Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 78

Issue No: 7

December 2023

ISSN 0300-5283 PP 2121/01/2013 (031329) MITA(P) 124/1/91

MJM

Official Journal of the Malaysian Medical Association

Volume 78 Number 7 December 2023

EDITORIAL BOARD

PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 0300-5283

The Medical Journal of Malaysia is published six times a year.
MJM is published bimonthly ie. January, March, May, July, September and November.

Advertisement Rates:
Enquiries to be directed to the Secretariat.

Subscription Rates:
Price per copy is RM100.00 or RM360.00 per annum, for all subscribers.

Secretariat Address:
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

Printed by: Digital Perspective Sdn. Bhd.
42-1, Level 1, Plaza Sinar, Taman Sri Sinar, 51200 Kuala Lumpur. Tel: 03-6272 3767
Email: dpsbkl@gmail.com

The Medical Journal of Malaysia
MJM

INSTRUCTION TO AUTHORS

The *Medical Journal of Malaysia* ***(MJM)*** welcomes articles of interest on all aspects of medicine in the form of original papers, review articles, short communications, continuing medical education, case reports, commentaries and letter to Editor. Articles are accepted for publication on condition that they are contributed solely to *The Medical Journal of Malaysia*.

NOTE: MJM is published bimonthly ie. January, March, May, July, September and November.

REQUIREMENTS FOR ALL MANUSCRIPTS
Please ensure that your submission to MJM conforms to the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Neither the Editorial Board nor the Publishers accept responsibility for the views and statements of authors expressed in their contributions.

The Editorial Board further reserves the right to reject papers read before a society. To avoid delays in publication, authors are advised to adhere closely to the instructions given below.

MANUSCRIPTS
Manuscripts should be submitted in English (British English). Manuscripts should be submitted online through *MJM Editorial Manager*, http://www.editorialmanager.com/mjm.

Instructions for registration and submission are found on the website. Authors will be able to monitor the progress of their manuscript at all times via the *MJM Editorial Manager*. For authors and reviewers encountering problems with the system, an online Users' Guide and FAQs can be accessed via the "Help" option on the taskbar of the login screen.

MJM charges a one-time, non-refundable Article Processing Charge (APC) upon submission. Waiver of the APC applies only to members of the editorial board, and authors whose articles are invited by the editor. In addition, recipients of the MJM Reviewer Recognition Award from the previous year may enjoy a waiver of the APC for the next calendar year (e.g. recipients of MJM Reviewer Recognition Award 2022 will enjoy waiver of APC for articles submitted between January and December 2023).

MJM
Member: RM500
Non Member: RM800
Overseas: USD200

MJM Case Report
Member: RM400
Non Member: RM500

Preparing your manuscript

The MJM Article Processing Charge is a non-refundable administrative fee. Payment of the APC does not guarantee acceptance of the manuscript. Submitted articles will only be sent for reviews once the MJM APC has been successful completed.

All submissions must be accompanied by a completed **Copyright Assignment Form**, **Copyright Transfer Form and Conflict of Interest Form** duly signed by all authors. Forms can be download from MJM website at https://www.e-mjm.org/

Manuscript text should be submitted as **Microsoft Word** documents. Tables and flow-charts should be submitted as **Microsoft Word** documents. Images should be submitted as separate **JPEG files** (minimum resolution of 300 dpi).

PEER REVIEW PROCESS
All submissions must include at least two (2) names of individuals who are especially qualified to review the work. All manuscripts submitted will be reviewed by the Editor in-charge before they are send for peer review. Manuscripts that are submitted to MJM undergo a double-blinded peer review and are managed online. Proposed reviewers must not be involved in the work presented, nor affiliated with the same institution(s) as any of the authors or have any potential conflicts of interests in reviewing the manuscript. The selection of reviewers is the prerogative of the Editors of MJM.

ELIGIBILITY AS AN AUTHOR
MJM follows the recommendation of the International Committee of Medical Journal Editors (ICMJE) for eligibility to be consider as an author for submitted papers. The ICMJE recommends that authorship be based on the following four (4) criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TYPES OF PAPERS
Original Articles:
Original Articles are reports on findings from original unpublished research. Preference for publications will be given to high quality original research that make significant contribution to medicine. Original articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. The main text of the articles should not exceed 4000 words, tables/illustrations/figures/images up to five (5) and references up to 40. Manuscript describing original research should conform to the IMRAD format, more details are given below.

Original articles of cross-sectional and cohort design should follow the corresponding STROBE check-lists; clinical trials should follow the CONSORT check-list.

Review Articles:
Review Articles are solicited articles or systematic reviews. ***MJM*** solicits review articles from Malaysian experts to provide a clear, up-to-date account of a topic of interest to medical practice in Malaysia or on topics related to their area of expertise. Unsolicited reviews will also be considered, however, authors are encouraged to submit systematic reviews rather than narrative reviews. Review articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. Systematic Review are papers that presents exhaustive, critical assessments of the published literature on relevant topics in medicine. Systematic reviews should be prepared in strict compliance with MOOSE or PRISMA guidelines, or other relevant guidelines for systematic reviews.

Short Communications:
Shorts communication are short research articles of important preliminary observations, findings that extends previously published research, data that does not warrant publication as a full paper, small-scale clinical studies, and clinical audits. Short communications should not exceed 1,500 words and shall consist of a Summary and the Main Text. The summary should be limited to 100 words and provided immediately after the title page. The number of tables/illustrations/figures/images should be limited to three (3) and the number of references to ten (10).

Continuing Medical Education (CME) Articles:
A CME article is a critical analysis of a topic of current medical interest. The article should include the clinical question or issue and its importance for general medical practice, specialty practice, or public health. It shall consist of a Summary and the Main Text. The summary should be limited to 500 words and provided immediately after the title page Upon acceptance of selected articles, the authors will be requested to provide five multiple-choice questions, each with five true/false responses, based on the article. For guideline, please refer to: Sivalingam N, Rampal L. Writing Articles on Continuing Medical Education for Medical Journals. Med J Malaysia. 2021 Mar;76(2):119-124.

Case Reports:
Papers on case reports (one to five cases) must follow these rules: Case reports should not exceed 2,000 words; with a maximum of two (2) tables; three (3) photographs; and up to ten (10) references. It shall consist of a Summary and the Main Text. The summary should be limited to 250 words and provided immediately after the title page. Having a unique lesson in the diagnosis, pathology or management of the case is more valuable than mere finding of a rare entity. Being able to report the outcome and length of survival of a rare problem is more valuable than merely describing what treatment was rendered at the time of diagnosis. There should be no more than seven (7) authors.

Please note that all Case Reports will be published in the new MJM Case Reports Journal (www.mjmcasereports.org).

Commentaries:
Commentaries will usually be invited articles that comment on articles published in the same issue of the ***MJM***. However, unsolicited commentaries on issues relevant to medicine in Malaysia are welcomed. They should not exceed 2,000 words. They maybe unstructured but should be concise. When presenting a point of view, it should be supported with the relevant references where necessary.

Letters to Editor:
Letters to Editors are responses to items published in ***MJM*** or to communicate a very important message that is time sensitive and cannot wait for the full process of peer review. Letters that include statements of statistics, facts, research, or theories should include only up to three (3) references. Letters that are personal attacks on an author will not be considered for publication. Such correspondence must not exceed 1,500 words.

Editorials:
These are articles written by the editor or editorial team concerning the ***MJM*** or about issues relevant to the journal.

STRUCTURE OF PAPERS
Title Page:
The title page should state the brief title of the paper, full name(s) of the author(s) (with the surname or last name bolded), degrees (limited to one degree or diploma), affiliation(s), and corresponding author's address. All the authors' affiliations shall be provided after the authors' names. Indicate the affiliations with a superscript number at the end of the author's degrees and at the start of the name of the affiliation. If the author is affiliated to more than one (1) institution, a comma should be used to separate the number for the said affiliation.

Do provide preferred abbreviated author names for indexing purpose, e.g. L Rampal (for Lekhraj Rampal), BS Liew (for Liew Boon Seng), B Abdullah (for Baharudin Abdullah), Hoe VC (for Victor Hoe Chee Wai).
Please indicate the corresponding author and provide the affiliation, full postal address and email.

Articles describing Original Research should consist of the following sections (IMRAD format): Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgment and References. Each section should begin on a fresh page.
Scientific names, foreign words and Greek symbols should be in italic.

Abstract and Key Words:
A structured abstract is required for Original and Review Articles. It should be limited to 500 words and provided immediately after the title page. Below the abstract provide and identify three (3) to 10 key words or short phrases that will assist indexers in cross-indexing your article. Use terms from the medical subject headings (MeSH) list from Index Medicus for the key words where possible. Key words are not required for Short Communications, CME articles, Case Reports, Commentaries and Letter to Editors.

Introduction:
Clearly state the purpose of the article. Summarise the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Materials and Methods:
Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly, identify the methods, apparatus (manufacturer's name and address in parenthesis), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well-known; describe new or substantially modified methods, give reasons for using them and evaluate their limitations.

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.

When appropriate, particularly in the case of clinical trials, state clearly that the experimental design has received the approval of the relevant ethical committee.

Results:
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.

Discussion:
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.

Conclusion:
Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgements:
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

Referencing guide:
The Medical Journal of Malaysia, follows the Vancouver numbered referencing style. Citations to someone else's work in the text, should be indicated by the use of a number. In citing more than one article in the same sentence, you will need to include the citation number for each article. A hyphen should be used to link numbers which are inclusive, and a comma used where numbers are not consecutive. The following is an example where works 1.3,4,5.have been cited in the same place in the text.

Several effective drugs are available at fairly low cost for treating patients with hypertension and reducing the risk of its sequelae.[1,3-5]

The list of all of the references that are cited in the article should be presented in a list labelled as 'References'. This reference list appears at the end of the paper. Authors are responsible for the accuracy of cited references and these should be verified by the author(s) against the original documents before the manuscript is submitted. It is important that the author should never place in the list of references a document that he or she has not seen. The Journals names should be abbreviated according to the style used in the Index Medicus. All authors when six or less should be listed; when seven or more list only the first six and add et al.

If you are citingthe author's name in your text, you must insert the citation number as well. Jewell BL (8) underlined that as focus in the SARS-CoV-2 pandemic shifts to the emergence of new variants of concern (VOC), characterising the differences between new variants and non-VOC lineages will become increasingly important for surveillance and maintaining the effectiveness of both public health and vaccination programme. If you are citing more than one author's name in your text and you want to cite author names in your text, use 'et al.' after the first author. Example: Rampal et al. (9) highlighted that the. disregard of the manuscript guidelines and instruction to authors of the journal you submit, is one of the common reasons for 'Rejection' of the article.

Example references Journals:
Standard Journal Article
Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

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.

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.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260–64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

Online articles
Webpage: Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

Other Articles:
Newspaper Article
Panirchellvum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).

Magazine Article
Rampal L.World No Tobacco Day 2021 -Tobacco Control in Malaysia. Berita MMA. 2021; May: 21-22.

Tables:
All tables and figures should have a concise title and should not occupy more than one printed page. The title should concisely and clearly explain the content of the table or figure. They should be numbered consecutively with Roman numerals (e.g Table I) and figures with Arabic numerals (e.g. Figure 1), and placed after the sections of the manuscript which they reflect, particularly the results which they describe on separate pages. Cite tables in the text in consecutive order. Indicate table footnotes with lower-case letters in superscript font. Place the information for the footnote beneath the body of the table. If a table will be submitted as a separate document, the filename should contain the surname of the first author and match its label in the manuscript (e.g., SMITH Table I).Vertical lines should not be used when constructing the tables. All tables and figures should also be sent in electronic format on submission of the manuscript as supplementary files through the journal management platform. Clinical Photographs should conceal the subject's identity. Tables and flow-charts should be submitted as Microsoft Word documents. Images should be submitted as separate JPEG files (minimum resolution of 300 dpi).

Photographs of Patients:
Proof of permission and/or consent from the patient or legal guardian must be submitted with the manuscript. A statement on this must be included as a footnote to the relevant photograph.

Colour reproduction:
Illustrations and diagrams are normally reproduced in black and white only. Colour reproductions can be included if so required and upon request by the authors. However, a nominal charge must be paid by the authors for this additional service; the charges to be determined as and when on a per article basis.

Abbreviations:
Use only standard abbreviations. The full-term for which an abbreviation stands should precede its first use in the abstract, article text, tables, and figures, unless it is a standard unit of measurement. Abbreviations shall not be used in the Title. Abbreviations should be kept to a minimum.

Formatting of text:
Numbers one to ten in the text are written out in words unless they are used as a unit of measurement, except in tables and figures. Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph. Do not use the automated formatting of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Submit the Manuscript in plain text only, removed all 'field codes' before submission. Do not include line numbers. Include only page number.

BEST PAPER AWARD
All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

CONTENTS Page

Original Articles

Clinical outcomes of children with COVID-19 infection in a low-risk centre in Malaysia

Tan Mei See, MBBS[1], Nur Amira Zulkifli, MBBS[1], Teng Wei, MD[1], Lim Pei Thong, MBBS[2]

[1]Paediatric Department, Hospital Kepala Batas, Pulau Pinang, Malaysia, [2]Clinic Research Unit, Hospital Seberang Jaya, Pulau Pinang, Malaysia

ABSTRACT

Introduction: According to WHO, long-COVID or post-COVID-19 condition is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. A systematic review and meta-analyses published in 2022, which mainly focus on the Western population, revealed that the prevalence of long COVID was 25.24%. Literature regarding long-COVID in children in Asia was scarce. The objectives of our study were to assess the long-term effect of COVID-19 infection in children and its correlation to their acute COVID-19 infection.

Materials and Methods: This study was conducted in Hospital Kepala Batas (HKB), a district hospital in Penang State, Malaysia, which was the designated regional COVID hospital during the pandemic. It was a retrospective observational study, where children who were admitted from November 2020 to March 2021, and attended follow-up clinics from Jan 2021 to May 2021, were recruited.

Results: This study comprised 90 subjects, from 3 months old to 12 years old, mean of 6.5 years old. When comparing asymptomatic and symptomatic children, children with co-morbidities were more likely to be symptomatic with a p-value of 0.045 using the Pearson Chi-square test. All our patients' symptoms resolved upon discharge. During follow-up at 2–4 months after COVID-19 infection, all children were reported as back to their usual selves. Fifteen patients had recurrent symptoms. Most of their symptoms pointed towards an acute infection. One patient had two episodes of illness, while the rest had one. The most common symptoms were cough, fever and runny nose. The average duration of illness of these 16 episodes was 4.5 days with a standard deviation of 2.48. None of these symptoms lasted more than seven days. None of them required hospital admission. None of them had recurrent COVID-19 infections. Tweleve out of 72 children who had been going to school stopped physical school after COVID-19 infection. Our findings differed from other studies. These could be due to the limitations that we faced.

Conclusion: Most children who contracted COVID-19 infection recovered fully after acute infection, and most of them recovered fully without long-term sequelae.

KEYWORDS:
Long COVID; post-Covid follow-up; children with COVID; paediatric COVID

INTRODUCTION

According to World Health Organisation (WHO), long COVID or post-COVID-19 condition is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.[1] This includes ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).[2] The United Kingdom (UK) Office for National Statistics estimated that 12.9% of UK children aged 2 to 11, still have symptoms 5 weeks after their first infection.[3] A systematic review and meta-analyses published in 2022, which mainly focus on the western population, revealed that the prevalence of long COVID was 25.24%, and the most prevalent clinical manifestations were mood symptoms (16.50%), fatigue (9.66%) and sleep disorders (8.42%). There were more than 40 long COVID symptoms in children and adolescents with a higher risk of persistent dyspnoea, anosmia/ageusia and/or fever compared to controls.[4] In a large cohort study which consisted of 659 286 children, the common symptoms post-infection were loss of taste or smell, myocarditis and cough. The incidence of at least one feature was 41.9% (95% Confidence Interval (CI), 41.4–42.4) among COVID-19 positive children versus 38.2% (95% CI, 38.1–38.4) among COVID-19 negative children, with an incidence proportion difference of 3.7% (95% CI, 3.2–4.2).[5] Literature regarding long COVID in children in Asia was scarce. We carried out this study during the country's Recovery Movement Control Order (RMCO) phase, where interstate travel was allowed.[6] During that time, Malaysia was undergoing the attack of Delta Wave. The objectives of our study were to assess the long-term effect of COVID-19 infection in children and its correlation to their acute COVID-19 infection at 4 months of follow-up.

MATERIALS AND METHODS

This study was conducted in Hospital Kepala Batas (HKB), a district hospital in Penang State, Malaysia, with 108 beds. Twenty-eight beds were dedicated to paediatrics. This hospital was a designated full COVID hospital during the pandemic. It received patients from the whole Seberang Prai

This article was accepted: 22 November 2023
Corresponding Author: Tan Mei See
Email: tanmeisee@yahoo.com

area. The study population included all children from age 1-month-old to 12 years old with positive COVID RT-PCR (Reverse transcription-polymerase chain reaction), who were admitted from November 2020 to March 2021 and attended follow-up clinic, either virtually or physically, from Jan 2021 to May 2021. Patients who did not come and were not contacted during follow-up were excluded. Although Malaysia already went into the country's RMCO, where there was still mandatory RTK testing and quarantine for those that were diagnosed with COVID-19 infection, interstate travel would be allowed, but only a few patients attended physical clinics. Most patients were followed up virtually by medical officers who worked in the paediatric department using hospital phone lines and documented in patients' case notes. Phone numbers of interviewees were recorded in patients' case notes during admission. Interviewees were the main caretakers. Most of them were parents to the children. For virtual clinic follow-up, children's well-being and the presence of any symptoms were determined during the virtual interview. For physical clinic follow-up, history taking and physical examination were done.

Data collection was by convenience sampling. Samples were identified via a monthly census of paediatric admissions to the Paediatric ward. Case notes were traced from the Electronic Hospital Information System (eHIS) and hospital record office. Demographic details of the patients, clinical presentation and follow-up outcomes were collected. The demographic variables included age, gender and ethnicity. Clinical presentation included the COVID-19 category, symptoms at presentation, chest X-ray findings, CT (cycle threshold)-value of RT-PCR result, co-morbidity, developmental milestone, transmission method and length of stay. Developmental milestone assessment was based on Denver II Scale. COVID-19 category was based on the Clinical Staging of COVID-19 for children.[7] Follow-up outcomes of recurrence symptoms, history of hospitalisation or clinic visit and attendance to school or childcare centre after discharge from the hospital and reason for absenteeism if any, were collected.

Data were entered into Microsoft Excel Sheet. No original records were photocopied. The data were analysed using the Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were presented as mean and standard deviation, and categorical variables were presented as frequency and percentage. Continuous variables were analysed using simple logistic regression based on one independent variable regardless of the type of variable, whilst categorical data were analysed using chi-square or Fischer's exact test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Ninety-seven children were admitted for COVID-19 during the study period. Seven children were excluded because they did not attend follow-up clinics either physically or virtually. 90 children were recruited, where 42 were in category 1, 39 in category 2, nine were in category 3 and none was in category 4 or 5. Their ages ranged from 3 months to 12 years old, mean 6.5 years, standard deviation 3.56 years. Among the symptomatic children, 64.6% had only one symptom at presentation. 16.7% had two symptoms, and the rest had three or more symptoms. The common symptoms were coryza (41.7%), fever (33.3%), cough (22.9%), anosmia (12.5%), sore throat (8.3%), diarrhoea (6.3%), chest discomfort (2.1%) and others (6.3%). Other symptoms were vomiting, poor oral intake and gum swelling. 90% of them had normal chest X-rays. Two children's RT-PCR was positive without CT value because the test was not done in our local health care system and there were no printout results attached in the case notes. The average CT value for our samples was 27.49. There were four obese children, three had bronchial asthma, two had allergic rhinitis and others had single kidney, epilepsy, congenital rubella and failure to thrive, respectively. Three children had isolated speech delay. When comparing asymptomatic and symptomatic children, as shown in Table I, children with co-morbidities were more likely to have symptomatic COVID-19 infection with a p value of 0.045. All our patients' symptoms resolved upon discharge.

During follow-up at 2–4 months after COVID-19 infection, all children were reported as well, active and back to their usual activities of daily living. Only 15 patients had recurrent symptoms. Most of their symptoms pointed towards acute infections. One patient had two episodes of acute infections, while 13 of them had one episode. One child complained of lethargy and dizziness for 2 days without evidence of infection. Eleven out of these 16 episodes of illness were presented by more than one symptom. The most common symptoms were cough (n = 12), fever (n = 9) and runny nose (n = 8). Other symptoms were vomiting, diarrhoea, sore throat, chest discomfort, lethargy and dizziness. Among these 16 episodes of illness, 12 visited the clinic, two visited the hospital casualty department, and two episodes did not need a clinic or hospital visit. Three of these episodes required salbutamol nebulisation, six were prescribed antibiotics. The average duration of illness is 4.5 days with a standard deviation of 2.48. None of these children developed new chronic symptoms after acute COVID-19 infection. None of them required hospital admission. None of them have recurrent COVID-19 infections. Among these 15 children, two had underlying bronchial asthma and allergic rhinitis and one had bronchial asthma prior to COVID-19 infections. When compared to the rest of the sample, the association between co-morbid and recurrent infection was not statistically significant, with a p-value of 0.121. The relation between co-morbidity and long COVID was not demonstrated in this study.

Before the pandemic, 80% of the children in our study were attending school or childcare centres, while the other 20% of them did not. Out of these 72 children, 12 of them stopped going to school and childcare after being infected with COVID-19, ranging from two days to two months. Six of them did not go to school for one week. Two did not state the duration. One did not go to school after the diagnosis of COVID-19 until the time of follow-up. Among the 12 of them who did not go to school, eight of them were due to recurrent symptoms, two were worried about getting reinfection, one said that would like to rest at home and one did not state the reason.

Table I: Comparison in demographic and clinical presentation between children with asymptomatic and symptomatic COVID-19 infection in Hospital Kepala Batas

Variables	Asymptomatic n = 42 n (%)	Symptomatic n = 48 n (%)	Crude OR (95% CI)	p value
Patients' demographics				
Age, yearsa	6.3 (3.41)	6.7 (3.72)	1.03 (0.92,1.16)	0.599[b]
< 1	4 (66.70)	2 (33.30)		0.555[c]
1–5	13 (43.30)	17 (56.70)		
6–13	25 (46.30)	29 (53.70)		
Gender				
Male	21 (48.80)	22 (51.20)		0.693[d]
Female	21 (44.70)	26 (55.30)		
Ethnicity				
Malays	39 (48.10)	42 (51.90)		0.504[c]
Chinese	2 (50.00)	2 (50.00)		
Indian	1 (20.00)	4 (80.00)		
Clinical presentation:				
CT-value of RT-PCR resulta	27.4 (6.93)	27.6 (5.77)	1.01 (0.94,1.08)	0.853[b]
Low CT value (<30)	25 (45.50)	30 (54.50)		0.783[d]
High CT value (30–40)	16 (48.50)	17 (51.50)		
Missing data	1	1		
Comorbid				
Have Comorbid	3 (20.00)	12 (80.00)		0.045[d]
No Comorbid	39 (52.00)	36 (48.00)		
Obesity	0 (0.00)	4 (100.00)		0.120[c]
No obesity	42 (48.80)	44 (51.20)		
Asthma	1 (33.30)	2 (66.70)		1.000[c]
No asthma	41 (47.10)	46 (52.90)		
Normal development	41 (47.10)	46 (52.90)		1.000[c]
Speech Delay	1 (33.30)	2 (66.70)		
Transmission method				
Close contact with family member	41 (46.60)	47 (53.40)		0.718[c]
Contact with family friends	1 (100.00)	0 (0.00)		
Contact with teacher	0 (0.00)	1 (100.00)		

CT - cycle threshold
Note: [a]Data presented are mean (standard deviation), [b]Simple Logistic Regression; cFisher's exact test; [d]Pearson Chi-square test; OR=Odds Ratio; 95% CI = 95% confidence interval

Table II: Comparison in follow-up outcome between children with asymptomatic and symptomatic COVID-19 infection in Hospital Kepala Batas

Follow-up outcome	Asymptomatic n = 42	Symptomatic n = 48	p value
Recurrent symptoms	8 (19.00)	7 (14.60)	0.571[a]
No recurrent symptoms	34 (81.00)	41 (85.40)	
Recurrent healthcare services visit	8 (19.00)	6 (12.50)	0.393[a]
No recurrent healthcare services visit	34 (81.00)	42 (87.50)	
Absence from school after COVID-19 infection	5 (11.90)	7 (14.60)	0.684[a]
Continue schooling after COVID-19 infection	27 (64.30)	33 (68.80)	

Note: [a]Pearson Chi-square test

As shown in Table II, there was no significant association between the COVID-19 severity in terms of risk of recurrent infection, health care facilities visits and school absentees.

DISCUSSION

During the time of the study, all children infected with COVID-19 needed to be admitted for isolation and observation. All our subjects were in category three or less because our centre was a low-risk centre. Nevertheless, none of these children deteriorated or needed step-up care. Furthermore, severe COVID-19 (category four and five) was less common in children.

To date, there are at least two long-term consequences that can occur following COVID-19 infection in children, namely multisystem inflammatory syndrome (MIS-C) and long COVID. Using the case definition released by the Centers for Disease Control and Prevention (CDC) in May 2020, the incidence of MIS-C the United State was estimated to be 5.1 cases per million person-months or 316 cases per million SARS-CoV-2 infections among persons aged <21 years.[8] None of our children developed MIS-C during the follow-up period. Contrary to the systematic review and meta-analysis published[4], as well as a recent paper published in Annals Academy of Medicine Singapore showing one in six children and younger persons in Singapore developed long COVID

with persistence of one or more symptoms after three months post-infection where persistent cough (7.4%), nasal congestion (7.6%) and fatigue (3.0%) were common symptoms[9], our study did not show any long COVID in our children. Despite having recurrent infections, none of them reported having chronic dry cough (7%), shortness of breath (6%), fatigue (4%) or headache (3%), as coded by another cohort study.[10]

During the study period, children attended school virtually and back to physical school in stages as instructed by the Malaysian Ministry of Education. The results of our study did show that the impact of COVID-19 on school attendance should not be underestimated.

Our findings differed from other studies. These could be due to the limitations that we faced. Firstly, our study was conducted among the local community who were admitted to our hospital, which was a low risk hospital, and the data was collected in a short duration. This might not represent the whole Malaysian population. Secondly, this study was conducted in the middle of the pandemic, which might not represent the whole clinical outcome of the changing variant of coronavirus. Thirdly, as per our general knowledge, recurrent infections were common in children. This study did not compare recurrent infection with children with other viral infections because during the study period, only children with COVID-19 infection were admitted to this hospital. And finally, the patient's symptoms were reported by parents, which carried the risk of recall biases and underreporting. Not all children attended the follow-up clinic physically.

CONCLUSION

In summary, most children who contracted COVID-19 infection recovered fully after acute infection, and most of them did not have long-term sequelae.

ACKNOWLEDGEMENT

We would like to thank Honorary Professor Dr ELC Ong, Consultant Infectious Diseases, Newcastle University Medicine for reviewing and editing the manuscript. We would like to thank the Director General of Health Malaysia for his permission to publish this article.

REFERENCES

1. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. The Lancet Infectious Diseases. 2021 Dec; 22(4): e102-7.
2. Clements W, Joseph T, Koukounaras J. UK NICE guidelines for EVAR: Cost implications for post-COVID Australian Public Health. CardioVascular and Interventional Radiology. 2021 Aug; 44(8): 1286-8.
3. Thomson H. Children with Long Covid. Science Direct New Scientist. 2021 Feb; 249(3323): 10-1.
4. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, et al. Long-COVID in children and adolescents: A systematic review and meta-analyses. Scientific reports. 2022 Jun; 12(1): 9950.
5. Rao S, Lee GM, Razzaghi H, Lorman V, Mejias A, Pajor NM, et al. Clinical features and burden of postacute sequelae of SARS-CoV-2 infection in children and adolescents. JAMA pediatrics. 2022 Oct; 176(10): 1000-9.
6. Ng CFS, Seposoa XT, Moi ML, Tajudin MABA, Madaniyazi L, Sahani M. Characteristics of COVID-19 epidemic and control measures to curb transmission in Malaysia. International Journal of Infectious Diseases. 2020 Dec; 101: 409-11.
7. Annex 2e Clinical management of confirmed COVID-19 case in adult and paediatric [Internet]. Minsitry of Health Malaysia. Updated May 2022 [cited Jun 2023]. Available from: https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX-2E-CLINICAL-MANAGEMENT-OF-CONFIRMED-COVID-19-31052022.pdf
8. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Network Open. 2021 Jun; 4(6): e2116420-e.
9. Li JH, Nadua K, Chong CY, Yung CY. Long COVID prevalence, risk factors and impact of vaccination in the paediatric population: A survey study in Singapore. ANNALS Academy of Medicine Singapore. 2023 Oct; 52(10): 522-32.
10. Bossley CJ, Kavaliunaite E, Harman K, Cook J, Ruiz G, Gupta A. Post–acute COVID–19 outcomes in children requiring hospitalisation. Nature Portfolio: Scientific Reports. 2022 May; 12(1): 8208.

Development, validation, and evaluation of allergic rhinitis symptoms and impact assessment (ARSIA) questionnaire

Muhammad Harith Mohamed Rouse, MD[1,2], Azliana Aziz, MMed[2], Baharudin Abdullah, MMed[2], Azidah Abdul Kadir, MMed[3], Wan Mohd Zahiruddin Wan Mohammad, MMed[4], Nor Shahida Abd Mutalib, MMed[1]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, Hospital Sultan Abdul Halim, Sungai Petani, Kedah, Malaysia, [2]Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, Kelantan, Malaysia, [3]Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, Kelantan, Malaysia, [4]Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa. It is among the most common diseases globally and usually persists throughout life. Allergic Rhinitis and Its Impact on Asthma (ARIA) is a well-established guideline applicable to AR and was updated regularly since 2001, aiming to improve the care for AR patients. We proposed a new questionnaire that addresses the severity of allergic rhinitis symptoms, specifically nasal symptoms, and its impact on quality of life in terms of specific vital activities such as sleeping, working, school performance, leisure, or sport, based on the ARIA guideline. The objective was to develop, validate and evaluate Allergic Rhinitis Symptoms and Impact Assessment (ARSIA) questionnaire among allergic rhinitis patients in Hospital Sultan Abdul Halim, Sungai Petani (HSAH), and Hospital Universiti Sains Malaysia (HUSM).

Materials and Methods: This is a prospective observational study to develop, validate and evaluate the ARSIA questionnaire based on ARIA guidelines. The sample will be obtained from the list of patients under follow-up in the ORL clinic HSAH and HUSM with ages of 18 to 60 years, patients clinically diagnosed with allergic rhinitis, and with positive skin prick test.

Results: A total of 150 patients with a positive skin prick test participated in this study. In the 'nasal symptom' and 'impact on daily activities' domains, calculated Cronbach's alpha shows a value of 0.878 and 0.811 respectively. The inter-item correlation was calculated to analyse internal consistency reliability. Items B3 and B4 were dropped from the questionnaire as both showed a low correlation with other items. New Cronbach's alpha for the daily activities domain was 0.830, which showed better internal consistency reliability.

All of the items were analysed for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Clinician diagnosis from the proforma was used as a comparison to the participant's responses. In the analysis, a cut-off points of 12 was used to classify the patient's nasal symptoms into intermittent or persistent, with a sensitivity of 75%, specificity of 86%, PPV of 95%, and NPV of 51%. Whereas, a cut-off point of 15 was used to classify the rhinitis impact on daily activities into mild or moderate/severe, with a sensitivity of 58%, specificity of 100%, PPV of 100%, and NPV of 42%.

The only item in the 'control' domain has been dropped out following a consensus of experts and judgement as it has not been used in the clinician diagnosis and thus, is unable to test for sensitivity, specificity, PPV, and NPV.

Conclusion: This newly developed, validated, and evaluated questionnaire is a good tool for the evaluation of allergic rhinitis symptoms and their impact on daily activities. It is important to understand that AR symptoms could have a significant impact on daily activities. Although further study and testing are needed, it provides an initial means for evaluating the patient condition and control level, as well as patients' perception of their rhinitis control.

KEYWORDS:
Allergic rhinitis; questionnaire; hypersensitivity; immunoglobulin E

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa, highly prevalent with rates of up to 50% in some populations.[1,2] It is among the most common diseases globally and usually persists throughout life.[1] The prevalence of self-reported AR has been estimated to be approximately 2 to 25% in children and 1% to greater than 40% in adults.[1,3,4] AR is a systemic disease affecting not only nasal function but general well-being as well. As a chronic condition, AR puts a considerable economic burden on sufferers.

Exposure of allergic patients to the allergen will result in increased immunoglobulin E (IgE) and induce IgE-mediated response. It can be manifested clinically as nasal congestion, rhinorrhoea, postnasal drainage, nasal itching, and sneezing.[4,5] Ocular symptoms are also frequent; allergic rhinoconjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip, and cough.

AR is frequently associated with asthma. There are about 15 to 38% of patients with asthma with AR, and rhinitis symptoms are present in 6 to 85% of patients with asthma.6–

This article was accepted: 22 November 2023
Corresponding Author: Azliana Aziz
Email: az_aziz@usm.my

8 AR also is a risk factor for asthma, and thus uncontrolled AR affects asthma control.[6,9]

AR might not appear to be serious as it does not associate with severe morbidity and mortality. Appropriate treatment will improve its symptoms, and thus the quality of life, and work and school performance.

The number of patients affected by allergies is increasing worldwide. The resulting allergic diseases lead to significant health care and social systems costs. Integrated care is needed for comprehensive care that later will lead to a better quality of life. Allergic Rhinitis and Its Impact on Asthma (ARIA) is a well-established guideline applicable to AR and was updated regularly since 2001, aiming to improve the care for AR patients. ARIA classifies the severity of AR into 'mild' or 'moderate/severe' based on the symptoms asked.[10] Despite the multiple treatment options mentioned by the guideline, AR is still treated sub-optimally. The most commonly used medications are oral antihistamines, which are not the most effective medication for moderate-severe AR symptoms.[11,12] This will lead to undertreated AR sufferers despite the high dependence on medication.[13,14]

Based on the ARIA guideline, we proposed a new questionnaire that specifically addresses the severity of allergic rhinitis symptoms and its impact on quality of life in terms of specific vital activities such as sleeping, working, school performance, leisure, or sport.

MATERIALS AND METHODS

There were two phases involved in this study. The first phase was the development of the questionnaire, followed by the second phase, which was the validation and reliability of the questionnaire. The data was measured for sensitivity, specificity, (PPV), and (NPV).

Phase 1: Development of Allergic Rhinitis Symptoms and Impact Assessment (ARSIA) questionnaire

This phase involved the development of a new questionnaire on allergic rhinitis symptoms and impact assessment based on ARIA guidelines. Few literatures were reviewed and analysed including ARIA.[10,15–17] Consultation from experts (consisting of three otorhinolaryngologists, one family medicine specialist, and one community medicine specialist) was also taken to develop this ARSIA questionnaire draft. The concepts identified in the literature review were used in the selection of items and the formation of the relevant questionnaire sections.

This newly drafted questionnaire was divided into two parts – the first part is demographics which include age, gender, ethnicity, occupation, educational level, marital status, smoking, allergic status, and current medication. The second part had three domains which consist of of 15 items. The domains include nasal symptoms (five items), impact on daily activities (nine items), and symptoms control (one item, refer to appendix).

