

## Original Investigation

# Factors Associated With 8-Year Mortality in Older Patients With Cerebral Small Vessel Disease

## The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study

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**IMPORTANCE** Gait and cognition have been related to mortality in population-based studies. This association is possibly mediated by cerebral small vessel disease (SVD), which has been associated with mortality as well. It is unknown which factors can predict mortality in individuals with SVD. Identification of high-risk patients may provide insight into factors that reflect their vital health status.

**OBJECTIVES** To assess mortality in patients with cerebral SVD and identify potential clinical and/or imaging factors associated with mortality.

**DESIGN, SETTING, AND PARTICIPANTS** A prospective, single-center cohort study was conducted. The present investigation is embedded in the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) study. Between January 17, 2006, and February 27, 2007, all participants underwent a cognitive and motor assessment and cerebral magnetic resonance imaging (MRI) including a diffusion tensor imaging sequence to assess microstructural integrity of the white matter. Participants were followed up until their death or November 24, 2014. Participants included 503 older adults with SVD noted on brain imaging. Data analysis was performed from November 26, 2014, to February 2, 2015.

**MAIN OUTCOMES AND MEASURES** Eight-year all-cause mortality.

**RESULTS** Of 503 participants (mean [SD] age, 65.7 [8.8] years; range, 50-85 years; 284 [56.5%] were male), 80 individuals (15.9%) died during a mean (SD) follow-up of 7.8 (1.5) years. In the final analysis, 494 (98.2%) were included, of whom 78 (15.8%) died. Gait speed, cognitive index, conventional MRI markers of SVD (white matter hyperintensity volume, brain volume, and lacunes), and diffusion measures of the white matter were associated with an 8-year risk of mortality independent of age, sex, and vascular risk factors. The prediction of mortality was determined using Cox proportional hazards models with backward stepwise selection and including age, sex, vascular risk factors, gait speed, cognitive index, MRI, and diffusion measures. Results are reported as hazard ratios (HRs) (95% CI). Older age (1.05 per 1-year increase [1.01-1.08]), lower gait speed (1.15 per 0.1-m/s slower gait [1.06-1.24]), lower gray matter volume (0.72 per 1-SD increase [0.55-0.95]), and greater global mean diffusivity of the white matter (1.51 per 1-SD increase [1.19-1.92]) were identified as the main factors associated with mortality. Cognitive index and other conventional SVD markers were not retained in the prediction model.

**CONCLUSIONS AND RELEVANCE** Gait, cognition, and imaging markers of SVD are associated with 8-year risk of mortality. In the prediction of mortality, an older age, lower gait speed, lower gray matter volume, and greater global mean diffusivity of white matter at baseline best predicted mortality in our population. Further research is needed to investigate the reproducibility of this prediction model and to elucidate the association between the factors identified and mortality.

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Cerebral small vessel disease (SVD) is prevalent on brain imaging of older adults.<sup>1</sup> It consists of white matter hyperintensities (WMHs) and lacunes of presumed vascular origin, microbleeds, and subcortical and cortical atrophy on conventional magnetic resonance imaging (MRI).<sup>2</sup> The radiologic spectrum of SVD extends beyond lesions visible on conventional MRI, including impaired WM microstructural integrity that can be assessed by diffusion tensor imaging (DTI).<sup>3</sup> The clinical presentation and long-term prognosis of SVD are both highly variable, including cognitive and motor impairment and mood disturbances, which could lead to functional decline<sup>4</sup> and death.<sup>5,6</sup> It is unknown which patients with SVD are at the highest risk for these adverse outcomes, especially mortality. Several population-based studies among community-dwelling older adults have shown that gait speed<sup>7</sup> and cognition<sup>8,9</sup> are important clinical characteristics associated with mortality; nevertheless, to our knowledge, whether this prediction was independent of the presence of SVD has not been investigated. We could hypothesize that this association is driven by SVD since SVD has been previously associated<sup>6,10</sup> with mortality, particularly, WMHs and lacunes. However, to our knowledge, it has never been investigated whether imaging characteristics of SVD have added value in the prediction of mortality regarding clinical factors such as gait and cognition.

