

# Screening for cognitive decline following single known stroke using the Mini-Mental State Examination

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**Background:** Progressive cognitive decline develops in a nontrivial minority of stroke survivors. Although commonly used to identify cognitive decline in older stroke survivors, the usefulness of the Mini-Mental State Examination (MMSE) as a screening tool for post-stroke cognitive decline across a wider range of ages is not well established. This study therefore investigated the usefulness of the MMSE for this purpose.

**Methods:** Twenty-seven subjects, aged 18–82 years, with a single known remote stroke were assessed using the MMSE. The frequency of cognitive impairment was determined by comparison of MMSE scores with population-based norms. Relationships between cognitive performance, motor impairments, age, gender, handedness, stroke laterality, and time since stroke also were explored.

**Results:** Age-adjusted MMSE scores identified mild cognitive impairment in 22.2% and moderate-to-severe cognitive impairment in 7.4% of subjects. Raw and age-adjusted MMSE scores were inversely correlated with time since stroke, but not with other patient or stroke characteristics.

**Conclusion:** A relationship between time since single known stroke and MMSE performance was observed in this study. The proportion of subjects identified as cognitively impaired in this group by Z-transformation of MMSE scores using previously published normative data for this measure comports well with the rates of late post-stroke cognitive impairment reported by other investigators. These findings suggest that the MMSE, when normatively interpreted, may identify cognitive decline in the late period following single known stroke. Additionally, the lack of a relationship between MMSE and Fugl-Meyer scores suggests that the severity of post-stroke motor impairments is unlikely to serve as a clinically useful indicator of the need for cognitive assessment. A larger study of stroke survivors is needed to inform more fully on the usefulness of normatively interpreted MMSE scores as a method of screening for post-stroke cognitive decline.

**Keywords:** stroke, Mini-Mental State Examination, cognitive decline, Fugl-Meyer evaluation, motor impairment

## Introduction

Improvement of acute stroke-induced cognitive impairments is expected over the months to years following stroke,<sup>1–8</sup> with as many as 30% of stroke survivors experiencing complete cognitive recovery by 18 months post-stroke.<sup>9</sup> Among persons who do not experience a complete recovery from post-stroke cognitive impairments, conventional clinical wisdom suggests that those individuals maintain persistent but stable cognitive impairments thereafter. However, a nontrivial minority of stroke

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survivors develop progressive cognitive decline over the first two years following a single known stroke.

For example, Ballard et al<sup>6</sup> performed cognitive assessments three and 15 months following stroke in 115 individuals without overt dementia in the immediate post-stroke period. Although 50% of these subjects demonstrated cognitive improvements by 15 months following stroke, 9% declined cognitively over that same time period. These subjects were without prior or subsequent known strokes, suggesting that even a single known stroke may provoke vascular dementia. Other studies offer similar evidence of cognitive decline in the months to years following stroke, with rates of dementia by two years post-stroke of 9%–31%.<sup>8–11</sup> In these studies, extended periods of observation after stroke (1–2 years) revealed higher rates of cognitive impairment than did studies with relatively short post-stroke observation periods (less than one year).

Other patient or stroke characteristics may facilitate the identification of persons at risk for post-stroke cognitive decline. Advanced age appears to be a risk factor for dementia following stroke,<sup>8</sup> with a one-year post-stroke prevalence of dementia of 7% in those aged <65 years and 53% in those aged >85 years.<sup>12</sup> Multivariate analyses of large stroke cohorts demonstrate associations between long-term post-stroke cognitive impairment and educational level,<sup>13</sup> lower socioeconomic status,<sup>14</sup> ethnicity (Afro-Caribbean, Asian),<sup>14</sup> stroke severity,<sup>13</sup> left hemispheric lesion,<sup>14</sup> prior cerebrovascular disease,<sup>13</sup> dysphasia,<sup>13</sup> visual field defect,<sup>14</sup> and urinary incontinence.<sup>14</sup> These studies suggest that some patient and/or stroke characteristics, as well as medical comorbidities (eg, prior cerebrovascular disease, incontinence), may serve to prompt clinicians to evaluate patients with such characteristics for post-stroke cognitive decline.

