Original research

Susceptibility vessel sign, a predictor of long-term outcome in patients with stroke treated with mechanical thrombectomy

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ABSTRACT

Background The absence of the susceptibility vessel sign (SVS) in patients treated with mechanical thrombectomy (MT) is associated with poor radiological and clinical outcomes after 3 months. Underlying conditions, such as cancer, are assumed to influence SVS status and could potentially impact the long-term outcome. We aimed to assess SVS status as an independent predictor of long-term outcomes in MT-treated patients.

Methods SVS status was retrospectively determined in consecutive MT-treated patients at a comprehensive stroke center between 2010 and 2018. Predictors of long-term mortality and poor functional outcome (modified Rankin Scale (mRS) ≥3) up to 8 years were identified using multivariable Cox and logistic regression, respectively.

Results Of the 558 patients included, SVS was absent in 13% (n=71) and present in 87% (n=487) on baseline imaging. Patients without SVS were more likely to have active cancer (P=0.003) and diabetes mellitus (P<0.001) at the time of stroke. The median long-term follow-up time was 1058 days (IQR 533–1671 days). After adjustment for active cancer and diabetes mellitus, among others, the absence of SVS was associated with long-term mortality (adjusted HR (aHR) 2.11, 95% CI 1.35 to 3.29) and poor functional outcome in the long term (adjusted OR (aOR) 2.90, 95% CI 1.29 to 6.55).

Conclusion MT-treated patients without SVS have higher long-term mortality rates and poorer long-term functional outcome. It appears that this association cannot be explained by comorbidities alone, and further studies are warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The absence of the susceptibility vessel sign (SVS) on admission susceptibility-weighted imaging is associated with lower successful reperfusion rates after mechanical thrombectomy (MT) and overall poorer outcomes at 3 months. Furthermore, the absence of the SVS is associated with underlying conditions, such as cancer and diabetes mellitus, which are known to impact overall long-term outcomes. Whether SVS alone is associated with long-term outcomes in patients with stroke undergoing MT remains unknown.

WHAT THIS STUDY ADDS

⇒ The absence of SVS is independently associated with poorer outcomes and higher mortality rates during long-term follow-up after MT, even after adjustment for underlying conditions and interventional parameters that are known to be associated with the absence of SVS and poor outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A thorough understanding of potential factors affecting long-term outcomes and SVS status is essential for stroke physicians. Special consideration should be given to factors which are already known to be associated with the absence of SVS in the acute phase. Future studies should elucidate the association between SVS and other underlying conditions in patients with stroke.

INTRODUCTION

Despite technical advances in stroke management, half the patients undergoing mechanical thrombectomy (MT) do not have a good functional outcome.[1] Several parameters obtainable by non-invasive admission imaging are known to impact patient outcome (eg, occlusion site, number of occluded vessels and infarct volumes).[1] The susceptibility vessel sign (SVS) can be assessed by susceptibility-weighted imaging (SWI) on admission and indicates a high proportion of deoxyhemoglobin which causes inhomogeneity in the magnetic field.[2–4] Pathohistologically, this could reflect a larger proportion of erythrocytes in the thrombus composition.[3] These erythrocyte-rich thrombi tend to induce signal loss on SWI (ie, indicating the

presence of the SVS), while fibrin- and platelet-rich thrombi do not show this loss of signal (ie, appearing as absence of SVS).[2] Prior studies have also shown that MRI-based SVS correlates with the CT-based hyperdense vessel sign (HVS) regarding the thrombus composition.[4 5] However, a direct transposition of the SVS evidence is not applicable and independent evidence for the HVS itself is required. Recent studies in patients with stroke undergoing MT reported that the absence of the SVS is associated with functional deterioration and an overall poorer outcome at 3 months.[6 7] The absence of SVS is assumed to be associated with underlying clinical conditions, such as cancer, which are known to impact overall long-term outcome.[8] Moreover, hypercoagulopathy, which is often observed in cancer patients, is associated with a higher percentage of fibrin- and platelet-rich thrombi.[9] Observational studies have also associated the absence of SVS with stroke of undetermined etiology; however, recent meta-analyses have not investigated stroke etiology in patients without SVS.[10–12] Therefore, the association between SVS and potential outcome drivers remains unclear,[8–12] and the extent to which the absence of SVS could be associated with patients' long-term outcome is presently unknown.[6 13 14] We hypothesized that SVS status could serve as an independent predictor of long-term outcome in MT-treated patients.

METHODS

Study cohort

All consecutive stroke patients treated with MT between January 1, 2010 and December 31, 2018 from our institution's prospective registry were retrospectively assessed for eligibility. Inclusion criteria were: (1) acute ischemic stroke treated with MT; (2) SWI performed as baseline imaging with SVS status available; (3) long-term outcome and follow-up time available. Only patients undergoing MT with the stent-retrievers were considered for the present study. Patients with intravenous thrombolysis (IVT) administered before SWI acquisition were excluded. Furthermore, patients receiving IVT before blood examination were excluded from analyses involving blood biomarkers. To avoid potential survivorship bias, all eligible patients were included in the main analyses even if they had died before the 3-month follow-up.[15] The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist was used for the present study.

Data collection

Baseline and 90-day follow-up data were extracted from the stroke registry. These included sex, age at admission, prestroke independence (defined as a modified Rankin Scale (mRS) score ≤2), prestroke anticoagulation/antiplatelet therapy, cerebrovascular risk factors (such as hypertension, diabetes mellitus, dyslipidemia, smoking, previous stroke, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS) score on admission, time between last known well and admission, time between last known well and groin puncture, IVT before MT, and site of occlusion. Sites of occlusion were defined as internal carotid artery, M1 segment of the middle cerebral artery (MCA), M2 segment of the MCA, other anterior occlusions, and posterior occlusions. The presence of active cancer (known or occult at the time of stroke) was determined retrospectively by two neurologists (MB and MK). The definition of active cancer and detailed characteristics of cancers found in the study cohort were previously published by Beyeler *et al*.[8] The assigned stroke etiology at discharge was defined by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification and extracted from the clinical information system.[16] The following laboratory values at admission were extracted: D-dimer in µg/L, hemoglobin in g/L, C-reactive protein (CRP) in mg/L, leukocytes in g/L, thrombocytes in g/L, fibrinogen in g/L, and international normalized ratio (INR).

