RESEARCH PAPER

Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3—6 months after stroke

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ABSTRACT

Objectives To determine the prognostic value of brief cognitive screening tests administered in the subacute stroke phase (initial 2 weeks) for the detection of significant cognitive impairment 3—6 months after stroke, the authors compared the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE).

Methods Patients with ischaemic stroke and transient ischaemic attack were assessed with both MoCA and MMSE within 14 days after index stroke, followed by a formal neuropsychological evaluation of seven cognitive domains 3—6 months later. Cognitive outcomes were dichotomised as either no—mild (impairment in ≤2 cognitive domains) or moderate—severe (impairment in ≥3 cognitive domains) vascular cognitive impairment. Area under the receiver operating characteristic (ROC) curve analysis was used to compare discriminatory ability.

Results 300 patients were recruited, of whom 239 received formal neuropsychological assessment 3—6 months after the stroke. 60 (25%) patients had moderate—severe VCI. The overall discriminant validity for detection of moderate—severe cognitive impairment was similar for MoCA (ROC 0.85 (95% CI 0.79 to 0.90) and MMSE (ROC 0.83 (95% CI 0.77 to 0.89)), p=0.96). Both MoCA (21/22) and MMSE (25/26) had similar discriminant indices at their optimal cutoff points; sensitivity 0.88 versus 0.88; specificity 0.64 versus 0.67; 70% versus 72% correctly classified. Moreover, both tests had similar discriminant indices in detecting impaired cognitive domains.

Conclusions Brief screening tests during acute admission in patients with mild stroke are predictive of significant vascular cognitive impairment 3—6 months after stroke.

INTRODUCTION

Post-stroke vascular cognitive impairment (VCI) is prevalent[1] (44%) with significant functional consequences.[2 3] The majority (57%) of VCIs are vascular cognitive impairment, no dementia (VCIND).[4] Patients with moderate VCIND are at elevated risk (HR=6.4) for incident dementia.[5] Although formal neuropsychological assessment is a reliable means of evaluating VCI, it is not practical for the assessment of all patients. Therefore, it is necessary to establish a sensitive screening tool for use in subacute stroke phase to identify high-risk groups for intensive reduction of vascular risk factors and improve prognosis.[6]

The widely used Mini-Mental State Examination (MMSE)[7] is reportedly poor in detecting VCI due to a lack of sensitivity to complex cognitive deficits,[8] while the Montreal Cognitive Assessment (MoCA)[9] was found to be more sensitive.[10 11] However, both MoCA and MMSE were recently reported to be equivalent and moderately sensitive (sensitivity: 0.67 vs 0.7, specificity: 0.9 vs 0.97) in detecting VCI at the post-acute stroke phase.[12] This was due to the high frequency of instrumental deficits (ie, language) to which the MMSE is more sensitive, while the MoCA may be more sensitive to impairments in executive function and visuo-motor-speed, particularly in patients with small vessel disease (SVD).[13] Hence, the recommended use of the MoCA over the MMSE in screening for VCI[14] remains to be empirically established.

The predictive ability of either MoCA or MMSE administered in the subacute stroke phase for cognitive impairment 3—6 months after stroke has not been studied. Thus, we aimed to: (1) examine whether the total scores of subacute MoCA and MMSE could predict moderate—severe VCI 3—6 months after stroke; (2) compare the discriminatory ability of subacute MoCA and MMSE scores using their respective optimal cut-off points in detecting impaired cognitive domains at 3—6 months after stroke.

METHODS

Subjects

Three hundred clinically stable patients (≥21 years of age) with a recent ischaemic stroke or transient ischaemic attack (TIA) (≤14 days) admitted to the stroke neurology service at the National University Health System of Singapore were recruited.

Patients were excluded if they had a major disability (modified Rankin scale[15] (mRS) >4), significant aphasia or dysarthria (National Institute of Health Stroke Score (NIHSS),[16] best language (Aphasia) and dysarthria score >1) that impeded cognitive assessment. Patients were also excluded if they had a major and active psychiatric illness and pre-existing dementia, and a score of >3.38 on the Informant Questionnaire on Cognitive Decline in the Elderly.[17 18] The Delirium Rating Scale-Revised-98[19] was used to exclude patients with

acute delirium. Stroke mechanism was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[20] criteria.

Standard protocol approvals and patient consent

This study was approved by the local ethics committee, and written informed consent was obtained from all participants or their legally acceptable representatives.