In this observational study, we prospectively investigated the cumulative mortality in a population of older adults with SVD after 8 years of follow-up. Our main objective was to identify baseline risk factors of all-cause mortality, including clinical (gait speed and cognition) and imaging (MRI and DTI measures) factors. We were especially interested in which of these variables were most predictive for all-cause mortality. This information may provide insight into factors that reflect the vital health status of older adults with SVD.

## Methods

### Study Population

The present study is embedded in the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) study, a prospective cohort study that investigates the risk factors and clinical consequences of functional and structural brain changes as assessed by MRI. A total of 503 older adults with SVD aged 50 to 85 years were included. The recruitment, study rationale, and protocol of the RUN DMC study have been reported.<sup>11</sup> Because the onset of SVD is often insidious and clinically heterogeneous with acute symptoms (transient ischemic attacks or lacunar syndromes) or subacute symptoms (cognitive, motor, and mood disturbances),<sup>12</sup> an SVD diagnosis was made on the basis of brain imaging and included the presence of WMHs and/or lacunes of presumed vascular origin.<sup>13</sup> Major referral reasons of the participants to our department included those corresponding to symptoms of SVD (eg, transient ischemic attack or minor stroke and cognitive disturbances). After inclusion, all participants were subsequently asked about acute or subacute symptoms of SVD. Main exclusion criteria were baseline parkinsonism, demen-

### Key Points

**Question:** Which clinical (gait and cognition) and/or imaging markers (magnetic resonance imaging and diffusion tensor imaging measures) can predict 8-year mortality in individuals with cerebral small vessel disease?

**Findings:** An older age, lower gait speed, lower gray matter volume, and greater global mean diffusivity of the white matter (reflecting a reduced microstructural integrity of the white matter) at baseline best predicted mortality in our population aged 50 to 85 years.

**Meaning:** These factors may reflect the vital health status of our population, although further research is needed to investigate the reproducibility of our prediction model and to elucidate the association between these factors and mortality.

tia, life expectancy of less than 6 months, non-SVD-related WM lesions (eg, multiple sclerosis), and MRI contraindications. Subsequently, the above-mentioned acute or subacute clinical symptoms of SVD were assessed by standardized structured assessments. Patients who were eligible because of a lacunar syndrome were included more than 6 months after the event to avoid acute effects on the outcomes.

Baseline assessment included a cognitive and motor examination and a cerebral MRI. The present study was conducted from January 17, 2006, to February 27, 2007. Participants were followed until their death or until November 24, 2014.

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. All participants signed an informed consent form; there was no financial compensation.

### Mortality

All-cause mortality was the primary outcome of this study. Information on vital status was first retrieved from the Dutch Municipal Personal Records database (<https://www.government.nl/topics/identification-documents/contents/the-municipal-personal-records-database>). Information on the cause of death was obtained from the general practitioner or treating physician and medical records. Subsequently, the cause of death was classified according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)*<sup>14</sup> by 1 rater (H.M.v.d.H.) and grouped as ischemic stroke, intracranial hemorrhage, cardiac cause, other vascular (when the cause of death was presumably vascular but did not meet the criteria for fatal stroke or cardiac cause), malignant neoplasms, infections, and miscellaneous.

### MRI Scanning and Processing

All participants underwent a cerebral MRI scan, including a 3-dimensional T1 magnetization prepared rapid acquisition gradient-echo (MPRAGE), fluid-attenuated inversion recovery (FLAIR), gradient-echo T2\*-weighted sequence and a DTI sequence on a 1.5-T scanner at baseline. Imaging details have been described elsewhere.<sup>11</sup>

White matter hyperintensities were manually segmented on the FLAIR images, and total WMH volume was calculated

by summing all segmented areas multiplied by section thickness, with a good interrater variability (intraclass correlation coefficient, 0.99). The ratings of lacunes and microbleeds (including subcortical and lobar ones) were revised according to the recently published Standards for Reporting Vascular changes on neuroimaging<sup>2</sup> by trained raters (including H.M.v.d.H. and I.W.M.v.U.) blinded to clinical information (intrarater and interrater reliabilities: weighted  $\kappa$  values, 0.87 and 0.95, respectively, for the presence of lacunes and 0.85 and 0.86, respectively, for the presence of microbleeds, calculated in a random sample of 10% of the scans).

