RESEARCH ARTICLE

Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: A multicenter prospective cohort study

Marios K. Georgakis[1] | Rong Fang[1] | Marco Düring[1,2] | Frank A. Wollenweber[1] | Felix J. Bode[3,4] | Sebastian Stösser[3,4] | Christine Kindlein[3,4] | Peter Hermann[5] | Thomas G. Liman[6,7] | Christian H. Nolte[6,7,8] | Lucia Kerti[7,9] | Benno Ikenberg[10] | Kathleen Bernkopf[10] | Holger Poppert[11] | Wenzel Glanz[12,13] | Valentina Perosa[12,13] | Daniel Janowitz[1] | Michael Wagner[3] | Katja Neumann[13] | Oliver Speck[13,14,15,16] | Laura Dobisch[13] | Emrah Düzel[13] | Benno Gesierich[1] | Anna Dewenter[1] | Annika Spottke[3,4] | Karin Waegemann[1,17] | Michael Görtler[12,13] | Silke Wunderlich[10] | Matthias Endres[6,7,9,18] | Inga Zerr[5,19] | Gabor Petzold[3,4] | Martin Dichgans[1,17]
on behalf of the DEMDAS Investigators*

[1]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

[2]Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland

[3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[4]Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn, Germany

[5]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany

[6]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[7]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

[8]Berlin Institute of Health (BIH), Berlin, Germany

Abstract

Introduction: It remains unknown whether the global small vessel disease (SVD) burden predicts post-stroke outcomes.

Methods: In a prospective multicenter study of 666 ischemic and hemorrhagic stroke patients, we quantified magnetic resonance imaging (MRI)–based SVD markers (lacunes, white matter hyperintensities, microbleeds, perivascular spaces) and explored associations with 6- and 12-month cognitive (battery of 15 neuropsychological tests) and functional (modified Rankin scale) outcomes.

Results: A global SVD score (range 0–4) was associated with cognitive impairment; worse performance in executive function, attention, language, and visuospatial ability; and worse functional outcome across a 12-month follow-up. Although the global SVD score did not improve prediction, individual SVD markers, assessed across their severity range, improved the calibration, discrimination, and reclassification of predictive models including demographic, clinical, and other imaging factors.

Discussion: SVD presence and severity are associated with worse cognitive and functional outcomes 12 months after stroke. Assessing SVD severity may aid prognostication for stroke patients.

[9] Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany

[10] Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

[11] Department of Neurology, Helios Klinikum München West, Munich, Germany

[12] Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[13] German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

[14] Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[15] Leibniz Institute for Neurobiology, Magdeburg, Germany

[16] Center for Behavioral Brain Sciences, Magdeburg, Germany

[17] German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[18] German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany

[19] German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany

Correspondence
Martin Dichgans, Institute for Stroke and Dementia Research, University Hospital LMU, Ludwig-Maximilians-University (LMU), Feodor-Lynen-Str. 17, 81377 Munich, Germany.
Email: martin.dichgans@med.uni-muenchen.de

Highlights
- In a multi-center cohort, we explored associations of small vessel disease (SVD) burden with stroke outcomes.
- SVD burden associates with post-stroke cognitive and functional outcomes.
- A currently used score of SVD burden does not improve the prediction of poor outcomes.
- Assessing the severity of SVD lesions adds predictive value beyond known predictors.
- To add predictive value in assessing SVD in stroke patients, SVD burden scores should integrate lesion severity.

1 | INTRODUCTION

The ever-growing proportion of stroke survivors worldwide[1] has shifted attention from early complications in the acute phase to long-term consequences after stroke.[2–4] Cognitive and functional deficits are present in up to 80% of stroke survivors, depending on the definition and timepoint of assessment.[3,5–7] These deficits are associated with disability,[8,9] dependency,[10] and morbidity,[11,12] thus posing a major burden to patients, caregivers, and health care systems. A more detailed understanding of the factors that predispose to long-term outcomes is required to counsel patients and to identify high-risk individuals who might benefit from targeted interventions.

Cerebral small vessel disease (SVD) accounts for ∼25% of all strokes[13,14] and is the leading cause of vascular dementia.[15] Imaging features of SVD on magnetic resonance imaging (MRI) include lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and enlarged perivascular spaces (PVSs).[16,17] Compared to the general population, stroke patients have a higher burden of SVD.[18,19] Individual SVD markers are associated with worse outcomes including higher risk for dementia, disability, stroke recurrence, and death,[19–21] but

their combined predictive value has not been explored systematically. As such, SVD measures have attracted attention both as a traceable risk factor and a predictor of poor outcomes post-stroke.

More recent studies have focused on integrative measures of global SVD burden, which are generated by quantifying the burden of individual lesions (lacunes, WMHs, CMBs, and enlarged PVSs) and combining them into a single score.[22–24] The MRI-based global SVD[25] score ranges from 0 to 4 (one point awarded for presence of each of the four SVD markers) and is strongly associated with cognitive performance[26] and risk of dementia in the general population.[27] Yet its performance for predicting cognitive and functional outcomes in stroke patients remains poorly defined. Previous studies focused on specific patient subgroups, such as patients with lacunar stroke[28] or those receiving thrombolysis,[29] used cognitive screening instruments rather than detailed neuropsychological testing for outcome assessments,[30,31] and had a short follow-up interval of 6 months post-stroke when recovery is still underway.[28,29,31] In addition, the predictive performance of assessing a global SVD score has not been compared to visual rating scores for the severity of individual SVD markers.[30,31]

Here we set out to determine whether the global burden of SVD assessed on baseline MRI predicts cognitive and functional outcomes up to 12 months after stroke. We explored the associations of the global SVD score, as well as individual SVD markers, with cognitive and functional end points. Furthermore, we tested the predictive value of the global SVD score for cognitive and functional impairment beyond known outcome predictors post-stroke and compared it to the predictive value gained by individual SVD markers. To address these aims, we used data from a prospective multicenter study in 736 ischemic and hemorrhagic stroke survivors, which was designed to identify predictors of long-term cognitive outcomes post-stroke.

2 | METHODS

2.1 | Study population

Participants for the current study were drawn from the DEM-DAS study (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke), a multicenter prospective hospital-based cohort study conducted across seven tertiary stroke centers in Germany. The study began as a single-center pilot study at Ludwig-Maximilians-University (LMU) Munich, Germany (DEDE-MAS [Determinants of Dementia After Stroke]; NCT01334749), which enrolled 136 patients between May 2011 and November 2013 and was subsequently expanded to the multicenter study (DEMDAS) with enrollment of an additional 600 patients between January 2014 and January 2019. Details on the study protocol and DEDE-MAS have been published previously.[32,33] A detailed description of the clinical and imaging protocols of the two studies is provided in the Supplement (Supplementary methods, Tables S1, S2, Figures S1, S2).

We recruited patients ≥18 years of age who were hospitalized for acute stroke with symptom onset within the last 5 days before admission, as defined by an acute focal neurological deficit in combination with an acute ischemic infarct and as documented by either a diffusion-weighted imaging (DWI)–positive lesion on cranial MRI, a new lesion on a delayed computed tomography (CT), or a hemorrhagic stroke as documented on CT or MRI. Eligible patients needed to have an available informant. Because the target population was patients with acute stroke and no pre-stroke dementia, prior stroke was not an exclusion criterion for this study. Patients were excluded if they had a diagnosis of dementia or if they scored >64 on a screening Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[34] with the informant at recruitment. Furthermore, we excluded patients with shortened life expectancy due to a diagnosis of a malignant disease; patients with contraindications for MRI; and patients with cerebral venous thrombosis, traumatic cerebral hemorrhage, intracerebral hemorrhage because of a vascular malformation, or purely meningeal or intraventricular hemorrhage.