Procedures

Baseline characteristics

Demographic information (age, gender, ethnicity, years of education), cognitive status (MoCA and MMSE), clinical information, vascular risk factors and neurological status (NIHSS and mRS) were collected.

Clinical outcome measures

Patients were followed up at 3–6 months after their index stroke for their neurological status, clinical outcomes and interval events. Medical records were used to verify these events (strokes or TIA, peripheral artery disease, intracranial haemorrhage, cardiac events or deaths from any of the above).

Cognitive measures

Patients were assessed using a formal neuropsychological battery locally validated for older Singaporeans,[21] which was administered by trained research psychologists blinded to the baseline MMSE and MoCA scores.

The non-memory domains of the formal neuropsychological battery included: (1) attention (digit span test,[22] visual span test[22] and auditory detection test[23]); (2) language (modified Boston naming[24] and category fluency[25]); (3) visuomotor speed (symbol digit modalities,[26] digit cancellation[27] and maze[28]); (4) visuoconstruction (visual reproduction subtest of the Wechsler Memory Scale-Revised[22] copy task, clock drawing[29] and the block design subtest of the Wechsler Adult Intelligence Scale-Revised[30]); (5) executive function (frontal assessment battery[31]).

The memory domains of the battery included: (1) verbal memory (word list[32] and story recall[22]); (2) visual memory (picture recall[22] and the visual reproduction subtest of the Wechsler Memory Scale-Revised[22]).

Education-adjusted cutoffs of 1.5 SD below the established norms were used on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. Diagnoses of dementia were made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[33] The Bayer-Activities of Daily Living Scale was administered to the informant to ascertain functional disabilities primarily due to cognitive impairment.[34] Patients with VCIND were impaired in at least one domain of the neuropsychological test battery, but did not meet the criteria for dementia. VCIND patients were further classified into VCIND mild (impairment in ≤2 cognitive domains) and VCIND moderate (impairment in ≥3 cognitive domains).[5] VCI patients were dichotomised into no–mild VCI (NCI and VCIND mild) and moderate–severe VCI (VCIND moderate and dementia).

Statistical analyses

Between-group comparisons were conducted using independent sample t-tests for quantitative variables, and a Pearson χ^2 tests for categorical variables. A logistic regression was performed to determine the predictors for the moderate–severe VCI 3–6 months after stroke. All the clinically relevant variables were included in the logistic regression using the enter method to determine the predictors for the moderate–severe VCI 3–6 months after stroke. A receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) was used to compare the discriminatory ability of the MoCA and MMSE for moderate–severe VCI and the impaired cognitive domains, using the standard method[35] of adjustment for MoCA, and the age and education adjustment using the regression analysis for MoCA and MMSE.

All statistical analyses were performed with SPSS V.19.0 for Windows.

RESULTS

Subject characteristics

The flow diagram of study participation as recommended by the STARD (Standards for Reporting of Diagnostic Accuracy) guidelines[36] is shown in figure 1. In the period from June 2009 to February 2011, 904 patients admitted to the National University Health System stroke neurology service were screened for eligibility and 300 were recruited. The major reasons for exclusion, in order of frequency, were as follows: (1) no consent (n=332); (2) significant aphasia or dysarthria (n=118); (3) major disability (n=59); (4) other physical or sensory conditions (eg, hearing or vision impairment) impeding cognitive assessment (n=32); (5) major and active psychiatric illnesses (n=19); (6) preexisting dementia (n=15); (7) stroke onset >14 days (n=14); (8) unstable clinical condition (n=13); (9) lack of language proficiency (n=2).

Recruited patients were mostly Chinese (71.3%) and men (67.6%) with a mean age of 60.2±11.8 years and a mean age of 7.5±4.1 years of formal education. Most patients (84.7%) had ischaemic stroke and a low level of disability (median NIHSS score=2 and median mRS score=2). The median interval between the stroke/TIA event and assessment was 3 days. Of the 300 eligible patients, 46 were diagnosed with TIA. Hence,

