit Project has showed that the drugs most commonly involved in anaphylaxis are antibiotics (48%) followed by neuromuscular blocking drug (NMBD) (25%).[1] Another study on anaphylaxis in anaesthesia also found that NMBDs (61%) were most responsible for anaphylaxis.4 Additionally, around 95% of reactions involving NMBD presented within 5 minutes.[1] Therefore, based on the evidence and timing of the event the cause of the anaphylaxis in this study was presumed to be rocuronium.

Although the patient had no previous anaesthetic history, evidence has shown that anaphylaxis can still occur as the quaternary ammonium group of the NMBD is found in many foods and over the counter drugs. Cross-sensitization through exposure to the ammonium group may explain why allergic reactions to NMBD can occasionally occur upon initial exposure to rocuronium.[5]

Adrenaline is the first-line treatment for anaphylaxis as it offers greater physiological benefits. In our case, the patient's deterioration could have been avoided if adrenaline had been administered first instead of noradrenaline. After the administration of adrenaline, noradrenaline was weaned off without any lowering of the blood pressure. The triggering threshold based on the total dose of vasopressor given before the single bolus dose of adrenaline is unknown. This provides a basis and direction for future research.

In conclusion, our case highlights the importance of identifying isolated refractory hypotension after the induction of general anaesthesia, as this may be the only indicator of anaphylaxis. We also recommend that intravenous adrenaline be administered earlier to such hypotensive patients who are refractory to fluids and repeated doses of vasopressors. This early identification will enable early administration of adrenaline and hence, improve morbidity and mortality.

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CASE REPORT

Mycotic iliac artery aneurysm with appendicitis in a pediatric patient

Sunil SP, Ms[1], Karthigesu Aimanan, Dr Surg[2], Ismazizi Z, Ms[1]

[1]Department of Surgery, Hospital Kuala Lumpur, Ministry of Health Malaysia, [2]Department of Surgery, Hospital Miri, Sarawak, Ministry of Health Malaysia

SUMMARY

Iliac aneurysms are rare in children, especially mycotic aneurysms. Re-vascularization is challenging given the infected field and concern on patency due to their growth potential and a longer life-span. We report a complex case of a mycotic iliac aneurysm in a child. A 12-years-old boy with a previous history of infective endocarditis was referred to us for a right common iliac mycotic aneurysm after presenting with pain. A balloon-expandable stent-graft was deployed across the aneurysm during the acute presentation. He improved post-operatively, but developed abdominal pain four weeks later. A repeat computed tomography (CT) imaging showed a new inflammation of the appendix which was adhered to the calcified wall of the aneurysm and an endoleak from the internal iliac artery. A laparotomy was performed and the right internal iliac artery ligated along with an appendicectomy and omental pedicle. Postoperatively the patient was well and discharged home. Six-month surveillance revealed a healthy child and imaging showed a patent stent-graft and no residual collection.

INTRODUCTION

Arterial aneurysms are rare in children, especially mycotic iliac aneurysms (MIA).[1] Conventional open repair of MIA raises the challenge of a suitable conduit and morbidity in an ill child. We report our management of a 12-year-old boy who developed a MIA due to infective endocarditis which was subsequently complicated with acute appendicitis. Herein we describe our approach of the management.

CASE REPORT

A 12-year-old boy presented with an acute lower abdominal pain of a week duration associated with fever and diarrhoea. He had previously been treated for infective endocarditis when he was 9 years old with a long course of penicillin after blood cultures grew Streptococcus pneumoniae. At that point he had no abdominal symptoms and there was no suspicion of an iliac aneurysm. Surveillance echocardiograms showed resolved vegetation and no valvular heart disease. On presentation at the Department of Surgery, Hospital Kuala Lumpur a tender mass was palpable on his right iliac fossa. He was febrile and tachycardic, though no significant leucocytosis and C-reactive protein (CRP) of 12mg/L. Computed tomography (CT) scan revealed a saccular aneurysm of the distal right common iliac artery (CIA), and a normal appendix (Figure 1).

