

# Dementia as a Predictor of Adverse Outcomes Following Stroke

## An Evaluation of Diagnostic Methods

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**Background and Purpose**—Although it is understood that dementia is a risk factor for adverse outcomes, little is known about the predictive validity of the numerous methods that have been proposed for its diagnosis. Thus, we performed the present study to assess the utility of a variety of diagnostic methods in the prediction of adverse outcomes following stroke.

**Methods**—We administered neuropsychological, neurological, and functional examinations to 244 patients (age,  $71.7 \pm 8.5$  years) 3 months after ischemic stroke. We diagnosed dementia using each of the following methods: (1) neuropsychological testing, requiring deficits in increasing numbers of cognitive domains, both with and without memory impairment, as well as functional impairment; (2) Mini-Mental State Examination (MMSE) score of  $<24$ ; and (3) neurologists' clinical judgment. We then used survival analyses to investigate the ability of diagnoses based on those methods to predict death and recurrent stroke during long-term follow-up.

**Results**—Log-rank tests and Cox proportional hazards analyses, with recurrent stroke entered as a time dependent covariate, determined that all of the paradigms were significant predictors of mortality, but the performance of paradigms based on neuropsychological testing was superior to the use of the MMSE and clinical judgment, particularly when memory impairment was required. Log-rank tests determined that paradigms based on neuropsychological testing were the only significant predictors of recurrent stroke and performed best when memory impairment was required.

**Conclusions**—Our results suggest that dementia diagnosis based on neuropsychological assessment and an operationalized paradigm requiring deficits in memory and other cognitive domains is superior to other conventional methods in its ability to identify patients at elevated risk of adverse outcomes following stroke. (*Stroke*. 1998;29:69-74.)

**Key Words:** dementia ■ mortality ■ neuropsychological tests ■ stroke, ischemic ■ stroke outcome

Although dementia is typically considered to be a primary consequence of a number of neurological diseases, it can also serve as a risk factor for other adverse outcomes. Many studies have reported that survival is reduced among patients with dementia, particularly in a setting of cerebrovascular disease.<sup>1-6</sup> It has also been reported that clinically stroke-free subjects with severe cognitive impairment are at an elevated risk of first stroke<sup>7</sup> and that stroke patients with dementia are at an elevated risk of long-term stroke recurrence compared with nondemented stroke patients.<sup>8</sup> The results of these studies suggest that the ability to accurately diagnose dementia could permit the identification of patients at risk of adverse events and the initiation of targeted interventions in those patients.

Prior studies have used a variety of methods in the diagnosis of dementia, most frequently relying on the clinical judgment of physicians or mental status testing. In part due to limitations in time and personnel, neuropsychological testing has been used less frequently. Despite the

numerous studies that have been performed on patients with dementia, however, few have attempted to investigate the validity of those diagnostic methods. Given that dementia can be considered to identify a patient who is "at risk," the investigation of the predictive validity of those approaches could be of particular importance. Thus, in the present study, we used variations of each of the diagnostic methods listed above to determine whether dementia was present or absent in a sample of patients with ischemic stroke and investigated the ability of those diagnoses to predict death and recurrent stroke. We attempted to answer three specific questions: (1) Is formal cognitive testing superior to the use of clinical judgment in the diagnosis of dementia? (2) If so, is dementia diagnosis based on neuropsychological assessment and an operationalized paradigm superior to mental status testing? and (3) Does a requirement of memory impairment significantly influence the predictive validity of operationalized paradigms based on neuropsychological assessment?

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## Subjects and Methods

### Subjects

As part of a prospective study of stroke and dementia,<sup>9</sup> we examined 244 patients (age, 71.7±8.5 years; education, 10.1±4.5 years) recruited within 30 days of ischemic stroke. Stroke was defined as the acute onset of a focal neurological deficit attributable to cerebrovascular disease and supported by CT scan (normal or relevant infarct). Eligibility criteria included age ≥60 years and the absence of any comorbid disorders that might limit survival or affect cognitive function, although patients were not excluded if a premorbid history of functional impairment suggested that they might also have Alzheimer's disease. Our sample was derived from a larger cohort of 297 patients. Forty-six of those patients were excluded from the present study because they were not examined 3 months after stroke, and 7 of those patients could not be diagnosed using each of the diagnostic paradigms that will be described below because they were unassessable in certain critical aspects of neuropsychological testing.