Automated segmentation on T1 images was performed using Statistical Parametric Mapping, version 5 (SPM5; <http://www.fil.ion.ucl.ac.uk/spm/software/>) to obtain gray matter (GM) and WM and cerebrospinal fluid probability maps. The volumes were calculated by summing all the voxel volumes belonging to the tissue class. All volumes, including WMHs, were normalized to the total intracranial volume (sum of GM, WM, and cerebrospinal fluid volumes)<sup>15</sup> to adjust for head size. Gray matter volume was composed of the volume of the neocortex, basal ganglia, and thalamus.

For DTI analysis, the diffusion-weighted images of each participant were realigned on the mean of the unweighted image using mutual information-based coregistration routines from SPM5. The diffusion tensor<sup>16</sup> and its eigenvalues were estimated using linear regression and spurious negative eigenvalues were set to zero, after which the tensor derivatives of fractional anisotropy and mean diffusivity (MD) were calculated.<sup>17</sup> The mean unweighted image was used to compute the coregistration variables to the anatomical T1 reference image, which were then applied to all diffusion-weighted images and results. All images were visually checked for motion artifacts and coregistration errors. The volume-averaged fractional anisotropy and MD were calculated in the total WM.

### Cardiovascular Risk Factors

Information on the presence of cardiovascular risk factors was investigated with structured questionnaires. The use of medication for treatment of any vascular risk factor was verified by a medication list from the pharmacy provided by the participant.

Information on smoking behavior was dichotomized into ever (current and former) and never smoking. Diabetes mellitus was considered to be present if the participant was receiving oral glucose-lowering drugs or insulin. Hypertension was defined as the use of blood pressure-lowering medication and/or a current systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher, assessed during baseline examination, with the mean determined after 3 measurements with the patient in a supine position after 5 minutes of rest.<sup>18</sup>

### Cardiovascular Diseases and Malignant Neoplasms

To identify cardiovascular disease or malignant neoplasms in the medical history, structured questionnaires were used and this information was subsequently retrieved by the participants' treating physician or from medical records and was verified thereafter. A history of cardiovascular disease was de-

defined as the presence of an ischemic stroke, intracerebral hemorrhage, transient ischemic attack, myocardial infarction, percutaneous coronary intervention, coronary bypass surgery, or peripheral arterial disease. A history of cancer was defined as the presence of any malignant neoplasm (mentioned in the ICD-10).<sup>14</sup>

### Measurement of Gait

Gait speed was assessed by using a 5.6-m electronic portable walkway (GAITRite; MAP/CIR Inc). This walkway system has an excellent test-retest reliability and validity.<sup>19,20</sup> Each participant was instructed to walk over the walkway at his or her usual speed. Participants started 2 m before the walkway and stopped 2 m behind it to measure steady-state walking. The mean gait speed (meters per second) of 2 walking episodes of each participant was used for analysis.

### Cognitive Assessment

Global cognitive function was evaluated by the Mini-Mental State Examination.<sup>21</sup> A cognitive index was constructed to obtain a more robust outcome measure for global cognition. The cognitive index was calculated as the mean of the *z* scores of the Speed Accuracy Tradeoff score of the 1-letter subtask of the Paper and Pencil Memory Scanning Task,<sup>22</sup> the mean of the Speed Accuracy Tradeoff score of the reading task of the Stroop test,<sup>23</sup> the mean of the Symbol-Digit Substitution task,<sup>24</sup> and the mean of the added score on the 3 learning trials of the Rey Auditory Verbal learning test and the mean of the delayed recall of this test.<sup>25</sup>

### Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics 20 for Windows (SPSS Inc) and R, version 2.15 (<http://www.R-project.org>) software packages. Cumulative mortality was estimated using Kaplan-Meier analysis and stratified for different imaging markers. Differences between the lowest and highest quartiles and presence vs absence were estimated with the log-rank test. Data analysis was performed from November 26, 2014, to February 2, 2015. Differences in baseline characteristics between survivors and those who died were tested by using an independent-samples *t* test,  $\chi^2$  test, or Mann-Whitney test when appropriate.