An endovascular approach was chosen for the treatment as open surgery would be associated with a higher morbidity. Furthermore, there was no suitable native conduit and we felt a synthetic graft was better suited once the child had completed adolescence. While under general anaesthesia the right femoral artery was exposed via a groin incision. Percutaneous access was not attempted as the profile of the stent-graft was 9Fr and we did not have access to vascular closure devises. After catheter-directed retrograde cannulation of the CIA, angiography revealed a stenotic proximal external iliac artery (EIA) due to the mass effect of the aneurysm. After dilatation with an 8mm PTA dilatation catheter, a 7mm x 58mm Lifestream BE stent-graft (Becton Dickinson, UK) was deployed across the mycotic aneurysm, proximally landing at the CIA and distally at the EIA. Post-deployment angiography revealed no filling of the sac, and the right internal iliac artery opacified from retrograde flow (Figure 2). Postoperatively the condition of the patient improved and had reduced CRP from 74.6mg/L to 9.4mg/L. Surveillance ultrasonography revealed an endoleak from the right IIA. As it was small, we planned for conservative treatment, and empirical ertapenem was given during the subsequent recovery as blood cultures did not yield any organisms.

Unfortunately his sepsis and abdominal pain recurred four weeks later while he was an inpatient. A repeat CT scan revealed gas pockets in the previous aneurysm sac, and the appendix was grossly inflamed and was adhered to the sac, which was not present on the previous imaging. Open drainage was performed as there was no accessible percutaneous window. Intraoperatively the sac was filled with pus and a perforated appendix densely adhered to the calcified wall. An appendicectomy was performed, the right internal iliac artery was ligated and an omental pedicle anchored into the sac after drainage and deroofing, avoiding exposure of the endograft. Intraoperative cultures showed mixed growth.

The patient made a full recovery after completing a course of intravenous metronidazole and ampicillin & salbactam over two months. On discharge he was prescribed oral metronidazole and ampicillin & salbactam for another two months. Erythrocyte sedimentation rate (ESR) and CRP continued to reduce and also the resolution of leucocytosis. All subsequent cultures were negative. He is on long term aspirin 100mg daily and oral ampicillin/sulbactam and remains under follow up. Surveillance imaging at 6 months showed no endoleak and good antegrade flow.

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Corresponding Author: Karthigesu Aimanan
Email: karthi_abim@yahoo.com

Fig. 1: CT abdomen, A- Normal appendix, B – Right CIA aneurysm.

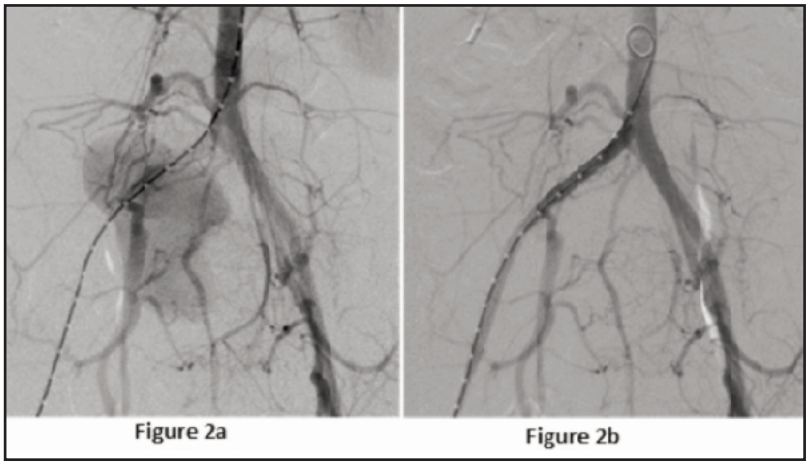

Fig. 2: DSA of right iliac artery before (2a) and after (2b) endograft deployment.