Imaging analysis

Imaging was performed on a 1.5T or 3T MRI scanner. The SWI sequences were performed as part of our institution's stroke protocol.[7] Technical details on MRI scanners and our institution's stroke protocol are shown in online supplemental eTable I. To summarize, the presence or absence of SVS was determined retrospectively by two independent neuroradiologists blinded to clinical data and patient outcome (NFB and EBA). The presence of SVS was determined as a distinct signal loss which directly corresponded to the site of angiographically-confirmed occlusion and for which there was no alternative explanation (ie, neighboring vein, petechial hemorrhage or microcalcification in the neighboring parenchyma). The absence of SVS was defined as the absence of signal loss despite a clearly visible occlusion on the first angiographic imaging run (figure 1A–B). Inter-rater reliability regarding SVS evaluation (dichotomized: present or absent) was very good (Cohen κ=0.873, P<0.001).[7] Alberta Stroke Program Early CT Score (ASPECTS) was assessed on diffusion-weighted imaging (DWI) by neuroradiologists with 5 years of experience. The final reperfusion grade was core lab adjudicated using the expanded Treatment in Cerebral Ischemia (eTICI) score.[17 18] A score of eTICI2b50 or higher was considered as successful reperfusion.

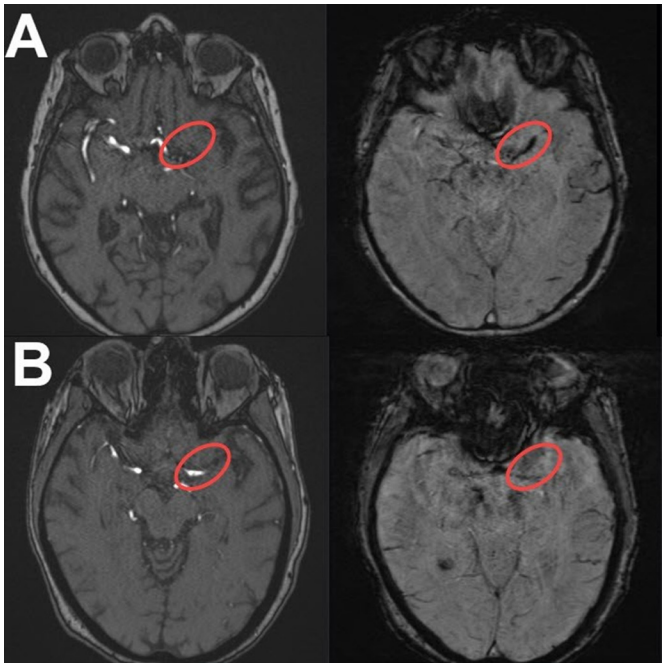

Figure 1 Susceptibility vessel sign assessment. Admission MRI. (A) TOF shows an occlusion in the M1-MCA segment on the left side (left panel) with a visible SVS sign on SWI (right panel). (B) Similar to the previous case, TOF again shows an occlusion in the M1-MCA segment on the left side (left panel); however, the SVS sign on SWI is absent (right panel). MCA, middle cerebral artery; SWI, susceptibility-weighted imaging; TOF, time-of-flight angiography.

Long-term follow-up

Patients who had survived or died in the long term were identified using the Swiss Population Registry (SPR), which records the vital status of Swiss residents monthly. Two neurologists (MB and LW) contacted the surviving patients, their next of kin or healthcare providers between September 2019 and June 2020 to assess long-term functional outcome based on the mRS. Details of the informed consent process and data collection are published elsewhere.[19] Long-term poor functional outcome was defined as mRS 3–6. For the survival analysis, follow-up time was defined as the time from the index ischemic stroke to the last update of the SPR or date of death, which is also reported in the SPR. For the functional outcome analysis, follow-up time was defined as the time from index ischemic stroke to the telephone interview or date of death extracted from the SPR.

Statistical analysis

Differences in baseline characteristics between patients with and without SVS were reported for continuous variables using median and interquartile range (IQR) and for categorical variables using frequency (percentage). Fisher's exact test and the Mann–Whitney U test were used to assess the differences between the two groups for categorical and continuous variables, respectively. For survival analyses, Kaplan–Meier curves with a log-rank test stratified by SVS status were plotted to display mortality rates during the long-term follow-up. Adjusted hazard ratios (aHRs) and their 95% confidence intervals (CI) were assessed with multivariate Cox regression analysis. For outcomes analysis, odds ratios or adjusted odds ratios (aOR) and their 95% CI were calculated from univariate and multivariate logistic regression, respectively. Multivariate regression analysis included the following clinically relevant covariates: age at admission, sex, diabetes mellitus, active cancer, prestroke independence, time from last known well to admission, NIHSS score on admission, occlusion site, ASPECTS at admission, IVT, successful reperfusion (binary variable)/eTICI grade (ordinal variable with a stepwise increase), stroke etiology according to TOAST and CRP. Interaction modeling was used to identify conditions that could impact the association between SVS and long-term follow-up based on previously reported findings (ie, SVS status*active cancer interaction term with long-term follow-up defined as the dependent variable).[8] For outcomes analyses (assessing the long-term mRS), subgroups with equal numbers of patients according to follow-up times were defined to limit the heterogeneity of the long-term follow-up due to the cross-sectional conduct of the telephone interview. Mixed-effects models with predefined follow-up times used as random effects were then applied. Due to the long recruitment period, sensitivity analyses were independently performed for the different follow-up groups. No imputation method was used for missing data. Statistical analyses were performed with Stata 16 (StataCorp) and R (version 3.6.0, R Core Team).

RESULTS

Study population

Of the 1317 patients undergoing MT, 577 had assessable SVS status. Of these, 19 had missing long-term follow-up data, resulting in 558 patients being finally included in the study (see online supplemental eFigure I). SVS was present in 87% of all patients (n=487/558) and absent in 13% (n=71/558) on baseline imaging.