Cox regression analysis was used to calculate hazard ratios (HRs) and 95% CIs for gait speed, cognitive index, and different imaging measures after adjustment for age, sex, and vascular risk factors. For the prediction models, we used the variables with a significance level of  $P \leq .10$  after adjustment for age, sex, and vascular risk factors. Because of the high correlation between DTI variables, only the MD of the WM was included in the model. Three Cox proportional hazards models were constructed to predict all-cause mortality. In the first model, age, sex, and vascular risk factors were entered simultaneously into the Cox model. For the next models these factors were fixed. Subsequently, gait speed and cognitive index (model 2) and imaging variables (MRI and DTI measures, model 3) were entered by a backward, stepwise selection procedure until these nonfixed variables had a significance level of  $P \leq .10$ . A fourth model was constructed by using a backward, step-

Table 1. Baseline Characteristics of the Study Population

Characteristic	Status at Follow-up		P Value
	Alive (n = 416)	Dead (n = 78)	
Baseline demographics			
Age (SD), y	64.5 (8.4)	72.1 (8.4)	<.001 <sup>a</sup>
Male sex, No. (%)	236 (56.7)	43 (55.1)	.79 <sup>b</sup>
Vascular risk factors at baseline, No. (%)			
Smoking	286 (68.8)	60 (76.9)	.15 <sup>b</sup>
Diabetes mellitus	44 (10.6)	19 (24.4)	.001 <sup>b</sup>
Hypertension	299 (71.9)	64 (82.1)	.06 <sup>b</sup>
Comorbidity at baseline, No. (%)			
Cardiovascular	195 (46.9)	48 (61.5)	.02 <sup>b</sup>
Malignant neoplasm	42 (10.1)	10 (12.8)	.47 <sup>b</sup>
Baseline clinical scores			
Gait speed, mean (SD), m/s	1.32 (0.26)	1.09 (0.28)	<.001 <sup>a</sup>
MMSE score, mean (SD)	28.3 (1.6)	27.5 (1.8)	<.001 <sup>c</sup>
Cognitive index, mean (SD)	0.08 (0.76)	-0.52 (0.68)	<.001 <sup>a</sup>
Baseline MRI characteristics <sup>d</sup>			
WMH volume, median (IQR), mL	6.0 (3.2-15.2)	17.7 (9.8-35.1)	<.001 <sup>c</sup>
WM volume, mean (SD), mL	470.5 (50.7)	433.6 (41.8)	<.001 <sup>a</sup>
GM volume, mean (SD), mL	636.9 (52.9)	597.6 (47.1)	<.001 <sup>a</sup>
Lacunae present, No. (%)	92 (22.1)	41 (52.6)	<.001 <sup>b</sup>
Microbleeds present, No. (%) <sup>e</sup>	62 (14.9)	19 (24.4)	.034 <sup>b</sup>
Territorial infarcts present, No. (%)	42 (10.1)	13 (16.7)	.09 <sup>b</sup>
Baseline DTI measures			
WM global FA, mean (SD)	0.33 (0.02)	0.32 (0.02)	<.001 <sup>a</sup>
WM global MD, mean (SD), $\times 10^{-4}$ mm <sup>2</sup> /s	8.8 (0.4)	9.3 (0.4)	<.001 <sup>a</sup>

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; IQR, interquartile range; MD, mean diffusivity; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; WM, white matter; WMH, WM hyperintensities.

<sup>a</sup> Independent-samples t test.

<sup>b</sup>  $\chi^2$  Test.

<sup>c</sup> Mann-Whitney test.

<sup>d</sup> Brain volumes are represented as normalized to the total intracranial volume.

<sup>e</sup> Two participants were excluded because of missing values of microbleeds at baseline (1 in each group).

Table 2. Cause of Death According to ICD-10 Classification

Cause of Death	Participants, No. (%)
Vascular	26 (33.3)
Ischemic stroke	5 (6.4)
Intracerebral hemorrhage	3 (3.8)
Cardiac cause	12 (15.4)
Other vascular <sup>a</sup>	6 (7.7)
Malignant neoplasm	20 (25.6)
Infection	12 (15.4)
Miscellaneous	15 (19.2)
Unknown	5 (6.4)

Abbreviation: ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

<sup>a</sup> Deaths that were presumably vascular but did not meet the criteria for fatal stroke or cardiac cause.

wise selection procedure for all covariates (age, sex, vascular risk factors, cognition, gait, and MRI and DTI measures); none of these were fixed. Models 1 to 3 were also constructed for vascular mortality; using the proportional hazards model of Fine and Gray,<sup>26</sup> causes of death other than vascular factors were considered a competing risk. Schoenfeld residuals were investigated to verify the proportionality of hazards. There were no indications that the proportional hazards assumption was violated.