DISCUSSION

The etiology of the aneurysm in our patient can be attributed to his previous bout of infective endocarditis in his childhood, as the calcified wall suggests a chronic process. In the classification proposed by Sarkar et al, this type of aneurysm is due to arterial infection from a systemic process and accounts for a third of reported cases.[1] The appendicitis in our patient developed while during recovery from the first surgery was not in fact the cause of the aneurysm, as initial imaging showed a normal appendix. We postulate that the appendicitis developed due to lymphoid hypertrophy secondary to inflammation from the mycotic aneurysm and foreign-body response after the stent-graft deployment.

In the literature, the surgical approach to treat mycotic aneurysms in children has generally been via an open technique. Iliac mycotic aneurysms due to infective endocarditis and tuberculosis have been described in an 8-year-old and a 12-year-old respectively, both having successful bypasses with synthetic grafts.[2,3] Nevertheless, patency is an issue in paediatric vascular bypasses, wherein late primary graft failures occur in up to a third of cases. Due to somatic growth, the dimensions of the conduit and technique of anastomosis play an important role. Both the diameter and length need to be considered when choosing and fashioning a graft. Autologous graft in this patient was not used due to the small calibre of the native veins of the child.

Stent-grafts on the other hand have a relatively fixed geometry, and are usually not performed in children. However, its role as a bridging procedure in an ill child is very attractive and can be extrapolated from adult series.[4] Stent-grafts have proven to be a feasible mode for treatment in MIA in adults, at least as a bridge to later definitive therapy when the physiologic condition of the patient is more favourable. Stenting in an adolescent in an acute setting has been reported using balloon-expandable stent-grafts.[4] Our choice of balloon-expandable stent-graft allows maximum inflation dilatation to 10mm. As the average adult Asian iliac artery is 11mm, this allows for future redilatation to nearly accommodate the increased blood flow required during his pubertal growth spurt. This hypothesis extrapolated from pediatric data on stent-graft use in coarctation of aorta has several drawbacks though. Neointimal hyperplasia and the risk of arterial wall injury have to be considered prior to redilatation, along with stent-graft shortening.

Keeping in mind the afore-mentioned growth spurt, the postoperative management entails various aspects, mainly

infection control and stent-graft patency. As this is a mycotic aneurysm which was complicated with an acute appendicitis, there remains a risk of endograft infection and subsequent pseudoaneurysm and blow-out. Choice of antimicrobial therapy is based on culture results though there is no consensus on duration of therapy.[5] Surveillance for infected grafts may be enhanced with white blood cell scintigraphy and single-photon emission computed tomography (SPECT/CT), though these modalities are hampered by its practicality.[5] Hence biochemical and clinical parameters remain the cornerstone of surveillance. Until the end of the adolescent growth spurt, surveillance should be done frequently as children may be asymptomatic of endograft thrombosis due to collateral vessels.

CONCLUSION

To our knowledge, this is the first reported case of a mycotic aneurysm in a child associated with a perforated appendix, successfully treated with a staged hybrid approach as a bridging therapy. The use of a stent-graft reduces the morbidity of the index surgery in an ill patient and allows for future bypass, at which point both target arteries and autologous conduits are bigger. Postprocedural surveillance is vital in the management to detect endograft thrombosis, especially during the growth spurt of puberty and detection of endograft infection.

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Uterine arteriovenous malformation – Possible association to uterine fibroids?

Farah Gan, MD, Vikneswaran Virasamy, MBBS, Yu Kok Kin, MBBS

Department of Obstetrics and Gynaecology, Selayang Hospital, Selangor

SUMMARY

A 32-year-old, gravida 2 para 0+1, was managed in Selayang Hospital, Selangor for uterine fibroids in pregnancy and placenta previa major. The lady went into preterm labour at 33 weeks, requiring emergency Caesarean section. Intraoperatively, we found a thinned-out bulge between the intramural uterine fibroids at the posterior uterine wall, which then perforated and was repaired. Persistent bleeding post operatively led to relaparotomy and hysterectomy. Histology of the uterus reported arteriovenous malformation (AVM). We postulate the possibility of these lesions co-existing with uterine fibroids. Screening for uterine AVMs in patients with fibroids may lead to early detection with option of embolization; deferring the need for hysterectomy.

