Clinical Sciences

The Prognostic Effects of Poststroke Cognitive Impairment No Dementia and Domain-Specific Cognitive Impairments in Nondisabled Ischemic Stroke Patients

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Background and Purpose—There is some evidence that poststroke dementia, cognitive impairment no dementia (CIND), and mild cognitive impairment predict for poor outcomes such as dementia, death, and institutionalization. However, few studies have examined the prognostic value of CIND, CIND severity, and domain impairments in a poststroke cohort.

Methods—A cohort of ischemic stroke patients with baseline cognitive assessments 3 months poststroke were followed up annually for outcomes of dependency, vascular events, and death for up to 5 years. Univariate and multivariate Cox proportional regression was performed to determine the ability CIND, CIND severity, and domain impairments to predict dependency, vascular outcomes, and death.

Results—Four-hundred nineteen patients without dementia (mean age 60±11 years, 32% female) were followed for a mean of 3.2 years. Older age, diabetes, more severe strokes, CIND-mild, and CIND-moderate were independently predictive of dependency. There were no independent predictors of recurrent vascular events. Older age, diabetes, and CIND-moderate were independently predictive of death. In analyses of individual cognitive domains, impairments in visuomotor speed were independently predictive of dependency.

Conclusions—In poststroke patients, CIND predicts dependency and death, while CIND severity discriminates patients with poor survival. Impairments in visuomotor speed independently predict dependency.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00161070.

(Stroke. 2011;42:883-888.)

Key Words: dementia ■ stroke ■ mild cognitive impairment ■ cognitive impairment no dementia

D ementia, cognitive impairment no dementia (CIND), and mild cognitive impairment (MCI) have become increasingly prevalent in aging populations. CIND is a broad concept that has been used to define impairments in any objective cognitive domain in neuropsychological testing in the absence of dementia.1 In community-based studies, CIND has been shown to predict for dementia, death, and institutionalization.2 One study found that poststroke CIND is a negative predictor of survival.3 Studies have also shown that poststroke dementia (PSD) increases the risk of recurrent vascular events.5,6 However, no studies to date have examined the effect of CIND on poststroke recurrent vascular events or dependency. We hypothesize that CIND is associated with dependency, recurrent vascular events, and death following ischemic stroke.

In a previous study from this cohort,6 we have shown that CIND severity predicts incident dementia; CIND-mild patients shared a similar risk profile with patients with no cognitive impairment (NCI), and CIND-moderate patients experienced a 6-fold increase in the risk of incident dementia. Because PSD has been associated with recurrent vascular events4 and death,7 we hypothesize that a similar association may exist with CIND severity and outcomes after stroke.

Previous studies that have examined the prognostic abilities of domain-specific impairments have found that visual memory impairments predict for disturbances in activities of daily living,8 whereas executive functioning and visuospatial impairments3,9 predict for poor survival after stroke. Therefore, in this study, we aimed to determine domain-specific

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predictors of dependency, recurrent vascular events, and death.

Methods

Subjects
All patients with recent transient ischemic attacks or nondisabling ischemic stroke who were seen in the Singapore General Hospital between 1999 and 2005 were screened for eligibility for the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). Detailed methodology for the main study has been previously reported. Briefly, patients were eligible if they were within 6 months of a transient ischemic attack (including transient monocular blindness) or a nondisabling ischemic stroke (grade ≤3 on the modified Rankin scale [mRS]) of presumed arterial origin. The exclusion criteria were: a possible cardiac source of embolism, high-grade carotid stenosis for which carotid endarterectomy or endovascular treatment was planned, moderate to severe leukoaraiosis on brain imaging (for randomization into anticoagulation), any blood coagulation disorder, any contraindication for aspirin or dipyridamole, and a limited life expectancy.

Patients recruited into ESPRIT were eligible to enter a cognitive substudy (ESPRIT-Cog) with the following additional exclusion criteria: confusion, severe aphasia (expressive or receptive), major psychosis diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria,12 or dominant upper-limb paralysis.