Baseline characteristics

The baseline characteristics of patients with and without SVS are summarized in table 1. SVS was more often absent in female than in male patients (63.4% vs 36.6%). Compared with patients with SVS, those without SVS were less independent at the time of the stroke (mRS≤2: 82.9% vs 93.0%, P=0.009), more likely to have active cancer (21.1% vs 5.1%, P<0.001), diabetes mellitus (26.8% vs 12.7%, P=0.003), had a lower NIHSS score at admission (9 vs 12, P=0.049), a higher likelihood of stroke of undetermined etiology (56.3% vs 39.6%, P=0.010), and a higher level of CRP (4.5 vs 3 mg/L, P=0.030). For imaging characteristics, there was no difference between the two groups with respect to the MRI field strength or time between last known well and admission imaging. Patients without SVS had a poorer prognosis at 3 months and also during the long-term follow-up (table 1).

Association between absence of SVS and long-term mortality

The median long-term follow-up time was 1058 days (IQR 533–1671 days). In patients in whom the SVS was absent it was 587 days (IQR 44–1334 days) and, for patients in whom SVS was present, it was 1132 days (IQR 590–1710 days). The mortality rate in patients without SVS was higher during the long-term follow-up (figure 2, log-rank test P<0.001). In multivariable Cox regression analyses (figure 3), long-term mortality was associated with absence of SVS (aHR 2.11, 95% CI 1.35 to 3.29), active cancer (aHR 3.08, 95% CI 1.93 to 4.91), diabetes mellitus (aHR 1.78, 95% CI 1.19 to 2.64), lower ASPECTS (aHR 1.14, 95% CI 1.05 to 1.23), older age at admission (aHR 1.07, 95% CI 1.05 to 1.09) and elevated CRP (aHR 1.004, 95% CI 1.001 to 1.007). Higher levels of reperfusion were correlated with lower rates of long-term mortality, whether dichotomized for successful reperfusion (aHR 0.46, 95% CI 0.30 to 0.69, figure 3) or according to increasing eTICI grade (aHR 0.82, 95% CI 0.74 to 0.91, online supplemental eFigure II). Interaction analyses found no influence of active cancer, diabetes mellitus or successful reperfusion/eTICI grade on the association between the absence of SVS and long-term mortality.

Association between absence of SVS and long-term functional outcome

For the analysis of functional outcome, follow-up groups were created, as summarized in online supplemental eFigure III. From the 476 patients with long-term outcome (mRS) available, 184 were included in the group with a follow-up time of 1.2 to 3 years (follow-up group 1), 150 in the group with a follow-up time of 3 to 5 years (follow-up group 2) and 142 in the group with a follow-up time of 5 to 9.5 years (follow-up group 3). Poor functional outcome (mRS 3–6) in the long term was associated with absence of SVS (aOR 2.90, 95% CI 1.29 to 6.55, online supplemental eFigure IV), active cancer (aOR 3.97, 95% CI 1.53 to 10.28), diabetes mellitus (aOR 2.85, 95% CI 1.39 to 5.85), low ASPECTS (aOR 1.23, 95% CI 1.07 to 1.40) and older age at admission (aOR 1.07, 95% CI 1.04 to 1.09). Higher levels of reperfusion were correlated with lower rate of poor functional outcome, whether dichotomized for successful reperfusion (aOR 0.32, 95% CI 0.16 to 0.67, online supplemental eFigure IV) or according to increasing eTICI score (aOR 0.75, 95% CI 0.63 to 0.88, online supplemental eFigure V). Again, interaction analyses found no influence of active cancer, diabetes mellitus or successful reperfusion/eTICI grade on the association between the absence of SVS and long-term poor functional outcome. In univariate sensitivity analyses of follow-up groups, the absence of

Table 1 Comparison of baseline characteristics, short-term and long-term outcomes between patients with and without susceptibility vessel sign