From a practical standpoint, particularly in the busy clinical practices of neurologists, psychiatrists, and primary care physicians caring for stroke survivors, screening for post-stroke cognitive decline presents several challenges. First, in a time-limited setting, it is often impractical to administer more than a brief measure of general cognition, such as the Mini-Mental State Examination (MMSE).<sup>15</sup> Formal neuropsychological testing is often useful for the identification and quantification of post-stroke cognitive impairments, but obtaining support for such testing is inconsistently available, especially in many managed care environments.<sup>16</sup> As such, the task of assessing post-stroke cognitive performance is often relegated to primary care physicians, neurologists, psychiatrists, and physiatrists, and therefore the office-based assessment of cognition is frequently limited to the MMSE.

While the MMSE is not a substitute for formal neuropsychological testing, it appears to be a useful measure for the assessment of post-stroke cognitive decline. For example, Laukka et al<sup>17</sup> suggest that the MMSE may be a useful measure with which to identify forthcoming vascular dementia in adults  $\geq 75$  years of age, and Madureira et al<sup>18</sup> found the MMSE to be a useful screening measure of cognition among older persons in the post-acute (three-month) period following stroke. However, the usefulness of the MMSE measure for the identification of post-stroke cognitive impairment across a broader age range and in the late (ie, more than one year) period following stroke has not been established.

Additionally, the types of stroke-related impairments associated with incipient post-stroke dementia noted above (eg, dysphasia, visual field defect, severity of initial stroke, urinary incontinence) are often challenging to identify and quantify in a brief office visit, particularly in non-neurological clinical settings. When such are identified, clinicians may be more likely to perform cognitive screening tests, assuming that the presence and severity of other stroke sequelae may serve as a gauge of the likelihood and/or severity of post-stroke cognitive impairments. However, it is possible that the relationship between cognitive and other stroke-related impairments may be an artifact of age, with older persons experiencing more frequent impairments in a variety of neurological and functional domains, regardless of whether there are causal relationships between such impairments. Accordingly, it would be useful to understand more fully the relationship between post-stroke motor and cognitive impairments in the late period following stroke, and particularly whether the former serve as a proxy with which to identify stroke survivors in need of more detailed cognitive assessment.

The present study was undertaken to address these issues by investigating the usefulness of the MMSE as a screening tool for post-stroke cognitive decline among younger stroke survivors, and particularly the utility of interpreting MMSE performance according to population-based norms for this purpose. Additionally, relationships between cognitive performance, motor performance, time since stroke, and a limited set of easily identified patient and stroke characteristics were investigated for the purpose of determining whether these variables serve usefully to identify survivors of remote strokes in need of cognitive assessment.

## Materials and methods

This study was approved by the HealthONE Alliance Institutional Review Board, and all subjects provided informed consent for study participation.

## Subjects

Individuals who experienced a single known stroke at least 12 months prior to study participation were recruited nationally via printed and Internet media for participation in a study examining the effects of constraint-induced movement therapy on chronic post-stroke upper extremity motor impairments. Participants were enrolled on the basis of the onset and persistence of moderate-to-severe upper extremity motor impairments following a single known stroke, with moderate-to-severe upper extremity motor impairment, defined as movement from a resting position limited to wrist extension of no more than 20°, metacarpophalangeal and interphalangeal joint extension of no more than 20°, but preserved ability to grasp a washcloth using any method of prehension. Subjects were also required to have the ability to sit at the bedside for 10 minutes without support, to follow directions using written, verbal, or demonstration instructions, and to have no other serious and/or uncontrolled medical conditions. Findings from the constraint-induced movement therapy protocol into which these subjects subsequently entered are described elsewhere.<sup>19–21</sup> Medical records were reviewed for the purpose of determining stroke type and laterality.

