Validation of T-MoCA in the screening of mild cognitive impairment in Chinese patients with atrial fibrillation

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Research article

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Abstract

Background: Atrial fibrillation (AF) is associated with high risk of mild cognitive impairment (MCI) and dementia. However, feasible and simple instruments that facilitates regular assessment of cognitive status in AF patients remain underdeveloped.

Methods: Cognitive function of 136 AF patients was first evaluated using T-MoCA. Cognitive function of 101 patients was then assessed through in-person interview by physicians who are blinded to telephone interview results, using both Clinical Dementia Rating (CDR) and Mini-Mental Status Evaluation (MMSE). Using CDR=0.5 as a reference standard, the ability of T-MoCA and MMSE to discriminate cognitive dysfunction, stratified by education level, was tested by receiver-operating curve (ROC) analysis. Net reclassification index was calculated for comparison between the performance of T-MoCA and MMSE.

Results: Thirty-five MCI patients were identified as MCI using the criteria of CDR=0.5. The areas under the ROC curve of T-MoCA were 0.80 (0.71-0.89), 0.83 (0.71-0.95), and 0.85 (0.64-0.92) for all patients, patients with high educational level, and patients with low education level, respectively. The optimal threshold was achieved at 16/17 with a sensitivity of 85.7% and a specificity of 69.7% in overall patients, 15/16 with a sensitivity of 88.2% and a specificity of 64.5% in the low educational level patients, and 16/17 with a sensitivity of 77.8% and a specificity of 87.9% in the high educational level patients. Compared to the criterion MMSE≤27 and MMSE norms for the Chinese community elderly, stratified T-MoCA threshold improves correct classification by 23.7% ($p=0.033$) and 30.3% ($p=0.020$) respectively.

Conclusion: T-MoCA is a feasible and effective method for MCI screening in patients with AF.

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in adults, and its prevalence has been increasing globally over the past decades[1]. AF is associated with high risk of stroke, heart failure, and impaired quality of life. However, cognitive dysfunction and dementia are the most concerning complications in AF patients. The risk of dementia is 2-fold higher in AF patients than that in population without AF[2]. Cognitive function decline accelerates even in AF patients at young age when compared to those without AF[3]. Mild cognitive impairment (MCI) is a preventable and reversible pre-dementia stage. Appropriate interventions can delay or even reverse cognitive impairment. Therefore, regular cognitive status follow-ups for AF patients is important for timely identification of those with cognitive impairment allowing subsequent interventions in clinical practice.

However, only a limited number of validated cognitive scales are available for MCI identification [4]. Montreal Cognitive Assessment (MoCA) scale is the most widely used instrument to screen for MCI. However, the MoCA scale requires an in-person interview, which limits the feasibility of regular follow-ups. Telephone interviewed Montreal Cognitive Assessment (T-MoCA) is a modified version of the MoCA scale. It has been validated as a reasonable screening tool for MCI in post-stroke patients in recent studies[5, 6]. Although with reasonable sensitivity and specificity in screening MCI in stroke patients, it has not yet been validated externally in populations with different comorbidities, nor has it been further validated in patients with different education levels. In the present study, we used the Chinese version of T-MoCA and examined its validity for MCI screening in Chinese AF patients.

Methods

Study design

Telephone cognitive assessment was first administered to AF patients using T-MoCA. Patients were divided into high educational level (≥ 12 years of education) and low educational level (< 12 years of education). Patients who have completed the telephone interview were invited for an in-person cognitive function assessment using Clinical Dementia Rating (CDR) and Mini-Mental Status Evaluation (MMSE). Using CDR = 0.5 as a reference standard for MCI, the sensitivity and specificity of T-MoCA were analyzed in overall population and educational subgroups. The performance of T-MoCA was also compared with the MMSE scale in MCI screening in AF patients.