This study was approved by the Institutional Review Board of Columbia–Presbyterian Medical Center, and all subjects provided informed consent.

### Patient Assessment Procedures

We administered a battery of neuropsychological tests developed for use in epidemiological studies of dementia<sup>10</sup> to all patients in either English or Spanish 3 months after stroke. The battery included measures of memory (the Selective Reminding Test and a multiple-choice recognition version of the Benton Visual Retention Test), orientation (the Mini–Mental State Examination [MMSE] orientation subtest), language (a 15-item version of the Boston Naming Test, letter and category fluency tests, and the repetition and complex ideation subtests of the Boston Diagnostic Aphasia Examination), visuospatial function (the Rosen Drawing Test and a multiple-choice matching version of the Benton Visual Retention Test), and abstract reasoning (the Similarities subtest of the Wechsler Adult Intelligence Scale–Revised and the Identities and Oddities subtest of the Mattis Dementia Rating Scale). Impairment on each neuropsychological subtest was identified based on a predetermined set of cutoff scores developed in a pilot study.<sup>10</sup> Patients were considered to be impaired within a specific cognitive domain when their scores on one or more of the subtests within that domain fell below the predetermined cutoffs.

As part of the same assessment, we administered the MMSE,<sup>11</sup> a popular mental status test tapping verbal memory, orientation, language, visuospatial function, and attention and mental control, and all patients were seen for comprehensive neurological examinations by neurologists specializing in cerebrovascular disease and dementia. We also administered the Blessed Functional Activity Scale,<sup>12</sup> which taps the cognitive aspects of activities of daily living, and we operationally defined functional impairment as a total score of ≥0.5 not solely attributable to physical disability. Based on the neurological examination and the Barthel Index,<sup>13</sup> which taps the physical aspects of activities of daily living, we calculated a total score for each patient on the Stroke Data Bank Stroke Severity Scale.<sup>14</sup>

### Diagnostic Paradigms

We examined multiple approaches to the diagnosis of dementia, all of which were based on assessments performed 3 months after stroke. First, based on neuropsychological testing, we required impairment in increasing numbers of cognitive domains as well as functional impairment. We also examined a modification of that method in which memory impairment was required to be one of the defective domains. Use of those paradigms permitted us to directly investigate the predictive validity of the following sets of codified criteria for the diagnosis of dementia: (1) deficits in memory and two or more other cognitive domains as well as functional impairment, as proposed for use in the diagnosis of vascular dementia by the International Workshop organized by the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN)<sup>15</sup>; (2) deficits in memory and one or more other cognitive domains as well as functional impairment, as presented in the fourth edition of the

*Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV)<sup>16</sup>; and (3) deficits in memory and an unspecified number of additional cognitive domains as well as functional impairment, as presented in the tenth edition of the *International Classification of Diseases* (ICD–10).<sup>17</sup> While the description of the criteria proposed for use in the diagnosis of vascular dementia by the State of California Alzheimer's Disease Diagnostic and Treatment Centers states that “most patients with dementia will exhibit deficits on more than one type of intellectual task,”<sup>18</sup> a specification of the number and type of deficits required for the diagnosis of dementia was explicitly withheld, rendering formal study of those criteria in the present manuscript inappropriate.

In addition to paradigms based on neuropsychological testing, we examined the use of the standard MMSE<sup>11</sup> cutoff of a total score of <24 in the diagnosis of dementia. We also examined a diagnosis of dementia based solely on the clinical judgment of the examining neurologists, who were blinded to the results of neuropsychological testing in making that determination.

### Patient Follow-up

In-person follow-up examinations were performed annually, and interim 6-month telephone calls were made to document subjects' vital status and identify any clinically evident recurrent strokes that may have occurred. Continuous screening of admissions to our medical center permitted us to identify additional recurrences as well as illnesses leading to subject death. Death was confirmed by review of medical records and death certificates, when available. Similar to our definition of the index stroke, recurrent stroke was defined as the acute onset of a focal neurological deficit attributable to cerebrovascular disease and supported by CT scan (normal or relevant infarct), if performed. We further required that the neurological deficit be clearly different from that of the index stroke, involve a different anatomic site or vascular territory from that of the index stroke, or be of a stroke subtype different from that of the index stroke. Only recurrent strokes occurring after the 3-month dementia assessment were considered in this study.

