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RESEARCH ARTICLE

Risk factors and clinical significance of post-stroke incident ischemic lesions

Rong Fang[1] | Marco Duering[1,2] | Felix J. Bode[3,4] | Sebastian Stösser[3,4] | Julius N. Meißner[3,4] | Peter Hermann[5,6] | Thomas G. Liman[7,8,9] | Christian H. Nolte[8,10,11] | Lucia Kerti[7,8] | Benno Ikenberg[12] | Kathleen Bernkopf[12] | Wenzel Glanz[13,14] | Daniel Janowitz[1] | Michael Wagner[3,15] | Katja Neumann[13] | Oliver Speck[14,16,17,18] | Emrah Düzel[14] | Benno Gesierich[1,2] | Anna Dewenter[1] | Annika Spottke[3,4] | Karin Waegemann[1,19] | Michael Görtler[13,14] | Silke Wunderlich[20] | Inga Zerr[5,6] | Gabor C. Petzold[3,4] | Matthias Endres[7,8,21,22,23] | Marios K. Georgakis[1,24] | Martin Dichgans[1,19,25,26] | on behalf of the DEMDAS investigators

[1]Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany
[2]Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland
[3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[4]Department of Vascular Neurology, University Hospital Bonn, Bonn, Germany
[5]Universitätsmedizin Göttingen, Klinik für Neurologie, Göttingen, Germany
[6]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany
[7]Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany
[8]German Center for Neurodegenerative Diseases (DZNE, Berlin), Berlin, Germany
[9]Department of Neurology, Carl Von Ossietzky University, Oldenburg, Germany
[10]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[11]Berlin Institute of Health (BIH), Berlin, Germany
[12]Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany
[13]Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[14]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
[15]Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, Bonn, Germany
[16]Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[17]Leibniz Institute for Neurobiology, Magdeburg, Germany
[18]Center for Behavioral Brain Sciences, Magdeburg, Germany
[19]German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany
[20]Department of Neurology, TUM School of Medicine, Technical University of Munich, Munich, Germany
[21]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany
[22]German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany
[23]Klinik und Hochschulambulanz für Neurologie, Charité - Universitätsmedizin Berlin, Berlin, Germany
[24]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[25]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[26]German Centre for Cardiovascular Research (DZHK, Munich), Munich, Germany

Marios K. Georgakis and Martin Dichgans have contributed equally to this study.

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

Names and affiliations of collaborators for the DEMDAS study are listed in the Appendix.

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Abstract

INTRODUCTION: While incident ischemic lesions (IILs) are not unusual on follow-up magnetic resonance imaging (MRI) following stroke, their risk factors and prognostic significance remain unknown.

METHODS: In a prospective multicenter study of 503 acute stroke patients, we assessed IILs on registered MRI images at baseline and 6 months, analyzing risk factors and clinical outcomes across 36 months.

RESULTS: At 6 months, 78 patients (15.5%) had IILs, mostly diffusion-weighted imaging-positive (72%) and clinically covert (91%). Older age and small vessel disease (SVD) lesions were baseline risk factors for IILs. IILs were associated with worse cognitive (beta for global cognition: −0.31, 95% confidence interval [CI]: −0.48 to −0.14) and functional outcomes (beta for modified Rankin scale [mRS]: 0.36, 95% CI: 0.14 to 0.58), and higher recurrent stroke risk (hazard ratio: 3.81, 95% CI: 1.35 to 10.69). IILs partially explained the relationship between SVD and poor cognition.

DISCUSSION: IILs are common and are associated with worse cognitive and functional outcomes and stroke recurrence risk. Assessing IILs following stroke might aid prognostication.

KEYWORDS
cerebral small vessel disease, cognitive impairment, functional outcome, incident ischemic lesions, recurrent stroke, stroke

Highlights

- Incident ischemic lesions (IILs) were assessed with registered baseline and 6-month magnetic resonance imaging (MRI) scans in a stroke cohort.
- IILs 6 months after stroke are present in one-sixth of patients and are mostly clinically silent.
- Small vessel disease burden is the main baseline risk factor for IILs.
- IILs are associated with cognitive and functional impairment and stroke recurrence.
- Assessing IILs by follow-up MRI aids long-term prognostication for stroke patients.

1 | BACKGROUND

Stroke mortality rates have declined worldwide over the past 30 years,[1] drawing attention to the long-term outcomes following stroke.[2–5] Cognitive and functional impairment affect up to 80% of stroke survivors[5–8] and are associated with disability,[9–11] dependency,[12,13] and death,[14–17] placing a major socioeconomic burden on healthcare systems. An understanding of the factors determining long-term outcomes after stroke is needed to identify high-risk patients and optimize strategies for prevention.

Up to 30% of stroke survivors are found to have incident (new) ischemic lesions (IILs) on follow-up magnetic resonance imaging (MRI) scans,[18,19] but few studies have assessed IILs weeks or months after stroke,[20–26] which is when patients typically return for a follow-up visit. Even less is known about the association between such lesions and long-term clinical outcomes. In a study of 270 stroke survivors, IILs at 30 days after stroke were associated with an increased rate of recurrent stroke and vascular events over a 4-year follow-up period.[22] However, data from large prospective studies are lacking, and the impact of IILs detected weeks or months after the index event on post-stroke cognitive and functional outcomes remains unknown.

The current study aimed to define the characteristics, baseline predictors, and clinical significance of IILs detected on MRI scans 6 months after stroke. Using paired (baseline and 6 months) MRI data from a multicenter, prospective cohort of 736 stroke patients, we (i) determined the frequency and imaging as well as clinical features of IILs 6 months after stroke, (ii) explored risk factors for IILs, and (iii) tested the associations of IILs with cognitive and functional outcomes, recurrent stroke, and mortality across a 36-month follow-up period.

RESEARCH IN CONTEXT

1. **Systematic review**: Our MEDLINE search yielded cross-sectional studies showing a prevalence of up to 30% of new incident ischemic lesions (IILs) on follow-up magnetic resonance imaging (MRI) after stroke. However, the characteristics, risk factors, and associated long-term cognitive, functional, and clinical outcomes of IILs have not been systematically explored.
2. **Interpretation**: IILs, although mostly clinically silent, are common at 6 months after stroke and are associated with small vessel disease (SVD) lesions at baseline. IILs are associated with worse cognitive and functional outcomes and a higher risk of stroke recurrence over 36 months. IILs partially mediated the relationship between SVD and poorer cognition.
3. **Future directions**: Future studies should explore whether assessing IILs on MRI as part of post-stroke follow-up care could aid risk stratification and patient selection for inclusion in future clinical trials.

2 | METHODS

2.1 | Study design and baseline assessments

Participants were from the DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke)-DEDEMAS ([Determinants of Dementia After Stroke]; NCT01334749) study, a multicenter prospective hospital-based cohort study in Germany. Details of the study rationale, protocol, and baseline characteristics have been published elsewhere.[3,27] We recruited consecutive patients ≥18 years old who had experienced an acute stroke of any stroke severity, with symptom onset within the last 5 days and no pre-stroke dementia and provided informed consent for the study. Stroke was defined by an acute focal neurological deficit combined with an acute ischemic infarct as documented on cranial MRI scans, a new lesion on a delayed computed tomography (CT) scan, or an intracerebral hemorrhage as documented on CT or MRI scans. Eligible patients needed to have an available informant. The key exclusion criteria were as follows: patients who had previously been diagnosed with dementia or patients who scored >64 in the screening Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) test with the informant at baseline, patients with cerebral venous thrombosis, traumatic cerebral hemorrhage, intracerebral hemorrhage because of a vascular malformation, purely meningeal or intraventricular hemorrhage, shortened life expectancy due to a malignant disease, and patients with contraindications for MRI. The enrollment started as a single-center pilot study at the Ludwig-Maximilians-University (LMU) University Hospital in Munich (DEDEMAS), which enrolled 136 patients between May 2011 and November 2013. It was subsequently expanded to a multicenter study (DEMDAS) conducted at seven tertiary stroke centers in Germany, which enrolled an additional 600 patients between January 2014 and January 2019. Participants in the current study attended face-to-face follow-ups at 6, 12, and 36 months. Brain MRI examinations were conducted at baseline and 6 months. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committees of all participating sites. All participants or their legal caregivers provided written informed consent. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[28]

2.2 | MRI scan acquisition and image processing

Participants underwent 3 Tesla MRI (all scanners Siemens Healthineers, Erlangen, Germany) examinations within 5 days of stroke onset and at 6 months (median 190 days [interquartile range {IQR}: 183 to 207 days]) using a standardized imaging protocol. The details on the neuroimaging parameters and the preprocessing steps are in the Supplement (Supplementary Methods).

