Original Article

Cognitive Deficit in Alzheimer's Patients with Normal Scores on the Mini-Mental State Examination

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Objective: To study the sensitivity and specificity of the Abbreviated MMSE in Alzheimer patients with normal MMSE scores.

Materials and Methods: A retrospective analytic study of 89 normal subjects and Alzheimer's patients with normal MMSE scores, aged 60 years or older, between 2015 and 2020, from the Memory Clinic, Ramathobodi Hospital. Pearson chi-square, Fisher's exact test, and Mann-Whitney U test were used to compare demographic data and MMSE score of each item between the normal subjects and the Alzheimer Disease (AD) subjects. The ROC curve was analyzed to find the proper cut-off points in the three models of the Abbreviated form ($p<0.05$).

Results: AD subjects showed different scores from the normal subjects with statistical significance in four subtests of full MMSE-Thai-2002, namely, date, attention/calculation, recall, and repetition ($p<0.001$, 0.001, 0.018, and 0.023, respectively). The Model 2 of the Abbreviated MMSE consisting of recall, date, and attention/calculation, was the most proper test to be used in the clinical setting. [AUC (95% CI): 0.905 (0.831 to 0.979)]. The proper cut-off point was seven out of nine with a sensitivity of 89.4%, specificity of 78.3%, of PPV 92.2%, and NPV of 72.2%.

Conclusion: The models of short MMSE was an option in case of normal scores in the full version of MMSE with recall impairment. There should be further studies in larger number of Alzheimer's patients, along with classification of daily life skills and other groups of brain diseases' patients.

Keywords: Alzheimer's disease; Abbreviated-MMSE; Normal MMSE scores

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The Mini-Mental State Examination (MMSE) developed by Folstein et al in 1975[(1)] is an Alzheimer's disease screening tool that has been popular over a period of time and translated in different languages worldwide, with the full score of 30 points. It consists of 11 subtests as orientation to time with 5 points, orientation to place with 5 points, registration with 3 points, attention/calculation with 5 points, delayed recall with 3 points, language skills with 8 points, and visual construction with 1 point. In Thailand, it was translated and prepared by the MMSE-Thai 2002 Committee and Institute of Geriatric Medicine, Department of Medical Services, Ministry of Public Health (1999)[(2)] and has been used under the name "MMSE-Thai 2002". The essence and the meanings of all 11 subtests in the original version remained in the Thai version, with the objectives to report research results at the international level and to screen patients with Alzheimer's disease in accordance with the standard in Thailand.

The original version of MMSE by Folstein with the full score of 30 points and the cut-off point at 23 points has sensitivity of 81% and specificity of 82%[(1)]. In Thailand, there are three levels of cut-off points for no cognitive impairment, classified by educational levels as the uneducated elderly with the full score of 23 points, the cut-off point at 14 points, sensitivity of 35.4%, and specificity of 56.3%, the elderly with primary education with the full score of 30 points, the cut-off point at 17 points, sensitivity of 56.6%, and specificity of 93.8%, and the elderly at higher education than the primary level with the full score of 30 points, the cut-off point at 23 points, sensitivity of 92.0%, and specificity of 92.6%[(2)]. MMSE was widely used in the previous studies as an Alzheimer's

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disease screening tool[3,4] because it was fast, which is around 10 to 15 minutes. Therefore, it was convenient to use, and no expertise was required. Its sensitivity and specificity are moderately efficient, with inclusive contents of all cognitive abilities to be measured[5]. It was found that MMSE was used by physicians to assess the elderly at the primary level up to 51%[6]. Most studies focused on the totals and used MMSE as a basic tool rather than consideration in subtests, causing interpretation errors[7]. That was because each type of Alzheimer's disease contained specific memory impairment in each aspect of cognition. However, it was found that patients with memory impairment, cognitive impairment, and Alzheimer's disease whose scores were equal to or over the normal criteria were not actually diagnosed with Alzheimer's disease[8].