Standard Protocol Approvals, Registrations, and Patient Consents
The study protocol was approved by Singapore General Hospital’s Institutional Review Board and Ethics Committee. Written informed consent was obtained from all patients or legal guardians. The ESPRIT trial was registered under http://clinicaltrials.gov with the identifier NCT00161070.

Neuropsychological Test Battery
Patients who consented to ESPRIT-Cog received their baseline cognitive assessment 3 to 4 months after their qualifying event, and then annually thereafter for up to 5 years. Trained research psychologists administered a neuropsychological test battery that has been validated for use in Singapore. The battery assessed 6 domains, 4 of which were nonmemory domains. Education-adjusted cutoffs of 1.5 standard deviations below established normal means were used on individual tests. Failure in at least half of the tests in a domain constituted failure in that domain. The assessment was administered in English, Malay, Mandarin, or Chinese dialects according to the subject’s habitual language. The entire battery took under 90 minutes to complete.

The nonmemory domains were: Attention, as defined by digit span,14 visual span,14 and auditory detection15; Language, as defined by modified Boston naming16 and category fluency17 (animals and food subtasks); Visuomotor speed, as defined by symbol digit modality test,18 digit cancellation,19 and maze ask;20 and Visuoconstruction, as defined by Weschler Memory Scale-Revised14 visual reproduction copy task, clock drawing,21 and Weschler Adult Intelligence Scale-Revised22 subtest of block design.

The memory domains were: Verbal Memory, as defined by word list recall23 (immediate, delayed, and delayed recognition) and story recall14 (immediate and delayed); and Visual Memory, as defined by picture recall14 (immediate, delayed, and delayed recognition) and Weschler Memory Scale-Revised visual eproduction14 (immediate, delayed, and delayed recognition).

Determination of CIND
As is commonly defined, patients with CIND were impaired in at least 1 domain of the neuropsychological test battery, but did not meet criteria for dementia. In keeping with our previous study, where severity of CIND predicted incident dementia, CIND was divided by a median split into CIND-mild (1 to 2 domains impaired) and CIND-moderate (3 to 6 domains impaired).

Baseline Risk Factors
Risk factor information was collected at baseline. Stroke subtype was classified according to the Oxfordshire Community Stroke Project by: total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct, or lacunar infarct. All patients had either computed tomography or magnetic resonance imaging as part of the diagnostic process. Vascular risk factor data, such as age, diabetes mellitus status, hypertension, hyperlipidemia, smoking status, ischemic heart disease, peripheral artery disease, as well as history of stroke, angina, and myocardial infarction, were obtained verbally from the patient and were confirmed with hospital records.

Outcome Measures
Patients were followed up annually for up to 5 years. Patients underwent full neuropsychological assessment at the outpatient clinic. If a recurrent vascular event had occurred, detailed hospital records were obtained to verify occurrence of the vascular event. Strokes, peripheral artery disease, intracranial bleeds, and any cardiac ischemia (stable and unstable angina, myocardial infarctions) or deaths from any of the above were considered to be a recurrent vascular event. Dependence was measured by the mRS, which is a commonly utilized scale in stroke studies (0=no symptoms, 1=symptoms, no disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, 6=death). The mRS was dichotomized by good outcome (0–2) and bad outcome (3–6). Patients with a mRS of 3 at baseline were considered dependent only if they progressed to mRS scores >3. Information pertaining to death was collected verbally and confirmed with hospital and/or death registry records at the end of the study.