## Outcome measures

Subjects completed pretreatment assessments using the MMSE<sup>15</sup> and the Fugl-Meyer evaluation of physical performance.<sup>22</sup> The MMSE is a brief cognitive assessment measure used commonly by physicians and allied health care providers in clinical practice. MMSE scores range between 0 and 30, with higher scores reflecting better performance. This measure was administered and scored using the method described by Folstein et al.<sup>15</sup> In order to account for the effect of age prior to interpreting MMSE scores, adjusted MMSE scores were calculated using the population-based norms reported by Crum et al.<sup>23</sup> Mild cognitive impairment was defined as an MMSE score  $\geq 1$  standard deviation (SD) below age-adjusted performance expectations,<sup>24</sup> and moderate or greater cognitive impairment was defined as an MMSE score  $\geq 2$  SD below age-adjusted performance expectations.

The Fugl-Meyer assessment generated a score for upper extremity performance (FM-UE) based on motor skill, coordination, and speed of upper extremity movement; FM-UE scores range from 0 to 66, with lower scores reflecting more severe impairment. The Fugl-Meyer assessment also generates a total motor performance score (FM-T) based on the FM-UE and also joint range of motion, pain, and sensory function, as well as lower extremity function. For the purpose of this study, FM-T scores ranged from 0 to 126 points, again

with lower scores reflecting more severe impairment. All administrations of the Fugl-Meyer assessment were completed by one occupational therapist following Fugl-Meyer testing guidelines<sup>22</sup> and employed a standardized assessment environment (ie, the same chair, testing equipment, and testing procedures used for every subject). Determination of handedness was also made during the course of Fugl-Meyer assessment. Test-retest reliability on both the FM-UE and FM-T were determined by repeat assessment of 10 randomly selected patients; for both measures, the Pearson product moment correlation was  $r = 0.96$  ( $P < 0.05$ ).

## Statistical analyses

All statistical analyses were performed using Statistica 6.0 (Statsoft Inc, Tulsa, OK). Pearson product moment correlation coefficients were calculated for age versus MMSE (raw and age-adjusted), age versus Fugl-Meyer (FM-UE or FM-T), time since stroke versus MMSE (raw and age-adjusted), time since stroke versus Fugl-Meyer (FM-UE or FM-T), and MMSE (raw and age-adjusted) versus Fugl-Meyer (FM-UE or FM-T). Student *t*-tests were used to investigate differences in MMSE and FM-T scores as a function of gender, laterality of stroke, and cerebral dominance. These analyses were cross-validated by dividing the study group into those with and without cognitive impairment (ie, age-adjusted performance  $\geq 1$  SD below norm-based expectations) and then using Student *t*-tests to investigate between-group differences in age, time since stroke, FM-UE, and FM-T.  $\chi^2$  analyses were used to investigate differences in gender, cerebral dominance, and laterality of stroke among subjects with and without cognitive impairment.

## Results

Twenty-seven subjects (10 of whom were female) were included. The study group is described in Table 1 (continuous variables of interest) and Table 2 (categorical variables of interest). Mild cognitive impairment was observed in 6/27 subjects (22.2%), and moderate or greater cognitive

**Table 1** Study group characteristics (continuous variables)

	Mean ( $\pm$ SD)	Median	Range
Age (years)	58.5 $\pm$ 16.8	60.0	18–82
Time post-stroke (years)	5.9 $\pm$ 5.2	3.5	1–20
MMSE	27.3 $\pm$ 3.4	28.0	14–30
Age-adjusted MMSE	-0.10 $\pm$ 1.6	0.4	-5.7–1.9
Fugl-Meyer (upper extremity)	30.3 $\pm$ 9.6	26.0	17–51
Fugl-Meyer (total)	84.8 $\pm$ 11.8	84.0	66–112

**Abbreviations:** SD, standard deviation; MMSE, Mini-Mental State Examination.

**Table 2** Study group characteristics (categorical variables)

Gender	17 men	63%
	10 women	37%
Handedness	23 right	85%
	3 left	11%
	1 mixed	4%
Hemispheric laterality of stroke	15 left	56%
	12 right	44%
Stroke type	17 ischemic	63%
	6 hemorrhagic	22%
	1 mixed	4%
	3 undetermined	11%