Despite MMSE as a tool that uses the totals for Alzheimer's disease screening, data obtained from each subtest could be useful to the Alzheimer Disease (AD) group from the normal group[6]. Therefore, the present study focused on patients with memory and cognitive impairment of AD whose totals of all subtests in MMSE-Thai 2002 were equal to or over the normal criteria. Each subtest was analyzed and compared with the normal group to select only the subtests with negative and positive sensitivity, specificity, and predictive values for screening patients with Alzheimer's disease. Then, these were organized into groups as a short screening form to be used as a guideline on clinical use of this tool for highest efficiency. The present study was implemented in patients receiving cognitive assessment at the Memory Clinic of Ramathibodi Hospital.

Objective

To study sensitivity and specificity of the short screening form obtained by MMSE score analysis in the AD group whose MMSE scores were equal to or over the normal criteria.

Materials and Methods

Samples

The present study was a retrospective analytic study using the data of 89 patients from the clinical psychological test report recorded at the Memory Clinic, Psychiatric Outpatient Unit, Ramathibodi Hospital, between January 2015 and January 2020.

Inclusion criteria

The participants aged 60 years or older at the test date at the Memory Clinic, Ramathibodi Hospital, between January 2015 and January 2020, diagnosed with memory and cognitive impairment of Alzheimer's disease in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[9], whose MMSE scores was 23 points or more, which is the cut-off for education higher than primary level, and were confirmed from the memory clinic conference by psychiatrists and neuro-radiologists, along with the control group where the participants were diagnosed as normal.

Human subjects protections

The implementation of the present study was approved by the Institutional Review Board (Ethics Committee), Faculty of Medicine Ramathibodi Hospital, Mahidol University, no. MURA2019/811 on 26 August 2019.

Instrument

MMSE-Thai 2002, with the request for permission and copyright payment to PAR, Inc. to use MMSE.

Data analysis

PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses to display number, percentage, median, and interquartile range (IQR). Pearson chi-square and Mann-Whitney test were used to compare demographic data between the normal group and the AD group.

For the analyses of differences among MMSE scores in each subtest in the AD group and the control group, Mann-Whiney U test and Fisher's exact test were used.

ROC curve and Youden index analysis were used to find proper cut-off points in the different subtests, compared with the normal group. The statistical significance of sensitivity and specificity of the subtests was set at 0.05.

Results

The 89 participants were divided into two groups with 23 diagnosed as normal and 66 patients with AD whose MMSE scores were equal to or over the normal criteria.

According to Table 1, the percentages of male and female in each group were similar with 26.1% of male and 73.9% of female in the normal group, and 28.8% of male and 71.2% of female in the AD group.

Age, years of education, and the total of MMSE of the normal group were significantly different from

Table 1. Demographic data between the normal group and the AD group whose MMSE scores were equal to or over the normal criteria

	Normal (n=23)	The AD group whose MMSE scores were equal to or over the normal criteria (n=66)	p-value
Sex; n (%)			0.80
Male	6 (26.1)	19 (28.8)	
Female	17 (73.9)	47 (71.2)	
Age (years); median [IQR]	66 [9.0]	73 [7.0]	<0.001*
Years of education (years); median [IQR]	16 [2.0]	16 [4.0]	0.026*
MMSE (score); median [IQR]	29 [3.0]	25 [2.0]	<0.001*

AD=Alzheimer's disease; MMSE=Mini-Mental State Examination; IQR=interquartile range

* Statistical significance, p<0.05

the AD group. To clarify, median (IQR) of age in the normal group and the AD group were 66.0 (9.0) and 73.0 (7.0) years, (p<0.001), and years of education were 16.0 (2.0) and 16.0 (4.0) years (p=0.026), respectively. The educational levels both groups were higher than primary level. The totals of MMSE were 29.0 (3.0) and 25.0 (2.0) points, respectively (p<0.001).

The differences of age, years of education, and MMSE scores should not affect data analysis in the present research as 1) MMSE Thai was implemented in the population aged over 60 years, with no age range classification, and 2) MMSE Thai used the basic educational level rather than years of education. The educational levels of both groups were higher than primary level.

The comparison of MMSE scores between the normal group and the AD group is displayed in Table 2.