RESEARCH IN CONTEXT

1. **Systematic review**: Our search in MEDLINE yielded multiple studies that have shown associations between neuroimaging markers of cerebral small vessel disease (SVD) and poor post-stroke outcomes. However, whether a global score of SVD burden that integrates different individual markers is associated with cognitive and functional outcomes after stroke has not been explored systematically.

2. **Interpretation**: Beyond individual lesions, SVD burden is associated with worse cognitive and functional outcomes 12 months after stroke. However, our results indicate that the currently used global SVD score does not improve the prediction of poor outcomes, partly because it does not consider the severity of individual SVD lesions.

3. **Future directions**: To add predictive value in assessing SVD burden in patients with stroke and to improve prognostication of poor cognitive and functional outcomes, future studies should aim to develop a global SVD score that integrates individual lesion severity.

2.2 | Standard protocol approvals, registrations, patient consent, and data availability

The current study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[35] DEDEMAS and DEMDAS were conducted according to the Declaration of Helsinki and were approved by the local ethics committees of all participating sites. All patients or their legal guardians provided written informed consent prior to study inclusion. Anonymized data are available upon reasonable request to the corresponding author.

2.3 | Baseline assessments

Study participants underwent a comprehensive interview using standardized questionnaires as well as clinical, cognitive, and laboratory assessments. Detailed information on sociodemographic data, family and medical history, and prescribed medications were recorded. Assessments further included physiological (e.g., blood pressure and body mass index measurement), clinical (e.g., National Institutes of Health Stroke Scale [NIHSS], Modified Rankin Scale [mRS], Glasgow Coma Scale [GCS]), and cognitive screening tests (Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]). Peripheral blood was drawn from all enrolled patients within a median of 1 day (interquartile range: 1—2 days) after stroke (>85% of samples were drawn in the morning) and biochemical assessments were performed as part of clinical routine.

2.4 | MRI acquisition, stroke lesion volume, and SVD score

Patients underwent cranial 3-Tesla MRI examinations within 3 (DEDE-MAS) or 5 (DEMDAS) days of stroke onset. Details on the imaging protocols are provided in the Supplement (Supplementary methods, Table S2). Acute stroke lesions were segmented on DWI images using a semi-automated procedure detailed in the Supplementary methods. Stroke lesion volume was normalized by total intracranial volume as measured from T1 images. We semi-quantitatively assessed SVD markers on baseline MRI using widely accepted consensus criteria.[17,25] The following individual SVD markers were assessed: (1) lacunes: a lacune was defined as a round or ovoid, subcortical, cerebrospinal fluid (CSF)-like signal lesion with an axial diameter between 3 mm to 15 mm on fluid-attenuated inversion recovery (FLAIR) and T1-weighted images; (2) white matter hyperintensities (or WMHs): periventricular and deep WMH lesions were graded from 0 to 3 according to the Fazekas scale[36] on FLAIR images; (3) cerebral microbleeds (or CMBs): small (2–10 mm), round signal voids on T2*-weighted images; (4) enlarged perivascular spaces (PVSs) in basal ganglia: PVSs are fluid-filled spaces that are visible as either linear or round/ovoid high signals on T2-weighted and low-signals on T1-weighted images (CSF–like signal) of an axial diameter <3 mm that follow the orientation of penetrating arterioles in basal ganglia and centrum semiovale.[37] PVSs were counted bilaterally in the basal ganglia, and the side with the higher number on T2-weighted and T1-weighted images was used for scoring, in line with Staals et al.[25] and according to a method first proposed by MacLullich et al.[38]: $0 = $ no PVSs, $1 = < 10$ PVSs, $2 = 11$ to 20 PVSs, $3 = 21$ to 40 PVSs, and $4 = > 40$ PVSs.[37] Lacunes, WMHs, CMBs, and PVSs within the stroke lesion were not considered when rating the images. All images were rated by an experienced, trained rater (R.F.) without knowledge of the clinical data, and doubtful cases were discussed with a senior imaging specialist (M.Dür.) in regular consensus meetings. To ensure the reproducibility of the ratings, inter-rater reliabilities were assessed by two trained raters (R.F. and A.D.) in a sub-sample of the images: κ for lacunes $= 0.720$, κ for WMHs $= 0.795$, κ for CMBs $= 0.725$, and κ for PVSs $= 0.815$. For each participant, we quantified the global cerebral SVD burden using a previously validated score ranging from 0 to 4.[25,37] One point was allocated for each of the following lesions (Table S3): (1) presence of lacunes, (2) periventricular WMH Fazekas grade 3 or deep WMH Fazekas grade 2 or 3, (3) presence of CMBs, and (4) PVS grade 2 or higher.

2.5 | Follow-up outcomes

Study participants underwent comprehensive cognitive and functional assessments by face-to-face interviews at 6 and 12 months post-stroke. A comprehensive neuropsychological battery of tests was performed and classified in five domains (executive function, memory, language, attention, and visuospatial function; Table S1, Supplementary methods). The memory domain was a composite of word-learning, recall, recognition, and figure-immediate and delayed recall tests. Miss-

ing values for individual tests, along with reasons for missingness are presented in Tables S4–S6. We calculated test-specific z-scores based on published norms corrected for age, sex, and education ("Neuropsychological test battery" section in Supplementary methods). We then calculated domain-specific z-scores by averaging the available test-specific z-scores per domain, as well as an average global cognitive score by averaging z-scores of five domains.[39] A z-score of < -1.5 in any of five domains was used to define cognitive impairment.[39] Definitions of domain-specific cognitive impairment were likewise based on domain-specific z scores of < -1.5. Functional outcomes were assessed with the modified Rankin scale (or mRS), a global functional scale focused on motor recovery (score range from 0 [no symptoms] to 5 [serious functional impairment]), the Barthel index (BI), which evaluates functional dependence (score range from 0 [fully dependent] to 100 [fully independent]),[40,41] and the instrumental activities of daily living (IADLs), which evaluates independence in eight daily activities (score range from 0 [no independence at any task] to 8 [full independence]).[33] For all tests, information from the patients and their informants was considered. We used two independent definitions of different levels of functional impairment based on two widely applied cutoffs of mRS (>1 and >2).[12,42,43]

2.6 | Statistical analysis

We compared baseline characteristics of study participants using χ^2 or Fisher exact test for categorical variables, a two-tailed t-test for variables following a normal distribution (age and body mass index) or Mann–Whitney U test for other continuous variables. To account for the repeated assessments of the main outcomes at two follow-up time-points, we applied generalized estimating equations (GEE) models to explore associations between baseline SVD lesions and cognitive and functional outcomes at 6 and 12 months after stroke. We tested (1) the global SVD score (range 0–4), (2) the four constituent sub-scores (0 or 1 for lacune presence, periventricular WMH grade >2 or deep WMH grade ≥ 2, CMB presence, PVS grade ≥ 2), and (3) the five individual SVD markers in their entire range (lacune counts, periventricular WMH grade, deep WMH grade, CMB counts, PVS grade). Using GEE, we fit generalized linear regression models for continuous cognitive and functional outcomes (z-scores for global cognitive performance and the five individual domains, mRS, IADL, BI) and logistic regression for binary outcomes (cognitive impairment: z-score < -1.5 in global cognitive performance or individual domains; functional impairment: mRS >1 and mRS >2). To explore the associations between baseline global SVD score and cognitive and functional outcomes at individual timepoints, we applied multiple linear and multivariable logistic regression analyses. We adjusted for age, sex, and educational years (basic model), as well as for cardiovascular risk factors (history of hypertension, diabetes, atrial fibrillation, prior stroke, current smoking, alcohol consumption, body mass index, circulating low-density lipoprotein cholesterol [LDL-C] levels), stroke severity (NIHSS score at baseline), pre-stroke mRS, cognitive impairment in the acute post-stroke phase (MoCA <26 or MMSE <24 if MoCA not available), and

normalized stroke lesion volume at baseline (main model). These factors were selected, as they have previously been reported to be associated with post-stroke outcomes.[6,31,33,44,45] In sensitivity analyses we also adjusted for apolipoprotein E (*APOE*) genotype (0, 1, or 2 ε4 alleles).