	All (n=558)	SVS present (n=487)	SVS absent (n=71)	P value
Baseline				
Age at admission median (IQR)	72.75 (61–80.7)	72.66 (60–80.86)	74.2 (62.44–80)	0.71
Sex (female), n/N (%)	286/558 (51.3%)	241/487 (49.5%)	45/71 (63.4%)	0.031
Independence before stroke (mRS ≤2), n/N (%)	551/557 (91.7%)	453/487 (93.0%)	58/70 (82.9%)	0.009
Anticoagulation (vitamin K-antagonist and NOAC) prior to stroke, n/N (%)	65/557 (11.7%)	56/486 (11.5%)	9/71 (12.7%)	0.84
Antiplatelet drugs prior to stroke, n./N (%)	178/557 (32%)	152/486 (31.3%)	26/71 (36.6%)	0.41
Risk factors, n/N (%)				
Diabetes	81/558 (14.5%)	62/487 (12.7%)	19/71 (26.8%)	0.003
Hypertension	366/558 (65.6%)	318/487 (65.3%)	48/71 (67.6%)	0.79
Dyslipidemia	323/556 (58%)	279/485 (57.5%)	44/71 (62.0%)	0.52
Smoking	140/557 (25.1%)	123/486 (25.3%)	17/71 (23.9%)	0.88
Previous stroke	62/558 (11.1%)	51/487 (10.5%)	11/71 (15.5%)	0.22
Active cancer	40/558 (7.1%)	25/487 (5.1%)	15/71 (21.1%)	<0.001
Stroke characteristics				
Time from last known well to admission in min, median (IQR)	126 (71–286)	126 (73–277)	146 (70–322)	0.83
NIHSS on admission, median (IQR)	12 (7–17)	12 (7–18)	9 (5–16)	0.049
3 Tesla MRI, n/N (%)	184/555 (33%)	157/484 (32%)	27/71 (38%)	0.35
Time from last known well to imaging in min, median (IQR)	161 (101–320)	161 (101–305)	170 (103–377)	0.51
ASPECTS score, median (IQR)	8 (6–9)	8 (6–9)	8 (7–9)	0.003
IVT prior to MT, n/N (%)	217/558 (38.9%)	192/487 (39.4%)	25/71 (35.2%)	0.52
Time from last known well to groin puncture in min, median (IQR)	234 (164–397)	233 (166–391)	268 (157–431)	0.60
Number of maneuvers, median (IQR)	1 (1–2)	1 (1–2)	1 (1–3)	0.76
Successful reperfusion, n/N (%)	474/552 (85.9%)	418/481 (86.9%)	56/71 (78.9%)	0.098
eTICI categories, n/N (%)				
eTICI 0	24/552 (4.35%)	18/481 (3.7%)	6/71 (8.5%)	0.51
eTICI 1	12/552 (2.17%)	11/481 (2.3%)	1/71 (1.4%)	
eTICI 2a	42/552 (7.61%)	34/481 (7.1%)	8/71 (11.3%)	
eTICI 2b50	64/552 (11.59%)	56/481 (11.6%)	8/71 (11.3%)	
eTICI 2b67	132/552 (23.91%)	117/481 (24.3%)	15/71 (21.1%)	
eTICI 2c	131/552 (23.73%)	116/481 (24.1%)	15/71 (21.1%)	
eTICI 3	147/552 (26.63%)	129/481 (26.8%)	18/71 (25.4%)	
Site of occlusion, n/N (%)				
ICA	94/558 (16.9%)	88/487 (18.1%)	6/71 (8.5%)	0.010
M1	292/558 (52.3%)	258/487 (53.0%)	34/71 (47.9%)	
M2	119/558 (21.3%)	100/487 (20.5%)	19/71 (26.8%)	
Posterior occlusion	44/558 (7.9%)	36/487 (7.4%)	8/71 (11.3%)	
Other anterior occlusion	9/558 (1.6%)	5/487 (1.0%)	4/71 (5.6%)	
Stroke etiology (TOAST), n/N (%)				
Cardioembolic	222/558 (39.8%)	196/487 (40%)	26/71 (37%)	0.016
More than one cause	1/558 (0.1%)	1 (0.2%)	0/71 (0%)	
Large artery atherosclerosis	73/558 (13.1%)	71 (15%)	2/71 (3%)	
Stroke of other determined etiology	28/558 (5%)	25 (5%)	3/71 (4%)	
Stroke of undetermined etiology	234/558 (41.9%)	194 (40%)	40/71 (56%)	
Stroke of undetermined etiology vs other etiologies, n/N (%)	233/558 (41.8%)	194/487 (40%)	40/71 (56.3%)	0.010
Baseline laboratory findings				
D-dimer, µg/L, median (IQR)	888 (497–1758)	869 (495.5–1743)	1020 (543–2731)	0.17
Hb, g/L, median (IQR)	135 (124–146)	136 (124–147)	130.5 (119–144)	0.11
CRP, mg/L, median (IQR)	3 (3–8)	3 (3–8)	4.5 (3–12.5)	0.030
Leukocytes, g/L, median (IQR)	8.3 (6.6–10.3)	8.21 (6.6–10.3)	8.8 (7.2–10.3)	0.21
Thrombocytes, g/L, median (IQR)	221 (180.5–268)	220 (182–268)	225 (177–278)	0.92

Continued

Table 1 Continued

	All (n=558)	SVS present (n=487)	SVS absent (n=71)	P value
Fibrinogen, g/L, median (IQR)	3.08 (2.56–3.7)	3.085 (2.59–3.67)	3.01 (2.385–4.055)	0.98
INR, median (IQR)	1.01 (1–1.07)	1 (1–1.07)	1.03 (1–1.08)	0.11
Stroke outcomes				
Death before 3 months, n/N (%)	102/558 (18.3%)	79/487 (16.2%)	23/71 (32.4%)	0.003
mRS at 3 months, median (IQR)	2 (1–4)	2 (1–4)	3.5 (1–6)	0.004
Poor functional outcome at 3 months (mRS 3–6), n/N (%)	239/539 (44.3%)	197/469 (42.0%)	42/70 (60.0%)	0.006
Long-term follow-up time, days, median (IQR)	1058 (533–1671)	1132 (590–1710)	587 (44–1334)	<0.001
Long-term deaths, n/N (%)	189/558 (33.9%)	151/487 (31.0%)	38/71 (53.5%)	<0.001
Long-term mRS, median (IQR)	3 (1–6)	2 (1–6)	6 (2–6)	<0.001
Long-term poor functional outcome (mRS 3–6), n/N (%)	248/476 (52%)	203/411 (49.4%)	45/65 (69.2%)	0.003

ASPECTS, Alberta Stroke Program Early CT Scores; CAD, coronary artery disease; CRP, C-reactive protein; eTICI, expanded treatment in cerebral infarction; Hb, hemoglobin; ICA, internal carotid artery; INR, international normalized ratio; IQR, interquartile range; IVT, intravenous thrombolysis; M1 and M2, first and second segment of the middle cerebral artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; SVS, susceptibility vessel sign; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

SVS was associated with poor functional outcomes in follow-up group 1 (OR 2.62, 95% CI 1.16 to 5.89) and follow-up group 3 (OR 5.06, 95% CI 1.10 to 23.21) but not in follow-up group 2 (OR 1.88, 95% CI 0.67 to 5.31). In the multivariate sensitivity analyses of the follow-up groups, the absence of SVS was not associated with poor functional outcomes in any of the follow-up groups (online supplemental eFigure VI).

DISCUSSION

This study's main finding is that the absence of SVS remained associated with poorer outcomes and higher mortality during the long-term follow-up even after adjustment for underlying conditions and interventional outcome parameters known to be associated with the absence of SVS and poor outcome (such as active cancer and diabetes mellitus).

