MRI Biomarkers of Vascular Damage and Atrophy Predicting Mortality in a Memory Clinic Population

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Background and Purpose—MRI biomarkers play an important role in the diagnostic work-up of dementia, but their prognostic value is less well-understood. We investigated if simple MRI rating scales predict mortality in a memory clinic population.

Methods—We included 1138 consecutive patients attending our memory clinic. Diagnostic categories were: subjective complaints (n=220), mild cognitive impairment (n=160), Alzheimer disease (n=357), vascular dementia (n=46), other dementia (n=136), and other diagnosis (n=219). Baseline MRIs were assessed using visual rating scales for medial temporal lobe atrophy (range, 0–4), global cortical atrophy (range, 0–3), and white matter hyperintensities (range, 0–3). Number of microbleeds and presence of infarcts were recorded. Cox-regression models were used to calculate the risk of mortality.

Results—Mean follow-up duration was 2.6 (±1.9) years. In unadjusted models, all MRI markers except infarcts predicted mortality. After adjustment for age, sex, and diagnosis, white matter hyperintensities, and microbleeds predicted mortality (white matter hyperintensities: hazard ratio [HR], 1.2; 95% CI, 1.0–1.4; microbleeds: HR, 1.02 95% CI, 1.00–1.03; categorized: HR, 1.5; 95% CI, 1.1–2.0). The predictive effect of global cortical atrophy was restricted to younger subjects (HR, 1.7; 95% CI, 1.2–2.6). An interaction between microbleeds and global cortical atrophy indicated that mortality was especially high in patients with both microbleeds and global cortical atrophy.

Conclusion—Simple MRI biomarkers, in addition to their diagnostic use, have a prognostic value with respect to mortality in a memory clinic population. Microbleeds were the strongest predictor of mortality. **(*Stroke*. 2009;40:492-498.)**

Key Words: dementia ■ magnetic resonance imaging ■ microbleeds ■ mortality ■ white matter

Predicting progression and outcome in dementia is clinically important. It provides important information for patients and caregivers and improves patient management. It also has scientific importance by giving insight in the possible pathological processes involved in progression of disease. The presence of dementia in general leads to an increased mortality, and several clinical and demographic characteristics have been identified that convey poor survival.[1–3] Old age, male gender, and comorbidity are associated with higher mortality, both in a general population[2] and among patients with dementia,[1,2,4] although some studies report that mortality attributable to dementia is higher in young subjects compared to older subjects.[5]

MRI has an established role in the diagnostic work-up of dementia, beyond the exclusion of potentially treatable causes of dementia.[6,7] MRI markers of atrophy can support a diagnosis of Alzheimer disease (AD)[8] and markers of cerebrovascular disease are an essential part of the NINDS-AIREN criteria for vascular dementia.[9] Moreover, global cortical atrophy (GCA) and medial temporal lobe atrophy (MTA) predict decline of cognitive function.[10,11] The relation between MRI markers of vascular disease and cognitive function is less clear; however, some studies suggest an association[12,13] but others fail to do so.[10,14]

Less is known about the value of MRI in predicting survival in memory clinic patients. A limited number of studies found a correlation between imaging markers and an increased risk of mortality, and only 1 of those studies[4] was conducted in a dementia population, using CT rather than MRI. The latter study described an association of temporoparietal atrophy and mortality within a population of AD patients. Other studies that described associations between imaging markers and mortality were conducted either in an elderly population without dementia,[15,16] or in other disease populations.[17–19] The aim of the current study was to investigate the prognostic value with respect to mortality of 5 simple MRI markers related to neurodegenerative and vascular disease in a memory clinic population.