To examine the value of assessing the global SVD score for predicting cognitive and functional impairment at 6 and 12 months after stroke,[46] we compared the performance of different logistic regression models: Model 1 included age, sex, education, vascular risk factors, NIHSS, and cognitive impairment in the acute phase; pre-stroke mRS; and normalized stroke lesion volume. Model 2 additionally included the global SVD score. Model 3 included individual SVD markers instead of the global SVD score. We tested model calibration with the Hosmer-Lemeshow test and compared the models with the integrated calibration index (ICI),[47] which is a commonly used method, derived by Loess-based smoothing function between the observed frequency of events and predicted risk from the models.[47] For discrimination, we compared areas under the receiver-operating characteristic (ROC) curves. Finally, we tested changes in reclassification between the models with the Net Reclassification Index (NRI).[48] We considered individuals at high risk for cognitive or functional impairment when their predicted risk was ≥30% and at low risk when their predicted risk was <10%. To account for multiple comparisons, we adjusted *P*-values using the false discovery rate (FDR) method and set statistical significance at an FDR-adjusted *P* < .05. Statistical analyses were performed with R v4.0.4.

3 | RESULTS

3.1 | Baseline characteristics and imaging features

A total of 736 participants were recruited at admission (for baseline characteristics see Table S7); 666 of them had baseline MRI scans suitable for a complete assessment of SVD lesions and were thus included in the current analyses (Figure 1). The most common reasons for missing MRI scans were unavailability of the scanner or patient refusal (Table S8). We found no significant differences at baseline between participants with and without a baseline MRI (Table S9).

The baseline characteristics of study participants entering the analyses are presented in Table 1 (mean age 67.9 ± SD 11.4 years, 66.7% men). Of the study participants, 10.7% had a prior history of stroke and their median mRS before the index event was 0 (IQR 0–0). The vast majority of index events represented ischemic strokes (97.3%), with a median NIHSS score at admission of 2 (IQR 1–5). The distribution of stroke lesions across vascular territories and the distribution of normalized lesion volumes are presented in Table S10 and Figure S3, respectively. Differences in demographics and cardiovascular risk profile between male and female study participants are presented in Table S11. Baseline characteristics were largely similar between the run-in DEDEMAS study and the multicenter expansion of DEMDAS, as well as across centers (Table S12), except for higher LDL-C levels in participants recruited to DEDEMAS.
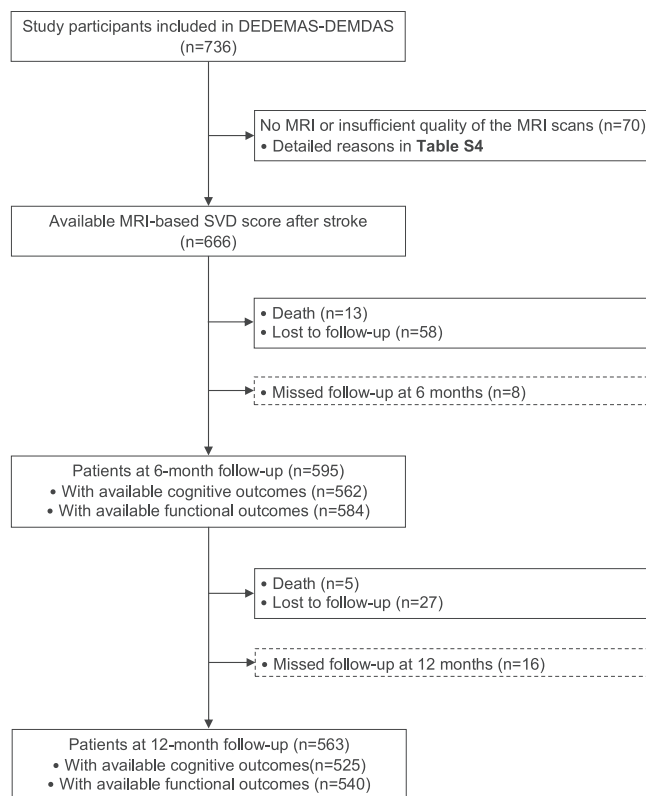

FIGURE 1 Flowchart of study participants and follow-up in the current study. DEDEMAS, Determinants of Dementia After Stroke; DEMDAS, DZNE (German Center for Neurodegenerative Diseases)-Mechanisms of Dementia After Stroke; MRI, magnetic resonance imaging; SVD, small vessel disease.

The frequency and burden of individual SVD markers is displayed in Figure 2. The most common SVD marker was WMH (46.8% of study participants had a Fazekas grade of ≥2 for deep lesions or >2 for periventricular lesions) followed by PVS (35.6% had a grade of ≥2 in the basal ganglia), lacunes (12.8%) and CMB (9.8%). When combined into the global SVD score, 38.9% of the participants had an overall score of 0 (no SVD lesions fulfilling the score criteria), 30.2% had a score of 1 (a single lesion type), 20.4% had a score of 2 (two lesion types), and only 8.1% and 2.4% of the participants had scores of 3 and 4, respectively.

3.2 | Association between global SVD score and cognitive and functional outcomes

A total of 595 (89%) and 563 (85%) participants were followed up at 6 or 12 months, respectively, after stroke and were thus included in our analyses (Figure 1, Method S1). Patients who died or were lost to follow-up were older, had a higher systolic blood pressure at baseline, and had a higher rate of cognitive impairment, as defined by their baseline MoCA scores (MoCA <26) (Table S13). At 6 months, 148 (27.6%) of the study participants met the criteria for cognitive impairment, 127 (21.7%) had an mRS score >1, and 50 (8.6%) had an mRS score >2, thus meeting one of the criteria for functional impairment. Cognitive

TABLE 1 Baseline characteristics of patients included in the analysis

Variables	n = 666
Demographic variables	
Age, y	67.9 ± 11.4
Male, n (%)	444 (66.7)
Education, y	13 (12–16)
Cardiovascular risk factors	
Hypertension, n (%)	515 (77.3)
Diabetes mellitus, n (%)	131 (19.7)
Current smoking, n (%)	155 (23.3)
Regular alcohol consumption,[a] n (%)	498 (74.8)
Atrial fibrillation, n (%)	133 (20.0)
Prior history of stroke, n (%)	71 (10.7)
BMI, kg/m^2	27.0 ± 4.3
SBP, mm Hg	140 (129–150)
DBP, mm Hg	80 (72–87)
HbA1c, %	5.7 (5.4–6.1)
LDL-C, mg/dL	126 (103, 154)
HDL-C, md/dL	48 (40–58)
Triglycerides, mg/dL	122 (92–170)
APOE genotype (n = 529), n (%)	
0 ε4 allele	421 (79.6)
1 ε4 allele	107 (20.2)
2 ε4 alleles	6 (1.1)
Index stroke classification, n (%)	
Ischemic stroke	648 (97.3)
TOAST subtype, n (%)	
Large artery atherosclerosis	172 (26.5)
Cardioembolism	144 (22.2)
Small artery occlusion	77 (11.9)
Other etiology	30 (4.6)
Undefined etiology	224 (34.6)
Hemorrhagic stroke	18 (2.7)
Clinical/cognitive assessment	
NIHSS score	2 (1–5)
mRS before stroke	0 (0–0)
BI score	100 (80–100)
IQCODE score	48 (48–49)
Baseline cognitive impairment,[b] (n = 643), n (%)	337 (52.4)
MRI variables	
Stroke lesion volume (mm3)	2248 (520, 11760)
Normalized stroke lesion volume[c] (%)	0.15 (0.03–0.77)

Note: Values are expressed as n (%), mean ± SD, or median (interquartile range).