INTRODUCTION

Uterine arteriovenous malformations (AVMs), although considered rare, have an important place in gynaecological practice due to risk of massive bleeding that is potentially life-threatening. There are numerous risk factors associated with this condition; encompassing nearly the entirety of uterine pathophysiology, as well as the normal physiologic changes of pregnancy.[1] As such, a high index of suspicion is required when faced with persistent or heavy uterine bleeding, after common causes have been ruled out. This case report highlights our encounter with a patient with multiple uterine fibroids, whose bleeding during Caesarean section was only later confirmed to be due to a uterine AVM. We hope to raise awareness of the possibility of these lesion co-existing with uterine fibroids when seen in women whose uterine bleeding remains uncontrolled despite routine measures.

CASE REPORT

We describe here a case of a 32 year old, gravida 2 para 0+1 who was followed up in Selayang Hospital, Selangor throughout her antenatal period for multiple uterine fibroids and placenta previa major. She had a complete miscarriage in the past, managed conservatively and not requiring curettage. She denied having any uterine surgeries done before.

She went into preterm labour at 33 weeks of gestation and required emergency Caesarean section. Intraoperatively she was reported to have a highly vascularised lower segment with a distorted uterine cavity. There were multiple intramural fibroids at the posterior wall of the uterus; largest of which measured 7x6cm, located at the left cornua.

Due to persistent bleeding, the uterus was exteriorised for optimal view. Interestingly, she was found to have a thinned-out bulge measuring 5x6cm, located right in between the fibroids previously mentioned at the posterior wall of the uterus, away from the placental implantation site. Gentle palpation over this lesion caused it to perforate; a defect of 1x2cm in measurement. Multiple haemostatic sutures had to be applied to secure the bleeding. Post operatively, she was transferred to the ICU for close monitoring.

She unfortunately continued to bleed (evidenced by persistent bleeding from the abdominal drain) and required relaparotomy the same night. Intraoperatively, she was found to be oozing from the friable area at the thinned-out bulge of the posterior uterine wall stated earlier. Hysterectomy was done; however, she had by then developed disseminated intravascular coagulopathy (DIVC). Abdominal packs were placed into the pelvic cavity; these were only removed 3 days later after her coagulation profile had improved. Her condition improved gradually and she was discharged home well on Day 15 post surgery. She remained well during her follow-up at 6 weeks post delivery.

Histology of the uterus reported the posterior wall to have groups of dilated and ectatic vessels with variable muscular wall thickness. There were an admixture of malformed vessels displaying muscular disruption with incomplete muscular wall and intimal protrusion; causing abrupt changes in thickness of medial and elastic layers of vessels and abnormal vascular dilatation. Elsewhere, some vessels were dilated and thin-walled where the uterine stroma form part of the vessel wall. These findings were in keeping with arteriovenous malformation. These were found to be in close proximity with two well-circumscribed intramural lesions composed of interlacing bundles of smooth muscle cells in sweeping fascicles. These smooth muscle cells are of bland-looking spindle cells having cigar shape nucleus and abundant bright eosinophilic cytoplasm with marked stromal hyalinization – suggestive of leiomyomata.

DISCUSSION

AVMs are rare vascular anomalies that are potentially life-threatening. There are difficulties in obtaining accurate incidence rate due to the rarity in reported cases; to date, there are fewer than 150 cases reported in the literature. A prospective study of 959 patients after abortions or delivery found sonographically evident uterine AVMs in 5.2% of women after dilatation and curettage, and in 0.22% of

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Corresponding Author: Farah Gan
Email: farah.gan88@gmail.com

women after delivery; however only 0.1% deemed clinically significant.[2] It is estimated from that study that the incidence of true uterine AVMs is <0.1% of women who have had abortion or delivered. Increased use of imaging modalities is likely to lead to identification of these lesions more frequently.

Arteriovenous malformations result from abnormal direct communication between an artery and a vein without an intervening capillary bed, causing diversion of blood flow into the venous system following the pressure gradient, and resulting in increased intraluminal pressure, high-velocity flow, and marked vascular enlargement of the venous system.[1] These lesions rarely occur in the uterus.