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Materials and Methods

Patients

The study population consisted of 1138 consecutive patients who visited the memory clinic of the Alzheimer Center, VU University Medical Center between 1993 and 2006, and underwent brain MRI. Brain MRI scans were performed as part of the routine clinical work-up. The other standardized clinical assessments included medical history, physical examination, neurological examination, laboratory tests, electroencephalography and neuropsychological examinations. Diagnoses were made in a multidisciplinary consensus meeting between neurologists, neuropsychologists, a clinical neurophysiologist, psychiatrist, geriatrician, and radiologist. We defined the following categories of diagnosis: subjective complaints (cognitive complaints in the absence of deficits on neuropsychological examination), mild cognitive impairment,[20,21] AD using the NINCDS-ADRDA criteria,[22] vascular dementia,[9] other dementia (including frontotemporal lobar degeneration,[23] dementia with Lewy bodies,[24] and other neurodegenerative disorders), and other diagnosis (including neurological, psychiatric, or other diagnoses and cases in which diagnosis was postponed, eg, awaiting further examinations).

The study was approved by the local medical ethical committee, and all patients gave written informed consent for their clinical data to be used for research purposes at the time of their first visit. Questionnaires were sent out to patients' general practitioners and follow-up was defined based on dates of survival or death on these questionnaires. When the questionnaire was not returned, last date of survival or date of death was retrieved from the patient's clinical record (n=287). Information about medical history was retrieved from the patients' clinical records.

MRI Protocol

The majority of MRI scans (n=998) were obtained on a 1.0-T system (Siemens Magnetom Impact Expert); 140 scans were obtained on a 1.5-T platform (Siemens Sonata Syngo or Siemens Vision). Scan protocol included: (1) 3-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence (coronal orientation, 148–176 slices; 1.5-mm slice thickness; field of view, 250 mm; 256×256 matrix; echo time (TE), 5.2–7.0 ms; repetition time (TR), 15 ms; inversion time (TI), 300 ms); (2) fluid-attenuated inversion recovery sequence (transverse orientation, 17 slices; slice thickness, 5 mm; slice gap, 1.5–2.0 mm; field of view, 250 mm; 256×256 matrix; TE, 101–105 ms; TR, 9000 ms; TI, 2200 ms); (3) T2-weighted turbo spin echo sequence (transverse orientation, 21 slices; slice thickness, 5 mm; slice gap, 1.5 mm; field of view, 250 mm; 256×256 matrix; TE, 119 ms; TR, 5775 ms); and (4) T2*-weighted gradient-echo sequence (transverse orientation, 19–21 slices; slice thickness, 5 mm; slice gap, 1.0 mm; field of view, 250 mm; 256×256 matrix; TE, 15–22 ms; TR, 600–800 ms; flip angle, 15°–20°).

MRI Assessment

Assessment of MRI consisted of 3 widely used visual rating scales (using previously described operationalization criteria[25–27]), a count of microbleeds, and assessment of the presence of large vessel infarcts. MTA was rated using a 5-point rating scale (0–4)[27] using oblique reconstructions of the magnetization-prepared rapid acquisition gradient-echo sequences, perpendicular to the long axis of the hippocampus. In the analysis, we used the average of MTA score for the left and right sides. GCA (range, 0–3)[26] and white matter hyperintensities (WMH) (range, 0–3)[25] were assessed on fluid-attenuated inversion recovery images. We defined microbleeds as round lesions with low signal on T2*-weighted images within the brain parenchyma (diameter <10 mm).[28] The total number of microbleeds was counted. Presence of ≥1 infarcts, including both territorial and watershed infarctions, was recorded.

The rating was performed by 3 observers, blinded to the patients' clinical data. The observers were trained using our standard training set (19 brains) to meet consistency requirements according to our standard operating procedure. The interrater-weighted Cohen κ scores were >0.90 for microbleeds, >0.80 for MTA and WMH scores, and >0.60 for GCA (against internally established gold standard). Intrarater-weighted Cohen κ scores were >0.90 for microbleeds, >0.80 for MTA, and >0.70 for GCA and WMH.

Because of missing sequences, or impaired quality of sequences, MTA could only be assessed in 1112 cases, GCA could only be assessed in 1090, and WMH could only be assessed in 1117. Because the T2*-weighted sequence has been included in the standard scan protocol more recently, microbleeds could be assessed in a smaller number of scans than the other measures (n=938).

