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Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after stroke: an observational study

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ABSTRACT

Objectives: To investigate the prognostic value of the neurocognitive status measured by screening instruments, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), obtained at the subacute stroke phase or the baseline (≤ 2 weeks), for functional outcome 3–6 months later.

Design: Prospective observational study.

Setting: Tertiary stroke neurology service.

Participants: 400 patients with a recent ischemic stroke or transient ischemic attack (TIA) received NIHSS, MoCA and MMSE at baseline and were followed up at 3-6 months later.

Primary outcome measures: At 3-6 months following index event, functional outcome was measured by the modified Rankin Scale (mRS) scores.

Results: Baseline NIHSS, MMSE and MoCA scores individually predicted mRS scores at 3–6 months, with NIHSS being the strongest predictor (NIHSS: R^2change=0.043, p<0.001). Moreover, baseline MMSE scores had a small but statistically significant incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months, while baseline MoCA scores did not [MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083]. However, in patients with more severe stroke at baseline (defined as NIHSS>2), both baseline MoCA and MMSE had significant and moderately large incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months [MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021].

Conclusion: Cognitive screening at the subacute stroke phase can predict functional outcome independently and improve the predictive value of stroke severity scores for functional outcome 3–6 months later, particularly in patients with more severe stroke.

ARTICLE SUMMARY

Article focus

- The prognostic value of neurocognitive status measured by brief screening instruments, the MoCA and the MMSE, individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), at subacute stroke phase for functional outcomes at 3–6 months is unknown.
- We examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS for functional outcome 3–6 months after stroke.
- We also explored the predictive ability of these measures in patients with differing stroke severity.

Key messages

- Cognitive screening at the subacute stroke phase can predict functional outcome independently. Neurocognitive status measured by baseline MMSE scores adds a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients.
- Unexpectedly, in patients with more severe stroke defined by baseline NIHSS score >2, neurocognitive status measured by both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later.

Strength and limitations of this study

- The main strength of this study is that we examined the prognostic value of neurocognitive status (MoCA and MMSE) and stroke severity (NIHSS) at subacute stroke phase systematically as a singular measure and in combination for mRS scores

3–6 month later in a large sample of stroke patients and in patients with differing stroke severity.

- An additional strength is the choice of 3–6 month follow-up because patients were more likely to resume their daily activities and usual roles within this time frame. Hence, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke.
- The limitation of this study is that we did not systematically examine rehabilitation services provided for patients from subacute stroke phase to 3-6 months follow-up.

INTRODUCTION

It is important for early intervention and focused management to have instruments available during the subacute stroke phase for predicting functional outcome 3–6 months later. Cognitive performance measured by the Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) administered at the subacute stroke phase predicted patients' functional outcomes at inpatient discharge.[1, 2] Furthermore, patients' post-stroke cognitive functioning measured by a brief neuropsychological battery 2–3 weeks following stroke predicted their functional outcomes 13 months later.[3] No study yet has investigated the utility of patients' neurocognitive status at the subacute stroke phase for predicting functional outcome at 3–6 months. A widely used stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), administered at the subacute stroke phase is predictive of patients' functional outcomes 3–6 months later,[4] but has limited representation of cognitive function.[5] Hence, whether the NIHSS and neurocognitive status at baseline are independently predictive o r have additive predictive value for functional outcomes at 3–6 months is unknown.

We therefore examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS at the subacute stroke phase for functional outcome 3–6 months later. In addition, we explored the predictive ability of these measures in patients with differing stroke severity.

METHODS

Subjects

The methodology of this study has been described previously.[6] Briefly, we recruited 400 consecutive patients (≥21 years old) with a recent ischemic stroke or transient ischemic attack

(TIA) (≤14 days) during their inpatient admission (subacute stroke phase or baseline) at the National University Health System in Singapore. Patients were excluded if they had a major physical disability or an active psychiatric disorder that would impede cognitive testing.

Standard protocol approvals and patient consent

This study was approved by the National Healthcare Group Domain-Specific Review Board (DSRB), and was conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or legally acceptable representatives.

Procedures

Patients were assessed using the NIHSS, modified Rankin Scale (mRS) (premorbid and baseline functioning), MMSE[7] and MoCA[8] at baseline. In addition, their mRS scores were collected at 3–6 months later. The NIHSS and mRS were administered by certified research personnel blinded to patients' neurocognitive status at baseline and 3-6 months follow-up. Similarly, the cognitive screening tests were administered by trained research psychologists blinded to patients' NIHSS and mRS scores. The patients' functional outcome was defined by the continuous scores of mRS.

Statistical analyses

Hierarchical regression analyses were conducted to examine the incremental contribution of baseline MMSE and MoCA compared with the baseline NIHSS in predicting functional outcomes defined by mRS scores at 3–6 months after stroke. In the initial analysis, the clinically-relevant or significant covariates (i.e., age, sex, years of education, number of cardiovascular risk factors, premorbid and baseline mRS) were entered in the first block. The cognitive screening variables (MMSE or MoCA) at baseline were entered in the second block and the NIHSS scores at baseline were entered in the third block (Model A1 and B1 for MMSE and MoCA, respectively). Subsequently, the order of entry was altered, with baseline

NIHSS scores entered in the second block and either baseline MMSE or MoCA entered at the third block (Model A2 and B2 for MMSE and MoCA, respectively). In order to explore predictive value in patients with differing stroke severity, we dichotomized the baseline NIHSS scores using a median split and repeated these analyses.

All statistical analyses were performed with IBM SPSS Statistics Version 20.0 for Windows.

RESULTS

Subject characteristics

The recruited patients were mostly Chinese (70.3%) and male (69.8%), with a mean age of 59.8 (11.6) years and a mean of 7.7 (4.3) years of formal education. Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0). The median interval between the stroke or TIA event and assessment was 2 days (range: 0–14).

At 3–6 months following the index event, patients who were lost to follow-up (n=12) were younger and their clinical condition was stabilized faster than those who completed the follow-up (age: 52.8±12.9 vs 60.0±11.5, p=0.03; interval days: 2.91±2.31 vs 2.08±0.90, p=0.01). 136 (35.1%) of patients had poor functional outcomes defined by mRS score >2 on follow-up. The population characteristics can be found in Table 1.

The Predictive Ability of the MoCA, MMSE and NIHSS

Using hierarchical regression analyses and controlling for baseline characteristics, the MMSE, MoCA and NIHSS—as singular measures—predicted mRS scores at 3–6 months after stroke (R^2 changes of 0.012, 0.007 and 0.043, with p-values 0.004, 0.029 and <0.001, respectively; Table 2). Baseline MMSE scores added a small but statistically significant prediction of

functional outcomes in addition to baseline NIHSS scores, while baseline MoCA scores did not (MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083).

Using a median split of baseline NIHSS scores at 2, patients with NIHSS scores ≤2 (median =1, range 0–2) were defined as having less severe stroke and those with NIHSS score >2 (median = 5, range 3–18) were defined as having more severe stroke. As shown in Table 3, in patients with NIHSS score >2, both baseline MMSE and MoCA had a significant and considerable incremental prediction for functional outcomes at 3-6 months in addition to baseline NIHSS scores (MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021), while neither baseline neurocognitive measure nor baseline NIHSS showed an incremental prediction for functional outcome in patients with less severe stroke (NIHSS score ≤2).

DISCUSSION

Cognitive screening at the subacute stroke phase can predict functional outcome at early convalescent stroke phase independently. Baseline MMSE scores add a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients. Unexpectedly, in patients with more severe stroke defined by baseline NIHSS score >2, both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later.

The contributions of our study are three-fold. First, our finding that neurocognitive status at the subacute stroke phase predicts functional outcome at 3–6 months is novel and consistent with previous studies in inpatient rehabilitation [1, 2] and at 13 months after stroke.[3] Second, MMSE scores at baseline add a small incremental prediction to baseline stroke severity scores for functional outcomes 3-6 months later. Third, both baseline MMSE

and MoCA showed a considerable incremental effect to the baseline NIHSS scores in predicting functional outcomes in patients with more severe stroke (NIHSS>2) while neither neurocognitive measure nor stroke severity score at baseline was predictive for functional outcome in patients with less severe stroke (NIHSS score ≤2). This may be explained by the higher recovery potential of patients with more neurological deficits compared to patients with less severe deficits.

There are several strengths of our study. First, we examined the prognostic value of NIHSS and cognitive status by systematically assessing baseline values individually and in combination in predicting patients' mRS scores 3–6 month after stroke. Although previous studies that investigated the predictive power of cognition included baseline NIHSS as a control variable (along with other baseline characteristics), they did not explore the role of baseline NIHSS as a predictor itself. [1–3] Second, we chose the 3–6 month follow-up period because prognosis of functional recovery can be made reliably within 12 weeks after stroke,[9] and patients were more likely to resume their daily activities and usual roles within this time frame. Therefore, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke. Third, we examined the predictive ability of neurocognitive status and stroke severity measures at baseline for functional outcome at 3-6 months in patients with differing stroke severity.

There are several limitations of this study. Our results may not be generalizable as the majority of patients had less severe stroke, nevertheless, a third had poor functional outcomes 3–6 months after stroke so better prognostic tools are required. We employed cognitive screening tests at baseline rather than formal neuropsychological assessments, for their brevity and utility by non-specialist personnel. We did not examine rehabilitation services systematically as this study was designed to investigate cognitive outcomes after stroke.

However, all patients received standard rehabilitation according to the institutional pathway. In addition, the mRS has been criticized for its lack of specificity,[5] however, it is a summary of outcomes in functioning and has been widely used in clinical trials as a primary efficacy measure.

In conclusion, neurocognitive status at the subacute stroke phase is independently predictive of functioning at early convalescent stroke phase. Baseline MMSE scores can add incremental prediction to baseline stroke severity score for functional outcome 3-6 months later. Moreover, in patients with more recovery potential, both baseline MMSE and MoCA can improve baseline stroke severity score in predicting functional outcomes 3–6 months later. We have previously shown that these screening tests administered at the subacute stroke phase could also predict cognitive outcomes 3–6 months later.[6] Therefore, the predictive value and brevity of the MMSE and MoCA warrants their routine use in the subacute stroke phase in clinical service and early acute stroke trials. Future studies may establish a modified scale combining the NIHSS and items from the MMSE and MoCA to improve the predictive ability for functional outcome.

