Cardiovascular risk factors of Alzheimer's disease and other neurocognitive disorders in Malaysia

Buhari Ibrahim, MSc[1,2], Subapriya Suppiah, MD[1], Albert Dayon Piersson, MSc[3,4], Rizah Mazzuin Razali, MD[5], Mazlyfarina Mohamad, PhD[3], Hasyma Abu Hassan, MD[1], Normala Ibrahim, MD[6]

[1]Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia, [2]Department of Physiology, Faculty of Basic Medical Sciences, Bauchi State University PMB 65, Gadau, Nigeria, [3]Centre for Diagnostic, Therapeutic and Investigative Studies, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Malaysia, [4]University of Cape Coast, School of Allied Health Sciences, Department of Imaging Technology & Sonography, Cape Coast, Ghana, [5]Geriatric Unit, Department of Medicine, Hospital Kuala Lumpur, Malaysia, [6]Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

ABSTRACT

Introduction: Risk factors for cardiovascular disease (CVD) have been increasingly implicated in the development of dementia but little is known about the effects in a Malaysian population. We aimed to determine the interaction between sociodemographic and CVD risk factors among the dementia and mild cognitive impairment (MCI) patients in Malaysia.

Materials and Methods: A cross-sectional study was conducted in the memory clinic at Hospital Kuala Lumpur (HKL). Medical records data from 2014 to 2019 were extracted. Mini Mental State Examination (MMSE) test was used to assess the neurocognitive function of patients.

Results: A total of 298 patients (30 MCI, and 268 dementia) were evaluated, with dementia patients consisting of 78 Alzheimer's disease (AD), 93 Vascular dementia (VaD), 94 Mixed dementia, 2 early-onset Alzheimer's disease (EOAD) and 1 Logopenic Progressive Aphasia type of AD (LPA). MCI and dementia were significantly associated with a history of CVD, particularly stroke (p=0.023).

Conclusion: Given that stroke significantly predicted the risk of developing vascular dementia among the patients in a central Malaysian population, lifestyle modifications are recommended to alleviate these risk factors of CVD.

KEYWORDS:
Alzheimer's disease, vascular dementia, cardiovascular, hypertension, Malaysian

INTRODUCTION

Dementia or major neurocognitive disorders (NCD) refers to the collection of heterogeneous disorders that occur because of progressive neurodegeneration and other pathologies of brain cells. Based on the Diagnostic and Statistical Manual for of Mental Disorders, Fifth Edition (DSM-5), the commonest major NCD is Alzheimer's disease (AD) that involves disturbances in the cognitive cerebral domains, such as memory, language, and executive functions.[1] On the other hand, mild cognitive impairment (MCI), which is a mild NCD, has been implicated in the spectrum of NCDs, and refers to a transitional state between normal ageing and dementia.[2] MCI is characterised by a decline in one's cognitive abilities in the memory domain of cognitive functions compared to the previous level of performance, provided the activities of daily living remain intact and the subject does not fulfil the criteria for AD.[3] Typically, AD accounts for more than 70% of all cases of dementia and most patients have late onset AD (LOAD) but some are also identified with early-onset AD (EOAD) that is likely hereditary in aetiology.[4] A survey in 2016, reported that AD affects nearly 40-50 million people worldwide, out of which approximately 23 million of them live in Asia, and more than 123,000 reside in Malaysia.[5] The second most prevalent form of dementia is vascular dementia (VaD),[6] and the third most common dementia subtype is mixed dementia, which is usually caused by a co-existence of AD and VaD. Other forms of dementias include fronto-temporal dementia (FTD) and Lewy-body dementia (DLB).[7,8] In addition, atypical AD subtypes such as language variant AD, known as the Logopenic variant of Primary Progressive Aphasia (lv-PPA) also exist.[9]