Statistical Analysis
ANOVA or χ2 analysis was used to test for significant differences between NCI, CIND-mild, and CIND-moderate patients. Analysis was performed in 3 stages. In the first stage, univariate regressions were performed to determine which baseline characteristics were predictive of dependency, recurrent vascular events, and death. Univariate regression analyses were repeated twice, once with CIND versus NCI as the indicator of baseline cognitive impairment, then with CIND severity as the indicator of baseline cognitive impairment. In the second stage of analysis, the analyses were repeated as multivariate regression models controlling for treatment allocation, with significant predictors in the univariate stage included in the models. In the third stage of analysis, individual domains of cognition were analyzed for their ability to predict dependency, recurrent vascular events, or death in both univariate analyses and multivariate analyses (in which domains of cognition were entered individually into regression models that adjusted for significant predictors of dementia from stage 1), and treatment allocation. For the outcome of dependency, we adjusted for stroke subtype, age, gender, diabetes mellitus, hypertension, and treatment allocation. For the outcome of vascular events, we adjusted for age, diabetes mellitus, and treatment allocation. For the outcome of death, we adjusted for age, gender, diabetes mellitus, hypertension, previous myocardial infarction, and treatment allocation. Cox proportional hazards models were used in all stages of analysis. Analyses were performed in Stata 10.0, and significance was determined with a 2-tailed α of 0.05 in stages 1 and 2 of analysis, whereas Bonferroni adjustment for multiple comparisons in stage 3 yielded an α of 0.008.

Results
A total of 458 patients were recruited into ESPRIT at the Singapore General Hospital site, of which 432 consented to participate in the ESPRIT-Cog substudy. Of these 432 patients, 13 had dementia at baseline and were therefore excluded from this study. We thus present data of 419
patients (mean age 60 ± 11 years, 32% women) who were followed for a mean of 3.2 years (Figure). There were 212 patients (51%) with NCI, 109 patients (26%) with CIND-mild, and 98 patients (23%) with CIND-moderate. The demographic characteristics of the study population stratified by baseline cognitive status are summarized in Table 1. Older, female, diabetic, hypertensive patients and those with more severe strokes (total/partial anterior circulation infarct) were more likely to have cognitive impairment.

During the course of the study, 28 patients died, 62 had a vascular event (40 ischemic stroke, 14 myocardial ischemia, 4 intracerebral hemorrhages, 4 peripheral artery disease), and 48 became dependent. The incidence of death was 0.2 per 1000 in NCI patients, 0.9 per 1000 in CIND-mild patients, and 1.4 per 1000 in CIND-moderate patients. The incidence of recurrent vascular events was 1.0 per 1000 in NCI patients, 1.8 per 1000 in CIND-mild patients, and 2.1 per 1000 in CIND-moderate patients. The incidence of dependency was 0.3 per 1000 in NCI patients, 1.9 per 1000 in CIND-mild patients, and 2.2 per 1000 in CIND-moderate patients.

Table 2 summarizes the result of univariate and multivariate Cox proportional hazards analysis predicting dependency, vascular events, and death. In univariate analysis, age, gender, diabetes mellitus, hypertension, stroke subtype, and cognitive impairments were associated with dependency. In multivariate analysis, age, stroke subtype, diabetes mellitus, and all definitions of cognitive impairment were significant predictors of dependency. In univariate analysis, age, diabetes mellitus, CIND, and CIND severity were associated with recurrent vascular events. However, there were no significant predictors of recurrent vascular events in multivariate analysis. In univariate analysis, age, diabetes mellitus, hypertension, and cognitive impairments were associated with death. In multivariate analysis predicting for death, age, diabetes mellitus, and CIND-moderate were all significant predictors of death.

Table 3 summarizes the results of the Cox proportional hazards analysis using domains of cognitive impairment to predict dependency, vascular events, and death. In univariate analysis, all domains predicted for dependency, whereas in multivariate analysis, only visuomotor speed independently predicted dependency (HR = 3.49, P = 0.002). In univariate analysis, language, visual memory, and visuomotor speed predicted vascular events; however, none remained significant in multivariate analysis. In univariate analysis, language, visual and verbal memory, visuomotor speed, and visuconstruction were significant predictors of death; however, none remained significant in multivariate analysis.

## Discussion

In this study, we determined the prognostic effect of cognitive impairment in poststroke patients without dementia. Specifically, we evaluated the effects of CIND, CIND severity, and domain-specific impairments on dependency, recurrent vascular events, and death.