In the nasal symptom domain, the 4-point Likert scale response was used for each item. It is further divided into two columns to separate symptoms within 4 weeks and within 6 months duration. In the column of symptoms in the last 4 weeks, responses are assigned to a score of 0 for 'never', 1 for '1-4 times per week', 2 for '5-6 times per week', and 3 for '7 days per week', while in the column of symptoms in the last 6 months, it is assigned a score as 0 for '1–4 consecutive weeks', 1 for '5–8 consecutive weeks', 2 for '9–12 consecutive weeks', and 3 for 'more than 12 consecutive weeks'.

The impact on daily activities domain used the 5-point Likert scale response to each item, and the response was assigned to a score of 1 for 'Never', 2 for 'Rarely', 3 for 'Sometimes', 4 for 'Often', and 5 for 'Extremely often'.

While the control domain used the 5-point Likert scale response to this item, the response was assigned a score of 1 for 'Never', 2 for 'Rarely', 3 for 'Sometimes', 4 for 'Most of the time', and 5 for 'Always'.

Phase 2: Validity and reliability of the ARSIA questionnaire

In the second phase, the ARSIA questionnaire was validated based on content, face, and construct validity.

Content Validation

Content validity assessed the relevance and representability of each item to a specific domain of the panel of experts. Setting up content validity is important for evaluating a questionnaire and should be the priority in developing an instrument. Content validity provides information on the representativeness and clarity of items and provides preliminary evidence on the construct validity. It helps improve an instrument through recommendations from experts.[18]

There are a few methods that can be used to assess the content validity of a questionnaire. The content validity index (CVI) is the most widely used method. There are two kinds of CVI; item-level CVI (I-CVI) and scale-level CVI (S-CVI).[18]

In this study, we invited five experts who pretested the questionnaire to evaluate for potential problems when used by respondents. Each expert independently rated the relevance of each item for each domain of the questionnaire to the conceptual framework using a 4-point Likert scale (1 = not relevant, 2 = somewhat relevant, 3 = relevant, 4 = very relevant). A CVI of at least 0.80 is considered adequate for accepting an item as valid.[18] Another parameter was the Scale-level CVI of averaging calculation method (S-CVI/Ave). S-CVI/Ave is calculated by taking the sum of the I-CVIs divided by the total number of items, and the value must be 0.90 and above to be considered acceptable content validity.[19]

Face Validation

Then, the face validity of the ARSIA questionnaire was conducted on ten respondents in the ORL clinic at Sultan Abdul Halim Hospital in printed form. Face validity is used to assess the comprehensibility and clarity of each item. Ten respondents were involved in the assessment. Instrument review by a sample of subjects that represents the target population is another important component of instrument development. The face validity index (FVI) is quantified as

Table I: Content validation for the ARSIA questionnaire

	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	I-CVI
Nasal symptom domain						
Q1	1	1	1	1	1	1
Q2	1	1	1	1	1	1
Q3	1	1	1	1	1	1
Q4	1	1	1	1	1	1
Q5	1	1	1	1	1	1
Impact on daily activities domain						
Q1	1	1	1	1	1	1
Q2	1	1	1	0	1	0.8
Q3	1	1	1	1	1	1
Q4	1	1	1	1	1	1
Q5	1	1	1	1	1	1
Q6	1	1	1	1	1	1
Q7	1	1	1	1	1	1
Q8	1	1	1	1	1	1
Q9	1	0	1	1	1	0.8
Control domain						
Q10	1	1	1	1	1	1
					S-CVI/Ave	0.97

Table II: Face validation for the ARSIA questionnaire

	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	I-FVI
Nasal symptom domain											
Q1	1	1	1	1	1	1	1	1	1	1	1
Q2	1	1	1	1	1	1	1	1	1	1	1
Q3	1	1	1	1	1	1	1	1	0	1	0.9
Q4	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	0	1	0.9
Impact on daily activities domain											
Q1	1	1	1	1	1	1	1	1	0	1	0.9
Q2	1	1	1	1	1	1	1	1	0	1	0.9
Q3	1	1	1	1	1	1	1	1	0	1	0.9
Q4	1	1	1	1	1	1	1	1	0	0	0.8
Q5	1	1	1	1	1	1	1	1	1	1	0.9
Q6	1	1	1	1	1	1	1	1	0	1	0.9
Q7	1	1	1	1	1	1	1	1	1	1	1
Q8	1	1	1	1	1	1	1	1	1	1	1
Q9	1	1	1	1	1	1	1	0	0	1	0.8
Control domain											
Q10	1	1	1	1	1	1	1	1	1	1	1
									S-FVI/Ave	0.93	

the thought processes of target users of an instrument.[20,21] In this study, we used the method to calculate the FVI based on the recommendation by Yusoff M 2019.[20] The items were rated based on a Likert scale ranging from 1 (not clear or not comprehensible) to 4 (very clear or very comprehensible). The item-face validity index (I-FVI) and scale-face validity index (S-FVI/Ave) were calculated. I-FVI is calculated as the number of respondents giving a rating of 3 to 4 for each item divided by the total number of respondents, and S-FVI/Ave is calculated based on the sum of the I-FVIs divided by the total number of respondents. The recommended FVI for ten respondents is at least 0.83.[20]

Psychometric Validation Study

For construct validity, a total of hundred and fifty patients who fulfilled the inclusion and exclusion criteria participated in this study. Cronbach's alpha was used to measure this questionnaire's construct validity and internal consistency. Each domain in the questionnaire is unidimensional.

Criterion validity was also conducted simultaneously with the construct validity. ORL specialist or attendant doctor did an assessment based on ARIA classification using clinical proforma.

After the validity was completed, the questionnaires were analysed to assess their sensitivity, specificity, PPV, and NPV. The internal consistency reliability, a Cronbach's alpha coefficient >0.70 is considered acceptable.[22]

The study was a cross-sectional study. It was conducted amongst patients who fulfilled inclusion and exclusion criteria, attending the Otorhinolaryngology Clinic Hospital Sultan Abdul Halim (HSAH) and Hospital Universiti Sains Malaysia (HUSM), from January 1, 2021, until December 31, 2021. The sample size was determined using a 2-Parameter Logic Item Response Theory (2-PL IRT) analysis. The required sample size for 2-PL IRT was by taking a ratio of 10:1 to each item, and it showed 150 participants were required.

Table III: Socio-demographics data of the participants

Variables	Mean (SD)	N (%)
Age	35.23 (12.34)	
<21	Range = 18-60	23(15.3)
21-30		35(23.3)
31-40		43(28.7)
41-50		27(18.0)
51-60		22(14.7)
Gender		
Male		50(33.3)
Female		100(66.7)
Ethnic		
Malay		127(84.7)
Chinese		3(2.0)
Indian		16(10.7)
Others		1(0.7)
Missing		3(2.0)
Occupation		
Non-professional		81(54.0)
Professional		69(46.0)
Education level		
Primary		5(3.3)
Secondary		72(48.0)
Tertiary		73(48.7)
Marital status		
Unmarried		51(34.0)
Married		99(66.0)
Smoking		
Yes		15(10.0)
Passive		6(4.0)
No		129(86.0)

Table IV: Sensitivity, specificity, PPV, and NPV for the 'nasal symptoms' domain

Cut-off point used	Sensitivity	Specificity	PPV	NPV
9 and less	61	94	97	42
10 and less	68	91	96	47
11 and less	74	89	96	49
12 and less	75	86	95	51

Table V: Sensitivity, specificity, PPV, and NPV for the 'impact on daily activities' domain

Cut-off point	Sensitivity	Specificity	PPV	NPV
10	16	100	100	26
11	23	100	100	28
12	28	100	100	30
13	34	100	100	32
14	40	100	100	33
15	58	100	100	42

The purposive sampling method was used for recruitment. Participants ranged from 18 years of age to 60 years of age, clinically diagnosed with allergic rhinitis, with a positive skin prick test. Exclusion criteria included a patient who has nasal polyposis or confirmed mucociliary disease, a patient with a nasal anatomical abnormality, and a patient with mental retardation, neuromuscular diseases, cardiovascular diseases, or psychological problems.

The questionnaire was hand-delivered to the patients who were willing to participate and hand-collected once they had completed the questionnaire. ORL specialists or doctors who attended the participant were required to fill up the proforma based on clinical assessment, and they will be blinded to the questionnaire scoring by the patient prior to the assessment.

Data Analysis (sensitivity, specificity, (PPV), and (NPV))

Data entry and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) version 26.0. The data entered were then checked for outliers and missing values. Descriptive statistics were employed to summarise the socio-demographic characteristics of subjects. The findings were presented based on the types and distribution of the data. Categorical data were presented as frequencies and percentages, while numerical data were presented as means and standard deviations (if normally distributed), or as

medians and interquartile ranges (if not normally distributed).

Specificity, sensitivity, PPV, and NPV of the questionnaire were calculated and tabulated. The sensitivity of a test helps rule out a disease when the test is negative, whereas a specificity of a test will rule out a disease when the test is positive. PPV and NPV are directly related to prevalence. PPV is the probability that a positive test will truly have that specific disease. While NPV is the probability of a negative test which will truly not have that specific disease.[23] The ARSIA questionnaire reliability was measured through internal consistency, inter-item correlation, and Cronbach's alpha coefficient. The questionnaire items were considered a good internal consistency if the total Cronbach's alpha value was more than 0.7.[24]

Ethical Considerations

Ethical approval was obtained from the Medical Research & Ethics Committee (MREC) of the Ministry of Health, Malaysia via the National Medical Research Register (NMRR), and the Human Research Ethics Committee of USM (JEPeM). Verbal consent was obtained from each participant prior to conducting this study.

RESULTS

Content Validity

The I-CVI relevancy for the nasal symptom domain ranges from 0.9 to 1, while for the impact on daily activities domain ranges from 0.8 to 1, and the control domain is 1 (Table I). The S-CVI/Ave is 0.97. In all of the domains (nasal symptoms, impact on daily activities, and control), the I-CVI is ≥0.8. Thus, 5 items in the nasal symptom domain, 9 items in the impact on daily activities domain, and 1 item in the control domain were kept. Modifications were made to a few items based on the suggestions of the experts. The final ARSIA questionnaire consists of 15 items.

Face Validity

The I-FVI for the nasal symptom domain ranges from 0.9 to 1, while for the impact on daily activities domain ranges from 0.8 to 1.0, and the control domain is 1 (Table II). All items were valid with I-FVI ranging from 0.80 to 1.00, S-FVI/Ave of 0.93 indicates the questionnaire was found to be very clear and easy to answer, and indicated the appearance and layout would be acceptable to the intended target group.

Psychometric Analysis

A total of 150 patients participated in this study consisting of 50 men and 100 women, with ages ranging from 18 to 60 years. The mean age was 35.2. The majority of them were Malays 127 (84.7%) (Table III). Three participants were missing ethnic data.

The participants' allergic status was asked, including food, dust, animal or insect, climate changes, smoke, and drugs. Among the participants, a majority of them had food and dust allergies and were on antihistamines with intranasal steroids. Every participant had a skin prick test evaluation at least once in their life.

Validity and Reliability of the Questionnaire

1- 'Nasal symptoms' domain

In the nasal symptom domain, there were five items (items A1-A5, refer to appendix), further divided into two columns to separate symptoms within 4 weeks and 6 months duration. The internal consistency reliability, a Cronbach's alpha coefficient >0.70 is considered acceptable.22 Cronbach's alpha was calculated from these ten items (five items with two columns each), showing a value of 0.878. All of the items were kept and further analysed for sensitivity, specificity, PPV, and NPV. Clinician diagnosis from the proforma was used as a comparison to the participants' responses.

In the analysis, a cut point of 12 was used to classify the patient's nasal symptoms into intermittent or persistent, with a sensitivity of 75%, specificity of 86%, PPV of 95%, and NPV of 51%. A score of 12 or less will turn into the intermittent group, whereas more than 12 is the persistent group (Table IV).

2- 'Impact on daily activities' domain

The impact on daily activities domain has nine items (items B1-B9) (refer to appendix). The internal consistency reliability, a Cronbach's alpha coefficient >0.70 is considered acceptable.[22] Cronbach's alpha of 0.811 was achieved, showing that all the items were good. The inter-item correlation was calculated to analyse internal consistency reliability. Item B3 (Due to your allergic rhinitis impact on you in the last 4 weeks, do you need to increase the use (dose or frequency) of your medicines?) and B4 (Due to your allergic rhinitis impact on you in the last 4 weeks, do you avoid any activities (for example, gardening, visiting a house with a dog or cat)?) showed a low correlation with other items. The ideal range of average inter-item correlation is 0.15 to 0.50.[25] Thus, items B3 and B4 were dropped from the questionnaire. New Cronbach's alpha was 0.830, which showed better internal consistency reliability after the items were dropped.

All of the remaining items were further analysed for sensitivity, specificity, positive PPV, and NPV. Clinician diagnosis from the proforma was used as a comparison to the participants' responses.

In the analysis, a cut point of 15 was used to classify the rhinitis impact on daily activities into mild or moderate/severe, with a sensitivity of 58%, specificity of 100%, PPV of 100%, and NPV of 42%. A score of 15 or less is considered mild, whereas more than 15 is considered moderate/severe (Table V).

3- 'Control' domain

The only item in this domain, C1 (due to your allergic rhinitis impact on you in the last 4 weeks, do you feel your allergy is controlled?) has been dropped out following a consensus of experts and judgment as it has not been used in the clinician diagnosis and thus, unable to test for sensitivity, specificity, PPV, and NPV.

Assessment of the Validated Items

For the impact on the daily activity domain, seven of nine items showed good inter-item correlation. However, two items

(B3 and B4) showed poor correlation with other items (less than 0.15) and thus have been dropped out.

In the control domain, the only item, that was C1, has been dropped out as it was not included in the physician's diagnosis in the proforma.

DISCUSSION

AR and nonallergic rhinitis (NAR) are considered one of the major global health concerns with increasing prevalence worldwide. AR is when the nasal symptoms are triggered by an allergen, whereas NAR is when nasal symptoms occur in relation to nonallergic, non-infectious triggers such as changes in weather, exposure to smoke or odours, hormonal related, or some drugs.[26]

The main factors highlighted in the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline include nasal symptoms and their impact on daily activities. It is used in classifying a patient's condition into 'intermittent' or 'persistent', and 'mild' or 'moderate/severe'. In the ARIA guidelines, intermittent symptoms are described as symptoms in less than 4 days per week or less than 4 consecutive weeks, whereas persistent symptoms are defined as nasal symptoms more than 4 days per week and more than 4 consecutive weeks. A patient with symptoms not affecting their daily activities is considered mild, whereas symptoms affecting their daily activities are considered moderate to severe AR.

The ARIA classification acknowledged the impact of a disease that was often qualified as trivial. The ARIA 'mild' and 'moderate/severe' classification has strengths and weaknesses. It is very simple to administer since it is based on yes or no answers. The ARIA duration and severity classifications have been implemented in several countries and patient populations. Cohort studies of adults and paediatric AR patients in Spain found that symptoms, Rhinitis Quality of Life Questionnaire, and visual analogue scale scores were significantly higher in 'moderate/severe' than in 'mild' AR.[27,28] The level of awareness and application of the ARIA severity classification is less. A study by Demoli et. al found that only about 54% of physicians were aware of the ARIA classification.[29]

The knowledge of ARIA classification by primary care practitioners did not influence the use of H1-antihistamine and/or intranasal steroid as a function of the patient's disease severity.[29] Researchers also found that ARIA severity did not significantly influence medication prescription.[30]

Patient education, allergen avoidance, and pharmacotherapy are required for the optimal treatment of AR patients.[31] Allergen immunotherapy is another option for treatment for certain patients. Skin prick test is the gold standard for allergy testing. Patients with uncertain allergy histories might benefit from this test for their allergen avoidance. The main goal for AR is to achieve good control and to reduce its impact on daily activities, work or school performance, sport or leisure, and sleep. A reliable AR control assessment tool is important and needed to evaluate this AR symptom. For pharmacotherapy in AR control, the patient should be prescribed an antihistamine and/or intranasal steroid spray. Patients with uncontrolled AR symptoms should be considered for increased medication dosage or additional other AR treatment. While for controlled AR, stepping-down treatment is recommended to identify the minimum medication needed to maintain control.[32] Most AR patients could get their symptoms controlled after a standard treatment as proposed by ARIA.

The ARIA guidelines state that treatment should be tailored to the severity of the disease, comorbidities, treatment availability, affordability, and patient preference. Thus, methods for measuring the disease severity and its control must be uniform, reproducible, quick, and easy to perform in routine practice.[33] Focus should be on the disease's impact on daily activities.

Few AR control tools have been validated including RCAT, CARAT, and ARCT, to assess the AR control levels. Recent ARCT has been validated in step-up and step-down medication strategies. They found that the AR control rate was similar in the ARCT group and the control group, whereas less medication use, and medical cost were found in the ARCT group.[31]

This study is aimed to develop, validate, and evaluate a tool to simultaneously assess AR symptoms and their impact on daily activities, based on ARIA guidelines.

Participants are required to answer demographic, allergy status and current medication in part 1 of the ARSIA questionnaire. In part 2(a) of the ARSIA questionnaire, participants are required to answer both in the 4 weeks and 6 months column, and the score will be summed up. Based on reliability statistics Cronbach alpha, sensitivity, specificity, PPV, and NPV compared to the physician diagnoses, showed all these items were good. In part 2(b), the impact on daily activities such as irritability, sleep disturbance, leisure, sport, school or work performance, troublesome symptoms, and relationship with a spouse were assessed.

We found that the ARSIA questionnaire has good internal consistency and internal validity.

We also observed a good correlation in terms of sensitivity, specificity, PPV, and NPV, compared to physician diagnoses that were made clinically based on ARIA guidelines.

These two parts of the questionnaire will give a score each and a comparison during each follow-up visit could be made. Reducing the total score indicates improvement in the nasal symptoms and their impact on daily activities, whereas increasing the score indicates worsening symptoms.

Further studies with larger datasets and involving multicentre are needed to establish the cut values for the ARSIA questionnaire. However, the existing data seems to suggest a score of '12 or less' for the symptoms indicates intermittent, 'more than 12' indicates persistent, '15 or less' for the impact on daily activities indicated mild, and 'more than 15' indicates moderate/severe.

In summary, this study showed that the ARSIA questionnaire has good internal consistency and internal validity, with good sensitivity, specificity, (PPV), and (NPV). Therefore, the ARSIA questionnaire can be used to rapidly screen for patients having rhinitis symptom control problems. It also can help patients in communicating with doctors about problems with their nasal disease. This patient assessed ARSIA questionnaire can complement the physician's assessment, and in addition, it should also perform well as a standalone measure of the patient's perception of their symptom control.

CONCLUSION

This newly developed, validated, and evaluated questionnaire is a good tool for the evaluation of allergic rhinitis symptoms and their impact on daily activities. It is important to understand that AR symptoms could have a significant impact on daily activities. Although further study and testing are needed, it provides an initial means for evaluating the patient's condition and control level, as well as patients' perception of their rhinitis control.

ACKNOWLEDGMENT

Special thanks to the nursing staff of ORL Clinic HSAH and HUSM for their full cooperation to make the research work successful and meaningful. Additionally, we are grateful to USM for the funding (1001/PPSP/8070011) that enabled us to accomplish the study's goals.

REFERENCES

1. Kateralis CH, Lee BW, Potter PC, Maspero JF, Cingi C, Lopatin A, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy 2012; 42: 186-207.
2. Bauchau V, Durham SR. Epidemiological characterisation of the intermittent and persistent types of allergic rhinitis. Allergy 2005; 60: 350-53.
3. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in prevalence of symptoms of asthma, allergic rhino-conjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 2006; 368: 733-43.
4. Bousquet J, Van Cauwenberge P, Khaltaev N. Aria workshop group, world health organisation. J Allergy Clin Immunol 2001; 108(55): 5147-334.
5. Keith PK, Desrosiers M, Laister T, Schellenberg RR, Waserman S. The burden of allergic rhinitis (AR) in Canada: perspectives of physicians and patients. Allergy Asthma Clin Immunol 2012; 8(1): 7.
6. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factors for asthma in nonatopic subjects: results from European community respiratory health survey. J Allergy Clin Immunol 1999; 104: 301-4.
7. Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample; data from the second national health and nutrition examination survey, 1976-80 (NHANES II). J Allergy Clin Immunol 1992; 90: 579-88.
8. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax 1991; 46: 895-901.
9. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992; 90: 250-56.
10. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organisation, GA (2)LEN and AllerGen). Allergy 2008; 63(suppl 86): 8-160.
11. Tan R, Cvetkovski B, Kritikos V, Price D, Yan K, Smith P, et al. Identifying the hidden burden of allergic rhinitis (AR) in community pharmacy: a global phenomenon. Asthma Res Pract 2017; 3: 8.
12. Williams A, Scadding G. Is reliance on self-medication and pharmacy care adequate for rhinitis patients? Int J Clin Pract 2009; 63(1): 98–104.
13. Bosnic-Anticevich S, Kritikos V, Carter V, Yan KY, Armour C, Ryan D, et al. Lack of asthma and rhinitis control in general practitioner-managed patients prescribed fixed-dose combination therapy in Australia. J Asthma 2018; 55(6): 684-94.
14. Tan R, Cvetkovski B, Kritikos V, Price D, Yan K, Smith P, et al. The burden of rhinitis and the impact of medication management within the community pharmacy setting. J Allergy Clin Immunol Pract 2018; 6(5): 1717-25.
15. Azevedo P, Correia de Sousa J, Bousquet J, Bugalho-Almeida A, Del Giacco SR, Demoly P, et al. WHO collaborative centre for asthma and rhinitis, montpellier. Control of allergic rhinitis and asthma test (CARAT): dissemination and applications in primary care. Prim Care Respir J 2013; 22(1): 112-6.
16. Nathan RA, Dalal AA, Stanford RH, Meltzer EO, Schatz M, Derebery J, et al. Qualitative development of the rhinitis control assessment test (RCAT), an instrument for evaluating rhinitis symptom control. Patient 2010; 3(2): 91-9.
17. Kennedy JL, Hubbard MA, Huyett P, Patrie JT, Borish L, Payne SC. Sino-nasal outcome test (SNOT-22): a predictor of postsurgical improvement in patients with chronic sinusitis. Ann Allergy Asthma Immunol 2013; 111(4): 246-51.e2.
18. Armstrong TS, Mendoza T, Gring I, Coco C, Cohen MZ, Eriksen L, et al. Validation of the M.D. anderson symptom inventory brain tumor module (MDASI-BT). J Neurooncol 2006; 80(1): 27-35.
19. Shi J, Mo X, Sun Z. Zhong Nan Da Xue Xue Bao Yi Xue Ban. [Content validity index in scale development]. Journal of Central South University. Medical sciences. 2012; 37(2): 152-5.
20. Yusoff M. Abc of response process validation and face validity index calculation. Educ Med J 2019; 11(3): 55-61.
21. Cook DA, Beckman TJ. Current concepts in validity and reliability for psychometric instruments: theory and application. Am J Med 2006; 119(2): 166.e167-166.e116.
22. Stephanie Glen. Cronbach's Alpha: Simple Definition, Use and Interpretation. From StatisticsHowTo.com: Elementary Statistics for the rest of us! [cited December 2022]. Available from: https://www.statisticshowto.com/probability-and-statistics/statistics-definitions/cronbachs-alpha-spss/.
23. Trevethan R. Sensitivity, specificity, and predictive values: foundations, pliabilities, and pitfalls in research and practice. Front Public Health 2017; 5: 307.
24. Hair J, Anderson R, Babin B, Black W. Multivariate Data Analysis: A Global Perspective. (Vol. 7), New York, USA: Pearson; 2010.
25. Stephanie Glen. Average Inter-Item Correlation: Definition, Example. From StatisticsHowTo.com: Elementary Statistics for the rest of us! [cited December 2022]. Available from: https://www.statisticshowto.com/average-inter-item-correlation/.
26. Tran NP, Vickery J, Blaiss MS. Management of rhinitis: allergic and non-allergic. Allergy Asthma Immunol Res 2011; 3(3): 148-56.
27. Del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients - the ADRIAL cohort study. Rhinology 2010; 48: 201-5.

28. Jáuregui I, Dávila I, Sastre J, Bartra J, del Cuvillo A, Ferrer M, et al. Validation of ARIA (allergic rhinitis and its impact on asthma) classification in a pediatric population: the PEDRIAL study. Pediatr Allergy Immunol 2011; 22: 388-92.
29. Rouve S, Didier A, Demoly P, Jankowsky R, Klossek JM, Annesi-Maesano I. Numeric score and visual analog scale in assessing seasonal allergic rhinitis severity. Rhinology 2010; 48: 285-91.
30. Ramirez LF, Urbinelli R, Allaert FA, Demoly P. Combining H1-antihistamines and nasal corticosteroids to treat allergic rhinitis in general practice. Allergy 2011; 66: 1501-502.
31. Zhu R, Wang J, Wu Y, Yang Y, Huang N, Yang Y, et al. The allergic rhinitis control test questionnaire is valuable in guiding step-down pharmacotherapy treatment of allergic rhinitis. J Allergy Clin Immunol Pract 2019; 7(1): 272-78.
32. Demoly P, Broue-Chabbert A, Wessel F, Chartier A. Severity and disease control before house dust mite immunotherapy initiation: ANTARES a French observational survey. Allergy Asthma Clin Immunol 2016; 12: 13.
33. Bousquet J, Schunemann HJ, Samolinski B, Baena-Cagnani CE, Bachert C, Bonini S, et al. Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 2012; 130: 1049-62.

Accuracy of bleeding volumetric measurement on head CT scan with sequence and helical techniques using manual and automatic methods: A phantom study

Darmini, MKes[1], Agustina Dwi Prastanti, MSi[1], Siti Daryati, MSc[1], Yeti Kartikasari, MKes[1], Akhmad Haris Sulistiyadi, MKes[1], Dwi Adi Setiawan, SST[2]

[1]Poltekkes Kemenkes Semarang, Radiodiagnostic and Radiotherapy Department, Semarang, Indonesia, [2]dr.Kariadi Central Hospital, Semarang, Indonesia

ABSTRACT

Introduction: There are two data acquisition methods for computed tomography (CT) scans, namely sequence and helical. Each of them has two ways of measuring the volume of bleeding in a head CT scan, namely by manual and automatic methods. So, it is necessary to have an analysis for measurement accuracy with these two methods in two data acquisitions. The purpose of this study was to compare and evaluate bleeding volumetric measurement accuracy of sequence and helical on head CT acquisition using manual and automatic methods.

Materials and Methods: This is quantitative research with a true experimental approach. Actual bleeding volume was simulated by an acrylic phantom containing Iodine contrast media (5 ml, 10 ml, 15 ml, and 20 ml). The phantom was scanned using routine CT protocol using the helical and sequence technique. Bleeding volume from each technique was measured manually using the Broderick formula and automatic software (ROI based). Accuracy was assessed by comparing the volume measurement result to the actual bleeding volume. Data was analysed using the Friedman test and by Wilcoxon.

Results: The standard deviation of measured bleeding volume from the manual and automatic measurements compared to the actual bleeding volume were (0.220; 0.236; 0.351; 0.057) and (0.139; 0.270; 0.315; 0.329) in helical technique, and (0.333; 0.376; 0.447; 0.476) and (0.139; 0.242; 0.288; 0,376) in sequence technique. There are differences in the measurement results from the helical and sequence techniques ($p < 0.05$) and using manual and automatic methods ($p < 0.05$).

Conclusion: The measurement of bleeding volume that has a standard deviation value compared to the actual volume is more accurate in the helical technique using the automatic method, while the sequence technique is the manual method.

KEYWORDS:
Bleeding volumetric measurement; head CT; helical; sequence

INTRODUCTION

Computed tomography (CT) scan is a fast and accurate imaging modality in diagnosing abnormalities in the head or brain.[1] It is very useful for emergency cases and the gold standard for brain injury and trauma brain injury (TBI) evaluation.[2] CT is the first-line modality of choice for evaluating the brain and the most often performed CT examination in many hospitals nowadays. CT scan is the first and foremost modality in the investigation of head trauma patients.[3] In some cases of suspected paediatric non-accidental trauma, skull radiographs are still performed as part of a skeletal survey in addition to CT, however this does not supplant the need for CT when TBI is clinically suspected. Although radiographs may help differentiate accessory sutures from fractures, this too may become obsolete as three-dimensional skull reformats are increasingly available in clinical practice.[4]

CT scans of the brain can be performed using either sequence or helical CT scanning techniques. In sequence scanning, the CT table moves through the rotating gantry, which images thin slices of the brain. Because the table advances only after each slice is scanned, this technique is time-consuming prone to potential misregistration and motion artifacts and has limited availability of the overlapping images used for postprocessing. In helical scanning, the CT table moves through the gantry at a constant speed as scanning occurs, resulting in faster scan times, continuous data acquisition, and continuous radiation.[5] This technique reduces the scan time, and with breath-hold technique can reduce the motion artifacts. Data acquisition in the helical technique is continuous, which results in an improvement in the post-processing of MPR and VRT reconstructions. It is not clearly stated that the helical CT produces such good-quality images to replace those of conventional CT. For example, studies have revealed that the axial technique yields better image quality, especially in structures with low contrast differences yet another study has shown that the two techniques attribute similar image quality. In addition, there are studies suggesting that the helical technique has a lower dose whereas others show the exact opposite.[6]

Bleeding in the brain due to trauma or stroke is one thing that requires evaluation to measure its volume. Intracranial

This article was accepted: 17 November 2023
Corresponding Author: Darmini
Email: da12mini@gmail.com

haemorrhage (ICH) that causes mass effect usually needs urgent neurosurgical evacuation. It is divided into five subtypes including intraventricular haemorrhage (IVH), intraparenchymal haemorrhage (IPH), subarachnoid haemorrhage (SAH), epidural haemorrhage (EDH), and subdural haemorrhage (SDH). The decision for surgical intervention for craniotomy is dependent on the injury type and the patient's neurologic exam. Only three potential subtypes of ICH that may necessitate surgical interventions: intraparenchymal haemorrhage (IPH), subdural haemorrhage (SDH), and epidural haemorrhage (EDH).[2] Head bleeding can occur in several places such as ICH, SAH, EDH and SDH. The location and volume of the bleeding can determine the mortality rate. So, accuracy in measuring bleeding volume with an easy and accurate method is important.[7]

Measurement of bleeding volume can use two methods, namely manual and automatic. Manually using the Broderick method and automatically using analyse software, the region of interest (ROI) was segmented from surrounding regions automatically by setting up threshold levels.[8] The Broderick method is performed by multiplying the bleeding diameter to the total length of the slice thickness. The automatic method calculates the volume by identifying the HU values in the bleeding area with volume evaluation software. The aim of this study was to compare and evaluate the bleeding volume measurement of sequence CT and helical CT of the brain using automatic and manual methods with standardised phantom.

MATERIALS AND METHODS

Study Design and Data Collection

This study was conducted in Roemani Muhammadiyah Hospital. This is an experimental study that analyses of actual bleeding volume simulated by an acrylic phantom with four tube sizes (diameter= 2 cm) containing iodine contrast media. Actual bleeding volume was simulated by an acrylic phantom as shown in Fig 1 with four tube sizes (diameter= 2 cm) containing iodine contrast media. The tube volume is 5 ml, 10 ml, 15 ml, and 20 ml respectively. The whole size of the phantom is 20 cm in diameter and 11 cm in thickness corresponds to the size of the average adult human head.

Preliminary Scanning

Preliminary scanning is performed to figure out the best filter. Filter H70s was chosen to get the best image contrast.

Radiological Data

Scanning was performed using six slice CT-scan (Siemens Emotion) with a routine head protocol (rotation time 1 second and slice thickness 2.5 mm, 130 kV; 250 mAs; 200 mm FOV; H70s filter; Hu min: 3069; HU max: 3071. Scanning for each tube volume (5 ml, 10 ml, 15 ml and 20 ml). Volume measurements repeated three times.

Measurement of bleeding with manual method (Fig 2A):

a. Slice selection: The 10th slice (the middle slice number). This slice representing the middle position of the entire length of the slices. The slice selection for the length measurement is give two measurements, the first measurement at the greatest diameter of the slices, and then the second measurement perpendicular to the first measurement.
b. Measure the thickness of bleeding with the Broderick formula:

    Volume = A x B x C / 2
    A = long diameter of bleeding
    B = diameter of bleeding width
    C = thickness of bleeding

Thickness of bleeding is the number of slices in which the bleeding is visualized multiplied by the slice thickness

Measurement of bleeding automatic method (Fig 2B):

a. Selection of the area in upper and lower limits of the lateral scan.
b. Apply the circle tool to the bleeding area in the axial image.
c. Determine the HU value for upper HU and lower HU (minimum HU value is 3069, maximum HU is 3071).

Data was analysed with the Friedman test followed by Wilcoxon (confidence level= 95%). Accuracy was assessed from the standard deviation value of the measurement results to the actual volume.

RESULTS

The results of measuring volume of bleeding on a head CT scan in the helical technique and sequence within manual and automatic measurement methods.

The results of calculating the helical technique using the manual method mean that the average value close to the actual volume in the helical technique is at a volume of 5 ml (4.39 cm^3) and 15 ml (11.40 cm^3). Whereas in the helical technique the automatic method is at a volume of 10 ml (8.09 cm^3) and 20 ml (18.93 cm^3) as shown in Table I.

The results of the helical technique calculation study using manual and automatic methods were carried out by means of a paired samples T-test with a significance value of 5 ml volume 0.000, 10 ml volume 0.000, 15 ml volume 0,001 and 20 ml volume 0.021 ($p < 0.05$). It can be concluded that there is a significant difference in the helical technique using automatic and manual methods as shown in Table II.

The results of the research on calculating the sequence technique using manual and automatic methods were carried out by the means of a paired samples T-test with the results of a significance value of 0.000 5 ml volume, 0.000 10 ml volume, 0.012 15 ml volume and 0.000 20 ml volume ($p < 0.05$). It can be concluded that there are significant differences in the sequence technique using automatic and manual methods as shown in Table II.

The automatic method has a smaller standard deviation in the helical technique, while the manual method with a volume of 5 ml has the same value, namely the standard deviation value is 0.139. Whereas at 10 ml, 15 ml and 20 ml, it is smaller in the sequence technique than the helical technique as shown in Table III.

Table I: The average value of bleeding volume using manual and automatic methods within helical and sequence scan modes

Volume	Helical		Sequence	
	Manual (cm^3)	Automatic (cm^3)	Manual (cm^3)	Automatic (cm^3)
5 ml	4,39	4,10	4,39	3,75
10 ml	7,87	8,09	8,05	7,27
15 ml	11,40	11,12	11,72	10,35
20 ml	15,05	18,93	14,20	13,55

Table II: Paired samples T-test result of bleeding volume using manual and automatic

Volume	Helical		Sequence	
	Sig. Value	p value	Sig. Value	p value
5 ml	0,000	< 0,05	0,000	< 0,05
10 ml	0,000	< 0,05	0,000	< 0,05
15 ml	0,001	< 0,05	0,012	< 0,05
20 ml	0,021	< 0,05	0,000	< 0,05

Table III: Standard deviation value with actual bleeding volume in manual and automatic method

Volume	Manual		Automatic	
	Helical	Sequence	Helical	Sequence
5 ml	0,139	0,139	0,220	0,333
10 ml	0,270	0,242	0,236	0,376
15 ml	0,315	0,288	0,351	0,447
20 ml	0,329	0,376	0,057	0,476

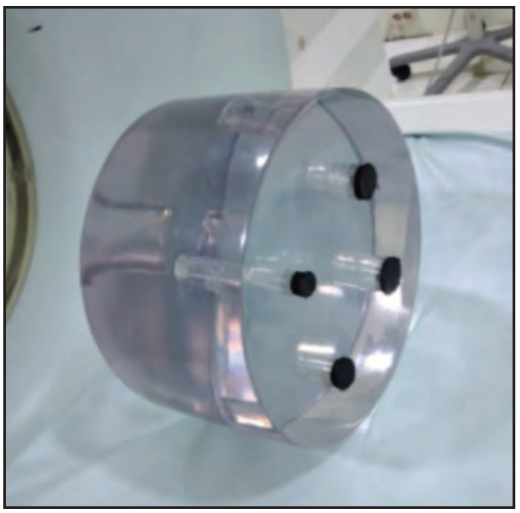

Fig. 1: Acrylic phantom.