For VaD, the clinical presentation is dependent on the causative agent. Specifically, a cerebrovascular accident or stroke may localise the area and extent of the brain injury, whereas VaD due to cardiovascular disease (CVD) is highly diffuse in its involvement and presents with a reduced rate of information processing, cognitive dysfunction, and an inability to perform tasks that require complex attention.[10] Apart from memory loss, VaD has been implicated in gait apraxia, and urinary incontinence.[11] Additionally, mixed dementia, presents with a combination of the symptoms of AD and VaD; namely memory loss, together with executive impairment and attention dysfunction.[9]

Clinical conditions such as stroke, atrial fibrillation, coronary heart disease (CHD), and heart failure are examples of CVDs. The CVDs have been increasingly implicated in the development of dementia.[12] It is postulated that there is a direct causal association between CVD and AD as cardiac disease leads to cerebral hypoperfusion and micro-emboli.[13] These mechanisms can cause neuronal damage, which along

This article was accepted: 12 February 2021
Corresponding Author: Subapriya Suppiah
Email: subapriya@upm.edu.my

with beta amyloid deposition and tau pathology, lead to the neurocognitive deficit of AD.[7,14] Stroke, which is a major type of CVD, can lead to 'post-stroke dementia' or VaD. Lacunar strokes caused by cerebral small vessels disease are known to cause VaD and can also increase the risk of developing AD.[15] Furthermore, ischemic brain damage, which is evidenced by white matter lesions on magnetic resonance imaging (MRI), is also associated with dementia.[15,16]

A previous community-based study conducted among elderly Malaysians revealed that the risk factors for dementia included older age, lack of formal education, female gender, very poor level of self-rated health quality, and Malay or Bumiputera ethnicity.[17] There is, however, a lack of information regarding the sociodemographic information and related risk factors pertaining to dementia patients in a hospital-based setup in Malaysia. In particular, it is of interest to identify the sociodemographic information and associated risk factors for patients having dementia at HKL, which is one of the largest tertiary referral centres in Malaysia that attends to dementia cases at a regular basis in their memory clinic.

To the best of our knowledge, to date only community-based studies pertaining to dementia have been conducted in Malaysia. Therefore, the present study is aimed to achieve the following objectives i.e., to estimate the frequency of MCI and the different subtypes of dementia among Malaysians attending the memory clinic HKL, to determine the differences in MMSE scores among the MCI and dementia patients and to determine the association between MCI or dementia with the sociodemographic and CVD risk factors.

MATERIALS AND METHODS

Study design and settings

A retrospective study was carried out using secondary data from the medical records of 298 patients (30 MCI and 268 dementia) attending the memory clinic of HKL between 2014 and 2019. The patients are residents of an urban region in Malaysia, specifically Kuala Lumpur.

The Memory Clinic at the Geriatric Unit, HKL has been operating since 2003. Patients who attend the clinic here are first screened by nurses who are well-trained in the assessment of cognitive function. Several cognitive assessment tools such as the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), the Saint Louis University Mental Status exam (SLUMS) were used to assess the' level of daily living activities of the patients before they were evaluated by the geriatricians. Furthermore, since 2013, the memory clinic incorporated a multidisciplinary approach involving allied health workers in the care of patients. For example, occupational therapists, pharmacists, speech and language therapist, physiotherapist, dietitians, special-need dentists, social workers and neuroradiologist were instrumental in providing the necessary services to the patients. This kind of multidisciplinary approach is thus essential in providing good quality of care for the patients.

Sample size determination

The sample size calculated was estimated based on the assumption that retrospective studies use statistical power instead of measuring sample sizes (also called post hoc power analysis).[18] Consequently, the GPower software was used to predict the actual sample size needed by choosing the effect size of 0.25, power (1-β err prob) of 0.95 and 4 number of groups for the ANOVA, the results yielded 280 NCD patients' data was needed to be recorded retrospectively based on the a study with similar endpoint.[19] However, during the data collection, 298 patients were found in the hospital records and hence all were considered for the analysis.