Abbreviations: APOE, apolipoprotein E; BI, Barthel index; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LDL-C, low-density lipoprotein cholesterol; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

[a]From a self-reported questionnaire.

[b]MoCA <26 or Mini-Mental Status Examination (MMSE) <24 when MoCA was not available (5.3% of total).

[c]Stroke lesion volume/total intracranial volume.

and functional outcomes both improved between 6 and 12 months after stroke. The proportion of individuals with cognitive impairment, an mRS >1, and an mRS >2 at 12 months, was 19.2% (N = 97), 19.8% (N = 107), and 5.9% (N = 32), respectively. As illustrated in Figure 3, patients with a higher global SVD score at baseline also scored lower in cognitive tests and higher in mRS at both 6 and 12 months after follow-up. Notably, the improvement from 6 to 12 months was evident across patient subgroups stratified by global SVD.

Baseline global SVD score was associated with both a worse cognitive performance and a higher mRS score across the 12 months of follow-up after adjustment for demographic characteristics, vascular risk factors, and index stroke features (beta for cognitive performance: −0.08, 95% confidence interval [CI]: −0.14 to −0.03, P = .005; beta for mRS: 0.14, 95% CI: 0.06 to 0.22, P = .0006, Figure 3C). Looking at binary outcomes, we likewise found significant associations between the baseline SVD score and global cognitive impairment (odds ratio [OR]: 1.31, 95% CI: 1.09, 1.58; P = .005), as well as functional impairment, defined either as mRS >1 (OR: 1.34, 95% CI: 1.13 to 1.60, P = .0009) or mRS >2 (OR: 1.42, 95% CI: 1.08 to 1.86, P = .01, Figure 3D). The analyses for individual cognitive domains revealed significant associations between the baseline global SVD score and performance in executive function and attention (Figure S4). Looking at binary outcomes, we found the baseline global SVD score to be significantly associated with impairment in all of the examined domains except memory (Figure S5).

The results were largely consistent across sensitivity analyses (Figures S4–S7). Specifically, the significant associations remained stable when adjusting only for age, sex, and education; when adjusting for APOE genotype on top of demographic, clinical, and imaging predictors; and when examining associations with the study outcomes at 6 and 12 months separately. The baseline global SVD score was not associated with changes in global cognitive performance or mRS from 6 to 12 months after stroke (P = .8183 and P = .1969, respectively; Figure S8).

3.3 | Individual SVD markers in association with cognitive and functional outcomes

We next explored the associations between the presence and extent of individual SVD lesions and cognitive and functional outcomes post-stroke (Figure 4). Following correction for multiple testing, no significant associations were noted between any of the four constituent sub-scores of the global SVD score (binary variables for each SVD marker) and any of the continuous or binary cognitive and functional outcomes across the first 12 months of follow-up. In contrast, there were multiple significant associations between individual SVD markers and study outcomes when SVD markers were analyzed in their entire severity range. Overall, lacune count showed the strongest associations, with significant associations for global cognitive score, domain-specific cognitive scores, mRS score, and the corresponding binary outcomes (all except memory). Both deep and periventricular WMH grades showed significant
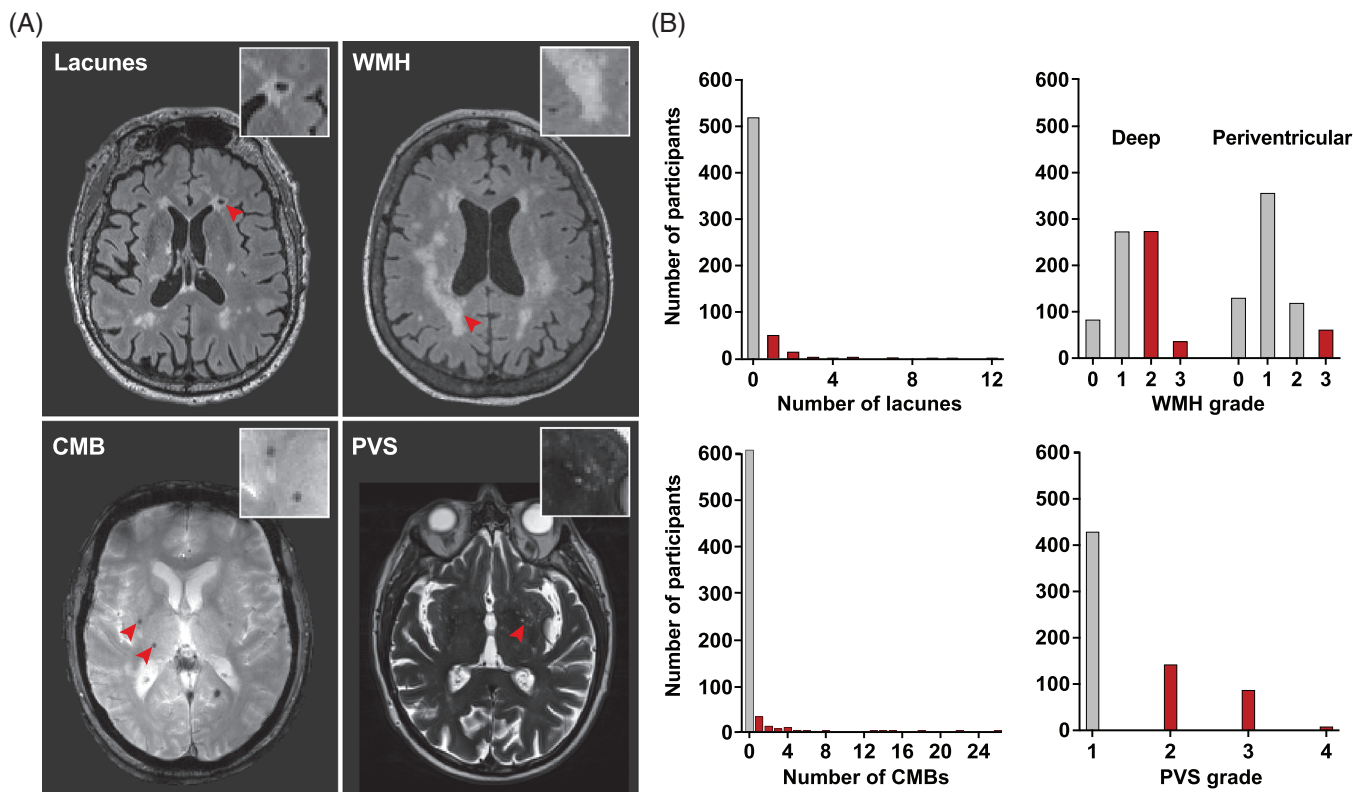
FIGURE 2 Magnetic resonance imaging (MRI) markers of cerebral small vessel disease (SVD) and the distribution of individual lesion types across the study population. (A) Representative images from patients included into the DEDEMAS (Determinants of Dementia After Stroke)-DEMDAS (DZNE [German Center for Neurodegenerative Diseases]-Mechanisms of Dementia After Stroke) study showing a lacune on axial fluid-attenuated inversion recovery (FLAIR) sequences, extensive white matter hyperintensities (WMHs) on FLAIR sequences, cerebral microbleeds (CMBs) on gradient echo T2-weighted (T2*) axial sequences, and enlarged perivascular spaces (PVSs) on T2-weighted images. The lesions are indicated by the arrowheads and also shown in enlargement in the upper corners of the respective images. (B) Distribution of individual lesion types across the study participants. Red bars represent the values that are given a point in the global SVD score (range of total score 0–4). WMHs were rated with the Fazekas scale and PVSs as recommended by Doubal et al.[37]

associations with worse outcomes in global cognition, executive function, attention, visuospatial ability, and functional status. CMB count was associated with a worse score in executive function on a continuous scale, whereas PVS grade was associated with functional impairment (Figure 4).