According to Table 2, when considering MMSE scores in each of the 11 subtests between the normal group and the AD group, it was found that the ones with significant differences of scores were date, attention/calculation, recall, and repetition. When considering p-value of each subtest from the highest to the lowest, there would be recall, date, attention/calculation, and repetition. It should be noted that in the AD group, no participant had the full score of 3 points from recall.

In the Orientation to place, registration, naming, verbal command, written command, writing, and visuoconstruction, the difference between the normal group and the AD group was insignificant.

According to Table 3, when comparing the totals of MMSE-Thai 2002 (full version) between the AD group and the normal group, significant difference was found. Median (IQR) were 25.0 (2.0) and 29.0 (3.0) (p<0.001), respectively.

The researchers developed the significantly different subtests into the three models of a short MMSE as follows:

Model 1: This model consisted of the totals from date, recall, attention/calculation, and repetition. The full score was 10 points. Median (IQR) in the AD group and the normal group were 6.0 (1.3) and 9.0 (2.0) (p<0.001), respectively.

Model 2: This model consisted of the totals from date, recall, attention/calculation. The full score was 9 points. Median (IQR) in the AD group and the normal group were 6.0 (2.0), 8.0 (1.0) (p<0.001), respectively.

Model 3: This model consisted of the totals from recall and attention/calculation. The full score was 8 points. Median (IQR) in the AD group and the normal group were 5.5 (1.0) and 7.0 (1.0) (p<0.001), respectively.

AUCs (95%CI) of MMSE-Thai 2002, Model 1, Model 2, and Model 3 were 0.920 (0.844 to 0.979), 0.895 (0.782 to 0.961), 0.905 (0.831 to 0.979), and 0.871 (0.782 to 0.961), respectively (Figure 1).

Sensitivity and specificity of MMSE and the 3 models of the short MMSE

Table 4 displays the scores of MMSE Thai, both full and short version, in the three models at the different cut-off points for the calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for screening and separating patients with AD whose MMSE scores were equal to or over the normal criteria from the normal group.

When considering sensitivity, specificity, PPV, and NPV at the different cut-off points of MMSE Thai, both full and short version, in the three models, it was found that the proper cut-off point of MMSE Thai was 26 points, with sensitivity of 87.9%, specificity of 87.0%, PPV of 95.1%, and NPV of 71.4%.

Table 2. The comparison of participants obtained from each subtest in MMSE between the normal group and the AD group whose scores were equal to or over the normal criteria

MMSE subtest	The normal group (n=23)	The AD group whose scores were equal to or over the normal criteria (n=66)	p-value
1. Orientation to time; n (%)			
1.1 Date	23 (100)	44 (66.7)	0.001*[a]
1.2 Day	22 (95.7)	58 (87.9)	0.44
1.3 Month	23 (100.0)	57 (86.4)	0.11
1.4 Year	22 (95.7)	55 (83.3)	0.17
1.5 Season	21 (91.3)	59 (89.4)	1.00
2. Orientation to place; n (%)			
2.1 Place	23 (100)	65 (98.5)	1.00
2.2 Floor	23 (100)	56 (84.8)	0.06
2.3 Subdistrict	21 (91.3)	54 (81.8)	0.51
2.4 Province	23 (100)	66 (100)	N/A
2.5 Region	23 (100)	65 (98.5)	1.00
3. Registration; n (%)	23 (100)	66 (100)	N/A
4. Attention/calculation; median [IQR]	5.0 [1.0]	4.0 [2.0]	0.018*[b]
5. Recall; n (%)			<0.001*[a]
0 point	0 (0.0)	5 (7.6)	
1 point	1 (4.3)	18 (27.3)	
2 points	4 (17.4)	43 (65.1)	
3 points	18 (78.3)	0 (0.0)	
6. Naming; n (%)			N/A
2 points	23 (100.0)	66 (100.0)	
7. Repetition; n (%)	15 (65.2)	25 (37.9)	0.023*[a]
8. Verbal command; n (%)			0.17
2 points	3 (13.0)	18 (27.3)	
3 points	20 (87.0)	48 (72.7)	
9. Written command; n (%)	23 (100.0)	64 (97.0)	1.00
10. Writing; n (%)	23 (100.0)	62 (93.9)	0.57
11. Visuoconstruction; n (%)	22 (95.7)	55 (82.4)	0.17