Long-term outcome and survival rates

Reports on the association between the SVS and functional outcome are conflicting. A single-center retrospective registry study reported that poor outcome was more common in patients with SVS (present vs absent: 57.1% vs 33.3%, P=0.02).[14] However, multivariable analysis identified only age and reperfusion as independent predictors of clinical outcome. Conversely, Bourcier *et al* reported higher rates of poor outcome among patients without SVS (present vs absent: 35% vs 74%, P=0.004) and this association was also perceptible after correcting for other cofactors known to be associated with functional outcome (aOR 8.7; 95% CI 1.1 to 69.4).[6] A post hoc analysis of the Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER) trial reported no difference in functional outcome at 3 months between patients with and without SVS (risk ratio (RR) 1.27, 95% CI 0.9 to 1.6; P=0.08); however, this trial was not powered to detect such an association.[13] A recent meta-analysis reported that patients with SVS were more likely to have a poor functional outcome at 3 months (RR 1.5,

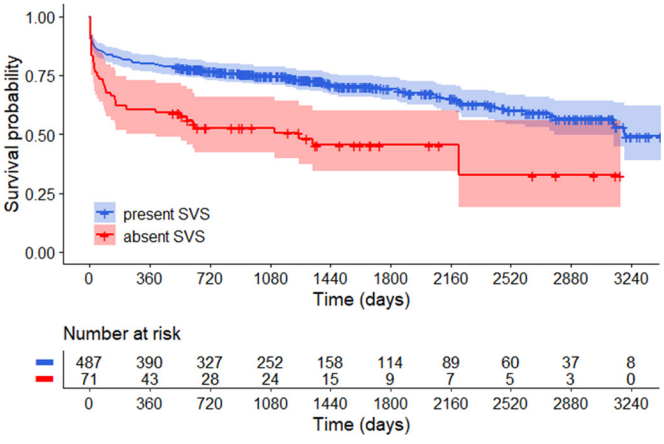

Figure 2 Long-term survival curve for patients with and without susceptibility vessel sign (SVS). Compared with patients in whom SVS was present (blue), patients in whom SVS was absent (red) had higher mortality rates during the long-term follow-up after ischemic stroke treated with mechanical thrombectomy (log-rank test, P<0.001).

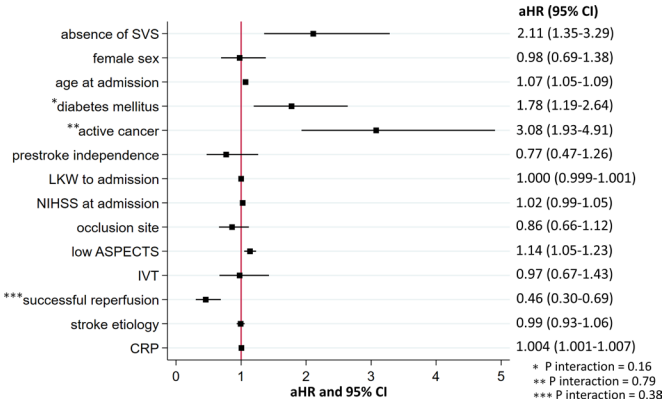

Figure 3 Association between long-term mortality and demographic characteristics, relevant risk factors, and stroke parameters. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) from the multivariate Cox regression analyses comparing long-term mortality and demographics, relevant risk factors and stroke parameters. Long-term mortality was associated with absence of SVS, diabetes mellitus, active cancer, low ASPECTS, older age at admission and increased CRP. Interaction analyses (*, **, ***) did not identify any substantial influence of diabetes mellitus, active cancer or successful reperfusion on the relationship between absence of SVS and long-term mortality. P interaction indicates P value for corresponding interaction terms. ASPECTS, Alberta Stroke Program Early CT Score; CRP, C-reactive protein; IVT, intravenous thrombolysis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign.

95% CI 1.3 to 1.7), although wide heterogeneity among the studies was noted (I^2=87.8%, P<0.001).[12]

Here we report similar results to those of Bourcier *et al*—namely, a poor 3-month outcome was more often observed in patients in whom SVS was absent. Moreover, this association was present even when looking at the adjusted long-term clinical outcome and survival rates. We assume that the non-significant results in the sensitivity analyses of follow-up groups are attributable to the small number of patients in each group, leading to imprecise estimates (online supplemental eFigure VI).[20] The association between SVS and long-term patient outcome could potentially be explained by thrombus composition: white thrombi are more common in patients without SVS and red thrombi in patients with SVS.[2] More specifically, red thrombi are easier to manipulate during the intervention and often yield higher reperfusion rates after the endovascular procedure.[21 22] Patients with SVS would therefore be more likely to have a favorable outcome, as they would tend to have higher reperfusion rates after MT. Another potential explanation for differences in long-term outcome between patients with and without SVS might reflect underlying conditions, which would affect the thrombus composition and also the long-term survival rates. An association between cancer, diabetes mellitus and the SVS has been previously described in the same cohort.[7 8] Fibrin-rich thrombi are strongly correlated with cancer-related stroke,[9] and changes of the inner lining of blood vessels caused by diabetes mellitus increase the chances of adhesion of thrombi that are rich in fibrin and have a low erythrocyte count.[23 24] Both conditions would therefore increase the chance of SVS being absent in this subgroup of stroke patients. However, we saw no significant interaction effect between these cofactors (successful reperfusion, active cancer and diabetes mellitus) and SVS status on long-term outcome rates. This further underlines present uncertainties between SVS and other factors that may affect the outcome.[8–12]

A potentially relevant finding of this study is that the CRP level was higher in patients with absent SVS and was also associated with a higher mortality event rate after adjustment for SVS (figure 3). Therefore, a potential underlying acute or chronic inflammation could be related to the formation of fibrin- and platelet-rich thrombi, the absence of SVS and, finally, a poorer long-term outcome.[25 26] Further prospective studies could include other potential causes of acute and chronic inflammation to elucidate the association between possible inflammatory factors impacting the outcome and the absence of SVS. More aggressive treatment of such underlying conditions could then improve long-term outcome rates.