We further explored associations between SVD and cognitive and functional outcomes separately for strokes in the left and right hemispheres, which showed similar results (Figures S9, S10). When we adjusted additionally for a surrogate lesion location score capturing the impact of strategic stroke locations on risk of post-stroke cognitive impairment,[49] the results were still consistent with those derived from our main models (Figure S11). To explore whether our results are robust to the presence of brain atrophy at the time of the stroke, we also adjusted our models for normalized whole brain volume, which returned highly consistent estimates (Figure S12). Excluding patients with a history of pre-stroke mood, anxiety, or psychotic disorders or further adjusting for depression (the Center for Epidemiological Studies-Depression) and apathy (Starkstein Apathy Scale), scores at 6 and 12 months after stroke also did not materially influence our results (Figures S13–S15). Finally, adjustments for study site did not change our main findings (Figure S16).

Predictive value of SVD burden for cognitive and functional outcomes

As a final step, we explored the value of assessing the global SVD score for predicting binary outcomes beyond well-established predictors, and how predictive models including the global SVD score perform in comparison with models considering the severity of individual SVD lesions. We compared the calibration, discrimination, and classification change between a model of established demographic, clinical, and imaging predictors (model 1), a model also including the global SVD score (model 2), and a model including all individual SVD markers across their severity range instead of the global SVD score (model 3).

Although the overall calibration of all models was good (all Hosmer-Lemeshow–derived goodness-of-fit P > .05, Table S19), model 3 that included the individual SVD markers showed a significantly better calibration for the prediction of both cognitive and functional impairment (defined by an mRS >1) at 12 months when compared to both model 1 and model 2 (Figure 5A). Similarly, model 3 improved discrimination significantly for prediction of cognitive impairment at 12 months post-stroke, as demonstrated by areas under the curve when compared to model 1 (c = 0.72, 95% CI: 0.66 to 0.78 vs 0.69,
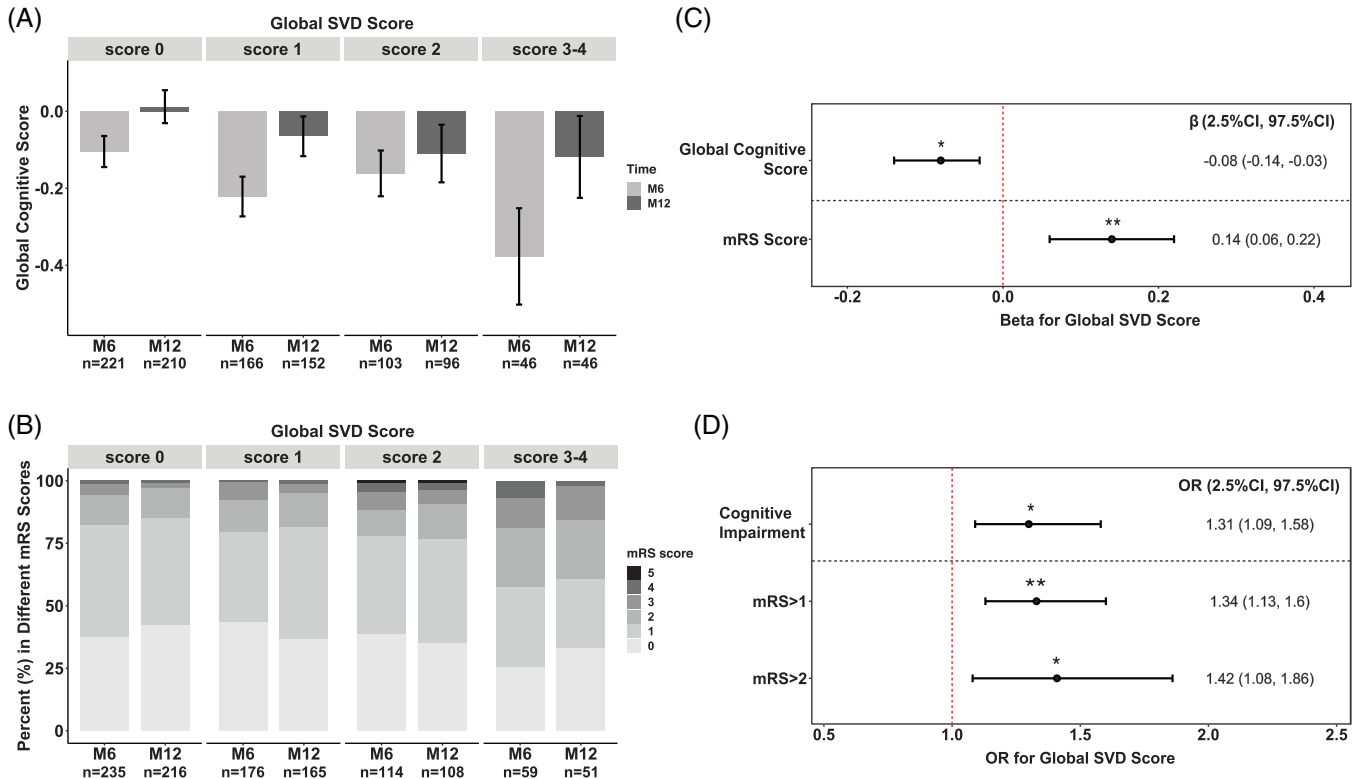
FIGURE 3 Associations between baseline global cerebral small vessel disease (SVD) score (1-point increment, range 0–4) and cognitive and functional outcomes across 12 months of follow-up after stroke. (A) Mean composite z-score of global cognitive performance at 6 (M6) and 12 months (M12) after stroke across categories of the global SVD score as assessed at baseline magnetic resonance imaging (MRI). Error bar represents standard error (SE) of the mean in each bar. (B) Distribution of the modified Rankin scale (mRS) scores across study participants at M6 and M12 across categories of the global SVD score as assessed at baseline MRI. (C) Associations of global SVD scores with global cognitive scores (composite z-score across five cognitive domains) and modified Rankin scale (mRS) scores across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS), and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). The association estimates represent betas (β's) and their 95% confidence intervals (CIs). (D) Associations of global SVD scores with cognitive impairment (composite z-score < −1.5 or z < −1.5 in any individual cognitive domain) and functional impairment (mRS >1 or mRS >2) across 12 months of follow-up after stroke incorporating both 6- and 12-month outcomes in logistic GEE models adjusted for the abovementioned variables. The association estimates represent odds ratios (ORs) and their 95% CIs. P-values are corrected for multiple comparisons with the false discovery rate (FDR) method. *Pcorr. < .05, **Pcorr. < .01

95% CI: 0.63 to 0.75; *P* = .036, Figure 5B). In contrast, we found no evidence of improved calibration or discrimination for cognitive impairment or functional impairment at 6 or 12 months when comparing model 2 that included the global SVD score with model 1 (Figure 5B, Figure S17, Table S20). Finally, we tested the reclassification changes between the three models Tables (S21, S22). Again, model 3 including individual SVD lesions outperformed model 1 and model 2 including the global SVD score in correctly reclassifying patients between low (<10%), intermediate (10% to <30%), and high risk (≥30%) for cognitive and functional impairment at 12 months.