To assist in the identification of IILs at 6 months, we used difference images between baseline and 6 months for diffusion-weighted imaging (DWI and trace image), fluid-attenuated inversion recovery (FLAIR), and T1-weighted (T1w) images. For registration and intensity bias correction, we used tools from the Advanced Normalization Tools (ANTs version 2.3.2).[29] The difference images were calculated by subtracting the intensity-normalized images at baseline from the registered 6-month follow-up images. All images were evaluated in a standardized reading setup (Figure 1A, Video S1, and Figure S1).

2.3 | Neuroimaging markers at baseline

Index acute stroke lesions were segmented on the preprocessed trace images using Otsu's method.[3] Baseline markers of small vessel disease (SVD), including lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs), were further assessed following widely accepted standards[30,31] and as previously reported.[3] Three types of indices were used to determine SVD burden (Supplementary Methods): (1) presence of SVD marker; (2) summary SVD score[3,31,32] (the score ranges from 0 to 4, with one point awarded for (i) the presence of lacunes, (ii) a Fazekas score[33] of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively); and (3) individual SVD markers.[3] An experienced, trained rater (R.F., board-certified neurologist) assessed all images blinded to the clinical data including various clinical outcomes, and doubtful cases were discussed with a senior neuroimaging specialist (M.Due.) in regular consensus meetings. To guarantee the reproducibility of the ratings, inter-rater reliabilities were evaluated by two trained raters (R.F. and A.D., PhD in neuroimaging) in a subset of the images, resulting in κ values of 0.720 for lacunes, 0.795 for WMHs, 0.725 for CMBs, and 0.815 for PVSs.

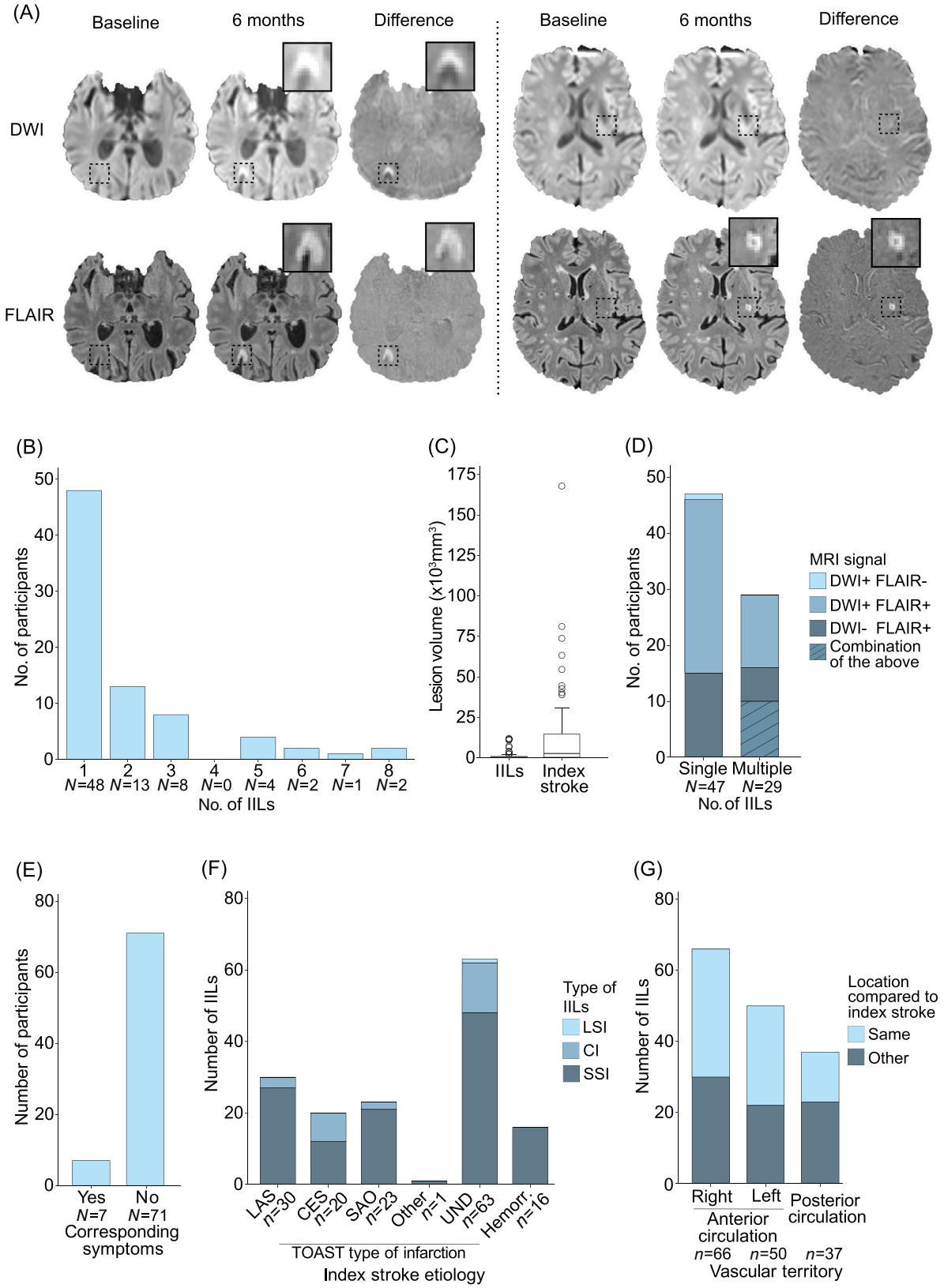

FIGURE 1 Characteristics of IILs at 6 months after stroke. (A) Examples of IILs on brain MRI scans at 6 months. Left: 77-year-old patient with incident DWI+/FLAIR+ cortical infarct; right: 59-year-old patient with incident DWI−/FLAIR+ small subcortical infarct. For more details see *Methods* and Figure S1 in Supplement. (B) Distribution of IIL counts among participants who had IILs ($N = 78$). (C) Boxplot of volume of IILs and index stroke in participants with IILs. (D) Number of participants with different MRI signals of IILs. (E) Number of participants with and without symptoms corresponding to IILs. (F) Number of IILs with different types of IILs stratified by index stroke. Fisher's exact tests were applied to

2.4 | IILs at 6 months after stroke

IILs were detected visually by comparing images at baseline and 6 months using three image contrasts (DWI, FLAIR, and T1w) and their respective different images to increase the sensitivity of the visual rating. Lesions were classified into three categories[34]: (1) DWI+/FLAIR− IILs: new lesions appearing hyperintense on 6-month DWI but isointense on FLAIR, primarily representing the early hyperacute phase (0 to 6 h) after stroke; (2) DWI+/FLAIR+ IILs: new lesions appearing hyperintense on 6-month DWI and hyper- or hypointense (cavitated) on 6-month FLAIR, typically present in the late hyperacute, acute, or subacute phases (6 h to 3 weeks). These two categories were further combined into one overarching DWI+ category: (3) DWI−/FLAIR+ IILs: new lesions appearing hyper- or hypointense (cavitated) on FLAIR at 6 months but isointense on DWI, indicating chronic lesions. Signals of IILs on T1w could be isointense or hypointense. One experienced rater (R.F.) visually screened all images for IILs while being blinded to clinical information. When uncertain, consensus meetings were held with a senior neuroimaging specialist (M.Due.).