SVS positivity is subject to time-dependent variations in deoxyhemoglobin; however, detection of SVS in our study seemed to be independent of MRI field strength and time from last known well to imaging.[3] Our results could be partly explained by our stringent inclusion criteria as we focused on patients presenting with large vessel occlusion in the early time window (see Methods). The acquisition of SWI sequences in institutions with available MRI for acute stroke diagnosis is of clinical relevance given the prognostic value of SVS (better reperfusion rate after thrombectomy and higher mid- and long-term survival) as well as its diagnostic value (detection of hemorrhage, concomitant microbleeds and recognition of underlying treatable conditions more quickly).[7 8 27] Despite the known time-consuming cost of acquiring SWI sequences, Fischer *et al* showed that conducting brain MRI at admission (compared with brain CT) showed no difference in door-to-puncture time in MT-treated patients, even those with early presentation and severe stroke.[28] Additionally, the development and implementation of faster SWI acquisition methods (highly accelerated wave–controlled aliasing in parallel imaging (CAIPI) SWI) should enable a reduction of SWI sequence acquisition times (currently ~5 min) by a factor of 3–5 in the future, making the SWI acquisition even more valuable.[29] Furthermore, as most sites use CT rather than MRI for acute stroke work-up, our findings must be confirmed in a CT-diagnosed stroke population to generalize the prognostic value of thrombus imaging characterization in the long-term outcome. Even if the correlation between SVS and HVS was described previously, the analyses performed in our study should be performed for HVS independently.[4 5]

Limitations

Our study has several limitations. First, it is a single-center retrospective study with all the commonly attributed biases. Second, even if no difference in the identification of SVS was found between 1.5T and 3T MRI in this study, this limitation may have influenced the sensitivity for detecting SVS and consequently the predictive value of the absence of SVS for poorer long-term outcomes. Third, due to the retrospective design, not all underlying conditions, potentially leading to the absence of SVS and poor long-term outcomes, were systematically documented and assessable. Furthermore, the lack of direct histological examination of the thrombus composition limits the broader interpretation of the study results. Fourth, although patients were treated with second-generation devices, the long recruitment period with not well-established MT procedures at the beginning of recruitment, could have introduced biased reperfusion success assessment due to interventionalist experience and in-hospital workflows. Fifth, in the sensitivity analyses of the follow-up groups, the number of patients per subgroup was insufficient and caution is advised when interpreting these results.

CONCLUSION

The absence of SVS is independently associated with poor long-term outcome and higher mortality rates in patients with stroke after MT. It appears that this association cannot be explained by already associated comorbidities alone, and further studies are warranted.

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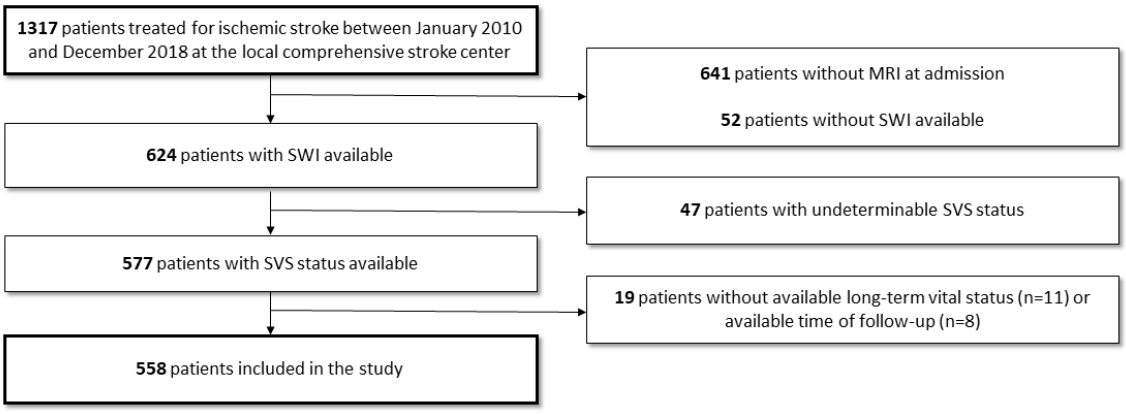
SUPPLEMENTAL MATERIALS

Susceptibility Vessel Sign, a Predictor of Long-Term Outcome in Stroke Patients Treated with Mechanical Thrombectomy

eTable I – Technical Information on SWI sequence

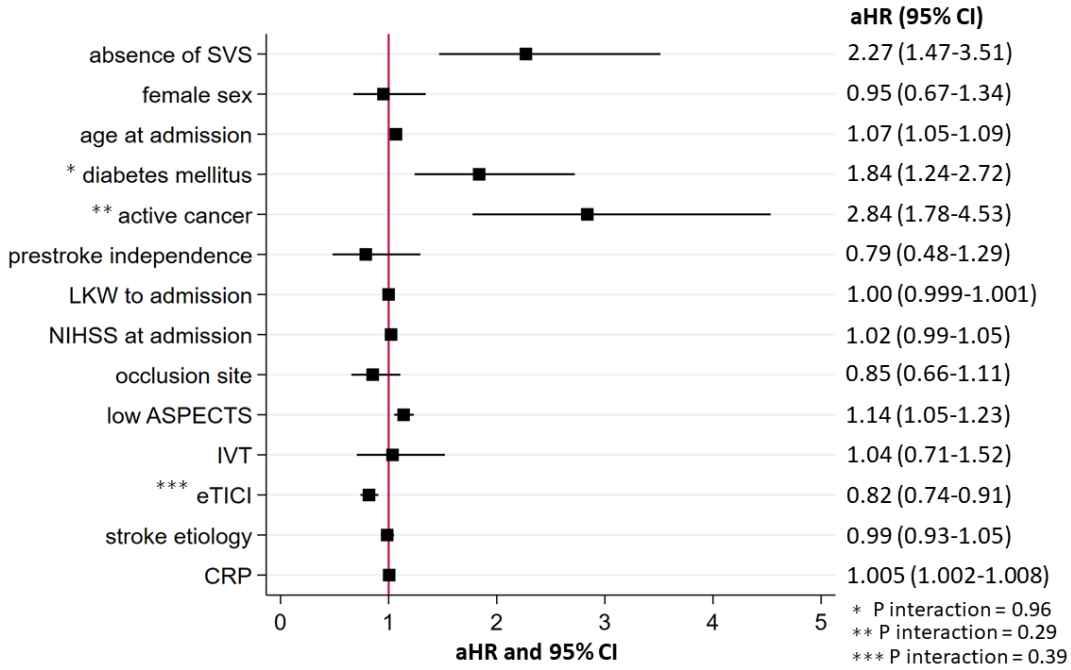
Field strength	1.5T	3T
MRI scanner	Avanto, Aera	Sykra, Prsima, Verio, Vida
MRI sequence included in standard stroke protocol	-ax DWI -ax FLAIR -ax SWI -ax intracranial TOF -ax DSC Perfusion -ax T1 post contrast -cor extracranial CE-MRA	-ax DWI -ax FLAIR -ax SWI -ax intracranial TOF -ax DSC Perfusion -ax T1 post contrast -cor extracranial CE-MRA
Scanner parameters for SWI	TR, 49 ms; TE, 40 ms; flip angle, 15.0°; section thickness, 1.6, 1.8, or 2.0 mm; and intersection gap, 0 mm.	TR, 27 ms; TE, 20 ms; flip angle, 15.0°; section thickness, 2.0 mm; and intersection gap, 0 mm.