4 | DISCUSSION

In this multicenter cohort of acute stroke patients, we found that the presence and severity of SVD burden on baseline MRI is associated with poor post-stroke cognitive and functional outcomes. Specifically,

we found that both a global SVD burden score and individual SVD markers (lacune count, WMH grade, CMB count, PVS grade) are associated with cognitive and functional impairment up to 12 months after stroke. Patients with a higher SVD burden at baseline performed worse in executive function, attention, language, and visuospatial ability across 12 months after stroke. Although the global SVD score did not improve prediction on top of demographic, clinical, and imaging factors, we found that considering individual SVD markers throughout their severity range led to better calibration, discrimination, and reclassification of predictive models for post-stroke cognitive and functional impairment. Collectively, our results provide further evidence for a detrimental role of SVD for post-stroke outcomes, but also highlight the need for a more accurate assessment of global SVD burden to improve prognostication for acute stroke patients.

Our findings extend the previous literature on the prognostic role of SVD markers in stroke patients.[22–24] Specifically, they support an additive effect of individual SVD lesions on post-stroke cognitive and
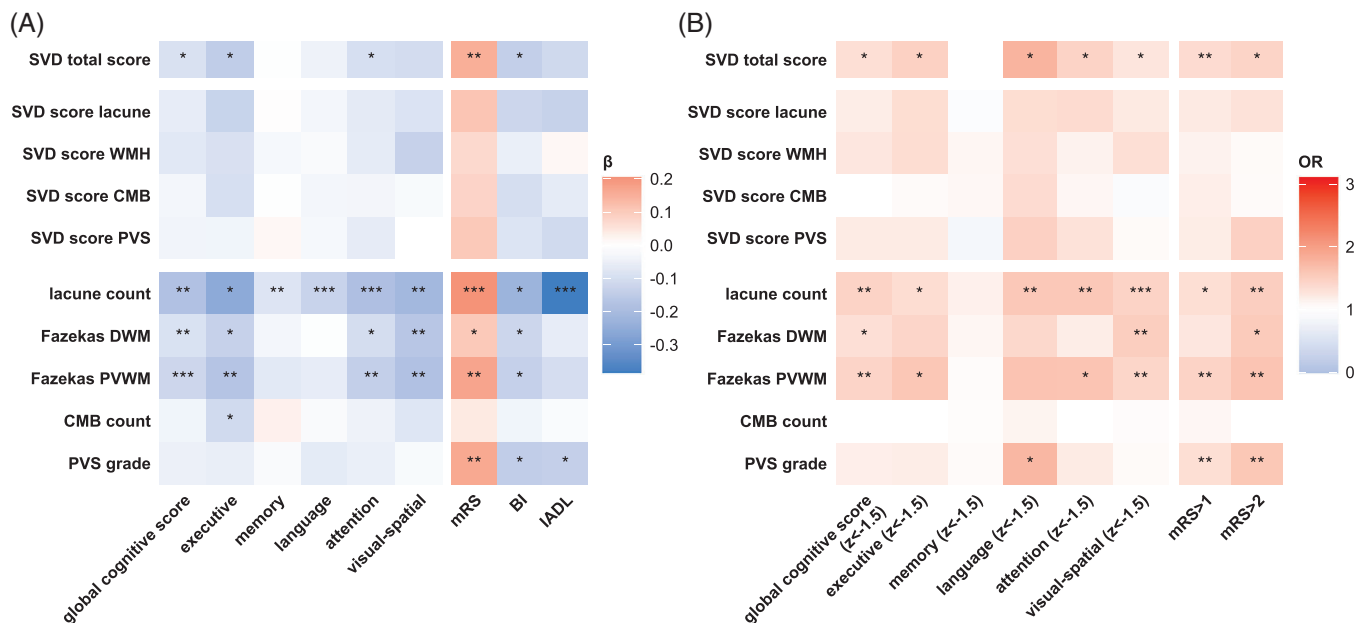
FIGURE 4 Heatmaps of the associations of global cerebral small vessel disease (SVD) score (1-point increment, range 0–4), individual components of the score (presence vs absence), and individual SVD lesion burden with cognitive and functional outcomes over 12 months of follow-up after stroke. (A) Associations with continuous outcomes: global cognitive score (composite z-score across five cognitive domains), individual cognitive domain scores, modified Rankin scale (mRS), Barthel index (BI), and instrumental activities of daily living (IADLs) across 12 months of follow-up after stroke. The heatmap includes standardized betas (β's) and their 95% confidence intervals (CIs) derived from generalized linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS), and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). (B) Associations with binary outcomes: global cognitive impairment (composite z-score < −1.5 or z < −1.5 in any individual cognitive domain) or cognitive impairment across each individual domains and functional impairment (mRS >1 or mRS >2) across 12 months of follow-up after stroke. The heatmap includes standardized odds ratios (ORs) and their 95% confidence intervals (CIs) derived from logistic GEE models adjusted for the abovementioned variables. P-values are corrected for multiple comparisons with the false discovery rate (FDR) method. NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment. *$P_{corr.}$ < .05, **$P_{corr.}$ < .01, and ***$P_{corr.}$ < .001

functional outcomes, as captured by a widely used global SVD score.[50] Despite the significant associations, this score did not add value for predicting cognitive and functional outcomes up to 12 months, in line with a previous study examining outcomes at 6 months post-stroke.[31] However, a deeper exploration revealed that a model considering the severity rather than presence of individual SVD lesions improves prediction. This suggests that a simple approach of awarding one point for the presence of each of the four hallmarks of SVD without considering the severity of individual lesion types results in a loss of relevant information. The finding has implications for future research, as it highlights the requirement to develop more efficient tools for SVD burden quantification. Such tools should ideally be both convenient to use in clinical practice and informative, including, for example, accurate and automated segmentation by machine-learning technologies, or a more detailed visual-rating scale that considers lesion severity. Such tools could inform analyses in observational studies that test predictive models for vascular cognitive impairment and the design of clinical trials that target SVD progression to ameliorate poor long-term outcomes.

Beyond clinical predictive purposes, our results provide further support that SVD is an independent risk factor for post-stroke out-

comes. Individual lesions contribute independently to poor outcomes and there seems to be a dose-response relationship for all lesion types, with the strongest dose relationship seen for lacune count. Although these results from an observational analysis cannot provide evidence of causality, we believe that the high consistency of these associations with the results from previous studies[19,20] is an indication that targeting SVD progression in stroke patients with SVD lesions at baseline might favorably influence cognitive outcomes. This is not yet part of post-stroke clinical care, but the Systolic Blood Pressure Intervention Trial-Memory and cognition IN Decreased hypertension (SPRINT-MIND) trial demonstrated that intensive blood pressure lowering in hypertensive adults without a history of diabetes or stroke can halt the progression of WMH volume[51] and lower the risk of mild cognitive impairment.[52] Studies incorporating serial imaging are needed to examine the associations between SVD progression and post-stroke cognitive outcomes.