DISCUSSION

The results of measuring volume of bleeding on a head CT scan in the helical technique and sequence within manual and automatic measurement methods

CT advantages for assessment of TBI include its sensitivity for demonstrating acute intra-axial and extra-axial haemorrhage, mass effect, ventricular size and bone fractures.[9] Post-traumatic blood may be epidural, subdural, subarachnoid, intraventricular or intraparenchymal. IPH may be related to brain contusion, that is, from injury to brain parenchyma after direct blow against the calvarium, or from diffuse axonal injury, also termed traumatic axonal injury or shear injury. So, it is necessary to have an analysis of the volume of bleeding in head trauma patients through the CT scan modality.[10]

Volume measurement plays an important role in further management, both surgical and non-surgical (conservative). The helical technique is a helical beam geometry that is used to obtain volume in a network. In this technique the x-ray tube is moved around the patient in a helical pattern with each scan. This technique produces a single slice of rotating x-ray tube. The advantage of this technique is relatively fast time.

The range of HU values used is smaller or larger, causing tissue with a smaller or larger HU value than the bleeding HU value to be counted as bleeding. The automatic volume method (SVE) has a longer processing time than the manual method, due to the process of segmenting the bleeding area and determining the HU value according to the type of

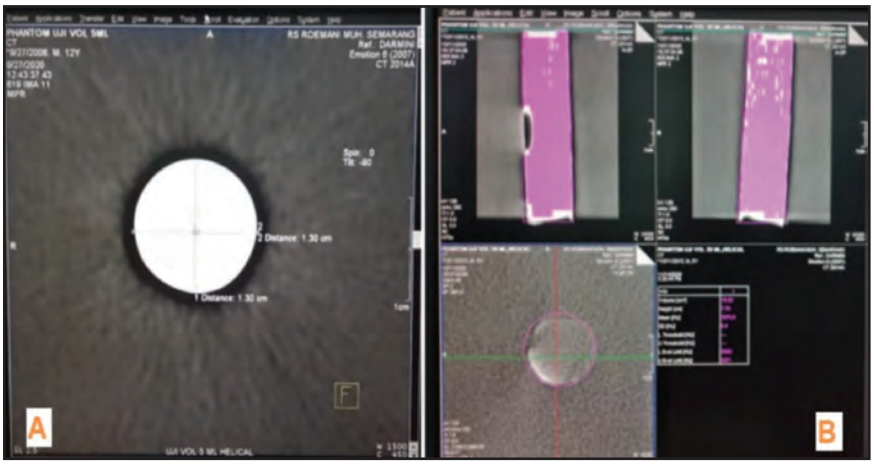

Fig. 2: Measurement of bleeding with manual method (A) and automatic method (B).

bleeding. Volumetric calculation manually (Broderick) looks more complicated according to data and calculations, but it's a process that have a faster processing time. In terms of accuracy, there is a tendency for the volume value of the manual method to be higher because it depends on the shape and size of the bleeding. In breeding with a regular form (regular), the manual method (Broderick) has a very small volume difference value compared to the automatic volume method, the average percentage value of the volume difference is 6%. However, in bleeding with irregular shapes (irregular) and bleeding with more than one point (multilobular) the manual method (Broderick) has a higher volume yield (overestimated) than the automatic volume method, the average percentage of the volume difference is 25%.

According to the researchers, the results in this study used the helical technique, the manual method, the results that were close to the actual size were at 5 ml volume, while in the automatic method, the values that were close to the actual volume were at volumes of 10 ml and 20. The different test results using manual and automatic methods, there were differences. Manual method ABC/2 is accurate with a fast process for bleeding volumes for small ones and there is a significant overestimation error for calculating bleeding volume, especially for irregular bleeding. and multilobular.[11] Volumetric calculations using the automatic volume method which is called Software Volume Evaluation (SVE) are strongly influenced by slice thickness or slice reconstruction, a thinner slice thickness will produce a more accurate volume measurement.[12] Although measurement of bleeding volume is currently mostly done by segmentation technique in ICH, it is still preceded by manual measurement with the ABC/2 formula.[13]

The results of measuring the volume of bleeding on a head CT scan in the sequence technique within manual and automatic measurement methods

In principle, the sequence technique of the X-ray tube and detector moves around the patient and collects data from first to last data points. Then the patient moves to the second position and the scan takes place automatically. Sequence technique is often called the axial scanning technique. During scanning the x-ray tube rotates around the patient to generate a specific set of data. To get another picture, the examination table must move to another position and set of data to produce images.[6]

The results of measuring the volume of bleeding in this study in the sequence technique, the values obtained are close to the actual volume using the manual method. This is consistent with that statement ABC/2 method is a valid method for estimation of ICH volume for both regular and irregular shaped hematomas.[14]

The standard deviation value of the measurement results of the bleeding volume of the sequence and helical techniques was compared with the actual volume

The automatic method has a smaller standard deviation in the helical technique, while the manual method with a volume of 5 ml has the same value, namely the standard deviation value is 0.139. Whereas at 10 ml, 15 ml and 20 ml, it is smaller in the sequence technique.

Data acquisition using the helical technique is volumetric in nature and has the advantage of reducing the radiation dose to patients.[15] Helical technique also has significant advantages over sequential CT techniques and therefore is likely to pave the way for the implementation of spiral CTs in cranial neuroradiology as a standard procedure.[16]

Based on the measurement results of the helical technique, the automatic method has a smaller standard deviation value, while the manual method sequence technique has a smaller standard deviation value. The automatic volume method (software volume evaluation) is a volume calculation by the computer software available on the CT scan tool. This method of volume calculation is used after all the parameters and the scanning process are complete. Calculation of the volume of bleeding based on this method is only used on CT scans with helical or helical techniques.[17] To obtain accurate information about the volume of bleeding it is critical to obtain the location and the shape of the bleeding regions for the diagnosis of cerebral haemorrhage, in which the algorithm needs to be improved.[18] Recently, fully automated algorithm method for measuring bleeding volume has also been developed. The fully automated algorithm quantified ICH volumes significantly faster than the semiautomated

and manual methods. Fully automated ICH segmentation may facilitate therapeutic decision-making and outcome prediction in patients with spontaneous, supratentorial ICH.[19] Several segmentation methods can also be used to estimate the estimated volume of bleeding, such as the Dynamic Graph Convolutional Neural Network (DGCNN) which predicts small-scale intracranial haemorrhage data set although a large dataset would be better.[20] But what is done in this study is to test the accuracy of calculating the volume of bleeding from the volume actual size and measured using the manually and automatically measurement methods within sequential and helical scan mode using a phantom.

This study has an update in discussing sequence and helical scanning techniques in determining the accuracy of bleeding volume measurements using phantom. In several existing studies for sequence and helical techniques often only discuss the radiation dose.[21]

This research has the limitation of not being able to assess masses, oedema, or midline shift. Because this research is a study using a phantom which is designed to simulate bleeding, the measurement of masses, oedema, or midline shift cannot be measured. Further research is needed to simulate irregular bleeding volume measurements, use of slice thickness variations and filter variations.

CONCLUSION

The results of the paired samples T test difference test were significant at 5 ml volume = 0.000, 10 ml volume 0.000, 15 ml volume = 0.012 and 20 ml volume = 0.000 ($p < 0.05$). Standard deviation value of the measurement results of the bleeding volume of the sequence technique and the helical technique compared to the actual volume of the helical technique measurement in the automatic method has a smaller standard deviation value. The most accurate method is the automatic method with the helical technique because it has a smaller standard deviation than the manual method with both techniques.

ACKNOWLEDGMENTS

We acknowledge the research grant received from Poltekkes Kemenkes Semarang with No: HK.02.03/6.1/3939/2020

REFERENCES

1. Kuo W, Häne C, Mukherjee P, Malik J, Yuh EL. Expert-level detection of acute intracranial hemorrhage on head computed tomography using deep learning. Proc Natl Acad Sci USA 2019; 116(45): 22737-45.
2. Inkeaw P, Angkurawaranon S, Khumrin P, Inmutto N, Traisathit P, Chaijaruwanich J, et al. Automatic hemorrhage segmentation on head CT scan for traumatic brain injury using 3D deep learning model. Comput Biol Med 2022; 146: 105530.
3. Davis T, Ings A. Head injury: triag investigation and early management of head Head injury: triage, assessment, investigation and early management of head injury in children, young people and adults (NICE guideline CG 176). Arch Dis Child Educ Pract Ed 2015; 100(2): 97-100.
4. Mutch CA, Talbott JF, Gean A. Imaging evaluation of acute traumatic brain injury. Neurosurg Clin N Am 2017; 27(4): 409-39.
5. Pace I, Zarb F. A comparison of sequential and spiral scanning techniques in brain CT. Radiol Technol 2015; 86(4): 373-8.
6. Dousi M, Fatsi A, Sotirakou K, Gkatzia N, Patelarou M, Theodosiou A. Helical vs conventional CT in routine head imaging. a comparison of dose and image quality using VGC analysis. J Radiol Clin Imaging 2021; 4(1): 36-049.
7. Rahmani F, Rikhtegar R, Ala A, Farkhad-Rasooli A, Ebrahimi-Bakhtavar H. Predicting 30-day mortality in patients with primary intracerebral hemorrhage: evaluation of the value of intracerebral hemorrhage and modified new intracerebral hemorrhage scores. Iran J Neurol 2018; 17(1): 47-52.
8. Divani AA, Majidi S, Luo X, Souslian FG, Zhang J, Abosch A, et al. The ABCs of accurate volumetric measurement of cerebral hematoma. Stroke 2011; 42(6): 1569-74.
9. Lolli V, Pezzulo M, Delpierre I, Sadeghi N. Emergency radiology special feature : review article MDCT imaging of traumatic brain injury. Br Inst Radiol 2015; 89: 1-14.
10. Kathleen R, Fink M. Imaging of head trauma. Semin Roentgenol 2016; 51(3): 143-51.
11. Huttner HB, Steiner T, Hartmann M, Köhrmann M, Juettler E, Mueller S, et al. Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 2006; 37(2): 404-8.
12. Prionas ND, Ray S, Boone JM. Volume assessment accuracy in computed tomography: a phantom study. J Appl Clin Med Phys 2010; 11(2): 168-80.
13. Hillal A, Sultani G, Ramgren B, Norrving B, Wasselius J, Ullberg T. Accuracy of automated intracerebral hemorrhage volume measurement on non –contrast computed tomography : a Swedish Stroke Register cohort study. Diagnostic Neuroradiol 2023; 65: 479–88.
14. Oge DD, Arsava EM, Pektezel MY, Gocmen R, Topcuoglu MA. Intracerebral hemorrhage volume estimation: is modification of the ABC/2 formula necessary according to the hematoma shape? Clin Neurol Neurosurg 2021; 207: 106779.
15. Roy C, Quin R, Labani A, Leyendecker P, Mertz L, Ohana M. Wide volume versus helical acquisition using 320-detector row computed tomography for computed tomography urography in adults. Diagn Interv Imaging 2018; 99(10): 653-62.
16. Wenz H, Maros ME, Meyer M, Förster A, Haubenreisser H, Kurth S, et al. Image quality of 3rd generation spiral cranial dual-source CT in Combination with an advanced model iterative reconstruction technique: a prospective intra-individual comparison study to standard sequential cranial CT using identical radiation dose. PLoS One 2015; 10(8): 1-14.
17. Scholtz JE, Wichmann JL, Bennett DW, Leithner D, Bauer RW, Vogl TJ, et al. Detecting intracranial hemorrhage using automatic tube current modulation with advanced modeled iterative reconstruction in unenhanced head single-and dual-energy dual-source CT. Am J Roentgenol. 2017; 208(5): 1089-96.
18. Wang N, Tong F, Tu Y, Chen H, Zhou Y, Tang J. Extraction of cerebral hemorrhage and calculation of Its volume on CT image using automatic segmentation algorithm extraction of cerebral hemorrhage and calculation of Its volume on CT image using automatic segmentation algorithm. J Phys Conf Ser 2019; (1187042088): 1-6.
19. Ironside N, Chen CJ, Mutasa S, Sim JL, Marfatia S, Roh D, et al. Fully automated segmentation algorithm for hematoma volumetric analysis in spontaneous intracerebral hemorrhage. AHA J 2019; 50: 3416-23.
20. Irene K, Masum MA, Yunus RE, Jatmiko W. Segmentation and approximation of blood volume in intracranial hemorrhage patients based on computed tomography scan images using deep learning method. Int Work Big Data Inf Secur IWBIS 2020; i(2020): 65-72.
21. Mahdavi M, Rahimi S, Eghlidospoor M. Evaluation of some spiral and sequential computed tomography protocols of adults used in three hospitals in Shiraz , Iran with American college of radiology and European commission guidelines. Polish J Radiol 2018; 83: 297-305.

ORIGINAL ARTICLE

A retrospective record review of tuberculous infections in rheumatoid arthritis patients on biologics in Malaysia

Abu Mansor Matardiah Nor Hashimah, DrIntMed[1], Ai Lee Lim, MBBS[1], Mollyza Mohd Zain, MMED[2], Suk Chyn Gun, MD[3], Liza Mohd Isa, MMED[4], Hwee Cheng Chong, MMED[5], Asmahan Mohamed Ismail, MMED[6], Sharifah Aishah Wan Mohamad Akbar, MBBS[7], Guo Ruey Ling, MBBS[8], Hairul Hadi Ariff, MMED[9], Chun Ruh Ng, MD[10], Seow Ching Ng, MBBS[11], Asmah Mohd, MMED[12], Eashwary Mageswaren, MMED[13]

[1]Rheumatology Unit, Department of Medicine, Hospital Pulau Pinang, Pulau Pinang, Malaysia, [2]Rheumatology Unit, Department of Medicine, Hospital Selayang, Selangor, Malaysia, 3Rheumatology Unit, Department of Medicine, Hospital Seremban, Negeri Sembilan Malaysia, [4]Rheumatology Unit, Department of Medicine, Hospital Putrajaya, Putrajaya, Malaysia, [5]Rheumatology Unit, Department of Medicine, Hospital Melaka, Melaka, Malaysia, [6]Rheumatology Unit, Department of Medicine, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia, [7]Rheumatology Unit, Department of Medicine, Hospital Umum Sarawak, Sarawak, Malaysia, [8]Rheumatology Unit, Department of Medicine, Hospital Sibu, Sarawak, Malaysia, [9]Rheumatology Unit, Department of Medicine, Hospital Queen Elizabeth, Sabah, Malaysia, [10]Rheumatology Unit, Department of Medicine, Hospital Sultan Ismail, Johor, Malaysia, [11]Rheumatology Unit, Department of Medicine, Hospital Sultanah Bahiyah, Kedah, Malaysia, [12]Rheumatology Unit, Department of Medicine, Hospital Pakar Sultanah Fatimah, Johor, Malaysia, [13]Rheumatology Unit, Department of Medicine, Hospital Tengku Ampuan Rahimah, Klang, Malaysia

ABSTRACT

Introduction: The aim of this study was to analyse the clinical characteristics of patients with rheumatoid arthritis receiving biologics therapy and investigate the association between types of biologics and tuberculosis (TB) infections in 13 tertiary hospitals in Malaysia.

Materials and Methods: This was a retrospective study that included all RA patients receiving biologics therapy in 13 tertiary hospitals in Malaysia from January 2008 to December 2018.

Results: We had 735 RA patients who received biologics therapy. Twenty-one of the 735 patients were diagnosed with TB infection after treatment with biologics. The calculated prevalence of TB infection in RA patients treated with biologics was 2.9% (29 per 1000 patients). Four groups of biologics were used in our patient cohort: monoclonal TNF inhibitors, etanercept, tocilizumab, and rituximab, with monoclonal TNF inhibitors being the most commonly used biologic. The median duration of biologics therapy before the diagnosis of TB was 8 months. 75% of patients had at least one co-morbidity and all patients had at least one ongoing cDMARD therapy at the time of TB diagnosis. More than half of the patients were on steroid therapy with an average prednisolone dose of 5 mg daily.

Conclusion: Although the study population and data were limited, this study illustrates the spectrum of TB infections in RA patients receiving biologics and potential risk factors associated with biologics therapy in Malaysia.

KEYWORDS:
Risk of tuberculosis; biologic therapy; tumour necrosis factor-alpha inhibitor; rheumatoid arthritis

INTRODUCTION

The World Health Organisation (WHO) estimates that 19 to 43% of the world's population is infected with *M. tuberculosis*; 18 million new cases and 12 million deaths from tuberculosis (TB) infection occur each year.[1] In Malaysia, the reported rate for TB infection is less than 100 cases per 100,000 population and the mortality rate was 5.5 cases per 100,000 population in 2015.[2]

Rheumatoid arthritis (RA) is a common, multisystemic autoimmune disease that can lead to deformities and functional limitations without appropriate treatment. The innate immune system in RA is important for maintaining the immune response and protecting against infection. It is also responsible for initiating the inflammatory response and activating the adaptive immune response.[3]

It is well known that RA patients have a four-fold higher rate of infections[4] and up to 13% infection-related mortality compared with the general population, especially TB infections.[5] Several factors predispose RA patients to infections, including the disease and its complications, cumulative doses of disease-modifying antirheumatic drugs (DMARDs),[2,4] prolonged use of steroids, and the advent of biologics therapy, which may further alter the immune system.

In one study,[6] RA patients treated with biologics had a 2.5-fold higher risk of TB infection compared with the biologic-naïve group. Tumour necrosis factor-alpha inhibitors (TNFα-i), particularly etanercept (ETN), had the lowest risk of TB infection compared with biologics in the same group.

To date, there are only a few studies reporting TB infections in RA patients treated with biologics therapy in Asian countries.[7,8] Most of the available studies aimed to analyse the adverse events associated with biologics therapy in RA

This article was accepted: 21 November 2023
Corresponding Author: Abu Mansor Matardiah Nor Hashimah
Email: norhashimahamm@yahoo.com

patients, especially infections.[9,10] In Malaysia, the risk of TB infection in RA patients receiving DMARDs or biologics therapy has not been reported. Although it is known that the risk is higher compared to the general population, it is important for us to know the data in relation to Malaysian population.

In this study, we analysed the baseline characteristics and demographic data of RA patients who received biologics therapy and investigate the association between types of biologics and tuberculosis infections in 13 tertiary hospitals in Malaysia.

MATERIALS AND METHODS

This was a retrospective study that included all RA patients who received biologics therapy from January 2008 to December 2018 at 13 tertiary hospitals in Malaysia. The aim of this study was to analyse the clinical characteristics of patients with RA receiving biologics therapy and investigate the association between types of biologics and tuberculosis infections in 13 tertiary hospitals in Malaysia. Ethics approval for the study was given by the National Medical Research Register (NMRR) under research number ID 58004. As this was a retrospective study, a consent waiver was granted by the research ethics committee.

All RA patients from rheumatology follow-up in 13 tertiary hospitals in Malaysia who received biologic therapy were included for this study. The inclusion criteria were patients: (i) diagnosed with RA based on the American College of Rheumatology (ACR) 2010 criteria;11 (ii) aged 18 years and older; and (iii) who received biologics therapy between January 2008 and December 2018. The exclusion criteria were RA patients: (i) with a concurrent diagnosis of psoriatic arthritis, spondyloarthritis or Bechet's disease; and (ii) who had received biologics therapy before January 2008 or after December 2018.

Patient demographics including age, sex, concomitant diseases (diabetes mellitus [DM], cardiovascular disease [CVD], chronic kidney disease [CKD], and chronic lung disease), screening prior to biologics therapy, treatment received for RA including conventional synthetic DMARDs (csDMARDs) and steroids, and treatment received for TB including TB infection and latent tuberculosis infection (LTBI) were obtained from the Malaysian National Inflammatory Arthritis Registry (MyNIAR), the Malaysian Rheumatology Biologic Registry (MARBLE), and the patient's medical records and recorded in the data collection forms. Data were expressed as mean ± standard deviation (SD) unless otherwise stated.

RESULTS

Patient Characteristics

During the study period from January 2008 to December 2018, 735 RA patients received biologics therapy. A total of 21 of the 735 patients were diagnosed with TB infection after treatment with biologics. Therefore, the calculated prevalence of TB infection in RA patients treated with biologics was 2.9% (29 per 1000 patients).

We were able to analyse only 21 patients diagnosed with TB infection because only limited data was available for the remaining patients. Of these 21 patients, 71.4% were women and the majority were of Malay ethnicity (52.45%). The median disease duration was 162 months. The sociodemographic characteristics of the subjects are shown in Table I.

Biologic Therapy

Four groups of biologics were used in our patient cohort: monoclonal TNFα-i, etanercept (ETN), interleukin-6; tocilizumab (TCZ), and anti-CD20; rituximab (RTX). Monoclonal TNFα-i was the most commonly used biologic (seven patients), namely, adalimumab (45.5%), infliximab (27.3%), golimumab (18.2%), or certolizumab (9.0%). The median duration of biologic therapy before diagnosis of TB was 8 months, with anti-CD20 having a minimum duration of 4.5 months. 16 (76.2%) had pulmonary TB, while the remaining 23.8% had extra-pulmonary TB, which included TB lymphadenitis, military TB, and disseminated TB (Table II).

Associated Risk Factors

Of the 21 patients, only 3 (14.3%) were smokers or had a history of smoking. Most of them had no history of TB (71.4%) and had never been treated for latent TB (71.4%). 75% of patients had at least one pre-existing disease, with hypertension (33.3%) being the most frequently reported comorbidity, followed by dyslipidaemia (19.0%) and ischemic heart disease (14.3%). As regards occupational status, 23.8% of patients were housewives, 14.3% worked in the hospital, and some had their own business (14.3%) or were retired (14.3%) (Table III).

All the patients had at least one ongoing cDMARDs therapy at the time of diagnosis TB. The most commonly used cDMARDs were leflunomide (71.4%), followed by methotrexate (61.9%) and sulfasalazine (38.1%). More than half had ongoing steroid therapy with an average steroid dose of 5 mg daily (Table III).

DISCUSSION

A paper published by Keane et al triggered the emergence of studies and registries on the risk of TB infections after biologics therapy.[8] Most of the available registries provided valuable data and estimates of the relative risk of TB associated with the use of different biologics. The result of our study showed that the calculated prevalence of TB infections in the Malaysian RA cohort treated with biologics was higher than in the Malaysian general population, and the incidence was almost comparable to reports from the Brazilian registry,[12] the Swedish population,[13] and the Korean population.[14] A French prospective study had reported a lower adjusted annual incidence rate of TB in patients receiving ETN, infliximab (IFX), and adalimumab (ADA).[15]

The median latency of TB infection after exposure to biologics in our patient cohort was 8 months, with the earliest being 4.25 months in patients exposed to anti-CD20, followed by 8.0 months for interleukin-6 (IL-6), 9.0 months for ETN, and 12.0 months for monoclonal TNFα-i. A retrospective

Table I: Sociodemographic data of the subjects

	Median	Min, Max
Demographic		
Age (years)	53	33, 82
Gender		
Male	6 (28.6)	
Female	15 (71.4)	
Race		
Malay	11 (52.4)	
Chinese	5 (23.8)	
Indian	5 (23.8)	
Duration of RA (months)	162	87, 336
Duration of biologic (months)	8.0	2.5, 72

RA: rheumatoid arthritis
Data presented as either counts (percentages) or median

Table II: Type of biologics, duration of therapy and tuberculosis infection

	ETN	Monoclonal TNF -i	Anti-CD20	IL-6	Total patients
Total number of patients (in percent)	6 (28.6)	7 (33.3)	2 (9.5)	6 (28.6)	21
Duration of biologics exposure before TB infection (months, median)	9.0	12.0	4.25	8.0	8.0
Steroid therapy at time of TB diagnosis (number of patients, dose)	2 (5mg)	3 (5mg) 1 (10mg) 1 (20mg)	1 (5mg) 1 (10 mg)	1 (5mg) 2 (2.5mg)	
History of TB infection	2 (9.5)	3 (14.3)	0	1 (4.8)	6
History of LTBI	1 (4.8)	2 (9.5)	0	3 (14.2)	6
Type of TB infection	4 PTB 2 EPTB	5 PTB 2 EPTB (Goli, Certo)	All PTB	5 PTB 1 EPTB	16 PTB 5 EPTB

ETN: etanercept, TNFα-i: tumour necrosis factor alpha-inhibitor, IL-6: interleukin-6, TB: tuberculosis, LTBI: latent tuberculosis infection, PTB: pulmonary tuberculosis, EPTB: extra pulmonary tuberculosis, Goli: golimumab, Certo: certolizumab pegol
Data presented as either counts (percentages) or median

Table III: Risk factors associated with tuberculosis infections in biologics therapy

Occupations	
Housewife	5 (23.8)
Hospital setting	3 (14.3)
Retired	3 (14.3)
Business	3 (14.3)
Office	2 (9.5)
Factory	2 (9.5)
Teacher	2 (9.5)
Driver	1 (4.8)
Smoking status	
Yes	3 (14.3)
No	18 (85.7)
History of TB infections before biologics therapy	
Yes	6 (28.6)
No	15 (71.4)
History of LTBI before biologics therapy	
Yes	6 (28.6)
No	15 (71.4)
Other co-morbidities	
Nil	5 (23.8)
1	4 (19.0)
2	7 (33.3)
3 and more	5 (23.8)
Number of DMARDs therapy at TB diagnosis	
1	6 (28.6)
2	8 (38.1)
3 and more	7 (33.3)
Steroid usage at TB diagnosis	
Yes	12 (57.1)
No	9 (42.9)

TB: tuberculosis, LTBI: latent tuberculosis infection, DMARDs: disease-modifying antirheumatic drugs
Data presented as counts (percentages)

Canadian study in 2006 found that the median time to diagnosis TB from IFX and ETN exposure was 4.25 and 19.75 months, respectively.[16] However, in the UK population, the median time from first TNFα-i exposure to diagnosis of TB was 13.4 months for ETN, 5.5 months for IFX, and 18.5 months for ADA.[17] Although the data were not comparable to our patient cohort, it suggests that we need to monitor the possibility of TB infection in patients receiving biologics as early as 4.25 months.

The association between TNFα-i therapy and reactivation of latent TB is well known. As mentioned in many studies[15,17,18] monoclonal TNFα-i was known to have a higher risk of TB infection compared with ETN. In the Korean population, two cases of TB were reported in 90 patients receiving IFX, and no case was reported in 103 patients receiving ETN.[19] In the UK registry, the incidence of TB was 1.5 per 1,000 patient-years for IFX and 0.5 per 1,000 patient-years for ETN.[20] A study of data from the British Society for Rheumatology Biologics Registry (BSRBR) confirmed a three- and four-fold risks of TB for IFX and ADA, respectively, compared with ETN.[17] Similarly, in our cohort, most patients who contracted TB were from the TNFα-i monoclonal group (33.3%). The TNFα-i agent inhibits the TNFα receptor, an important cytokine involved in the defence against infection, particularly mycobacterial infection, through a number of mechanisms include inhibition of reactivation of dormant bacilli.[21]

In the present study only two patients who had TB infection after RTX, none of whom had a prior history of TB. An open-label extension study by Keystone et al showed that the rate of severe infections was low in patients treated with RTX.[22] A 2-year, multicentre, randomised, double-blind, placebo-controlled trial of RTX therapy showed that RA patients had significant improvement in their disease activity after an inadequate response to TNFα-i. This study also found no evidence of TB reactivation with rituximab.[23] In patient treated with RTX, peripheral blood remains clear of B cells for 6 to 2 months after a single therapy. However, the reduction in B cells is not necessarily dramatic, and the long-lived plasma cells, the main source of protective antibodies, are not eliminated. Because RTX acts primarily on the humoral immune response, the risk of acquiring TB or reactivating latent TB is very low.[24] This is important in clinical practice because RTX may be one of the options for the treatment of RA patients at risk of developing TB, especially in patients with prior TB infection.

Data from the randomised controlled trials have shown that the newer TNFα-i monoclonal antibodies, such as golimumab (Goli) and certolizumab pegol (Certo), do not have an increased TB risk compared with placebo.[18] The risk of severe infections also appears to be significantly lower with these agents than with other TNFα-i.[18] In our patient pool, we had two patients receiving Goli and one patient with Certo who had TB infection after treatment.

Because TB disease is highly endemic in Malaysia, screening for TB is mandatory in all patients before starting the treatment with biologics. Methods used for TB screening in Malaysia include the tuberculin skin test (TST), chest radiograph, direct smear of sputum for acid-fast bacilli, and the most recent method available is the interferon-gamma release assay (IGRA). TST is the standard method for identifying LTBI, but it has low specificity and does not distinguish between infection with nonspecific mycobacteria or a reaction due to BCG vaccination. In contrast, IGRA is more specific and sensitive for LTBI but has not been validated in patients taking TNFα-i.[25] False-negative results in TST or IGRA may occasionally be observed especially in immunosuppressed patients treated with biologics, corticosteroids, or DMARDs.[26] Park et al. reported that serial TST combined with IGRA may be useful for the identification of false-negative results for LTBI and new TB infections in patients undergoing long-term anti-TNF therapy.[27]

Reactivation of LTBI has become a major concern since the introduction of IFX for RA.[8] In our cohort of patients who were found to have LTBI, isoniazid (INH) prophylaxis was administered for at least 6 to 9 months, with a treatment duration of at least 1 to 2 months before starting treatment with biologics. Several guidelines have recommended this treatment regimen on the basis of studies reporting up to a 10-fold increased risk of reactivation of latent TB in patients undergoing TNFα-i therapy and a decrease with appropriate prophylaxis in the same group of individuals.[21] Starting TNFα-i therapy after 1 month of TB prophylaxis in patients with RA who tested positive for LTBI significantly reduced the risk of TB reactivation. However, if the activity of the underlying disease and the general condition of the patient permit, it is preferable to wait another 1 month, because the side effects of therapy with isoniazid occur mainly in the first 2 months. Although the risk of LTBI reactivation is not the same with all biologics, screening for LTBI is strongly recommended in all current guidelines when initiating therapy with a TNFα-i.[28]

Older age, male sex, use of corticosteroids, and the presence of comorbidities such as DM, chronic obstructive pulmonary disease (COPD), and CKD were all significant risk factors for the development of TB in the cohort of RA.[29] We also attempted to assess the potential risk factors that might contribute to the development of TB infections in our patient cohort but were unable to analyse the correlation because of very limited data. We had expected that patients with a history of smoking or active smoking, a history of previous TB infections or LTBI, and occupational status might contribute to TB infection, but this was not the case. However, patients with ongoing steroid use and DMARDs and at least one comorbidity had a higher percentage of TB infections than the other patients. Comorbidities in our patients included hypertension, dyslipidaemia, ischemic heart disease, and diabetes mellitus.

We also investigated the types of TB infection in our patient cohort and up to 76% of them had pulmonary TB infection. The rest (five patients in total) had extrapulmonary TB (EPTB) infection, which included TB lymphadenitis and disseminated TB. Two of them received ETN, two received monoclonal TNFα-i, and one IL-6. TB lymphadenitis is known to be the most common EPTB reported in Malaysia,[30] but it is somewhat different in other countries.[31] Severe immunosuppression increases the risk of developing EPTB, as opposed to PTB alone.[30,31] To our knowledge, there has been no study addressing the association between biologics therapy and EPTB per se. Diagnosis of EPTB is also clinically challenging because of its atypical clinical features, but the risk of developing extrapulmonary tuberculosis was definitely

higher in RA patients. It is also difficult to distinguish symptoms such as fever and elevated inflammatory markers from other infections or a RA disease flare. In addition, TST results may be false-negative in cases of EPTB.[26]

There are some limitations to this study. This study did not have enough data from RA patients without biologics therapy, which would make it difficult to assess the association between risk factors in patients on and off biologics. Assessing risk factors in patients before and during biologics therapy would help improve treatment success without interruption and reduce the risk of infection for patients. Although the number of cases that developed TB in our study cohort was limited and the assessment of risk factors was not robust, we drew some conclusions about which biologics could be used in patients who previously had TB infections. This study also lacked data on disease activity before and after TB infections in patients treated with biologics. We were unable to assess treatment outcome in patients with TB infections. We anticipate that it will be difficult for patients with TB infections to control their disease activity because treatment options are limited during this time. It would be helpful to have the full data on this so that we can evaluate the impact of TB not only on the patient's infection status but also on disease control. We also were not able to compare whether RA disease alone is a risk factor for TB without biologics therapy.

A prospective cohort study of TB infections in patients with RA receiving biologics in the Malaysian population and the effects of different classes of biologics could provide useful information to help clinicians in the prevention of TB in this patient group.

CONCLUSION

Although the study population and data were limited, the findings of this study illustrate the spectrum of TB infections in RA patients receiving biologics and potential risk factors associated with biologics therapy. The incidence rates and types of biologics associated with TB appear comparable to other Asian and Western data. Identification of high-risk patients and appropriate screening before biologics therapy is an important tool to reduce the risk of progression to active TB. Patients with negative screening tests may need to be closely followed and monitored for possible TB reactivation. Effective prophylaxis helps to significantly reduce the risk of infection or TB reactivation in patients treated with biologics.

ACKNOWLEDGMENTS

We would like to thank the Director General of Health Malaysia for allowing us to publish the paper.

REFERENCES

1. World Health Organisation. Global tuberculosis report 2020. 2020; 1-232. Accessed from: https://iris.who.int/bitstream/handle/10665/336069/9789240013131-eng.pdf?sequence=1.
2. Disease Control Division, Ministry of Health Malaysia. National Strategic Plan for Tuberculosis Control (2016–2020). 2011; 1-119. Accessed from: http://www.moh.gov.my.
3. Pabón-Porras MA, Molina-Ríos S, Flórez-Suárez JB, Coral-Alvarado PX, Méndez-Patarroyo P, Quintana-López G. Rheumatoid arthritis and systemic lupus erythematosus: pathophysiological mechanisms related to innate immune system. SAGE Open Med 2019; 7: 1-24.
4. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003; 30: 1436-39.
5. Bouza E, Moya JGL, Muiioz P. Infections in systemic lupus erythematosus and rheumatoid arthritis. Infect Dis Clin North Am 2001; 15(2): 335-61.
6. Arkema EV, Jonsson J, Baecklund E, Bruchfeld J, Feltelius N, Askling J, et al. Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? Ann Rheum Dis 2014; (0): 1-6.
7. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT study group. Lancet 1999; 354: 1932-39.
8. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor a–neutralising agent. N Engl J Med 2001; 345(15): 1098-104.
9. Shobha V, Chandrashekara S, Rao V, Desai A, Jois R, Dharmanand BG, et al. Biologics and risk of tuberculosis in autoimmune rheumatic diseases: a real-world clinical experience from India. Int J Rheum Dis 2019; 22(2): 280-7.
10. Ji X, Hu L, Wang Y, Man S, Liu X, Song C, et al. Risk of tuberculosis in patients with rheumatoid arthritis treated with biological and targeted drugs: meta-analysis of randomised clinical trials. Chin Med J (Engl) 2022; 135(4): 409-15.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an american college of rheumatology/european league against rheumatism collaborative initiative. Arthritis Rheum 2010; 62(9): 2569-81.
12. Yonekura CL, Oliveira RDR, Titton DC, Ranza R, Ranzolin A, Hayata AL, et al. Incidence of tuberculosis among patients with rheumatoid arthritis using TNF blockers in Brazil: data from the Brazilian registry of biological therapies in rheumatic diseases. Rev Bras Reumatol 2017; 57(S2): S477-S83.
13. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cōster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005; (52): 1986-92.
14 Jung SM, Ju JH, Park MS, Kwok SK, Park KS, Kim HY, et al. Risk of tuberculosis in patients treated with anti-tumor necrosis factor therapy: a nationwide study in South Korea, a country with an intermediate tuberculosis burden. Int J Rheum Dis 2015; 18(3): 323-30.
15. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French research axed on tolerance of bio-therapies registry. Arthritis Rheum 2009; 60(7): 1884-94.
16. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006; 46(6): 717-22.
17. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British society for rheumatology biologics register (BSRBR). Ann Rheum Dis 2010; 69(3): 522-28.
18. Dobler CC. Biologic agents and tuberculosis. Microbiol Spectr 2016; 4(6): 1-12.
19. Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol 2007; 34(4): 706–11.

20. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British society for rheumatology biologics register. Arthritis Rheum 2006; 54: 2368-76.
21. Borekci S, Atahan E, Demir Yilmaz D, Mazican N, Duman B, Ozguler Y, et al. Factors affecting the tuberculosis risk in patients receiving anti-tumor necrosis factor-α treatment. Respiration 2015; 90: 191-8.
22. Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis; an open-label extension analysis. Arthritis Rheum 2007; 56(12): 3896-908.
23. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomised, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54: 2793-806.
24. Alkadi A, Alduaiji N, Alrehaily A. Risk of tuberculosis reactivation with rituximab therapy. Int J Health Sci 2017; 11(2): 41-4.
25. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-g assay for the development of active tuberculosis disease after recent infection with mycobacterium tuberculosis. Am J Respir Crit Care Med 2008; 177: 1164-70.
26. Nogi S, Arinuma Y, Komiya A, Hashimoto A, Matsui T, Tohma S. Clinical utility of neutrophil CD64 to detect extrapulmonary tuberculosis in three patients with rheumatoid arthritis undergoing treatment with biologics. Case Rep Rheumatol 1028; 2018: 1-6.
27. Park JH, Seo GY, Lee JS, Kim TH, Yoo DH. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol 2009; 36(10): 2158-63.
28. Iannone F, Cantini F, Lapadula G. Diagnosis of latent tuberculosis and prevention of reactivation in rheumatic patients receiving biologic therapy: International recommendations. J Rheumatol Suppl 2014; 91: 41-6.
29. Liao TL, Lin CH, Chen YM, Chang CL, Chen HH, Chen DY. Different risk of tuberculosis and efficacy of isoniazid prophylaxis in rheumatoid arthritis patients with biologic therapy: A nationwide retrospective cohort study in Taiwan. Plos One 2016; 11(4): 1-14.
30. Nissapatorn V, Kuppusamy I, Rohela M, Khairul Anuar A, Fong MY. Extrapulmonary tuberculosis in peninsular malaysia: retrospective study of 195 cases. Southeast Asian J Trop Med Public Health 2004; 35: 39-45.
31. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of risk factors for extrapulmonary tuberculosis. Clin Infect Dis 2004; 38: 199-205.

ORIGINAL ARTICLE

Links between socio-demographic characteristics and body mass index to colorectal cancer in North Borneo, Malaysia: A case–control study

Edawati Hamsah, MSc[1], Fredie Robinson, PhD[1], Firdaus Hayati, DrGenSurg[2], Norkiah Arsat, PhD[3], Nirmal Kaur, MPH[4], Ratha Krishnan Sriram, MS[5], Sentilnathan Subramaniam, DrGenSurg[5], Nithya Devi Kandasami, DrGenSurg[6], Chung Ket Lai, MS[7], Khasnizal Abd Karim, MS[8]

[1]Department of Public Health Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, [2]Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, [3]Department of Nursing, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, [4]Non-Communicable Unit, Department of Public Health, Ministry of Health, Malaysia, Sabah Health State Department, Kota Kinabalu, Sabah, Malaysia, [5]Colorectal Unit, Department of Surgical, Queen Elizabeth Hospital, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia, [6]Department of Surgery, Keningau Hospital, Ministry of Health Malaysia, Keningau, Sabah, Malaysia, [7]Department of Surgery, Sandakan Hospital, Ministry of Health Malaysia, Sandakan, Sabah, Malaysia, [8]Department of General Surgery, Teluk Intan Hospital, Ministry of Health Malaysia, Teluk Intan, Perak, Malaysia

ABSTRACT

Introduction: The fourth leading cause of cancer-related mortality and morbidity worldwide is colorectal cancer (CRC). Numerous reasons have contributed to the massive rise in CRC cases, for which Asian nations differ significantly in terms of risk incidence rates. The objectives of this study were to, first, identify the socio-demographic characteristics of those of North Borneo ethnicity and body mass index (BMI) and, second, determine the association of these factors with CRC. This research will contribute to preventing this form of cancer.

Materials and Methods: This study is an analysis of a matched case-control study with a ratio of 1:2. The case group contained 206 respondents, and the control group contained 412. All CRC cases were confirmed with the histological results. The control group was matched for links between age, sex and ethnicity with CRC. The Statistical Package for Social Sciences Statistics (SPSS) IBM version 28.0 was used to conduct descriptive analysis using chi-squared testing and simple logistic regression. The statistical significance was P < 0.05.

Result: Overall, 618 respondents took part in this survey, of which 256 (41.4%) were female and 362 (58.6%) were male. The maximum age was 76, with a mean age ± SD of 53.17 ± 11.4. Those of Bajau ethnicity comprised 24.6% (152) of the population, followed by Dusun with 22.8% (141), Kadazan with 17.6% (109%), other North Borneo ethnic groups with 15.5% (96), Bugis with 9.7% (60), Brunei with 4.4% (27) and other predominant races with 5.3% (33). Regression analyses revealed that the incidence of CRC in North Borneo, Malaysia, was substantially correlated with income, occupation, other linked diseases and BMI.

Conclusion: Various risk factors are linked to CRC, based on the findings related to socio-demographic characteristics and BMI. Therefore, to lower the nationwide prevalence of CRC, national public health campaigns should include collaboration with the regional authorities to highlight the incidence and risk factors of CRC based on ethnicity.

KEYWORDS:
Colorectal cancer; Ethnicity; Malaysia; Obese; Overweight; Sociodemographic

INTRODUCTION

Colorectal cancer (CRC), a leading cause of cancer-related morbidity and mortality, is the fourth leading cause of cancer deaths worldwide.[1] In 2018, 550,000 men and 470,000 women were affected by CRC, of which there are approximately one million new cases yearly. The number of new cases of CRC includes about 1,096,000 and 704,000 new cases of rectal cancer among men and women, respectively.[1] In Asian countries, incidence rates vary widely, and CRC cases have increased dramatically in certain economically mature parts of the continent.[2] This pattern can also be observed in Malaysia. CRC incidence rates are the highest among those of Chinese ethnicity, and CRC is the second most common cancer in both males and females, with an age-specific incidence of 10.2 per 100,000 females.[3]

Evidence from worldwide literature demonstrates that the CRC risk can be attributed to genetics, gender, ethnic origin, geographical region and environmental conditions.[4] In addition, meta-analysis research showed a considerably increased incidence of CRC associated with obesity.[5,6] The findings from 13 different meta-analysis cohort studies revealed weight gain or BMI were related to an elevated risk of colon cancer.[7,8] Compared to those of normal weight, obesity is associated with a 7%–60% higher risk of CRC; updated reviews suggest a 30%–70% higher risk and links to the population's lifestyle.[9,10] Therefore, the variety of cultures

This article was accepted: 21 November 2023
Corresponding Author: Firdaus Hayati
Email: firdaushayati@gmail.com

and technological changes mean that individual variations, age-related differences, body composition and ethnic factors must be considered when diagnosing CRC.[5]

In Asian countries, common risk factors are positively associated with CRC, such as positive family history, obesity and old age.[11–13] Understanding risk factors that compare various differences in demographics and resources would facilitate the prevention of CRC in Asia.[13] Studies in Malaysia have revealed the prevalence of CRC risk factors and their reduction in the Malaysian population as areas that should be investigated more extensively.[7] Thus far, most studies have represented only the three major ethnicities in Malaysia (Malay, Chinese and Indian) when exploring the risk factors of CRC.[14] To the best of the authors' knowledge, few studies have examined the socio-demographic characteristics of the indigenous population in North Borneo, Malaysia and their association with CRC incidence.

The population of North Borneo is approximately 3.59 million and comprises 32 ethnic groups, of which 28 are indigenous.[15] These multiple ethnic groups are characterised by diverse languages, cultures, and high genetic diversity, but they can communicate effectively in the Sabah Malay dialect.[16] Although the majority professed either Islam or Christianity, some retain ancient beliefs and practices. The latter group are not always genetically homogenous.[17] Therefore, understanding population-based differences concerning CRC will improve clinical practice and increase the resources available to facilitate the prevention of CRC in Malaysia. The objectives of this paper were to, first, identify links between socio-demographic characteristics—focusing on age, gender, ethnicity, religion, residential areas, marital status, education, income and occupation—and CRC incidence and, second, determine the association between BMI and CRC in those of North Borneo ethnicity.

MATERIALS AND METHODS

This is an analysis of a matched case–control study with a ratio of 1:2. CRC cases were taken from four district general hospitals (Queen Elizabeth Hospital, Duchess of Kent Hospital, Tawau Hospital, and Keningau Hospital) between 2019 and 2022. Using a multilevel research approach, the control group was matched for age, sex, ethnicity and place of residence to avoid potential bias.

The target population for the cases was all CRC patients (male and female) registered and reported in the Sabah Cancer Registry or the National Cancer Registry within three years of diagnosis (from 2019 to 2021). Participants in the control group were matched with cases in age (within five years), sex, and ethnicity in the same district and of the same ethnic group in Sabah. Based on the CRC risk, the sample size was determined (odds ratio [OR] = 1.78, 95% confidence interval [CI], P2 = 0.546). To identify odds ratios greater than 2.0 or lower than 0.6 with an 80% power, the sample size was matched to two controls (206:412) for age, sex and ethnicity. However, 2 years after the study began, new CRC cases were included to account for patients who had passed away.

Data collection commenced in March 2020 after obtaining research approval from the Malaysian Ministry of Health and Ethics Committee. Further support from the selected hospitals, clinics and Sabah State Health Departments was obtained to allow access to cancer registry lists, hospital records of diagnoses and patients' medical records. The investigator met selected respondents from the case group who visited one of four selected general hospitals in Sabah. Meanwhile, the control subjects met in the community and at their chosen health clinic. All the respondents were selected using purposive sampling. All the eligible respondents gave written informed consent to their participation before the interviews.

The subjects in the case groups were confirmed CRC patients diagnosed based on histopathological examination (HPE), registered in the Sabah State Cancer Register or the National Cancer Registry, and alive, regardless of their family history of cancer. These requirements helped to establish a comprehensive and reliable source for identifying cases. The control group was free of CRC participants with no family history of colorectal or any other form of cancer. Each respondent was matched by age, sex, gender and ethnicity to minimise potential confounding factors and enhance the comparability between groups. All the control subjects were screened for CRC using a faecal immunochemical blood test (iFOBT). The results needed to be negative, with no signs or symptoms of the disease. Respondents in both the case and control groups had to be indigenous to North Borneo and belong to one of the region's major ethnicities—such as Kadazan, Dusun, Bajau, Bugis, Brunei, Murut, Sungai, Bisaya, Jawa, Lundayeh, Rungus, Suluk, Irranun, Cocos, Kegayan or Tidung—or to another predominant race, such as Malay, Chinese or Indian. All the respondents had to be at least five years old to ensure their potential environmental exposure to the risk of CRC. To ensure the validity and reliability of data collection, participants were excluded if they could not provide written consent or had difficulties understanding or answering the questionnaire.

All the study respondents were interviewed face-to-face and given a standardised self-report questionnaire. These structured questionnaires were cross-culturally adapted to the research topic and valid for use in the local context. The questionnaire was divided into two sections. Section A (socio-demographic characteristics) covered the respondents' details, such as their age, gender (male or female), ethnicity (North Borneo ethnicity), religion (Muslim, Christian, Buddhist, Hindu or other), area or place of residence (by district), marital status (single, married, widow/widower/divorced), educational status (no formal education, primary, secondary, tertiary), household income (less than RM1000, RM1000-RM3000, RM3000 and above) and current employment (based on the International Labour Organisation criteria: self-employed, retired). Section B covered measurements of the respondent's anthropometric details.

A literature review of the studies, journals and books relevant to this topic validated the questionnaire's content. Face validity was used to assess the questionnaire. It was pre-tested with 30 respondents not included in the study sample to

ensure they understood the questions and statements. To gather more information, interviews were also conducted with the patients' family members and the medical professionals in charge of the patients. A document review was conducted of the patients' case notes, and hospital documents were reviewed to obtain the respondents' HPE results and notification reports. The North Borneo dialect uses the Malaysian national language, *Bahasa Melayu*, which was used when communicating with and interviewing the respondents.

Direct measurements of anthropometric data (weight, height and waist circumferences) were performed after the interview with each subject. Validated and calibrated instruments were utilised following Malaysian Health Ministry protocol standards. The participants wore light clothing and no shoes, and individual accessories were removed. According to standard procedures, body weight was measured to the nearest 0.1 kg using a digital SECA scale (model Seca Clara 803, Seca GmbH & Co. KG., Hamburg, Germany). The parameter used to determine underweight, normal weight, overweight, and obese was the BMI, which is calculated according to the formula BMI = weight (kg)/height (m^2). The BMI values were calculated as the ratio of weight in kilograms to the square of the height in metres (kg/m^2) and categorised based on the WHO 1998 guideline and the Asian BMI cutoff values. Every participant was divided into one of four categories based on the Asian BMI cutoff points: BMI 18.5 kg/m^2 (slim or underweight), BMI between 18.5 and 24.9 kg/m^2 (normal), BMI between 25 and 29.9 kg/m^2 (overweight) and BMI > 30 kg/m^2 (obesity).

According to standard procedures, waist circumference (WC) was measured with a non-elastic measuring tape Seca 201 (SECA, Vogel & Halke GmbH & Co. KG, Hamburg, Germany) and recorded to the closest 0.1 centimetres.[18] After the participant took several successive natural breaths, WC was measured at a level parallel to the floor, halfway between the top of the iliac crest and the lower edge of the last perceptible rib in the midaxillary line.[19] The waist circumferences were classified based on the cutoff established by the International Diabetes Federation (IDF)/Western Pacific World Health Organization/International Obesity Task (WHO/IASO/IOTF,2000) for Asians (90 cm in men and 80 cm in women).[20]

Patient privacy and confidentiality were maintained. Respondent selection was voluntary, so they were given the choice to participate, with no attention paid to any conflict of interest. They also had the right to withdraw from the study at any time. Informed consent was obtained from the respondents who wished to participate in the study, the confidentiality of which was assured. Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia NMRR: 19-3905-52394 and the University of Malaysia Sabah Research Ethics Committee (UMS/FPSK 6.9/100-6/1/95).

The Statistical Package for Social Sciences Statistics (SPSS) IBM version 28.0 was used to analyse the data. The data collected from the respondents were analysed according to their group. The normality tests showed that the data had a normal distribution. The socio-demographic data were analysed using the Pearson chi-squared test. Categorical data were expressed as frequencies, and percentages were presented descriptively and expressed as frequency (percentage, %) distribution. The current variables only used simple logistic regression on the effect size to determine the various socio-demographic factors associated with CRC. Simple regression was also used to determine the association between BMI and CRC. Hosmer and Lemeshow recommended this p-value as they found that using $p < 0.05$ might not enable certain significant variables to be identified.[21] No adjustments were made for confounding factors in the statistical analysis. The significance level was set as $p < 0.05$. The outcomes are presented as crude and odds ratios (OR) with a 95% confidence interval (CI) and the corresponding p values.

RESULTS

This case-control study involving 618 participants was conducted between March 2020 and December 2022. According to Table I, of the 206 cases and 412 controls, most participants were 61–65 years old, with 19.3% being 21.8% in the case group and 18.7% in the control group. The mean age of the participants was 53.17 (11.4) years old. Of the seven ethnic groups identified in this survey, Bajau comprised the greatest percentage (24.8%), followed by Dusun (22.3%), Kadazan (18.0%), other North Borneo groups (15.5%), Bugis (9.7%), other major races (5.3%) and Brunei (4.4%). Most participants (58.6%) were male, making up a majority of 59.2% in the case group and a majority of 58.3% in the control group. The participants were predominantly Muslim (59.4%) and married (78.3%). A total of 53.1% were secondary school graduates. Table II lists the socio-demographic characteristics with regard to CRC, including the respondents' incomes, occupations and BMI values.

The average monthly income of the wealthiest households was RM1000 (227.25 USD), and 38.2% earned between RM1000 and RM3000 (681.74 USD). The unemployment rate among the participants was 35.6%, while retirees comprised 15.0%. Following the International Labor Organization criteria, professionals made up 15.3% of the participants in the control group and 13.9% of those in the case group. Sales and service professionals comprised the next-largest group in both categories, accounting for 11.0% in each. Although the majority (61.7% of the respondents in the case and control groups) did not report receiving any treatment, 15.0% of the respondents from the case group and 41.0% of those from the control group did, receiving additional treatment for conditions such as hypertension, diabetes mellitus and cholesterol.

Table II also summarises the BMI values of the participants. It is statistically significant that CRC was associated with most respondents in the case group (48.5% vs. 63.1% in the control group), with a p-value of 0.001. Males with a waist circumference of less than 90 cm represented the majority of these, followed by men with a waist circumference beyond 90 cm. The mean (SD) of the case group is 3.62, whereas that of the control group is 3.42.

Table I: Frequency distribution of socio-demographic background of the participants

Variable	Case (206) n (%)	Control (412) n (%)
Age of respondent		
>25	4 (1.9)	8 (1.9)
26–30	5 (2.4)	10 (2.4)
31–35	10 (4.9)	22 (5.3)
36–40	14 (6.8)	26 (6.3)
41–45	13 (6.3)	31 (7.5)
46–50	23 (11.2)	39 (9.5)
51–55	34 (16.5)	72 (17.5)
56–60	37 (18.0)	82 (19.9)
61–65	45 (21.8)	77 (18.7)
>65	21 (10.2)	45 (10.9)
Mean age±SD (years) 53.17 ± 11.4		
Min–Max age 18–76 years		
Gender		
Male	122 (59.2)	240 (58.3)
Female	84 (40.8)	172 (41.7)
Ethnicity		
Bajau	51 (24.8)	101 (24.5)
Dusun	46 (22.3)	95 (23.1)
Kadazan	37 (18.0)	72 (17.5)
Bugis	20 (9.7)	40 (9.7)
Brunei	9 (4.4)	18 (4.4)
Other North Borneo ethnicity[a]	32 (15.5)	64 (15.5)
Other predominant race[b]	11 (5.3)	22 (5.3)
Religion		
Muslim	125 (60.7)	242 (58.7)
Christian	76 (36.9)	164 (39.8)
Buddha	5 (2.4)	5 (1.2)
Free thinker	0	1 (0.2)
Marital status		
Married	158 (76.7)	326 (79.1)
Divorce	14 (6.8)	19 (4.6)
widow	15 (7.3)	25 (6.1)
Single	19 (9.2)	42 (10.2)
Education		
None	16 (7.8)	16 (7.8)
Primary	45 (21.8)	87 (21.1)
Secondary	106 (51.5)	222 (53.9)
Higher education	39 (18.9)	87 (21.1)

[a](Murut, sungai, Bisaya, Jawa,Lundayeh, Rungus, Suluk, Irranun, Cocos, Kegayan, Tidung)
[b](Chinese, Malay)

DISCUSSION

Ethnicity age-adjusted incidence has often been interpreted to account for the differences in the prevalence of CRC worldwide. In addition, ethnicity, geographic variation, being younger, and gender have been linked to increased risk.[20–23] However, classification systems with four consensus molecular (CMS) subtypes of CRC are yet to be defined.[24] Some people in Asia, particularly the Chinese, Koreans and Japanese, live in similar environments and have similar lifestyles and dietary behaviours, unlike multi-ethnic populations like those of Singapore and Malaysia.[25,26] Cancer incidence and survival differences between indigenous and non-indigenous populations have been reported.[27,28] Surprisingly, the reported CRC prevalence was below the national norm. Malays, Chinese, Indians and others (including foreigners) are not representative of the indigenous communities in North Borneo, Malaysia (Sabah).[29,30]

The population of Sabah was projected to be 3,418.8 million in 2020. There are 36 officially recognised ethnic groups in North Borneo. The majority of the population (698,300) are of the Kadazan/Dusun ethnic group, followed by the Bajau (592,400) and Murut (112,900).[31] However, the study found that the highest incidence of CRC in selected districts was among the Bajau, with 24.8%, followed by the Dusun (22.3%), Kadazan (18.0%), and others in North Borneo (15.5%). These results may have been obtained due to these groups being the majority ethnicities in that area, and the findings do not represent the whole country. Following other research in Malaysia, the main ethnic groups reflected the increased risk factors for CRC.[32]

Most of those in the case group were found to be between the ages of 61 and 65, while 59.2% were male and 40.8% were female. In contrast, a global study in 2018 placed CRC risk third among men and second among women.[3] In Asian countries such as Korea and Japan, CRC is more significant in women than men, and it has surpassed all other cancer-

Table II: Univariate analysis of risk factors for colorectal cancer

Variable	Case (206) n (%)	Control (412) n (%)	OR	95% CI Lower	Upper	p value
Income						0.004
RM 1000–RM 3000	72 (35.0)	16 (39.8)	1.756	1.164	2.648	
> RM 3000	60 (29.1)	236 (38.2)	1.953	1.276	2.989	
< RM 1000	74 (35.9)	90 (23.3)	Ref			
Occupational						0.001
Manager	5 (2.4)	11 (2.7)	0.9	0.212	3.822	
Professional	23 (11.2)	63 (15.3)	2.073	0.678	6.339	
Technician and associate professional	4 (1.9)	9 (2.2)	1.05	0.277	3.985	
Clerical support workers	8 (3.9)	17 (4.1)	2.631	0.81	8.543	
Service and sales worker	13(6.3)	55 (13.3)	0.487	0.14	1.7	
Skilled agricultural, forestry and fishery worker	14 (6.8)	13 (3.2)	0.9	0.178	4.549	
Craft and related trades workers	5 (2.4)	7 (1.7)	0.15	0.013	1.676	
Plant and machine operators and assemblers	4(1.9)	2 (0.5)	3	0.786	11.445	
Elementary occupation	7 (3.4)	37 (9)	2.4	0.215	26.822	
Armed force	3 (1.5)	5 (1.2)	0.9	0.316	2.565	
Pensioner	32 (15.5)	61 (14.8)	1.125	0.375	3.377	
Not working	88 (42.7)	132 (32)	Ref			
Other related diseases						<0.001
HPT, DM, and cholesterol	31 (15)	169 (41)	3.25	2.09	5.055	
HPT, DM, and others	0	15 (3.6)	96322	0		
Others	5 (2.4)	15 (3.6)	1.789	0.635	5.039	
Chemotherapy	43 (20.9)	0	0	0		
Not on any treatment	127 (61.7)	213 (61.7)	Ref			
BMI						<0.001
Healthy weight	64 (31.1)	79 (19.2)	0.178	0.063	0.499	
Overweight	26 (12.6)	68 (16.5)	1.674	1.135	2.47	
Obesity	100 (48.5)	260 (63.1)	1.396	0.871	2.237	
Underweight	16 (7.8)	5 (1.2)	Ref			

OR = odds ratio, CI = confidence interval, BMI=Body mass index, and Ref = Reference

related causes as the second-most significant cause of death globally.[33,34] CRC has overtaken breast disease as the second-most frequent cancer in both men and women. The gender disparity may be partly due to lifestyle factors such as higher rates of smoking and drinking alcohol among men, as well as fewer doctor visits or cancer screenings.[32]

The earliest age at which diagnosis of CRC occurred was 18; however, between the ages of 41 and 50, the incidence rose by 17.5%. Between the ages of 61 and 65, it increased by 21.8% between notified cases.[23] These results agree with those of other studies in which indigenous people had a threefold higher risk of CRC than Chinese people.[3] It subsequently had CRC at age 50, climbs by 30% until age 55 and peaks at 70 years for both sexes.[3,23] In contrast, other studies have revealed a higher burden of prevalent CRC in people aged 45–49, based on observed incidence rates, and an increase among people younger than 40.[3]

Unique to this study, 66.5% of CRC cases were found to be diagnosed in patients between the ages of 51 and more than 65; however, most of these represent the majority of the primary ethnicity of North Borneo, Malaysia. These findings are in accordance with the Malaysian clinical practice guidelines for managing CRC. Recent studies have also shown that beginning screening at age 40 or 45 is cost-effective, and cancer screening models must be updated with the most current data regarding age and incidence of CRC.[33,34] In contrast to this study, by the ages of 41–50, 17.5% of the respondents in the control group were free from CRC because they attended CRC screening with the iFOBT (Immunological Faecal Blood Test).

Studies have also revealed that the country's population is divided between Muslims and Christians, with 60.7% of the respondents being Muslims and 36.9% being Christians.[29] Furthermore, only a small number of socio-demographic relationships were found not to be statistically significant. However, socioeconomic status was found to be a significant risk factor for CRC, with the majority of the respondents having a household income of less than RM1000 per month. The majority (51.5%) also had secondary-level schooling as their highest level of education. However, earlier research established a correlation between updated rates of CRC screening, income, and BMI category.[21,35]

The relationship between occupation and the onset of CRC has not been extensively studied. However, several studies have demonstrated that there are differences between the incidence of CRC in a variety of occupational groups. Some workers have more significant occupational exposure to particular agents, including those in the textile industry, automotive industry, petrochemical industry, beverage industry, iron and steel industry and railway industry, as well as dockyard workers and firefighters.[36] Our findings did not suggest exposure to any of these, but a connection between CRC and occupation was discovered. However, most respondents (220, or 35.6%) were unemployed, pensioners (15.0%) or professionals (13.9%), based on the International Standard Classification of Occupations (ISCO). Furthermore,

the results showed that 11.0% were sales and service workers, while 7.1% were employed at stalls, at markets or in elementary occupations. This association may be because North Borneo, Malaysia (Sabah) has the third-highest population working in the informal sector, with 165.5% of the population working in the unregistered sector (the informal sector establishment category includes establishments not registered with CCM and professional bodies, as well as establishments with fewer than ten workers and where all or at least one type of the goods produced are meant for sale or barter transactions).[29]

According to the findings shown in Table II, 51.7% of the respondents in the control group were healthy or not receiving any treatment, whereas 61.7% of those in the case group only received treatment for CRC. Additionally, respondents diagnosed with hypertension, diabetes mellitus, or hypercholesterolaemia were less common in the case group than the control group (15.0% vs. 41.0%). Co-morbid illnesses (diabetes, hypertension, dyslipidemia, coronary heart disease, gallbladder disease, arthritis and constipation) are more common in CRC patients with a Western lifestyle. As the data illustrate, CRC was significantly associated with the three morbid disorders of hypertension, hypercholesterolaemia, and diabetes mellitus, which were more prevalent in the control group than the case group. This aligned with the inverse relationship between blood cholesterol and the risk of CRC frequently noted in earlier research. In contrast, a small number of additional studies found a non-significant relationship between metformin use and decreased CRC risk in those with DM type II.[37] However, statins, antihypertensives and metformin use among patients and controls have not been fully documented. Although CRC risk factors vary from country to country, it is critical to investigate the disease further among healthy individuals.

Obesity is rapidly becoming a severe health problem because of lifestyle changes. Being overweight and being obese are two highly modifiable risk factors that significantly affect the incidence and mortality of CRC.[38] As shown in Table II, there is a substantial correlation between obesity and CRC, with 63.1% of the case group being obese and 31.1% being of normal weight. These results may be explained by the fact that obese people had a 33% higher risk of CRC than those of normal weight.[39] However, a study on CRC and obesity conducted in Malaysia in 2017 found that this country had a lower population attributable fraction (PAF) for overweight than Korea and Brazil. The PAF reflects the percentage of cases (both exposed and unexposed). Findings from 13 distinct meta-analysis cohort studies revealed that weight gain as determined by BMI or weight was marginally related to an elevated risk of colon cancer.[4] Further research is required to better understand the underlying biological mechanisms linking obesity to CRC.

Gender differences, the age of onset of metabolic syndrome, and BMI appear inconsistently associated with an increased risk of CRC. Consistent with the literature, the current findings show a significant correlation between all the anthropometric variables (weight, BMI and waist circumference) and CRC risk. Regardless of gender, the case group's average BMI was slightly higher than that of the control group, at 3.62 (1.054) and 3.42 (0.837), respectively. That is consistent with the findings of three further meta-analyses, which showed that both BMI and waist size were linked to the risk of CRC.[33,40] The strong correlation between the two sexes supports our findings on the association between BMI and CRC, as opposed to two studies from China that indicated a significant increase in colon cancer in men but not women.[40]

One limitation of the study is that the generalisability of these findings only represented a few specific ethnicities. The findings could only be generalised to some of the population of Sabah for reasons of ethnicity. Although all the socio-demographic factors were extensively discussed, it is unfortunate that not all the CRC cases registered in all the general hospitals in North Borneo could be included. Moreover, occupational exposure to the particular agent linked to CRC was not explored in this study. These areas require further research to determine whether an actual difference exists with regard to gender.

CONCLUSION

The authors concluded that there is a risk variance for CRC among the ethnic groups in North Borneo, Malaysia. The study showed various socio-demographic characteristics are linked to CRC based on socio-demographic characteristics and BMI. Therefore, national public health campaigns should include collaboration with the regional authorities to highlight the incidence and risk factors of CRC based on ethnicity to lower the nationwide prevalence of CRC.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394-424.
2. Veettil SK, Lim KG, Chaiyakunapruk N, Ching SM, Abu Hassan MR. Colorectal cancer in Malaysia: Its burden and implications for a multiethnic country Asian Journal of Surg. 2017;40:481-9.
3. Malaysia Cancer Statistics-Data and Figure Peninsular Malaysia (2016). National Cancer Registry. Ministry of Health Malaysia. Cited Jan 2022. Available from URL: http://www.makna.org.my/PDF/MalaysiaCancerStatistics.pdf.
4. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. J Natl Cancer Inst. 2017; 109(8): djw322.
5. Morrison DS, Parr CL, Lam TH, Ueshima H, Kim HC, Jee SH, et al . Behavioural and metabolic risk factors for mortality from colon and rectum cancer: analysis of data from the Asia-Pacific Cohort Studies Collaboration. Asian Pac J Cancer Prev. 2013; 14: 1083-1087
6. Chen Q, Wang J, Yang J, Jin Z, Shi W, Qin Y, et al. Association between adult weight gain and colorectal cancer: a dose–response meta-analysis of observational studies. Int J Cancer. 2015; 136(12): 2880-9.
7. Karahalios A, English DR, Simpson JA. Weight change and risk of colorectal cancer: A systematic review and meta-analysis. Am J Epidemiol. 2015; 181(11): 832-45.
8. World Cancer Research Fund/American Institute for Cancer Research: Food, Nutrition, Physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
9. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013; 62: 933-7.

10. Frezza EE, Wachtel MS, International MCh. Influence of obesity on the risk of developing colon cancer. Gut. 2006; 55: 285-1.
11. Hilmi I, Hartono JL, Goh KL. Negative perception in those at highest risk - potential challenges in colorectal cancer screening in an urban Asian population. Asian Pacific J Cancer Prev. 2010; 11: 815.
12. Su TT, Goh JY, Tan J, Muhaimah AR, Pigeneswaren Y, Khairun NS, et al. Level of colorectal cancer awareness: a cross-sectional exploratory study among multi-ethnic rural population in Malaysia. BMC Cancer. 2013; 13: 376.
13. Azeem S, Gillani SW, Siddiqui A, Jandrajupalli SB, Poh V, Syed Sulaiman SA. Diet and colorectal cancer risk in Asia-a systematic review. Asian Pac J Cancer Prev. 2015; 16: 5389-96.
14. Naing C, Lai PK, Mak JW. Immediately modifiable risk factors attributable to colorectal cancer in Malaysia BMC Public Health. 2017; 17: 637
15. Wise MR. Indigenous groups of Sabah: an annotated bibliography of linguistic and anthropological sources. Malaysia 2018: The Natural History Publications
16. Yew CW, Hoque MZ, Kitingan JP, Minsong A, Voo CLY, Ransangan J, et al. Genetic relatedness of indigenous ethnic groups in northern Borneo to neighbouring populations from Southeast Asia, as inferred from genome-wide SNP data. Ann Hum Genet. 2018; 82(4): 216-2261–11
17. Rundi C, Fielding K, Godfrey-Faussett P, Rodrigues LC, Mangtani P. Delays in seeking treatment for symptomatic tuberculosis in Sabah, East Malaysia: factors for patient delay. Int J Tuberc Lung Dis. 2011; 15: 1231-8.
18. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr. 2007; 86: 556-6.
19. Larsson SC, Wolk A. Body mass index and risk of multiple myeloma: A meta-analysis. Int J Cancer 2007; 121: 2512-16.
20. Jung KW, Park S, Kong HJ, Won YJ, Lee JY, Seo HG, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2009. Cancer Res Treat. 2012; 44: 11-24.
21. Sekeres MA, Maciejewski JP, List AF, Steensma DP, Artz A, Swern AS, et al. Perceptions of Disease State, Treatment Outcomes, and Prognosis Among Patients with Myelodysplastic Syndromes: Results from an Internet-Based Survey. The Oncologist. 2011; 16: 904-11.
22. Valan A, Najid F, Chandran P, Abd Rahim A, Chuah JA, Roslani AC. Distinctive clinicopathological Characteristics of Colorectal Cancer in Sabahan Indigenous Populations, Asian Pac J Cancer Prev. 2021; 22(3): 749-755.
23. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics. CA Cancer J Clin 2020; 70: 145-64.
24. Yue Xi, Pengfei Xu. Global colorectal cancer burden in 2020 and projections to 2040, Translational Oncology 2021;14: 101174.
25. Pourhoseingholi MA. Epidemiology and burden of colorectal cancer in Asia-Pacific region: what shall we do now? Transl Gastrointest Cancer. 2014 ;3: 169-73.
26. Chiu HM, Hsu WF, Chang LC, Wu MH. Colorectal cancer screening in Asia. Curr Gastroenterol Rep. 2017; 19: 47.
27. Dachs GU, Currie MJ, McKenzie F, Jeffreys M, Cox B, Foliaki S, Marchand LL, Robinson BA. Cancer disparities in indigenous Polynesian populations: Māori, Native Hawaiians, and Pacific people. The Lancet. 2008; 9: 473-84.
28. Moor JS, Cohen RA, Shapiroc JA, Nadelc MR, Sabatinoc SA, Yabroffa KR, Fedewad S, et al. Colorectal cancer screening in the United States: Trends from 2008 to 2015 and variation by health insurance coverage. Prev Med. 2018; 112: 199-206.
29. Hassan Abu MR, Wan Khamizar WK, Othman Z, Nik Mustapha NR, Mohd Said R, Leong TW, et al. The second annual national cancer patient registry report- colorectal cancer 2008-2013. Clin Res Centre. 2014.
30. Azizah AM, Nor Saleha IT, Noor Hashimah A, Asmah ZA, Mastulu W. Malaysian National Cancer Registry Report 2007-2011. 2016.
31. Ulaganathan V, Kandiah M , Zalilah MS, Faizal JA, Fijeraid H, Normayah K, et al. Colorectal Cancer and the Metabolic Syndrome: a Malaysian Multi-Centric Case-Control Study Asian Pacific Journal of Cancer Prevention. 2012; 13: 3873-7.
32. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359-86.
33. Abualkhair WH, Zhou M, Ahnen D, Yu Q, Wu XC, Karlitz JJ. Trends in incidence of early-onset colorectal cancer in the United States among those approaching screening age. JAMA Netw Open. 2020; 3: 1920407.
34. Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-effectiveness and national effects of initiating colorectal cancer screening for average-risk persons at age 45 years instead of 50 years. Gastroenterology. 2019; 157: 137-48
35. Azad NS, Leeds IL, Wanjau W, Shin EJ, Padula WV. Cost-utility of colorectal cancer screening at 40 years old for average-risk patients. Prev Med. 2020; 133: 106003.
36. Sing SM, Paszat LF, Li C, He J, Vinden C, Rabeneck L. Association of socioeconomic status and receipt of colorectal cancer investigations: A population-based retrospective cohort study. Can. Med. Assoc. J. 2004; 171: 461-465.
37. Puntoni R, russo l, Zannini D, Vercelli M, Gambaro RP, Valerio F, et al. Mortality among dock-yard workers in Genoa, Italy. Tumori. 1977; 63: 91-6.
38. Liu Y, Tang W, Wang J, Xie L, Li T, He Y, et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. Cancer Causes Control. 2014; 25(2): 237-49.
39. Ezzati M, Hoorn SV, Rodgers A, Lopez AD, Mathers CD, Murray CJ. Comparative risk assessment collaborating group. Estimates of global and regional potential health gains from reducing multiple major risk factors. Lancet. 2003; 362: 271-80.
40. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013; 8: 53916

Comparing risk factors for hepatitis B infection between indigenous and non-indigenous population in Pahang based on a 5-year database

Rifhan Rasuli, MPH, Mariam Mohamad, MD, Siti Sara Yaacob, DrPH

Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia

ABSTRACT

Introduction: Despite substantial progress in reducing hepatitis B prevalence in the general population, the indigenous population in Malaysia continues to face a significant burden of infection, with high seroprevalence rates. It is hypothesised that transmission patterns differ between the indigenous and non-indigenous populations. This study aimed to compare key risk factors for hepatitis B transmission in indigenous and non-indigenous cases.