MRI: magnet resonance imaging; T: Tesla; TR: repetition time; TE: time-to-echo. Device manufacturer: Siemens Healthcare GmbH, Erlangen, Germany. All the scanners were upgraded between 2016 – 2018 with slight modification of scanning parameters.



eFigure I – Study flowchart

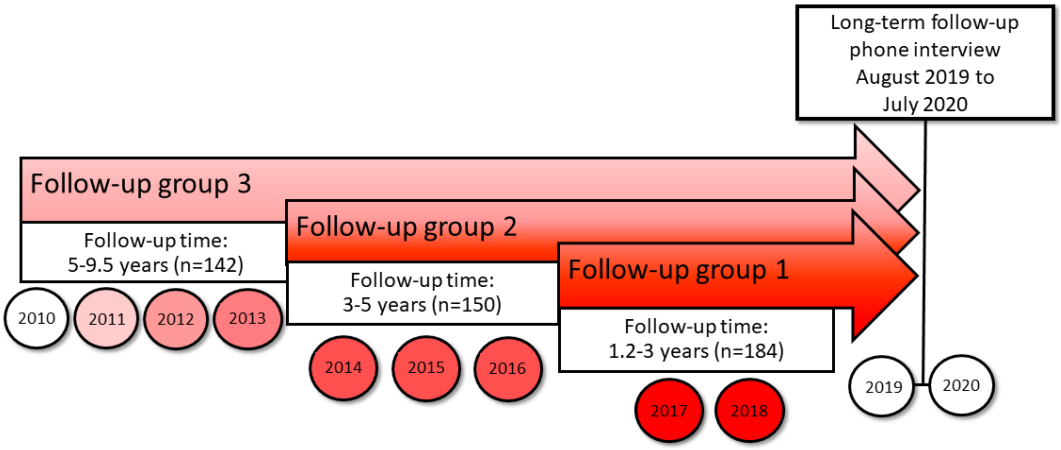
Inclusion and exclusion of study participants. MRI indicates magnetic resonance imaging; SVS, susceptibility vessel sign; and SWI susceptibility-weighted imaging.



eFigure II – Association between long-term mortality and other covariates

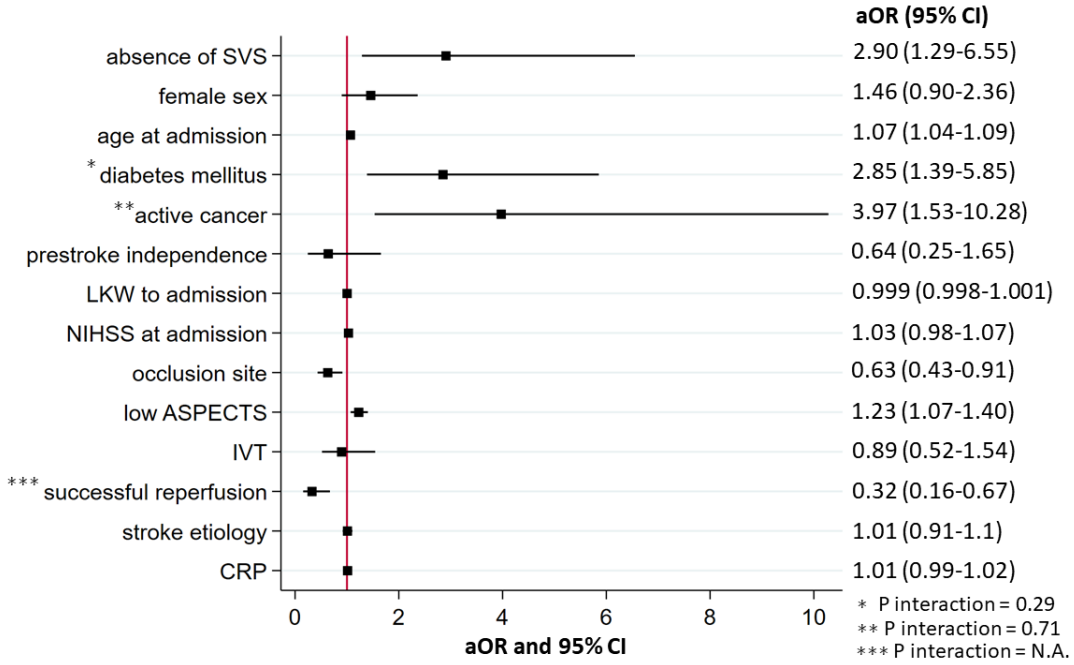
These included demographic characteristics, relevant risk factors, and stroke parameters (including eTICI as ordinal variable for the reperfusion outcome).

aHR indicates adjusted hazard ratio; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; CRP, C-reactive protein; eTICI, expanded treatment in cerebral infarction; IVT, intravenous thrombolysis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign. P interaction indicates P-value for corresponding interaction terms.