Statistical Methods

For statistical analyses, SPSS version 12.0.1 for windows was used. Differences between groups were analyzed using χ^2 test and Student *t* test. Kaplan-Meier survival curves were constructed for the scores of the visual rating scales. To estimate the risk of mortality associated with the MRI markers, Cox proportional hazards models were used. We performed the analyses for microbleeds in 2 ways, using the total number of microbleeds, and using a categorization (0, 1–2, ≥3), because the latter allows for easier comparison with the hazard ratios (HR) of the other MRI markers. Per MRI marker, we applied 5 models. Each MRI marker was entered univariately (model 1); adjusted for age and sex (model 2); adjusted for age, sex, and diagnosis (model 3); and additionally adjusted for history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction (model 4). Finally, all MRI measures were entered simultaneously in model 5, with all covariates from model 4. To investigate the predictive effects of WMH and microbleeds in further detail, we repeated the analysis, entering them as categorical variables to model 3. To assess interactions between age and MRI markers, and mutual interactions between the MRI markers, we subsequently introduced bivariate interaction terms. For the assessment of interactions with age, we entered age as a dichotomous variable, based on median age (68 years). The models used to assess interactions between MRI markers contained 2 MRI markers and their interaction term with age, sex, and diagnosis as covariates. Finally, we repeated the analyses for the group of AD patients only, using the same 4 Cox proportional hazard models.

Results

Baseline characteristics for all patients are shown in Table 1. The total number of patients who had died at follow-up was 153 (13%), after a mean follow-up duration of 2.6 (±1.9) years. The mean duration of follow-up did not differ between patients who had deceased and those who were alive at follow-up ($P=1.0$). There were 628 (55%) men and 510 (45%) women. Mortality was higher in men compared with women ($P<0.001$). Mean age at the time of MRI was 66 years (±11), and age at MRI was higher among patients who had deceased compared with those who were still alive at follow-up ($P<0.001$). The numbers of patients per category of diagnosis were: subjective symptoms, 220 (19%); mild cognitive impairment, 160(14%); AD, 357 (31%); vascular dementia, 46 (4%); other dementia, 136 (12%); and other diagnosis, 219 (19%). Mortality was higher among patients with dementia compared with the patients in the subjective symptoms and mild cognitive impairment groups ($P<0.001$ for AD and vascular dementia; $P<0.005$ for other dementia). Mean mini-mental state examination score was lower in the patients who had deceased at follow-up compared with those who were still alive. Mean mini-mental state examination, by diagnosis, ranged from 29 (subjective symptoms) to 21 (AD).

The Figure shows Kaplan-Meier survival curves for the MRI markers in the overall population. Cox proportional hazard models (Table 2) show that all MRI markers except infarcts predicted mortality in the univariate analysis and

Table 1. Baseline Characteristics

	Alive	Deceased	Total
Total	985 (87%)	153 (13%)	1138
Sex			
Female	463 (91%)	47 (9%)	510
Male	522 (83%)	106 (17%)*	628
Age	66 (11)	71 (9)†	66 (11)
Duration of follow-up	2.6 (1.9)	2.6 (1.9)	2.6 (1.9)
Diagnosis			
Subjective complaints	213 (97%)	7 (3%)	220
MCI	150 (94%)	10 (6%)	160
AD	284 (80%)	73 (20%)‡	357
Vascular dementia	31 (67%)	15 (33%)‡	46
Other dementia	109 (80%)	27 (20%)‡	136
Other diagnosis	198 (90%)	21 (10%)	219
MMSE	25 (5)	22 (6)†	25 (5)
Hypertension§	248 (89%)	32 (11%)	280
Diabetes§	69 (80%)	17 (20%)	86
Hyperchol§	80 (88%)	11 (12%)	91
MI§	42 (82%)	9 (18%)	51

Data represent absolute number (percentage) of patients except for age, follow-up and MMSE, where numbers represent mean (SD). Percentages are relative to the numbers shown in the column 'Total'.