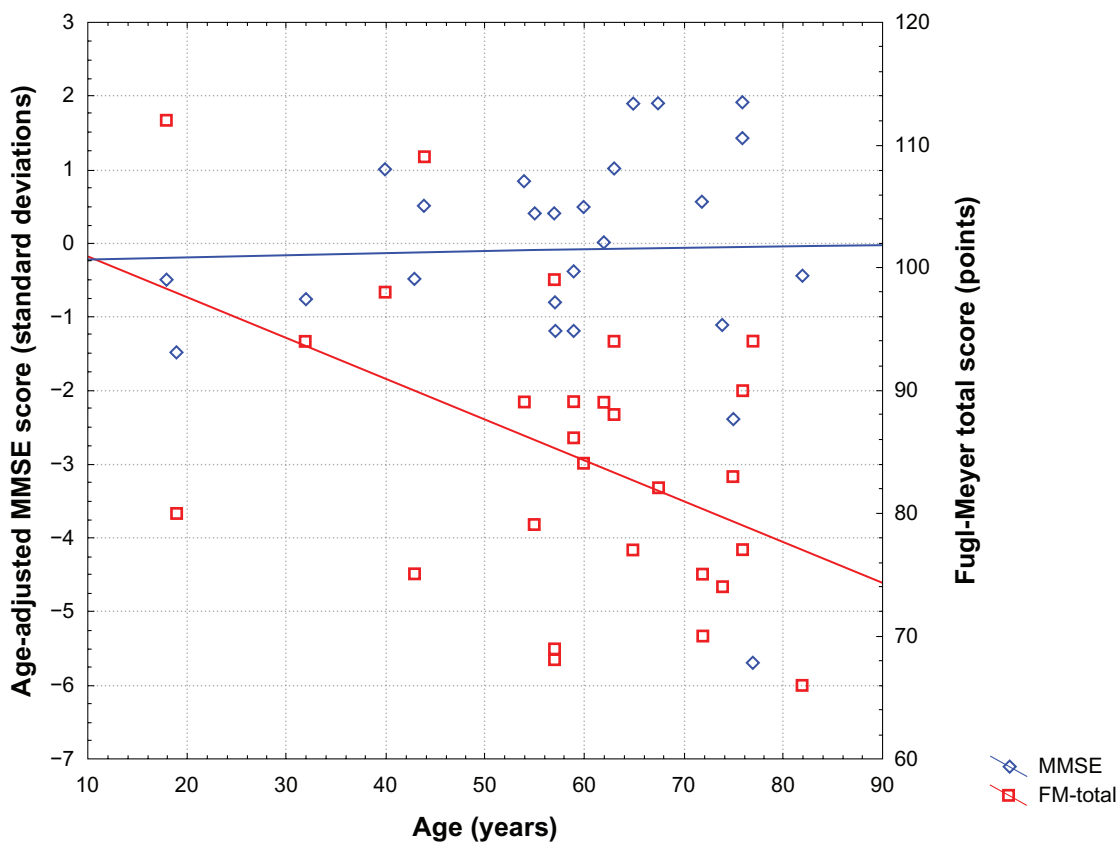
impairment was observed in 2/27 subjects (7.4%). Time since stroke was inversely correlated with both raw and age-adjusted MMSE scores ( $r = -0.65$ ,  $P < 0.001$ , and  $r = -0.59$ ,  $P < 0.002$ , respectively), but not with FM-UE or FM-T scores. Age was not correlated with raw or age-adjusted MMSE scores, but age was inversely correlated with FM-UE and FM-T scores (both  $r = -0.47$ ,  $P < 0.02$ ). Neither raw nor age-adjusted MMSE scores correlated with FM-UE or FM-T scores. Relationships between age-adjusted MMSE scores, FM-T scores, and age are presented in Figure 1, and relationships between age-adjusted MMSE

scores, FM-T scores, and time since stroke are presented in Figure 2. Raw and age-adjusted MMSE scores did not differ as a function of gender, cerebral dominance, or laterality of stroke. Similarly, FM-UE or FM-T scores did not differ as a function of gender, cerebral dominance, or laterality of stroke.