IILs were manually segmented using ITK-SNAP (version 3.8.0, www.itksnap.org)[35] and further classified into three types based on their size and location: (1) small subcortical infarct (SSI), which refers to a lesion up to 20 mm in diameter on the axial plane in the territory of penetrating arteries, following the criterion adopted by STRIVE;[30] (2) large (>20 mm in diameter) subcortical infarct (LSI); and (3) cortical infarct (CI). The clinical manifestations of IILs were also extracted. Data on ischemic stroke symptoms after the index stroke were collected at the 6-month in-person follow-up visit by a physician. All recurrent stroke reports were confirmed through medical records, including clinical manifestations and neuroimaging information, as documented by the treating physicians. Symptomatic IILs referred to confirmed recurrent infarcts that were associated with acute clinical manifestations. Asymptomatic IILs were not associated with clinical symptoms.

2.5 | Follow-up outcomes across 36 months after stroke

2.5.1 | Cognitive and functional outcomes

Participants underwent detailed in-person cognitive and functional evaluations at 6, 12, and 36 months. The evaluations included a comprehensive neuropsychological test battery (15 tests) covering five domains: executive function, memory, language, attention, and visuospatial function.[3] Domain-specific *z*-scores were obtained by averaging the scale-specific *z*-scores[36–39] within each domain, and an average global cognitive score was derived by averaging the *z*-scores from all five domains. Cognitive impairment was defined as a *z*-score of < -1.5 in any of the five domains, and domain-specific cognitive impairments were defined according to domain-specific *z*-scores of < -1.5.[40] Functional outcomes were assessed using the modified Rankin scale (mRS), the Barthel index (BI),[41,42] and the instrumental activities of daily living (IADLs).[43] Functional impairment was defined based on two widely adopted cutoffs of mRS (>1 and >2).[17,44]

2.5.2 | Recurrent stroke and mortality

Information on recurrent stroke between 6 and 36 months, which was defined as the occurrence of neurological deficits caused by a newly diagnosed stroke, was obtained from reports from the patients or informants during annual follow-ups and an inspection of their medical records complying with the published procedure.[3] For participants who did not attend the scheduled follow-up visits, we followed a standardized protocol for establishing contact with them or their informants.[3] In short, a trained study nurse initially contacted participants by telephone and, if unsuccessful, called their informant or sent a mail questionnaire. In case of no response, the data manager checked with the local registration office for the participant's information related to mortality or new address, and the contact process was repeated if a new address was found.

2.6 | Statistical analysis

Baseline risk factors of IILs at 6 months were explored by applying logistic regression analysis for IIL presence and quasi-Poisson regression analysis for IIL number to obtain more accurate standard errors (SEs) adjusting the overdispersed data. We applied a main model adjusting for age, sex, and the National Institutes of Health Stroke Scale (NIHSS), as well as an additional model further adjusting for history of hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, body mass index (BMI), low-density lipoprotein-cholesterol (LDL-C) levels, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or computed tomography angiography [CTA], if ultrasound not available), and normalized index stroke volume.

compare categorical differences across all six groups and between any pair of groups. The results showed a significant difference across all six groups; CES had a higher proportion of CI-IILs than LAS, SAO, and Hemorr. Strokes, with all *p*-values being <.05. SSI refers to a lesion up to 20 mm in diameter on the axial plane in the territory of penetrating arteries, following STRIVE criteria.[30] LSI refers to a lesion located in the subcortex with an axial diameter above 20 mm. CI refers to a lesion located in the cortex of any size. (G) Number of IILs in locations compared to the vascular territories of the index stroke. *N* represents the number of participants; *n* represents the number of IILs. CES, cardioembolic stroke; CI: cortical infarct; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; Hemorr., hemorrhagic stroke; IIL, incident ischemic lesion; LAS, large artery stroke; LSI, large subcortical infarct; MRI, magnetic resonance imaging; SAO, small artery occlusion; SSI, small subcortical infarct; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Associations between IIL presence and number at 6 months and clinical outcomes were assessed across 36 months after stroke using the cognitive and functional evaluations at 6-, 12-, and 36-month follow-ups. Generalized estimating equations (GEEs) with a first-order autoregressive working correlation structure and robust SEs were used to account for repeated outcomes. Linear GEE analyses were fitted for continuous outcomes, and logistic GEE analyses were fitted for binary outcomes. For stability and interpretability,[45] we chose five covariables in the main model: age, sex, NIHSS, educational years, and cognitive impairment in the acute phase (MoCA < 26 or MMSE < 24 if MoCA is not available), considering that these variables are strong predictors of poststroke cognitive/functional outcomes in the previous literature.[3,43,46–48] In sensitivity analysis, we utilized two additional models: (1) the main model plus history of hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume and (2) a model adjusting for apolipoprotein E (*APOE*) genotype (0, 1, or 2 ε4 alleles) on top of all covariates. The aforementioned models showed no multicollinearity, as indicated by variance inflation factors (VIF) <2 for all included variables.[49,50] We assumed the missingness of the adjusted covariates was at random and used multiple imputation methods to replace missing data.[51] All missing ratios were below 4% with missing data on cognitive impairment in the acute phase, LDL-C, and normalized index stroke volume. Linear, ordinal logistic and logistic regressions were further applied to examine the relationship of IIL presence and number with outcomes at 6, 12, and 36 months, separately.

Because non-stroke death is a competing risk for recurrent stroke, we calculated the cumulative incidence of recurrent stroke using the cumulative incidence function, and the difference between the presence and absence of IIL groups was estimated by Gray's test.[52] Associations of IILs (presence and number) and recurrent stroke between 6 and 36 months were assessed by competing-risk regression models (cause-specific and Fine-Gray subdistribution hazard models), with non-stroke death representing the competing risk.[53,54] Data from patients who were lost to follow-up or who did not experience recurrent strokes between 6 and 36 months were censored at the last visit, at which the patients were present or at the last contact. Considering stroke history as a consistent risk factor for recurrent stroke,[55,56] the main model was adjusted for age, sex, NIHSS, and whether there was a recurrent clinical stroke between the index stroke and 6 months. An additional model further adjusted for hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume. Further sensitivity analyses were conducted in patients after excluding those who had recurrent clinical strokes between the index stroke and 6 months. Associations of IILs (presence and number) and mortality between 6 and 36 months were calculated using Cox proportional hazard models. The main model was adjusted for age, sex, and NIHSS, and a second model included further adjustments for hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume.

We further performed mediation analysis[57–59] with the R package mediation version 4.5.0 to test whether IILs explain the associations between baseline SVD burden and cognitive outcomes at 36 months that we previously reported.[3] SVD presence (dichotomous) was treated as the exposure (X), IIL presence (dichotomous) was treated as the mediator (M), and the global cognitive score (continuous) or cognitive impairment (dichotomous) was regarded as the outcome (Y). Confidence intervals were estimated by bootstrapping 10,000 times. In the main analysis, no covariates were adjusted, whereas sensitivity analyses were adjusted for age, sex, and NIHSS score. Additional sensitivity analyses set the summary SVD score, an ordinal (0 to 4) variable, as the exposure in the aforementioned mediation models.

In all analyses, we adjusted for multiple comparisons setting as a statistical significance threshold a false discovery rate (FDR)-derived *p*-value < .05. Statistical analyses were performed using R version 4.3.0 (R Foundation).