Our study has several methodological strengths. The results were derived from a prospective multicenter study that was designed specifically to identify predictors of post-stroke cognitive impairment and disability. As such, all enrolled patients underwent a 3-Tesla MRI examination using a state-of-the-art, high-quality imaging protocol that
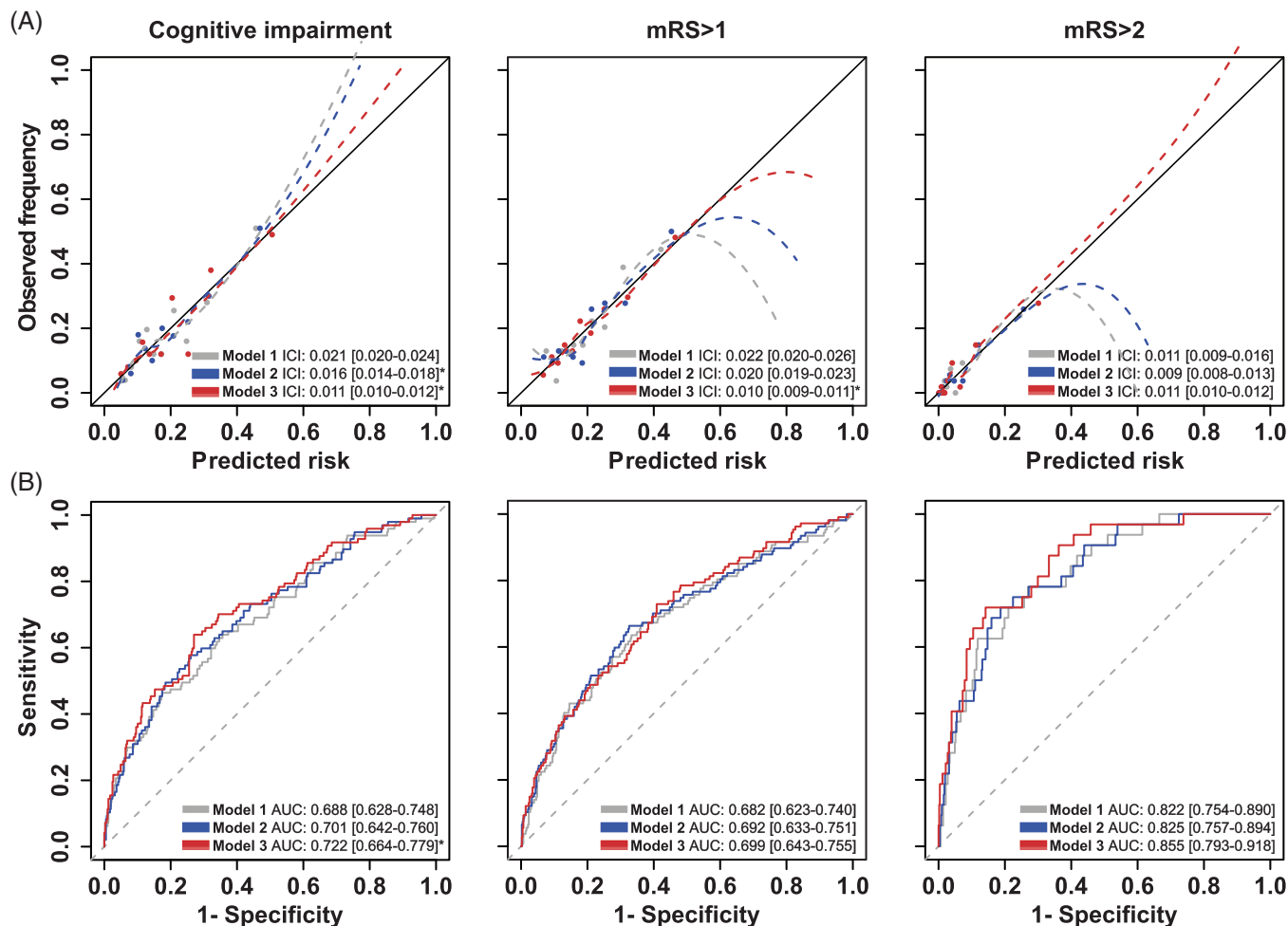
FIGURE 5 Calibration curves and receiver-operating characteristic (ROC) curves for predicting cognitive and functional impairment at 12 months post-stroke derived from models not considering cerebral small vessel disease (SVD), including the global SVD score, and including individual SVD lesions and their burden. The (A) calibration curves and (B) ROC curves were derived from three models predicting cognitive impairment (composite z-score < −1.5 or z < −1.5 in any individual cognitive domain) (left panel), and functional impairment defined by the modified Rankin scale (mRS) scores <1 (middle panel) and <2 (right panel). Model 1 includes age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS) and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). Model 2 includes the global SVD score on top of these predictors. Model 3 includes individual SVD markers instead of the global SVD score on top of these predictors (lacune count, deep and periventricular white matter hyperintensity (WMH) Fazekas grades, cerebral microbleed counts, and grade of perivascular spaces). The calibration curves are derived from Loess-based smoothing functions of the observed frequency against the predicted risk. Curves closer to the midline are indicative of better calibration. The integrated calibration index (ICI) indicates the deviation of the curves from the midline and as such lower values are indicative of better calibration. On the contrary, higher area under the ROC curve (AUC) values are indicative of better discrimination. 95% confidence intervals are presented in brackets. AUC, area under the ROC curve; ICI, integrated calibration index; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment. *P < .05 when compared to model 1

was standardized across all participating sites, allowing a comprehensive and detailed assessment of both stroke and SVD markers with high reliability. The standardized protocol across centers enabled us to pool data from more than 650 participants at an individual patient level, thereby maximizing statistical power. Furthermore, we examined patients over serial in-person follow-up visits with an extensive neuropsychological battery, which resulted in a comprehensive assessment of cognitive outcomes across multiple domains.

Our study also has limitations. First, because of the extensive imaging and neuropsychological protocol, our cohort consisted primarily

of patients with mild stroke (median NIHSS 2), who were more likely to consent to inclusion. This is reflected by the relatively low burden of SVD lesions and favorable cognitive and functional outcomes, when compared to previous studies. Consequently, our study might not be representative of the larger stroke population, where more severe stroke might be associated with challenges in assessing both SVD lesions due to masking by large infarcts and cognitive outcomes due to stroke-related motor and non-motor deficits. It is important to note, however, that it represents a population of less severely affected patients, who might benefit most from preventive interventions. Along

the same lines, the majority of the participants (97%) had an ischemic stroke, possibly as a result of an under-representation of patients with hemorrhagic stroke, who are usually more severely affected. In addition, there was an over-representation of male patients (67%), whereas the average level of education was generally high (median of 13 educational years), thus possibly limiting the generalizability of the study findings to the general stroke population. Second, we had a lost-to-follow-up rate of 15.5% across the first year after stroke, which might introduce attrition bias in our results. Yet, these patients did not significantly differ from the patients ultimately included in the analyses. Third, for 9.5% of the patients it was not possible to obtain MRI imaging at baseline, despite our efforts to be as inclusive as possible. Again, these events were related primarily to technical issues and these patients did not differ with regard to their baseline demographic and clinical characteristics when compared to patients included in the analyses. Fourth, the neuropsychological test battery at 6- and 12-month follow-up visits included identical test material, which may have led to some improvements at 12 months because of practice effects, and thus to an underestimation of the rates of cognitive impairment at 12 months after stroke. Fifth, the available SVD burden scores are surrogate markers of SVD lesions that are visible on MRI and do not capture the real burden of SVD pathology at the level of the microvasculature. Sixth, we acknowledge that we needed to adjust our analyses for a large number of potential confounders, which have been associated previously with both SVD burden and post-stroke outcomes. Although this could theoretically have introduced instability in our main models, the consistency of the association estimates for SVD markers with those derived from models only adjusted for demographic variables (age, sex, education) is reassuring. Finally, the classification of individual neuropsychological tests under specific cognitive domains, although standard in the field, is an inherent limitation because several tests require input from different domains, but also an intact motor output, which might not be the case for patients with a recent stroke.