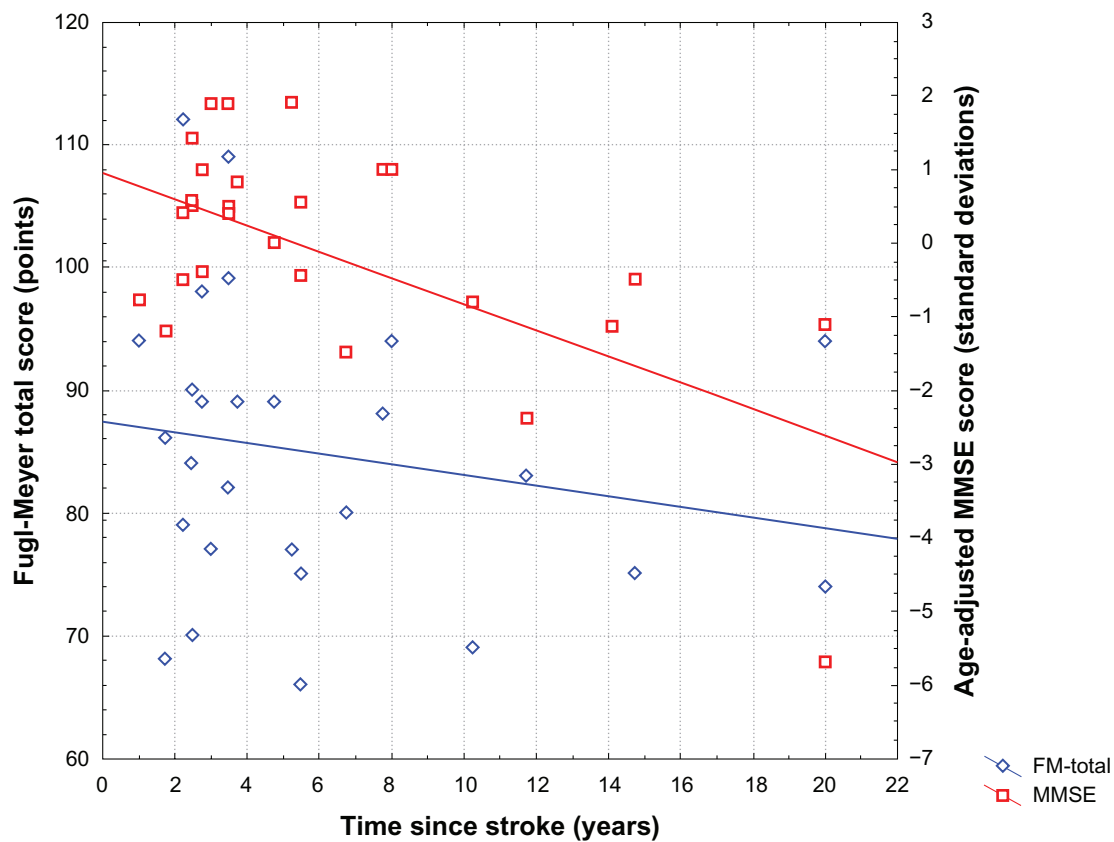
After dividing subjects into groups with and without cognitive impairment, there were no significant differences between these groups with respect to age, gender, cerebral dominance, laterality of stroke, FM-UE, or FM-T scores. However, time since injury was significantly longer among subjects with MMSE-determined cognitive impairment ( $10.3 \pm 8.4$  years) when compared with subjects performing within normal limits for age on this measure ( $4.6 \pm 3.2$  years,  $t = 2.6$ ,  $P < 0.02$ ).

## Discussion

The present findings suggest that the MMSE, particularly when interpreted using age-adjusted normative data, may be useful in the identification of post-stroke cognitive impairment among both younger and older adult stroke survivors. This suggestion is consistent with the conclusions of other investigators<sup>25-27</sup> and the American Heart Association.<sup>28</sup>



**Figure 1** Relationships between age-adjusted Mini-Mental State Examination (MMSE) scores and age, and Fugl-Meyer total (FM-Total) scores and age.