Table 1. Population characteristics according to the functional outcome

Characteristics N (%)	mRS 0–2 (*n* = 252)		mRS >2 (*n* = 136)		Univariate Analysis *P*
Age, mean (SD)	57.9	(10.8)	63.8	(11.8)	< 0.001
Gender, female*	68	(27.0%)	52	(38.2%)	0.02
Education, *y* (mean, SD)	9.8	(4.3)	6.3	(3.7)	< 0.001
Ethnicity					0.09
Chinese	188	(74.6%)	87	(64.0%)	
Malay	40	(15.9%)	36	(26.5%)	
Indian	22	(8.7%)	12	(8.8%)	
Others	2	(0.8%)	1	(0.7 %)	
Stroke classification					0.001
SAO	114	(45.2%)	60	(44.1%)	
LAA	29	(11.5%)	30	(22.1%)	

Characteristics N (%)	mRS 0–2 (*n* = 252)		mRS >2 (*n* = 136)		Univariate Analysis *P*
CE	31	(12.3%)	25	(18.4%)	
UND	11	(4.4%)	7	(5.1%)	
OC	1	(0.4%)	1	(0.7%)	
TIA	66	(26.2%)	13	(9.6%)	
NIHSS (median)*	1		4		< 0.001
Premorbid mRS (median)	0		0		<0.001
Baseline mRS (median)*	1		3		< 0.001
Mean interval between stroke/TIA and assessment	2.4	(2.0)	3.8	(2.5)	< 0.001
Cognitive screening tests					
MMSE (mean, SD)	25.7	(3.3)	22.6	(4.3)	< 0.001
MoCA (mean, SD)	22.0	(4.8)	18.1	(5.5)	< 0.001
Number of cardiovascular risk factors (median)	2		3		<0.001

Characteristics N (%)	mRS 0–2 (*n* = 252)		mRS >2 (*n* = 136)		Univariate Analysis *P*
Recurrent vascular events (no., %)	10	(4.0%)	8	(6.0%)	0.37

*P <0.050 for logistic regression for binary outcome of mRS scores of 0–1 and ≥ 2.

mRS = modified Rankin scale; **SD**= Standard Deviations; **SAO =** small artery occlusion; **LAA**= large artery atherosclerosis; **CE** = cardioembolism; **UND** = undetermined etiology; **OC** = other determined etiology; **TIA**= transient ischemic attack; **NIHSS** = National Institute of Health Stroke Score; **MMSE=**Mini-Mental State Examination; **MoCA=**Montreal Cognitive Assessment.

Table 2. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS scores

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	54.10	<0.001
A1	2	Baseline MMSE	−0.1 (0.031)	0.47	0.012	8.48	0.004
	3	Baseline NIHSS	0.3 (<0.001)	0.51	0.038	29.00	<0.001
A2	2	Baseline NIHSS	0.3 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MMSE	−0.1 (0.031)	0.51	0.006	4.71	0.031
B1	2	Baseline MoCA	−0.08 (0.083)	0.47	0.007	4.80	0.029
	3	Baseline NIHSS	0.31 (<0.001)	0.51	0.040	31.10	<0.001
B2	2	Baseline NIHSS	0.31 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MoCA	−0.08 (0.083)	0.51	0.004	3.02	0.083

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

Table 3. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS for subsample of patients with NIHSS scores>2 at baseline

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	21.68	<0.001
A1	2	Baseline MMSE	−0.18 (0.010)	0.49	0.036	10.94	0.001
	3	Baseline NIHSS	0.22 (0.001)	0.53	0.034	11.07	0.001
A2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MMSE	−0.18 (0.010)	0.53	0.021	6.83	0.010
B1	2	Baseline MoCA	−0.16 (0.021)	0.49	0.029	8.51	0.004
	3	Baseline NIHSS	0.22 (0.001)	0.52	0.040	12.07	0.001
B2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MoCA	−0.16 (0.021)	0.52	0.017	5.42	0.021

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

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Contributors: Y. Dong drafted the original manuscript. Statistical analysis was conducted by Ms. Y Dong with the guidance from Dr. J Crawford. All authors contributed to one of: study design, conceptualization, analysis, interpretation of the data, drafting or revision of the manuscript for intellectual content.

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ABSTRACT

Objectives: To investigate the prognostic value of the neurocognitive status measured by screening instruments, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), obtained at the subacute stroke phase or the baseline (≤ 2 weeks), for functional outcome 3–6 months later.

Design: Prospective observational study.

Setting: Tertiary stroke neurology service.

Participants: 400 patients with a recent ischemic stroke or transient ischemic attack (TIA) received NIHSS, MoCA and MMSE at baseline and were followed up at 3-6 months later.

Primary outcome measures: At 3-6 months following index event, functional outcome was measured by the modified Rankin Scale (mRS) scores.

Results: Baseline NIHSS, MMSE and MoCA scores individually predicted mRS scores at 3–6 months, with NIHSS being the strongest predictor (NIHSS: R^2change=0.043, p<0.001). Moreover, baseline MMSE scores had a small but statistically significant incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months, while baseline MoCA scores did not [MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083]. However, in patients with more severe stroke at baseline (defined as NIHSS>2), both baseline MoCA and MMSE had significant and moderately large incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months [MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021].

Conclusion: Cognitive screening at the subacute stroke phase can predict functional outcome independently and improve the predictive value of stroke severity scores for functional outcome 3–6 months later, particularly in patients with more severe stroke.

ARTICLE SUMMARY

Article focus

- The prognostic value of neurocognitive status measured by brief screening instruments, the MoCA and the MMSE, individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), at subacute stroke phase for functional outcomes at 3–6 months is unknown.
- We examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS for functional outcome 3–6 months after stroke.
- We also explored the predictive ability of these measures in patients with differing stroke severity.

Key messages

- Cognitive screening at the subacute stroke phase can predict functional outcome independently. Neurocognitive status measured by baseline MMSE scores adds a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients.
- Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, neurocognitive status measured by both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

Strength and limitations of this study

- The main strength of this study is that we examined the prognostic value of neurocognitive status (MoCA and MMSE) and stroke severity (NIHSS) at subacute

stroke phase systematically as a singular measure and in combination for mRS scores 3–6 month later in a large sample of stroke patients and in patients with differing stroke severity.

- An additional strength is the choice of 3–6 month follow-up because patients were more likely to resume their daily activities and usual roles within this time frame. Hence, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke.
- The limitation of this study is that we did not systematically examine rehabilitation services provided for patients from subacute stroke phase to 3-6 months follow-up.

INTRODUCTION

It is important for early intervention and focused management to have instruments available during the subacute stroke phase for predicting functional outcome 3–6 months later. Cognitive performance measured by the Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) administered at the subacute stroke phase predicted patients' functional outcomes at inpatient discharge (1, 2). Furthermore, patients' post-stroke cognitive functioning measured by a brief neuropsychological battery 2–3 weeks following stroke predicted their functional outcomes 13 months later (3). No study yet has investigated the utility of patients' neurocognitive status at the subacute stroke phase for predicting functional outcome at 3–6 months. A widely used stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), administered at the subacute stroke phase is predictive of patients' functional outcomes 3–6 months later (4), but has limited representation of cognitive function (5). Hence, whether the NIHSS and neurocognitive status at baseline are independently predictive or have additive predictive value for functional outcomes at 3–6 months is unknown.

We therefore examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS at the subacute stroke phase for functional outcome 3–6 months later. In addition, we explored the predictive ability of these measures in patients with differing stroke severity.

METHODS

Subjects

The methodology of this study has been described previously (6).[6] Briefly, we recruited 400 consecutive patients (≥21 years old) with a recent ischemic stroke or transient ischemic

attack (TIA) (≤14 days) during their inpatient admission (subacute stroke phase or baseline) at the National University Health System in Singapore. Patients were excluded if they had a major physical disability or an active psychiatric disorder that would impede cognitive testing.

Standard protocol approvals and patient consent

This study was approved by the National Healthcare Group Domain-Specific Review Board (DSRB), and was conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or legally acceptable representatives.

Procedures

Patients were assessed using the NIHSS, modified Rankin Scale (mRS) (premorbid and baseline functioning), MMSE (7) and MoCA (8) at baseline. In addition, their mRS scores were collected at 3–6 months later. The NIHSS and mRS were administered by certified research personnel blinded to patients' neurocognitive status at baseline and 3-6 months follow-up. Similarly, the cognitive screening tests were administered by trained research psychologists blinded to patients' NIHSS and mRS scores. The patients' functional outcome was defined by the continuous scores of mRS.

Statistical analyses

Between-group differences were examined using independent-sample *t* test for quantitative variables and Pearson's χ^2 test for categorical variables. Hierarchical regression analyses were conducted to examine the incremental contribution of baseline MMSE and MoCA compared with the baseline NIHSS in predicting functional outcomes defined by mRS scores at 3–6 months after stroke. In the initial analysis, the clinically-relevant or significant covariates (i.e., age, sex, years of education, number of cardiovascular risk factors, premorbid and baseline mRS) were entered in the first block. The cognitive screening variables (MMSE or MoCA) at baseline were entered in the second block and the NIHSS scores at baseline

were entered in the third block (Model A1 and B1 for MMSE and MoCA, respectively). Subsequently, the order of entry was altered, with baseline NIHSS scores entered in the second block and either baseline MMSE or MoCA entered at the third block (Model A2 and B2 for MMSE and MoCA, respectively). In order to explore predictive value in patients with differing stroke severity, we dichotomized the baseline NIHSS scores using a median split and repeated these analyses.

All statistical analyses were performed with IBM SPSS Statistics Version 20.0 for Windows.

RESULTS

Subject characteristics

The recruited patients were mostly Chinese (70.3%) and male (69.8%), with a mean age of 59.8 (11.6) years and a mean of 7.7 (4.3) years of formal education. Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0). The median interval between the stroke or TIA event and assessment was 2 days (range: 0–14).