Patients selection

The inclusion criteria included Malaysian patients at the HKL memory clinic, having all the relevant clinical data, i.e., the diagnosis of the type of NCD was available, the age, gender, education level, marriage status, and comorbid disease. Foreigners and patients who were not diagnosed with dementia between the periods of 2014 to 2019 were excluded from the study.

Secondary source of data

The data was collected manually by going through the files of the patients that met the inclusion criteria for our study. The primary data extracted from the files of patients included age, gender, race, marital status, level of education, occupation, and the Mini Mental State Examination (MMSE) test scores. The MMSE test is an example of a widely used tool for the objective assessment of dementia.[20] It is comprised of 30 questions aimed at evaluating memory, registration, recall, calculation, language, attention, and orientation, as well as visuospatial abilities.[21] Normally a total score of 24 and below indicates significant cognitive impairment and dementia. However, sociodemographic factors such as age, duration of formal education and other factors affect the scores at an individual level.[22]

Diagnostic criteria

The patients were diagnosed with the specific subtypes of NCDs by the clinicians based on the standardised criteria using DSM-5 and MMSE test scores. Although there is no consensus for the diagnosis of mixed dementia, several international references such as the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) and the National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN) have proposed diagnostic criteria that differ from each other. Therefore, mixed dementia was diagnosed following the harmonization of criteria outlined by the ADDTC and NINDS-AIREN, such as the presence of focal neurological symptoms and evidence of significant CVD.[23]

Ethical Approval

This study was approved by the Medical Research Ethics Committee (MREC) of National Medical Registration Registry (NMRR) Malaysia (NMRR-19-2719-49105) and the Ethics Committee for Research Involving Human Subjects of Universiti Putra Malaysia (JKEUPM-2019-328)

Table I: Association between socio-demographic risk factors and neurocognitive disorders among the memory clinic patients at Hospital Kuala Lumpur, Malaysia

	MCI (n=30) (10.24%)	AD (n=78) (26.62%)	VaD (n=93) (31.1%)	Mixed dementia (n=94) (32.1%)	Total (n=293) (100%)	F/X2	p value
Age (years)	74 (7.22)	75.47(8.90)	75.48 (7.77)	77.35 (7.49)	75.93 (7.98)	1.77	0.153
Gender							
Male	17 (56.7)	35 (44.9)	44 (47.3)	36 (40.4)	133 (46)	2.24	0.524
Female	13 (43.3)	43 (55.1)	49 (52.7)	53 (59.6)	156 (54)		
Race							
Malay/Bumiputera	5 (16.7%)	21 (27.3)	32 (34.8)	27 (28.7)	85 (29)	4.55	0.603
Chinese	17 (56.7)	37 (48.1)	37 (40.2)	46 (48.9)	137 (46.8)		
Indian	8 (26.7)	19 (24.7)	23 (25)	21 (23.3)	71 (24.2)		
Years of education:							
≤ 6 years	9 (34.6)	39 (54.9)	45 (57)	55 (62.5)	148 (56.1)	6.39	0.094
≥ 6 years	17 (65.4)	32 (45.1)	34 (43)	33 (37.5)	116 (43.9)		
Marital status:							
Unmarried	7 (29.2)	13 (22)	18 (25.4)	28 (35)	66 (28.2)	3.23	0.358
Married	17 (7.3)	46 (78)	53 (74.6)	52 (65)	168 (71.8)		
Employment							
Yes	18 (78.3)	40 (80.0)	47 (77.0)	52 (75.4)	157 (77.3)	0.369	0.946
No	5 (21.7)	10 (20.0)	14 (23.0)	17 (24.6)	46 (22.7)		
Diabetes mellitus							
Yes	10 (33.3)	29 (37.2)	46 (50)	41 (43.6)	126 (42.9)	4.077	0.253
No	20 (66.7)	49 (62.8)	46 (50)	53 (56.4)	168 (57.1)		
Hypertension							
Yes	17 (56.7)	47 (60.3)	68 (73.9)	64 (68.1)	196 (66.7)	5.051	0.168
No	13 (43.3)	31(39.7)	24 (26.1)	30 (31.9)	98 (33.3)		
Hypercholesterolemia							
Yes	1 (3.3)	3 (2.8)	1 (1.1)	2 (2.1)	7 (2.4)	1.53	0.676
No	29 (96.7)	75 (96.2)	91 (98.9)	92 (97.9)	287 (97.6)		
Stroke							
Yes	1 (3.3)	3 (3.8)	15 (16.3)	13 (13.8)	32 (10.9)	9.374	0.023*
No	29 (96.7)	75 (96.2)	77 (83.7)	81 (86.2)	262 (89.1)		
Heart disease							
Yes	0 (0.0)	1 (1.3)	1 (1.1)	4 (4.3)	6 (2)	3.574	0.311
No	30 (100)	77 (98.7)	91 (98.9)	90 (95.7)	288 (98)		