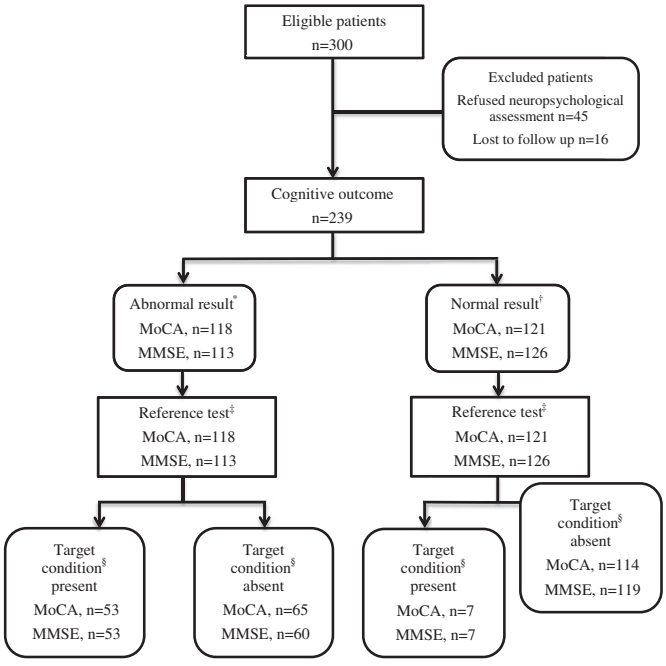

Figure 1 Flow diagram of participation. *Montreal Cognitive Assessment (MoCA) abnormal result ≤21; Mini-Mental State Examination (MMSE) abnormal result ≤25. †MoCA normal result ≥22; MMSE normal result ≥25. ‡Reference test: neuropsychological battery. §Target condition: moderate–severe cognitive impairment (VCIND moderate and dementia; n=60).

a total of 254 ischaemic stroke patients were classified using the TOAST criteria. Most (n=133, 44.3%) stroke patients were classified as having had a small artery occlusion, with a further 18.0% (n=54) with large artery atherosclerosis, 16.0% (n=48) with cardio-embolism, 5.7% (n=17) with undetermined aetiology and 0.7% (n=2) with stroke of other determined aetiology (OC). When compared with the non-included subjects, recruited patients were significantly younger with less severe neurological status (age: 60.2±11.8 years vs 65.4±14 years; median NIHSS score: 2 vs 4; median mRS score: 2 vs 3, p<0.01).

At 3–6 months following the index event, 239 patients (80%) completed a formal neuropsychological assessment (see table 1), 45 (15%) declined testing, 16 (5.3%) were lost to follow-up (one deceased, one coma and 14 not contactable). There were no significant differences in the baseline demographic and clinical characteristics of patients who did or did not complete a formal neuropsychological assessment.

Most participants had NCI (42.3%) but a large proportion had VCIND: VCIND mild (32.6%) and VCIND moderate (22.2%) followed by a small minority with dementia (2.9%). As shown in table 1, patients with moderate–severe VCI were significantly older, women, of Malay or Indian ethnicity, less educated, more neurologically impaired, and assessed later after their index stroke. They were also more likely to have a history of hypertension, ischaemic heart disease, previous stroke/TIA and significantly lower cognitive screening test scores. However, they were less likely to have a history of smoking. The Geriatric Depression Scale[37] scores did not differ significantly between groups, nor did the TOAST stroke subtype. The proportion of patients with moderate–severe cognitive impairment did not differ between those with (30%, 3 out of 10) or without recurrent stroke, or TIA (25%, 57 out of 229) on follow-up (p=0.73). Logistic regression showed that age, ethnicity, history of smoking and ischaemic heart disease, previous stroke or TIA, and baseline NIHSS and MoCA scores predicted moderate–severe cognitive impairment at 3–6 months after stroke (p<0.05).

Comparison of the discriminant ability of the MoCA and the MMSE

ROC AUCs were similar between the MoCA and MMSE scores (MoCA 0.85 (95% CI 0.79 to 0.90) vs MMSE 0.83 (95% CI 0.77