AD=Alzheimer's disease; MMSE=Mini-Mental State Examination; IQR=interquartile range; N/A=not available

[a] p<0.05 by Fisher's exact test, [b] p<0.05 by Mann-Whitney U test

Table 3. The comparison of the totals of MMSE-Thai 2002 and the 3 models of the short MMSE

MMSE	Full score	AD group whose scores were equal to or over the normal criteria; median (IOR)	Normal; median (IOR)	p-value	Area under curve (95% CI)
MMSE-Thai 2002	30	25.0 (2.0)	29.0 (3.0)	<0.001*	0.92 (0.84 to 0.99)
Model 1a	10	6.0 (1.3)	9.0 (2.0)	<0.001*	0.89 (0.78 to 0.96)
Model 2b	9	6.0 (2.0)	8.0 (1.0)	<0.001*	0.91 (0.83 to 0.98)
Model 3C	8	5.5 (1.0)	7.00 (1.0)	<0.001*	0.87 (0.78 to 0.96)

AD=Alzheimer's disease; MMSE=Mini-Mental State Examination; IQR=interquartile range; CI=confidence interval

[a] Consisted of date, recall, attention/calculation, and repetition; [b] Consisted date, recall, and attention/calculation; [c] Consisted recall and attention/calculation

* Statistical significance, p<0.05

The proper cut-off point of Model 1 was 8 points, with sensitivity of 92.4%, specificity of 60.9%, PPV of 87.1%, and NPV of 73.7%. The most proper cut-off point of Model 2 was 7 points, with sensitivity of 89.4%, specificity of 78.3%, PPV of 92.2%, and NPV of 72.0%. And the most proper cut-off point of Model 3 was 6 points, with sensitivity of 81.8%, specificity of 78.3%, PPV of 95.1%, and NPV of 60.0%.

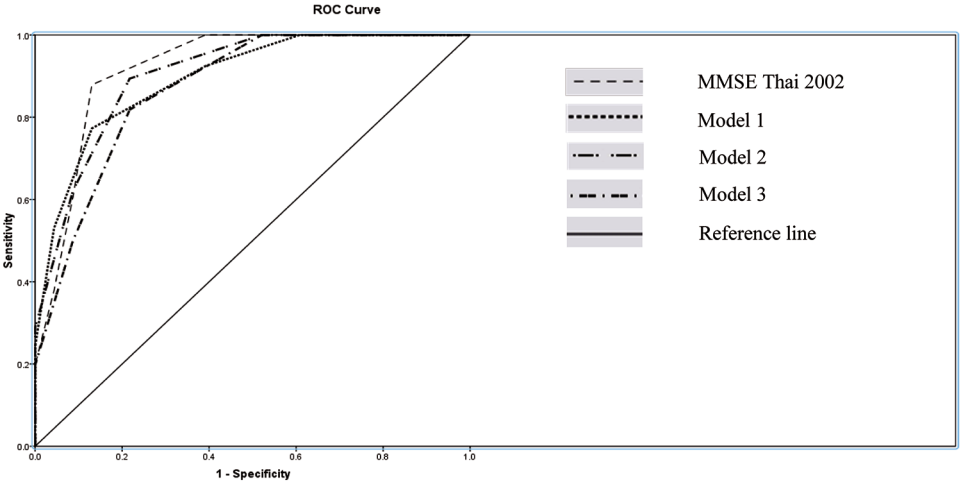

Figure 1. ROC curve of the totals of MMSE-Thai 2002 and the 3 models of the short MMSE.