The C statistic was used to assess the discriminatory performance of the different prediction models. An increase of C statistic values by 0.025 or more was considered a significant improvement of accuracy.<sup>7</sup> Furthermore, the Akaike information criterion (AIC) was used to investigate the goodness of fit of the models.<sup>27</sup> The most appropriate model is the one with the lowest AIC value.<sup>28</sup> We considered a decrease of 10 or more values as significantly improved goodness of fit.

## Results

The study population consisted of 503 participants; 493 individuals (98.0%) were white, with a mean (SD) age at baseline of 65.7 (8.8) years and a mean follow-up duration of 7.8 (1.5) years. Eighty participants (15.9%) died during the follow-up period. The 8-year cumulative all-cause mortality was 14.5% (95% CI, 11.3-17.6). Nine participants were excluded because of imaging artifacts (4 [44.4%]) and missing values on gait or cognitive tests (5 [55.6%]); 2 of these 9 individuals had died. **Table 1** reports the baseline characteristics of the study population (494 [98.2% of the original population]). The cause of death was vascular related in 26 (33.3%) of the participants (**Table 2**).

The **Figure** shows the cumulative mortality stratified for different imaging characteristics. All-cause 8-year mortality was highest in participants with lacunae and microbleeds, with

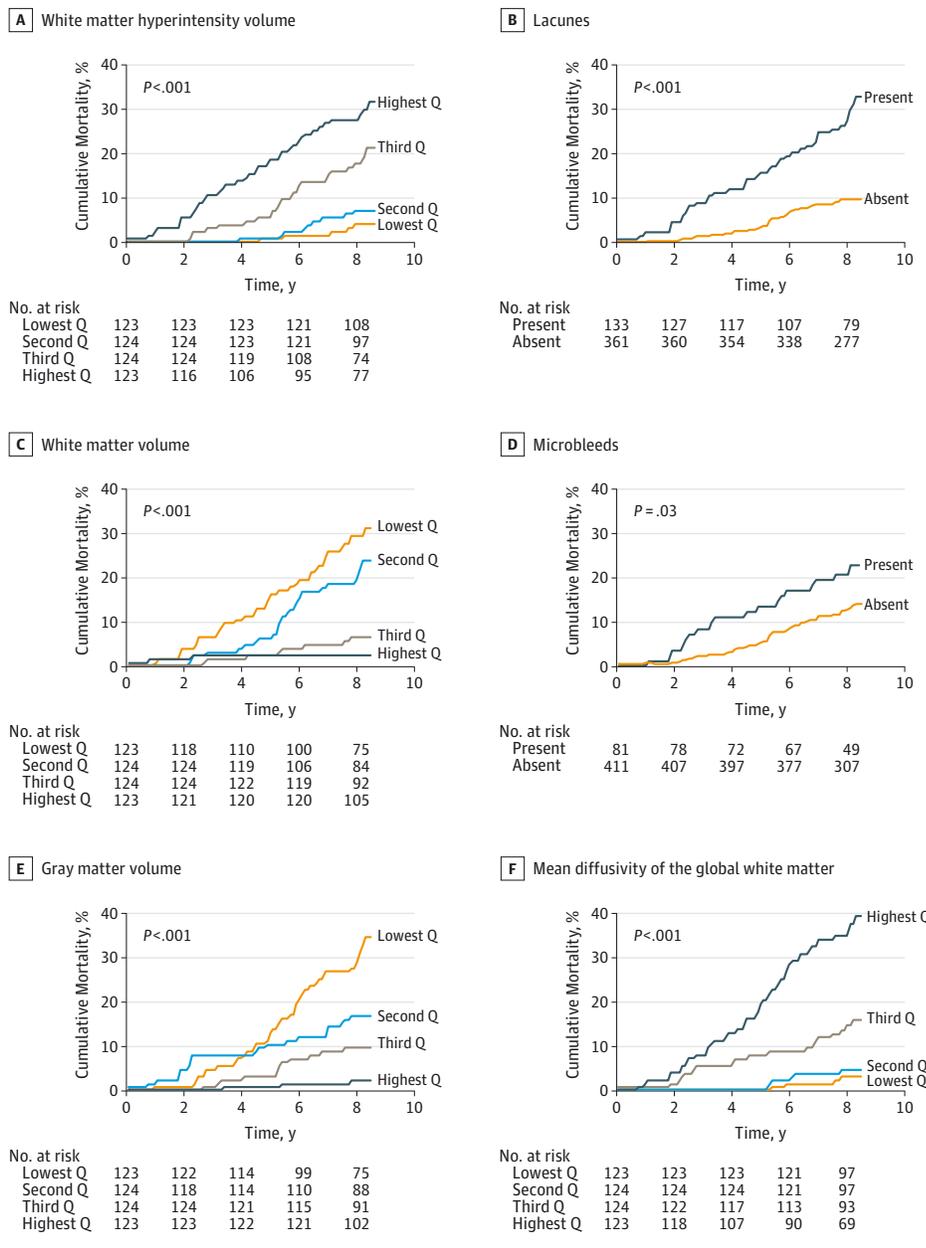
the highest WMH volume and MD of the WM and the lowest WM and GM volumes.