At 3–6 months following the index event, patients who were lost to follow-up (n=12) were younger and their clinical condition was stabilized faster than those who completed the follow-up (age: 52.8±12.9 vs 60.0±11.5, p=0.03; interval days: 2.91±2.31 vs 2.08±0.90, p=0.01). We defined favorable functional outcome as mRS score ≤1 and poor functional outcome as mRS score ≥2. This dichotomized mRS scores for favorable and poor functional outcome is commonly used and is in keeping with the recommendation from previous analyses (9). The majority of the patients (n=252, 64.9%) had good functional outcomes (mRSscore ≤1) while approximately one third of the patients (n=136, 35.1%) had poor

functional outcomes (mRS score ≥2). Patients with poor functional outcome were significantly older, women, of Malay ethnicity, less educated, more neurologically impaired with poorer premorbid and baseline functioning, and assessed later following cerebrovascular event. They also had more stroke classification of large artery occlusion and cardioembolic stroke, as well as higher number of cardiovascular risk factors. In addition, patients with poorer functional outcome had significantly lower scores of the MMSE and the MoCA. The population characteristics of patients with favorable and poor functional outcomes can be found in Table 1.

The Predictive Ability of the MoCA, MMSE and NIHSS

Using hierarchical regression analyses and controlling for baseline characteristics, the MMSE, MoCA and NIHSS—as singular measures—predicted mRS scores at 3–6 months after stroke (R^2 changes of 0.012, 0.007 and 0.043, with *p*-values 0.004, 0.029 and <0.001, respectively; Table 2). Baseline MMSE scores added a small but statistically significant prediction of functional outcomes in addition to baseline NIHSS scores, while baseline MoCA scores did not (MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083).

Using a median split of baseline NIHSS scores at 2, patients with NIHSS scores ≤2 (median =1, range 0–2) were defined as having less severe stroke and those with NIHSS score >2 (median = 5, range 3–18) were defined as having more severe stroke. As shown in Table 3, in patients with NIHSS score >2, both baseline MMSE and MoCA had a significant and considerable incremental prediction for functional outcomes at 3-6 months in addition to baseline NIHSS scores (MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021), while neither baseline neurocognitive measure nor baseline NIHSS showed an incremental prediction for functional outcome in patients with less severe stroke (NIHSS score ≤2).

DISCUSSION

Cognitive screening at the subacute stroke phase can predict functional outcome at early convalescent stroke phase independently. Baseline MMSE scores add a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients. Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

The contributions of our study are three-fold. First, our finding that neurocognitive status at the subacute stroke phase predicts functional outcome at 3–6 months is novel and consistent with previous studies in inpatient rehabilitation (1, 2) and at 13 months after stroke (3). Second, MMSE scores at baseline add a small incremental prediction to baseline stroke severity scores for functional outcomes 3-6 months later. Third, both baseline MMSE and MoCA showed a considerable incremental effect to the baseline NIHSS scores in predicting functional outcomes in patients with more severe stroke (NIHSS>2) while neither neurocognitive measure nor stroke severity score at baseline was predictive for functional outcome in patients with less severe stroke (NIHSS score ≤2). This may be explained by the higher recovery potential of patients with more neurological deficits compared to patients with less severe deficits.

There are several strengths of our study. First, we examined the prognostic value of NIHSS and cognitive status by systematically assessing baseline values individually and in combination in predicting patients' mRS scores 3–6 month after stroke. Although previous studies that investigated the predictive power of cognition included baseline NIHSS as a control variable (along with other baseline characteristics), they did not explore the role of

baseline NIHSS as a predictor itself (1-3). Second, we chose the 3–6 month follow-up period because prognosis of functional recovery can be made reliably within 12 weeks after stroke (10), and patients were more likely to resume their daily activities and usual roles within this time frame. Therefore, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke. Third, we examined the predictive ability of neurocognitive status and stroke severity measures at baseline for functional outcome at 3-6 months in patients with differing stroke severity.

There are several limitations of this study. First, our results may not be generalizable as the majority of patients had less severe stroke, nevertheless, a third had poor functional outcomes 3–6 months after stroke so better prognostic tools are required. Second, we employed cognitive screening tests at baseline rather than formal neuropsychological assessments, for their brevity and utility by non-specialist personnel. Third, we did not examine rehabilitation services systematically as this information was not collected . However, all patients received standard rehabilitation according to the institutional pathway. Fourth, the mRS has been criticized for its lack of specificity (5), however, it is a summary of outcomes in functioning and has been widely used in clinical trials as a primary efficacy measure. Last, we did not consider other predictive scores (e.g., PLAN score (11), iScore (12), six simple variable (13) and five simple variable scores (14)) for our models primarily due to the following reasons: 1) None of these scores include a cognitive measure.; 2) PLAN scores are developed using more severe functional outcome measure, such as mRS scores of 5 to 6 at discharge**.** Similarly, iScore has been used to estimate poor functional outcome defined by mRS 3 to 5. ; 3) Six simple variable and five simple variable scores require Glasgow Coma Scale which we did not collect in this study. Therefore, we are unable to adopt these models to predict functional outcome in this study. However, in line with our aims, we included

significant and clinically relevant predictors as control variables (age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS) in our models.

In conclusion, 4.3% of the functional outcome after 3-6 months can be predicted early after admission by NIHSS, with its many functional and only few cognitive items. Premorbid and baseline factors alone however, explain almost half of the variance. In addition, neurocognitive status at the subacute stroke phase is independently predictive of functioning at early convalescent stroke phase. Baseline MMSE scores can add incremental prediction to baseline stroke severity score for functional outcome 3-6 months later. Moreover, in patients with more recovery potential, both baseline MMSE and MoCA can improve baseline stroke severity score in predicting functional outcomes 3–6 months later. We have previously shown that these screening tests administered at the subacute stroke phase could also predict cognitive outcomes 3–6 months later (6). In addition, MoCA administration has been reported to be applicable to the majority of acute stroke patients (ischemic or hemorrhagic) (82.5%),and therefore feasible to be used in acute stroke phase (15). Therefore, the predictive value and brevity of the MMSE and MoCA warrants their routine use in the subacute stroke phase in clinical service and early acute stroke trials. However, the current instruments (NIHSS in combination with MMSE or MoCA) could only predict for 51% of the functional outcome. Therefore, it would be helpful if a better prognostic tool can improve the prediction for functional outcome to 70%-80%. Future studies may establish a modified scale combining the NIHSS and items from the MMSE and MoCA to improve the predictive ability for functional outcome.

Table 1. Population characteristics according to the functional outcome defined by mRS scores at 3-6 months after stroke

Characteristics N (%)	mRS 0–1 (*n* = 252)		mRS ≥2 (*n* = 136)		Univariate Analysis *P*
Age, mean (SD)	57.9	(10.8)	63.8	(11.8)	< 0.001
Gender, female	68	(27.0%)	52	(38.2%)	0.02
Education, *y* (mean, SD)	9.8	(4.3)	6.3	(3.7)	< 0.001
Ethnicity					0.039
Chinese	188	(74.6%)	87	(64.0%)	
Malay	40	(15.9%)	36	(26.5%)	
Indian and others	24	(9.5%)	13	(9.6%)	
Stroke classification					<0.001
SAO	114	(45.2%)	60	(44.1%)	
LAA	29	(11.5%)	30	(22.1%)	
CE	31	(12.3%)	25	(18.4%)	

Characteristics N (%)	mRS 0–1 (*n* = 252)		mRS ≥2 (*n* = 136)		Univariate Analysis *P*
UND and OC	12	(4.8%)	8	(5.9%)	
TIA	66	(26.2%)	13	(9.6%)	
NIHSS (mean, SD)	1.46	(1.83)	5.04	(3.68)	< 0.001
Premorbid mRS (median)	0.06	(0.29)	0.54	(1.05)	<0.001
Baseline mRS (median)	1.28	(1.20)	3.04	(1.21)	< 0.001
Mean interval (days) between stroke/TIA and assessment	2.4	(2.0)	3.8	(2.5)	< 0.001
Cognitive screening tests					
MMSE (mean, SD)	25.7	(3.3)	22.6	(4.3)	< 0.001
MoCA (mean, SD)	22.0	(4.8)	18.1	(5.5)	< 0.001
Number of cardiovascular risk factors (median)	2		3		<0.001
Recurrent vascular events (no., %)	10	(4.0%)	8	(6.0%)	0.37

Characteristics N (%)	mRS 0–1 ($n = 252$)	mRS ≥2 ($n = 136$)	Univariate Analysis P

mRS = modified Rankin scale; **SD**= Standard Deviations; **SAO =** small artery occlusion; **LAA**= large artery atherosclerosis; **CE** = cardioembolism; **UND** = undetermined etiology; **OC** = other determined etiology; **TIA**= transient ischemic attack; **NIHSS** = National Institute of Health Stroke Score; **MMSE=**Mini-Mental State Examination; **MoCA=**Montreal Cognitive Assessment.

Table 2. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS scores

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	54.10	<0.001
A1	2	Baseline MMSE	−0.1 (0.031)	0.47	0.012	8.48	0.004
	3	Baseline NIHSS	0.3 (<0.001)	0.51	0.038	29.00	<0.001
A2	2	Baseline NIHSS	0.3 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MMSE	−0.1 (0.031)	0.51	0.006	4.71	0.031
B1	2	Baseline MoCA	−0.08 (0.083)	0.47	0.007	4.80	0.029
	3	Baseline NIHSS	0.31 (<0.001)	0.51	0.040	31.10	<0.001
B2	2	Baseline NIHSS	0.31 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MoCA	−0.08 (0.083)	0.51	0.004	3.02	0.083

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

Table 3. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS for subsample of patients with NIHSS scores>2 at baseline

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	21.68	<0.001
A1	2	Baseline MMSE	−0.18 (0.010)	0.49	0.036	10.94	0.001
	3	Baseline NIHSS	0.22 (0.001)	0.53	0.034	11.07	0.001
A2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MMSE	−0.18 (0.010)	0.53	0.021	6.83	0.010
B1	2	Baseline MoCA	−0.16 (0.021)	0.49	0.029	8.51	0.004
	3	Baseline NIHSS	0.22 (0.001)	0.52	0.040	12.07	0.001
B2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MoCA	−0.16 (0.021)	0.52	0.017	5.42	0.021

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

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Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after stroke: an observational study

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ABSTRACT

Objectives: To investigate the prognostic value of the neurocognitive status measured by screening instruments, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), obtained at the subacute stroke phase or the baseline (≤ 2 weeks), for functional outcome 3–6 months later.

Design: Prospective observational study.

Setting: Tertiary stroke neurology service.

Participants: 400 patients with a recent ischemic stroke or transient ischemic attack (TIA) received NIHSS, MoCA and MMSE at baseline and were followed up at 3-6 months later.