Table 4. Sensitivity and specificity at the different cut-off points

MMSE	Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MMSE-Thai 2002	27	93.9	73.9	91.2	80.9
	26	87.9	87.0	95.1	71.4
	25	60.6	91.3	95.2	44.7
	24	37.9	95.7	96.2	34.9
	23	19.7	100	100	30.3
Model 1a	9	100	39.1	82.5	100
	8	92.4	60.9	87.1	73.7
	7	77.3	87.0	94.4	57.1
Model 2b	8	100	47.8	84.6	100
	7	89.4	78.3	92.2	72.0
	6	62.1	91.3	95.3	45.7
Model 3C	7	100	47.8	84.6	100
	6	81.8	78.3	91.5	60.0
	5	50.0	91.3	94.3	38.9

MMSE=Mini-Mental State Examination; PPV=positive predictive value; NPV=negative predictive value

[a] Consisted of date, recall, attention/calculation, and repetition; [b] Consisted date, recall, and attention/calculation; [c] Consisted recall and attention/calculation

Discussion

According to the present study, it was found that the subtests in MMSE-Thai version 2002 are efficient predictors to separate patients with Alzheimer's disease with the totals under the normal criteria from the normal group when they used recall, date, and attention/calculation. These subtests were cognitive assessment in terms of recall, orientation to time such as date and attention. These required working memory, episodic memory, and semantic memory conforming to memory impairment found in Alzheimer's disease[10,11]. These symptoms were caused by brain dysfunction in term of cognitive impairment[12]. The early and most prominent sign was memory impairment, starting from loss of new memory and short memory, thus, episodic memory. Moreover, such brain pathology also affected the scores of MMSE in the different subtest such as attention/calculation and orientation to time as the primary indicators of Alzheimer's disease[8,13,14-17]. The results of the present research also conformed to the previous studies, which found that the subtests with highest sensitivity for prognosis of early-stage Alzheimer's disease, such as recall, orientation to time, and attention/calculation. The other subtests were with sensitivity of middle stage and late stage of the disease[18-24].

For recall, which was to instruct patients to repeat three words after hearing and being intervened by other tasks, with the full score of three points, it was found that patients with Alzheimer's disease whose score was two points or 65.1% and patients with Alzheimer's disease whose score was one point or 27.3% had high correlation coefficients ($p<0.001$) when comparing with the normal group. These conformed to the research of Feher et al (1992)[25], who found that if recall was below three points, there would be high sensitivity but rather low specificity. However, if recall was below two points, there would be balance between sensitivity and specificity. That was because recall was for memory assessment after a short time. Episodic memory could separate the group with MMSE scores under the normal criteria from the normal group. A study found that the subtest to separate the severity of Alzheimer's disease was

recall[19], which could significantly separate patients with mild Alzheimer's disease from the normal group ($p<0.0001$). This conformed to the present study, which found that date was with efficient predictive values after recall because the assessment was related to delayed episodic memory that required attention and interest. What was more, it was also found that patients with Alzheimer's disease lost episodic memory more quickly than cognitive domains in other aspects[19,10]. Ashford et al (1989)[15] and Galasko et al (1990)[21] found that recall, day, and date were the best subtests to separate patients with mild Alzheimer's disease from the normal group. Evidence of the study supported that episodic memory deterioration was related to lesions around hippocampus and loss of nerve cells around entorhinal cortex, which connected between hippocampus and neocortex[22].

Another subtest from the present research with high correlation coefficient was attention/calculation. The present research only used 100–7 as to let patients calculate in their mind by subtracting 100 with 7 each time. It can be said that this test required memory and rules to remember the instruction of how to proceed in sequence, the remains after subtraction, and what numbers that were subtracted by 100. Focus/attention was also indispensable because it was calculation in mind. This subtest truly required fluid intelligence. It was to use the learned ability for problem-solving, along with working memory. Proceeding 100–7 for five times was sequential subtraction, with perception, planning, and focus/attention required for successful thinking[26]. Likewise, Carlamagno et al (1999)[26] studied and found the two factors behind the symptom of dyscalculia in patients with Alzheimer's disease, which was the deterioration of assessment in numbers and focus/attention for accurate calculation. Feher et al (1992)[25] found that attention/calculation generated proper sensitivity and specificity for the neuropsychological test, similarly to recall.