Gait speed, cognitive index, conventional MRI markers of SVD (except for microbleeds), and diffusion measures of the WM were identified as potential risk factors of all-cause mortality (Table 3). The presence of territorial infarcts was not associated with mortality.

In the prediction of all-cause mortality (Table 4), model 2 shows that gait speed and cognitive index added substantially to model 1. In model 3, imaging parameters were also included; GM volume and global MD of the WM were retained in the model together with gait speed. Cognitive index and other imaging markers were not retained in the

prediction model. This last model predicted the best mortality in our population. When we applied backward stepwise selection for all covariates mentioned in model 3, the following covariates were retained (reported as HR [95% CI]): age (1.05 per 1-year increase [1.01-1.08];  $P = .01$ ), gait speed (1.15 per 0.1-m/s slower gait [1.06-1.24];  $P = .001$ ), GM volume (0.72 per 1-SD increase [0.55-0.95];  $P = .02$ ), and global MD of the WM (1.51 per 1-SD increase [1.19-1.92];  $P = .001$ ). This model was as accurate as model 3 (C statistic, 0.79 [95% CI, 0.72-0.85] and AIC, 854.8). When cardiovascular morbidity and malignant neoplasms were additionally added as fixed covariates, the above-mentioned prediction models were not substantially altered.

Figure. Cumulative Mortality Stratified by Imaging Characteristics



Cumulative mortality was estimated using Kaplan-Meier analysis; this was stratified for different magnetic resonance imaging markers. The differences between the lowest and highest quartiles and presence vs absence were estimated with the log-rank test. Q indicates quarter.

**Table 3. Association Between Baseline Factors and All-Cause Mortality**

Characteristic	HR (95% CI) <sup>a</sup>	P Value <sup>b</sup>	HR (95% CI) <sup>c</sup>	P Value <sup>b</sup>
<b>Clinical scores</b>				
Gait speed, per 0.1-m/s slower gait	1.19 (1.10-1.28)	<.001	1.17 (1.08-1.26)	<.001
MMSE	0.89 (0.79-1.01)	.07	0.91 (0.81-1.03)	.15
Cognitive index	0.54 (0.38-0.77)	.001	0.59 (0.41-0.84)	.004
<b>MRI measures<sup>d</sup></b>				
WMH volume, per 1-SD increase, mL <sup>e</sup>	1.65 (1.28-2.15)	<.001	1.62 (1.24-2.11)	<.001
WM volume, per 1-SD increase, mL	0.71 (0.54-0.92)	.009	0.74 (0.57-0.97)	.03
GM volume, per 1-SD increase, mL	0.61 (0.47-0.81)	.001	0.65 (0.49-0.86)	.003
No. of lacunes	1.28 (1.09-1.49)	.002	1.23 (1.05-1.44)	.01
No. of microbleeds <sup>f</sup>	1.02 (0.96-1.09)	.52	1.01 (0.95-1.09)	.69
Territorial infarcts, presence	1.39 (0.77-2.54)	.28	1.25 (0.69-2.29)	.46
<b>DTI measures</b>				
WM global FA, per 1-SD increase	0.70 (0.57-0.87)	.001	0.70 (0.56-0.87)	.002
WM global MD, per 1-SD increase, $\times 10^{-4}$ mm <sup>2</sup> /s	1.70 (1.35-2.14)	<.001	1.68 (1.32-2.13)	<.001