Primary outcome measures: At 3-6 months following index event, functional outcome was measured by the modified Rankin Scale (mRS) scores.

Results: Baseline NIHSS, MMSE and MoCA scores individually predicted mRS scores at 3–6 months, with NIHSS being the strongest predictor (NIHSS: R^2change=0.043, p<0.001). Moreover, baseline MMSE scores had a small but statistically significant incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months, while baseline MoCA scores did not [MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083]. However, in patients with more severe stroke at baseline (defined as NIHSS>2), both baseline MoCA and MMSE had significant and moderately large incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months [MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021].

Conclusion: Cognitive screening at the subacute stroke phase can predict functional outcome independently and improve the predictive value of stroke severity scores for functional outcome 3–6 months later, particularly in patients with more severe stroke.

ARTICLE SUMMARY

Article focus

- The prognostic value of neurocognitive status measured by brief screening instruments, the MoCA and the MMSE, individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), at subacute stroke phase for functional outcomes at 3–6 months is unknown.
- We examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS for functional outcome 3–6 months after stroke.
- We also explored the predictive ability of these measures in patients with differing stroke severity.

Key messages

- Cognitive screening at the subacute stroke phase can predict functional outcome independently. Neurocognitive status measured by baseline MMSE scores adds a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients.
- ~~Unexpectedly~~Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥~~>~~2, neurocognitive status measured by both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

Strength and limitations of this study

- The main strength of this study is that we examined the prognostic value of neurocognitive status (MoCA and MMSE) and stroke severity (NIHSS) at subacute

stroke phase systematically as a singular measure and in combination for mRS scores 3–6 month later in a large sample of stroke patients and in patients with differing stroke severity.

- An additional strength is the choice of 3–6 month follow-up because patients were more likely to resume their daily activities and usual roles within this time frame. Hence, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke.
- The limitation of this study is that we did not systematically examine rehabilitation services provided for patients from subacute stroke phase to 3-6 months follow-up.

INTRODUCTION

It is important for early intervention and focused management to have instruments available during the subacute stroke phase for predicting functional outcome 3–6 months later. Cognitive performance measured by the Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) administered at the subacute stroke phase predicted patients' functional outcomes at inpatient discharge (1, 2).~~[1, 2]~~ Furthermore, patients' post-stroke cognitive functioning measured by a brief neuropsychological battery 2–3 weeks following stroke predicted their functional outcomes 13 months later (3).~~[3]~~ No study yet has investigated the utility of patients' neurocognitive status at the subacute stroke phase for predicting functional outcome at 3–6 months. A widely used stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), administered at the subacute stroke phase is predictive of patients' functional outcomes 3–6 months later (4),~~[4]~~ but has limited representation of cognitive function (5).~~[5]~~ Hence, whether the NIHSS and neurocognitive status at baseline are independently predictive o~~-~~r have additive predictive value for functional outcomes at 3–6 months is unknown.

We therefore examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS at the subacute stroke phase for functional outcome 3–6 months later. In addition, we explored the predictive ability of these measures in patients with differing stroke severity.

METHODS

Subjects

The methodology of this study has been described previously (6).[6] Briefly, we recruited 400 consecutive patients (≥21 years old) with a recent ischemic stroke or transient ischemic

attack (TIA) (≤14 days) during their inpatient admission (subacute stroke phase or baseline) at the National University Health System in Singapore. Patients were excluded if they had a major physical disability or an active psychiatric disorder that would impede cognitive testing.

Standard protocol approvals and patient consent

This study was approved by the National Healthcare Group Domain-Specific Review Board (DSRB), and was conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or legally acceptable representatives.

Procedures

Patients were assessed using the NIHSS, modified Rankin Scale (mRS) (premorbid and baseline functioning), MMSE[7] and MoCA[8] at baseline. In addition, their mRS scores were collected at 3–6 months later. The NIHSS and mRS were administered by certified research personnel blinded to patients' neurocognitive status at baseline and 3-6 months follow-up. Similarly, the cognitive screening tests were administered by trained research psychologists blinded to patients' NIHSS and mRS scores. The patients' functional outcome was defined by the continuous scores of mRS.

Statistical analyses

Between-group differences were examined using independent-sample *t* test for quantitative variables and Pearson's χ^2 test for categorical variables. Hierarchical regression analyses were conducted to examine the incremental contribution of baseline MMSE and MoCA compared with the baseline NIHSS in predicting functional outcomes defined by mRS scores at 3–6 months after stroke. In the initial analysis, the clinically-relevant or significant covariates (i.e., age, sex, years of education, number of cardiovascular risk factors, premorbid and baseline mRS) were entered in the first block. The cognitive screening variables (MMSE or MoCA) at baseline were entered in the second block and the NIHSS scores at baseline

were entered in the third block (Model A1 and B1 for MMSE and MoCA, respectively). Subsequently, the order of entry was altered, with baseline NIHSS scores entered in the second block and either baseline MMSE or MoCA entered at the third block (Model A2 and B2 for MMSE and MoCA, respectively). In order to explore predictive value in patients with differing stroke severity, we dichotomized the baseline NIHSS scores using a median split and repeated these analyses.

All statistical analyses were performed with IBM SPSS Statistics Version 20.0 for Windows.

RESULTS

Subject characteristics

The recruited patients were mostly Chinese (70.3%) and male (69.8%), with a mean age of 59.8 (11.6) years and a mean of 7.7 (4.3) years of formal education. Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0). The median interval between the stroke or TIA event and assessment was 2 days (range: 0–14).

At 3–6 months following the index event, patients who were lost to follow-up (n=12) were younger and their clinical condition was stabilized faster than those who completed the follow-up (age: 52.8±12.9 vs 60.0±11.5, p=0.03; interval days: 2.91±2.31 vs 2.08±0.90, p=0.01). We defined favorable functional outcome as mRS score ≤1 and poor functional outcome as mRS score ≥2. This dichotomized mRS scores for favorable and poor functional outcome is commonly used and is in keeping with the recommendation from previous analyses (9). The majority of the patients (n=252, 64.9%) had good functional outcomes (mRSscore ≤1) while approximately one third of the patients (n=136, 35.1%) had poor

functional outcomes (mRS score ≥2). Patients with poor functional outcome were significantly older, women, of Malay ethnicity, less educated, more neurologically impaired with poorer premorbid and baseline functioning, and assessed later following cerebrovascular event. They also had more stroke classification of large artery occlusion and cardioembolic stroke, as well as higher number of cardiovascular risk factors. In addition, patients with poorer functional outcome had significantly lower scores of the MMSE and the MoCA. The population characteristics of patients with favorable and poor functional outcomes can be found in Table 1.~~136 (35.1%) of patients had poor functional outcomes defined by mRS score >2 on follow-up. The population characteristics can be found in Table 1.~~

The Predictive Ability of the MoCA, MMSE and NIHSS

Using hierarchical regression analyses and controlling for baseline characteristics, the MMSE, MoCA and NIHSS—as singular measures—predicted mRS scores at 3–6 months after stroke (R^2 changes of 0.012, 0.007 and 0.043, with *p*-values 0.004, 0.029 and <0.001, respectively; Table 2). Baseline MMSE scores added a small but statistically significant prediction of functional outcomes in addition to baseline NIHSS scores, while baseline MoCA scores did not (MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083).

Using a median split of baseline NIHSS scores at 2, patients with NIHSS scores ≤2 (median =1, range 0–2) were defined as having less severe stroke and those with NIHSS score >2 (median = 5, range 3–18) were defined as having more severe stroke. As shown in Table 3, in patients with NIHSS score >2, both baseline MMSE and MoCA had a significant and considerable incremental prediction for functional outcomes at 3-6 months in addition to baseline NIHSS scores (MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021), while neither baseline neurocognitive measure nor baseline NIHSS showed an

incremental prediction for functional outcome in patients with less severe stroke (NIHSS score ≤2).

DISCUSSION

Cognitive screening at the subacute stroke phase can predict functional outcome at early convalescent stroke phase independently. Baseline MMSE scores add a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients. Additionally,~~Unexpectedly,~~ in patients with more severe stroke defined by baseline NIHSS score ≥~~>~~2, both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

The contributions of our study are three-fold. First, our finding that neurocognitive status at the subacute stroke phase predicts functional outcome at 3–6 months is novel and consistent with previous studies in inpatient rehabilitation ~~[~~(1, 2)~~]~~ and at 13 months after stroke (3).~~[3]~~ Second, MMSE scores at baseline add a small incremental prediction to baseline stroke severity scores for functional outcomes 3-6 months later. Third, both baseline MMSE and MoCA showed a considerable incremental effect to the baseline NIHSS scores in predicting functional outcomes in patients with more severe stroke (NIHSS>2) while neither neurocognitive measure nor stroke severity score at baseline was predictive for functional outcome in patients with less severe stroke (NIHSS score ≤2). This may be explained by the higher recovery potential of patients with more neurological deficits compared to patients with less severe deficits.

There are several strengths of our study. First, we examined the prognostic value of NIHSS and cognitive status by systematically assessing baseline values individually and in

combination in predicting patients' mRS scores 3–6 month after stroke. Although previous studies that investigated the predictive power of cognition included baseline NIHSS as a control variable (along with other baseline characteristics), they did not explore the role of baseline NIHSS as a predictor itself (1-3). ~~[1–3]~~ Second, we chose the 3–6 month follow-up period because prognosis of functional recovery can be made reliably within 12 weeks after stroke (10),~~[9]~~ and patients were more likely to resume their daily activities and usual roles within this time frame. Therefore, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke. Third, we examined the predictive ability of neurocognitive status and stroke severity measures at baseline for functional outcome at 3-6 months in patients with differing stroke severity.