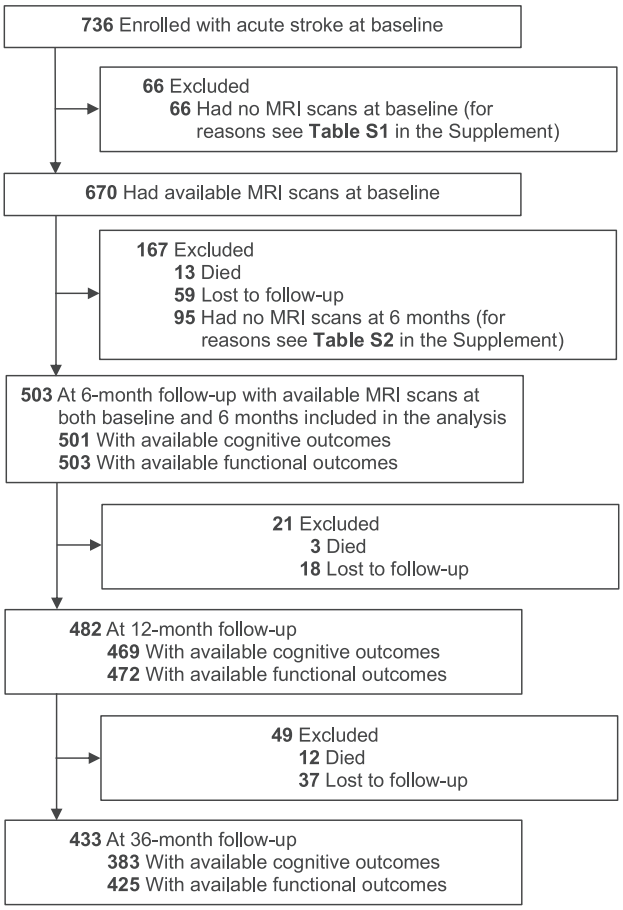

FIGURE 2 Study profile. MRI, magnetic resonance imaging.

3 | RESULTS

3.1 | Frequency and characteristics of IILs

Among 736 recruited participants, 503 had paired MRI scans (baseline and 6 months after the index stroke) and were included in current analyses (Figure 2). Reasons for missing MRIs at each time point are

listed in Tables S1,S2. Compared with the 233 participants who were excluded from the analyses, the included participants were younger, had a higher educational level, had lower HbA_{1c} and triglyceride levels, less frequently had a history of atrial fibrillation, large artery disease, and cardio-embolic stroke, more frequently had stroke related to other etiology, had less prestroke disability, less cognitive impairment, and a lower SVD burden at baseline (Table S3).

We detected a total of 153 IILs in 78 out of 503 (15.5%) participants at 6 months. The baseline characteristics of the 503 participants (mean age 66.7 ± SD 11.1 years, 32.0% female) and a comparison of participants with and without IILs are presented in Table 1. Compared to participants without IILs, participants with IILs were older, more frequently had a history of hypertension, had a lower BI, a higher proportion of cognitive impairment, and a greater SVD burden.

Among participants with IILs: (1) 48 (62%) had only one IIL and the median number of IILs was one (IQR: 1 to 2) (Figure 1B); (2) the overall volume of IILs per patient (median: 302 mm^3, IQR: 100 to 902 mm^3) was an order of magnitude smaller than the index stroke lesion volume (median volume in participants with IILs: 2656 mm^3, IQR: 344 to 14,672 mm^3) (Figure 1C); (3) among participants with informative DWI and FLAIR images at both time points ($N = 76$, Table S4), 45 (59%) had DWI+ IILs ($N = 1$ with DWI+/FLAIR−; $N = 44$ with DWI+/FLAIR+), 21 (28%) had DWI−/FLAIR+ IILs, and 10 (13%) had both DWI+ and DWI−/FLAIR+ IILs (Figure 1D); (4) only 7 (9%) had corresponding clinical symptoms (Figure 1E, Table S5); (5) the majority ($n = 125$, 81.7%) had SSI-IILs, whereas few had CI-IILs ($n = 27$, 17.6%) or LSI ($n = 1$, 0.7%)-IILs, regardless of the index stroke etiology (although CI-IILs were proportionally more common in cardioembolic stroke, as to be expected) (Figure 1F); (6) about half of the IILs (78/153, 51.0%) occurred in the same vascular territory as the index stroke (Figure 1G); (7) IILs were observed throughout the brain, most frequently in the white matter (100 IILs, 65.4%), followed by cortex (27, 17.6%), subcortical gray matter (12, 7.8%), brainstem (7, 4.6%), and cerebellum (7, 4.6%) (Figure S2).

3.2 | Associations between baseline characteristics and IILs at 6 months

In age-, sex-, and NIHSS-adjusted logistic regression analyses of potential risk factors at baseline, the following variables associated with IIL presence 6 months after stroke: age (odds ratio [OR]: 1.05, 95% confidence interval: 1.02 to 1.08, $p < .001$), SVD burden including the presence of SVD marker (OR: 3.47, 95% confidence interval: 1.81 to 7.08, $p < .001$), summary SVD score (OR: 1.68, 95% confidence interval: 1.33 to 2.14, $p < .001$), and all individual SVD markers (OR for lacune count: 1.46, 95% confidence interval: 1.13 to 2.04, $p = .01$; deep white matter [DWM] Fazekas score: 1.93, 95% confidence interval: 1.32 to 2.86, $p < .001$; periventricular white matter [PVWM] Fazekas score: 1.66, 95% confidence interval: 1.20 to 2.31, $p = .002$; CMB count: 1.11, 95% CI: 1.002 to 1.23, $p = 0.04$; PVS grade: 1.62, 95% CI: 1.16 to 2.27, $p = 0.005$). In analyses further adjusting for vascular risk factors and normalized index stroke volume for IIL presence, as well as exploring risk factors for the IIL number, associations with SVD burden remained stable (Table 2).

3.3 | Associations between IILs and long-term clinical outcomes

3.3.1 | Cognitive and functional outcomes

Among the 503 participants included, 503 (100%), 482 (95.8%), and 433 (86.1%) attended the follow-up visits at 6, 12, and 36 months, respectively (Figure 2). At 6 months, 151 (30.3%), 96 (19.1%), and 30 (6.0%) participants had cognitive impairment, mRS > 1, and mRS > 2, respectively. Corresponding numbers at 12 months were 100 (21.6%), 83 (17.6%), and 21 (4.5%) and at 36 months 66 (17.4%), 70 (16.5%), and 22 (5.2%).

Participants with IILs at 6 months had a lower composite global cognitive score and a higher mRS at 6, 12, and 36 months compared to those without IILs (Figure 3A,B). Accordingly, patients with IILs exhibited a higher occurrence of cognitive impairment, mRS > 1, and mRS > 2 at each follow-up visit (all $p < .05$) (Figure S3). After adjusting for age, sex, NIHSS, educational status, and cognitive impairment at baseline, IILs presence was significantly associated with a lower global cognitive score and a higher mRS score across the 36-month follow-up (beta for global cognitive score: −0.31, 95% confidence interval: −0.48 to −0.14, $p < .001$; beta for mRS: 0.36, 95% confidence interval: 0.14 to 0.58, $p = .001$; Figure 3C). Looking at binary outcomes, significant associations were likewise observed in both cognitive (OR: 2.86, 95% confidence interval: 1.82 to 4.49, $p < .001$) and functional impairment (OR for mRS > 1: 2.41, 95% confidence interval: 1.56 to 3.71, $p < .001$; OR for mRS > 2: 2.81, 95% confidence interval: 1.46 to 5.38, $p = .002$; Figure S4). The IIL presence was further associated with all individual cognitive domains and functional tests when considering both continuous and binary outcomes (Figure 3C, Figures S4,S5). Sensitivity analyses showed that significant associations between IIL presence/number and cognitive and functional outcomes remained consistent when additionally accounting for vascular risk factors and normalized index stroke volume, when additionally accounting for *APOE* genotype (Figures S4–S7), and when exploring associations at 6, 12, and 36 months, respectively (Figures S8 to S11).