Study population

Three hundred and four consecutive patients in the waiting list for AF ablation in Beijing Anzhen Hospital, a tertiary medical center in Beijing, China, were invited from January 2019 to July 2019 to participate in a telephone interview by trained physicians using T-MoCA. Among them, 159 refused to participate and 9 did not finish the interview (2 patients had hearing problems, 2 patients did not speak Mandarin, and 5 patients had other reasons); In total, 136 patients completed the T-MoCA interview (Fig. 1). Within this cohort, 28 patients were not in-person interviewed before they received catheter ablation. In order to avoid possible impact of catheter ablation on cognitive impairment[7], no further in-person interview was performed in those patients. Another 7 patients withdrew their consent to participate. In the end, 101 patients participated in an in-person cognitive interview within one month after the telephone interview.

Data collection

Data on history of hypertension, diabetes, coronary heart disease, heart failure, smoking, and alcohol use were collected in all patients during the in-person interview. Results of laboratory tests were extracted from a medical chart by a cardiologist.

Telephone interviewed Montreal Cognitive Assessment (T-MoCA)

T-MoCA is a simplified version of MoCA from which trail making, visual structure and naming are removed. It consists of digit span, attention, calculation, repetition, verbal fluency, abstraction, recall, and orientation, with a maximum score of 22. Since the Chinese version of MoCA has been widely validated and applied in previous reports[8, 9], the items of T-MoCA Chinese version are picked out from the MoCA while the sequence and combination of the items in T-MoCA were kept same with those in MoCA. Instructions for each item were strictly adhered to standardize the process of interview.

Standard cognitive function assessment

Clinical Dementia Rating (CDR) was used as a standard cognitive function assessment. CDR is a widely used semi-structured clinical measure for global cognitive status. It comprises six domains (memory; judgment and problem-solving; orientation; community affairs; home and hobbies; and personal care). The information in CDR are provided by assessing patients directly and by asking those who are familiar with the patient. All CDR raters were required to be certified (https://knightadrc.wustl.edu/CDR/CDR.htm). An online algorithm was used to calculate CDR scores (https://biostat.wustl.edu/~adrc/cdrpgm/index.html). CDR = 0.5 is used in clinical practice for MCI diagnosis in Chinese speaking populations[10, 11]. Therefore, we used CDR = 0.5 as the reference standard for T-MoCA validation.

The Mini-Mental Status Evaluation (MMSE) is a widely used scale for screening cognitive impairment[12]. Although limited by low sensitivity, it is commonly used by clinicians as it is easy to apply [4]. The threshold of MMSE for MCI varies in different studies[13]. A recently published data for the Chinese community elderly population proposed a stratified criterion (27/28 for those with a ≥ 7 years of education, 24/25 for those with an 1–6 years of education, and 19/20 for illiterates)[14]. In the present study, we used this criterion as a comparison to the T-MoCA in MCI screening.

Statistical analysis

Data analysis was conducted using R3.5.1. Normative data were presented as mean [SD] and compared using the t-test, while non-normative data were presented as median [interquartile range] and compared using the Mann-Whitney U test. Categorical data were presented as count (frequency) and compared using the Chi-square test or Fisher's exact test.

The pROC package was used for the receiver operating curve (ROC) analysis. Sensitivities and specificities for different thresholds were calculated in the overall patients and in patients with low educational level and high educational level respectively. The optimal threshold was defined as the score with highest Youden index among all scores with sensitivity > 75% and specificity > 60%. When reasonable sensitivity and specificity cannot satisfy simultaneously, the optimal threshold was simply determined by Youden index. The area under the curve (AUC) of T-MoCA and MMSE was compared using Delong's test. The net reclassification index (NRI) of optimal thresholds of T-MoCA against the optimal threshold of MMSE in the present study and optimal thresholds suggested by the MMSE normative data of the Chinese community elderly population were calculated to assess whether and to what extent T-MoCA outperforms MMSE in screening MCI.

Sample size is estimated by PASS 15.0 prior to the study. Under the null hypothesis of a sensitivity of 0.5, a minimum of 13 cases has 0.8 power to detect a sensitivity of 0.82 in the previous study at a significance level of 0.05. And a minimum of 36 cases account for 0.9 power to detect a sensitivity of 0.75, under the null hypothesis of a sensitivity of 0.5 and a significance level of 0.05. Therefore, assuming the prevalence of MCI in AF population is 30%-40%, a sample size of 100 patients was considered.