There are several limitations of this study. First, ~~O~~our results may not be generalizable as the majority of patients had less severe stroke, nevertheless, a third had poor functional outcomes 3–6 months after stroke so better prognostic tools are required. Second, ~~W~~we employed cognitive screening tests at baseline rather than formal neuropsychological assessments, for their brevity and utility by non-specialist personnel. Third, ~~W~~we did not examine rehabilitation services systematically as this -information was not collected ~~study was designed to investigate cognitive outcomes after stroke~~. However, all patients received standard rehabilitation according to the institutional pathway. ~~In addition~~Fourth, the mRS has been criticized for its lack of specificity (5),~~[5]~~ however, it is a summary of outcomes in functioning and has been widely used in clinical trials as a primary efficacy measure. Last, we did not consider other predictive scores (e.g., PLAN score (11), iScore (12), six simple variable (13) and five simple variable scores (14)) for our models primarily due to the following reasons: 1) None of these scores include a cognitive measure.; 2) PLAN scores are developed using more severe functional outcome measure, such as mRS scores of 5 to 6 at

discharge. Similarly, iScore has been used to estimate poor functional outcome defined by mRS 3 to 5. ; 3) Six simple variable and five simple variable scores require Glasgow Coma Scale which we did not collect in this study. Therefore, we are unable to adopt these models to predict functional outcome in this study. However, in line with our aims, we included significant and clinically relevant predictors as control variables (age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS) in our models.

In conclusion, 4.3% of the functional outcome after 3-6 months can be predicted early after admission by NIHSS, with its many functional and only few cognitive items. Premorbid and baseline factors alone however, explain almost half of the variance. In addition, ~~In conclusion,~~ neurocognitive status at the subacute stroke phase is independently predictive of functioning at early convalescent stroke phase. Baseline MMSE scores can add incremental prediction to baseline stroke severity score for functional outcome 3-6 months later. Moreover, in patients with more recovery potential, both baseline MMSE and MoCA can improve baseline stroke severity score in predicting functional outcomes 3–6 months later. We have previously shown that these screening tests administered at the subacute stroke phase could also predict cognitive outcomes 3–6 months later (6).~~[6]~~ In addition, MoCA administration has been reported to be applicable to the majority of acute stroke patients (ischemic or hemorrhagic) (82.5%),and therefore feasible to be used in acute stroke phase (15). Therefore, the predictive value and brevity of the MMSE and MoCA warrants their routine use in the subacute stroke phase in clinical service and early acute stroke trials. However, the current instruments (NIHSS in combination with MMSE or MoCA) could only predict for 51% of the functional outcome. Therefore, it would be helpful if a better prognostic tool can improve the prediction for functional outcome to 70%-80%.

Future studies may establish a modified scale combining the NIHSS and items from the MMSE and MoCA to improve the predictive ability for functional outcome.

Table 1. Population characteristics according to the functional outcome defined by mRS scores at 3-6 months after stroke

Characteristics N (%)	mRS 0–12 (*n* = 252)		mRS >>2 (*n* = 136)		Univariate Analysis *P*
Age, mean (SD)	57.9	(10.8)	63.8	(11.8)	< 0.001
Gender, female*	68	(27.0%)	52	(38.2%)	0.02
Education, *y* (mean, SD)	9.8	(4.3)	6.3	(3.7)	< 0.001
Ethnicity					0.039
Chinese	188	(74.6%)	87	(64.0%)	
Malay	40	(15.9%)	36	(26.5%)	
Indian and others	224	(9.58.7%)	123	(9.68.8%)	
~~*Others*~~	~~2~~	~~(0.8%)~~	~~1~~	~~(0.7 %)~~	
Stroke classification					≤0.001
SAO	114	(45.2%)	60	(44.1%)	
LAA	29	(11.5%)	30	(22.1%)	

Characteristics N (%)	mRS 0–12 (*n* = 252)		mRS >=2 (*n* = 136)		Univariate Analysis *P*
CE	31	(12.3%)	25	(18.4%)	
UND and OC	121	(4.84%)	87	(5.91%)	
~~*OC*~~	~~1~~	~~(0.4%)~~	~~1~~	~~(0.7%)~~	
TIA	66	(26.2%)	13	(9.6%)	
NIHSS (~~median~~ mean, SD)~~*~~	1.46	(1.83)	5.04	(3.68)	<0.001
Premorbid mRS (median ~~median~~)	0.06	(0.29)	0.54	(1.05)	<0.001
Baseline mRS (median ~~median~~)~~*~~	1.28	(1.20)	3.04	(1.21)	<0.001
Mean interval (days) between stroke/TIA and assessment	2.4	(2.0)	3.8	(2.5)	<0.001
Cognitive screening tests					
MMSE (mean, SD)	25.7	(3.3)	22.6	(4.3)	<0.001
MoCA (mean, SD)	22.0	(4.8)	18.1	(5.5)	<0.001
Number of cardiovascular risk factors (median)	2		3		<0.001

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Characteristics N (%)	mRS 0–12 (*n* = 252)		mRS ~~>~~≥2 (*n* = 136)		Univariate Analysis *P*
Recurrent vascular events (no., %)	10	(4.0%)	8	(6.0%)	0.37

~~*P<0.050 for logistic regression for binary outcome of mRS scores of 0–1 and ≥ 2.~~

mRS = modified Rankin scale; **SD**= Standard Deviations; **SAO =** small artery occlusion; **LAA**= large artery atherosclerosis; **CE** = cardioembolism; **UND** = undetermined etiology; **OC** = other determined etiology; **TIA**= transient ischemic attack; **NIHSS** = National Institute of Health Stroke Score; **MMSE**=Mini-Mental State Examination; **MoCA**=Montreal Cognitive Assessment.

Table 2. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS scores

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	54.10	<0.001
A1	2	Baseline MMSE	−0.1 (0.031)	0.47	0.012	8.48	0.004
	3	Baseline NIHSS	0.3 (<0.001)	0.51	0.038	29.00	<0.001
A2	2	Baseline NIHSS	0.3 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MMSE	−0.1 (0.031)	0.51	0.006	4.71	0.031
B1	2	Baseline MoCA	−0.08 (0.083)	0.47	0.007	4.80	0.029
	3	Baseline NIHSS	0.31 (<0.001)	0.51	0.040	31.10	<0.001
B2	2	Baseline NIHSS	0.31 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MoCA	−0.08 (0.083)	0.51	0.004	3.02	0.083

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

Table 3. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS for subsample of patients with NIHSS scores>2 at baseline

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	21.68	<0.001
A1	2	Baseline MMSE	−0.18 (0.010)	0.49	0.036	10.94	0.001
	3	Baseline NIHSS	0.22 (0.001)	0.53	0.034	11.07	0.001
A2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MMSE	−0.18 (0.010)	0.53	0.021	6.83	0.010
B1	2	Baseline MoCA	−0.16 (0.021)	0.49	0.029	8.51	0.004
	3	Baseline NIHSS	0.22 (0.001)	0.52	0.040	12.07	0.001
B2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MoCA	−0.16 (0.021)	0.52	0.017	5.42	0.021

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

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Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after mild stroke and transient ischemic attack: an observational study

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Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after mild stroke and transient ischemic attack: an observational study

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ABSTRACT

Objectives: To investigate the prognostic value of the neurocognitive status measured by screening instruments, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), obtained at the subacute stroke phase or the baseline (≤ 2 weeks), for functional outcome 3–6 months later.

Design: Prospective observational study.

Setting: Tertiary stroke neurology service.

Participants: 400 patients with a recent ischemic stroke or transient ischemic attack (TIA) received NIHSS, MoCA and MMSE at baseline and were followed up at 3-6 months later.

Primary outcome measures: At 3-6 months following index event, functional outcome was measured by the modified Rankin Scale (mRS) scores.

Results: Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0), while a minority of patients had TIA (20.3%). Baseline NIHSS, MMSE and MoCA scores individually predicted mRS scores at 3–6 months, with NIHSS being the strongest predictor (NIHSS: R^2change=0.043, p<0.001). Moreover, baseline MMSE scores had a small but statistically significant incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months, while baseline MoCA scores did not [MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083]. However, in patients with more severe stroke at baseline (defined as NIHSS>2), both baseline MoCA and MMSE had significant and moderately large incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months [MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021].

Conclusion: Cognitive screening at the subacute stroke phase can predict functional outcome independently and improve the predictive value of stroke severity scores for functional outcome 3–6 months later, particularly in patients with more severe stroke.

ARTICLE SUMMARY

Article focus

- The prognostic value of neurocognitive status measured by brief screening instruments, the MoCA and the MMSE, individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), at subacute stroke phase for functional outcomes at 3–6 months is unknown.
- We examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS for functional outcome 3–6 months after mild stroke and transient ischemic attack.
- We also explored the predictive ability of these measures in patients with differing stroke severity.

Key messages

- Cognitive screening at the subacute stroke phase can predict functional outcome independently. Neurocognitive status measured by baseline MMSE scores adds a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients.
- Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, neurocognitive status measured by both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

Strength and limitations of this study

- The main strength of this study is that we examined the prognostic value of neurocognitive status (MoCA and MMSE) and stroke severity (NIHSS) at subacute stroke phase systematically as a singular measure and in combination for mRS scores 3–6 month later in a large sample of stroke patients and in patients with differing stroke severity.
- An additional strength is the choice of 3–6 month follow-up because patients were more likely to resume their daily activities and usual roles within this time frame. Hence, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke.
- The limitation of this study is that we did not systematically examine rehabilitation services provided for patients from subacute stroke phase to 3-6 months follow-up.

INTRODUCTION

It is important for early intervention and focused management to have instruments available during the subacute stroke phase for predicting functional outcome 3–6 months later. Cognitive performance measured by the Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) administered at the subacute stroke phase predicted patients' functional outcomes at inpatient discharge (1, 2). Furthermore, patients' post-stroke cognitive functioning measured by a brief neuropsychological battery 2–3 weeks following stroke predicted their functional outcomes 13 months later (3). No study yet has investigated the utility of patients' neurocognitive status at the subacute stroke phase for predicting functional outcome at 3–6 months. A widely used stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), administered at the subacute stroke phase is predictive of patients' functional outcomes 3–6 months later (4), but has limited representation of cognitive function (5). Hence, whether the NIHSS and neurocognitive status at baseline are independently predictive or have additive predictive value for functional outcomes at 3–6 months is unknown.

We therefore examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS at the subacute stroke phase for functional outcome 3–6 months later. In addition, we explored the predictive ability of these measures in patients with differing stroke severity.

METHODS

Subjects

The methodology of this study has been described previously (6).[6] Briefly, we recruited 400 consecutive patients (≥21 years old) with a recent ischemic stroke or transient ischemic

attack (TIA) (≤14 days) during their inpatient admission (subacute stroke phase or baseline) at the National University Health System in Singapore. Patients were excluded if they had a major physical disability or an active psychiatric disorder that would impede cognitive testing.

