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Diagnostic performances of the susceptibility vessel sign on MRI for the prediction of macroscopic thrombi features in acute ischemic stroke

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Abstract:

Background: The “white” compared to “Red-Black” visual aspect of the thrombus on withdrawal with mechanical thrombectomy for acute ischemic stroke was related to atypical etiologies like infective endocarditis. The susceptibility vessel sign (SVS) and the two-layered SVS (TL-SVS) could help predict outcome and cardio-embolic etiology of acute ischemic stroke. We aimed to evaluate the diagnostic performance of the SVS and TLSVS to predict the visual aspect of the thrombus.

METHODS: We included patients treated by mechanical thrombectomy and screened with MRI for the SVS and the TL-SVS for whom thrombus photograph was available. Photographs underwent a double-blind evaluation by neuroradiologists who classified the thrombus as “White” or “Red-Black”. Logistic regression assessed the association of Red-Black thrombus and age, sex, baseline National Institutes of Health Stroke Scale, occlusion site, the IVr-tPA administration, SVS and TL-SVS. We calculated the diagnostic performances of the SVS to predict a Red-Black type thrombus.

RESULTS: Between May 2017 and July 2018, 139 patients were included in the study. On multivariate analysis, only SVS was an independent predictor for Red-Black thrombus (Odd ratio 8.31, 95%CI 2.30 to 32, pvalue<0.001). Concerning SVS diagnostic performances, the specificity was 0.58 (95%CI 0.28 to 0.85), the sensitivity was 0.87 (95%CI 0.80 to 0.93), the negative predictive value was 0.30 (95% 0.13 to 0.53), the positive predictive value was 0.96 (95%CI 0.90 to 0.99) and accuracy was 0.85 (95%CI 0.78 to 0.90).

CONCLUSION: The SVS on MRI provides a good prediction accuracy to anticipate the macroscopic visual aspect of the thrombus after mechanical thrombectomy for acute ischemic stroke.

Key words: Magnetic resonance imaging; Stroke; thrombus; thrombectomy

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Abstract:

Background and purpose: The “white” compared to “Red-Black” visual aspect of the thrombus at withdrawal with mechanical thrombectomy (MT) for acute ischemic stroke (AIS) was related to atypical etiologies like infective endocarditis. The susceptibility vessel sign (SVS) and the two-layered SVS (TL-SVS) could help predict outcome and cardio-embolic etiology of AIS. We aim to evaluate the diagnostic performance of the SVS and TLSVS to predict the visual aspect of the thrombus.

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CONCLUSION: The SVS on MRI provides a good prediction accuracy to anticipate the macroscopic visual aspect of the thrombus after MT for AIS.

INTRODUCTION

In 20%–40% of cases the etiology of acute ischemic stroke (AIS) remains uncertain despite complete diagnostic investigation. (1) Correlations between the histological microscopic features of the thrombus and the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) categories have been found. (2–5) However, from the macroscopic point of view, only one case report has considered the chromatic visual aspect of the retrieved thrombus. (6) Recently, the “white” visual aspect of the thrombus at the moment of withdrawal has been related to atypical etiologies, in particular infective endocarditis. (7) Furthermore, these “white” thrombi, often related to a fibrin-rich content, are harder to extract with mechanical thrombectomy (MT) devices using a stent retriever. (8–10) Indeed, a white, firm and more organized thrombus can be difficult to engage in the stent retriever struts, as it adheres more strongly to the vessel wall. (9,11,12) Beside conventional histological examinations, a gross and macroscopic examination of the thrombi retrieved just after MT could offer an original and complementary approach to assess thrombi retrieved from large vessel occlusions.

The susceptibility vessel sign (SVS) can be identified on MRI T2* gradient recalled echo (GRE) sequences and corresponds to a localized hypo intense signal at the site of the thrombus. (13,14) Studies have shown that qualitative evaluation of SVS could help predict recanalization and clinical outcome after MT. (15,16) Moreover, the two-layered susceptibility vessel sign (TL-SVS) has been reported to predict cardio-embolic stroke. (17,18)

However, no study has evaluated the relationship between the gross visual aspect (white or red/black) of the thrombus at the moment of withdrawal and these latter radio-markers in MRI. The purpose of the study was to evaluate the diagnostic performance of the SVS and TLSVS to predict the visual aspect at the moment of withdrawal of the thrombus.