Materials and Methods: This is a comparative cross-sectional study using secondary data from the *eNotifikasi* system and hepatitis B case investigation forms between 2018 and 2022 from four district health offices in Pahang, Malaysia. Demographic data, hepatitis B vaccination status and risk factors were assessed. Data analysis employed were independent chi-squared tests, t-tests and binary logistic regression.

Results: The study included 285 cases (141 indigenous and 145 non-indigenous). Among the indigenous cases, 72.3% were unvaccinated and 59.6% reported a history of infected mother, followed by percutaneous exposure, multiple sexual partners, and sharing syringe. The odds for those with a history of an infected mother being indigenous group is 2.5 times (95% CI: 1.4–4.4) compared to those with a history of an infected mother being non-indigenous group.

Conclusion: Significant difference exists in hepatitis B risk factors between indigenous and non-indigenous populations. The main risk factor for indigenous community is history of infected mother. Thus, the necessity of incorporating hepatitis B screening into the current practice of antenatal HIV screening, specifically targeting the indigenous community, should be given consideration.

KEYWORDS:
Hepatitis B, indigenous peoples, risk factors

INTRODUCTION

Hepatitis B infection poses a major global public health challenge, leading to the development of chronic liver diseases such as cirrhosis and hepatocellular carcinoma, resulting in an estimated 820,000 deaths each year.[1] Despite its highly infectious nature, this disease is preventable through vaccination, screening and the implementation of harm reduction programmes.[2]

The transmission of hepatitis B occurs through four main routes, namely perinatal, percutaneous, sexual and close person-to-person contact, often facilitated via open cuts and sores.[3] In areas with a high prevalence of infection, vertical transmission is believed to be the primary mode of transmission.[4]

Over the years, Malaysia has made outstanding progress in reducing the prevalence of hepatitis B infection within its general population. From an intermediate seroprevalence rate of 5.2% in the 1990s,[5] the country has achieved a remarkable decline, with current rates ranging between 1.1%[6] and 1.7%.[7] Despite this, the indigenous population in Malaysia continues to face a considerable burden of hepatitis B infection, with high seroprevalence rates of 8.7%[8] and 10.3%.[9]

The higher prevalence of hepatitis B among indigenous populations compared to the general population is a well-known phenomenon. Similar trends have been observed in other countries as well. For instance, in Australia, the seroprevalence of hepatitis B virus among indigenous Australians is reported to be 6.1%, significantly higher than the rate of 1.6% among non-indigenous Australians.[10] Likewise, high endemicity of hepatitis B infection has been found among certain indigenous communities in Mexico and Venezuela in Latin American countries.[11]

In the general population, hepatitis B cases predominantly occur among Malay males aged between 20 and 40 years, with intravenous drug abuse being the main transmission route.[6] However, there is a scarcity of research exploring the risk factors for hepatitis B transmission, specifically within the indigenous community in Malaysia. A study conducted by Sahlan et al.[8] shed some light on this issue, revealing that among the indigenous community, hepatitis B cases mostly involve males above 35 years of age, and potential modes of transmission include perinatal exposure, tattooing and body piercing. However, it is important to note that this study had a small sample size and focused solely on the Negrito tribes.

Indigenous people in the Peninsular Malaysia are classified into three main groups: Negrito, Senoi and Proto-Malay.

This article was accepted: 22 November 2023
Corresponding Author: Mariam Mohamad
Email: mariammd@uitm.edu.my

Among them, a notable proportion, accounting for 37.9%, reside in the state of Pahang.[12] As a result, Pahang is noteworthy for having the highest number of indigenous communities compared to other states in the Peninsular Malaysia. The indigenous population in Pahang is estimated to be approximately 80,924 individuals,[13] constituting approximately 5% of the state's total population.

Given the notably higher prevalence of hepatitis B infection within the indigenous community compared to the general population, it is postulated that there may exist distinct patterns of transmission in contrast to the non-indigenous population. Therefore, this study aimed to compare the key risk factors for hepatitis B transmission between the indigenous and non-indigenous cases.

MATERIALS AND METHODS

Study Design

This is a comparative cross-sectional study using secondary data obtained from *eNotifikasi* (online infectious disease notification system for Ministry of Health Malaysia) and hepatitis B case investigation forms (HepB/Ix/1-2008 form) that were available at the district health offices. These forms were employed by the district health inspectors during field investigations for each notified hepatitis B case in the *eNotifikasi* system.

Locations and Study Population

The study was conducted in four district health offices, namely Rompin, Pekan, Kuala Lipis and Temerloh. These districts were selected because they have the highest number of indigenous population within the state. Data collection for the study was carried out in June 2023. The study population comprised individuals diagnosed and reported with hepatitis B infection in the state of Pahang, while the sampling frame consisted of hepatitis B infection cases reported in the *eNotifikasi* system within the four selected districts from the year 2018 to 2022.

Data Collection and Sampling Strategy

The inclusion criteria were individuals in the four selected districts who were registered as having hepatitis B based on *eNotifikasi* system between the year 2018 and 2022 with positive hepatitis B surface antigen (HbsAg). This was based on the Ministry of Health's Case Definitions for Infectious Diseases in Malaysia,[14] which defined a confirmed chronic hepatitis B case as the presence of HbsAg in the patient's blood for a duration of more than 6 months. However, considering the challenges in accurately determining the exact duration of positive HbsAg, the criterion for chronic illness was simplified to include individuals who tested positive for HbsAg alone, as suggested by Terrault et al.[3]

Exclusion criteria encompassed non-Malaysian individuals, cases lacking an investigation form and cases with incomplete data specifically pertaining to hepatitis B vaccination status and risk factors.

The relevant information, such as hepatitis B immunisation status and risk factors for hepatitis B infection, was extracted from the investigation forms. In cases where multiple risk factors were reported, all of these factors were included in the analysis.

Initially, this study intended to classify the cases into two groups: indigenous and non-indigenous, followed by random sampling method. However, during the data collection phase, it became apparent that a significant number of randomly selected subjects did not meet the inclusion and exclusion criteria, particularly concerning the availability of investigation forms. As a result, the cases were still categorised into two groups, but the sampling strategy subsequently shifted to universal sampling, involving the examination of all hepatitis B investigation forms available at the district health offices.

Sample Size

The sample size for this study was determined using OpenEpi software version 3.01. The calculation took into account the prevalence rates of hepatitis B infection in both the general population and the indigenous population in Pahang. The prevalence of hepatitis B infection in the general population (1.7%) was derived from the National Health and Morbidity Survey (NHMS) 2020[7], while the prevalence among the indigenous population in Pahang (10.3%) was obtained from the study by Mohd Firdaus et al.[9]

To achieve a statistical power of 80% and a significance level (alpha) of 0.05, a sample size of 240 was initially calculated. Considering a potential 20% rate of missing data, the minimum required sample size for this study was adjusted to 288 (144 for each group).

Data Analysis

The collected data was entered into SPSS software version 28.0 for analysis. The investigation forms identified multiple risk factors for hepatitis B infection, which were regrouped in this study to facilitate analysis. The final classification of the risk factors for the transmission is as follows:

i) Infected mother—refers to cases where the mother has a reported history of hepatitis B infection
ii) Infected spouse/partner—refers to cases where the spouse/partner has a reported history of hepatitis B infection
iii) History of medical procedures—any history of healthcare procedure, such as surgery, dental treatment, blood transfusion and haemodialysis[20]
iv) History of percutaneous exposure—any history of process that involves puncturing through the skin, such as acupuncture, tattooing and body piercing[20]
v) Sharing syringes—refers to a history of sharing syringes and/or needles while intravenously administering illegal substances
vi) Multiple sexual partners—refers to a history of engaging in high-risk sexual practices involving multiple partners

A comparison of socio-demographic characteristics and risk factors for hepatitis B infection between the two groups was conducted using independent chi-squared tests and t-tests. Subsequently, binary logistic regression was performed to compare the risk factors for hepatitis B infection between indigenous and non-indigenous cases, while adjusting for age at diagnosis and hepatitis B vaccination status, which

Table I: Comparing the socio-demographic characteristics for hepatitis B transmission between the indigenous and non-indigenous cases in four districts in Pahang, 2018– 2022 (n = 285)

		Indigenous (n = 141) n (%)[a]	Non-indigenous (n = 144) n (%)[a]	Total (n = 285) n (%)[b]	p value
Sex	Male	65 (46.1)	81 (56.3)	146 (51.2)	0.087
	Female	76 (53.9)	63 (43.8)	139 (48.8)	
Age at diagnosis (years)[c]		34.4 (16.5)	47.5 (16.5)	41.0 (17.8)	<0.001
Area of residence	Urban	1 (0.7)	42 (29.2)	43 (15.1)	<0.001
	Rural	140 (99.3)	102 (70.8)	242 (84.9)	
Districts	Rompin	86 (61.0)	62 (43.1)	148 (51.9)	<0.001
	Pekan	48 (34.0)	38 (26.4)	86 (30.2)	
	Kuala Lipis	7 (5.0)	16 (11.1)	23 (8.1)	
	Temerloh	0 (0.0)	28 (19.4)	28 (9.8)	
No hepatitis B vaccination		102 (72.3)	125 (86.8)	227 (79.6)	0.002

[a]Within the indigenous or non-indigenous group.
[b]Within total sample.
[c]Mean (SD).

Table II: Comparing the risk factors for hepatitis B transmission between the indigenous and non-indigenous cases in four districts in Pahang, 2018 – 2022 (n = 285)

Risk factors	Indigenous	Non-indigenous (n = 141) n (%)[a]	Total[b] (n = 144) n (%)[a]	p value (n = 285)
Infected mother	84 (59.6)	45 (31.3)	129 (45.3)	0.002
History of percutaneous exposure	17 (12.1)	11 (7.6)	28 (9.8)	0.210
Multiple sexual partners	9 (6.4)	15 (10.4)	24 (8.4)	0.220
Infected spouse/partner	11 (7.8)	5 (3.5)	16 (5.6)	0.112
Sharing syringes	3 (2.1)	13 (9.0)	16 (5.6)	0.011
History of medical procedures	2 (1.4)	10 (6.9)	12 (4.2)	0.020
Undetermined	28 (19.9)	53 (36.8)	81 (28.4)	0.002

[a]Within the indigenous or non-indigenous group.
[b]Within total sample.

Table III: Comparing the risk factors for hepatitis B infection between the indigenous and non-indigenous cases, adjusted for age at diagnosis and hepatitis B vaccination status, in four districts in Pahang, 2018–2022 (n = 285)

Mode of transmission	Indigenous vs non-indigenous						
	ß	S.E.	Wald	df	p value	Adjusted OR[a]	95% CI OR
Infected mother	0.89	0.30	8.87	1	0.030	2.45	1.36, 4.40
History of percutaneous exposure	0.57	0.46	1.52	1	0.218	1.77	0.72, 4.37
Multiple sexual partners	–0.17	0.50	0.12	1	0.727	0.84	0.32, 2.23
Infected spouse/partner	1.06	0.59	3.28	1	0.070	2.90	0.92, 9.17
Sharing syringes	–1.19	0.69	2.96	1	0.085	0.31	0.08, 1.18
History of medical procedures	–1.02	0.82	1.54	1	0.215	0.36	0.07, 1.81

OR = odds ratio.
[a]Adjusted for age at diagnosis and hepatitis B vaccination status.

were identified as statistically significant confounding factors. A p-value of less than 0.05 was considered statistically significant, and consequently, adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Ethics Approval

This study received approval from both the Faculty Ethics Review Committee, Faculty of Medicine, MARA University of Technology (UiTM), and the Medical Research and Ethics Committee, Ministry of Health Malaysia. All procedures conducted during this study strictly adhered to the guidelines set forth by the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP), the Malaysia Good Clinical Practice Guidelines and the principles outlined in the Declaration of Helsinki.

The patients' information was securely stored in a password-protected electronic file on a personal computer accessible only to authorised researchers. To ensure additional security measures, no printed copies of the information were made, maintaining its exclusive digital format.

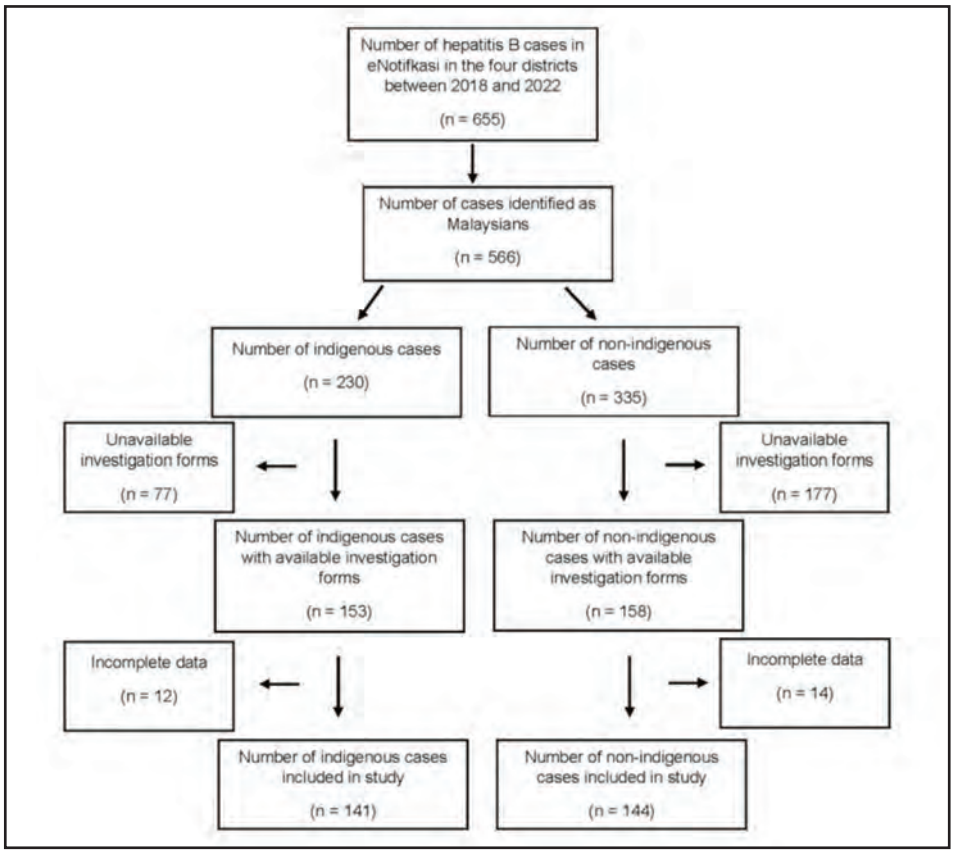

Fig. 1: Flow diagram of sampling.

RESULTS

Between 2018 and 2022, a total of 655 hepatitis B cases were registered in the four districts of Pahang. Among these cases, 566 were identified as Malaysians. After applying other exclusion criteria (a lack of an investigation form or incomplete data on the investigation form), 285 cases (141 indigenous and 144 non-indigenous cases) remained and were therefore included in the final analysis of this study (Fig.1).

The mean age for all cases was 41.0 (17.8) years. The indigenous group had a younger age profile, with individuals averaging 34.4 (16.5) years, while the non-indigenous group had an older mean age of 47.5 (16.5) years. The majority of the cases (84.9%) resided in rural areas, with the indigenous group almost exclusively located in rural areas (99.3%). In contrast, only 70.8% of non-indigenous cases resided in rural areas (Table I).

A notable proportion (79.6%) has not received prior hepatitis B vaccination. Specifically, 72.3% of indigenous cases and 86.8% of non-indigenous cases reported no history of hepatitis B vaccination. Of these cases, 45.3% reported a history of their mother being infected with hepatitis B, while 9.8% reported a history of percutaneous exposure. Other factors reported included multiple sexual partners (8.4%) and sharing syringes or having infected partners (both 5.6%) (Table II).

Table III presents the odds ratios and corresponding 95% confidence intervals, adjusted for age at diagnosis and vaccination status, of the risk factors for hepatitis B infection. The odds for those with a history of an infected mother being indigenous group is 2.5 times (95% CI: 1.4–4.4) compared to the odds of those with a history of an infected mother being non-indigenous group.

DISCUSSION

In the socio-demographic findings of this study, a remarkable 13-year gap emerged between the two groups, indicating that indigenous cases were diagnosed at an earlier age. This difference could be linked to the pilot implementation of universal hepatitis B screening among pregnant women in Pahang since 2019, as part of the National Strategic Plan For Hepatitis B And C 2019–2023.[6,15] This initiative likely led to intensified contact tracing and screening efforts, especially among the younger family members, such as husbands and children. Given the presumption that vertical transmission is more prevalent in the indigenous people, it is possible that the detection of positive cases among their younger generation is higher. Nevertheless, the statistical analysis for this study has been appropriately adjusted for age.

Moreover, almost all indigenous individuals in this study were found to reside in the rural areas. This pattern is likely a reflection of cultural ties, consistent with findings from a study among indigenous people in Australia, which

demonstrated a stronger cultural attachment among those living in the remote areas.[16] Similar observations were noted in Malaysia, where the unique customs and taboos of some indigenous groups were found to be significantly influenced by the remoteness of their settlements.[17] Since the 1980s, resettlement programmes have been implemented in Malaysia to facilitate the provision of public utilities and amenities, as well as to improve the socio-economic profile of the indigenous people,[18] but the locations of these resettlements have been concentrated in the rural areas. However, in more recent times, the impact of modernisation has emerged as a factor contributing to the erosion of cultural beliefs among these communities,[17,19] potentially signalling a shift in this residential trend in the future.

Our study found that a substantial proportion (79.6%) of hepatitis B cases were found to have no history of prior hepatitis B vaccination. Other notable risk factors for the infection included having an infected mother (45.3%), percutaneous exposure (9.8%), having multiple sexual partners, sharing syringes and having infected spouses or partners. Most of these findings differ from the NHMS 2020, which indicated a higher prevalence of histories of medical procedures (dental and surgical procedures) associated with hepatitis B infection among the general population.[20] It is also noteworthy to highlight that in NHMS 2020, zero respondent reported any history of unsafe sexual practices or injectable substance use. The only common similarity observed between NHMS 2020 and this study is the presence of a family history of hepatitis B and percutaneous exposure as the risk factors for hepatitis B infection.[20]

These variations can be attributed to differences in methodology. The NHMS 2020 utilised multistage random sampling from the general population, specifically adult populations aged 15 and above,[7,21] encompassing both healthy participants and those with hepatitis B. In contrast, our study's sample population specifically concentrated on individuals diagnosed with hepatitis B infection. Additionally, the NHMS 2020 employed self-administered questionnaires to assess participants' risk factors,[20] whereas our study relied on investigation forms completed by health inspectors who performed face-to-face interviews with the patients. Moreover, as the NHMS 2020 was conducted nationally,[21] unlike our study which focused solely on one East Coast state in the Peninsular Malaysia, it is likely that there are disparities in demographic characteristics, socio-economic conditions and healthcare infrastructures among these diverse populations.

Our study found that the risk factors of hepatitis B transmission between the indigenous and non-indigenous population are different. Among the indigenous population, mother-to-child transmission is a significant risk factors as compared to non-indigenous population. This is consistent with previous research conducted in Malaysia[8] and Australia,[22] which also identified vertical transmission as a primary mode of hepatitis B transmission among aboriginal communities. The high prevalence of hepatitis B among the indigenous population likely contributes to the heightened risk of vertical transmission.[4] Additionally, limited access to preventive interventions might exacerbate this issue. A systematic review by Akter et al.[23] suggested that the indigenous women in lower- and middle-income countries face challenges in accessing maternal healthcare services due to culturally insensitive intervention programmes, along with financial and logistical barriers. Similar phenomenon has also been observed in Malaysia, where the indigenous community experiences unequal accessibility to healthcare services.[24,25]

Contrary to Sahlan et al.[8], this study discovered that percutaneous exposure, such as tattooing or body piercing, is not a significant risk factor for hepatitis B infection among indigenous population as compared to non-indigenous population. This discrepancy may be attributed to variations in the indigenous populations studied. Sahlan et al.[8] focused on the Negrito tribe (Bateq and Mendriq), whereas this study primarily involved the Proto-Malay tribe (Jakun) in Rompin and Pekan districts and the Senoi tribe (Semai) in Kuala Lipis district, with only a small proportion of the Negrito tribe (Bateq) in Kuala Lipis. Further research is required to comprehend the prevailing trends of tattooing or body piercing within the indigenous population, particularly among the younger generation.

In addition, a cross-sectional study on indigenous populations in Peru highlighted sexual contact as a significant risk factor for hepatitis B infection,[26] which was not observed in this study. This disparity may stem from the differences in the study design. While our study sample population focused exclusively on individuals diagnosed with hepatitis B, the Peru study included both healthy participants and those with hepatitis B. Furthermore, substantial variations in socio-economic conditions, healthcare infrastructures, and cultural practices likely exist between Peru and Malaysia, potentially influencing the observed differences in risk factors across these populations.

Recognising the distinct pattern of risk factors for hepatitis B infection among the indigenous population, it is important to adopt targeted strategies in an effort to address this issue. This is in line with WHO's recommendation that indigenous people need tailored approaches in the prevention, care and treatment of hepatitis B infection.[2] Therefore, it is recommended to implement perinatal hepatitis B screening programme specifically targeting the indigenous community. Additionally, once a hepatitis B infection is diagnosed, appropriate interventions and treatments for both the mothers and their children should be promptly administered, such as immunoprophylaxis with hepatitis B immunoglobulin and antiviral treatment.[27]

Strengths and Limitations

This is the first study comparing the risk factors for hepatitis B transmission between the indigenous and non-indigenous groups in Malaysia. This study's strength lies in the more reliable data on the risk factors for hepatitis B transmission since the investigations were conducted by health inspectors, who were presumed to possess a deep understanding of the local culture and norms, through face-to-face interviews with the cases. Furthermore, the risk factors analysed in this study were adjusted for age and hepatitis B vaccination status, thus accounting for potential confounding variables to provide a more accurate understanding of the situation.

One limitation of this study is the reliance on secondary data, which consisted of readily available information only. This constraint restricts the study's ability to address additional questions that may be of interest to the researchers. Regarding data collection, it is important to acknowledge that the quality of the data depended heavily on the competence and experience of the health inspectors performing the investigations. Without proper systematic pre-data collection training similar to other research utilising primary data, the standardisation of the interview process could not be guaranteed, increasing the risk of interviewer bias.

Another aspect contributing to the study's limitations is the exclusion of cases, specifically, 38.7% of indigenous cases and 57% of non-indigenous cases were not included due to missing investigation forms or incomplete data, which may potentially give rise to selection bias. As a result, universal sampling method was employed to mitigate selection bias and enhance the validity of this study.

CONCLUSION

Significant differences exist in hepatitis B risk factors between indigenous and non-indigenous populations. The main risk factor for indigenous community is the history of infected mother. Therefore, the necessity of incorporating hepatitis B screening into the current practice of antenatal HIV screening, specifically targeting the indigenous community, should be given consideration. In addition, it is essential to maximise the coverage of hepatitis B vaccination to effectively address the transmission risk within these communities.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We also express our sincere gratitude to the Pahang Health State Department for granting us permission to conduct this study and for the assistance provided by their dedicated health staffs during data collection. Additionally, we would like to extend our appreciation to the Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM) for their valuable support throughout the study.

REFERENCES

1. World Health Organisation. Fact sheets on hepatitis B [Internet]. World Health Organisation official website. 2022 Jun 24 [cited 2022 Dec 28]. Accessed from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. World Health Organisation. Global hepatitis report 2017. World Health Organisation; 2017.
3. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67(4): 1560-99.
4. Veronese P, Dodi I, Esposito S, Indolfi G. Prevention of vertical transmission of hepatitis B virus infection. World J Gastroenterol 2021; 27(26): 4182.
5. Merican I, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, et al. Chronic hepatitis B virus infection in Asian countries. J Gastroenterol Hepatol 2000; 15(12): 1356-61.
6. Ministry of Health Malaysia. National Strategic Plan For Hepatitis B And C 2019-2023. Ministry of Health Malaysia; 2019.
7. Mohamed Haris H, Abdul Mutalip MH, Muhammad EN, Abd Hamid HA, Mohd Hisham MF, Rodzlan Hasani WS, et al. Seroprevalence of Hepatitis B Virus among Adults in Malaysia. National Health & Morbidity Survey (NHMS) 2020: Communicable Diseases. Ministry of Health Malaysia; 2020.
8. Sahlan N, Fadzilah MN, Muslim A, Shaari SA, Rahman A, Hoh BP. Hepatitis B virus infection: Epidemiology and seroprevalence rate amongst Negrito tribe in Malaysia. Med J Malaysia 2019; 74(4): 320-5.
9. Firdaus MA, Poh TH. Incidence of chronic Hepatitis B among Orang Asli in Pahang. IIUM Med J Malaysia 2016; 15(1): 99.
10. Davies J, Li SQ, Tong SY, Baird RW, Beaman M, Higgins G, et al. Establishing contemporary trends in hepatitis B sero-epidemiology in an Indigenous population. PLoS One 2017; 12(9): e0184082.
11. Russell NK, Nazar K, Del Pino S, Alonso Gonzalez M, Diaz Bermudez XP, Ravasi G. HIV, syphilis, and viral hepatitis among Latin American indigenous peoples and Afro-descendants: a systematic review. Revista Panamericana de Salud Pública. 2019; 43: e17.
12. Department of Orang Asli Development Malaysia. Suku Kaum Orang Asli Semenanjung Malaysia [Internet]. Laman Web Rasmi Jabatan Kemajuan Orang Asli. 2021 Nov 29 [cited 2022 Nov 11]. Accessed from: https://www.jakoa.gov.my/orang-asli/suku-kaum/
13. Pahang Health State Department. Mesyuarat Perkhidmatan Kesihatan Orang Asli (PKOA) Jabatan Kesihatan Negeri Pahang Bersama Jabatan Kemajuan Orang Asli (JAKOA) Pahang Peringkat Negeri Pahang Tahun 2022 [PowerPoint slides]. Pahang Health State Department; 2022.
14. Ministry of Health Malaysia. Case Definitions for Infectious Diseases in Malaysia, 3rd edition. Disease Control Division, Ministry of Health Malaysia; 2017.
15. Ministry of Health Malaysia. Towards Elimination of Viral Hepatitis In Malaysia Through Multisectoral Collaboration, 2019. Ministry of Health Malaysia; 2020.
16. Dockery AM. Culture and wellbeing: The case of Indigenous Australians. Soc Indicat Res 2010; 99: 315-32.
17. Ghani EK, Muhammad K, Hassan R. Understanding the influence of remoteness on culture and socio-economic of the Orang Asli in Malaysia. PalArch's J Archaeol Egypt/Egyptol 2020; 17(2): 366-76.
18. Syed Hussain TPR, Krishnasamy DS, Gholam Hassan AA. Resettlement of the Orang Asli and development plan for Orang Asli community in Malaysia. J Techno-Social. 2017; 9(1): 32-43.
19. Masron T, Masami F, Ismail N. Orang Asli in Peninsular Malaysia: population, spatial distribution and socio-economic condition. J Ritsumeikan Soc Sci Humanit 2013; 6: 75-115.
20. Ahmad FH, Harith AA, Shahein NA, Abd Aziz NS, Pardi M, Mohd Sallehuddin S, et al. Personal Risk Factors of Hepatitis B. National Health & Morbidity Survey (NHMS) 2020: Communicable Diseases. Ministry of Health Malaysia; 2020.
21. Abdul Mutalip MH, Fikri Mahmud MA, Lodz NA, Rodzlan Hasani WS, Ibrahim Wong N, Sahril N, et al. Introduction. National Health & Morbidity Survey (NHMS) 2020: Communicable Diseases. Ministry of Health Malaysia; 2020.
22. Australian Government Department of Health. Third National Hepatitis B Strategy 2018 – 2022. Department of Health and Aged Care; 2019.
23. Akter S, Davies K, Rich JL, Inder KJ. Indigenous women's access to maternal healthcare services in lower-and middle-income countries: a systematic integrative review. Int J Public Health 2019; 64: 343-53.
24. Chew CC, Lim XJ, Low LL, Lau KM, Kari M, Shamsudin UK, et al. The challenges in managing the growth of indigenous children in Perak State, Malaysia: A qualitative study. Plos One 2022; 17(3): e0265917.

25. Saifullah MK, Masud MM, Kari FB. Vulnerability context and well-being factors of Indigenous community development: a study of Peninsular Malaysia. AlterNative 2021; 17(1): 94-105.
26. Ormaeche M, Whittembury A, Pun M, Suárez-Ognio L. Hepatitis B virus, syphilis, and HIV seroprevalence in pregnant women and their male partners from six indigenous populations of the Peruvian Amazon Basin, 2007–2008. Int J Infect Dis 2012; 16(10): e724-30.
27. Akmal S, Mohamed Ghazali IM. Strategies To Eliminate Mother to Child Transmission of Hepatitis B In Malaysia. Technology Review. Malaysian Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia; 2020.

ORIGINAL ARTICLE

Diffusion-weighted imaging in hyperacute haemorrhagic stroke patients presenting within thrombolysis window

Mohd Fandi Al Khafiz Kamis, MD[1], Azril Ishak, MD[1], Norafida Bahari, MD[1], Mohd Naim Mohd Yaakob, MD[1], Ezamin Abdul Rahim, MD[1], Janudin Baharin, MD[2], Iskasymar Ismail, MD[3], Mohamad Khairi Mahmood, MD[1], Hilwati Hashim, MD[4], Ahmad Sobri Muda, MD[1]

[1]Department of Radiology, Hospital Sultan Abdul Aziz Shah (HSAAS), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia, [2]Department of Neurology, Hospital Hospital Sultan Abdul Aziz Shah (HSAAS), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia, [3]Hospital Hospital Sultan Abdul Aziz Shah (HSAAS), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia, [4]Department of Radiology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Malaysia

ABSTRACT

Introduction: Diffusion-weighted imaging (DWI) in magnetic resonance imaging (MRI) has been proposed as the first line of neuroimaging for acute ischaemic stroke. The reliability of DWI in detecting intracranial haemorrhage, however, is still unproven, compared with susceptibility-weighted imaging (SWI) and CT scan which being considered the gold standard. This study seeks to establish the reliability of DWI as a first-line imaging modality to detect the intracranial haemorrhage in the patients present within the thrombolysis window.

Materials and Methods: A retrospective cross-sectional analysis was performed on patients who presented to our institution from April 2020 until July 2021 for acute stroke and had MRI brain as first-line neuroimaging. A total of 31 subjects were included in this study. Two radiologists assessed the signal patterns in DWI sequence and compared them with SWI and CT Brain, whenever available, as the gold standard for observing the presence of intracranial haemorrhage.

Results: The majority of patients with hyperacute bleed proven to be revealed on SWI or CT, thus showed characteristics of central hyperintensity and peripheral hypointense rim, on DWI. Slightly more than half (51.6%) presented with mild to moderate NIHSS scores (1–15). The sensitivity, specificity, positive predictive value and negative predictive value of DWI in detecting intracranial intra-axial haemorrhages were exceptionally high. There is strong interobserver level of agreement in identifying central haemorrhagic signal intensity [kappa = 0.94 (0.06), p < 0.05].

Conclusion: This study supported the DWI sequence as a reliable sequence in MRI, to detect intracranial haemorrhage in hyperacute stroke.

KEYWORDS:
Acute stroke; haemorrhagic; magnetic resonance imaging; diffusion-weighted imaging

INTRODUCTION

Haemorrhage accounts for 15–30% of hyperacute stroke, rapid neuroimaging is readily available in many centres and advocated in many recommendations.[1-3] To ensure a safe and optimal acute management, it is critical to exclude the intracranial haemorrhage, where intravenous thrombolysis and mechanical thrombectomy are contraindicated.[4,5] Non-contrasted computed tomography (CT) and magnetic resonance imaging (MRI) are effective tools to exclude intracranial haemorrhage in hyperacute stroke. Although more than 90% of centres are using CT as the first line of neuroimaging, there are now more centres adopting an MRI-first policy in hyperacute stroke.[7,8]

Diffusion-weighted imaging (DWI) provides a more accurate measure of infarct core volume, which is valuable as the first sequence in hyperacute stroke. However, the DWI is not routinely used to evaluate haemorrhage. Kang et al.[9] described the signal intensity of hyperacute haemorrhage as observed on the DWI as hyperintense core and focal areas of variable hypointensity. These are consistently found in all patients with hyperacute haemorrhage. According to the authors, the hypointense areas are not caused by susceptibility artefact due to paramagnetic substances such as intracellular deoxyhemoglobin or methaemoglobin but may be related to the T2 shine-through effect caused by vasogenic oedema surrounding the haematoma.[9]

Our centre is a newly established teaching hospital which adopted the MRI-first policy for hyperacute stroke using the Putra Acute Stroke.[10] This study was performed to share early experience conducting the reliability of DWI as the first sequence to detect the intracranial haemorrhage in MRI on acute stroke patients who presented within the thrombolysis window.