Sensitivity analysis was conducted in patients without a history of stroke.

Results

Characteristics of patients with MCI and with normal cognitive function

Among the 101 AF patients receiving both T-MoCA interviews and in-person assessments, 35 patients were identified as MCI by in-person CDR assessment. Patients with and without MCI were not significantly different in age, sex, education level, medical history, smoking and drinking habit, left atrial diameter, left ventricular ejection fraction (LVEF), and CHA_2DS_2-VASc score (Table 1). T-MoCA scores in patients with and without MCI were 15 [13–16] and 17 [16–19], respectively ($p < 0.001$). MMSE scores in patients with and without MCI were 26 [24-27.5] and 28 [27–29], respectively($p < 0.001$). (Fig. 2).

Table 1
Demographics of MCI and cognitively normal participants.

	CDR = 0.5 (n = 35)	CDR = 0 (n = 66)	P value
Male gender	20 (57.1)	40 (60.6)	0.736
Age, years	62.8 [7.5]	61.3 [8.7]	0.388
Senior high school or above	18 (51.4)	35 (53.0)	0.878
Paroxysmal AF	25 (71.4)	49 (59.1)	0.221
Hypertension	25 (71.4)	38 (57.6)	0.171
Heart failure	4 (11.4)	6 (9.1)	0.735
Diabetes	8 (22.9)	17 (25.8)	0.748
CHD	8 (22.9)	11 (16.7)	0.449
Stroke	6(17.1)	4 (6.1)	0.091
Smoking	14 (40.0)	27 (40.9)	0.929
Drinking	7 (20.0)	14 (21.2)	0.886
Left atrial diameter, mm	38.4 [3.9]	39.0 [5.6]	0.529
Ejection fraction, %	60.9 [6.7]	61.9 [4.9]	0.398
CHA_2DS_2-VASc	2 [1–3]	2 [1–4]	0.148

Data are mean [SD], median [interquartile range], or n (%). AF, atrial fibrillation; CHD, coronary heart disease.

Sensitivity and specificity of T-MoCA and MMSE

The area under the curve for T-MoCA was 0.80 (0.71–0.89). Sensitivity and specificity for different thresholds are shown in Appendix Table 1. The optimal threshold of 16/17 in the overall population had a sensitivity of 85.7% and specificity of 69.6%. Stratifying the patients by educational level increased the AUC to 0.83(0.71–0.95) in patients with low educational level and 0.85(0.64–0.92) in patients with high educational level, respectively. The optimal threshold 16/17 had a sensitivity of 77.8% and specificity of 88.6% in the high educational level group, and optimal threshold 15/16 had a sensitivity of 70.6% and specificity of 90.3% in the low educational level group. (Table 2)

Table 2
Optimal thresholds of T-MoCA and corresponding parameters in overall population and educational level subgroups using CDR as reference standard.

	Optimal threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Overall(n = 101)	16/17	85.7	69.7	60.0	90.2
Low educational level(n = 48)	15/16	88.2	64.5	60.0	91.3
High educational level(n = 53)	16/17	77.8	88.6	77.8	88.6

The AUCs of MMSE were 0.75(0.63–0.83), 0.72(0.58–0.85), and 0.80(0.64–0.92) in the overall study population, in patients with high educational level, and in patients with low educational level respectively, not significantly different with that of T-MoCA (Fig. 3). The optimal sensitivity (75.0%) and specificity (59.4%) of MMSE for screening MCI were achieved at a threshold of 27/28 in the overall population. A sensitivity of 64.7% and a specificity of 81.3% were achieved in patients with low educational level at an optimal threshold of 25/26. However, the sensitivity is too low for MMSE to be a screening tool in the high educational level group (Appendix Table 2).

Net reclassification improvement (NRI)

Compared with the optimal threshold of MMSE (≤ 27) in the present study, the stratified T-MoCA threshold (< 16 for the low educational level group and < 17 for the high educational level group) improved correct classification by 23.7% ($p = 0.033$). Stratified (NRI = 0.303, $p = 0.020$) thresholds also significantly improved classification when comparing with MCI criteria from MMSE norms of Chinese community elderly patients[14]. (Table 3)

Table 3
Net reclassification index for T-MoCA by MMSE criteria for MCI.