Mainly acquired, uterine AVMs are typically associated with damage to uterine tissue; development of abnormal vascular connections between arteries and veins may occur during the healing process. They usually follow a history of previous uterine trauma – e.g. curettage procedures, caesarean section, or pelvic surgery.[3] Acquired arteriovenous communications are analogous to fistula formation, but more complex and numerous, likely due to the rich vascularity and dense network of anastomoses within the uterus. With increased surgical gynaecological procedures in current practice, the prevalence of uterine AVMs will likely increase.

Outside the context of pregnancy, acquired AVMs are associated with uterine infections, inflammation, endometriosis, gynaecological malignancies, and exposure to diethylstilbestrol (DES).[3] The pathophysiolgy behind non-surgical-related cases of uterine AVMs (such as in the case described above) remain unclear.

Uterine fibroids have occasionally been described in cases of uterine AVMs.[4] AVMs are histologically reflected by abrupt changes in the thickness of the medial and elastin layer of the vessels. During the course of fibroid development, the abnormal increase in muscle growth is accompanied by dysregulation of its normal vascular pattern. From available studies, there appear to be alterations in the distribution of vessels in the myometrium around the fibroid as well. The gradient of vessel size seen in non-fibroid myometrium, is lost in the myometrium around the fibroid.[5] It is proposed that the loss of the vessel size gradient could lead to vascular pressure changes and predispose to the formation of uterine AVMs.

Given the rarity of the condition and its nonspecific ultrasound findings, the diagnosis of uterine AVM is often challenging. Traditionally, and as with our case, AVM was diagnosed by laparotomy and histopathologic examination of the uterus after a hysterectomy. With advancing technology, colour and spectral Doppler ultrasound is now widely used to detect this condition; revealing multiple enlarged uterine vessels, intense signalling, and apparent multidirectional flow indicative of turbulent high-velocity flow within low-resistance vessels. CT, MRI, CTA, and MRA can be used to better delineate the AVM. Digital subtraction angiography (DSA) however remains the gold standard for diagnosing AVMs, though rarely performed due to its invasive nature.[1]

Endovascular management with transcatheter embolization of uterine artery is the mainstay of therapy for uterine AVMs as it is effective, can be done without general anaesthesia, and maintains fertility.[1] Cases refractory to endovascular interventions can be treated definitively with hysterectomy.

Many uterine AVMs spontaneously resolve without requiring treatment. Growing evidence suggests that conservative management with flow monitoring and imaging may be appropriate for patients who are asymptomatic with lower-flow lesions. There have also been case reports describing the use of gonadotropin-releasing hormone (GnRH) agonists, oral contraceptives, as well as methylergonovine maleate to treat uterine AVMs in stable patients.[1]

Described in this case report was a woman in her early 30s, now with only one child. While screening for uterine AVMs (i.e. by means of ultrasound Doppler scan) in all patients with uterine fibroid in pregnancy may not be practical, it would have led to the early detection of this lesion with the option of embolization; hence deferring the need for a hysterectomy. Although rare, there are case reports available on successful uterine artery embolization during an ongoing pregnancy, not resulting in any acute complication to the mother or the developing foetus.

CONCLUSION

Uterine AVMs may present with torrential uterine bleeding, potentially leading to life-threatening haemorrhage. As such, they should be considered as part of the differential diagnoses when faced with unexplained heavy uterine bleeding, so as to avoid any unnecessary intervention which may significantly worsen the bleeding or delay treatment. As far as screening goes, awareness of this condition, recognition of its imaging features, as well as a high index of suspicion is essential in maximizing the chances of a favourable outcome, especially in the presence of risk factors.