**Figure 2** Relationship between age-adjusted Mini-Mental State Examination (MMSE) scores and time since stroke, and between Fugl-Meyer total (FM-Total) scores and time since stroke.

Our findings clarify these suggestions by demonstrating that the usefulness of the MMSE for this purpose relies upon Z-transforming scores on this measure. Age influences MMSE performance, and the magnitude of the effect of age on MMSE performance increases with advancing age. Accordingly, interpreting MMSE scores in a manner that adequately controls for the potential confound of age-related performance decrements necessitates Z-transforming raw MMSE scores using the best available normative data.<sup>23</sup> In this study, age-adjusted MMSE scores identified 22.2% of subjects in this study with cognitive impairment of at least mild severity, 50% of whom were  $\leq 60$  years of age (see Figure 1). Moderate or greater cognitive impairment (ie, vascular dementia) was identified in 7.4% of subjects, consistent with frequencies identified in studies using more extensive neuropsychological testing batteries.<sup>8-11</sup> By comparison, using raw MMSE cutoff scores of  $\leq 25$  or  $\leq 24$  would identify only 18.5% or 7.4%, respectively, of subjects in this group as cognitively impaired. The even more conservative cutoff score of  $< 20$  (for “organicity”), originally proposed by Folstein et al,<sup>15</sup> would identify only 1/27 (3.7%) of subjects in this sample as cognitively impaired.

Therefore, we suggest that using raw MMSE score cutoff values to establish cognitive impairment is not appropriate, and may explain why some other groups conclude (perhaps erroneously) that this measure underestimates the frequency of post-stroke cognitive decline.<sup>29-32</sup> Conversely, applying a less conservative raw MMSE cutoff score of  $\leq 26$  to our sample overidentifies subjects (29.6%) as having cognitive impairments of at least mild severity. Collectively, these observations suggest that the MMSE may be useful as an assessment for clinically significant post-stroke cognitive decline, and that the interpretation of MMSE scores for this purpose is best undertaken by comparing individual scores with published normative data.<sup>23</sup>

Cognitive performance as assessed by both raw and age-adjusted MMSE scores was inversely correlated with time since stroke, but was not correlated with the severity of post-stroke motor impairments, age, gender, cerebral dominance, or laterality of stroke. By contrast, the severity of post-stroke motor impairment was correlated with age, but was not correlated with time since stroke or the other patient or stroke characteristics assessed in this study. The pattern of relationships between cognitive performance, motor function, age,



and time since stroke observed in this study is complex. These relationships are considered individually and collectively in the service of considering their potential application to the care and future study of stroke survivors.

The correlation between cognitive performance and time since stroke suggests a time-related decline in cognition in the late period following stroke. Importantly, that decline is not accounted for by age, post-stroke motor impairment, or the other subject and stroke characteristics evaluated in this study. Although the association between increased severity of cognitive impairment and time since stroke observed in this study is likely to be multifactorial, two interpretations are immediately forthcoming.

First, it is possible that the cognitive performance of these subjects simply reflects their pre-stroke cognitive baseline, persistent and stable cognitive impairments since the time of stroke, or both, and that the apparent relationship between time since stroke and cognitive impairment is spurious. The strength of the association between time since stroke and both raw MMSE and age-adjusted MMSE scores suggests that the likelihood of a Type I error in this analysis is small, but this possibility cannot be dismissed entirely in light of the relatively small sample size of the present study.

Second, and more likely, our present findings suggest that a nontrivial minority of stroke survivors develop progressive cognitive decline in the late post-stroke period. That decline may result from the cumulative effects of additional (including otherwise clinically “silent”) cerebrovascular disease,<sup>33–37</sup> the induction of Alzheimer’s-type neuropathology by cerebrovascular disease,<sup>38–41</sup> or both of these and/or other factors.<sup>42–46</sup> This interpretation is concordant with findings from other similar studies,<sup>24,37,47–49</sup> and suggests that a single known stroke is probably understood most usefully as an overt manifestation of an underlying cerebrovascular process that in a substantial minority of individuals will result in gradual cognitive decline.