MATERIALS AND METHODS

The retrospective data were collected from our acute stroke registry. All cases presented within the acute stroke treatment window and triggering the stroke code who had MRI as the first neuroimaging were then evaluated. All cases that

This article was accepted: 30 November 2023
Corresponding Author: Ahmad Sobri Muda
Email: asobri@upm.edu.my

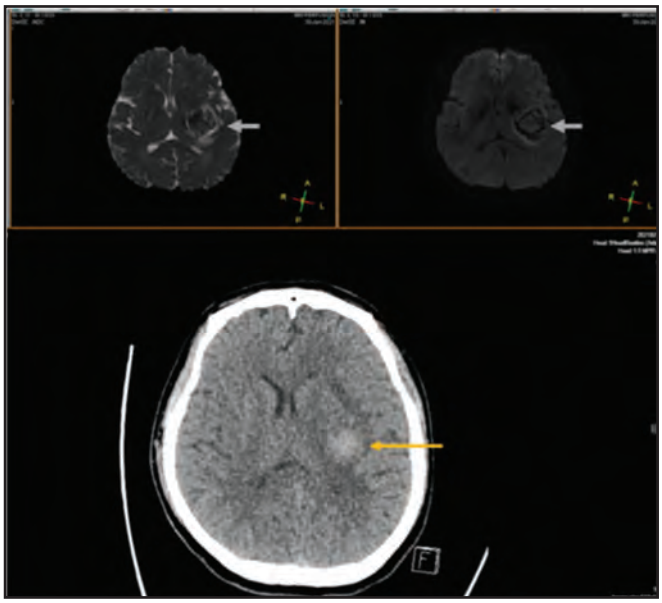

Fig. 1: DWI shows central hyperintensity with surrounding hypointensity rim with the outer hyperintense rim in b-1000 and ADC, representing oedema (arrows). Comparison to SWI and CT of the same patient.

underwent MRI using Philips Ingenia 3.0 Tesla by employing the Putra Acute Stroke protocol.[10]

Putra Acute Stroke Protocol for acute stroke consists of three main sequences: diffusion-weighted imaging (DWI), Fluid Attenuated Inversion Recovery (FLAIR), and MR angiography (time of flight). Additional sequences were also applied, which include susceptibility-weighted imaging (SWI), Perfusion imaging and BB (Black Blood) post-contrast, when necessary. The decision for treatment is usually achieved after the third sequence and IV thrombolysis will be given inside the MRI room if indicated. Thrombolysis will not be given if the initial sequence shows a haemorrhagic lesion on the DWI.

Two radiologists with at least 5 years of experience in general radiology reviewed all the MRI images. Each observer documented the demographic data, National Institute of Health Stroke Scale (NIHSS) score, characteristic appearance of the haemorrhagic lesion on DWI, ADC value and compared with SWI or CT Brain, whichever is available. Intra-observer agreements were calculated for the appearance of suspected haemorrhage on the DWI by correlating the findings with the SWI sequence. Observers were blinded to the patient's identity and MRI report. The intra-observer reliability and agreement were tested by Kappa coefficient statistical test.

RESULTS

There were a total of 345 patients who presented with hyperacute stroke from April 2020 to July 2021. In this study, 281 cases with ischaemic stroke, transient ischaemic stroke, or normal findings, and further 14 cases of stroke mimics were excluded. Another 11 patients who had extra-axial

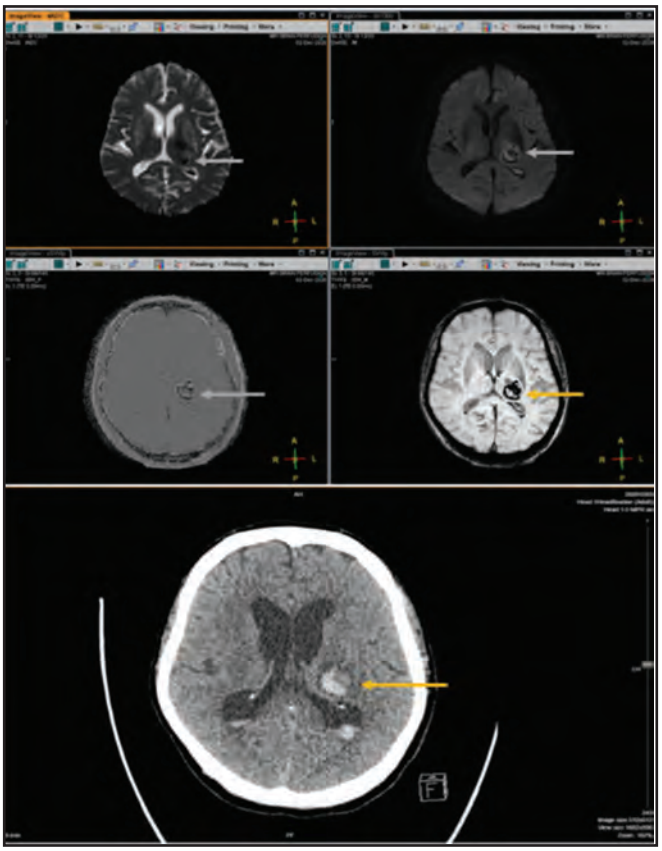

Fig. 2: Another hyperacute haemorrhagic stroke patient with left basal ganglia bleed, showing similar central hyperintense area with surrounding hypointense rim (arrows). Comparison to SWI and CT brain of the same patient.

haemorrhages and microhemorrhages were also excluded. The remaining 39 subjects had a haemorrhagic stroke with SWI confirming the presence of haemorrhages. However, eight subjects presented beyond thrombolysis windows from the onset, and thus were excluded. Only a total of 31 patients were included in this study.

Of the 31 patients with haemorrhagic stroke included in this study, the majority were men (81%) and the mean age was 58.1 years (95% of patients were 34.7– 81.5 years old). Sixteen patients (51.6%) presented with mild to moderate NIHSS scores (1–15). A majority (65%) of intra-axial haemorrhagic lesions occurred within the basal ganglia, followed by the cerebral cortex (25%) and the posterior fossa (10%).

The features in the DWI were variable intensities of the central area with peripheral hypointense rim and outer rim of oedema. The signal intensity was classified as either predominantly hyperintense or hypointense, or heterogeneous. There is a very high agreement among the observers, who noted that most subjects (58%–61%) demonstrated hyperintense central area while a significant percentage of the subjects (25–29%) showed hypointense central area. Nearly all subjects demonstrated peripheral hypointensity (96.8%) with the remaining being heterogeneous.

There was excellent percentage agreement (100%) demonstrated between the two radiologists in terms of identifying and localising the haemorrhage, based on the DWI sequences (b-1000 and ADC) in comparison to the SWI.

DISCUSSION

CT scan is still a preferred imaging technique to rule out the haemorrhage in hyperacute stroke. Few authors studied the feasibility of DWI versus conventional imaging in assessing the intracranial haemorrhage.[6,7,9,11] DWI detects the restricted diffusion resulting from cell death, which includes haemorrhagic changes.[9,11] The T2 effect contributed to the DWI signal due to the presence of paramagnetic haemoglobin by-products, deoxyhaemoglobin and methaemoglobin.[12]

In acute haematoma, DWI typically shows a markedly hyperintense core due to the paramagnetic effect of intracellular deoxyhemoglobin and methaemoglobin and a thin markedly hypointense rim (Fig. 1). From this study, the authors concluded that DWI is more accurate in detecting, characterising and staging the hyperacute, medium and large-sized acute and early subacute haemorrhages. DWI, however, is not sensitive in characterising the small haemorrhages, which, in other gradient echo sequences like SWI or GRE as necessary.[13] Kang et al.[9] also supported the findings of central hyperintensity representing diamagnetic oxyhaemoglobin and a peripheral hypointense rim representing early conversion to paramagnetic deoxyhemoglobin in the hyperacute haematomas.

In this study, DWI demonstrated three main components in haemorrhagic stroke, central area of hyperintensity with a small percentage of heterogeneous central intensities, surrounding peripheral rim of hypointensity and outer rim of peripheral oedema. All cases in this study concurred with the SWI, and some cases corresponded well with the CT, in confirming the presence of haemorrhage (Fig. 2). This experience demonstrated that the DWI features are vivid and easily differentiated, which may not require a very experienced neuroradiologist to elicit the findings of haemorrhagic stroke. Despite SWI or GRE sequences being used as the gold standard to detect hemorrhagic stroke in MRI, this study supported the notion that DWI has high sensitivity and specificity in order to identify the haemorrhage in hyperacute stroke.

LIMITATIONS

Small retrospective series of only 31 subjects without validation against the gold standard are among the limitations of this study. However, we believe this series will give useful insights to your esteemed readers.

CONCLUSIONS

In the acute stroke imaging procedure, DWI with ADC may be a viable substitute for CT to rule out hemorrhagic stroke. This study also demonstrated that the MRI-first policy for hyperacute stroke patients won't affect the ability to identify hemorrhagic stroke patients.

ACKNOWLEDGMENTS

The authors would like to acknowledge Farid Bajuri (ORCID iD: 0000-0003-1517-7282) from the Department of Aerospace Engineering, Faculty of Engineering, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia on the formatting and arrangement of the manuscript.

REFERENCES

1. Aziz ZA, Lee YYL, Ngah BA, Sidek NN, Looi I, Hanip MR, et al. Acute Stroke Registry Malaysia, 2010-2014: Results from the National Neurology Registry. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association [Internet]. 2015 [cited 2019 May 19];24(12):2701-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26338106
2. Neelamegam M, Looi I, Cheah WK, Narayanan P, Abdul Hamid AM, Ong LM. Stroke incidence in the South West District of the Penang Island, Malaysia. Preventive Medicine. 2013;57:S77–9.
3. Loo KW, Gan SH. Burden of Stroke in Malaysia. International Journal of Stroke [Internet]. 2012 Jan 20 [cited 2019 Jul 7];7(2):165–7. Available from: http://www.medic.usm.my/images/files/pub-march/mac_cited05%20.pdf
4. Malaysian Society of Neurosciences, Clinical Practice Guidelines: Management of Ischaemic Stroke (3rd edition). CVNS 2021; 3: 1-155.
5. Chia PK, Mohamad NA, Inche Mat LN, Itam@Ismail I, Yusof Khan AHK, Loh WC, et al. Regional Emergency Stroke Quick-Response (RESQ) Network: A Proposed Paradigm of Malaysia Stroke Care Services. Malaysian J Med Health Sci 2020; 16: 353-61.
6. Vilela P, Rowley HA. Brain ischemia: CT and MRI techniques in acute ischemic stroke. European Journal of Radiology. 2017; 96: 162-72.
7. Provost C, Soudant M, Legrand L, Ben Hassen W, Xie Y, Soize S, et al. Magnetic Resonance Imaging or Computed Tomography Before Treatment in Acute Ischemic Stroke. Stroke [Internet]. 2019 Mar [cited 2020 Jan 28]; 50(3): 659–64. Available from: https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.118.023882
8. Sølling C, Mahmoud Ashkanian, Hjort N, Carsten Gyldensted, Andersen G, Østergaard L. Feasibility and logistics of MRI before thrombolytic treatment. Acta Neurologica Scandinavica. 2009; 120(3): 143-9.
9. Kang BK, Na DG, Ryoo JW, Byun HS, Roh HG, Pyeun YS. Diffusion-Weighted MR Imaging of Intracerebral Hemorrhage. Korean Journal of Radiology [Internet]. 2001 Dec 31 [cited 2023 May 8];2(4):183–91. Available from: https://synapse.koreamed.org/articles/1027489
10. Muda AS, Kamis MFAK, Mohd Yaakob MN, Abdul Rahim E, Mahmood MK, Md Noh MSF, et al. Putra acute stroke protocol. CVNS 2021; 3: 12-4.
11. Cavusoglu M, Duran S, Sözmen Cılız D, Tufan G, Hatipoglu Çetin HG, Ozsoy A, et al. Added value of diffusion-weighted magnetic resonance imaging for the diagnosis of perianal fistula. Diagnostic and Interventional Imaging [Internet]. 2017 May [cited 2020 Apr 20];98(5): 401-8. Available from: https://isiarticles.com/bundles/Article/pre/pdf/148544.pdf
12. Whang JS, Kolber M, Powell DK, Libfeld E. Diffusion-weighted signal patterns of intracranial haemorrhage. Clin Radiol. 2015 Aug;70(8):909-16. doi: 10.1016/j.crad.2015.04.006. Epub 2015 Jun 4. PMID: 26050534.
13. Fiebach JB, Schellinger PD, Gass A, Kucinski T, Siebler M, Villringer A, et al. Stroke Magnetic Resonance Imaging Is Accurate in Hyperacute Intracerebral Hemorrhage. Stroke. 2004 Feb; 35(2): 502-6.

Demographics and characteristics of endoscopic findings among COVID-19 patients with upper gastrointestinal bleeding in a single centre

Mohamed Amin Kader, MMed[1], Tang Yuan Chin, MRCP[2]

[1]Department of Medicine, Hospital Sultanah Nora Ismail, Batu Pahat, Johor, Malaysia, [2]Department of Gastroenterology and Hepatology, Hospital Selayang, Selangor, Malaysia

ABSTRACT

Introduction: Novel coronavirus 19 disease (COVID-19) pandemic poses healthcare providers challenges in the endoscopic suite. It is unclear whether it affects the endoscopic manifestations of upper gastrointestinal (GI) bleeding. This retrospective study was done to review demographic data, site of lesions and need of interventions for those lesions.

Materials and Methods: Oesophagoduodenoscopy (OGDS) reports of COVID-19 patients with indication of upper GI bleeding from March 2021 to April 2022 were reviewed. Data of 35 patients were then analysed.

Results: Of the 35 patients, 8.6% (n = 3) were female and 91.4% (n = 32) were males. A total of 31.4% (n = 11) were below 50 years and 68.6% (n = 24) were 50 and above. 34.3% (n = 12) with lesions requiring endoscopic intervention, 34.3% (n = 12) with lesions not requiring endoscopic intervention, 31.4% (n = 11) has no significant stigmata of recent haemorrhage. Among subgroup requiring endoscopic intervention, 50% (n = 6) are non-variceal bleeding (NVUIB), and 50% (n = 6) are variceal bleeding (VUGIB). Among NVUGIB, 16.7% (n = 1) is gastric and duodenal angiodysplasia requiring argon plasma coagulation, 50% (n = 3) are duodenal F2A ulcer requiring thermoablation, 16.7% (n = 1) is gastric F2A ulcer requiring hemoclip, and 16.6% (n = 1) is Cameron's ulcer requiring hemoclip. Among VUGIB, 100% (n = 6) are oesophageal varices requiring endoscopic variceal banding (EVL).

Conclusions: Lower proportion of NVUGIB among COVID-19 patients raises hypothesis on whether prothrombotic state of COVID-19 is a protective factor of NVUGIB. Studies with larger sample size are needed to establish significance.

KEYWORDS:
COVID-19; upper gastrointestinal bleeding; endoscopic findings

INTRODUCTION

The novel coronavirus 19 disease (COVID-19) was initially described to have started at the Wuhan province, China in December 2019.[1] What initially started as a national problem quickly evolved into a global pandemic which still has dire consequences till now.[2] The COVID-19 disease causes a range of symptoms. From being asymptomatic till it causes fever, diarrhoea, anosmia, myalgia, arthralgia till causing multiorgan failure and death.[3] The COVID-19 too has been described to cause a variety of gastrointestinal (GI) symptoms. Recent evidence suggests that COVID-19 patients have an increased risk to develop venous thromboembolism disorders.[4,6] Hence, thromboprophylaxis may be needed in these patients to prevent it. This in turn causes a variety of side effects especially in terms of upper gastrointestinal bleeding (UGIB). A proportion of patients with a severe course of COVID-19 disease are also exposed to stress ulcers which in turn can also cause UGIB.

Routinely UGIB including non-variceal upper gastrointestinal bleeding (NVUGIB) and variceal upper gastrointestinal bleeding (VUGIB) are managed endoscopically after stabilisation within 24 hours, as suggested by the recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines.[11] However in these patients especially with the ill COVID-19 patients, the risk of cardiopulmonary complications needs to be addressed too. Thus, proper resuscitation, stabilisation and timing of endoscopy are crucial for these patients.

The aim of this study is to review demographic data, site of the UGIB lesions and need for intervention in those lesions in Hospital Kuala Lumpur (HKL) which is the national tertiary centre for Malaysia. To date, this would be the first study to assess UGIB in COVID-19 patients in HKL.

MATERIALS AND METHODS

Oesophagoduodenoscopy (OGDS) reports of COVID-19 patients with indication of UGIB from March 2021 to April 2022 were reviewed. Data of 35 patients were then analysed. These indications include signs and symptoms of overt UGIB such as malaena, haematemesis, significant drop in haemoglobin (>2g/dl), presence of blood or coffee ground in the Ryles tube aspirate. Patients who were confirmed to have COVID -9 disease either by a nasopharyngeal swab polymerase chain reaction (PCR) or rapid test kit-antigen (RTK-Ag) were then included in this study. These patients were then scoped within Day 1 to Day 7 of the COVID-19 illness. The OGDS were performed either in the endoscopy

This article was accepted: 02 December 2023
Corresponding Author: Mohamed Amin
Email: zuraidaamin1@gmail.com

Table I: Forrest classification for gastroduodenal ulcers

Stage	Characteristics
Ia	Spurting haemorrhage
Ib	Oozing haemorrhage
IIa	Visible vessel
IIb	Adherent clot
IIc	Black spot in ulcer crater
III	Clean base ulcer

Table II: Demographic characteristics of patients with COVID-19 and UGIB

Variables	Number	Percentage
Gender		
Male	32	91.4%
Female	3	8.6%
Age		
Below 50	11	31.4%
50 and above	24	68.6%
SRH		
Needing intervention	12	34.3%
Not needing intervention	12	34.3%
No SRH	11	31.4%

UGIB-upper gastrointestinal bleeding; SRH-stigmata of recent haemorrhage

Table III: UGIB requiring intervention

Variables	Number	Percentage
Bleeder requiring intervention (n = 12)		
NVUGIB	6	50%
VUGIB	6	50%
NVUGIB (n = 6)		
Angiodysplasia needing argon plasma coagulation	1	16.7%
Duodenal ulcer needing thermoablation	3	50%
Gastric ulcer needing hemoclip	1	16.7%
Cameron's ulcer needing hemoclip	1	16.6%
VUGIB (n = 6)		
OV needing banding	6	100%

UGIB-upper gastrointestinal bleeding; NVUGIB-non-variceal upper gastrointestinal bleeding; VUGIB- variceal upper gastrointestinal bleeding; OV-oesophageal varices

suite or at bedside OGDS. The exclusion criteria were patients younger than 18 years of age, pregnant or moribound from terminal course of COVID-19 patients and those with lower gastrointestinal bleeding (LGIB) were excluded from this study.

If needed, the upper GI endoscopy was then performed by experienced endoscopist with a standby endoscopy team available 24 hours. The endoscopy team wore proper personal protective equipment (PPE) during the endoscopic procedure. The endoscopic findings of NVUGIB were then classified according to Forrest classification for gastroduodenal ulcers. Forrest classifications are detailed in Table I.

Gastroduodenal ulcers with active bleeding (Forrest Ia, Ib, IIa) and active oesophageal variceal bleeding (active or recent stigmata of recent haemorrhage) were dealt with endoscopically. All the bleeding episodes were endoscopically managed requiring no further radiological or surgical intervention.

Patients demographic characteristics (gender, age below or above 50), non-variceal or variceal UGIB were then characterized. The findings were then analysed using SPSS version 10.0. This research was registered in accordance with National Medical Research Register Malaysia RSCH ID-22-05756-W7L.

RESULTS

There was a total of 35 patients with a positive COVID-19 test (confirmed either by a positive nasopharyngeal swab PCR or a positive saliva test) during the study period in HKL who manifested UGIB signs and symptoms (Table II). All of these patients were inpatients. Signs and symptoms include malaenic stools, haematemesis, coffee ground aspirate and significant drop in haemoglobin (>2g/dL).

Of the 35 patients, 8.6% (n = 3) were female and 91.4% (n = 32) were males. 31.4% (n = 11) were below 50 years and 68.6% (n = 24) were 50 and above. Upper GI endoscopy was performed after proper resuscitation and stabilization within 24 hours period from time of referral.

A total of 34.3% (n = 12) with lesions requiring endoscopic intervention, 34.3% (n = 12) with lesions not requiring endoscopic intervention, 31.4% (n = 11) has no significant stigmata of recent haemorrhage. Among subgroup requiring endoscopic intervention, 50% (n = 6) were non variceal bleeding (NVUGIH), and 50% (n = 6) were variceal bleeding (VUGIH). Among NVUGIH, 16.7% (n = 1) is gastric and duodenal angiodysplasia requiring argon plasma coagulation, 50% (n = 3) were duodenal F2a ulcer requiring thermoablation, 16.7% (n = 1) is gastric F2a ulcer requiring hemoclip, and 16.6% (n = 1) is Cameron's ulcer requiring hemoclip (Table III). Among VUGIH, 100% (n = 6) were oesophageal varices requiring banding. All of these patients had successful endoscopic haemostasis.

DISCUSSION

Our study is a retrospective descriptive study showing the characteristics of endoscopic findings in COVID-19 patients with UGIB. COVID-19, which is still an ongoing global pandemic has had devastating outcomes both in a health and economic perspective. Millions were infected globally with the corona virus and thousands more had passed away.[2] To date, there are an over of 4 million COVID-19 cases in Malaysia. COVID-19 can cause a variety of signs and symptoms involving the respiratory system, venous thromboembolism and also manifesting as gastrointestinal manifestations.[3] Among these manifestations include diarrhoea, enterocolitis and gastrointestinal bleeding. COVID-19 patients who are admitted as inpatients are considered high risk groups and tend to deteriorate further.[4] In these patients, thromboembolism is a recognised risk factors for upper GI bleeding. In our retrospective study, we did not have any data in regard to the oral anticoagulants or thromboprophylaxis the patients received.

COVID-19 patients can exhibit a variety of coagulation abnormalities. These include hypercoagulability, thrombosis risk and bleeding risk.[4] Hypercoagulability remains the more common complication in COVID-19 as compared to bleeding.[4]

Hypercoagulable state is a recognized association with COVID-19.[4] The degree of hypercoagulability depends on the systemic inflammatory response which the patient mounts. Fibrinogen and D-dimer may be increased. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be prolonged5. These patients may also exhibit a positive lupus anticoagulant (LA).[5] Pathogenesis of these abnormalities are to be yet to known.

Thrombosis risk is another complication of COVID-19. One of it would be venous thromboembolism (VTE). VTE risk was in the range of 5 to 10% in ICU patients and <5% in hospitalised patients.[6] Risks include stroke, myocardial infarction and pulmonary embolism.

Bleeding does happen in COVID-19 patient though not as common as the above complications.[7] Incidences may vary especially in patients who are already on anticoagulation or thromboprophylaxis. Patients on anticoagulation either for venous thromboembolism might be on novel oral anticoagulants such as rivaroxaban and oral warfarin.8 Thromboprophylaxis treatment include enoxaparin sodium (Clexane) or subcutaneous heparin which in turn can have a higher risk of bleeding. Another postulation for bleeding would include thrombocytopenia. Patients with COVID-19 may develop immune thrombocytopenia (ITP) with bleeding complication.[8,9] Bleeding can be minor or major bleeding such as UGIB which may eventually be life threatening if not detected early.

UGIB is a medical emergency.[10] Initial measures of resuscitation include proper airway protection, intravenous access and fluids. Blood products needs to be cross matched and made available as soon as possible.[10] Endoscopic services with an experienced team such as the one in HKL should be on standby and be made available once the need arises. Ideally patients' needs to be resuscitated and stabilised adequately prior to endoscopy. Patients can be scoped within a time frame of 24 hours after adequate resuscitation as per latest guidelines statement.[10,11] Some of the methods used to achieve endoscopic haemostasis include injection, thermo-coagulation methods and by deploying hemoclips.[12]

One of the aims of the study is to assess the demographics of the UGIB cases in COVID-19 patients. To date, this would be the first study done in Malaysia evaluating the incidence and endoscopic characterization of UGIB in COVID-19 patients. A larger sample size will be needed to further risk stratify and assess the risk factors of UGIB in COVID-19 patients.

This study also has limitations. The first is that this study is retrospective, which introduces bias. Incidences of UGIB might have been over or underestimated. Second, the number of cases is limited and therefore a larger sample size will be needed to assess the risk factors of UGIB in COVID-19 patients.

CONCLUSION

Thrombotic events remain the main challenge in Covid-19 patients. This demographic analysis does, however, indicate that UGIB is still a real phenomenon and should not be disregarded.

REFERENCES

1. Yong SS, Sia JKM. COVID-19 and social wellbeing in Malaysia: A case study. Curr Psychol 2021; 12: 1-15.
2. Dyer O. Covid-19: China stops counting cases as models predict a million or more deaths [cited Jan 2023]. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.
3. Seyed Alinaghi S, Afsahi AM, MohsseniPour M, Behnezhad F, Salehi MA, Barzegary A, et al. Late complications of covid-19; a systematic review of current evidence. Arch Acad Emerg Med 2021; 9(1): e14.
4. Mauro A, De Grazia F, Lenti MV, Penagini R, Frego R, Ardizzone S, et al. Upper gastrointestinal bleeding in COVID-19 inpatients: Incidence and management in a multicentre experience from Northern Italy. Clinics and Research in Hepatology and Gastroenterology 2021; 45(3): 101521.
5. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res 2020; 194: 101-15.
6. Sridharan GK, Vegunta R, Rokkam VRP, Meyyur Aravamudan V, Vegunta R, Khan SR, et al. Venous thromboembolism in hospitalized covid-19 patients. Am J Ther 2020; 27(6): e599-e610.

7. Thomas MR, Scully M. Clinical features of thrombosis and bleeding in COVID-19. Blood 2022; 140(3): 184-95.
8. Nakamura J, Tsujino I, Yachi S, Takeyama M, Nishimoto Y, Konno S, et al. Incidence, risk factors, and clinical impact of major bleeding in hospitalized patients with COVID-19: a sub-analysis of the CLOT-COVID Study. Thrombosis J 2022; 20: 53.
9. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 2020; 99(6): 1205-8.
10. Thiebaud PC, Yordanov Y, Galimard JE, Raynal PA, Beaune S, Jacquin L, et al. Management of upper gastrointestinal bleeding in emergency departments, from bleeding symptoms to diagnosis: a prospective, multicentre, observational study. Scand J Trauma Resusc Emerg Med 2017; 25(1): 78.
11. Gralnek, Ian M, Stanley, AJ, Morris, AJ, Camus, M, Lau, J, Lanas, A. et al. Endoscopic Diagnosis and Management of Nonvariceal Upper Gastrointestinal Hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021. Endoscopy 2021; 53(03): 300–32. https://doi.org/10.1055/a-1369-5274.
12. Anjiki H, Kamisawa T, Sanaka M, Ishii T, Kuyama Y. Endoscopic haemostasis techniques for upper gastrointestinal haemorrhage: a review. World J Gastrointest Endosc2010; 2(2): 54–60. https://doi.org/10.4253/wjge.v2.i2.54.

Predictive risk factors for pneumothorax following fluoroscopic-guided transbronchial lung biopsy

Ng Boon Hau, MMED[1], Low Hsueh Jing, MMED[2], Nik Nuratiqah Nik Abeed, MMED[1], Soo Chun Ian, MRCP[3], Mohd Imree Azmi, MMED[4], Mas Fazlin Mohamad Jailaini, MMED[1], Azat Azrai Azmel, MMED[1], Mohamed Faisal Abdul Hamid, MMED[1], Andrea Ban Yu-Lin, MMED[1]

[1]Respiratory Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia, [2]Department of Anaesthesia and Critical Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia, [3]Respiratory Unit, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia, [4]Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Fluoroscopic-guided transbronchial lung biopsy (FG-TBLB) is routinely performed via bronchoscopy to diagnose focal peripheral lesions and diffuse lung disease. Identifying the risk factors of FG-TBLB-related pneumothorax can assist the operator in taking pre-emptive measures to prepare for this potential complication.

Materials and Methods: We retrospectively analysed data from 157 patients who underwent FG-TBLB, with the primary outcome being procedure-related pneumothorax. We assessed several risk factors for pneumothorax following FG-TBLB: patient characteristics, location of biopsy, number of biopsies and computed tomography pattern. Univariate and multivariate logistic regression analyses were performed.

Results: One-hundred fifty-seven patients were included [mean (SD) age 57.9 (16.2) years; 60.5% male]. The most common location for FG-TBLB was the right upper lobe (n=45, 28.7%). The mean (SD) number of biopsy samples was 6.7 (2.1). Radiographic evidence of pneumothorax was reported in 12 (7.6%) patients, with 11 of those requiring intercostal chest tube intervention (mean air leak time: 5.7 days and 1 had persistent air leak requiring autologous blood patch pleurodesis. None experienced pneumothorax recurrence. Female gender and upper lobe location of the biopsy were identified as predisposing factors for pneumothorax. In the multivariable analysis, upper lobe biopsies were associated with a higher risk of pneumothorax (OR 0.120; 95% CI 0.015–0.963; p = 0.046).

Conclusion: The overall rate of pneumothorax is low. We recognise the increased risk of pneumothorax associated with upper lobe biopsy. These findings suggest that clinicians should exercise caution when performing FG-TBLB in this region and consider alternative biopsy locations whenever feasible. We suggest adequate planning and preparation should be implemented to minimise the risk of pneumothorax following FG-TBLB.

KEYWORDS:
Pneumothorax; transbronchial lung biopsy; bronchoscopy; fluoroscopy; diffuse lung disease

INTRODUCTION

Fluoroscopic-guided transbronchial lung biopsy (FG-TBLB) is a commonly used diagnostic procedure for evaluating pulmonary nodules and parenchymal lung diseases. While it is a minimally invasive procedure with a relatively low risk of complications, pneumothorax remains a recognised and potentially serious complication.[1] The incidence of pneumothorax following FG-TBLB varies widely across studies,[1] and a better understanding of the risk factors associated with this complication is needed. This study aims to determine the rate of pneumothorax following FG-TBLB and identify any risk factors that may predispose patients to this complication.

MATERIALS AND METHODS

Study Population and Data Acquisition

This was a single-centre retrospective cohort study at a university teaching hospital. The study population included all adults aged 18 years or older who underwent FG-TBLB between January 1st, 2020 and December 31st, 2022, and their medical records were reviewed. We investigated the risk factors, management and intervention of pneumothorax following FG-TBLB.

Patient Preparation

In this study, all FG-TBLB procedures were performed with the patient in the supine position, under conscious sedation. Patients received moderate sedation with individualised doses of midazolam (ranging from 1 to 5 mg) and fentanyl (ranging from 25 to 100 mcg). Before bronchoscopy, local pharyngeal anesthaesia was administered with 2% lidocaine. Additionally, topical anaesthesia with 2% lidocaine solution was used to anesthetise the airways. These standardised sedation and anaesthesia protocols were implemented to ensure patient comfort and safety during the procedure.

Bronchoscopic Procedure

Informed written consent was obtained from all patients before bronchoscopy, and thin-section computed tomography (CT) thorax with 0.5-mm slice thickness was performed on all patients before the procedure. The bronchoscopists evaluated and discussed the CT images to identify the bronchus sign and target lesion. In this study, FG-

This article was accepted: 06 December 2023
Corresponding Author: Boon Hau Ng
Email: ngboonhau@hotmail.com

Table I: Characteristics of the study cohort

Variables	n = 157
Sex	
Male	95 (60.5%)
Female	62 (39.5%)
CT indication for biopsy	
Nodule or mass	65 (41.4%)
Diffuse lung disease	15 (9.6%)
Infiltrates of unknown aetiology	77 (49%)
Location of biopsy	
Upper lobes	77 (49%)
Middle lobes	23 (14.6%)
Lower lobes	57 (36.4%)
Number of biopsies obtained	
1-4	6 (3.8%)
>5 (more than 6)	151 (96.2%)
Histopathological findings	
Normal	26 (16.6%)
Non-specific inflammation	53 (33.8%)
Malignancy	40 (25.5%)
Granulomatous inflammation	30 (19.1%)
Interstitial lung disease pathology	5 (3.1%)
Others	3 (1.9%)

Table II: Comparative analysis between patients with and without pneumothorax

Variables	No pneumothorax (n =145)	Pneumothorax (n =12)	OR (95% CI)	p value
Sex				
Male	92 (63.4%)	3 (25%)	1	
Female	53 (36.6%)	9 (75%)	5.208 (1.350 – 20.081)	*0.017
CT indication for biopsy				
Nodule or mass	62 (42.8%)	3 (25%)	1	
Diffuse lung disease	15 (10.3%)	0 (0%)	INFINITE	0.999
Infiltrates of unknown aetiology	68 (46.9%)	9 (75%)	2.735 (0.708 – 10.564)	0.144
Location of biopsy				
Upper lobes	67 (46.2%)	10 (83.3%)	1	
Middle lobes	22 (15.2%)	1 (8.3%)	0.305 (0.037 – 2.515)	0.270
Lower lobes	56 (38.6%)	1 (8.3%)	0.120 (0.015 – 0.963)	*0.046
Number of biopsies obtained				
1-4	5 (3.4%)	1 (8.3%)	1	
>5	140 (96.6%)	11 (91.7%)	0.393 (0.042 – 3.665)	0.412
Histopathological findings				
Normal	25 (17.2%)	1 (8.3%)	1	
Inflammation	49 (33.8%)	4 (33.3%)	2.041 (0.216 – 19.24)	0.533
Malignancy	38 (26.2%)	2 (16.7%)	1.316 (0.113 – 15.293)	0.826
Granulomatous	27 (18.6%)	3 (25%)	2.778 (0.271 – 28.482)	0.390
Interstitial lung disease	4 (2.8%)	1 (8.3%)	6.25 (0.322 – 121.334)	0.226
Others	2 (1.4%)	1 (8.3%)	12.5 (0.55 – 284.12)	0.113

*p < 0.05

TBLB was performed by five bronchoscopists with varying years of clinical experience ranging from 2 to 20 years. The bronchoscopy procedure involved at least three bronchoscopists, including one operator, one assistant, and one who monitored the patient's general condition. A fiberoptic flexible bronchoscope (Pentax EB-1990i, Japan) was used, and TBLB was performed by passing the closed forceps peripherally to the desired location under fluoroscopic guidance. Before TBLB, adrenaline 5 ml (1:10000) was flushed into the pre-selected segmental bronchus. Blood pressure, heart rate, and oxygen saturation were monitored during the bronchoscopy to ensure patient safety.

Diagnosis and Management of Pneumothorax

Immediately and 4 hours after FG-TBLB, an upright portable chest x-ray was performed on all patients. The attending bronchoscopist carefully reviewed the post-procedure chest X-ray to identify cases of pneumothorax. When pneumothorax was diagnosed, the attending bronchoscopist made decisions regarding the need for intercostal chest tube insertion or conservative management based on the patient's symptoms and the severity of pneumothorax. Oxygen supplementation was administered to all patients with pneumothorax to maintain an oxygen saturation of >95%.