3.3.2 | Recurrent stroke and mortality

Between 6 and 36 months, 7/78 (9.0%) of participants with IILs and 10/425 (2.4%) without IILs experienced a (clinically overt) recurrent stroke ($p = .009$), and 5/78 (6.4%) with IILs and 11/425 (2.6%) without IILs died ($p = .09$). In competing-risk regression analyses, the IIL presence was associated with a significantly higher risk of stroke recurrence from 6 to 36 months after stroke (Table S6) (1) when adjusting for age, sex, NIHSS, and recurrent clinical stroke between baseline and 6 months (cause-specific hazard ratio [csHR]: 3.81, 95% confidence

TABLE 1 Baseline characteristics of all participants.

Baseline characteristics	No. (%) All (*N* = 503)	With IILs (*N* = 78)	No IILs (*N* = 425)	*p*-value, with versus no IILs[a]
Age, mean (SD), years	66.7 (11.1)	70.9 (9.8)	65.9 (11.2)	**<0.001**
Sex[b]				
Male	342 (68.0)	56 (71.8)	286 (67.3)	0.51
Female	161 (32.0)	22 (28.2)	139 (32.7)	
Education, median (IQR), years	13 (12 to 17)	13 (11 to 16)	13 (12 to 17)	0.27
Cardiovascular risk factors				
Hypertension	380 (75.5)	67 (85.9)	313 (73.6)	**0.03**
Diabetes mellitus	94 (18.7)	17 (21.8)	77 (18.1)	0.54
Current smoking	118 (23.5)	17 (21.8)	101 (23.8)	0.82
Atrial fibrillation	87 (17.3)	13 (16.7)	74 (17.4)	>0.99
Prior history of stroke	49 (9.7)	11 (14.1)	38 (8.9)	0.23
Large artery disease[c]	157 (31.2)	28 (35.9)	129 (30.4)	0.40
BMI, mean (SD), kg/m^2	27.0 (4.2)	26.5 (4.1)	27.1 (4.2)	0.23
SBP, median (IQR), mmHg	139 (128 to 150)	144 (132 to 151)	138 (128 to 150)	0.14
DBP, median (IQR), mmHg	80 (72 to 87)	80 (73 to 87)	80 (72 to 87)	0.70
HbA_{1c}, median (IQR), %	5.7 (5.4 to 6.1)	5.7 (5.3 to 6.2)	5.7 (5.4 to 6.0)	0.49
LDL-C, median (IQR), mg/dL	124 (103 to 153)	126 (107 to 160)	124 (103 to 150)	0.41
HDL-C, median (IQR), mg/dL	48 (40 to 58)	46 (38 to 56)	48 (40 to 59)	0.26
Triglycerides, median (IQR), mg/dL	124 (94 to 172)	135 (94 to 173)	123 (94 to 168)	0.39
APOE genotype (*n* = 410)				
0 ε4 allele	318 (77.6)	52 (81.3)	266 (76.9)	0.27
1 ε4 allele	85 (20.7)	10 (15.6)	75 (21.7)	
2 ε4 allele	7 (1.7)	2 (3.1)	5 (1.4)	
Stroke classification				
Ischemic stroke	490 (97.4)	75 (96.2)	415 (97.6)	0.44
TOAST subtype				
Large artery atherosclerosis	122 (24.3)	21 (28.0)	101 (24.3)	0.33
Cardioembolism	99 (19.7)	11 (14.7)	88 (21.2)	
Small artery occlusion	63 (12.5)	11 (14.7)	52 (12.5)	
Other etiology	24 (4.8)	1 (1.3)	23 (5.5)	
Undefined etiology	182 (36.2)	31 (41.3)	151 (36.4)	
Hemorrhagic stroke	13 (2.6)	3 (3.8)	10 (2.4)	0.44
Clinical/cognitive assessment				
NIHSS score, median (IQR)	2 (1 to 5)	3 (1 to 5)	2 (1 to 5)	0.42
mRS[d] before stroke				
0	426 (84.7)	62 (79.5)	364 (85.6)	0.30
1	53 (10.5)	10 (12.8)	43 (10.1)	
2	11 (2.2)	2 (2.6)	9 (2.1)	
3	13 (2.6)	4 (5.1)	9 (2.1)	
BI score, median (IQR)	100 (85 to 100)	95 (80 to 100)	100 (90 to 100)	**0.01**
IQCODE score, median (IQR)	48 (48 to 49)	48 (48 to 49)	48 (48 to 49)	0.51
Baseline cognitive impairment[e]	236/490 (48.2)	48/74 (64.9)	188/416 (45.2)	**0.003**
MRI variables				
Primary stroke lesion volume, median (IQR), mm^3	2168 (452 to 12,262)	2656 (344 to 14,672)	2152 (480 to 11,544)	0.94
Total intracranial volume, median (IQR), $\times 10^6$ mm^3	1.56 (1.44 to 1.65)	1.58 (1.44 to 1.65)	1.56 (1.44 to 1.65)	0.65

(Continues)

TABLE 1 (Continued)

Baseline characteristics	No. (%) All (*N* = 503)	With IILs (*N* = 78)	No IILs (*N* = 425)	*p*-value, with versus no IILs[a]
Presence of SVD marker[f]	293/502 (58.4)	65/78 (83.3)	228/424 (53.8)	**<0.001**
Summary SVD score[g]				
0	209/502 (41.6)	13/78 (16.7)	196/424 (46.2)	**<0.001**
1	155/502 (30.9)	30/78 (38.5)	125/424 (29.5)	
2	90/502 (17.9)	15/78 (19.2)	75/424 (17.7)	
3 to 4	48/502 (9.6)	20/78 (25.6)	28/424 (6.6)	
Lacune count				
0	445 (88.5)	57 (73.1)	388 (91.3)	**<0.001**
1	41 (8.2)	14 (17.9)	27 (6.4)	
2	11 (2.2)	3 (3.8)	8 (1.9)	
≥3	6 (1.2)	4 (5.1)	2 (0.5)	
Fazekas DWM score				
0	71 (14.1)	4 (5.1)	67 (15.8)	**<0.001**
1	213 (42.3)	23 (29.5)	190 (44.7)	
2	200 (39.8)	44 (56.4)	156 (36.7)	
3	19 (3.8)	7 (9.0)	12 (2.8)	
Fazekas PVWM score				
0	112 (22.3)	9 (11.5)	103 (24.2)	**<0.001**
1	269 (53.5)	35 (44.9)	234 (55.1)	
2	89 (17.7)	23 (29.5)	66 (15.5)	
3	33 (6.6)	11 (14.1)	22 (5.2)	
CMB count				
0	454/502 (90.4)	65/78 (83.3)	389/424 (91.7)	**0.01**
1	22/502 (4.4)	3/78 (3.8)	19/424 (4.5)	
2	8/502 (1.6)	4/78 (5.1)	4/424 (0.9)	
≥3	18/502 (3.6)	6/78 (7.7)	12/424 (2.8)	
PVS grade[h]				
1	335 (66.6)	38 (48.7)	297 (69.9)	**<0.001**
2	110 (21.9)	21 (26.9)	89 (20.9)	
3	56 (11.1)	18 (23.1)	38 (8.9)	
4	2 (0.4)	1 (1.3)	1 (0.2)	
IILs volume, median (IQR), mm^3	NA	302 (100 to 902)	NA	NA

Note: SI conversion factors: to convert a percentage of total HbA_{1c} to the proportion of total HbA_{1c}, multiply by 0.01; LDL-C and HDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. Bold indicates statistically significant at $p < .05$.