### Statistical Analyses

We performed log-rank tests to determine whether dementia diagnoses based on each of the methods described above were significant predictors of death and recurrent stroke. In addition, given that dementia may be a significant predictor of recurrent stroke,<sup>8</sup> which may in turn be a significant predictor of death,<sup>19</sup> we performed Cox proportional hazards analyses, adjusting for recurrent stroke as a time-dependent covariate, to ensure that any significant association we might recognize between a diagnostic method and death would not be an artifact of that paradigm's ability to predict recurrent stroke. The log-rank test and Cox proportional hazards analysis provide estimates of the risk of an outcome given the presence of a factor compared with the risk of that outcome without the presence of that factor during a defined time period.

## Results

### Frequencies of Dementia and Adverse Outcomes

Tables 1 and 2 and Tables 3 and 4 present the frequencies of dementia associated with the use of each diagnostic method stratified by the occurrence of death and recurrent stroke, respectively. Regarding the frequency of dementia, the less restrictive neuropsychological paradigms diagnosed dementia in more than half of our cohort. In contrast, a requirement of deficits in all domains as well as functional impairment diagnosed dementia in one tenth of the cohort, whereas most of the paradigms requiring memory impairment diagnosed dementia in one fourth of the cohort. Regarding the diagnostic methods that did not involve neuropsychological testing, use of the MMSE diagnosed dementia in one third of the cohort while clinical judgment diagnosed dementia in one fifth of the cohort. Essentially, the patients who were found to be demented based on clinical judgment were a subset of the patients

**TABLE 1. Prediction of Death During Follow-Up by Dementia Status: Performance of Neuropsychological Paradigms**

Diagnostic Method	Dementia (%)	Death, n		Log-Rank	Wald
		Yes	No		
≥1 Defective domain+FI	Yes (66.4)	55	107	4.45*	4.50*
	No	17	65		
≥2 Defective domains+FI	Yes (54.5)	48	85	5.44*	5.27*
	No	24	87		
≥3 Defective domains+FI	Yes (41.4)	43	58	14.14†	15.82†
	No	29	114		
≥4 Defective domains+FI	Yes (26.2)	34	30	26.19‡	19.58‡
	No	38	142		
MI+FI	Yes (28.3)	36	33	26.53‡	21.90‡
	No	36	139		
MI+≥1 defective domain+FI	Yes (28.3)	36	33	26.53‡	21.90‡
	No	36	139		
MI+≥2 defective domains+FI	Yes (26.2)	33	31	23.12‡	18.20‡
	No	39	141		
MI+≥3 defective domains+FI	Yes (21.7)	29	24	24.33‡	17.52‡
	No	43	148		
All domains+FI	Yes (11.1)	17	10	25.08‡	17.84‡
	No	55	162		

Wald values are based on Cox proportional hazards analyses, with recurrent stroke entered as a time-dependent covariate.

FI indicates functional impairment; MI, memory impairment.

\* $P < .05$ ; † $P < .001$ ; ‡ $P < .0001$ .

who were found to be demented based on neuropsychological paradigms requiring memory impairment, while that group of patients was a subset of those who were found to be demented based on MMSE performance. Although it was not a primary focus of this study, it is worthy of note that a sole requirement of functional impairment diagnosed dementia in three fourths of the cohort.