Statistical Analysis

We analyse the clinical factors related to pneumothorax, including gender, lesion location, number of biopsies, CT pattern, and histopathological diagnosis. Data were presented in mean (standard deviation [SD]) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Associations between the variables and the incidence of pneumothorax were first examined by univariate logistic regression and presented as odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable logistic regression was performed to calculate OR with 95% CI for post-procedure pneumothorax. We used logistic regression to identify significant associations between these variables and pneumothorax.

RESULTS

Patient and Target Lesion Characteristics

A total of 157 patients who underwent FG-TBLB were included in the analysis. Demographics and procedure-related data are listed in Table I. The mean (SD) age was 57.9 (16.2) years, with 60.5% male. The most frequent indication was unknown pulmonary infiltrates (n = 77, 49%).

Twelve (7.6%) patients developed pneumothorax following FG-TBLB. Eleven (91.7%) required intercostal chest tube insertion with the mean (SD) 5.7 (6.2) days chest tube duration. One patient had a persistent air leak and required autologous blood patch pleurodesis. None of the patients experienced pneumothorax recurrence.

The mean (SD) number of biopsy samples was 6.7 (2.1). The most common location for FG-TBLB was the right upper lobe (n = 45, 28.7%), followed by the right lower lobe (n = 42, 26.8%), left upper lobe (n = 27, 17.2%), left lower lobe (n = 21, 13.4%), right middle lobe (n = 14, 8.9%) and lingula (n = 8, 5.1%).

The histopathological diagnoses were as follows: lung cancer or other malignancy (n = 40, 25.5%), granulomatous disease (n = 30, 19.1%), non-specific inflammation (n = 53, 33.8%), interstitial lung disease (n = 5, 3.1%; 3 organising pneumonia, 1 interstitial fibrosis, 1 pulmonary alveolar proteinosis) and others (n = 3, 1.9%; include 2 pulmonary hamartomas and 1 silicosis). This study's total diagnostic yield of FG-TBLB was 83.4% (n = 131).

Predictive Factors for Pneumothorax

In the univariate analysis, female gender and biopsy location were identified as independent predisposing factors for pneumothorax. However, in the multivariable analysis, a significantly higher risk of pneumothorax was observed for FG-TBLB obtained from the upper lobes (odds ratio [OR] 0.120; 95% confidence interval [CI] 0.015–0.963; p = 0.046). Table II presents a comparative evaluation between patient groups with and without radiological evidence of pneumothorax.

DISCUSSION

TBLB is a commonly utilised procedure for diagnosing diffuse infiltrative lung diseases, as well as pulmonary nodules or masses. In immunocompromised individuals presenting with pulmonary infiltrates of unknown origin, TBLB is considered valuable in establishing a microbiological or tissue diagnosis. Despite the usefulness of TBLB in diagnosing various lung diseases, it is essential to recognise that the procedure carries potential complications. Notably, a study has reported the incidence of pneumothorax (1–4%) associated with TBLB.[2]

Our study revealed an incidence of FG-TBLB-related pneumothorax at 7.6%, consistent with the data reported in the BTS guideline and COMET trial.[3,4] Our study establishes that the risk factors associated with FG-TBLB-related pneumothorax include lesions in the upper pulmonary lobes, consistent with findings reported in previous studies.[5-8] Specifically, Huang et al.[7] reported that out of 13 pneumothorax cases, 10 occurred after TBLB from the upper lobes, although this association was not statistically significant (OR 3.34, p = 0.149) due to the small number of pneumothorax cases.[7] The higher risk of TBLB-related pneumothorax involving the upper lobes may be due to the prominence of subpleural blebs in the upper lobes and the greater distention and reduced compliance of alveoli in this region, likely resulting from the pleural pressure gradient.[9] However, in contrast to our findings, Izbicki et al.[10] reported that none of the post-procedural pneumothorax resulted from an upper lobe TBLB.

The performance of bronchoscopy under sedation carries a risk of respiratory depression, which is further complicated by the development of pneumothorax and a subsequent reduction in arterial PO2 levels. Pneumothorax during TBLB is typically due to injury of the visceral pleura caused by biopsy forceps.[11] Sedation may mask pleural pain that indicates the onset of pneumothorax. Recent studies using advanced tools such as robotic bronchoscopy or endobronchial ultrasonography with a guide sheath have reported rates of pneumothorax at 3.7% and 3.2%, respectively, suggesting that complete prevention of pneumothorax may be challenging.[12,13] Therefore, early identification of procedure-related pneumothorax and the availability of an intercostal chest tube device on-site are crucial, as suggested by our study and others.

In previous studies, the optimal number of biopsies for optimal diagnostic yield was reported to be 4–10[14], and the BTS guidelines recommend using fluoroscopy during TBLB and obtaining at least 5 or 6 samples.[4] However, our study found no association between the number of biopsies and the risk of pneumothorax, which is consistent with the results reported by Herout et al.[6]

Computed tomography is widely used to diagnose and evaluate pulmonary diseases. The findings of CT are helpful in determining the optimal site for transbronchial lung biopsy (TBLB). Our study showed no association between the CT pattern of nodular, diffuse or infiltrate types and the risk of pneumothorax during TBLB. This finding is consistent with a recent study conducted by Herout et al. However, Bae et al. reported a higher risk of pneumothorax in nodular lesions. The difference in the results of our study and the study conducted by Bae et al. may be due to differences in patient populations, sample size or the specific techniques used for TBLB. Further studies are needed to determine the impact of CT pattern on the risk of pneumothorax during TBLB.[15]

One potential limitation of the present study pertains to its single-centre, retrospective design. Given the variability in bronchoscopy protocols, including differences in biopsy techniques, sedation practices and fluoroscopy usage across institutions, it is possible that the risk of procedure-related pneumothorax may differ in ways not captured by our data. Therefore, caution should be exercised when generalising our findings to other settings.

CONCLUSION

In conclusion, our study demonstrated that FG-TBLB from the upper pulmonary lobe is associated with the highest risk of pneumothorax. These findings suggest that clinicians should exercise caution when performing FG-TBLB in this region and consider alternative biopsy locations whenever feasible. Furthermore, given the potential for pneumothorax as a post-procedural complication, appropriate measures should be taken to ensure prompt detection and management of this event.

ACKNOWLEDGEMENTS

This study was approved by the UKM ethics committee with the project code: HTM-2023-016.

REFERENCES

1. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax. 2001; 56 (Suppl 1): i1-21.
2. Centonze CP, Davenport MS, White ES, Kazerooni EA. Routine Chest radiography for the evaluation of pneumothorax following bronchoscopy. Acad Radiol 2019; 26(5): 585-90.
3. Galli JA, Panetta NL, Gaeckle N, Martinez FJ, Moore B, Moore T, et al. Pneumothorax after transbronchial biopsy in pulmonary fibrosis: lessons from the multicenter COMET Trial. Lung 2017; 195(5): 537-43.
4. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013; 68(Suppl 1): i1.
5. Ishak M, Chakraborty D, Kassirian S, Dhaliwal I, Mitchell MA. Risk of iatrogenic pneumothorax based on location of transbronchial biopsy: a retrospective cohort study. BMC Res Notes 2023; 16(1): 14.
6. Herout V, Heroutova M, Merta Z, Jr IC, Brat K. Transbronchial biopsy from the upper pulmonary lobes is associated with increased risk of pneumothorax – a retrospective study. BMC Pulmon Med 2019; 19(1): 56.
7. Huang Y, Huang H, Li Q, Browning RF, Parrish S, Turner JF, Jr., et al. Transbronchial lung biopsy and pneumothorax. J Thorac Dis 2014; 6(Suppl 4): S443–7.
8. Fernández-Bussy S, Labarca G, Zagolin M, Oyonarte M, Isamit D, Jalilie A, et al. [Immediate complications following flexible bronchoscopy: retrospective analysis of 1079 procedures]. Rev Med Chil 2014; 142(3): 299-304.
9. Agostoni E. Mechanics of the pleural space. Physiol Rev 1972; 52(1): 57-128.
10. Izbicki G, Romem A, Arish N, Cahan C, Azulai H, Chen-Shuali C, et al. Avoiding routine chest radiography after transbronchial biopsy is safe. Respiration 2016; 92(3): 176-81.
11. Maritato KC, Colon JA, Kergosien DH. Pneumothorax. Compendium (Yardley, PA). 2009; 31(5): 232 42; quiz 42.
12. Chen AC, Pastis NJ, Jr., Mahajan AK, Khandhar SJ, Simoff MJ, Machuzak MS, et al. Robotic bronchoscopy for peripheral pulmonary lesions: a multicenter pilot and feasibility study (BENEFIT). Chest 2021; 159(2): 845-52.
13. Gotoh Y, Yamaguchi T, Yatsuya H, Ikeda A, Okamura T, Sakakibara Y, et al. Predictive risk factors for pneumothorax after transbronchial biopsy using endobronchial ultrasonography with a guide sheath. BMC Pulm Med 2021; 21(1): 181.
14. Roethe RA, Fuller PB, Byrd RB, Hafermann DR. Transbronchoscopic lung biopsy in sarcoidosis. Optimal number and sites for diagnosis. Chest 1980; 77(3): 400-2.
15. Bae K, Jeon KN, Lee SJ, Kim HC, Ha JY, Park SE, et al. Severity of pulmonary emphysema and lung cancer: analysis using quantitative lobar emphysema scoring. Medicine (Baltimore) 2016; 95(48): e5494.

Establishing transducers-dependent sensorineural acuity level normative data among young Malaysian adults

Mohd Normani Zakaria, PhD[1], Evlin Grecia Ensin, BSc[1], Mahamad Almyzan Awang, MClinAud[1], Rosdan Salim, MMed[2], Nik Adilah Nik Othman, MMed[2], Mohd Fadzil Nor Rashid, PhD[1]

[1]Audiology Programme, School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Department of Otorhinolaryngology Head and Neck Surgery (ORL-HNS), School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: The sensorineural acuity level (SAL) test was developed as an alternative assessment to estimate bone conduction (BC) thresholds in cases where masking problems occur in pure tone audiometry (PTA). Nevertheless, prior to its clinical application, the respective SAL normative data must be made available. As such, the present study was carried out to establish SAL normative data using an insert earphone and two different commercially available bone transducers. Additionally, to determine the effect of earphone type on SAL test results, it was also of interest to compare the present study's findings with those of a previous study (that used a headphone to derive SAL normative data).

Materials and Methods: In this repeated-measures study, 40 Malaysian adults (aged 19–26 years) with normal hearing bilaterally (based on PTA results) were enrolled. They then underwent the SAL test based on the recommended protocol by Jerger and Tillman (1960). The SAL normative data for each ear were obtained by calculating the differences between air conduction (AC) thresholds in quiet and AC thresholds in noise by means of insert earphone, B71 and B81 bone vibrators.

Results: The SAL normative values were comparable between the ears ($p > 0.05$), and the data were pooled for subsequent analyses ($n = 80$ ears). Relative to B81 bone transducer, B71 bone vibrator produced statistically higher SAL normative data at all frequencies ($p < 0.05$). The SAL normative values established by the present study were statistically lower than those of the previous study (that utilised headphones) at most of frequencies tested ($p < 0.05$).

Conclusions: The SAL normative data produced by the two bone vibrators were significantly different. The SAL normative values were also affected by the type of earphone used. While conducting the SAL test on Malaysian patients, the information provided by this study can be useful to guide the respective clinicians in choosing the appropriate normative data.

KEYWORDS:
Sensorineural acuity level test; bone conduction; headphones; insert earphones; normative data

INTRODUCTION

Hearing loss is a common medical abnormality among babies, children and adults.[1-3] As such, significant advancements have been made in the field of diagnostic audiology aiming to provide accurate hearing diagnoses in clinical settings.[4-9] Some audiological tests are subjective in nature, i.e., the patients are required to give full cooperation during the testing (which can be challenging when assessing children). The availability of objective audiological tests would overcome the limitations of the subjective hearing assessments.[1] Moreover, by combining routine and advanced audiological tests, better clinical decisions can be made at the site of lesion testing. Identifying hearing problems in a timely manner is imperative so that appropriate treatment options can take place to achieve a better prognosis.[1,10]

The severity of hearing loss and the type of hearing loss are two important indicators in diagnosing hearing status.[1,11] Pure tone audiometry (PTA) has been regarded as the gold standard test for hearing diagnosis as both severity and type of hearing loss can be documented conveniently across speech frequencies.[1,4,11] In the PTA testing, headphones or insert earphones are used to determine air conduction (AC) thresholds that represent the severity of hearing loss. As reported elsewhere, normal hearing is defined if AC thresholds ≤ 20 dB HL.[1,4] That is, those with AC thresholds exceeding 20 dB HL are considered to have hearing loss. By placing a bone transducer on the mastoid area in the PTA testing, bone conduction (BC) thresholds are obtained. In this regard, it has been well demonstrated that the skull vibration mainly stimulates the inner ear and that the BC thresholds represent the status of cochlear.[1] By combining AC and BC thresholds, air-bone gaps (ABGs) represent the type of hearing loss.[1] Herein, significant ABGs (with normal BC thresholds) indicate the presence of conductive hearing loss (CHL, which occurs due to abnormalities affecting the outer and middle ears). On the other hand, if both AC and BC thresholds are abnormal with no significant ABGs, the type of hearing loss is known as sensorineural hearing loss (SNHL, which occurs due to damage affecting the inner ear). Meanwhile, when all parts of the ears are affected, it is known as mixed hearing loss (MHL). Getting the exact type of hearing loss is undoubtedly important as each type of hearing loss requires a specific treatment option.[1]

This article was accepted: 13 December 2023
Corresponding Author: Mahamad Almyzan Awang
Email: almyzan@usm.my

It is worth noting that when the pure tones at high-intensity levels are delivered by the insert earphones in the PTA testing, the skull may vibrate, and the BC pathway can be stimulated.[1] Consequently, the respective tones can be heard by the opposite ear. If the tested ear has poorer hearing than the non-tested ear, the hearing status recorded from the test ear will be invalid (i.e., better than it is supposed to be). This cross-hearing phenomenon must be addressed to achieve accurate hearing diagnoses. In this matter, masking procedure is typically carried out so that valid AC and BC thresholds can be obtained in the PTA testing.[1] That is, the masking noise will be delivered to the non-test ear (to eliminate cross-hearing) while presenting the tones to the test ear. To assist hearing healthcare professionals in deciding on the needs of masking, masking rules have been established.[1] Nevertheless, during the masking procedure, overmasking (i.e., providing "too much" masking noise) can occur, typically when assessing patients with large ABGs.[1] In this case, the exact BC thresholds cannot be measured, and the type of hearing loss is uncertain. As getting the accurate type of hearing loss is crucial, alternative solutions must be made available.

One of the feasible options to obtain valid BC thresholds (in the presence of overmasking) is to apply a sensorineural acuity level (SAL) test.[12-15] The procedure of this test has been well described in the literature.[13-15] It is worth mentioning that before this test can be applied in clinical settings, SAL normative data must be established first. To obtain this information, a group of healthy, normal-hearing participants is required. After the completion of PTA, a masking noise is delivered continuously at a maximum intensity level by the respective bone transducer that is placed on the forehead of the participant. While wearing headphones (or insert earphones) that deliver pure tones, he/she is asked to press the response button when the tones are heard (in the presence of masking noise). The AC thresholds in noise are then determined at specific frequencies. Subsequently, the SAL normative data are derived by computing the differences between AC thresholds in noise and AC thresholds provided by PTA at each of frequencies.[12,13] These data are then averaged across the participants to provide a better estimation.[14] To estimate the masked BC threshold of a hearing-impaired patient, a similar procedure is applied. That is, the AC threshold in noise at a specific frequency is obtained, and it is then subtracted from the respective SAL normative data (at a similar frequency). This value provides the amount of estimated ABG.[13] Herein, since the AC threshold in quiet is known (as provided by the PTA), the exact BC threshold can now be estimated.[12,13] Taken together, the following equation is used to calculate the estimated BC threshold at a specific frequency: Estimated BC = AC in quite – (AC in noise – SAL normative data).

Valid SAL normative data gathered from particular populations are essential for using the SAL test in clinical settings.[12,14] For example, the SAL normative data established among Malaysian adults were found to be different from those of Caucasian adults.[14] There has also been some variation in the methods employed by the previous studies in establishing the normative data for the SAL test. In particular, different types of earphones and bone transducers were used across the studies.[13-19] Sensibly, different study outcomes (as well as normative data) would be produced if the methods employed were different in some ways. Headphones and insert earphones have different characteristics, and they are used for specific applications.[1] Among others, headphones are useful when testing patients with no access to the AC pathway (e.g., canal atresia).[1] On the other hand, apart from having larger interaural attenuation values (relative to the headphones), insert earphones are recommended when assessing those with collapsed ear canals.[1,20] It is well known that in certain cases, when the headphones are placed against the pinna, the ear canal may partially or completely collapse.[1,20,21] This condition is more common among older adults and must be identified accordingly during the PTA testing to overcome the presence of "false" ABGs at high frequencies.[1,21,22] In clinical settings, Radioear B71 bone vibrator has been widely used in the PTA testing.[1,14] The newly designed Radioear B81 bone vibrator has been gaining an interest among clinicians and researchers nowadays due to its superior characteristics. Specifically, relative to the conventional B71 bone transducer, it was found to produce higher output levels with less vibrotactile responses and harmonic distortions at low frequencies.[23,24]

It is rather surprising that even though the interest in studying the clinical usefulness of the SAL test began in the 1950s, not many subsequent studies have been published since then. More recently, Awang and his colleagues conducted a study to compare the SAL normative data between two types of bone transducers.[14] In their study that utilised headphones, 42 Malaysian adults were tested, and the performance of commercially available Radioear B71 and B81 bone transducers was studied. As reported, the SAL normative data produced by the bone transducers were found to be statistically different at all test frequencies, implying the significant effect of the bone vibrator type on the SAL test results.[14] Herein, it is not known if a similar pattern would be observed if other types of transducers (e.g., insert earphones) are used.

Collectively, the present study was carried out to establish SAL normative data using insert earphones and two different bone transducers (i.e., B71 versus B81). Additionally, it was also of interest to compare the findings gathered from the present study and the study outcomes reported by Awang et al.[14] (that utilised headphones) to determine the effect of earphone type on the SAL normative data.

MATERIALS AND METHODS

Participants

In the present study that utilised a repeated-measures research design, 40 Malaysian young adults (aged 19–26 years) were enrolled. They were chosen randomly among students and staff members of the respective institution. They were all in good health and had no prior history of hearing problems. They were found to have a clear ear canal and an intact tympanic membrane on both sides, based on otoscopic and tympanometric assessments. According to the air conduction (AC) testing, their hearing was normal bilaterally, with hearing thresholds of 20 dB or less at

Table I: Mean and standard deviation (SD) of normative data for the sensorineural acuity level (SAL) test when tested with B71 and B81 bone transducers at specific frequencies (the respective statistical test results, i.e., p value and Cohen's effect size (d) are also shown)

Frequency (Hz)	Transducer	Mean ± SD (dB)	p value	Effect size (d)
250	B71	41.4 ± 7.3	< 0.001*	0.89
	B81	33.1 ± 7.6		
500	B71	53.2 ± 8.8	< 0.001*	0.94
	B81	44.8 ± 7.3		
1000	B71	62.9 ± 7.1	< 0.001*	0.63
	B81	57.0 ± 8.2		
2000	B71	60.3 ± 10.0	< 0.001*	0.76
	B81	51.4 ± 8.5		
4000	B71	58.0 ± 9.4	< 0.001*	0.90
	B81	50.1 ± 8.3		

*Significance at $p < 0.05$.

Table II: The respective statistical test results when the data of the present study (that used insert earphones) are compared with the findings reported by Awang et al. (2021) that employed headphones for establishing the normative data for the sensorineural acuity level (SAL) test

Frequency (Hz)	Transducer	Mean ± SD (dB)		p value
		Present study	Awang et al. study	
250	B71	41.4 ± 7.3	46.3 ± 8.2	< 0.001*
	B81	33.1 ± 7.6	38.5 ± 9.1	< 0.001*
500	B71	53.2 ± 8.8	61.1 ± 7.2	< 0.001*
	B81	44.8 ± 7.3	51.7 ± 8.1	< 0.001*
1000	B71	62.9 ± 7.1	66.5 ± 8.0	< 0.001*
	B81	57.0 ± 8.2	59.4 ± 7.2	0.010*
2000	B71	60.3 ± 10.0	60.0 ± 8.7	0.824
	B81	51.4 ± 8.5	54.9 ± 9.8	< 0.001*
4000	B71	58.0 ± 9.2	58.4 ± 9.8	0.706
	B81	50.1 ± 8.3	50.0 ± 8.1	0.936

*Significance at $p < 0.05$.

frequencies ranging from 250 to 8000 Hz. Each participant signed a consent form prior to the data collection, and the study was approved by the respective institutional review board, which is in line with the 1975 Declaration of Helsinki and its later amendments.

Test Procedure

The PTA and SAL tests were conducted using a two-channel audiometer (GSI 61, Grason-Stadler Inc., USA) in a dedicated soundproof room within the Audiology Clinic, University Hospital. Prior to the assessments, adequate instructions were given to each of the participants. The PTA testing was conducted based on the standard protocol, and AC and BC thresholds were obtained according to the established Hughson–Westlake method.[1] Insert earphones (ER-3A, Etymotic Research, Illinois, USA) were used to measure AC thresholds (from 250 to 8000 Hz), while both B71 and B81 transducers were employed to determine BC thresholds (from 250 to 4000 Hz) for both ears. In the BC testing, the bone transducer was placed on the mastoid of each ear, and the order in which transducer was to be used was randomised across the participants to avoid any potential bias. Each participant was asked to press the response button whenever tones were heard (regardless of the loudness of tones). Only the AC thresholds in quiet obtained in the PTA testing would be used subsequently to derive the SAL normative data.

Following the PTA testing, the SAL test was carried out using the procedure recommended by Jerger and Tillman.[13] In particular, insert earphones were inserted into each ear while the bone vibrator was placed on the forehead (Fig. 1). A narrowband noise of masking at a maximum intensity level was delivered continuously via the bone transducer, while a pure tone was presented to one ear through the insert earphones. The participants were told to ignore the noise and only press the response button when they heard the tone. For each ear, the AC thresholds in noise at frequencies of 250, 500, 1000, 2000, and 4000 Hz were measured. The differences between AC thresholds in quiet (by PTA) and AC thresholds in noise (by SAL test) were used to calculate the SAL normative data. Likewise, to avoid potential bias, the order in which the transducers were to be used was randomised across the participants.

The SAL normative data at each frequency were gathered from all participants. Mean, standard deviation (SD) and percentage were utilised to express the data as applicable. The Shapiro–Wilk normality test revealed that the data for each ear were normally distributed ($p > 0.05$). As such, the paired t-test was used to compare the SAL normative data between the left and right ears. This analysis was again used to compare the SAL normative data between B71 and B81 bone transducers at each frequency. On the other hand, the one-sample t-test was used to compare the data from the present study with those published by Awang et al.[14] The

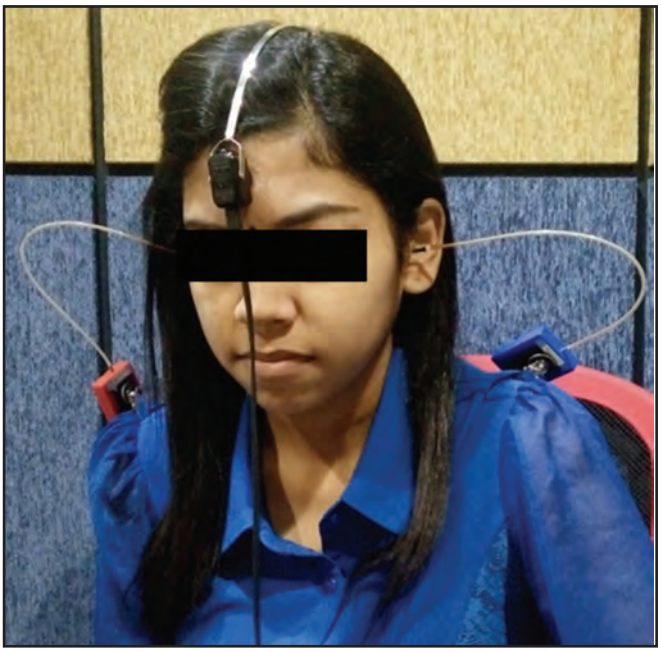

Fig. 1: The sensorineural acuity level (SAL) test procedure of a representative subject.

statistical significance level was set at $p < 0.05$. Additionally, to support the results of the hypothesis testing, Cohen's effect size (d) was measured. Herein, d = 0.2, d = 0.5 and d = 0.8 represent small, medium and large effect sizes, respectively.[25] All data were analysed using the JASP statistical software (version 0.17.1, University of Amsterdam, Netherlands).

RESULTS

In terms of ethnicity, Malay adults made up 75.0% of the total participants, followed by Chinese (15.0%) and other ethnic groups (10.0%). Their mean age was 22.9 ± 1.2 years, and the majority of them were females (65.0%).

The SAL test was successfully completed by each of the participants. The data for left and right ears were then combined (a total of 80 ears) for further analysis because it was determined that the SAL normative data did not statistically differ between the left and right ears at all tested frequencies ($p > 0.05$ using the paired t-test).

Table I shows mean, SD and statistical results when the SAL normative data were compared between the two bone transducers (n = 80 ears). As clearly revealed, the B71 bone transducer produced statistically higher SAL normative data relative to the B81 bone vibrator at all frequencies ($p < 0.05$). These findings were in line with the moderate to large effect sizes (d = 0.63–0.94).

Recall that the present study employed insert earphones and the respective bone transducers to generate the SAL normative data among healthy young adults. As stated earlier, the present study also aimed to compare the SAL normative data gathered from the present study and the findings reported by Awang et al.[14] that employed headphones for establishing their SAL normative data. The results of this comparison are shown in Table II. The different performance between these transducers (insert earphones and headphones) was elaborated in the discussion section.

DISCUSSION

Even though the PTA testing has been used utilised widely in clinical practice, obtaining masked thresholds can be troublesome due to masking problems. The emergence of the SAL test has provided an alternative solution for estimating masked BC thresholds (so that the type of hearing loss can be confirmed). As previously mentioned, the literature on the SAL test is currently limited, and more studies are warranted to further unveil the diagnostic usefulness of this test.

In the PTA testing, the commercially available audiometers are typically equipped with either Radioear B71 or B81 bone vibrators. The newly designed B81 bone transducer was developed with the intention of overcoming the limitations of the B71 bone transducer.[23,24] In the present study, the SAL normative data were established by means of insert earphones and the two bone transducers. As revealed, the SAL normative values produced by the B71 bone transducer were significantly higher than those of the B81 bone vibrator. Given the different designs and characteristics of the bone transducers, these findings were rather sensible. Similar outcomes were reported by Awang and his colleagues when comparing the performance of B71 and B81 bone vibrators in the SAL test.[14] They proposed that the differences in the SAL normative values might be due to several reasons including the increased sensation of vibrotactile of the B71 bone transducer. The different capabilities of the two transducers in delivering masking noise at maximum levels were also proposed as the reason for the discrepancies in the SAL normative data.[14] Even though these notions appear to be reasonable, future research is needed to further shed light on this issue. In this regard, performing the SAL test on adults with severe SNHL (with poor BC thresholds and enhanced vibrotactile sensations) can be advantageous to understand the mechanism of SAL test when tested with the two bone transducers.

To determine the possible effect of the earphone type on the SAL normative values, the present study's findings were compared with the data reported by Awang et al.[14] As shown in Table II, with the B71 bone vibrator, the SAL normative data were significantly lower in the present study than in the study by Awang et al.[14] at 250, 500 and 1000 Hz frequencies ($p < 0.05$). Whereas at 2000 and 4000 Hz, the SAL normative data between the studies were comparable ($p > 0.05$). Likewise, with the B81 bone transducer, the present study revealed statistically lower SAL normative data relative to the study by Awang et al.[14] at the majority of frequencies (i.e., 250 Hz, 500 Hz, 1000 Hz and 2000 Hz). At 4000 Hz, the SAL normative data between the two studies did not differ significantly with $t(79) = 0.081$, $p = 0.936$. This comparison was considered appropriate, as the methods employed by both studies were almost similar. Specifically, both studies were carried out among Malaysian participants with comparable sample sizes and age ranges (i.e., 42 adults aged 19–27 years in the study by Awang et al.[14]). Furthermore, both studies employed the similar SAL test procedure, i.e., based on the protocol recommended by Jerger and Tillman.[13]

It is worth stating that the data gathered from studies involving other ethnic groups (e.g., Caucasian adults) may not be appropriate to be compared.[14] Apart from methodological differences (e.g., different sample sizes, different types of earphones and bone transducers, etc.),[14,17,18] anatomical factors including head size and bone density may also contribute to the variation in the SAL normative data.[26-29] It was found that at most of the frequencies tested, the SAL normative data produced by the present study (with insert earphones) were statistically lower than those reported by Awang et al.[14] (that utilised headphones). Since both transducers were designed differently and for specific applications, the obtained results were somehow anticipated. Awang and his colleagues employed the Telephonics TDH-39 supra-aural headphones (that rest on the ear and do not completely enclose the ear) to derive the SAL normative values.[14] The insert earphones used in the present study consist of a tube that delivers pure tone signals through compressible earplugs that are placed in the ear canal. As mentioned before, this transducer is useful for assessing those with collapsed ear canals to avoid misdiagnosis of the type of hearing loss.[20-22] Of note, since the output of both transducers is calibrated in dB HL, AC and BC thresholds obtained in the PTA testing (by both transducers) should be comparable. In line with this, previous studies revealed that both transducers had similar intra-subject reliability and test–retest stability.[30,31] In this regard, the differences in the SAL normative data by the two transducers might be due to differences in AC thresholds in noise (obtained in the SAL test). That is, relative to headphones, less threshold shifts were observed (in the presence of noise given by the bone transducer) when insert earphones were used. As shown in Table II, the mean difference between the earphones can be as large as 7.9 dB (for B71 bone vibrator at 500 Hz). This difference can be considered clinically large (i.e., more than ± 5 dB),[1] and the accuracy of the SAL test can be affected. Further studies are therefore warranted to determine which transducer is more accurate in predicting BC thresholds when testing hearing-impaired patients.

The present study had several limitations. Firstly, the sample size used was modest (n = 40), and perhaps better study results would be obtained if more participants were recruited. Nevertheless, recall that the data for left and right ears were pooled (n = 80 ears) as an effort to enhance the statistical power. Furthermore, the effect size analysis was also employed to support the p values. As reported elsewhere, unlike the p value approach, the effect size analysis provides the magnitude of difference between the groups of interest and is less affected by the sample size.[32,33] In fact, the hypothesis testing and effect size results were found to be consistent with each other, indicating that the desired study outcomes had been achieved. Secondly, the SAL normative data were gathered only from a group of healthy young adults. Obtaining similar data from other age groups should be the next step. Lastly, only those with normal hearing were enrolled in the present study. As such, further studies involving hearing-impaired groups are beneficial to verify the appropriateness of the SAL normative data obtained in the present study.

CONCLUSIONS

The SAL test is particularly useful to determine exact BC thresholds (to avoid misdiagnosis) in cases where the masking procedure fails to do so. Nevertheless, prior to its application, the SAL normative data must be made available. In the present study, insert earphones and two different bone transducers were employed to establish the respective SAL normative data. The SAL normative data produced by the commercially available Radioear B71 and B81 bone transducers were found to be statistically different at all frequencies. Additionally, insert earphones and headphones produced significantly different SAL normative data at the majority of frequencies. The information provided by the present study can be useful to hearing healthcare practitioners in determining which SAL normative data to be applied in clinical settings.

ACKNOWLEDGEMENT

This project was funded by the Short-Term Grant (Universiti Sains Malaysia) with Project Code: 304/PPSK/6315335.

REFERENCES

1. Katz J, Chasin M, English K, Hood L, Tillery KL. Handbook of clinical audiology. Philadelphia, PA: Lippincott Williams Wilkins, 2015.
2. Villavisanis DF, Lin FR, Deal JA. Quantification of hearing loss research on children compared with older adults. JAMA Otolaryngol Head Neck Surg 2019; 145(3): 283-5.
3. Abdul Wahid SN, Md Daud MK, Sidek D, Abd Rahman N, Mansor S, Zakaria MN. The performance of distortion product otoacoustic emissions and automated auditory brainstem response in the same ear of the babies in neonatal unit. Int J Pediatr Otorhinolaryngol 2012; 76(9): 1366-9.
4. Romli M, Wan Mohamad WN, Awang MA, Aw CL, Zakaria MN. The clinical value of bilateral bone conduction testing in hearing diagnosis. Indian J Otol 2020; 26(3): 182-5.
5. Lih AC, Zakaria MN, Mohamad RA, Nor Rashid MF. Effects of ethnicity and gender on the middle ear function in Asian adults. Indian J Otol 2017; 23: 94-7.
6. Abdul Wahab NA, Wahab S, Abdul Rahman AH, Sidek D, Zakaria MN. The hyperactivity of efferent auditory system in patients with schizophrenia: a transient evoked otoacoustic emissions study. Psychiatry Investig 2016; 13(1): 82-8.
7. Zakaria MN, Jalaei B, Wahab NA. Gender and modulation frequency effects on auditory steady state response (ASSR) thresholds. Eur Arch Otorhinolaryngol 2016; 273(2): 349-54.
8. Zakaria MN, Jalaei B, Aw CL, Sidek D. Are speech-evoked auditory brainstem response (speech-ABR) outcomes influenced by ethnicity? Neurol Sci 2016; 37(6): 943-8.
9. Jalaei B, Zakaria MN, Mohd Azmi MH, Nik Othman NA, Sidek D. Gender disparities in speech-evoked auditory brainstem response in healthy Adults. Ann Otol Rhinol Laryngol 2017; 126(4): 290-5.
10. Yoshinaga-Itano C. Benefits of early intervention for children with hearing loss. Otolaryngol Clin North Am 1999; 32(6): 1089-102.
11. Wan Mohamad WN, Romli M, Awang MA, Abdullah R, Lih AC, Zakaria MN. The presence of unusual bone conduction thresholds in pure tone audiometry. Indian J Otol 2020; 26(1): 54-7.
12. Awang MA, Zakaria MN, Salim R, Rashid MFN. Overcoming masking problems in pure tone audiometry: better understanding is needed regarding sensorineural acuity level (SAL) test. Int J Disabil Hum Dev 2021; 20(1): 21-5.