With regards to dependency, we found that poststroke CIND predicted for dependency. Both CIND-mild and CIND-moderate were predictive of poor functional prognosis when compared with NCI patients. We also found that visuomotor speed independently predicted for dependency after stroke. This is in keeping with a previous study of poststroke patients that showed that visual memory and neglect independently predicted for persistent disturbances in basic activities of daily living, whereas visual perception and construction difficulties independently predicted persistent disturbances in instrumental activities of daily living.
In the present study, we found that CIND predicted poor survival. This is in agreement with both population-based studies and poststroke studies in which CIND predicts poor survival, and with studies of PSD that have shown that PSD increases the risk of death by 2- to 6-fold. In addition, CIND severity was differentially predictive of poor survival, with CIND-moderate patients 3 to 4 times more likely to die compared with NCI patients, whereas CIND-mild patients had a nonsignificant increase in risk. This novel finding is in line with our previous study that showed that CIND severity is a prognostic factor for incident dementia in poststroke patients.6 In our study, there were no independent cognitive domains that predicted for death. This is in contrast to a previous study of poststroke outcomes, where deficits in executive functions and visuospatial/construction abilities independently predicted poor survival. We believe that the difference in findings could be caused by both the conservative use of a Bonferroni adjustment and by the relatively lower rates of death in our study (2 deaths per 1000 patient-years versus 59 per 1000 patient-years in the earlier study), which could in turn be a reflection of our differing study lengths (5 years versus 12 years).

In this study, we found no association between CIND, CIND severity, or individual domains of impairment and recurrent vascular events. Although there have been no previous studies that have analyzed the association between poststroke CIND and recurrent vascular events, PSD has previously been shown to increase the risk of recurrent vascular events. There remains some controversy regarding the role of PSD in recurrent vascular events, as leukoaraiosis has been shown to be more predictive than is PSD for recurrent vascular events.

Our study has several limitations. The inclusion/exclusion criteria limit recruitment to those without dominant upper-limb paralysis and who had a baseline mRS ≤3. This may limit the generalizability of our findings, as these criteria have resulted in a younger population in ESPRIT than in most stroke populations. Information pertaining to the baseline National Institute of Health Stroke Scale (NIHSS) score was unavailable, and therefore we were unable to control for neurological impairments among this stroke cohort. However, we used the Oxfordshire Community Stroke Project stroke subtype classification as a means of controlling for stroke severity in our analysis. An additional limitation to our

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<th>Vascular Events (1 Missing)</th>
<th>Death</th>
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<td>Univariate</td>
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<td>HR 0.95 CI</td>
<td>HR 0.95 CI</td>
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<td>1.00 . . . . .</td>
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</table>

**Table 2. Cox Regression Analysis of Baseline Characteristics Predicting Dependency, Recurrent Vascular Events, and Death**

HR indicates hazard ratio; CI, confidence interval; NCI, no cognitive impairment; CIND, cognitive impairment no dementia; TIA, transient ischemic attack; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct.

*Reference group.
†Adjusted for treatment allocation.
Table 3. Cox Proportional Hazards Models of Domains of Cognitive Impairment Predicting for Dependency, Vascular Events, and Death

|                      | Dependency | Vascular Events | Death
|----------------------|------------|----------------|--------
|                      | HR        | P            | HR     | P            | HR     | P            |
| Attention            | 2.77      | 0.006        | 1.11   | 0.798        | 2.57   | 0.055        |
| Language             | 2.94      | 0.003        | 2.16   | 0.018        | 3.60   | 0.005        |
| Verbal Memory        | 2.47      | 0.009        | 1.51   | 0.159        | 3.45   | 0.006        |
| Visual Memory        | 2.04      | 0.014        | 1.79   | 0.011        | 2.97   | 0.004        |
| Visuoconstruction    | 3.52      | <0.001       | 1.51   | 0.069        | 2.58   | 0.012        |
| Visuomotor Speed     | 6.78      | <0.001       | 2.12   | 0.001        | 3.29   | 0.003        |