In conclusion, our results support that both the presence and severity of SVD in patients with acute stroke are associated with poor cognitive and functional outcomes across 12 months after stroke. They further suggest that the development of an aggregate SVD burden score capturing the severity of individual lesion types would be necessary to improve clinical prognostication of stroke patients.

CONFLICTS OF INTEREST

Mattias Endres received grants from Bayer and fees paid to the Charité from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work. Author disclosures are available in the supporting information.

REFERENCES

1. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 Study. *Neuroepidemiology*. 2015;45(3):161-176.
2. Hachinski V, Einhaupl K, Ganten D, et al. Preventing dementia by preventing stroke: the Berlin Manifesto. *Alzheimers Dement*. 2019;15(7):961-984.
3. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol*. 2009;8(8):741-754.
4. Pendlebury ST, Rothwell PM. Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 2019;18(3):248-258.
5. Sexton E, McLoughlin A, Williams DJ, et al. Systematic review and meta-analysis of the prevalence of cognitive impairment no dementia in the first year post-stroke. *Eur Stroke J*. 2019;4(2):160-171.
6. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009;8(11):1006-1018.
7. Koton S, Pike JR, Johansen M, et al. Association of ischemic stroke incidence, severity, and recurrence with dementia in the atherosclerosis risk in communities cohort study. *JAMA Neurol*. 2022;79(3):271-280.
8. Fride Y, Adamit T, Maeir A, et al. What are the correlates of cognition and participation to return to work after first ever mild stroke? *Top Stroke Rehabil*. 2015;22(5):317-325.
9. Melkas S, Oksala NK, Jokinen H, et al. Poststroke dementia predicts poor survival in long-term follow-up: influence of prestroke cognitive decline and previous stroke. *J Neurol Neurosurg Psychiatry*. 2009;80(8):865-870.
10. Nys GM, van Zandvoort MJ, de Kort PL, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology*. 2005;64(5):821-827.
11. Oksala NK, Jokinen H, Melkas S, et al. Cognitive impairment predicts poststroke death in long-term follow-up. *J Neurol Neurosurg Psychiatry*. 2009;80(11):1230-1235.
12. Ganesh A, Luengo-Fernandez R, Wharton RM, et al. Time course of evolution of disability and cause-specific mortality after ischemic stroke: implications for trial design. *J Am Heart Assoc*. 2017;6(6):e005788.
13. Sudlow CL, Warlow CP, Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. *Stroke*. 1997;28(3):491-499.
14. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373(9675):1632-1644.
15. Iadecola C, Duering M, Hachinski V, et al. Vascular cognitive impairment and dementia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019;73(25):3326-3344.

16. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696.

17. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838.

18. Wen W, Sachdev PS, Extent and distribution of white matter hyperintensities in stroke patients: the Sydney Stroke Study. *Stroke*. 2004;35(12):2813-2819.

19. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(1):81-94.

20. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology*. 2019;92(12):e1298-e1308.

21. Charidimou A, Turc G, Oppenheim C, et al. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis. *Stroke*. 2017;48(8):2084-2090.

22. Pasi M, Sugita L, Xiong L, et al. Association of cerebral small vessel disease and cognitive decline after intracerebral hemorrhage. *Neurology*. 2021;96(2):e182-e192.

23. Yilmaz P, Ikram MK, Niessen WJ, Ikram MA, Vernooij MW. Practical small vessel disease score relates to stroke, dementia, and death. *Stroke*. 2018;49(12):2857-2865.

24. Jokinen H, Koikkalainen J, Laakso HM, et al. Global burden of small vessel disease-related brain changes on MRI predicts cognitive and functional decline. *Stroke*. 2020;51(1):170-178.

25. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228-1234.

26. Staals J, Booth T, Morris Z, et al. Total MRI load of cerebral small vessel disease and cognitive ability in older people. *Neurobiol Aging*. 2015;36(10):2806-2811.

27. Amin Al Olama A, Wason JMS, Tuladhar AM, et al. Simple MRI score aids prediction of dementia in cerebral small vessel disease. *Neurology*. 2020;94(12):e1294-e1302.

28. Zhi N, Zhang L, Wang Y, et al. Modified cerebral small vessel disease score is associated with vascular cognitive impairment after lacunar stroke. *Aging (Albany NY)*. 2021;13(7):9510-9521.

29. Arba F, Inzitari D, Ali M, et al. Small vessel disease and clinical outcomes after IV rt-PA treatment. *Acta Neurol Scand*. 2017;136(1):72-77.

30. Liang Y, Chen YK, Liu YL, et al. Cerebral small vessel disease burden is associated with accelerated poststroke cognitive decline: a 1-year follow-up study. *J Geriatr Psychiatry Neurol*. 2019;32(6):336-343.

31. Coutureau J, Asselineau J, Perez P, et al. Cerebral small vessel disease MRI features do not improve the prediction of stroke outcome. *Neurology*. 2021;96(4):e527-e537.

32. Wollenweber FA, Zietemann V, Rominger A, et al. The Determinants of Dementia After Stroke (DEDEMAS) Study: protocol and pilot data. *Int J Stroke*. 2014;9(3):387-392.

33. Zietemann V, Georgakis MK, Dondaine T, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. *Neurology*. 2018;91(20):e1838-e1850.

34. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. *Br J Psychiatry*. 1988;152:209-213.

35. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.

36. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, immerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149(2):351-356.

37. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*. 2010;41(3):450-454.

38. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1519-1523.

39. Knopman DS, Beiser A, Machulda MM, et al. Spectrum of cognition short of dementia: Framingham Heart Study and Mayo Clinic Study of Aging. *Neurology*. 2015;85(19):1712-1721.

40. Palmcrantz S, Wall A, Vreede KS, et al. Impact of intensive gait training with and without electromechanical assistance in the chronic phase after stroke-A multi-arm randomized controlled trial with a 6 and 12 months follow up. *Front Neurosci*. 2021;15:660726.

41. Mahoney FI, Barthel DW. Functional evaluatoin: the Barthel Index. *Md State Med J*. 1965;14:61-65.

42. Synhaeve NE, Schaapsmeerders P, Arntz RM, et al. Cognitive performance and poor long-term functional outcome after young stroke. *Neurology*. 2015;85(9):776-782.

43. Maldaner N, Sosnova M, Sarnthein J, Bozinov O, Regli L, tienen MN. Predicting functional impairment in patients with chronic subdural hematoma treated with burr hole Trepanation-The FIT-score. *Clin Neurol Neurosurg*. 2019;182:142-147.

44. Jampathong N, Laopaiboon M, Rattanakanokchai S, Pattanittum P. Prognostic models for complete recovery in ischemic stroke: a systematic review and meta-analysis. *BMC Neurol*. 2018;18(1):26.

45. Burton L, Tyson SF. Screening for cognitive impairment after stroke: a systematic review of psychometric properties and clinical utility. *J Rehabil Med*. 2015;47(3):193-203.

46. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. *JAMA*. 2017;318(14):1377-1384.

47. Austin PC, Steyerberg EW. The Integrated Calibration Index (ICI) and related metrics for quantifying the calibration of logistic regression models. *Stat Med*. 2019;38(21):4051-4065.

48. Pencina MJ, D'Agostino RB, Sr, D'Agostino RB, Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.

49. Weaver NA, Kuijf HJ, Aben HP, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. *Lancet Neurol*. 2021;20(6):448-459.

50. Jickling GC, Chen C. Rating total cerebral small-vessel disease: does it add up? *Neurology*. 2014;83(14):1224-1225.

51. SPRINT MIND Investigators for the SPRINT Research Group, Nasrallah IM, Pajewski NM, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA*. 2019;322(6):524-534.

52. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321(6):553-561.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.