Standard protocol approvals and patient consent

This study was approved by the National Healthcare Group Domain-Specific Review Board (DSRB), and was conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or legally acceptable representatives.

Procedures

Patients were assessed using the NIHSS, modified Rankin Scale (mRS) (premorbid and baseline functioning), MMSE (7) and MoCA (8) at baseline. In addition, their mRS scores were collected at 3–6 months later. The NIHSS and mRS were administered by certified research personnel blinded to patients' neurocognitive status at baseline and 3-6 months follow-up. Similarly, the cognitive screening tests were administered by trained research psychologists blinded to patients' NIHSS and mRS scores. The patients' functional outcome was defined by the continuous scores of mRS.

Statistical analyses

Between-group differences were examined using independent-sample *t* test for quantitative variables and Pearson's χ^2 test for categorical variables. Hierarchical regression analyses were conducted to examine the incremental contribution of baseline MMSE and MoCA compared with the baseline NIHSS in predicting functional outcomes defined by mRS scores at 3–6 months after stroke. In the initial analysis, the clinically-relevant or significant covariates (i.e., age, sex, years of education, number of cardiovascular risk factors, premorbid and baseline mRS) were entered in the first block. The cognitive screening variables (MMSE or MoCA) at baseline were entered in the second block and the NIHSS scores at baseline

were entered in the third block (Model A1 and B1 for MMSE and MoCA, respectively). Subsequently, the order of entry was altered, with baseline NIHSS scores entered in the second block and either baseline MMSE or MoCA entered at the third block (Model A2 and B2 for MMSE and MoCA, respectively). In order to explore predictive value in patients with differing stroke severity, we dichotomized the baseline NIHSS scores using a median split and repeated these analyses.

All statistical analyses were performed with IBM SPSS Statistics Version 20.0 for Windows.

RESULTS

Subject characteristics

The recruited patients were mostly Chinese (70.3%) and male (69.8%), with a mean age of 59.8 (11.6) years and a mean of 7.7 (4.3) years of formal education. Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0), while a minority of patients had TIA (20.3%). The median interval between the stroke or TIA event and assessment was 2 days (range: 0–14).

At 3–6 months following the index event, patients who were lost to follow-up (n=12) were younger and their clinical condition was stabilized faster than those who completed the follow-up (age: 52.8±12.9 vs 60.0±11.5, p=0.03; interval days: 2.91±2.31 vs 2.08±0.90, p=0.01). We defined favorable functional outcome as mRS score ≤1 and poor functional outcome as mRS score ≥2. This dichotomized mRS scores for favorable and poor functional outcome is commonly used and is in keeping with the recommendation from previous analyses (9). The majority of the patients (n=252, 64.9%) had good functional outcomes (mRSscore ≤1) while approximately one third of the patients (n=136, 35.1%) had poor

functional outcomes (mRS score ≥2). Patients with poor functional outcome were significantly older, women, of Malay ethnicity, less educated, more neurologically impaired with poorer premorbid and baseline functioning, and assessed later following cerebrovascular event. They also had more stroke classification of large artery occlusion and cardioembolic stroke, as well as higher number of cardiovascular risk factors. In addition, patients with poorer functional outcome had significantly lower scores of the MMSE and the MoCA. The population characteristics of patients with favorable and poor functional outcomes can be found in Table 1.

The Predictive Ability of the MoCA, MMSE and NIHSS

Using hierarchical regression analyses and controlling for baseline characteristics, the MMSE, MoCA and NIHSS—as singular measures—predicted mRS scores at 3–6 months after stroke (R^2 changes of 0.012, 0.007 and 0.043, with *p*-values 0.004, 0.029 and <0.001, respectively; Table 2). Baseline MMSE scores added a small but statistically significant prediction of functional outcomes in addition to baseline NIHSS scores, while baseline MoCA scores did not (MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083).

Using a median split of baseline NIHSS scores at 2, patients with NIHSS scores ≤2 (median =1, range 0–2) were defined as having less severe stroke and those with NIHSS score >2 (median = 5, range 3–18) were defined as having more severe stroke. As shown in Table 3, in patients with NIHSS score >2, both baseline MMSE and MoCA had a significant and considerable incremental prediction for functional outcomes at 3-6 months in addition to baseline NIHSS scores (MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021), while neither baseline neurocognitive measure nor baseline NIHSS showed an incremental prediction for functional outcome in patients with less severe stroke (NIHSS score ≤2).

DISCUSSION

Cognitive screening at the subacute stroke phase can predict functional outcome at early convalescent stroke phase independently. Baseline MMSE scores add a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients. Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

The contributions of our study are three-fold. First, our finding that neurocognitive status at the subacute stroke phase predicts functional outcome at 3–6 months is novel and consistent with previous studies in inpatient rehabilitation (1, 2) and at 13 months after stroke (3). Second, MMSE scores at baseline add a small incremental prediction to baseline stroke severity scores for functional outcomes 3-6 months later. Third, both baseline MMSE and MoCA showed a considerable incremental effect to the baseline NIHSS scores in predicting functional outcomes in patients with more severe stroke (NIHSS>2) while neither neurocognitive measure nor stroke severity score at baseline was predictive for functional outcome in patients with less severe stroke (NIHSS score ≤2). This may be explained by the higher recovery potential of patients with more neurological deficits compared to patients with less severe deficits.

There are several strengths of our study. First, we examined the prognostic value of NIHSS and cognitive status by systematically assessing baseline values individually and in combination in predicting patients' mRS scores 3–6 month after stroke. Although previous studies that investigated the predictive power of cognition included baseline NIHSS as a control variable (along with other baseline characteristics), they did not explore the role of

baseline NIHSS as a predictor itself (1-3). Second, we chose the 3–6 month follow-up period because prognosis of functional recovery can be made reliably within 12 weeks after stroke (10), and patients were more likely to resume their daily activities and usual roles within this time frame. Therefore, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke. Third, we examined the predictive ability of neurocognitive status and stroke severity measures at baseline for functional outcome at 3-6 months in patients with differing stroke severity.

There are several limitations of this study. First, our results may not be generalizable as the majority of patients had less severe stroke, nevertheless, a third had poor functional outcomes 3–6 months after stroke so better prognostic tools are required. Second, we employed cognitive screening tests at baseline rather than formal neuropsychological assessments, for their brevity and utility by non-specialist personnel. Third, we did not examine rehabilitation services systematically as this information was not collected. However, all patients received standard rehabilitation according to the institutional pathway. Fourth, the mRS has been criticized for its lack of specificity (5), however, it is a summary of outcomes in functioning and has been widely used in clinical trials as a primary efficacy measure. Last, we did not consider other predictive scores (e.g., PLAN score (11), iScore (12), six simple variable (13) and five simple variable scores (14)) for our models primarily due to the following reasons: 1) None of these scores include a cognitive measure.; 2) PLAN scores are developed using more severe functional outcome measure, such as mRS scores of 5 to 6 at discharge**.** Similarly, iScore has been used to estimate poor functional outcome defined by mRS 3 to 5. ; 3) Six simple variable and five simple variable scores require Glasgow Coma Scale which we did not collect in this study. Therefore, we are unable to adopt these models to predict functional outcome in this study. However, in line with our aims, we included

significant and clinically relevant predictors as control variables (age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS) in our models. Our prediction models can be applied to patients with mild ischemic stroke and TIA, especially in those with NIHSS score >2. The routine cognitive screening at subacute stroke phase with either MoCA or MMSE could add incremental predictive value to the NIHSS of patients with NIHSS score >2 for functional outcomes at 3-6 months. However, this model has yet to be validated externally, therefore it may not be generalizable to other stroke population.

In conclusion, 4.3% of the functional outcome after 3-6 months can be predicted early after admission by NIHSS, with its many functional and only few cognitive items. Premorbid and baseline factors alone however, explain almost half of the variance. In addition, neurocognitive status at the subacute stroke phase is independently predictive of functioning at early convalescent stroke phase. Baseline MMSE scores can add incremental prediction to baseline stroke severity score for functional outcome 3-6 months later. Moreover, in patients with more recovery potential, both baseline MMSE and MoCA can improve baseline stroke severity score in predicting functional outcomes 3–6 months later. We have previously shown that these screening tests administered at the subacute stroke phase could also predict cognitive outcomes 3–6 months later (6). In addition, MoCA administration has been reported to be applicable to the majority of acute stroke patients (ischemic or hemorrhagic) (82.5%),and therefore feasible to be used in acute stroke phase (15). Therefore, the predictive value and brevity of the MMSE and MoCA warrants their routine use in the subacute stroke phase in clinical service and early acute stroke trials. However, the current instruments (NIHSS in combination with MMSE or MoCA) could only predict for 51% of the functional outcome. Therefore, it would be helpful if a better prognostic tool can improve the prediction

for functional outcome to 70%-80%. Future studies may establish a modified scale combining the NIHSS and items from the MMSE and MoCA to improve the predictive ability for functional outcome.

Table 1. Population characteristics according to the functional outcome defined by mRS scores at 3-6 months after stroke

Characteristics N (%)	mRS 0–1 ($n = 252$)		mRS ≥2 ($n = 136$)		Univariate Analysis *P*
Age, mean (SD)	57.9	(10.8)	63.8	(11.8)	< 0.001
Gender, female	68	(27.0%)	52	(38.2%)	0.02
Education, *y* (mean, SD)	9.8	(4.3)	6.3	(3.7)	< 0.001
Ethnicity					0.039
Chinese	188	(74.6%)	87	(64.0%)	
Malay	40	(15.9%)	36	(26.5%)	
Indian and others	24	(9.5%)	13	(9.6%)	
Stroke classification					<0.001
SAO	114	(45.2%)	60	(44.1%)	
LAA	29	(11.5%)	30	(22.1%)	
CE	31	(12.3%)	25	(18.4%)	

Characteristics N (%)	mRS 0–1 (*n* = 252)		mRS ≥2 (*n* = 136)		Univariate Analysis *P*
UND and OC	12	(4.8%)	8	(5.9%)	
TIA	66	(26.2%)	13	(9.6%)	
NIHSS (mean, SD)	1.46	(1.83)	5.04	(3.68)	< 0.001
Premorbid mRS (median)	0.06	(0.29)	0.54	(1.05)	<0.001
Baseline mRS (median)	1.28	(1.20)	3.04	(1.21)	< 0.001
Mean interval (days) between stroke/TIA and assessment	2.4	(2.0)	3.8	(2.5)	< 0.001
Cognitive screening tests					
MMSE (mean, SD)	25.7	(3.3)	22.6	(4.3)	< 0.001
MoCA (mean, SD)	22.0	(4.8)	18.1	(5.5)	< 0.001
Number of cardiovascular risk factors (median)	2		3		<0.001
Recurrent vascular events (no., %)	10	(4.0%)	8	(6.0%)	0.37

Characteristics N (%)	mRS 0–1 ($n = 252$)	mRS ≥2 ($n = 136$)	Univariate Analysis P

mRS = modified Rankin scale; **SD**= Standard Deviations; **SAO =** small artery occlusion; **LAA**= large artery atherosclerosis; **CE** = cardioembolism; **UND** = undetermined etiology; **OC** = other determined etiology; **TIA**= transient ischemic attack; **NIHSS** = National Institute of Health Stroke Score; **MMSE=**Mini-Mental State Examination; **MoCA=**Montreal Cognitive Assessment.