Univariate†

|                      | Dependency | Vascular Events | Death
|----------------------|------------|----------------|--------
| Attention            | 1.04      | 0.925         |        |              |        |              |
| Language             | 1.67      | 0.190         | 2.17   | 0.027        | 2.33   | 0.072        |
| Verbal Memory        | 1.45      | 0.325         |        |              | 2.83   | 0.027        |
| Visual Memory        | 1.05      | 0.870         | 1.32   | 0.314        | 1.74   | 0.155        |
| Visuoconstruction    | 1.18      | 0.215         |        |              | 1.26   | 0.390        |
| Visuomotor Speed     | 3.49      | 0.002         | 1.48   | 0.176        | 1.41   | 0.444        |

Multivariate‡

|                      | Dependency | Vascular Events | Death
|----------------------|------------|----------------|--------
| Attention            | 1.04      | 0.925         |        |              |        |              |
| Language             | 1.67      | 0.190         | 2.17   | 0.027        | 2.33   | 0.072        |
| Verbal Memory        | 1.45      | 0.325         |        |              | 2.83   | 0.027        |
| Visual Memory        | 1.05      | 0.870         | 1.32   | 0.314        | 1.74   | 0.155        |
| Visuoconstruction    | 1.18      | 0.215         |        |              | 1.26   | 0.390        |
| Visuomotor Speed     | 3.49      | 0.002         | 1.48   | 0.176        | 1.41   | 0.444        |

HR indicates hazard ratio.

*Multivariable models included domains of cognition individually in each regression model along with treatment allocation as well as variables that were significant at the univariate stage of analyses.

†Adjusted for stroke subtype, age, sex, diabetes mellitus, hypertension, as well as the treatment allocation.

‡Adjusted for age, diabetes mellitus, and treatment allocation.

§Adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, as well as treatment allocation.

Conclusion

The study was that the majority of patients had baseline computed tomography as opposed to magnetic resonance imaging scans, which are superior in the determination of stroke subtypes. We were also unable to control for prestroke dependency. However, we hypothesize that the inclusion criteria of mRS <3 would limit the effect of prestroke dependency in our study population. Furthermore, although the cognitive battery utilized was validated by administration to an elderly community population in Singapore, more studies need to be performed using other cognitive instruments to confirm the predictive abilities of the CIND-moderate classification. In addition, we recognize that our classifications of CIND did not adopt the typical threshold of less than 1 standard deviation from the mean, but instead adopted the usual MCI threshold of <1.5 standard deviations from the mean. Hence, additional studies are needed to validate the operationalized criteria for CIND in different populations that are at high risk of developing dementia. Furthermore, we did not utilize MCI subtypes (amnestic single-domain MCI, amnestic multiple-domain MCI, nonamnestic single-domain MCI, nonamnestic multiple-domain MCI) in our analysis, as the number of outcomes was small. In addition, we chose to examine CIND and not MCI, as strokes may produce a spectrum of cognitive changes, but may not necessarily produce prominent amnesia, as is emphasized in the MCI subtypes. Therefore, larger studies may be required to examine the comparative predictive abilities of MCI and CIND subtypes. Lastly, the use of the conservative Bonferroni correction method in all analyses pertaining to domain-specific impairments may underestimate the contributions of these domains. In this study, without the use of a correction method, there was an effect of the language domain on vascular events as well as the verbal memory on death. However, we suggest that such findings require additional confirmation. In conclusion, we suggest that CIND severity is predictive of recurrent dependency and death in a highly selected population of nondisabled ischemic stroke patients.

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要介助, 脳卒中, 血管イベント, 死亡を予測する認知機能障害領域の Cox 比例ハザードモデル

Table 3 要介助, 血管イベント, 死亡を予測する認知機能障害領域の Cox 比例ハザードモデル

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HR はハザード比を示す。

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