The median duration of follow-up from the baseline dementia assessment until patient death or the end of patient surveillance was 56.5 months. Seventy-two deaths (29.5% of the cohort) and 46 recurrent strokes (18.9% of the cohort) occurred. Recurrent stroke and pneumonia or other infectious diseases were each the primary cause of one fourth of the deaths in our cohort; the remaining deaths resulted from myocardial infarction or other

**TABLE 2. Prediction of Death During Follow-Up by Dementia Status: Performance of Nonneuropsychological Paradigms**

Diagnostic Method	Dementia (%)	Death, n		Log-Rank	Wald
		Yes	No		
MMSE<24	Yes (37.7)	37	55	8.63†	9.37†
	No	35	117		
MMSE<24+FI	Yes (34.8)	36	49	11.22‡	11.22‡
	No	36	123		
Clinical judgment	Yes (16.4)	21	19	15.07‡	8.26†
	No	51	153		
Clinical judgment+FI	Yes (16.4)	21	19	15.07‡	8.26†
	No	51	153		
FI	Yes (75.4)	59	125	2.40	4.09*
	No	13	47		

Wald values are based on Cox proportional hazards analyses, with recurrent stroke entered as a time-dependent covariate.

MMSE indicates Mini-Mental State Examination; FI, functional impairment.

\* $P < .05$ ; † $P < .01$ ; ‡ $P < .001$ .

**TABLE 3. Prediction of Recurrent Stroke During Follow-Up by Dementia Status: Performance of Neuropsychological Paradigms**

Diagnostic Method	Dementia (%)	Recurrent Stroke, n		Log-Rank
		Yes	No	
≥1 Defective domain+FI	Yes (66.4)	33	129	0.64
	No	13	69	
≥2 Defective domains+FI	Yes (54.5)	29	104	1.60
	No	17	94	
≥3 Defective domains+FI	Yes (41.4)	23	78	1.51
	No	23	120	
≥4 Defective domains+FI	Yes (26.2)	18	46	4.86*
	No	28	152	
MI+FI	Yes (28.3)	19	50	4.74*
	No	27	148	
MI+≥1 defective domain+FI	Yes (28.3)	19	50	4.74*
	No	27	148	
MI+≥2 defective domains+FI	Yes (26.2)	18	46	4.78*
	No	28	152	
MI+≥3 defective domains+FI	Yes (21.7)	15	38	4.00*
	No	31	160	
All domains+FI	Yes (11.1)	9	18	4.45*
	No	37	180	

FI indicates functional impairment; MI, memory impairment.

\* $P < .05$ .

forms of cardiovascular disease, systemic malignancy, or other causes, in decreasing order of frequency.

### Dementia As a Predictor of Adverse Outcomes

As shown in Tables 1 and 2, log-rank tests and Cox proportional hazards analyses, adjusting for recurrent stroke as a time dependent covariate, demonstrated that paradigms based on neuropsychological assessment were the best predictors of

**TABLE 4. Prediction of Recurrent Stroke During Follow-Up by Dementia Status: Performance of Nonneuropsychological Paradigms**

Diagnostic Method	Dementia (%)	Recurrent Stroke, n		Log-Rank
		Yes	No	
MMSE<24	Yes (37.7)	20	72	0.73
	No	26	126	
MMSE<24+FI	Yes (34.8)	19	66	1.01
	No	27	132	
Clinical judgment	Yes (16.4)	11	29	2.79
	No	35	169	
Clinical judgment+FI	Yes (16.4)	11	29	2.79
	No	35	169	
FI	Yes (75.4)	33	151	0.49
	No	13	47	

MMSE indicates Mini-Mental State Examination; FI, functional impairment.

death, particularly when memory impairment was specifically required. While the less restrictive neuropsychological paradigms, the MMSE, clinical judgment, and the use of a sole criterion of functional impairment were all significant predictors of death in the Cox proportional hazards analyses, they were the weakest of the predictors. Similarly, as shown in Tables 3 and 4, log-rank tests demonstrated that dementia diagnoses based on neuropsychological paradigms requiring memory impairment or deficits in four or more cognitive domains as well as functional impairment were the only significant predictors of recurrent stroke.

Given that age and stroke severity are established predictors of stroke outcome, we performed additional Cox proportional hazards analyses to assess the utility of a neuropsychological paradigm that performed well in the preceding analyses, which required deficits in memory and one or more additional cognitive domains as well as functional impairment, in the prediction of death and recurrent stroke while adjusting for those factors, with age coded as 80+ years and 70 to 79 years versus 60 to 69 years and baseline Stroke Severity Scale score coded as  $\geq 7$  versus  $< 7$ . We found that dementia diagnosed using that paradigm remained a significant independent predictor of death while adjusting for the significant effects of baseline Stroke Severity Scale score and the nonsignificant effects of age as well as after further adjusting for the significant effects of recurrent stroke as a time-dependent covariate. Similarly, dementia diagnosed using that paradigm remained a significant independent predictor of recurrent stroke while adjusting for the nonsignificant effects of age and baseline Stroke Severity Scale score.