Table 2. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS scores

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	54.10	<0.001
A1	2	Baseline MMSE	−0.1 (0.031)	0.47	0.012	8.48	0.004
	3	Baseline NIHSS	0.3 (<0.001)	0.51	0.038	29.00	<0.001
A2	2	Baseline NIHSS	0.3 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MMSE	−0.1 (0.031)	0.51	0.006	4.71	0.031
B1	2	Baseline MoCA	−0.08 (0.083)	0.47	0.007	4.80	0.029
	3	Baseline NIHSS	0.31 (<0.001)	0.51	0.040	31.10	<0.001
B2	2	Baseline NIHSS	0.31 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MoCA	−0.08 (0.083)	0.51	0.004	3.02	0.083

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

Table 3. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS for subsample of patients with NIHSS scores>2 at baseline

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	21.68	<0.001
A1	2	Baseline MMSE	−0.18 (0.010)	0.49	0.036	10.94	0.001
	3	Baseline NIHSS	0.22 (0.001)	0.53	0.034	11.07	0.001
A2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MMSE	−0.18 (0.010)	0.53	0.021	6.83	0.010
B1	2	Baseline MoCA	−0.16 (0.021)	0.49	0.029	8.51	0.004
	3	Baseline NIHSS	0.22 (0.001)	0.52	0.040	12.07	0.001
B2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MoCA	−0.16 (0.021)	0.52	0.017	5.42	0.021

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

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Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after mild stroke and transient ischemic attack: an observational study

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ABSTRACT

Objectives: To investigate the prognostic value of the neurocognitive status measured by screening instruments, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), obtained at the subacute stroke phase or the baseline (≤ 2 weeks), for functional outcome 3–6 months later.

Design: Prospective observational study.

Setting: Tertiary stroke neurology service.

Participants: 400 patients with a recent ischemic stroke or transient ischemic attack (TIA) received NIHSS, MoCA and MMSE at baseline and were followed up at 3-6 months later.

Primary outcome measures: At 3-6 months following index event, functional outcome was measured by the modified Rankin Scale (mRS) scores.

Results: Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0), while a minority of patients had TIA (20.3%). Baseline NIHSS, MMSE and MoCA scores individually predicted mRS scores at 3–6 months, with NIHSS being the strongest predictor (NIHSS: R^2change=0.043, p<0.001). Moreover, baseline MMSE scores had a small but statistically significant incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months, while baseline MoCA scores did not [MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083]. However, in patients with more severe stroke at baseline (defined as NIHSS>2), both baseline MoCA and MMSE had significant and moderately large incremental predictive value to the baseline NIHSS for mRS scores at 3-6 months [MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021].

Conclusion: Cognitive screening at the subacute stroke phase can predict functional outcome independently and improve the predictive value of stroke severity scores for functional outcome 3–6 months later, particularly in patients with more severe stroke.

ARTICLE SUMMARY

Article focus

- The prognostic value of neurocognitive status measured by brief screening instruments, the MoCA and the MMSE, individually and in combination with the stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), at subacute stroke phase for functional outcomes at 3–6 months is unknown.
- We examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS for functional outcome 3–6 months after mild stroke and transient ischemic attack.
- We also explored the predictive ability of these measures in patients with differing stroke severity.

Key messages

- Cognitive screening at the subacute stroke phase can predict functional outcome independently. Neurocognitive status measured by baseline MMSE scores adds a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients.
- Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, neurocognitive status measured by both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

Strength and limitations of this study

- The main strength of this study is that we examined the prognostic value of neurocognitive status (MoCA and MMSE) and stroke severity (NIHSS) at subacute stroke phase systematically as a singular measure and in combination for mRS scores 3–6 month later in a large sample of stroke patients and in patients with differing stroke severity.
- An additional strength is the choice of 3–6 month follow-up because patients were more likely to resume their daily activities and usual roles within this time frame. Hence, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke.
- The limitation of this study is that we did not systematically examine rehabilitation services provided for patients from subacute stroke phase to 3-6 months follow-up.

INTRODUCTION

It is important for early intervention and focused management to have instruments available during the subacute stroke phase for predicting functional outcome 3–6 months later. Cognitive performance measured by the Montreal Cognitive Assessment (MoCA) and the Mini-mental State Examination (MMSE) administered at the subacute stroke phase predicted patients' functional outcomes at inpatient discharge (1, 2). Furthermore, patients' post-stroke cognitive functioning measured by a brief neuropsychological battery 2–3 weeks following stroke predicted their functional outcomes 13 months later (3). No study yet has investigated the utility of patients' neurocognitive status at the subacute stroke phase for predicting functional outcome at 3–6 months. A widely used stroke severity scale, the National Institute of Health Stroke Scale (NIHSS), administered at the subacute stroke phase is predictive of patients' functional outcomes 3–6 months later (4), but has limited representation of cognitive function (5). Hence, whether the NIHSS and neurocognitive status at baseline are independently predictive or have additive predictive value for functional outcomes at 3–6 months is unknown.

We therefore examined the predictive ability of MMSE and MoCA individually and in combination with the NIHSS at the subacute stroke phase for functional outcome 3–6 months later. In addition, we explored the predictive ability of these measures in patients with differing stroke severity.

METHODS

Subjects

The methodology of this study has been described previously (6).[6] Briefly, we recruited 400 consecutive patients (≥21 years old) with a recent ischemic stroke or transient ischemic

attack (TIA) (≤14 days) during their inpatient admission (subacute stroke phase or baseline) at the National University Health System in Singapore. Patients were excluded if they had a major physical disability or an active psychiatric disorder that would impede cognitive testing.

Standard protocol approvals and patient consent

This study was approved by the National Healthcare Group Domain-Specific Review Board (DSRB), and was conducted in conformity with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or legally acceptable representatives.

Procedures

Patients were assessed using the NIHSS, modified Rankin Scale (mRS) (premorbid and baseline functioning), MMSE (7) and MoCA (8) at baseline. In addition, their mRS scores were collected at 3–6 months later. The NIHSS and mRS were administered by certified research personnel blinded to patients' neurocognitive status at baseline and 3-6 months follow-up. Similarly, the cognitive screening tests were administered by trained research psychologists blinded to patients' NIHSS and mRS scores. The patients' functional outcome was defined by the continuous scores of mRS.

Statistical analyses

Between-group differences were examined using independent-sample *t* test for quantitative variables and Pearson's χ^2 test for categorical variables. Hierarchical regression analyses were conducted to examine the incremental contribution of baseline MMSE and MoCA compared with the baseline NIHSS in predicting functional outcomes defined by mRS scores at 3–6 months after stroke. In the initial analysis, the clinically-relevant or significant covariates (i.e., age, sex, years of education, number of cardiovascular risk factors, premorbid and baseline mRS) were entered in the first block. The cognitive screening variables (MMSE or MoCA) at baseline were entered in the second block and the NIHSS scores at baseline

were entered in the third block (Model A1 and B1 for MMSE and MoCA, respectively). Subsequently, the order of entry was altered, with baseline NIHSS scores entered in the second block and either baseline MMSE or MoCA entered at the third block (Model A2 and B2 for MMSE and MoCA, respectively). In order to explore predictive value in patients with differing stroke severity, we dichotomized the baseline NIHSS scores using a median split and repeated these analyses.

All statistical analyses were performed with IBM SPSS Statistics Version 20.0 for Windows.

RESULTS

Subject characteristics

The recruited patients were mostly Chinese (70.3%) and male (69.8%), with a mean age of 59.8 (11.6) years and a mean of 7.7 (4.3) years of formal education. Most patients (79.8%) had a mild ischemic stroke and less disability (median NIHSS =2, median mRS =2, median premorbid mRS =0), while a minority of patients had TIA (20.3%). The median interval between the stroke or TIA event and assessment was 2 days (range: 0–14).

At 3–6 months following the index event, patients who were lost to follow-up (n=12) were younger and their clinical condition was stabilized faster than those who completed the follow-up (age: 52.8±12.9 vs 60.0±11.5, p=0.03; interval days: 2.91±2.31 vs 2.08±0.90, p=0.01). We defined favorable functional outcome as mRS score ≤1 and poor functional outcome as mRS score ≥2. This dichotomized mRS scores for favorable and poor functional outcome is commonly used and is in keeping with the recommendation from previous analyses (9). The majority of the patients (n=252, 64.9%) had good functional outcomes (mRSscore ≤1) while approximately one third of the patients (n=136, 35.1%) had poor

functional outcomes (mRS score ≥2). Patients with poor functional outcome were significantly older, women, of Malay ethnicity, less educated, more neurologically impaired with poorer premorbid and baseline functioning, and assessed later following cerebrovascular event. They also had more stroke classification of large artery occlusion and cardioembolic stroke, as well as higher number of cardiovascular risk factors. In addition, patients with poorer functional outcome had significantly lower scores of the MMSE and the MoCA. The population characteristics of patients with favorable and poor functional outcomes can be found in Table 1.

The Predictive Ability of the MoCA, MMSE and NIHSS

Using hierarchical regression analyses and controlling for baseline characteristics, the MMSE, MoCA and NIHSS—as singular measures—predicted mRS scores at 3–6 months after stroke (R^2 changes of 0.012, 0.007 and 0.043, with *p*-values 0.004, 0.029 and <0.001, respectively; Table 2). Baseline MMSE scores added a small but statistically significant prediction of functional outcomes in addition to baseline NIHSS scores, while baseline MoCA scores did not (MMSE: R^2changes=0.006, p=0.03; MoCA: R^2changes= 0.004, p=0.083).