Abbreviations: BI, Barthel index; BMI, body mass index; CMB, cerebral microbleed; DBP, diastolic blood pressure; DWM, deep white matter; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein-cholesterol; IIL, incident ischemic lesion; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NA, not applicable.; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular space; PVWM, periventricular white matter; SBP, systolic blood pressure; SD, standard deviation; SVD, small vessel disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WMH, white matter hyperintensity.

[a]Categorical variables were analyzed using the χ^2 or Fisher's exact test, a two-tailed *t* test was employed for continuous variables with a normal distribution, and the Mann–Whitney U test was used for other continuous variables.

[b]Self-reported.

[c]Large artery disease is defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of >50% on ultrasound or computed tomography angiography (CTA) if ultrasound is not available.

[d]A global functional scale ranges from 0 (no symptoms) to 5 (serious functional impairment).

[e]Montreal Cognitive Assessment (MoCA) <26 or Mini-Mental State Examination (MMSE) <24 when MoCA was not available (2.6% of total).

[f]Summary SVD score is equal to or greater than 1.

[g]Summary SVD score ranges from 0 to 4, with 1 point awarded for (i) the presence of lacunes, (ii) a Fazekas score of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively.

[h]PVSs were counted bilaterally in the basal ganglia, and the side with the higher number was used for scoring: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = > 40 PVSs.[3,31,32]

TABLE 2 Relationship between baseline risk factors and IILs at 6 months after stroke.

	Presence of IILs at 6 months after stroke[a]		Number of IILs at 6 months after stroke[b]	
Potential risk factor at baseline	**OR (95% CI)[c]**	**OR (95% CI)[d]**	**RR (95% CI)[c]**	**RR (95% CI)[d]**
Demographic factor				
Age (years)	**1.05 (1.02 to 1.08)**	**1.05 (1.02 to 1.09)**	1.02 (0.998 to 1.05)	1.02 (0.99 to 1.06)
Sex (0 = male vs 1 = female)	0.73 (0.42 to 1.25)	0.73 (0.41 to 1.26)	0.63 (0.31 to 1.17)	0.65 (0.31 to 1.24)
NIHSS score	1.00 (0.94 to 1.04)	0.99 (0.93 to 1.05)	1.00 (0.93 to 1.04)	0.98 (0.90 to 1.05)
Cardiovascular risk profile				
History of hypertension	1.67 (0.87 to 3.51)	1.71 (0.86 to 3.68)	1.45 (0.70 to 3.38)	1.45 (0.68 to 3.52)
History of diabetes (yes vs no)	1.16 (0.62 to 2.08)	1.20 (0.62 to 2.25)	1.19 (0.58 to 2.30)	1.26 (0.59 to 2.51)
Current smoking (yes vs no)	1.26 (0.66 to 2.29)	1.22 (0.63 to 2.28)	1.24 (0.60 to 2.38)	1.21 (0.58 to 2.38)
Prior stroke history (yes vs no)	1.40 (0.65 to 2.84)	1.72 (0.77 to 3.59)	1.63 (0.71 to 3.30)	1.86 (0.78 to 3.90)
History of atrial fibrillation (yes vs no)	0.66 (0.32 to 1.26)	0.72 (0.34 to 1.44)	0.82 (0.36 to 1.69)	0.83 (0.34 to 1.81)
BMI/SD	0.94 (0.71 to 1.22)	0.92 (0.68 to 1.22)	0.92 (0.66 to 1.25)	0.90 (0.63 to 1.24)
LDL-C/SD	1.24 (0.97 to 1.58)	1.32 (1.03 to 1.70)	1.06 (0.79 to 1.40)	1.15 (0.86 to 1.54)
Large artery disease[e] (yes vs no)	1.28 (0.76 to 2.13)	1.08 (0.63 to 1.84)	0.997 (0.53 to 1.79)	0.88 (0.46 to 1.62)
Normalized primary stroke lesion volume[f]/SD	1.17 (0.91 to 1.46)	1.27 (0.99 to 1.59)	1.19 (0.93 to 1.46)	1.23 (0.95 to 1.52)
SVD lesion burden				
Presence of SVD marker[g]	**3.47 (1.81 to 7.08)**	**3.33 (1.68 to 7.04)**	**4.19 (1.93 to 10.25)**	**4.17 (1.78 to 11.18)**
Summary SVD score[h]	**1.68 (1.33 to 2.14)**	**1.71 (1.33 to 2.21)**	**1.93 (1.55 to 2.39)**	**2.01 (1.57 to 2.58)**
Lacune count	**1.46 (1.13 to 2.04)**	**1.48 (1.14 to 2.09)**	**1.31 (1.17 to 1.42)**	**1.35 (1.19 to 1.51)**
DWM Fazekas score	**1.93 (1.32 to 2.86)**	**1.91 (1.29 to 2.90)**	**2.66 (1.78 to 4.03)**	**2.71 (1.76 to 4.25)**
PVWM Fazekas score	**1.66 (1.20 to 2.31)**	**1.66 (1.19 to 2.34)**	**2.20 (1.61 to 3.00)**	**2.22 (1.60 to 3.07)**
CMB count	1.11 (1.002 to 1.23)	1.11 (1.001 to 1.24)	**1.13 (1.08 to 1.18)**	**1.14 (1.08 to 1.20)**
PVS grade[i]	**1.62 (1.16 to 2.27)**	**1.65 (1.17 to 2.33)**	**1.93 (1.37 to 2.69)**	**1.95 (1.37 to 2.74)**

Note: Bold indicates statistically significant ORs/RRs at $p < .05$, corrected for multiple comparisons with false discovery rate (FDR) method.

Abbreviations: BMI, body mass index; CI, confidence interval; CMB, cerebral microbleed; DWM, deep white matter; IIL, incident ischemic lesion; LDL-C, low-density lipoprotein-cholesterol; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVS, perivascular space.; PVWM, periventricular white matter; RR, rate ratio; SD, standard deviation; SVD, small vessel disease; WMH, white matter hyperintensity.

[a]Logistic regression analysis was applied to explore the baseline risk factors of the presence of IILs at 6 months.

[b]Quasi-Poisson regression analysis was applied to explore the baseline risk factors of the number of IILs at 6 months.

[c]Adjusted for age, sex, and NIHSS score at baseline.

[d]Adjusted for age, sex, NIHSS score, hypertension history, diabetes history, current smoking, prior stroke history, atrial fibrillation history, BMI, LDL-C, stenosis of brain vessels, and normalized primary stroke lesion volume at baseline.

[e]Large artery disease is defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of >50% on ultrasound or computed tomography angiography (CTA) if ultrasound is not available.

[f]Primary stroke lesion volume/total intracranial volume.

[g]Summary SVD score is equal to or greater than 1.

[h]Summary SVD score ranges from 0 to 4, with 1 point awarded for (i) the presence of lacunes, (ii) a Fazekas score of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively.

[i]PVSs were counted bilaterally in the basal ganglia, and the side with the higher number was used for scoring: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = >40 PVSs.[3,31,32]

interval: 1.35 to 10.69, $p = .01$; subdistribution HR [sdHR]: 3.77, 95% confidence interval: 1.31 to 10.83, $p = .01$; Figure 3D), (2) when additionally adjusting for vascular risk factors and normalized index stroke volume (csHR: 3.43, 95% confidence interval: 1.24 to 9.49, $p = .02$; sdHR: 3.37, 95% confidence interval: 1.24 to 9.12, $p = .02$), and (3) when excluding those who had recurrent clinical strokes between baseline and 6 months. No significant association was found between IILs and mortality (Figure S12).