### Discussion

Although it was not a primary focus of this study, it is worthwhile to review potential explanations for the importance of dementia as a predictor of recurrent stroke and death.<sup>6,8</sup> First, patients with dementia after stroke tend to have more severe cerebrovascular disease than nondemented patients, including characteristics such as a larger total volume of infarction and a greater number of vascular risk factors. Thus, in certain patients, dementia may serve as a surrogate for those characteristics that are actually increasing the risk of recurrent stroke and death. Second, patients with dementia might have more difficulty adhering to their medication regimens, with inconsistencies in compliance potentially resulting in less effective stroke prophylaxis and an elevated risk of recurrent stroke and death. Third, physicians might be hesitant to prescribe anticoagulant medications to demented stroke patients when otherwise indicated because of the adverse consequences that could result from inconsistent compliance or accidents such as falls.

The results of our study suggest that dementia diagnosis based on neuropsychological assessment has superior predictive validity compared with other conventional methods and would be a worthwhile component of many stroke outcome studies. While all paradigms were significant predictors of death, paradigms based on neuropsychological assessment performed best and were the only significant predictors of recurrent stroke. Functional information was a standard component of the neuropsychological paradigms that we exam-

ined, but those paradigms remained superior even after identical information regarding functional impairment was added to paradigms based on use of the MMSE and clinical judgment, suggesting that the more extensive assessment of cognitive function was the basis for their superior predictive validity. In particular, a requirement of memory impairment appeared to be central to the superior performance of paradigms based on neuropsychological assessment. Although we found that dementia diagnosis based on neuropsychological assessment provides predictive information beyond that of established factors such as age and stroke severity, it was not our intention to suggest that dementia could be considered to be an adequate sole predictor of the adverse outcomes that we studied. Instead, our findings suggest that dementia diagnosed using neuropsychological testing and an operationalized paradigm should be incorporated into multivariate predictor models, along with variables such as dementia subtype and severity, stroke subtype and severity, infarct characteristics, vascular risk factors, and demographic variables.

If we can assume that superior performance in the prediction of adverse outcomes can serve as evidence of the validity of diagnoses based on a certain paradigm, the prevalence or frequency of dementia that results from the use of such a paradigm should be considered to be most accurate because it is best able to identify “true” cases of dementia. The paradigms that predicted adverse outcomes best were those based on neuropsychological assessment and requiring memory impairment, and they identified dementia in approximately one fourth of our cohort. Thus, our findings provide support for the NINDS-AIREN, DSM-IV, and ICD-10 paradigms, but they do not suggest that any one of those codified paradigms is superior. While a paradigm requiring impairment in  $\geq 4$  cognitive domains, regardless of whether memory impairment was specifically evident, performed well, memory impairment was likely to have been present in patients diagnosed with dementia by that paradigm because of the large number of cognitive domains that were required to be impaired. Despite those findings, it should not be inferred that the sole presence of memory impairment is adequate for the diagnosis of dementia. As illustrated by the frequencies of dementia presented in Tables 1 and 3, all patients with memory impairment had deficits in one or more additional cognitive domains, and most patients with memory impairment had deficits in two or more additional cognitive domains. Based on our findings and consistent with the results of prior studies,<sup>20–22</sup> we can infer that the MMSE and the less restrictive neuropsychological paradigms overdiagnosed dementia, whereas clinical judgment underdiagnosed dementia.