Using a median split of baseline NIHSS scores at 2, patients with NIHSS scores ≤2 (median =1, range 0–2) were defined as having less severe stroke and those with NIHSS score >2 (median = 5, range 3–18) were defined as having more severe stroke. As shown in Table 3, in patients with NIHSS score >2, both baseline MMSE and MoCA had a significant and considerable incremental prediction for functional outcomes at 3-6 months in addition to baseline NIHSS scores (MMSE: R^2changes=0.021, p=0.010; MoCA: R^2changes=0.017, p=0.021), while neither baseline neurocognitive measure nor baseline NIHSS showed an incremental prediction for functional outcome in patients with less severe stroke (NIHSS score ≤2).

DISCUSSION

Cognitive screening at the subacute stroke phase can predict functional outcome at early convalescent stroke phase independently. Baseline MMSE scores add a small incremental prediction to baseline stroke severity scores for functional outcomes at 3-6 months in stroke patients. Additionally, in patients with more severe stroke defined by baseline NIHSS score ≥2, both baseline MMSE and MoCA improve the predictive value of stroke severity scores for functional outcome 3–6 months later. However, the incremental predictive value of the MMSE and MoCA is relatively smaller than the NIHSS.

The contributions of our study are three-fold. First, our finding that neurocognitive status at the subacute stroke phase predicts functional outcome at 3–6 months is novel and consistent with previous studies in inpatient rehabilitation (1, 2) and at 13 months after stroke (3). Second, MMSE scores at baseline add a small incremental prediction to baseline stroke severity scores for functional outcomes 3-6 months later. Third, both baseline MMSE and MoCA showed a considerable incremental effect to the baseline NIHSS scores in predicting functional outcomes in patients with more severe stroke (NIHSS>2) while neither neurocognitive measure nor stroke severity score at baseline was predictive for functional outcome in patients with less severe stroke (NIHSS score ≤2). This may be explained by the higher recovery potential of patients with more neurological deficits compared to patients with less severe deficits.

There are several strengths of our study. First, we examined the prognostic value of NIHSS and cognitive status by systematically assessing baseline values individually and in combination in predicting patients' mRS scores 3–6 month after stroke. Although previous studies that investigated the predictive power of cognition included baseline NIHSS as a control variable (along with other baseline characteristics), they did not explore the role of

baseline NIHSS as a predictor itself (1-3). Second, we chose the 3–6 month follow-up period because prognosis of functional recovery can be made reliably within 12 weeks after stroke (10), and patients were more likely to resume their daily activities and usual roles within this time frame. Therefore, the findings established in this study can guide early intervention from baseline to 3-6 months after stroke. Third, we examined the predictive ability of neurocognitive status and stroke severity measures at baseline for functional outcome at 3-6 months in patients with differing stroke severity.

There are several limitations of this study. First, our results may not be generalizable as the majority of patients had less severe stroke, nevertheless, a third had poor functional outcomes 3–6 months after stroke so better prognostic tools are required. Second, we employed cognitive screening tests at baseline rather than formal neuropsychological assessments, for their brevity and utility by non-specialist personnel. Third, we did not examine rehabilitation services systematically as this information was not collected. However, all patients received standard rehabilitation according to the institutional pathway. Fourth, the mRS has been criticized for its lack of specificity (5), however, it is a summary of outcomes in functioning and has been widely used in clinical trials as a primary efficacy measure. Last, we did not consider other predictive scores (e.g., PLAN score (11), iScore (12), six simple variable (13) and five simple variable scores (14)) for our models primarily due to the following reasons: 1) None of these scores include a cognitive measure.; 2) PLAN scores are developed using more severe functional outcome measure, such as mRS scores of 5 to 6 at discharge**.** Similarly, iScore has been used to estimate poor functional outcome defined by mRS 3 to 5. ; 3) Six simple variable and five simple variable scores require Glasgow Coma Scale which we did not collect in this study. Therefore, we are unable to adopt these models to predict functional outcome in this study. However, in line with our aims, we included

significant and clinically relevant predictors as control variables (age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS) in our models. Our prediction models can be applied to patients with mild ischemic stroke and TIA, especially in those with NIHSS score >2. The routine cognitive screening at subacute stroke phase with either MoCA or MMSE could add incremental predictive value to the NIHSS of patients with NIHSS score >2 for functional outcomes at 3-6 months. However, this model has yet to be validated externally, therefore it may not be generalizable to other stroke population.

In conclusion, 4.3% of the functional outcome after 3-6 months can be predicted early after admission by NIHSS, with its many functional and only few cognitive items. Premorbid and baseline factors alone however, explain almost half of the variance. In addition, neurocognitive status at the subacute stroke phase is independently predictive of functioning at early convalescent stroke phase. Baseline MMSE scores can add incremental prediction to baseline stroke severity score for functional outcome 3-6 months later. Moreover, in patients with more recovery potential, both baseline MMSE and MoCA can improve baseline stroke severity score in predicting functional outcomes 3–6 months later. We have previously shown that these screening tests administered at the subacute stroke phase could also predict cognitive outcomes 3–6 months later (6). In addition, MoCA administration has been reported to be applicable to the majority of acute stroke patients (ischemic or hemorrhagic) (82.5%),and therefore feasible to be used in acute stroke phase (15). Therefore, the predictive value and brevity of the MMSE and MoCA warrants their routine use in the subacute stroke phase in clinical service and early acute stroke trials. However, the current instruments (NIHSS in combination with MMSE or MoCA) could only predict for 51% of the functional outcome. Therefore, it would be helpful if a better prognostic tool can improve the prediction

for functional outcome to 70%-80%. Future studies may establish a modified scale combining the NIHSS and items from the MMSE and MoCA to improve the predictive ability for functional outcome.

Table 1. Population characteristics according to the functional outcome defined by mRS scores at 3-6 months after stroke

Characteristics N (%)	mRS 0–1 (*n* = 252)		mRS ≥2 (*n* = 136)		Univariate Analysis *P*
Age, mean (SD)	57.9	(10.8)	63.8	(11.8)	< 0.001
Gender, female	68	(27.0%)	52	(38.2%)	0.02
Education, *y* (mean, SD)	9.8	(4.3)	6.3	(3.7)	< 0.001
Ethnicity					0.039
Chinese	188	(74.6%)	87	(64.0%)	
Malay	40	(15.9%)	36	(26.5%)	
Indian and others	24	(9.5%)	13	(9.6%)	
Stroke classification					<0.001
SAO	114	(45.2%)	60	(44.1%)	
LAA	29	(11.5%)	30	(22.1%)	
CE	31	(12.3%)	25	(18.4%)	

Characteristics N (%)	mRS 0–1 (*n* = 252)		mRS ≥2 (*n* = 136)		Univariate Analysis *P*
UND and OC	12	(4.8%)	8	(5.9%)	
TIA	66	(26.2%)	13	(9.6%)	
NIHSS (mean, SD)	1.46	(1.83)	5.04	(3.68)	< 0.001
Premorbid mRS (median)	0.06	(0.29)	0.54	(1.05)	<0.001
Baseline mRS (median)	1.28	(1.20)	3.04	(1.21)	< 0.001
Mean interval (days) between stroke/TIA and assessment	2.4	(2.0)	3.8	(2.5)	< 0.001
Cognitive screening tests					
MMSE (mean, SD)	25.7	(3.3)	22.6	(4.3)	< 0.001
MoCA (mean, SD)	22.0	(4.8)	18.1	(5.5)	< 0.001
Number of cardiovascular risk factors (median)	2		3		<0.001
Recurrent vascular events (no., %)	10	(4.0%)	8	(6.0%)	0.37

Characteristics N (%)	mRS 0–1 ($n = 252$)	mRS ≥2 ($n = 136$)	Univariate Analysis P

mRS = modified Rankin scale; **SD**= Standard Deviations; **SAO =** small artery occlusion; **LAA**= large artery atherosclerosis; **CE** = cardioembolism; **UND** = undetermined etiology; **OC** = other determined etiology; **TIA**= transient ischemic attack; **NIHSS** = National Institute of Health Stroke Score; **MMSE=**Mini-Mental State Examination; **MoCA=**Montreal Cognitive Assessment.

Table 2. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS scores

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	54.10	<0.001
A1	2	Baseline MMSE	−0.1 (0.031)	0.47	0.012	8.48	0.004
	3	Baseline NIHSS	0.3 (<0.001)	0.51	0.038	29.00	<0.001
A2	2	Baseline NIHSS	0.3 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MMSE	−0.1 (0.031)	0.51	0.006	4.71	0.031
B1	2	Baseline MoCA	−0.08 (0.083)	0.47	0.007	4.80	0.029
	3	Baseline NIHSS	0.31 (<0.001)	0.51	0.040	31.10	<0.001
B2	2	Baseline NIHSS	0.31 (<0.001)	0.50	0.043	33.00	<0.001
	3	Baseline MoCA	−0.08 (0.083)	0.51	0.004	3.02	0.083

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

Table 3. Hierarchical regression of mRS scores at 3–6 months after stroke on baseline MMSE, MoCA and NIHSS for subsample of patients with NIHSS scores>2 at baseline

Model	Block	Variables	Final β (p)	R^2	R^2change	*F* change	*p*-value
	1	Controls[a]		0.46	0.460	21.68	<0.001
A1	2	Baseline MMSE	−0.18 (0.010)	0.49	0.036	10.94	0.001
	3	Baseline NIHSS	0.22 (0.001)	0.53	0.034	11.07	0.001
A2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MMSE	−0.18 (0.010)	0.53	0.021	6.83	0.010
B1	2	Baseline MoCA	−0.16 (0.021)	0.49	0.029	8.51	0.004
	3	Baseline NIHSS	0.22 (0.001)	0.52	0.040	12.07	0.001
B2	2	Baseline NIHSS	0.22 (0.001)	0.51	0.049	15.33	<0.001
	3	Baseline MoCA	−0.16 (0.021)	0.52	0.017	5.42	0.021

[a] Block 1 variables for Block 2 and 3 variables in the models (A1, A2, B1, B2) include age, sex, education, composite of cardiovascular risk factors, premorbid mRS and baseline mRS.

MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Score.

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