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A sinister rash in a lady with breast malignancy

Wen Foong Tan, MRCP, Sook Yee Michelle Voo, AdvMDerm

Department of Dermatology, Hospital Queen Elizabeth, Ministry of Health, Sabah, Malaysia

SUMMARY

Cutaneous metastasis may be the first presentation of an undiagnosed malignancy or a relapse of a previously treated malignancy. We describe a case of a 64-year-old lady with cutaneous metastases from breast carcinoma, who presented with two uncommon rash morphology-carcinoma erysipeloides (CE) and annular erythema. Histopathological examination showed infiltration of neoplastic cells in the dermal lymphatics and staging CT showed distant metastases. She is currently on palliative chemotherapy. A high index of suspicion and early referral to a dermatologist is crucial for early diagnosis for a patient who presents with an inflammatory skin lesion that is refractory to treatment, particularly if the patient has a previous history of malignancy.

INTRODUCTION

Metastases to the skin account for about 0.6-10.4% of all metastases.[1] They may represent the first presentation of an occult malignancy, a relapse of a previously treated malignancy or first indicator of metastasis. The most common internal malignancy that metastasises to the skin in women is breast carcinoma. This may be explained by the location of breast tumours which are superficial and in contiguity with the skin of the chest wall, as compared to visceral malignancy.[1] The presentation of cutaneous metastases may vary from the more common being single or multiple erythematous papules, plaques, nodules or ulcers to the uncommon variants including carcinoma erysipeloides (CE), carcinoma telangiectaticum, carcinoma en curaisse, alopecia neoplastica, metastasis to the inframammary crease and zosteriform pattern.[1,2]

CASE REPORT

We describe a 64-year-old lady who presented with a 3-month history of painless swelling of her right upper limb with itchy rash at her trunk. The right upper limb became warm and more erythematous 2 days prior to presentation, associated with fever. She was diagnosed with right upper limb cellulitis and was treated with intravenous cefuroxime. After completion of a course of antibiotic, the swelling over the right upper limb improved and the rash over her chest, right upper limb and back were less erythematous but persisted. Opinion of a dermatologist was sought. Of note, she had a history of invasive ductal carcinoma of the right breast (T2N3M0, HER2 positive, oestrogen/progesterone receptors negative) and had undergone right mastectomy with axillary lymph node clearance 7 years ago, followed by adjuvant chemotherapy (5-fluorouracil, epirubicin, cyclophosphamide for 3 cycles and docetaxel for 3 cycles), radiotherapy and transtuzumab for 17 cycles. However, she developed right chest wall recurrence 2 years ago and was treated with 6 cycles of docetaxel. She underwent computed tomography (CT) scan at that time which did not show any distant metastases. She denied applying any topical medication on the areas.

On examination, there were well defined irregular erythematous annular patches coalescing into a polycyclic configuration over her chest extending into the left breast (Figure 1a). Her right upper limb was diffusely erythematous and indurated (Figure 1b). Similar annular patches and plaques were seen at the left flank (Figure 2a) and her back (Figure 2b). There was no palpable breast nodules or lymphadenopathy.

Differentials that were considered were CE and radiation dermatitis. Skin biopsies were taken from the erythematous patch over her right upper arm, left chest and left flank. Histological evaluation revealed irregular nests of malignant cells in tubular formation within the dermis and the lumen of vessels. The malignant cells were pleomorphic with fine to coarse nuclear chromatin and prominent nucleoli. Mitotic figures were also seen. The surrounding stroma was desmoplastic with lymphoplasmacytic cells and histiocytes infiltration. Immunohistochemistry studies showed positivity to mammaglobin, HER2 and E-cadherin. The endothelial cells were immunoreactive to CD31. Staging CT showed bilateral pleural effusion and bony metastases.

She was started on capecitabine for 3 cycles, followed by gemcitabine/carboplatin for 6 cycles. The rash over her trunk resolved after completion the chemotherapy. However, she had recurrent pleural effusion and pericardial effusion requiring drainage.

The rash over her chest, abdomen and back recurred 6 months after the gemcitabine/carboplatin chemotherapy and she is currently on treatment with vinorelbine.