Note: Data were expressed as n (%) or mean ± SD; Significant difference between risk of MCI and de¬mentia was determined by One-way ANOVA test or Chi-square test ($\chi 2$) at 0.05 level of significance; *p<0.05

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences (SPSS software Version 23.0, SPSS Inc., Chicago, IL, USA) and the level of significant was set at p value less than 0.05. Chi-square test was used to determine the association between socio-demographic risk factors among patients with NCDs while One-way ANOVA test was used to determine the means difference in terms of age of the patients with NCDs. Simple descriptive statistic and one-way ANOVA were employed in analysing the MMSE test scores among various subtypes of NCD patients.

RESULTS

As shown in Figure 1, the distribution of the patients based on the NCDs showed that mixed dementia was the highest type of NCD (Figure 1). This was closely followed by VaD (31.2%), and AD (26.2%). MCI patients made up 10.1% of the patient population. We also identified 2 patients with EOAD and one patient with LPA, respectively. There were no patients diagnosed with FTD during our study period.

To compare the mean MMSE scores among patients with NCDs, One-way ANOVA test was used and revealed a statistical significance [F (3, 263) = 17.28, p < 0.001] mean difference between the scores in the MCI and the dementia groups. Moreover, the results from the post hoc Dunnett's C test revealed that there is a significant means difference (p < 0.05) between MMSE scores of patients with MCI and those with AD, VaD and mixed dementia. MCI patients had the highest MMSE scores (mean 24.88±4.84), followed by VaD (mean 18.28±6.49), mixed dementia (mean 14.98±7.28), and the lowest score was among the AD (mean 14.81±7.26) as shown in Figure 2.

To determine the association between the sociodemographic and CVD risk factors and NCDs, Chi-square and One-way ANOVA tests were performed. The results indicate that only a history of stroke was significantly associated with NCDs (p=0.023) (Table I). All other factors did not significantly associate with NCDs.

DISCUSSION

We have identified that the frequency of mixed dementia and VaD exceeded that of AD cases and that of EOAD, whereas LPA type of dementia presented with the least frequency in HKL. Hence, it is evident from our study that the