In contrast with post-stroke cognitive performance, motor performance remained relatively more stable as a function of time since stroke. However, motor performance demonstrated a clear age-related decline. The quality of motor function varies with normal aging,<sup>50</sup> and clinically apparent motor decline begins in the fifth decade of life. By contrast, the Crum et al<sup>23</sup> data suggest that significant age-related decline in MMSE scores is not expected until the eighth decade of life. These observations might suggest that age may more strongly influence motor performance than cognitive performance among relatively younger stroke survivors. Given that the mean age in the present study was

$58.5 \pm 16.8$  years, the present observation of a relationship between age and post-stroke motor performance, but not between age and MMSE scores, is not entirely unexpected.

It is also important to note that the severity of motor impairments experienced by the subjects in this study were just short of plegia of the affected limb or hemibody. The lack of correlation between post-stroke cognitive performance and motor performance is therefore even more important to highlight here. If in this group there is no significant association between motor and cognitive performance, then severity of motor impairments seems unlikely to serve usefully as an indicator of post-stroke cognitive impairments.

The present study suffers from several limitations, including its development as a secondary analysis of cognition in a sample of stroke survivors recruited for a different purpose (constraint-induced movement therapy of post-stroke motor impairments), cross-sectional rather than longitudinal assessment of cognition and motor function, nonblinded assessments, lack of a matched comparison sample, lack of extensive demographic data (eg, educational levels, ethnicity, primary language, socioeconomic status), absence of overall stroke severity metrics (eg, National Institutes of Health Stroke Scale<sup>51</sup>), lack of ascertainment of potential confounds such as neuropsychiatric conditions (ie, depression, anxiety, substance use) and neuroactive medications on cognitive and motor performance, and lack of assessment with the formal neuropsychological testing needed to establish the validity of the rates of cognitive impairment identified by Z-transformed MMSE scores. Of particular note, the recruitment strategy for the constraint-induced movement therapy study may at least in part contribute to the lack of correlation between motor and cognitive performance in the present sample. As noted earlier, subjects were required to be able to follow directions using written, verbal, or demonstration instructions. This requirement reduces the likelihood of enrolling subjects with functionally significant language impairments, and would tend to bias MMSE scores towards the less impaired range. Accordingly, these subjects were less likely than the general stroke population to demonstrate an association between motor and cognitive (including language) abilities. It is possible that, if subjects with more overt impairments of language had been included in the present study, a correlation between motor and cognitive performance might have been observed. Conversely, the finding of an association between time since stroke and cognitive performance despite the apparent selection bias against patients with aphasia is that much more noteworthy, because it suggests that post-stroke language disturbances alone are unlikely to explain the MMSE scores observed in these subjects.

In summary, the present findings suggest that the MMSE may serve as a useful screening measure of post-stroke cognitive performance across a wide age range, particularly when MMSE scores are interpreted with respect to population-based norms rather than raw MMSE cutoff scores. Additionally, the present study findings suggest that clinicians should remain vigilant for the development of progressive cognitive decline throughout the post-stroke period, and that such vigilance should be maintained regardless of a patient's age and/or severity of post-stroke motor impairments. Given the morbidity and mortality risks posed by post-stroke cognitive impairment<sup>52-54</sup> and promise of emerging therapies for the treatment of vascular dementia,<sup>55-61</sup> routine screening for cognitive impairments among stroke survivors is necessary if such treatments are to be offered early in the course of vascular dementia, when preservation of function may yield the greatest benefits for affected persons and their families. The present findings suggest that identification of cognitive impairments rests upon direct assessment of cognition, and that recognition of other patient or stroke characteristics are neither suitable substitutes nor reliable prompts for post-stroke cognitive assessment. Prospective studies are needed to validate the present findings, including direct comparison of the rates of cognitive impairment identified by Z-transformed MMSE scores versus formal neuropsychological testing, and to investigate further their clinical implications.

## Acknowledgments

The authors gratefully acknowledge the support provided for this study by the Spalding Community Foundation, the HealthONE Alliance, and HealthONE Spalding Rehabilitation Hospital, Aurora, CO.

## Disclosure

The authors report no conflicts of interest in this work.

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