Table 1 Population characteristics according to the cognitive outcome

Characteristics N (%)	No–mild cognitive impairment (n=179)	Moderate–severe cognitive impairment (n=60)	Univariate analysis p Value	Logistic regression p Value
Age, mean (SD)*	57.6 (10.3)	67.9 (11.7)	<0.001	0.011
Gender, female (%)	47 (26.3)	26 (43.3)	0.013	0.810
Education, *y* (mean, SD)	8.1 (3.9)	5.7 (3.8)	<0.001	0.264
Ethnicity*			0.019	0.047
Chinese (%)	141 (78.8)	35 (58.3)		
Malay (%)	25 (14.0)	15 (25.0)		
Indian (%)	12 (6.7)	9 (15.0)		
Others (%)	1 (0.6)	1 (1.7)		
Stroke classification			0.289	0.308
SAO (%)	85 (47.5)	21 (35.0)		
LAA (%)	27 (15.1)	16 (26.7)		
CE (%)	30 (16.8)	10 (16.7)		
UND (%)	8 (4.5)	4 (6.7)		
OC (%)	1 (0.6)	1 (1.7)		
TIA (%)	28 (15.6)	8 (13.3)		
Baseline NIHSS (median)*	1	4	<0.001	0.023
Baseline mRS (median)	1	3	<0.001	0.618
Delirium rating scale (mean, SD)	2.3 (1.7)	4.1 (1.7)	<0.001	0.344
Mean interval between				
Stroke/TIA and assessment	3.0 (2.1)	4.4 (2.9)	<0.001	0.428
Cognitive screening tests				
Baseline MMSE (mean, SD)	25.9 (3.1)	20.9 (4.4)	<0.001	
Baseline MoCA (mean, SD)*	22.5 (4.5)	15.7 (4.8)	<0.001	
IQCODE, mean (SD)	3.0 (0.2)	3.2 (0.4)	0.004	0.193
Risk factors				
Hyperlipidaemia (%)	141 (78.8)	47 (78.3)	0.943	0.385
Hypertension (%)	119 (66.5)	49 (81.7)	0.026	0.778
Diabetes mellitus (%)	64 (35.8)	26 (43.3)	0.294	0.289
Ever smoked (%)*	79 (44.4)	16 (27.1)	0.019	0.015
Previous ischaemic heart disease (%)*	29 (16.2)	24 (40.0)	<0.001	0.006
Previous stroke/TIA (%)*	27 (15.1)	20 (33.3)	0.002	0.005
Atrial fibrillation (%)	20 (11.2%)	10 (16.7)	0.266	0.360
Previous peripheral artery disease (%)	5 (2.8%)	2 (3.3)	0.830	0.832
3–6 Months geriatric depression scale (mean, SD)	3.0 (3.3)	3.6 (3.5)	0.381	

*p<0.050 for logistic regression.
AD, Alzheimer's Disease; CE, cardio-embolism; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LAA, large artery atherosclerosis; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score; OC, stroke of other determined cause; SAO, small artery occlusion; TIA, transient ischaemic attack; UND, undetermined aetiology.

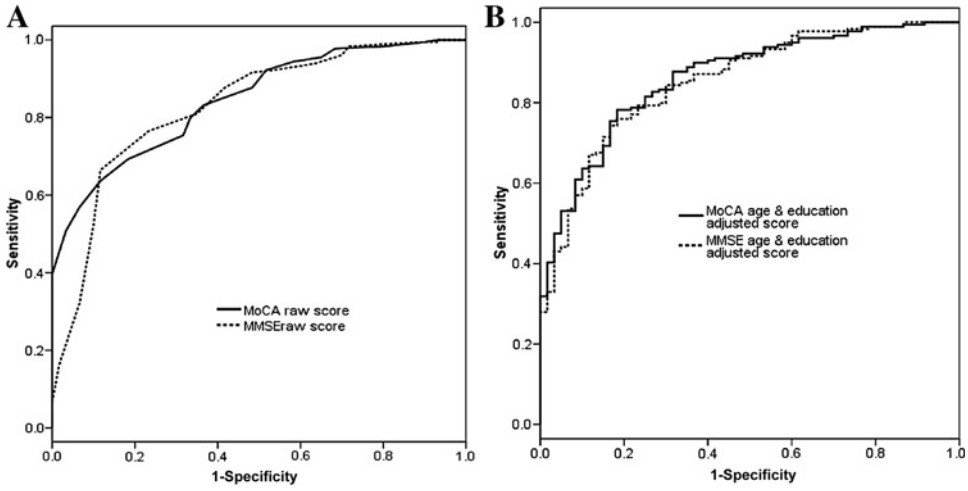

Figure 2 (A) Receiver operating characteristic curve analysis: Montreal Cognitive Assessment (MoCA) versus Mini-Mental State Examination (MMSE) using the raw scores. (B) Receiver operating characteristic curve analysis: MoCA versus MMSE using the age- and education-adjusted score.