DISCUSSION

Here we highlight the need to consider the diagnosis of skin metastases in patients with underlying solid organ tumour presenting with erythematous, indurated skin eruption. Interestingly, our patient had CE and annular erythema which are two morphological variants of skin metastases. In this case, radiation dermatitis was another differential however, it was less likely as the erythematous indurated appearance of radiation dermatitis usually occurs in the

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Corresponding Author: Wen Foong Tan
Email: wftan85@gmail.com

Fig. 1: a) Well defined irregular erythematous annular patches coalescing into a polycyclic configuration over her chest extending into the left breast; b) Diffuse erythema and induration of right upper limb.

Fig. 2a, 2b : Erythematous annular patches and plaques at the left flank and back.[1]

[1]Written consent had been obtained from the individual for publication of her images.

setting of acute radiation dermatitis. In contrast, chronic radiation dermatitis typically presents more than 90 days after radiation therapy and the cutaneous findings are epidermal thinning, edema, dyspigmentation and telangiectasia.[1,3]

CE also known as inflammatory metastatic carcinoma, is a rare presentation of cutaneous metastasis from a primary internal malignancy. CE is most frequently associated with breast carcinoma with intraductal carcinoma being the most common. Other primary tumour sites include the pancreas, stomach, colon, rectum, lung, ovary, prostate, parotid gland and melanoma.[1] The prevalence of CE as a clinical manifestation of cutaneous metastases from breast carcinoma is about 3%. In CE, malignant cells disseminate from the affected lymph nodes to the cutaneous lymphatics in the dermis and subcutaneous tissue.[2] These malignant cells form tumour emboli that obstruct the lymphatics, giving rise to peau d'orange appearance due to localised lymphedema. The rash in CE is described as a unilateral erythematous patch or plaque with a well-demarcated border.[1] The rash is usually distributed in proximity to the primary tumour and may progress to involve the back, arm and the contralateral side. CE may mimic other inflammatory conditions such as cellulitis, erysipelas, dermatophytosis, mastitis and contact dermatitis.

Our patient also had annular erythematous patches with polycyclic configuration. This morphology had been described in several reports of local recurrence of breast carcinoma. In these cases, the annular lesions were described to occur adjacent to the previous surgical scar except in one case where there was involvement of the back. This annular morphology is due to the spread of tumour cells via the lymphatics, not direct spread.[4] Tan et al postulated that the remaining cancer cells which did not respond to the initial chemotherapy had invaded the dermal lymphatics giving rise to this annular morphology.[5] Differential diagnoses to

consider include erythema chronicum migrans, erythema annulare centrifugum, drug-induced subacute cutaneous lupus and tinea corporis. Histological examination will help to clinch the diagnosis of cutaneous metastasis.[4]

Histopathological examination of both CE and annular erythema show infiltration of metastatic tumour cells into the superficial and deep lymphatics. The endothelial cells in the involved dermal lymphatics stain positively with CD31 and podoplanin, further supporting the predominant spread via lymphatic channels.[1,4,5] Other markers such as cathepsin D, mammaglobin, E-cadherin, pankeratins, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), gross cystic disease fluid protein-15 (GCDFP-15), progesterone and estrogen receptors may improve diagnosis accuracy of breast carcinoma as the primary site.[1,2] In reported cases of annular erythema, there were overexpression of HER2 and negative markers for hormonal receptors.[4]

Features that may suggest the diagnosis of cutaneous metastasis include prolonged duration of rash, absence of fever or leucocytosis, negative cultures, and no improvement despite antibiotic treatment. In these cases, early biopsy facilitates the diagnosis. The prognosis of the patient will depend on the behaviour and type of the primary tumour and its treatment response. With regard to breast carcinoma, cutaneous metastasis portends advanced stage of disease with poor prognosis. The main treatment options include systemic chemotherapy, immunotherapy, hormonal therapy with or without radiation.[2]

CONCLUSION

Inflammatory skin lesions, in particular those that are refractory to conventional treatment in a patient with history of malignancy could be the first sign of a relapse or metastasis. A high degree of suspicion and prompt referral to the dermatologist may lead to early diagnosis and intervention.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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