13. Jerger J, Tillman T. A new method for the clinical determination of sensorineural acuity level (SAL). Arch Otolaryngol 1960; 71: 948-55.
14. Awang MA, Don AHM, Salim R, Sul'ain MD, Zakaria MN. The normative data for sensorineural acuity level (SAL) test among young adults: comparisons between B71 and B81 bone transducers. Int J Stat Med Res 2021; 10: 161-8.
15. Awang MA, Suhaimi MAA, Salim R, Othman NAN, Sul'ain MD, Rashid MFN, et al. Are the normative values of sensorineural acuity level (SAL) test affected by head circumferences of subjects? Int J Stat Med Res 2022; 11: 169-74.
16. Kapoor P, Zangmo N, Garg LN, Saini A, Gupta M. Threshold shift validity by documenting sensorineural acuity level: a useful tool for masking. Int J Otorhinolaryngol Head Neck Surg 2020; 6(5): 913-7.
17. Beattie RC, Daily LB. Bone-conduction force values for the sensorineural acuity level (SAL) test. J Aud Res 1982; 22(1): 51-60.
18. Goetzinger CP, Porter TA. Study of the sensorineural acuity level test. J Am Audiol Soc 1976; 1(4): 135-44.
19. Keys JW, Milburn B. The sensorineural acuity level (SAL) technique: an experiment with some observations. Arch Otolaryngol 1961; 73(6): 710-6.
20. Bess JC. Ear Canal Collapse: A Review. Arch Otolaryngol 1971; 93(4): 408-12.
21. Randolph LJ, Schow RL. Threshold in accuracy in an elderly clinical population: ear canal collapse as a possible cause. J Speech Hear Res 1983; 26: 54-8.
22. Dourado EC, Corona AP, Ferrite S. Ear canal collapse prevalence and associated factors among users of a center of prevention and rehabilitation for disabilities, Rev CEFAC 2017; 19(6): 749-55.
23. Eichenauer A, Dillon H, Clinch B, Loi T. Effect of bone conduction harmonic distortions on hearing thresholds. J Acoust Soc Am 2014; 136(2): EL96-102.
24. Jansson KJ, Håkansson B, Johannsen L, Tengstrand T. Electro-acoustic performance of the new bone vibrator Radioear B81: a comparison with the conventional Radioear B71. Int J Audiol 2015; 54(5): 334-40.
25. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum, 1988.
26. Ngeow WC, Aljunid ST. Craniofacial anthropometric norms of Malays. Singapore Med J 2009; 50: 525-8.
27. Leslie WD. Clinical review: Ethnic differences in bone mass-clinical implications. J Clin Endocrinol Metab 2012; 97(12): 4329–40.
28. Tobias JH, Cook DG, Chambers TJ, Dalzell N. A comparison of bone mineral density between Caucasian, Asian and Afro-Caribbean women. Clin Sci (Lond) 1994; 87(5): 587-91.
29. Helzner EP, Cauley JA, Pratt SR, Wisniewski SR, Talbott EO, Zmuda JM, et al. Hearing sensitivity and bone mineral density in older adults: the Health, Aging and Body Composition Study. Osteoporos Int 2005; 16(12): 1675-82.
30. Lindgren F. A comparison of the variability in thresholds measured with insert and conventional supra-aural earphones. Scand Audiol 1990; 19(1): 19-23.
31. Stuart A, Stenstrom R, Tompkins C, Vandenhoff S. Test-retest variability in audiometric threshold with supraaural and insert earphones among children and adults. Audiology 1991; 30(2): 82-90.
32. Zakaria MN. The values of effect size in statistical decision for clinical research. Aud Vestib Res 2017; 26(1): 1-3.
33. Sullivan GM, Feinn R. Using effect size-or why the p value is not enough. J Grad Med Educ 2012; 4(3): 279-82.

A study of neuropsychiatric manifestations in COVID-19 infection in inpatients and its long-term outcomes in Malaysia

Siew Kian Chow, MRCP (UK)[1], Diana Fui Sing Yap, MPharm. Clin. (National University of Malaysia)[2], Jian Hao Sim, MRCP (UK)[1], Pei Sun Tan, MRCP (UK)[1], YiYun Kok, MRCP (UK)[1], Nicholas Hee Ken Yoong, MRCP (UK)[1], Xin Min Teow, MBBS (MAHE)[1], Azreeni Syafiqa Binti Md Najib, MD (National University of Malaysia)[1], Nur Arina Binti Mohmad Hairin, MBBS (JUST)[1], Pek Woon Chin, FRCP (RCPE)[1]

[1]Medical Department of Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor, Malaysia, [2]Pharmacy Department, Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor, Malaysia

ABSTRACT

Introduction: This study aimed to determine the prevalence and association between the severity of COVID-19 and short and long-term neuropsychiatric symptoms, as well as the risk factors for the development of these symptoms.

Materials and Methods: A prospective observational study was conducted between 1st October 2021 till September 2022 in the state of Johor, Malaysia. 300 patients with confirmed SARS-CoV-2 infection were randomly selected and followed up for six months. Data were analysed by using Chi-square test, Fisher's Exact test, Paired t test and Multiple logistic regression.

Results: The prevalence of short-term neuropsychiatric symptoms was 78%, with anosmia being the most prevalent symptom. Long-term symptoms were found in 22.75% of patients, with headache being the most prevalent (p= 0.001). COVID-19 Stage 2 and 3 infections were associated with a higher risk of short-term neuropsychiatric symptoms, OR for Stage 2 infection was 5.18 (95% CI: 1.48-16.97; p=0.009) and for Stage 3 infection was 4.52 (95% CI: 1.76-11.59; p=0.002). Complete vaccination was a significant predictor of long-term symptoms with adjusted OR 3.65 (95% CI 1.22-10.91; p=0.021).

Conclusion: This study demonstrated that neuropsychiatric symptoms were common among COVID-19 patients in Johor, Malaysia and the risk of these symptoms was associated with the severity of the infection. Additionally, complete vaccination does not completely protect against long-term neuropsychiatric deficits. This is crucial for continuous monitoring and addressing neuropsychiatric symptoms in COVID-19 survivors.

KEYWORDS:
COVID-19; neuropsychiatric; vaccine

INTRODUCTION

In December 2019, a cluster of atypical 'viral pneumonia' like cases broke out in Wuhan, China, and this unravelled the pandemic to the whole world. This new disease, named COVID-19, is caused by a novel coronavirus called SARS-CoV-2. Up to 1st April 2023, WHO have reported 762,791,152 confirmed cases of COVID-19, including 6,897,025 deaths, while locally in Malaysia, our numbers stand at 5,052,337 confirmed cases with 36,982 deaths.[1] SARS-CoV-2 virus changes over time. This may affect the virus's properties, transmission rate, performances of vaccines, severity of the disease, detection rate by the diagnostic tools and effectiveness of treatment. Omicron as an example of Variant of Concern (VOC), which requires more meticulous public health actions, e.g. notify to local authority, enhancing preventive measures, and more studies on therapeutic medicine and vaccine effectiveness.

Studies have shown that COVID-19 does not solely affect the respiratory system but is multi-systemic as well. The most common central nervous system (CNS) symptoms include hyposmia or anosmia, ageusia, headache and myalgia, while symptoms indicating encephalopathy (e.g. delirium) are less common.[2,3,4] Even patients who have recovered from COVID-19 can develop long-term sequelae or persistent symptomatology (SPS). The CNS SPS made up 20.8%, and the most prevalent SPS is persistent anosmia or dysgeusia (7.2%) followed by headache (5.3%).[5] Patients may also experience psychological issues such as increased stress, anxiety or depression.[6] Thus, neuropsychiatric symptoms comprise neurological and psychiatric symptoms. Heneka et al.[7] suggested that patients recovered from COVID-19 are at high risk for neurodegenerative disease, e.g. Alzheimer's disease.

There are several postulations regarding the mechanism of SARS-CoV-2 invading the nervous system. Direct effect of SARS-CoV-2 such as its high binding affinity to human receptor angiotensin-converting enzyme 2 (ACE2) found in lung, interstitial epithelium and endothelium tissues of blood–brain barrier, haematogenous dissemination and invades into CNS via olfactory nerve. Other routes of infection are reportedly through the peripheral nervous system via retrograde neuronal routes. Apart from that, SARS-CoV-2 also can affect the nervous system indirectly. For instance, it can cause cytokine release syndrome which is due

This article was accepted: 13 December 2023
Corresponding Author: Chow Siew Kian
Email: siewkian90@gmail.com

to over-activity of the body's immune system, in which there is torrential release of cytokines leading to a harmful level of inflammation which can interfere with organ function. Moreover, SARS-CoV-2 also causes prothrombotic conditions, which may lead to debilitating complications, e.g. acute ischaemic stroke. On top of that, sepsis may be a catastrophic complication of COVID-19 infection, which may lead to multi-organ failure.[8,9]

The effects of COVID-19 infection can be devastating and long lasting. Therefore, this study aimed to determine the prevalence and association between the severity of COVID-19 and short and long-term neuropsychiatric symptoms, as well as the risk factor for the development of these symptoms. This, in turn, can aid medical practitioners and caretakers in managing these symptoms.

MATERIALS AND METHODS

We conducted a prospective observational study at the Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor (government-assigned hospital for treatment of COVID-19) between 1st October 2021 till September 2022. This study was registered at National Medical Research Register with registration number NMRR-21-1720-61044. In addition, ethical approval was obtained from the Malaysia Medical Research and Ethics Committee (MREC).

We included patients admitted to the hospital and diagnosed with COVID-19 based on clinical data, epidemiological history and nasopharyngeal swab or sputum for polymerase chain reaction (PCR) to SARS-CoV-2. Patients were categorised into five severity stages according to Malaysia Ministry of Health COVID-19 protocol.[10] Clinical stage of COVID-19 are as follow: stage 1 is asymptomatic; stage 2 is symptomatic but no pneumonic changes on chest X-ray (CXR); stage 3 is symptomatic and has pneumonic changes on CXR; stage 4 is symptomatic, has pneumonic changes on CXR and required supplemental oxygen; stage 5 is critically ill with multiorgan involvement. Stage 1, 2 and 3 were categorized as mild severity, whereas stages 4 and 5 were categorised as severe stage. Upon admission, all patients underwent a full history taking, physical examination, blood sampling for tests and CXR.

Considering 90% confidence interval, margin of error 0.05, detectable difference of 35% based on previous study7 and a potential dropout rate of 20%, a sample size of 300 patients was randomly selected by using a random number generator application. They were assessed in the ward and then followed up at 6 months via telephone consultation (video call or phone call). Subjects' contacts were kept confidential and only used for study purposes. Telecommunication benefitted patients by eliminating the hassle of travelling and reducing the exposure risk to COVID-19 in the community.

Cognitive function in patients was evaluated by using the six-items screener.[11] A score of 2 or 3 indicates a need for further screening and diagnostic testing. Patient Health Question-9 (PHQ-9)[12] was used to evaluate depression while General Anxiety Disorder-7 (GAD 7)[13] for assessing anxiety. Patients with moderate to severe depression or anxiety disorder were informed and with their permissions, referred to a psychiatrist for further evaluation.[14] Apart from that, Confusion Assessment Method (CAM-S) short-form worksheets was used to assess delirious patients.[15] Permission to use these neuropsychiatric evaluation tools (PHQ-9, GAD-7, six-item screener and CAM-S) in this study was granted by the respective authors.

Subjects' personal information in this study would be handled confidentially. They would not be informed about the individual study findings. However, they would be informed about the study findings collectively if they opted to.

Inclusion criteria included hospitalised patients aged 18 years old and above with confirmed PCR to SARS-CoV-2 (confirmed cases according to the Malaysia Ministry of Health). Thus, patients with compatible clinical symptoms and imaging tests (suspected cases) but negative PCR tests were excluded. Other exclusion criteria were patients who did not require hospitalisation, passed away during the study period, defaulted on post-COVID-19 follow up and those declined to participate in the study. Apart from that, patients with severe neurological disorders which impede participation in the study, e.g. stroke with impaired cognitive functions, severe dementia, chronic headache prior to COVID-19 infection and those with psychiatric disorders prior to COVID-19 infection, e.g. major depression disorder, generalised anxiety disorder, bipolar disorder and schizophrenia were excluded.

Ethical considerations

The ethical implications of the study adhered to the principles of the Declaration of Helsinki Declaration. The database was anonymized, and no identification data was used in the analyses. Informed consent was taken for each patient enrolled in the study. Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia and other relevant approvals prior to the start of any study-related activities.

Statistical Analysis

Data were analysed as descriptive and analytical statistics. In this study, patients were grouped as experiencing short-term or long-term neuropsychiatric symptoms, if they experienced any of the neuropsychiatric symptoms upon admission or in the post 6 months. Chi-square test, Fisher's Exact test or Paired t-test were applied to evaluate the association between patients' social demographic background, the severity of COVID-19 infection, the development of early neuropsychological symptoms and the persistence of these symptoms 6 months post COVID-19 infection, where appropriate. Multiple logistic regression was used to predict the development of early neuropsychological symptoms and the persistence of these symptoms 6 months later.

RESULTS

Baseline Characteristics

From October 2021 until June 2022, 300 patients with confirmed COVID-19 infection were enrolled into the study and followed up after 6 months. 255 (85%) patients were

Table I: Baseline characteristic of study cohort (n=300)

Baseline characteristic	Number of patients, n (%)
Gender	
Male	122 (40.7)
Female	178 (50.3)
Age, mean (+SD)	47.09 (+16.57)
Race	
Malay	247 (82.3)
Chinese	26 (8.7)
Indian	21 (7.0)
Others	6 (2.0)
Risk factors	
No	93 (31.0)
Yes	207 (69.0)
Types of risk factor	
Cardiovascular	53 (17.7)
Respiratory	49 (16.3)
Endocrinology	16 (5.3)
Obstetrics and Gynecology	14 (4.7)
Renal	10 (3.3)
Oncology	4 (1.3)
Multiple comorbid[a]	61 (20.3)
Covid-19 severity	
Stage 1	23 (7.7)
Stage 2	152 (50.7)
Stage 3	34 (11.3)
Stage 4	62 (20.7)
Stage 5	29 (9.7)
Oxygen requirement	
No	212 (70.7)
Yes	88 (29.3)
Steroid use	
No	209 (69.7)
Yes	91 (30.3)
Intensive Care Unit admission	
No	294 (98.0)
Yes	6 (6.0)
Covid-19 vaccination status	
Incomplete	59 (19.7)
Complete	241 (80.3)

Data are given as number (percentage) unless otherwise indicated. [a]Multiple comorbid defined as patients suffered from two or more types of risk factors (cardiovascular, respiratory, endocrinology, obstetrics and gynecology, renal or oncology).

Table II: Prevalence of short-term and long-term neuropsychiatric symptoms

Neuropsychiatric characteristics	Short term (n = 300)	Long term (n = 255)	p value*
Number of patients with neuropsychiatric symptoms, n (%)	234 (78.00)	58 (22.75)	0.001[a]
Average number of neuropsychiatric symptoms per patients, mean (+ SD)	3.40 (+1.930)	2.09 (+1.218)	<0.001c
Neuropsychiatric symptoms, n (%)			
Ageusia	115 (38.33)	3 (1.18)	0.054[b]
Anosmia	137 (45.67)	5 (1.96)	0.178[b]
Myalgia	109 (36.33)	19 (7.45)	<0.001[a]
Headache	109 (36.33)	20 (7.84)	<0.001[a]
Delirium, mean (+SD) (assessed using CAM-S scores)	0 (+0.130)	0 (+0.000)	0.318[c]
Stroke	2 (0.67)	2 (0.78)	0.016[b]
Paresthesia	18 (6.00)	12 (4.71)	<0.001[b]
Movement disorder	0 (0.00)	1 (0.39)	-
Seizure	1 (0.33)	1 (0.39)	0.004[b]
Depressive severity (assessed using PHQ-9 scores)			
Mild	220 (73.33)	56 (21.96)	0.884[b]
Moderate to severe	14 (4.66)	2 (0.78)	
Anxiety severity (assessed using GAD-7)			
Mild	230 (76.66)	56 (21.96)	0.504[b]
Moderate to severe	4 (1.71)	2 (0.78)	
Sleep disturbance	56 (18.67)	17 (6.67)	<0.001[b]
Loss of concentration	15 (5.00)	5 (1.96)	<0.001[b]
Memory disturbance	13 (4.33)	12 (4.71)	0.001[b]
Cognitive impairment (assessed using six-item screener)	27 (9.00)	6 (2.35)	0.375[b]

Data are presented as number (percentage) unless otherwise indicated. *p-value <0.05 considered statistically significant. aChi-square test. bFisher's exact test. cPaired t test. SD, standard deviation, CAM-S, Confusion Assessment Method, PHQ-9, Patient Health Question-9, GAD-7, General Anxiety Disorder-7.

Table III: Association and predictors of short-term neuropsychiatric symptoms (n = 300) in logistic regression models

Characteristics	Short term Neuropsychiatric symptoms		Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
	Yes (n = 234)	No (n = 66)				
Socio-demographic data						
Age, mean (+SD)	46.58 (+16.343)	48.91 (+17.358)	0.99 (0.98–1.01)	0.313	0.99 (0.97–1.01)	0.330
Race, n (%)						
Malay	197 (81.88)	50 (75.76)	1		1	
Non-Malay	37 (15.81)	16 (24.24)	0.59 (0.30–1.14)	0.115	0.58 (0.29–1.19)	0.139
Risk factors, n (%)						
No	72 (30.77)	21 (31.82)	1		1	
Yes	162 (69.23)	45 (68.18)	1.05 (0.58–1.89)	0.871	0.79 (0.41–1.54)	0.487
Clinical data						
COVID-19 severity, n (%)						
Stage 1	11 (4.70)	12 (18.18)	1		1	
Stage 2	120 (51.28)	32 (48.48)	4.09 (1.65–10.13)	0.002*	4.52 (1.76–11.59)	0.002*
Stage 3	27 (11.54)	7 (10.61)	4.21 (1.31–13.51)	0.016*	5.18 (1.48–16.98)	0.009*
Stage 4	52 (22.22)	10 (15.15)	5.67 (1.96–16.40)	0.001*	2.75 (0.45–16.87)	0.274
Stage 5	24 (10.26)	5 (7.58)	5.24 (1.48–18.53)	0.010*	2.20 (0.24–20.18)	0.486
Oxygen requirement, n (%)						
No	159 (67.95)	53 (80.30)	1		1	
Yes	75 (32.05)	13 (19.70)	1.92 (0.99–3.74)	0.054	3.28 (0.60–17.94)	0.170
Intensive Care Unit admission, n (%)						
No	229 (97.86)	65 (98.48)	1		1	
Yes	5 (2.14)	1 (1.52)	1.42 (0.16–12.36)	0.751	1.08 (0.10–12.50)	0.946
COVID-19 vaccination status+, n (%)						
Incomplete	45 (19.23)	14 (21.21)	1		1	
Complete	189 (80.77)	52 (78.78)	1.13 (0.58–2.22)	0.721	1.52 (0.72–3.26)	0.270

CI, confidence interval; OR, odds ratio. *p value <0.05 considered statistically significant. +Complete COVID-19 vaccination status defined as individual who received complete primary dose vaccination series (2 doses for CoronaVac®, Comirnaty®, COVID-19 AstraZeneca®) at least 14 days before SARS-CoV-2 virus infection.

Table IV: Association and predictors of long-term neuropsychiatric symptoms (n= 255) in logistic regression models

Characteristics	Long term neuropsychiatric symptoms		Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
	Yes (n=58)	No (n=197)				
Sociodemographic Data						
Age, Mean (+SD)	43.67 (+14.867)	47.86 (+16.916)	0.99 (0.97–1.00)	0.091	0.98 (0.96–1.00)	0.073
Race, n (%)						
Malay	48 (82.76)	159 (80.71)	1		1	
Non-Malay	10 (17.24)	38 (19.29)	0.87 (0.41–1.88)	0.726	1.30 (0.55–3.05)	0.548
Risk Factors, n (%)						
No	23 (39.66)	61 (30.96)	1		1	
Yes	35 (60.34)	136 (69.04)	0.68 (0.37– 1.25)	0.217	0.76 (0.39–1.47)	0.415
Clinical Data						
COVID-19 Severity, n (%)						
Stage 1	5 (8.62)	18 (9.14)	1		1	
Stage 2	35 (60.34)	99 (50.25)	1.27 (0.44–3.69)	0.657	1.35 (0.45–4.07)	0.592
Stage 3	2 (3.45)	28 (14.21)	0.28 (0.05–1.47)	0.127	0.27 (0.04–1.59)	0.144
Stage 4	14 (24.14)	32 (16.24)	1.58 (0.49–5.09)	0.448	0.78 (0.07–8.91)	0.842
Stage 5	2 (3.45)	20 (10.15)	0.36 (0.06– 2.09)	0.255	0.11 (0.01–2.61)	0.171
Oxygen Requirement, n (%)						
No	42 (72.41)	145 (73.60)	1		1	
Yes	16 (27.59)	52 (26.40)	1.06 (0.55–2.05)	0.857	2.98 (0.32–28.09)	0.340
Intensive Care Unit Admission, n (%)						
No	57 (98.28)	194 (98.48)	1		1	
Yes	1 (1.72)	3 (1.52)	1.14 (0.12–11.12)	0.914	6.18 (0.28–135.88)	0.248
COVID-19 vaccination status+, n (%)						
Incomplete	5 (8.62)	36 (18.27)	1		1	
Complete	53 (91.38)	161 (81.73)	2.37 (0.89–6.35)	0.086	3.65 (1.22–10.91)	0.021*

CI, confidence interval; OR, odds ratio. *p value <0.05 considered statistically significant. +Complete COVID-19 vaccination status defined as individual who received complete primary dose vaccination series (2 doses for CoronaVac®, Comirnaty®, COVID-19 AstraZeneca®) at least 14 days before SARS-CoV-2 virus infection

reassessed after 6 months. Table I shows the baseline sociodemographic and clinical characteristics of the entire cohort. The mean age of the study population was 47.09 (+16.57) with females (178, 50.3%) and Malay (247, 82.3%) predominance. Majority of them were admitted as Stage 2 Covid-19 infection (152, 50.7%) and have completed their COVID-19 vaccination (241, 80.3%).

Prevalence of Short-Term and Long-Term Neuropsychiatric Symptoms

In this study, the prevalence of the short-term neuropsychiatric symptoms in the study cohort was 78% (n = 234). Among those with short-term symptoms, the mean number of neuropsychiatric symptoms suffered per patient was 3.40 +1.930. In contrast, a majority of those suffering from short-term neuropsychiatric symptoms improved post 6 months of study follow-up with only 58 (22.75%) of the patients showing persistence with long-term symptoms (p = 0.001). From those post 6 months cohort with long-term neuropsychiatric symptoms, the mean number of symptoms suffered per patients was 2.09+1.218. After 6 months post COVID-19 infection, the mean number of persistent neuropsychiatric symptoms suffered per patient was statistically significantly reduced (p < 0.001).

The most prevalent short-term neurological symptoms were anosmia (46%), ageusia (38%), headache and myalgia (36%). On the other hand, the most prevalent long-term neurological symptoms were headache (7.8%), myalgia (7.6%) and sleep disturbance (6.7%). From a psychological aspect, about 73% and 76% have mild depressive and anxiety symptoms respectively during both initial and subsequent assessments (Table II). Besides, ageusia, anosmia, delirium, anxiety, depressive and cognitive impairment were among those neuropsychiatric symptoms that were found to be persistent post 6 months of evaluation (p>0.05) while movement disorder cannot be assessed in this study due to the small sample size (n = 1).

Associations and Predictors of Short- and Long-Term Neuropsychiatric Symptoms

The univariate analysis (Table III) demonstrated no statistically significant association between sociodemographic characteristics (age, race) and clinical characteristics (risk factors, oxygen requirements, ICU admission, COVID-19 vaccination status) with the manifestation of short-term neuropsychiatric symptoms (p > 0.05). COVID-19 disease severity was reported to be the only influencing predictor that affected the development of short-term symptoms. After adjusting and controlling all the possible confounding variables under the multivariate logistic regression, patients presented with COVID-19 Stage 2 and 3 infections appeared to have 4 to 5 times higher risk of suffering from short-term neuropsychiatric symptoms compared to other stages of infections. The reported adjusted OR for Stage 2 infection was 5.18 (95% CI: 1.48– 16.98; p = 0.009) and for Stage 3 infection was 4.52 (95% CI: 1.76–11.59; p = 0.002).

Following 6 months of study follow-up, COVID-19 vaccination status was found to be a significant predictor for long-term neuropsychiatric sequelae in multiple regression analysis. Interestingly, while vaccination status did not show to affect short-term symptoms, those with complete COVID-19 vaccination demonstrated approximately 3.6 times higher risk of long-term deficits with adjusted OR 3.65 (95% CI 1.22–10.91; p = 0.021). From another perspective, although COVID-19 disease severity was shown to be associated with short-term symptoms, it did not become an influencing predictor post 6 months of follow-up (p>0.05). Furthermore, our 6 months post-data implied that persistent neuropsychiatric deficits were independent from other socio-demographic characteristics (age, race) and clinical characteristics (risk factors, oxygen requirements, ICU admission) from the regression analysis with p > 0.05 (Table IV).

DISCUSSION

SARS-CoV-2 affects multiple systems acutely and also brings long-term effects to human health, known as long COVID. This study mainly focuses on the neurological and psychological impacts of COVID in acute infection and long-term effects later in life. We enrolled 300 patients who were diagnosed with COVID-19 infection and followed up in 6 months' time to assess for persistent neuropsychiatric symptoms. After 6 months, 255 patients were reassessed. We extensively outlined the neuropsychiatric symptoms, sociodemographic (age, gender, race, risk factors, comorbidities) and clinical variables (COVID stage, oxygen requirement, steroid use, ICU admission, vaccine status) observed within the cohort. This comprehensive list aimed to offer a detailed exploration of the cohort's clinical profile and contribute to a nuanced understanding of the study population.

Our mean age of expectancy was found to be lower compared to previous studies conducted in Mediterranean cohorts, specifically in Italy, Brazil and Spain.[5] This variance can be attributed to the overall lower life expectancy in Malaysia, a Southeast Asian country characterised by its diverse population comprising three main ethnic groups—Malays, Chinese and Indians. Despite the cultural and demographic differences, our study revealed no significant correlation between race and the occurrence of neuropsychiatric syndromes in both short and long-term period. Furthermore, it is a well-established fact that individuals with comorbidities often face heightened risks of severe illnesses or complications during acute illness. Consequently, our study was strategically designed to explore the potential relationship between comorbidities and neuropsychiatric symptoms. Interestingly, our findings defied expectations, as the study did not unveil a clear correlation between a patient's premorbid conditions and the subsequent development of neuropsychiatric symptoms.

From this study, we found that 78% of cohorts exhibited short-term neuropsychiatric symptoms while 22.75% experienced persistent symptoms. The number of patients with short-term symptoms was higher, whereas the number of patients with long-term symptoms fell between other studies.[5,6,7,16,17,18] This difference could be attributed to people being more anxious and paying closer attention to symptoms when experiencing less severe respiratory symptoms. Additionally, increased knowledge about the effects of COVID-19 on various systems may contribute to higher

awareness and education among the public, leading to more reported symptoms.

The most prevalent short-term neurological symptoms were anosmia (46%), ageusia (38%), headache and myalgia (36%). These results were similar to other studies.[17,18] The most prevalent long-term neuropsychiatric symptoms were headache (7.8%), myalgia (7.6%) and sleep disturbance (6.7%). All of these neuropsychiatric manifestations were the results of direct invasion of SARS-COV-2 virus into CNS via olfactory nerve or interaction with angiotensin-converting enzyme 2 (ACE2) receptors on the endothelial cells of the blood–brain barrier (BBB), systemic inflammation and massive cytokine release, cerebrovascular changes and complications of multi-organ dysfunction.[2,4,7] Additionally, there has been a hypothesis concerning the activation of the PYD domains-containing protein 3 (NLRP3) inflammasome and interleukin-1β, which causes the pathological accumulation of neurodegeneration-associated peptides. These peptides, such as fibrillar amyloid-β, induce or worsen neurodegenerative processes, ultimately leading to functional impairment in Alzheimer's Dementia. The heightened secretion of IL-1β through the activation of NLRP3 can induce neuroinflammation, neuronal death and cognitive impairments. This process might play a role in the pathogenesis of Alzheimer's Disease (AD).[19,20] In our study, 4.7% of patients suffer memory disturbance as a long-term sequelae ($p < 0.05$). This raises the concern of COVID-19-infected patients tending to suffer neurodegenerative disease in the future and further follow-up studies are warranted.

Noteworthy, mild depression and mild anxiety were highly prevalent among acute infection and during long-term follow-up ($p > 0.5$). This could be due to multifactorial, e.g. worrying of one's own health, societal stigmatisation, isolation policy, financial restraint due to worldwide economic recession, post-traumatic stress disorder (PTSD) and fear of long-term impact on health. Prevalence of PTSD symptoms in COVID19-19 was 9%.[14] The intense stressors linked to COVID-19 encompassed experiences such as undergoing treatments during severe illness (fear of death in critical situations, pain resulting from medical interventions like endotracheal intubation and central line insertion, and dealing with any complications), as well as witnessing the severe illness or death of beloved family members. Depression and anxiety have been identified as potential contributors to a decline in concentration, with a 5% decrease in the short term and a 1.96% decrease in the long term. Additionally, these psychological factors are associated with sleep disturbances, manifesting as an 18.67% occurrence in the short term and a 6.67% occurrence in the long term ($p < 0.05$).

Our study showed that patients with mild COVID-19 were associated with short-term neuropsychiatric symptoms. COVID-19 Stage 2 and 3 infections appeared to have 4 to 5 times higher risk of suffering from short-term neuropsychiatric symptoms compared to other stages of infections. Misra S et al. reported that mild COVID-19 patients have a higher tendency to get alteration in smell and taste.[18] It could be due to our first line defense—nasal cavity which acts as mechanical protection to prevent spreading of COVID-19 virus to the whole body. Thus, those patients suffer less severe symptoms of the disease. Apart from that, those severe COVID-19 patients are more ill and may not be able to give clear history or attention to neuropsychiatric symptoms as they are suffering from more severe lung inflammation and/or other organ involvements. Hence, severity of COVID-19 may predict the development of neuropsychiatric symptoms in acute infection.

COVID-19 vaccine is generally safe and provides strong protection from detrimental effects of COVID-19 and greatly reduces the rate of hospitalisation. It has short, tolerable side effects after injection. Nonetheless, this study found that those who completed COVID-19 vaccination (received at least two doses of COVID-19 vaccine eg Pfizer, AstraZenaca and Sinovac) at least 14 days before infection with SARS-CoV-2 virus, demonstrated approximately 3.6 times higher risk of long-term neuropsychiatric symptoms. This is contrary to other studies, which showed favourable results of COVID-19 vaccine on long covid.[21,22] It could be explained by the difference in duration of follow-up, as this study has a longer cohort period of 6 months, different SARS-CoV-2 variants, and different socio-demographic background. Another possible reason could be due to the existence of other factors affecting neuropsychiatric symptoms, e.g. mild depression symptoms that might be affected by stress of daily living. Moreover, perception of patients is subjective, and belief or fear of vaccines will bring long-term side effects. Those non-specific symptoms may be over-reported by the cohort.

LIMITATIONS

The limitations of this study include a small sample size, particularly in the incomplete vaccinated group, which accounted for only 16% of the study population at the end of the study. Secondly, it is not possible to confirm that the long-term neuropsychiatric symptoms were solely caused by COVID-19 since there was no comparison group. Thirdly, those suffering severe COVID-19 infection may not be able to provide a clear history and under-report the neuropsychiatric symptoms.

CONCLUSION

This study highlighted that neuropsychiatric symptoms were common among COVID-19 patients in Johor, Malaysia and most of these symptoms improved after 6 months. The most prevalent short-term neurological symptoms were anosmia, ageusia, headache and myalgia whereas the most frequent long-term neurological symptoms were headache, myalgia and sleep disturbance. Additionally, the risk of these symptoms was associated with the severity of the infection. Nonetheless, socio-demographic and premorbid did not correlate with short and long-term neuropsychiatric symptoms. Moreover, complete vaccination did not fully protect against long-term neuropsychiatric deficits. These findings emphasise the importance of monitoring and addressing neuropsychiatric symptoms in COVID-19 patients. Further follow-up and monitoring for any potential neuropsychiatric symptoms or neurodegenerative disease is warranted.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia and Head of Department for permission to publish this article.

REFERENCES

1. World Health Organization. WHO COVID-19 Dashboard [Internet]. World Health Organisation 2023. https://covid19.who.int. Accessed 1 April 2023.
2. Ermis U, Rust MI, Bungenberg J, Costa A, Dreher M, Balfanz P, et al. Neurological symptoms in COVID-19: a cross-sectional monocentric study of hospitalized patients. Neurological Research and Practice. 2021; 3(1): 17.
3. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clinical Neurology and Neurosurgery. 2020; 194: 105921.
4. Sharifian-Dorche M, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. Journal of the Neurological Sciences. 2020; 417: 117085.
5. Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, Pérez-Contreras M, Fernández-Martínez NF, Ruiz-Montero R, et al. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. BMC Med. 2021; 19(1): 129.
6. Kumar S, Veldhuis A, Malhotra T. Neuropsychiatric and Cognitive Sequelae of COVID-19. Front Psychol. 2021;12:577529.
7. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther. 2020; 12(1): 69.
8. Abdel Hafez SMN. Can Covid-19 attack our nervous system? J Chem Neuroanat. 2021; 117: 102006.
9. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. Cell.
2020; 183(1): 16-27.e1.
10. Ministry of Health Malaysia. Annex 2E: Clinical Management of Confirmed COVID-19 Case in Adult and Paediatric. https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX-2E-CLINICAL-MANAGEMENT-OF-CONFIRMED-COVID-19-31052022.pdf Accessed 28 April 2022.
11. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-Item Screener to Identify Cognitive Impairment Among Potential Subjects for Clinical Research. Medical Care. 2002; 40(9): 771-81.
12. Spitzer RL. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. JAMA. 1999; 282(18): 1737.
13. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. Arch Intern Med. 2006; 166(10): 1092-97.
14. Ministry of Health Malaysia. Post Covid 19 Management Protocol 2021, 1st Edition. https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX_50_POST_COVID-19_MANAGEMENT_PROTOCOL_12JULY2021.pdf Accessed 28 April 2022.
15. Inouye SK, Kosar CM, Tommet D, Schmitt EM, Puelle MR, Saczynski JS, et al. The CAM-S: Development and Validation of a New Scoring System for Delirium Severity in 2 Cohorts. Ann Intern Med. 2014; 160(8): 526-33.
16. Hampshire A, Trender W, Chamberlain SR, Jolly A, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine. 2021; 39: 101044.
17. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77(6): 683-90.
18. Misra S, Kolappa K, Prasad M, Radhakrishnan D, Thakur KT, Solomon T, et al. Frequency of Neurologic Manifestations in COVID-19: A Systematic Review and Meta-analysis. Neurology. 2021; 97(23): e2269-81.
19. Potere N, Del Buono MG, Caricchio R, Cremer PC, Vecchié A, Porreca E, et al. Interleukin-1 and the NLRP3 inflammasome in COVID-19: Pathogenetic and therapeutic implications. EBioMedicine. 2022; 85: 104299.
20. Wang H, Lu J, Zhao X, Qin R, Song K, Xu Y, et al. Alzheimer's disease in elderly COVID-19 patients: potential mechanisms and preventive measures. Neurol Sci. 2021; 42(12): 4913-20.
21. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. BMJ Med. 2023; 2(1): e000385.
22. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. BMJ. 2022; 377: e069676.

Acknowledgement
December Issue 2023

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Dr Aida Abdul Aziz
2. Dr Aida Abdul Rashid
3. Dr Adli Ali
4. Dr Andrew Chang Kean Wei
5. Prof Dr Andrew Yu-Lin Ban
6. Dr Chan Tha A Hing
7. Dr Chan Yean Yean
8. Dr Cheng Joo Thye
9. Dr Fauzi Abdul Rani
10. Dr Karthigesu Aimanan
11. Dr Kumar Harirajah
12. Dr Liew Boon Seng
13. Dr Mawaddah Azman
14. Dr Mohd Azmi bin Sulaiman
15. Dr Navin Kumar Devaraj
16. Dr Neil Rane
17. Dr Noor Alaudin Abdul Wahab
18. Dr Nour El Huda Abd Rahim
19. Dr Salman Amiruddin
20. Dr Saraswathi Bina Rai
21. Dr Siti Soraya Ab Rahman
22. Dr Sivananthan Asokumar
23. Dr Wan Mohd Zahiruddin Wan Mohammad