to 0.89), p=0.43) and age- and education-adjusted scores (MoCA 0.86 (95% CI 0.81 to 0.91) vs MMSE 0.85 (95% CI 0.80 to 0.91), p=0.69) to detect moderate–severe VCI 3–6 months after stroke as shown in figure 2A,B.We further adjusted the baseline scores of MoCA and MMSE using all significant predictors (age, ethnicity, history of smoking and ischaemic heart disease, previous stroke or TIA and baseline NIHSS) and education. The AUCs remained equivalent between the adjusted baseline scores of MoCA and MMSE (MoCA 0.91 (95% CI 0.87 to 0.95) vs MMSE 0.90 (95% CI 0.86 to 0.94), p=0.55) in detecting moderate–severe VCI. Optimal cut-off points of the standard adjustment method were 21/22 (sensitivity: 0.88; specificity: 0.64; positive predictive value: 0.45; negative predictive value: 0.94; 70% correctly classified) for the MoCA and 25/26 (sensitivity: 0.88; specificity: 0.67; positive predictive value: 0.47; negative predictive value: 0.94; 72% correctly classified) for the MMSE. Moreover, the ROC AUCs were also similar between the MoCA and MMSE scores (0.89 (95% CI 0.82 to 0.96) vs 0.85 (95% CI 0.76 to 0.94), p=0.27) and age- and education-adjusted scores (0.91 (95% CI 0.84 to 0.97) vs 0.88 (95% CI 0.79 to 0.96), p=0.37) to detect moderate–severe VCI in SVD patients alone at 3–6 months after stroke as shown in figure 3A,B. Hence, both MoCA and MMSE had similar discriminant indices with good sensitivity and moderate specificity to detect moderate–severe VCI 3–6 months after stroke.

Using the optimal cut-off points for MoCA and MMSE, there was no difference between either screening test in predicting cognitive impairment in a specific domain, as determined by formal neuropsychological testing 3–6 months after stroke (table 2).

DISCUSSION

The principal finding of this study is that brief cognitive screening tests administered in the subacute stroke phase can predict significant cognitive impairment 3–6 months after stroke, as determined by formal neuropsychological evaluations, and may therefore be clinically useful. Both MoCA and MMSE were sensitive in detecting instrumental deficits such as impairment in language and visuoconstruction domains and impairment in attention, verbal and visual memory, visuomotor speed and executive function domains.

Our findings, that both MoCA and MMSE were of equivalent discriminatory abilities, differ from previous comparative studies.[11 12] This could be due to the use of a formal neuropsychological assessment to determine cognitive impairment which is more comprehensive and able to accurately detect impairment of multiple cognitive domains.

We used formal neuropsychological evaluation 3–6 months after stroke as the gold standard to measure cognitive status after stroke as this is more relevant to standard clinical practice since patients generally improve after their initial stroke.[38]

The similar AUCs of both screening instruments in our study were consistent with a study in patients with Parkinson's disease.[39] However, it was unexpected that the MoCA was not

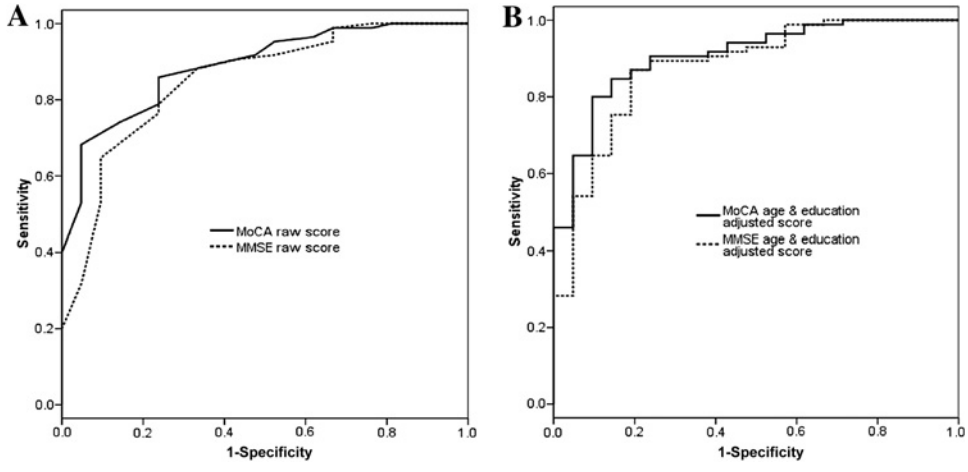

Figure 3 (A) Receiver operating characteristic curve analysis for small vessel disease: Montreal Cognitive Assessment (MoCA) versus Mini-Mental State Examination (MMSE) using the raw scores. (B) Receiver operating characteristic curve analysis for small vessel disease: MoCA versus MMSE using the age- and education-adjusted score.