	Stratified T-MoCA (16/17for high education and 13/14 for low education)		
	NRI	Z	P value
MMSE ≤ 27	0.237	1.84	0.033
Norms of Chinese community elder population*	0.303	2.05	0.020

*An education stratified MCI criteria in MMSE norms of Chinese community elderly population, which is 27/28 for ≥ 7 years of education,24/25 for 1–6 years of education and 19/20 for illiterates

Sensitivity analysis

We further excluded 11 patients with previous stroke or TIA. In this non-stroke AF population, optimal T-MoCA thresholds for MCI remained the same, with an AUC of 0.80(0.70–0.89) in the overall population and 0.82(0.67–0.97), 0.84(0.72–0.96) in the low and high educational group respectively. (Appendix Table 3)

Discussion

Among these consecutively enrolled patients on the AF ablation waiting list, the prevalence of MCI is 35%. This high prevalence underscores the necessity of timely identification of MCI in order to prevent or reverse cognitive deterioration. Our study expanded the validation of T-MoCA, a simple telephone cognition assessment tool, to be used in MCI screening in patients with AF. T-MoCA improved the correct classification by at least 23% compared to MMSE.

MoCA score highly depends on cultural background. The optimal threshold for MCI is 26 in studies using the English version[15], whereas the optimal threshold is much lower in studies using the Chinese and Korean versions[8, 16]. Similarly, in the present study, the optimal threshold of T-MoCA in the overall population was 2 points lower than that in previous studies[5, 6]. We also noticed that the optimal threshold in low education group is 1 point lower than that in the high education group. This highly conforms to the clinical MoCA assessment in which 1 additional score is added to patients with < 12 years of education. And unlike the ceiling effect in MMSE, T-MoCA has reasonable sensitivity and specificity in both low and high education groups. In the sensitivity analysis, parameters of ROC curves for non-stroke AF patients remained almost unchanged, demonstrating that T-MoCA can also be applied in patients with and without a history of stroke.

T-MoCA has several advantages in the cognitive screening of AF patients. Firstly, it only takes about 10 minutes to complete the test, rendering it widely accepted by both patients and physicians. Secondly, T-

MoCA can be easily accessed by those unable to attend an in-person interview. These patients are often elderly, frail, or actively disabled, which are all independent factors associated with cognitive impairment[17, 18], and should therefore be followed-up more closely. Excluding these patients from the clinical study would favor selection bias and underestimate the prevalence of MCI in the population. Thirdly, although there are many other telephone cognitive assessment tools, the majority were developed based on Alzheimer's MCI/dementia population and have a greater emphasis on memory[19]. However, mechanism of AF associated cognitive impairment is more complex. MCI in AF patients are more likely to be cerebrovascular origin[20, 21], with multiple brain lesions, including cerebral small vessel disease and ischemic cerebral lesions[22]. These lesions typically impair attention and executive function[23]. T-MoCA is derived from a post-stroke population that may have a similar pathophysiological background to AF. Moreover, T-MoCA comprises various items that assess various cognitive domains. Delayed recall reflects episodic memory that is typical of Alzheimer's MCI/dementia[24], while items that reflect attention, working memory, processing speed, and language are necessary for vascular MCI/dementia assessment[25]. Moreover, telephone interview is highly cost-effective, and can greatly reduce the loss to follow-up in clinical studies, particularly large ones with long-term follow up.

Despite the stress on comprehensive management for patients with AF in guidelines[26], primary and secondary prevention of MCI is often neglected. Patients with AF have a higher risk of MCI and dementia, which in turn affects the prognosis of AF, generating a vicious circle. Effective anticoagulation has been reported to be associated with alleviation of cognitive impairment in prospective cohorts[27–29]. Catheter ablation, albeit possibly associated with temporary cognitive impairment after the procedure[7], is associated with lower risk of dementia in the long term[30].Physical exercise is reported to be associated with improved cognition trajectories and reduced brain lesions in patients with MCI[31]. In recent years, several cognitive training systems have been developed and are recommended for clinical use to maintain cognitive status or even reverse MCI[32].