MCI indicates mild cognitive impairment; AD, Alzheimer disease; MMSE, Mini-Mental State Examination; hyperchol, hypercholesterolemia; MI, myocardial infarction.

*$P<0.001$ (χ^2; compared with female patients).

†$P<0.001$ (t test).

‡$P<0.005$ (χ^2; compared with both subjective complaints and MCI).

§Available for n=1096 (hypertension), n=1111 (diabetes), n=1121 (hypercholesterolemia) and n=1123 (myocardial infarction).

after adjustment for age and sex (models 1 and 2). Microbleeds had the strongest impact on mortality, which became especially clear after additional adjustment for diagnosis (model 3), while WMH also had a modest predictive effect. The effects were largely unchanged after entering history of hypertension, diabetes, hypercholesterolesterolemia, and myocardial infarction to the analysis. In the model in which all MRI measures were entered simultaneously, microbleeds remained a predictor of mortality, independent of the other MRI measures. To assess the predictive effects of microbleeds and WMH in more detail, we entered them as categorical variables to model 3. For both markers, the predictive effects mainly depended on the group with severe abnormality (severe WMH [no WMH=reference]: HR, 1.7; 95% CI, 1.0–2.8; $P=0.06$; many [≥3] microbleeds [no microbleeds=reference]: HR, 2.4; 95% CI, 1.4–4.3; $P<0.05$). The HR for 1 and 2 WMH (no WMH=reference) were 1.0 (95% CI, 0.6–1.5; $P=0.94$) and 1.0 (95% CI, 0.6-.8; $P=0.90$), respectively. For 1 to 2 microbleeds, HR was 0.8 (95% CI, 0.4–1.6; $P=0.60$).

There was an interaction between age and GCA ($P<0.01$), but there was no significant interaction between age and the other MRI markers. To explore how the predictive effect of GCA was modified by age, we stratified the patients by median age (68 years). Adjusted for sex and diagnosis, GCA was a predictor of mortality in the younger patients (HR, 1.7; 95% CI, 1.1–2.6; $P<0.05$), but not in older patients (HR, 1.0; 95% CI, 0.8–1.3; $P=0.80$).

When entering bivariate interaction terms between pairs of MRI markers to model 3, we found 2 interactions. First, there was an interaction between MTA and GCA ($P<0.05$). The risk of mortality related to MTA was highest in patients with a low GCA score, and the risk of mortality related to GCA was highest in patients with low MTA scores. Second, we found an interaction between GCA and number of microbleeds ($P<0.05$). The risk of mortality for patients with microbleeds was highest in those who additionally had high GCA scores. The risk of mortality for patients with both severe cortical atrophy (GCA score=3) and ≥3 microbleeds was 6-times the risk found in patients without cortical atrophy and microbleeds (HR, 5.8; 95% CI, 1.5–22.9; $P<0.05$).

Finally, we repeated the analyses for the group of AD patients only (n=357). Mean age was 70 years (±9) and there were relatively more female (196; 55%) than male patients (161; 45%). Results were largely comparable with the results in the total population (Table 3). After adjustment for age and sex, the predictive effect of MTA and GCA disappeared, whereas the number of microbleeds predicted mortality in the group of AD patients independent of age and sex. The overall predictive effect of WMH did not reach significance in any of the models. The presence of infarcts did not predict mortality. The effects were not altered after adjusting for the additional covariates in model 3, and the predictive effect of microbleeds was independent of the other MRI variables.

Discussion

The main finding of this study is that baseline MRI biomarkers, especially microbleeds and to a lesser extent WMH, predicted mortality in a memory clinic population. Large-vessel infarcts did not predict mortality. The predictive effect of cortical atrophy was restricted to the younger patients. When we restricted the analysis to AD patients only, findings were largely comparable.