3.4 | Mediating effects of IILs at 6 months in relationships between baseline SVD burden and cognitive outcomes at 36 months

Finally, given that SVD is associated with cognitive impairment after stroke,[3] we tested the hypothesis that IILs at 6 months partly mediate the relationship between baseline SVD burden and cognitive outcome at 36 months. A mediation analysis showed a significant

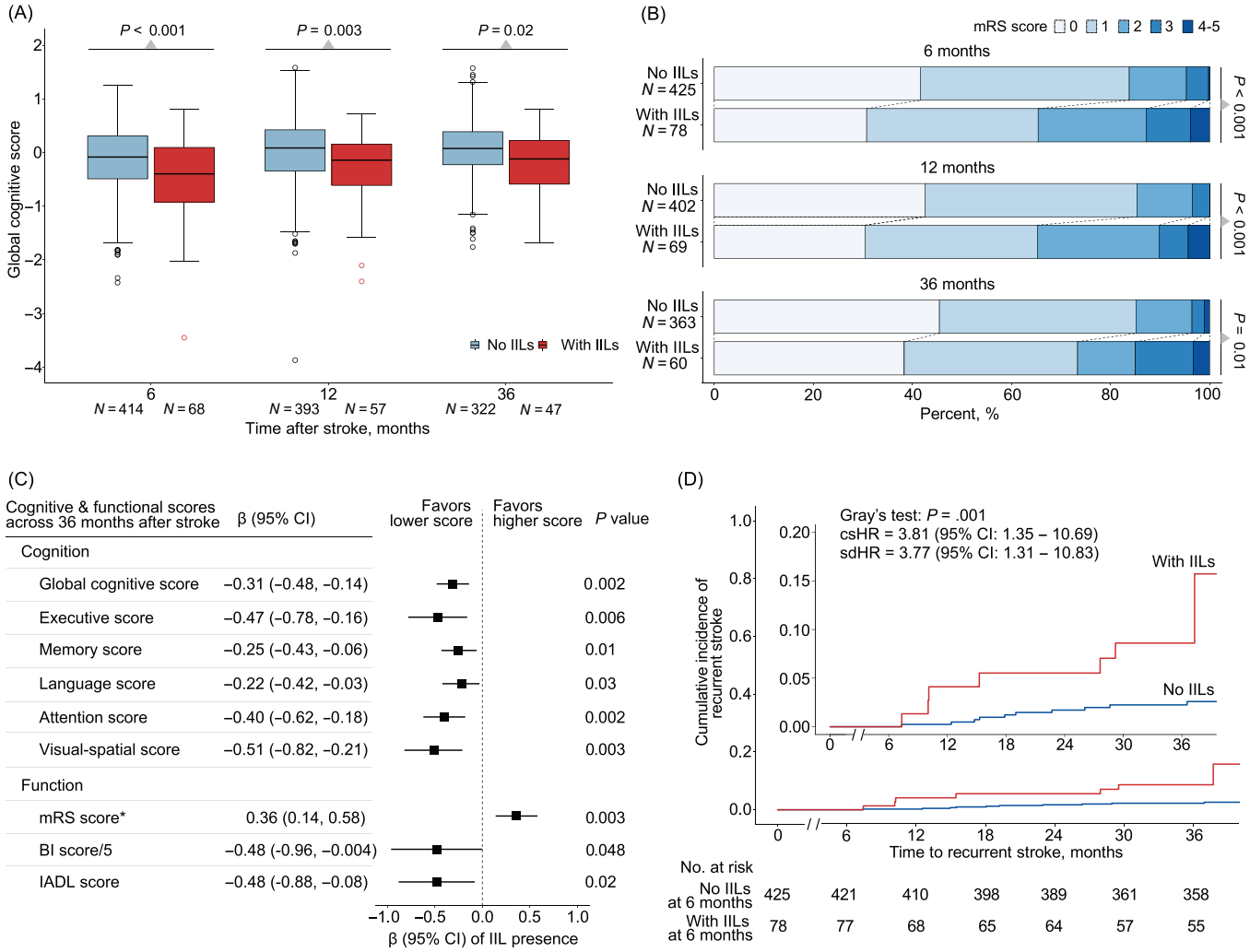

FIGURE 3 Associations between IILs at 6 months and cognitive and functional outcomes, as well as recurrent stroke over 36 months after the index stroke. (A) Median and interquartile range of *z*-scores of global cognitive performance at 6, 12, and 36 months stratified by IIL status. (B) Distributions of mRS score at 6, 12, and 36 months stratified by IIL status. (C) Associations of presence of IILs with cognitive and functional scores across 36 months using linear GEEs. The models in C adjusted for age, sex, NIHSS score, educational years, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA is not available) at baseline. *p*-values were corrected for multiple comparisons with the FDR method. (D) Cumulative incidence curve of recurrent stroke stratified by presence and absence of IILs based on the competing-risk model. Hazard ratios associated with the presence of IILs for recurrent stroke between 6 and 36 months after the index stroke were calculated using competing-risk regression models (cause-specific and subdistribution hazard models) incorporating the competing risk of non-stroke death. The two models adjusted for age, sex, and NIHSS score at baseline and recurrent clinical stroke between baseline and 6 months. BI, Barthel index; CI, confidence interval; csHR, cause-specific hazard ratio; FDR, false discovery rate; IILs, incident ischemic lesions; GEE, generalized estimating equation; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; sdHR, subdistribution hazard ratio.*mRS assesses functional outcome, with a score ranging from 0 (no symptoms) to 5 (serious functional impairment)

indirect effect of SVD marker presence at baseline on global cognitive performance at 36 months through IIL presence (beta: −0.02, 95% confidence interval: −0.06 to −0.002, p = .02) representing 14.3% of the total effect. Similar results were obtained for the binary outcome (OR for cognitive impairment: 1.03, 95% confidence interval: 1.01 to 1.07, p = .002; mediation effect: 26.7%) (Figure S13). The results remained significant after adjusting for age, sex, and NIHSS, as well as when using the summary SVD score as the exposure (Table S7).

4 | DISCUSSION

The main finding from this study is that IILs detected on MRI scan 6 months after stroke were associated with both worse cognitive and functional outcomes and with a higher risk of stroke recurrence. Compared to study participants without IILs, those with IILs had about three-fold higher odds of cognitive impairment, 2.5-fold higher odds of functional impairment, and a four-fold increased risk of stroke recurrence across the 3-year follow-up.

Almost one out of six patients had IILs. Several observations suggest that IILs in the current cohort mostly related to cerebral SVD: first, apart from age, SVD burden was the main baseline predictor for IILs, with all individual SVD markers predicting IILs. Second, the majority of lesions were small, which is consistent with data on IILs in older people with SVD[60] and in line with the definition of DWI+ lesions in the updated STRIVE-2 criteria.[30] Third, the majority of lesions affected the white matter and were localized in subcortical brain structures regardless of index stroke etiology. IILs in subcortical regions are associated with a risk factor profile of SVD in the general population.[61] Additionally, the statistical finding of a mediation effect of IILs on the relationship between SVD and worse cognitive and functional outcomes provides key mechanistic insights. SVD neuroimaging markers are surrogates of SVD pathologies, the commonest of which is arteriolosclerosis.[62,63] Our results suggest that existing SVD pathology in stroke patients contributes to the emergence of IILs, which then influence cognitive and functional performance. However, we cannot rule out mechanisms other than SVD, such as cardioembolism or hypoperfusion due to stenotic atherosclerotic lesions.