There are several limitations to the present study. We did not administer detailed multiple neuropsychological testing for different cognitive domains to patients because some patients with severely symptomatic AF cannot tolerate a more than one-hour mental storm, while CDR, comprises partly of informers inquiry, may be more tolerable for its shorter patient testing. One of the questions during follow-up interviews relates to the memory of scale items after repeated interviews, making it necessary to design equivalents for each item of the scale in the future. It is also hard to accurately assess the level of cooperation by a patient during a telephone interview, which might be addressed by introducing video interview in the future.

Conclusion

Our study showed that T-MoCA is an effective cognitive test that performs better than MMSE for MCI screening in patients with AF. It may be used as a highly feasible tool in clinical practice for timely identification of MCI in AF patients.

Declarations

Ethics statement

The present study was conducted ethically in accordance to the World Medical Association Declaration of Helsinki. Patients signed a written informed consent before the in-person interview and clinical data collection.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Disclosure

Changsheng Ma has received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer-Ingelheim (BI), and Bayer for giving lectures. Jianzeng Dong has received honoraria from Johnson & Johnson for giving lectures. The other authors have no conflict of interest.

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Author Contribution

YW-L, C-J, CH-S and CS-M is responsible for the conception and design of the study. YW-L and JY-L translated T-MoCA into simplified Chinese. XB-L and JR-Z conducted the telephone interview. YW-L and ZY-W conducted the in-person interview. BL-X and WW-Z supervised the process of cognitive assessment and MCI diagnosis. R-B, RB-T, N-L, XY-G, CX-J, SN-L, DY-L, RH-Y, and JZ-D is responsible for AF diagnosis and interpretation of clinical data. YW-L, C-J and Y-B drafted the manuscript, and X-D, CH-S, CS-M critically appraised the manuscript and approved the final version. All authors have the access to all of the data, read the manuscript. and agreed to be accountable for all aspects of the work.