Of the 5 MRI markers we investigated, presence of microbleeds was the strongest predictor of mortality. Where MTA and GCA are important markers in the diagnostic process, because they can both help differentiate neurodegenerative disease from controls[8] and are related to cognitive function,[10,11] we found that their value in predicting mortality is strongly related to diagnosis. Whereas the relation between markers of small-vessel disease and cognitive function remains less clear,[10,12–14] and microbleeds at present do not have an important role the diagnostical process of dementia, we show that the number of microbleeds and, to a lesser extent, WMH are clinically relevant markers because they predict mortality in this population. Our finding that infarcts do not predict mortality within a memory clinic population is in line with findings by others.[4]

To our knowledge, this is the first study assessing the predictive value of microbleeds with respect to mortality in a population other than a stroke population. Recent studies have shown that the prevalence of microbleeds on MRI is relatively high within a dementia population, and that the presence of microbleeds is related to age, diagnosis, and the

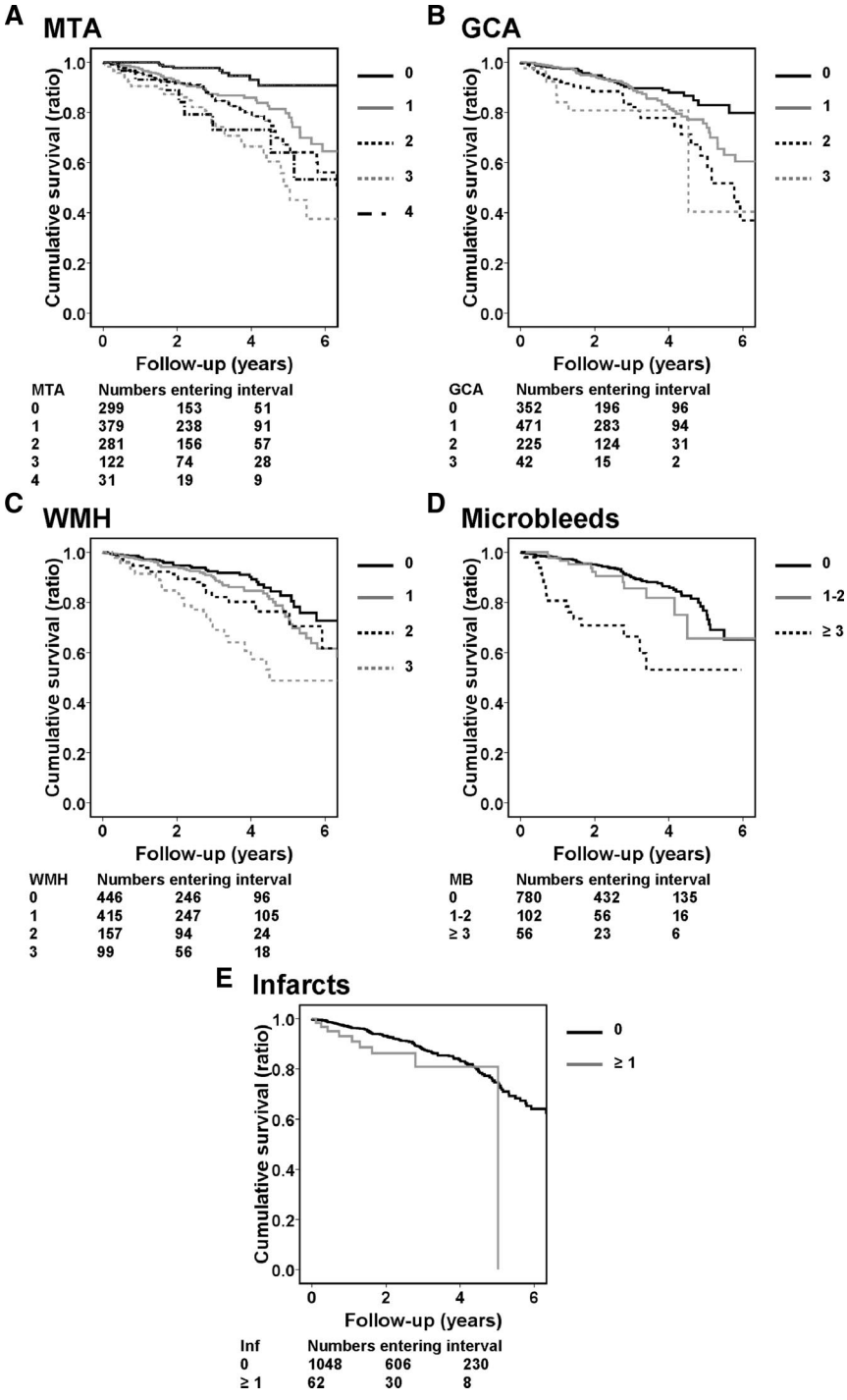

Figure. Kaplan-Meier survival curves of MRI markers. Kaplan Meier curves for (A) MTA; (B) GCA; (C) WMH; (D) microbleeds; and (E) infarcts. Lines represent cumulative survival for each different MTA, GCA and WMH score and for number of microbleeds. Tables under the curves represent the number of patients entering the intervals of 0, 2, and 4 years of follow-up.

presence of other findings of vascular pathology on MRI.[28–30] Although 2 studies have described a relation between the presence of microbleeds on MRI and severity of cognitive impairment within a vascular dementia [31] and a stroke[32] population, the clinical significance of microbleeds is not fully clear at present. We add an important piece of information by showing that microbleeds are associated with poorer survival. Although microbleeds are highly prevalent among patients with intracerebral hemorrhages and ischemic stroke, literature about the risk of future cerebrovascular events is scarce.