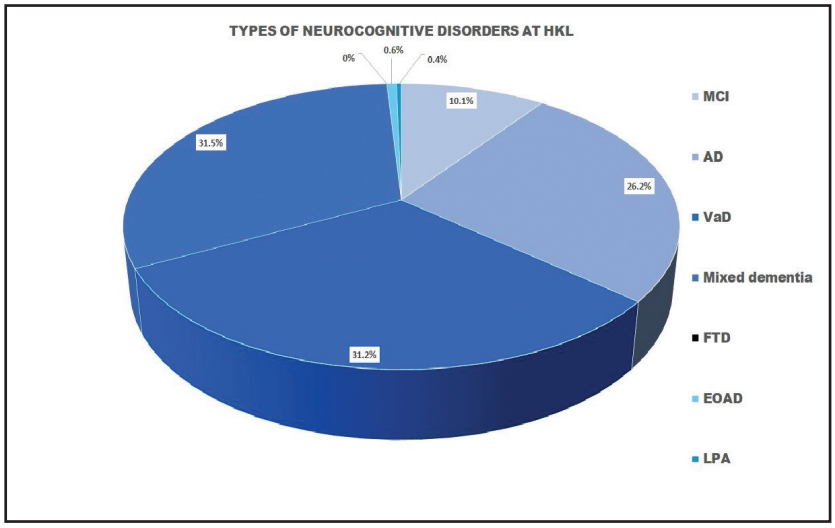

Fig. 1: Distribution of the patients with Neurocognitive disorders attending the memory clinic in Hospital Kuala Lumpur, Malaysia. AD=Alzheimer's disease, EOAD= Early-onset Alzheimer's disease, LPA = Logopenic Progressive Aphasia type of AD, MCI = Mild cognitive impairment, NCD= neurocognitive disorder, VaD= Vascular dementia

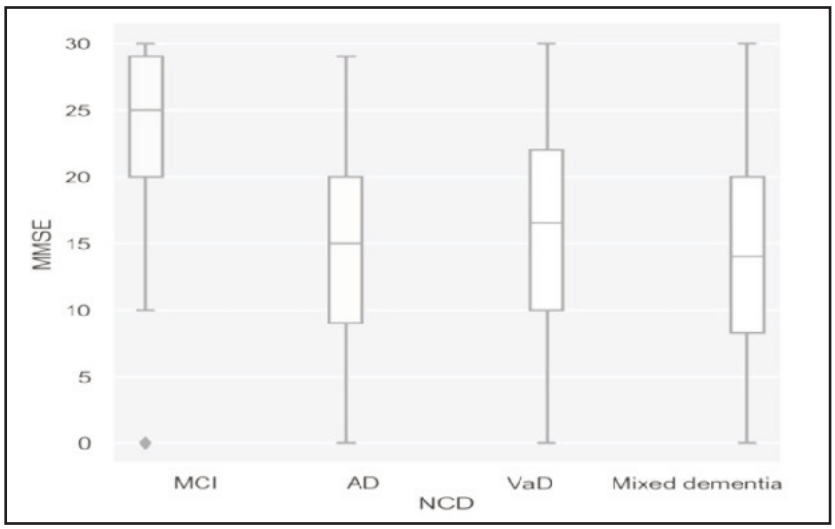

Fig. 2: Mean difference between the Mini Mental State Examination test scores for the various neurocognitive disorders subtypes of the patients attending the memory clinic in Hospital Kuala Lumpur, Malaysia. (MCI=Mild cognitive impairment, AD=Alzheimer's disease, VaD=Vascular dementia).

prevalence of VaD and mixed dementia, i.e., the NCDs with a vascular pathology, are more common than the primary degenerative dementia or AD among the urban Malaysian hospital-based population. Unlike other studies in the Western countries that indicated AD was the more prevalent type of dementia in their population,[21,22,24] our results showed that VaD and mixed dementia are more common among Malaysians living in Kuala Lumpur. This may be due to the comorbidity of hypertension as a major risk factor for CVD and the inherent excess dietary salt intake that is prevalent in many Asian populations, specifically in Malaysia.[25,26]

The MMSE scores of patients with MCI differed significantly ($p < 0.001$) from those with dementia, whereby MCI patients had overall higher scores compared to patients with dementia. This result agrees with previously published studies proving the usefulness of MMSE test in classifying healthy control from patients with MCI and dementia.[27,28] The MMSE test is normally administered to patients as the first line screening tool to determine the level of cognitive impairment in patients. Ordinarily, patients with less severe cognitive impairment tend to have higher scores in this neurocognitive test and conversely those at moderate and advanced stage of disease would normally have lower scores. Nevertheless, the interpretation of the test scores also depends on the age and level of education of the patients.[29] Therefore, our result agrees with previous evidence indicating that MMSE test scores, either taken alone or in combination with other tools for testing cognitive impairment, can help clinicians make prompt decisions for the early referral or therapeutic intervention of NCDs.[28,29]