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Figures

Figure 1. Study design and participants enrollment

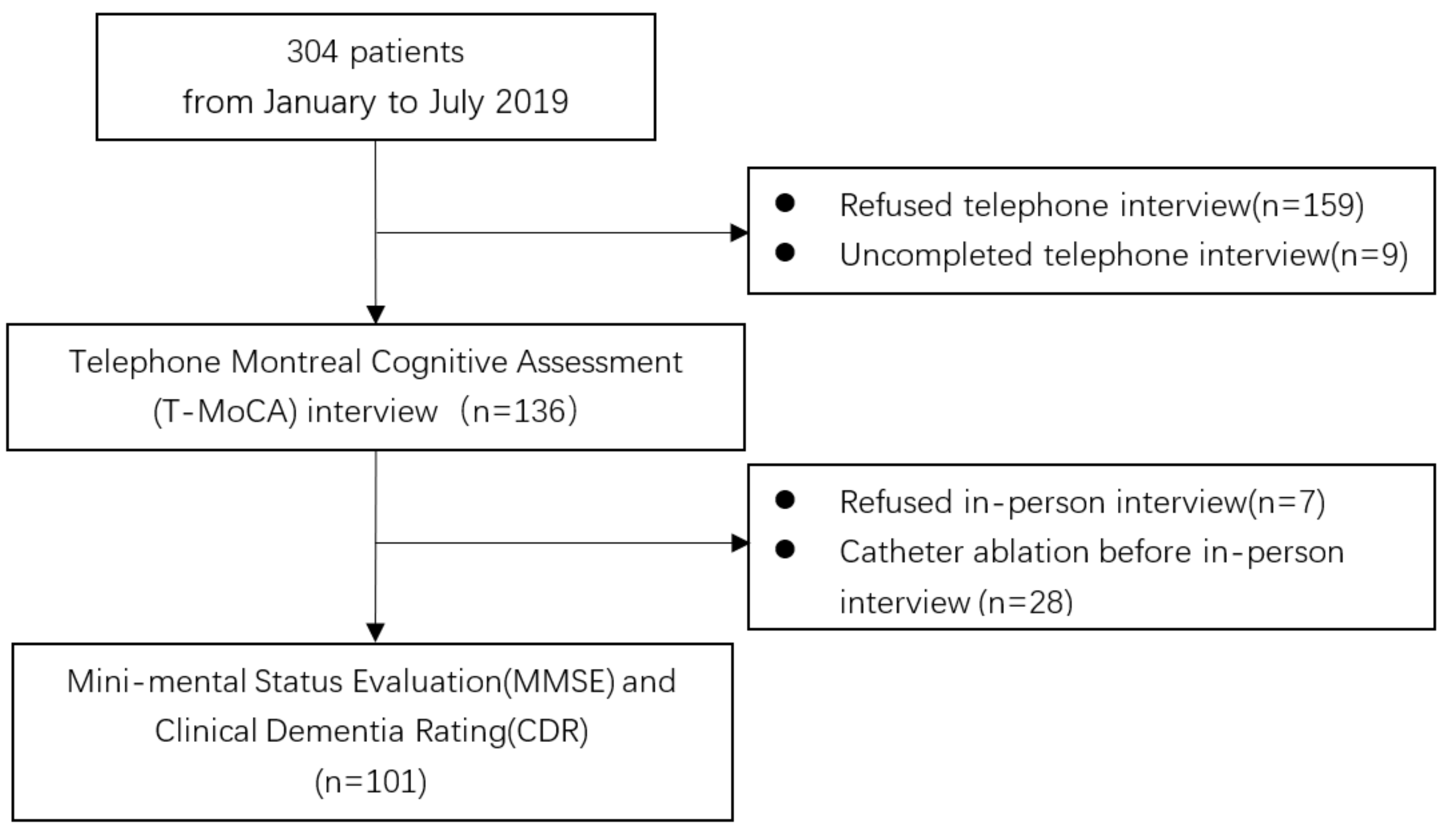

Figure 1

Study design and participants enrollment

	MCI	Cognitively normal	P value
T-MoCA	15.0[13.0-16.0]	17.0 [16.0-19.0]	<0.001
MMSE	26.0[24.00-27.5]	28.0 [27.0-29.0]	<0.001

Data are median[interquartile range]