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; HR, hazard ratio; MD, mean diffusivity; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SVD, small vessel disease; WM, white matter; WMH, WM hyperintensity.

<sup>a</sup> Adjusted for age and sex.

<sup>b</sup> Cox regression analysis.

<sup>c</sup> Adjusted additionally for vascular risk factors (smoking, diabetes mellitus, and hypertension).

<sup>d</sup> Brain volumes are represented normalized to the total intracranial volume.

<sup>e</sup> Log transformed.

<sup>f</sup> Two participants were excluded because of missing values of microbleeds at baseline.

**Table 4. Baseline Indicator Variables Retained in Cox Regression Models for Prediction of All-Cause Mortality**

Characteristic	HR (95% CI)					
	Model 1	P Value	Model 2	P Value	Model 3	P Value
<b>Demographics</b>						
Age, per 1-y increase	1.11 (1.08-1.14)	<.001	1.08 (1.05-1.12)	<.001	1.06 (1.02-1.09)	.003
Male sex	0.63 (0.38-1.04)	.07	0.76 (0.45-1.29)	.31	0.73 (0.43-1.25)	.25
<b>Vascular risk factors</b>						
Smoking	1.83 (1.01-3.32)	.046	1.69 (0.93-3.09)	.09	1.65 (0.89-3.04)	.11
Diabetes mellitus	2.14 (1.24-3.68)	.006	1.64 (0.94-2.88)	.08	1.60 (0.91-2.80)	.10
Hypertension	0.96 (0.53-1.74)	.88	0.88 (0.48-1.61)	.68	0.71 (0.38-1.32)	.27
<b>Clinical scores</b>						
Gait speed, per 0.1-m/s slower gait	NI		1.13 (1.04-1.23)	.006	1.13 (1.04-1.22)	.002
Cognitive index	NI		0.72 (0.49-1.05)	.09	NR	
<b>MRI and DTI measures</b>						
WMH volume, per 1-SD increase, mL <sup>a</sup>	NI		NI		NR	
WM volume, per 1-SD increase, mL	NI		NI		NR	
GM volume, per 1-SD increase, mL	NI		NI		0.75 (0.56-0.99)	.04
Lacunes, per No. increase	NI		NI		NR	
MD of WM, per 1-SD increase, $\times 10^{-4}$ mm <sup>2</sup> /s	NI		NI		1.53 (1.19-1.96)	.001
C statistic (95% CI)	0.74 (0.68-0.81)		0.77 (0.71-0.84)		0.80 (0.73-0.86)	
AIC	880.6		868.8		856.4	

Abbreviations: AIC, Akaike information criterion; DTI, diffusion tensor imaging; GM, gray matter; HR, hazard ratio; MD, mean diffusivity; MRI, magnetic resonance imaging; NI, not included in the model; NR, not retained in the

model; SVD, small vessel disease; WM, white matter; WMH, WM hyperintensity.

<sup>a</sup> Log transformed.

Hazard ratios of the same magnitude were found for vascular mortality compared with all-cause mortality (model 3 with age, sex, and vascular risk factors as fixed factors; reported as HR [95% CI]): gait speed (1.11 per 0.1-m/s slower gait [0.97-1.28];  $P = .13$ ), GM volume (0.72 per 1-SD increase [0.45-1.13];  $P = .15$ ), and the MD of the WM (1.85 per 1-SD increase [1.29-2.65];  $P < .001$ ), with other causes of death considered a competing risk. However, because of the small number of patients ( $n = 26$ ), significance was lost for gait speed and GM volume and only the MD of the WM was retained in the model (eTable in the Supplement).