Our study also revealed that lower levels of education was positively associated with dementia but failed to achieve statistical significance. This may be due to better educated individuals were more likely to seek hospital treatment and thus our patient population was skewed towards urban families with better knowledge and resourcefulness to seek treatment for their afflicted family members. Previously, population-based research supported the understanding that lower level of education correlated with dementia and MCI.[17,30] It is hypothesised that a lower levels of education, or no formal education, tends to be correlated with dementia due to less involvement in complex brain activity, which affects one's cognitive reserve and exposes one to early brain cells pathological insult.[31] However, the association between the level of education and dementia was said to vary between developed and developing countries, whereby low level of education in dementia is more pronounced in the latter countries.[32]

Moreover, a low level of education (not statistically significant in our study) and a history of stroke (statistically significant in our study) were associated with dementia in our population. These results are comparable with a previous study conducted among the urban population in Beijing China, whereby the elderly people with a lower level of education, having limited physical activity and a history of stroke were noted to have a higher risk for developing dementia.[33] Furthermore, similar to what has been observed in our study among the urban Malaysian population, a study in China also revealed that multi-infarct dementia or VaD was relatively more common than AD with a ratio of 3:2.[33]

Low average educational attainment and high CVD risk profile have been postulated to be the cause of VaD being more prevalent in developing countries.34 Nevertheless, an excellent explanation for educational level affecting the development of dementia can be derived by the Lifespan Developmental Model proposed by Sharp and Gatz, 2011, whereby educational factor is deemed as a surrogate indicator of cognitive development in a two-stage approach, i.e., (i) pre-education factors, e.g., parental socioeconomic status (SES), genetics, and socio-emotional influences and (ii) post-education factors, e.g., adult SES (particularly in developed regions), which is associated with occupational and environmental exposures, including the type of food intake, exercise and lifestyle habits.[32] Thus, this model indicates that the level of education does not directly affect the risk for developing dementia directly, but acts as a proxy through its influence on a multitude of factors across the lifespan of the patients.[32]

Hypertension being one of the modifiable risk factors in the spectrum of CVD, was noted to significantly predicted the development of VaD in our study population. This finding is corroborated by the results from a review conducted by Kalaria et al., 2018 whereby hypertension, diabetes mellitus, and obesity were implicated in the increased risk of developing dementia.[35] Additionally, a study among patients having VaD in India reported that stroke, hypertension, and diabetes mellitus, acting by the mechanism of causing small vessel disease, were important risk factors that gave rise to predominantly a subcortical type of VaD.[36]

The implication of this study is on improving the healthcare services by educating the public regarding lifestyle modifications and optimising the control of hypertension and diabetes mellitus, which are modifiable risk factors of CVD.

LIMITATIONS

The MMSE was used in this study as a screening tool to identify dementia and MCI among the patient population. However, other studies have suggested that the MoCA is a better screening tool for MCI.[37-39] Thus, future prospective studies may consider MoCA for evaluating their subjects. Additionally, our study has a relatively small sample size. Thus, future multicentre studies may reveal more significant modifiable risk factors for dementia. Furthermore, comparison with age and gender-matched cognitively healthy controls will allow more sophisticated statistical evaluation of the predictors of dementia in this population. Another limitation is that the diagnosis of the dementia subtypes was based on the expertise of the clinicians and not by the gold standard such as a biopsy. Alternatively, diagnostic imaging can play a role in the management of dementias, whereby the structural and functional information can be availed to exclude potential secondary causes and offer additional information to differentiate the dementia subtypes, especially in atypical cases.[40] Nevertheless, our clinicians followed the criteria developed by the ADDTC and NINDS-AIREN. Understanding the mechanisms that lead to dementia is crucial in the planning of interventional strategies, hence futures studies will need to evaluate the complete risk factors profile that includes physical examinations of neuropsychological deficits, food intake, physical activity, biochemical indices, genetic profiling, together with a complete panel of comorbidities and medications.