Table 2 Discriminant indices of Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) in detecting cognitive domain impairment

	MoCA 21/22					MMSE 25/26				
Cognitive domains	**Sen**	**Spec**	**PPV**	**NPV**	**Correctly classified**	**Sen**	**Spec**	**PPV**	**NPV**	**Correctly classified**
Attention	1.00	0.65	0.24	1.00	0.68	0.88	0.65	0.22	0.98	0.68
Language	0.90	0.55	0.17	0.98	0.58	0.90	0.58	0.18	0.98	0.61
Verbal memory	0.88	0.78	0.71	0.91	0.82	0.83	0.78	0.70	0.88	0.80
Visual memory	0.78	0.83	0.83	0.77	0.80	0.76	0.83	0.83	0.76	0.79
Visuo-construction	0.85	0.75	0.80	0.81	0.81	0.80	0.73	0.77	0.76	0.77
Visuomotor speed	0.79	0.77	0.73	0.83	0.78	0.77	0.80	0.75	0.82	0.79
Executive function	1.00	0.58	0.27	1.00	0.64	0.97	0.60	0.27	1.00	0.65

NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spec, specificity.

superior to the MMSE in detecting moderate–severe VCI, even among patients with SVD. The National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Harmonisation Standards[14] for VCI recommend the MoCA over the MMSE as the latter was thought to be insensitive to executive dysfunction and the 'more subtle memory impairments often encountered in VCI'. These findings may be due to the following: (1) we focused on the detection of moderate–severe VCI; these patients had impairment on multiple cognitive domains with approximately half having more than three domains impaired.[5] Hence, the psychometric superiority of the MoCA to lesser degrees of cognitive impairment may not be apparent in moderate–severe VCI. However, in our sample, ROC analysis also failed to show superiority of the MoCA in discriminating NCI from VCIND mild (data not shown); (2) VCIND patients may also have underlying AD[40]; thus, executive dysfunction may not be the most prominent feature, and so, the MoCA may not have an advantage over the MMSE. In our patient population, three domains were impaired in over 50% of patients (visual memory, visuoconstruction and visuomotor speed) while only 17% of patients were impaired in executive function; (3) that the younger age and lower formal educational attainments of Singaporean patients compared with patients in Western studies affected the comparison between MoCA and MMSE[10 39]; however, when we compared patients in our study with lower (≤6 years) and higher educational levels, and of younger (<60 years) and older age, no statistical significant difference in ROC curve analysis could be found (data not shown). In conclusion, consistent with a previous study,[9] either MoCA or MMSE could be used to screen for VCI at the subacute stroke phase. Moreover, both instruments could predict the moderate–severe cognitive impairment 3–6 month after stroke.

Patients who are older, women, of Malay or Indian ethnicity and with less education are also more likely to have moderate–severe VCI 3–6 months after stroke. In addition, more severe baseline neurological disability, and the presence of vascular risk factors such as hypertension, ischaemic heart disease, previous stroke/TIA, are also associated with moderate–severe VCI 3–6 months after stroke. These findings are consistent with the previous studies.[5]

There are several limitations in our study. First, our results may not be generalisable to all stroke populations, as the majority of our patients were younger and were less disabled with milder neurological deficits than non-included stroke patients admitted to the same hospital in Singapore. However, a significant proportion (25%) of this milder stroke group had moderate–severe VCI at 3–6 months after stroke, which may escape clinical attention if not detected by early screening. Hence, validated cognitive screening tests administered at the subacute stroke phase are valuable for the identification of such patients who are at higher risk for incident dementia. Second, we used the frontal assessment battery, a useful bedside measure,[31] to test for executive function rather than formal executive function instruments such as the trail making test. Third, a large proportion of the variation in cognitive functioning may be lost due to dichotomising cognitive performance instead of using a weighted continuous score of the formal neuropsychological battery. However, dichotomising cognitive performance was adopted in our study for the following reasons: (1) it has been validated in a stroke population in Singapore[5]; (2) it is more feasible for clinical implementation compared with the use of weighted continuous scores. Fourth, 20% of patients did not complete a formal neuropsychological assessment. However, no significant different characteristics were observed between the patients who underwent a formal neuropsychological assessment compared with those who did not. Finally, patients who had moderate–severe VCI were tested approximately one and half days later than those with no–mild VCI, which may reflect the limitation that patients who are clinically unstable may not be amenable to cognitive screening.

When administered in the subacute phase after stroke, the prognostic value of MoCA and MMSE, as determined by ROC curve analysis, is equivalent for detecting patients at higher risk for incident dementia. Either of the screening instruments correctly identified 70–72% of patients and may be considered for implementation in routine clinical practice and for research studies.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement YHD has full access to all of the data and has the right to publish any and all data separate and apart from any sponsor. There are no additional unpublished data to others.

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