An important strength of operationalized diagnostic paradigms lies in their high level of reliability,<sup>23,24</sup> in contrast to the use of clinical judgment, which has been shown to have only moderate reliability in the recognition of physiological signs and symptoms in neurological examination.<sup>25</sup> In the Stroke Data Bank,<sup>26</sup> dementia diagnosis based solely on clinical judgment resulted in a frequency of dementia of 16.0%, with a  $\kappa$  coefficient of 0.34 suggesting that interrater reliability was only moderate. Solari et al<sup>27</sup> performed a record review based on 50 patients presenting with possible cognitive impairment of varied etiology and reported a  $\kappa$  coefficient of 0.49 for

agreement on dementia diagnosis among four neurologists using DSM-III-R<sup>28</sup> criteria. Similarly, Fratiglioni et al<sup>29</sup> reported only moderate interrater reliability for the use of DSM-III-R criteria, and they suggested that interrater reliability could be improved by providing operationalized guidelines for the definition of impairment in cognitive function. In the present study, dementia diagnosis based on clinical judgment performed reasonably well in the prediction of mortality, but skilled neurologists specializing in stroke and dementia provided those diagnoses. Evidence in support of their specialized knowledge lies in the failure of the addition of a requirement of functional impairment to enhance the utility of that paradigm, suggesting that those neurologists had already incorporated functional information into their determinations, as noted in a prior study.<sup>30</sup> Thus, it is likely that the utility of clinical judgment is reduced when it is used by less specialized neurologists.

While dementia or similar concepts have long been in use, only recently have efforts been made to operationally define that disorder. It is informative to review the history of criteria for the diagnosis of dementia through the successive editions of the *Diagnostic and Statistical Manual of Mental Disorders*. In DSM-I,<sup>31</sup> the term “chronic brain syndrome” was used rather than dementia and diagnosis was treated descriptively, with impairment in orientation, memory, intellectual functions, and judgment, as well as lability and shallowness of affect, thought to be characteristic, but functional deficits were neither discussed nor required to reach that diagnosis. In DSM-II,<sup>32</sup> “senile and presenile dementia” were described as subtypes of organic brain syndrome and the psychoses. Much as in DSM-I, those disorders continued to be treated descriptively rather than operationally defined, but the inability to meet the ordinary demands of life had become an implied criterion. While impairment in multiple cognitive domains was discussed in both DSM-I and DSM-II, neither text described how cognitive abilities should be assessed.

A significant conceptual advance occurred with the publication of DSM-III,<sup>33</sup> which presented an operationalized definition of dementia in order to enhance the reliability of that diagnosis. Memory impairment was now specifically required, as well as impairment in one or more additional cognitive domains, including abstract thinking, judgment, and other higher cortical functions (eg, aphasia and apraxia), and bedside tasks were suggested that might be administered to assess those abilities. Impairment in social or occupational functioning was also explicitly required. While the criteria for dementia diagnosis were essentially unchanged with the publication of DSM-III-R, further significant modifications were made in DSM-IV.<sup>16</sup> Deficits in memory and one or more other cognitive domains, as well as impairment in social or occupational functioning, continued to be required, but it was noted that those deficits should represent a significant decline from a previously higher level of functioning. In addition, for the first time, neuropsychological assessment was explicitly recommended. It is worthy of note that the criteria for dementia diagnosis proposed by the International Workshop of the NINDS-AIREN<sup>15</sup> and presented in ICD-10<sup>17</sup> are quite similar to those in DSM-IV<sup>16</sup> and also include the recommendation that neuropsychological testing be performed. Alternatively, other influential guidelines have avoided the use of operation-

alized criteria for the diagnosis of dementia but also recommend the use of neuropsychological testing.<sup>18</sup>

While neuropsychological assessment is more labor intensive than the administration of a mental status test or a neurological examination, the significantly greater predictive power of that technique could permit the early identification of patients at risk of adverse outcomes and provide an opportunity for the initiation of targeted interventions. Neuropsychological assessment can also provide more precise information regarding the pattern of cognitive deficits exhibited by patients than the other methods, which can be useful when efforts are being made to define the subtype of dementia.<sup>34</sup> Recently, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology published a position paper stating that the utility of neuropsychological assessment is "established" for the assessment of patients with dementia as well as chronic stroke.<sup>35</sup> While future studies should investigate alternative diagnostic paradigms and varied neuropsychological test batteries in patients with stroke to determine whether additional precision in the prediction of adverse outcomes is possible, it is our belief that the widespread adoption of these methods would facilitate the recognition and treatment of patients with dementia and, potentially, reduce the significant public health burden associated with that disorder.

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