CONCLUSION

Vascular dementia and mixed dementia are more common than Alzheimer's disease in our urban HKL population. Modifiable risk factors for cardiovascular disease are significantly associated with dementia. Hence, lifestyle modifications, optimised blood pressure control, and monitoring other CVD risk factors are recommended to delay the development of dementia.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Alan Pok Wen Kin and Dr Elizabeth Chong Gar Mit of the Memory Clinic, Hospital Kuala Lumpur for assisting in the data collection. The authors also thank Mr. Umar Ahmad from the Medical Genetics Unit, Department of Anatomy, Faculty of Basic Medical Sciences, Bauchi State University, Gadau, Nigeria for his assistance in the statistics and data analysis.

FUNDING

We would like to acknowledge the Research Management Centre (RMC) Universiti Putra Malaysia and the Ministry of Education Malaysia in providing the financial support for

this research. This research was financially supported by the Ministry of Education Malaysia research grant, under the Fundamental Research Grant Scheme (FRGS) with the reference code number: FRGS/1/2019/SKK03/UPM/02/4 and project code: 04-01-19-2119FR and project number 5540244.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest to disclose.

REFERENCES

1. American Psychiatric Association A. Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association, editors. Arlington, VA: American Psychiatric Association; 2013.
2. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med 2014; 275(3): 214-28.
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 270-9.
4. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 263-9.
5. Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology 2019; 18(1): 88-106.
6. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. Arteriosclerosis, Thrombosis, and Vascular Biology 2019; 39(8): 1542-9.
7. Suppiah S, Didier M-A, Vinjamuri S. The Who, When, Why, and How of PET Amyloid Imaging in Management of Alzheimer's Disease—Review of Literature and Interesting Images. Diagnostics 2019; 9(2): 65.
8. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996; 47(5): 1113-24.
9. Leyton CE, Hodges JR. Towards a clearer definition of logopenic progressive aphasia. Curr Neurol Neurosci Rep 2013;13(11):396.
10. Vijayan M, Reddy PH. Stroke, Vascular Dementia, and Alzheimer's Disease: Molecular Links. J Alzheimers Dis 2016; 54(2): 427-43.
11. Culebras A, Anwar S. Sleep Apnea Is a Risk Factor for Stroke and Vascular Dementia. Current Neurology and Neuroscience Reports 2018; 18(8): 53.
12. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med 2014; 12: 130.
13. Goldberg I, Auriel E, Russell D, Korczyn AD. Microembolism, silent brain infarcts and dementia. J Neurol Sci 2012; 322(1-2): 250-3.
14. Suppiah S, Ching SM, Nordin AJ, Vinjamuri S. The role of PET/CT amyloid Imaging compared with Tc99m-HMPAO SPECT imaging for diagnosing Alzheimer's disease. Med J Malaysia 2018; 73(3): 141-6.
15. Cai Z, Wang C, He W, Tu H, Tang Z, Xiao M, et al. Cerebral small vessel disease and Alzheimer's disease. Clin Interv Aging 2015; 10: 1695-704.
16. Ye S, Dong S, Tan J, Chen L, Yang H, Chen Y, et al. White-Matter Hyperintensities and Lacunar Infarcts Are Associated with an Increased Risk of Alzheimer's Disease in the Elderly in China. J Clin Neurol 2019; 15(1): 46-53.
17. Hamid TA, Krishnaswamy S, Abdullah SS, Momtaz YA. Sociodemographic risk factors and correlates of dementia in older Malaysians. Dement Geriatr Cogn Disord 2010; 30(6): 533-9.
18. Zhang Y, Hedo R, Rivera A, Rull R, Richardson S, Tu XM. Post hoc power analysis: is it an informative and meaningful analysis? General Psychiatry 2019; 32(4): e100069.