## Discussion

This study shows that older age, lower gait speed, lower GM volumes, and greater global MD of the WM at baseline significantly increased the 8-year risk of mortality in individuals 50 years or older with SVD and together had the best predictive ability for all-cause mortality in our population. Cognitive performance and conventional MRI markers of SVD (including WMH volume, WM volume, and lacunes) did not significantly contribute to the prediction of mortality, although these factors were associated

with 8-year mortality after adjustment for age, sex, and vascular risk factors.

This is a unique longitudinal study that assesses potential clinical and imaging risk factors of mortality in patients with SVD. The strengths of this study include the large sample size, the complete follow-up for mortality, and its longitudinal and single-center design, which allowed us to consistently collect gait, cognitive, and imaging measures. Furthermore, all imaging data were analyzed with the reviewers blinded to clinical information with good intrarater and interrater variability.<sup>11</sup>

Some limitations need to be addressed. First, the observational design of the study prevents us from elucidating the exact association between the baseline factors identified and mortality. However, it is conceivable that these factors reflect the vital health status of our participants rather than their having a direct causal association with mortality. Second, because age is the strongest predictor of mortality,<sup>29</sup> the additional predictive value of gait speed, GM volume, and global MD of the WM was relatively low. Nonetheless, risk factors or diseases underlying slower gait, lower GM volume, or lower WM microstructural integrity might be modifiable. Further research is needed to investigate whether treatment of these underlying risk factors results in improved survival. Third, our results on vascular mortality should be interpreted with caution owing to limited statistical power. Fourth, we could not exclude the possibility that residual confounding by unmeasured variables (eg, socioeconomic status and genetics) or years of uncontrolled vascular risk factors could, at least in part, have explained our results. Finally, although this was a hospital-based cohort study, we believe that our results can be generalized to patients with SVD referred to a general neurologic clinic because we included all consecutive patients with SVD and there were no restrictions for admission to our department.

Of the clinical factors included in our prediction model, gait speed was retained in all models and cognitive performance was not retained after including imaging markers. A possible explanation for this finding might be that gait relies not only on intact cerebral networks but also on the functioning of several organ systems, including respiratory, circulatory, musculoskeletal, and peripheral nerve systems.<sup>7</sup> As a result, slower gait might not be primarily caused by dysfunction of one system (eg, the brain) but is probably due to accumulation of pathology among several organ systems, which is in accordance with the results of one recent study.<sup>30</sup> Because cognition is less affected by damage to other organ systems com-

pared with the brain, it could be that the association between cognitive performance and mortality is mediated by SVD. Cognitive performance has been related<sup>31,32</sup> to conventional markers of SVD and DTI measures. In our prediction model, cognitive index was not retained in the model when these imaging markers were added.

Another interesting finding was that the microstructural integrity of the WM seems to be more important in the prediction of mortality in our population than the conventional MRI markers of SVD because none of these markers were retained in the prediction model. An explanation for this finding might be that diffusion abnormalities in the WM probably better reflect the overall WM damage of our population since most of our participants had mild to moderately severe SVD at baseline. Conventional MRI markers of SVD probably reflect a small amount of WM abnormalities because it has been suggested that changes in diffusion measures precede the development of WMHs.<sup>3</sup> Furthermore, other (neurodegenerative) abnormalities may have influenced the microstructural integrity of the WM of our participants and the association with mortality.

Gray matter volume has been associated with mortality in population-based studies.<sup>33</sup> We showed that this factor had a significant contribution in the prediction of mortality in a population with SVD. Because 17 (21.8%) of the patients who died had developed dementia during the follow-up of our study, this may be an explanation for the observed association between lower GM volume at baseline and mortality. However, the causes of increased mortality in patients with dementia have not been fully elucidated.<sup>34</sup>

## Conclusions

This study showed that, in the prediction of mortality in older adults with SVD, older age, lower gait speed, lower GM volume, and a greater global MD of the WM were the factors primarily associated with 8-year all-cause mortality. These factors probably reflect the vital health status of this group. Further studies are needed to investigate the reproducibility of our prediction model on mortality. Furthermore, research is needed to elucidate the exact association between these risk factors and mortality and should investigate whether, for example, intervention in these risk factors (eg, by treatment of SVD and/or treatment of the underlying causes of gait impairment) could improve life expectancy in older adults with SVD.

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