[33,34] It is tempting to assume that the observed association between microbleeds and mortality is accounted for by cerebrovascular causes of death. However, because we were not able to collect data about cause of death of all deceased patients and because the reason of death was too often unknown, we were not able to perform analysis on these data. Further studies should address the important issue of the relation of microbleeds (and other MRI findings) and cause of death.

Our data suggest that not merely the presence, but rather the number, of microbleeds predicts the risk of mortality. The categorized (0, 1–2, ≥3 microbleeds) analysis shows that only the presence of many (≥3) microbleeds predicts mortality. It should, however, not be concluded that there

Table 2. Risk Estimates of Mortality: Overall Population (n=1138)

	Model 1	Model 2	Model 3	Model 4	Model 5
MTA	1.5 (1.3–1.7)*	1.3 (1.1–1.5)*	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.8–1.4)
GCA	1.6 (1.3–2.0)*	1.3 (1.0–1.6)†	1.2 (0.9–1.4)	1.2 (1.0–1.5)	1.2 (0.9–1.6)
WMH	1.5 (1.2–1.7)*	1.3 (1.1–1.5)*	1.2 (1.0–1.4)‡	1.2 (1.0–1.4)‡	1.1 (0.9–1.4)
MB N	1.02 (1.01–1.03)*	1.02 (1.01–1.03)*	1.01 (1.00–1.03)†	1.01 (1.00–1.03)†	. . .
MB categories	2.0 (1.5–2.6)*	1.5 (1.2–2.0)*	1.4 (1.1–1.9)†	1.6 (1.2–2.1)*	1.6 (1.1–2.2)*
Infarcts	1.7 (0.9–3.4)	1.4 (0.7–2.7)	1.2 (0.6–2.4)	1.2 (0.6–2.4)	0.6 (0.3–1.4)

Data represent HR (95% CI) for mortality.

Model 1: uncorrected; model 2: adjusted for age and sex; model 3: adjusted for age, sex, and diagnosis; model 4: adjusted for age, sex, diagnosis, and history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction; model 5: all MRI measures entered in 1 model, with covariates of model 4. In model 5, microbleeds were entered as a categorical variable, and results were comparable with the total number of microbleeds (data not shown).

MB N indicates number of microbleeds (total N; range, 0–200); MB categories, microbleeds (0, 1–2, ≥3).

MTA, mean of score for left and right side, range, 0–4; GCA, range, 0–3; WMH, range, 0–3; infarcts, presence of ≥1 large-vessel infarcts.

*$P<0.01$.

†$P<0.05$.