When the subtests with the efficient predictive values were organized into groups, and the three models were used for prognosis of Alzheimer's disease, and to compare with MMSE-Thai version 2002 (full version), it was found that the full version of MMSE was MMSE-Thai version 2002 was the most proper one for prognosis of Alzheimer's disease in patients with Alzheimer's disease whose MMSE scores were equal to or over the normal criteria when comparing with the normal group. When selecting the proper cut-off point by considering AUC close to 1, sensitivity, and specificity, it was found that the best correlation coefficient was on the cut-off point at 26 points out of 30 points. This was considered from ROC (AUC 0.920, sensitivity of 60.6%, specificity of 91.3%, PPV of 95.1%, and NPV of 71.4%), which AUC was regarded as excellent, with moderate sensitivity, and high specificity as well as PPV and conforming to the international research[13,18,27]. The only difference was that the cut-off point changed from 23 to 26 points. This meant if the same cut-off point at 23 points had been used for screening the selected AD group, ROC would have been poor. Thus, AUC of 0.920, sensitivity of 19.7%, specificity of 100.0%, PPV of 100.0%, and NPV of 30.3% was good. Therefore, Model 2 was selected in the present research, consisting of recall, date, and attention/calculation, which was the subtests with efficient predictive values after the best one. Model 2 had the full score of 9 points and the proper cut-off point at 7 points with AUC of 0.905, sensitivity of 89.4%, specificity of 78.3%, PPV of 92.2%, and NPV of 72.2%. Therefore, it was the most proper model to be used as the short MMSE because of highly positive AUC, specificity, and prediction, along with the properties of the three subtests, as recall, date, and attention/calculation for screening patients with Alzheimer's disease whose MMSE scores in the full version were equal to or over the normal criteria. This conformed to the previous international studies that supported the properties of those subtests for prognosis of Alzheimer's disease[14-16,28].

Limitation

For the strengths of the present study, the samples were evaluated for neuropsychology and diagnosed as patients with cognitive and memory impairment in accordance with Alzheimer's disease criteria. This was confirmed by the memory clinic conference by psychiatrists and neuro-radiologists. For the weaknesses of the present study, there were small number of the samples in the normal group for the comparative study. Binary logistic regression was used for analysis to apply for the comparative study between the normal group and the AD group. Another limitation is it was a retrospective study. Therefore, it was likely that the index test results (MMSE) were available to the assessors/physicians of the reference standard. In addition, the present study did not classify the stage levels of patients with Alzheimer's disease. Therefore, it was regarded as the study on the overall patients with Alzheimer's disease. There should also be further studies by increasing the number of patients in the normal group. Their symptoms/signs should also be classified for further acknowledgement of data

whether or not it conforms to the short MMSE and how it conforms or not conform to it. Further studies on patients with dementia should be implemented, such as patients with vascular dementia.

Conclusion

It has been well known that MMSE is a tool for screening cognition in various aspects. Assessors usually focus on total scores. This might cause false negatives. As a result, patients are not diagnosed properly. However, according to the results of the present research, Model 2 was selected, of which subtests were recall, date, attention/calculation. It was an efficient predictive model and proper to be organized into groups as a short MMSE for assessing patients with Alzheimer's disease whose MMSE scores in the full version were equal to or over the normal criteria, with recall below three points. The subtests in Model 2 can be used for further screening to find the risk of Alzheimer's disease in a certain patient. Therefore, this short MMSE is proper to be used as the next step to help further diagnosis in case the full version of MMSE contains the full scores under the normal criteria so that screening and diagnosis will be more accurate.

What is already known on this topic?

Previous studies developed short MMSE to detected cognitive impaired patients such as psychiatric conditions, Alzheimer disease, Vascular dementia, and medical/neurological conditions and found group of MMSE subtests corresponded well to identify the cases.

What this study adds?

The present study focused on the group of MMSE subtests that differentiated AD patients with normal MMSE scores from normal subjects and the results suggested that Abbreviated MMSE was able to apply to the risk of AD patients with normal MMSE scores. However, there was also found that subtest Recall related to delayed recall memory was the most efficient on cognitive impaired patients, especially for Alzheimer disease.

Conflicts of interest

The authors declare no conflict of interest.

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