Most of the IILs were positive on DWI scans and were not associated with clinical manifestations, which is consistent with the observation in a sporadic SVD cohort,[60] where DWI+ lesions were common and silent. DWI+ is widely seen in acute ischemic stroke, with cytotoxic edema being the most common underlying pathophysiology, resulting from ion and water shifts.[64] Diffusion restriction may also occur in other brain diseases, such as demyelination, infection, and metabolic disorders, each with different clinical presentations and anatomical distributions.[65] Nevertheless, the nature and pathophysiology of SVD-related DWI+ lesions remain undefined. Acute IILs might have been overestimated since FLAIR+ largely coexisted with DWI+ in this study, and DWI+ might occur due to T2 shine-through. However, with a diffusion weighting of $b = 1000$ s/mm^2 as used in the current study, T2 shine-through is mostly absent.[66–68] Hence, DWI hyperintensities at 6 months indicate that the lesions occurred within the recent 10 to 20 days.[34] This may suggest that we missed many IILs without clinical symptoms by scanning at only one time point, with some of them eventually disappearing. Considering the evidence that transient DWI+ lesions do not necessarily indicate complete recovery from injury,[69] exploring the dynamics and determinants of IILs after stroke remains an interesting and important topic.

There is currently no guidance for assessing the clinical relevance of IILs on MRI scans performed as part of follow-up care after a stroke. It is also unclear how patients with IILs on follow-up scans should be managed. Our results suggest that the availability of paired MRI scans 6 months after stroke aids prognostication. Our results further imply that follow-up MRI might be suited to select high-risk patients even months after stroke for inclusion in secondary prevention trials. Such trials seem warranted given the substantial increase in stroke recurrence rate and both cognitive and functional decline in study participants with IILs. The four clinical studies (dose-finding trials of PACIFIC-STROKE[23,70] and AXIOMATIC-SSP,[24] DATAS II trial,[25] and ATTUNE[26]) show it is possible to integrate follow-up MRI for the assessment of covert infarcts as an endpoint in secondary stroke prevention trials. Selecting patients based on IILs for intensified preventive treatment would be a different approach, targeting a different population and time interval after stroke but should be equally feasible. On the other hand, although there is limited evidence from randomized trials, the European Stroke Organisation (ESO) guidelines have recommended securing blood pressure control, as well as smoking cessation, healthy diet, good sleep habits, and avoiding obesity and stress in patients with covert cerebral SVD, specifically WMHs and lacunes, to prevent adverse clinical outcomes.[71] Stroke patients with SVD-related covert IILs fall within these recommendations. Several clinical trials have shown that anticoagulation[23–25,70] did not prevent incident MRI-detected brain infarcts after stroke, which is to be expected given the predominant role of SVD in IILs that we demonstrated in our study. However, a post hoc analysis of the PACIFIC stroke trial further revealed that FXIa inhibition was associated with numerically fewer incident cortical covert infarcts, which highlights the importance of IIL subtyping in defining underlying mechanisms and predicting responses to different preventive strategies.[70]

Our study is limited by the preferential recruitment of patients with mild stroke, which in part relates to the requirement for comprehensive imaging and neuropsychological assessment. Related to this, there was an overrepresentation of patients with ischemic stroke. Despite our efforts to be as inclusive as possible, the requirement for paired baseline and follow-up MRI scans resulted in a high attrition rate, a common issue in real-world neuroimaging research,[22,72] and the selection for less severely affected patients could have led to an underestimation of IILs and adverse outcomes after stroke. Although our findings may not be fully representative of an unselected stroke population, they likely reflect patients who can follow up with MRI and would benefit from personalized approaches. As one of the technical limitations, the use of identical neuropsychological tests at follow-up visits might have led to learning effects and an underestimation of cognitive impairment rates at 12 and 36 months. Surveillance for symptomatic IILs or recurrent strokes, originally derived from patients' or caregivers' reports, may introduce recall bias. In neuroimaging, it is indeed challenging to differentiate old small subcortical infarcts from non-specific WMHs, and this cannot be fully resolved with MRI. To address this issue, we used the STRIVE-2[30] guidelines as guidance, taking other imaging features into account, such as small cavitations, which are more indicative of small subcortical infarcts than newly formed WMHs, and held consensus meetings with a senior neuroimaging expert. Strengths include the standardized 3T MRI protocol enabling advanced image processing and image reading on registered scans in a standardized reading environment. Also, follow-up MRI scans were conducted at an interval compatible with clinical practice.[73–75] As such, our data could aid clinical prognostication.

In conclusion, IILs are common on MRI scans 6 months after stroke and are associated with adverse outcomes. Assessing IILs on follow-up MRI aids prognostication and might help in selecting high-risk patients suited for inclusion in secondary prevention trials.

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CONFLICT OF INTEREST STATEMENT

Dr. Duering reports consulting for Roche, serving on the scientific advisory board for Biogen, and receiving speaker honoraria from Sanofi Genzyme, all outside of the submitted work. Dr. Nolte reports speaker honoraria and/or lecture fees from Abbott, Alexion, AstraZeneca, BMS, Daiichi Sankyo, Novartis, Pfizer, and Takeda, all outside the submitted work. Dr. Endres reported receiving grants from Bayer and fees paid to the Charité – Universitätsmedizin Berlin from Amgen, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, BMS, Daiichi Sankyo, Sanofi, and Pfizer, all outside the submitted work. Other (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid): European Academy of Neurology (Board of directors, unpaid), German Society of Neurology (Member, unpaid), International Society of Cerebral Blood Flow Metabolism (Member, unpaid), American Heart Association/American Stroke Association (Member, unpaid), World Stroke Organization (Member, unpaid), European Stroke Organisation (Fellow, unpaid), German Center of Neurodegenerative Diseases (personal contract, paid). All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants or their legal caregivers provided written informed consent, and the study was approved by the local ethics committees of all participating sites.

ORCID

Rong Fang https://orcid.org/0000-0002-5663-9407
Christian H. Nolte https://orcid.org/0000-0001-5577-1775
Matthias Endres https://orcid.org/0000-0001-6520-3720
Martin Dichgans https://orcid.org/0000-0002-0654-387X

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SUPPORTING INFORMATION

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

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APPENDIX

Collaborators for the DEMDAS study

Last name	First name	Email	Affiliation 1	Affiliation 2	Affiliation 3
Wittenberg	Tatjana	tatjana.wittenberg@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin		
Scheitz	Jan F.	jan.scheitz@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	
Prüß	Harald	harald.pruess@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany	
Sperber	Pia Sophie	pia.sperber@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	
Nave	Alexander H.	alexander-heinrich.nave@charite.de	Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Berlin Institute of Health (BIH), Germany
Kufner Ibaroule	Anna	anna.kufner@charite.de	Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Berlin Institute of Health (BIH), Germany
Ebrahimi	Taraneh	taraneh.ebrahimi@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany		
Nordsiek	Julia	julia.nordsiek@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany	
Beckonert	Niklas	niklas.beckonert@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany		
Schmitz	Matthias	matthias.schmitz@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Goebel	Stefan	stefan.goebel@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Schütte-Schmidt	Julia	julia.schuette@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		

Last name	First name	Email	Affiliation 1	Affiliation 2	Affiliation 3
Nuhn	Sabine	sabine.nuhn@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Volpers	Corinna	corinna.volpers@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Dechent	Peter	peter.dechent@med.uni-goettingen.de	Department of Cognitive Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Bähr	Mathias	mbaehr@gwdg.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany	German Center for Neurodegenerative Diseases (DZNE), Göttingen 37075, Germany	Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany
Tiedt	Steffen	steffen.tiedt@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, 81377 Munich, Germany.		
Huber	Christiane	Christiane.Huber@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany		
Stöcker	Tony	tony.stoecker@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany		
Kellert	Lars	Lars.kellert.@med.uni-muenchen.de	Department of Neurology, University Hospital, LMU Munich, 81377 Munich, Germany		
Bartenstein	Peter	Peter.Bartenstein@med.uni-muenchen.de	Department of Nuclear Medicine, University Hospital, LMU Munich, 81377 Munich, Germany		