19. Song D, Yu DS, Li PW, He G, Sun Q. Correlates of Health-Related Quality of Life Among Chinese Older Adults with Mild Cognitive Impairment. Clin Interv Aging 2019; 14: 2205-12.
20. Arevalo-Rodriguez I, Smailagic N, Roqué IFM, Ciapponi A, Sanchez-Perez E, Giannakou A, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2015; 2015(3): Cd010783.
21. Mantzavinos V, Alexiou A. Biomarkers for Alzheimer's Disease Diagnosis. Curr Alzheimer Res 2017; 14(11): 1149-54.
22. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res 2018; 7.
23. Sengupta P, Ganguly J, Pal S, Ghosal M. Pattern of cognitive deficits in vascular dementia. Indian J Med Res 2019; 149(4): 503-7.
24. Garre-Olmo J, Garcia-Ptacek S, Calvó-Perxas L, Turró-Garriga O, López-Pousa S, Eriksdotter M. Diagnosis of Dementia in the Specialist Setting: A Comparison Between the Swedish Dementia Registry (SveDem) and the Registry of Dementias of Girona (ReDeGi). J Alzheimers Dis 2016; 53(4): 1341-51.
25. Eshkoor SA, Hamid TA, Nudin SS, Mun CY. Importance of hypertension and social isolation in causing sleep disruption in dementia. Am J Alzheimers Dis Other Demen 2014; 29(1): 61-6.
26. Trieu K, Webster J. Report on reducing salt intake in Malaysia: An interim evaluation of what works. Malaysia: Ministry of Health Malaysia and WHO; 2019.
27. Benson AD, Slavin MJ, Tran TT, Petrella JR, Doraiswamy PM. Screening for Early Alzheimer's Disease: Is There Still a Role for the Mini-Mental State Examination? Prim Care Companion J Clin Psychiatry 2005; 7(2): 62-9.
28. Kim JW, Lee DY, Seo EH, Sohn BK, Park SY, Choo IH, et al. Improvement of dementia screening accuracy of mini-mental state examination by education-adjustment and supplementation of frontal assessment battery performance. J Korean Med Sci 2013; 28(10): 1522-8.
29. Pradier C, Sakarovitch C, Le Duff F, Layese R, Metelkina A, Anthony S, et al. The Mini Mental State Examination at the Time of Alzheimer's Disease and Related Disorders Diagnosis, According to Age, Education, Gender and Place of Residence: A Cross-Sectional Study among the French National Alzheimer Database. PLOS ONE 2014; 9(8): e103630.
30. Palmer K, Kabir ZN, Ahmed T, Hamadani JD, Cornelius C, Kivipelto M, et al. Prevalence of dementia and factors associated with dementia in rural Bangladesh: data from a cross-sectional, population-based study. International Psychogeriatrics 2014; 26(11): 1905-15.
31. Zhang MY, Katzman R, Salmon D, Jin H, Cai GJ, Wang ZY, et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. Ann Neurol 1990; 27(4): 428-37.
32. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord 2011; 25(4): 289-304.
33. Li G, Shen YC, Chen CH, Zhau YW, Li SR, Lu M. A three-year follow-up study of age-related dementia in an urban area of Beijing. Acta Psychiatr Scand 1991; 83(2): 99-104.
34. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. Biomed Res Int 2014; 2014: 908915.
35. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology 2018; 134(Pt B): 226-39.

36. Alladi S, Kaul S, Meena AK, Somayajula S, Umadevi M, Reddy JM. Pattern of Vascular Dementia in India: Study of Clinical Features, Imaging, and Vascular Mechanisms From a Hospital Dementia Registry. Journal of Stroke and Cerebrovascular Diseases 2006; 15(2): 49-56.
37. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53(4): 695-9.
38. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology 2009; 73(21): 1738-45.
39. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. BMC Geriatr 2015; 15: 107.
40. Siti Aishah Abdul A, Loh Jia L, Fathinul Fikri Ahmad S, Abdul Jalil N, Normala I, Arlina N, et al. Voxel-wise analysis of 18F-fluorodeoxyglucose metabolism in correlation with variations in the presentation of Alzheimer's disease: a clinician's guide. Medical Journal of Indonesia 2019; 28(3).