‡$P<0.1$.

is a strict threshold going from 2 to 3 microbleeds. Rather, our results indicate that the presence of multiple microbleeds does predict mortality, whereas the presence of some microbleeds is not associated with an increased risk of mortality.

The interaction between microbleeds and cortical atrophy resulted in a 6-fold increased risk of death for patients with severe cortical atrophy and multiple microbleeds in comparison with subjects without cortical atrophy and microbleeds. Literature shows that atrophy is present in vascular disease,[35,36] and vascular damage often occurs in AD.[37] Moreover, neuropathological studies have suggested that neurodegenerative disease and vascular pathology act in synergy, resulting in a higher risk of dementia and more severe cognitive impairment.[38,39] In vivo studies using MRI have shown similar results.[40,41] We extend on these findings by showing that patients expressing both types of pathology on MRI are at a far higher risk of mortality than patients with either of them. Although one might hypothesize that microbleeds and cortical atrophy could coexist as a representation of amyloid-angiopathy, recent findings that microbleeds seem to have no or only little influence on cerebral atrophy in CADASIL[36] suggest that different pathological pathways might be involved as well. Age modified the relation between cortical atrophy and mortality. In the younger patients GCA predicts mortality, but it does not do so in the older patients. This might explain why the overall effect of GCA did not reach statistical significance in the overall population.

Among the limitations of this study is the fact that, rather than an epidemiological population-based study in which a given number of subjects is followed for a fixed number of years, our study is a cohort study in a clinical setting. The consequentially high variability in duration of follow-up was, nevertheless, accounted for in the statistical analyses. Second, although the cohort consists of a clinically important selection of patients, the results might not be applicable to a general population. In the Cox-proportional hazards models, age, sex, diagnosis, and vascular risk factors were included as covariates. We were not able to include other predictors of mortality that have been described, such as (nonvascular)

Table 3. Risk Estimates of Mortality: Patients With AD (n=357)

	Model 1	Model 2	Model 3	Model 4
MTA	1.2 (1.0–1.5)‡	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.0 (0.7–1.4)
GCA	1.4 (1.0–1.9)‡	1.2 (0.9–1.7)	1.3 (0.9–1.9)	1.5 (0.9–2.4)
WMH	1.2 (0.9–1.6)	1.1 (0.9–1.5)	1.1 (0.9–1.5)	1.1 (0.8–1.7)
MB N	1.07 (1.04–1.11)*	1.07 (1.03–1.11)*	1.07 (1.03–1.11)*	. . .
MB categories	1.7 (1.1–2.5)†	1.6 (1.0–2.4)†	1.8 (1.1–2.8)†	1.8 (1.1–3.0)†
Infarcts	2.3 (0.8–6.3)	2.0 (0.7–5.6)	1.8 (0.6–5.2)	0.9 (0.2–3.2)

Data represent HR (95% CI) for mortality.

Model 1: uncorrected; model 2: adjusted for age and sex; model 3: adjusted for age, sex, and history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction; model 4: all MRI measures entered in 1 model, with covariates of model 3. In model 4, microbleeds were entered as a categorical variable, and results were comparable with the total number of microbleeds (data not shown).

GCA, range, 0–3; infarcts, presence of ≥1 large-vessel infarcts; MB categories, microbleeds (0, 1–2, ≥3); MB N, total number, range, 0–55; MTA, mean of score for left and right side, range, 0–4; WMH, range, 0–3.

*$P<0.01$.

†$P<0.05$.

‡$P<0.1$.

comorbidity and physical performance, because these data, derived from clinical files, were not uniformly assessed and were less complete than data on vascular risk factors. No conclusions about the comparison between the predictive values of MRI variables and other predictors of mortality, such as age, diagnosis, and comorbidity, can be drawn from our results. Taken into account that MRI is at present widely available, as it is used in the diagnostic work-up of memory clinic patients, our finding that simple MRI markers, in addition to their diagnostic value, have prognostic value in predicting mortality is clinically important. The information obtained from MRI should be weighted together with other clinical variables such as comorbidity in planning of patient care and information given to patients and caregivers about prognosis.

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Disclosure

None.

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