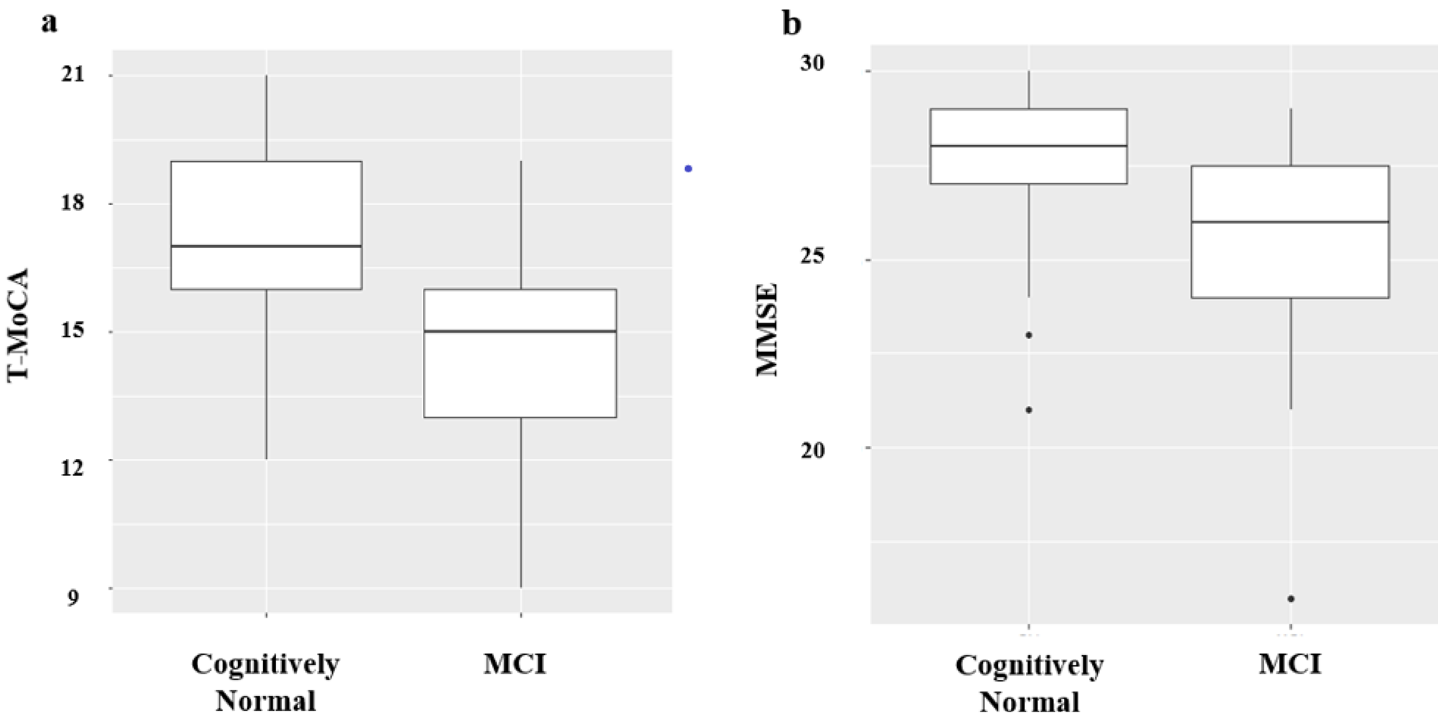

Figure 2

Boxplots showing the distribution of T-MoCA and MMSE scores in MCI and cognitively normal patients.

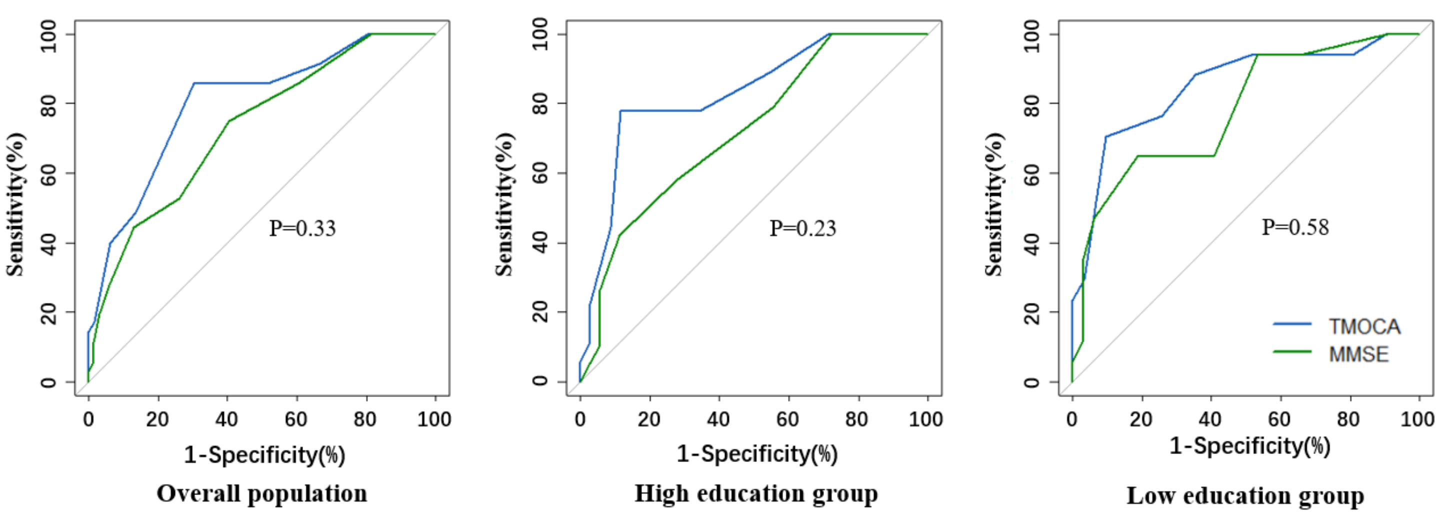

Figure 3

Comparison of ROC curves for T-MoCA and MMSE in overall population and different educational groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfiles.docx