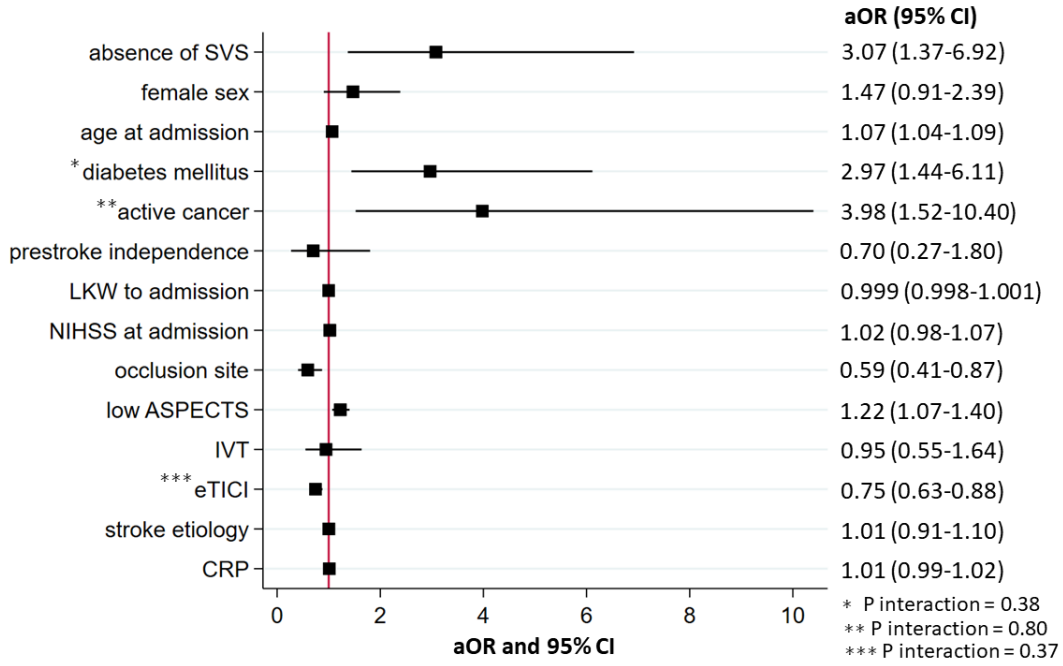
eFigure III – Follow-up time and establishment of follow-up groups

Patients treated with mechanical thrombectomy between January 2010 and December 2018 and with available SVS status were included. Surviving patients were contacted for long-term follow-up by telephone interview between August 2019 and July 2020. Because of the heterogeneous follow-up times, three follow-up groups of approximately equal size were established (1.2–3 years, 3–5 years, 5–9.5 years) to guarantee statistical power (see Methods).



eFigure IV – Association between long-term poor functional outcome (defined as mRS 3–6) and demographics, relevant risk factors and stroke parameters in the multivariate logistic regression model

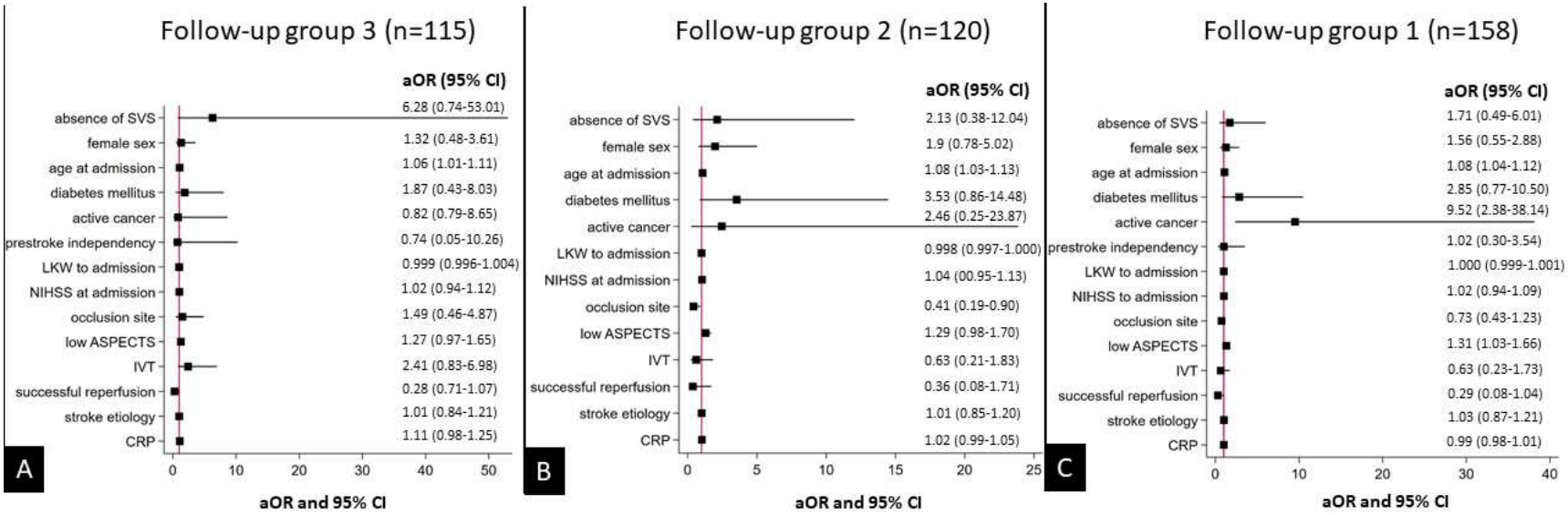
This figure summarizes the association between long-term poor functional outcome and demographics, relevant risk factors, and stroke parameters. Adjusted odds ratios (aOR) and 95% confidence intervals are reported. Absence of SVS, diabetes mellitus, low ASPECTS and older age at admission were associated with poor long-term functional outcome. Interaction analyses (∗ and ∗∗) did not identify any substantial influence of the diabetes mellitus and active cancer on the association between absence of SVS and long-term poor functional outcome. Successful reperfusion was omitted from interaction analyses because of collinearity. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CRP, C-reactive protein; IVT, intravenous thrombolysis; LKW, last known well; N.A., not applicable; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign.



eFigure V – Association between long-term poor functional outcome (defined as mRS 3–6) with eTICI

This analysis included demographics, relevant risk factors and stroke parameters (including eTICI as ordinal variable for the reperfusion outcome) in the multivariate logistic regression model.

aOR indicates adjusted odds ratio; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; CRP, C-reactive protein; eTICI, expanded treatment in cerebral infarction; IVT, intravenous thrombolysis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign.



eFigure VI – Association between long-term poor functional outcome (defined as mRS 3–6) and other covariates in the different follow-up groups

This sensitivity analysis of the different follow-up groups (described in eFigure III) included demographics, relevant risk factors and stroke parameters in the multivariate logistic regression model. The number of patients included in the multivariate analysis in each group is indicated in parenthesis.

aOR indicates adjusted odds ratio; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; CRP, C-reactive protein; IVT, intravenous thrombolysis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale and SVS, susceptibility vessel sign.