METHODS

Study population

From May 2017 and July 2018, we included patients with large anterior intracranial vessel occlusion, referred to two experienced centers, treated by MT (with stent-like retrievers, contact aspiration or with combined technique), with or without intravenous (IV) recombinant tissue plasminogen activator (tPA), and for whom a photograph of the retrieved thrombus was taken and available. From the current analysis, patients not being imaged with susceptibility-weighted imaging (SWI) or gradient-recalled echo T2 (GRE T2) sequence before treatment, or for whom thrombus photograph for evaluation of the macroscopic appearance of the thrombus (color) was of poor clarity were excluded.

The institutional review boards waived the approval or patient informed consent for this study.

Database and etiologies

A prospective and registered multicenter database (ETIS Registry, NCT03776877) was used to export the data of the AIS for each patient after a 3-month follow-up. Clinical data, such as age, sex, baseline and 24-hour National Institutes of Health Stroke Scale (NIHSS) score were collected for each patient. Other variables such as the occlusion site, the IV tPA administration, the MT technique, the final modified Thrombolysis in Cerebral Infarction score (mTICI) and the parenchymal hemorrhage after 24-hours were also collected. An extensive research for the etiology of the AIS was performed. The presence of atrial fibrillation (AF), dissection and atheroma was verified using normal ECG or ECG Holter when required, carotid Doppler ultrasound, CT angiography/MR angiography, and DSA.

MRI examination

MR imaging in Center 1 was performed on a 1.5T magnet (Sonata; Siemens, Erlangen, Germany) with a phased array head coil. First, a GRE T2* imaging was performed to screen for intracranial hemorrhage and SVS. Acquisition parameters for GRE T2* were the following: TR, 800 ms; TE, 30 ms; section thickness, 5 mm; intersection gap, 1 mm; FOV, 250x250 mm; flip angle, 20°. MR examinations in Center 2 were performed on a 3T magnet (Magnetom Skyra; Siemens, Erlangen, Germany) with a phased array head coil. Acquisition parameters for GRE T2* were the following: TR, 26 ms; TE, 20 ms; section thickness, 2 mm; intersection gap, 1 mm; FOV, 230x230 mm; flip angle, 15°.

Occlusion of the MCA (either M1 and/or M2) was classified as MCA occlusion. Occlusion involving the ICA terminus, extending or not to M1, was classified as ICA occlusion. The SVS was defined as a hypointense signal on T2* within a vessel, exceeding the size of the homologous contralateral artery diameter (Fig 2,3 and 4). (13) The TL-SVS was defined as an SVS that contained a low-intensity core surrounded by a signal of higher intensity. (18) All MR images were analyzed without knowing the macroscopic aspect of thrombus or the etiology of AIS by a junior radiologist (XX and XX) and in case of discrepancy an experienced neuroradiologist (XX) analyzed images in consensus.

Retrieved thrombi and macroscopic features

Methods for the examination of the macroscopic features of retrieved thrombi have previously been described. (7) Briefly, all the retrieved thrombi were immediately rinsed and collected under sterile conditions. A photograph of each thrombus positioned on a white gauze was taken with a smartphone. In the consensus statement by De Meyer et al, standardization of the terminology for description of the gross appearance was suggested. (5) All the photos underwent a double-blind evaluation performed by two senior interventional neuroradiologists who classified the thrombus as

“white” or “red/red-black”. In cases of discordance between the first two observers, a third physician, a vascular neurologist, provided the final evaluation.

Statistical analysis

Results were expressed as mean, SD, median, minimum and maximum for quantitative variables and as count and percentage for categorical variables. After resolving discordance by a third independent evaluation, patients were divided into two groups by thrombus color. Usual bivariate parametric (χ^2 test or Fisher exact test) statistical tests were used for group comparisons, considering either “SVS+” and “SVS-” or “TLSVS+” and “TLSVS-” thrombi. Inter-reader and intra-reader agreements for the SVS, TL-SVS and thrombus color were calculated using Kappa Cohen with 95% CI. Logistic regression analysis was used to assess the association of the Red/Red-Black type thrombus and age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, occlusion site, the IV r-tPA administration, center, SVS and TL-SVS. First, a univariate analysis was performed, and only factors with a P value $\leq .25$ were selected for the multivariate analysis. All statistical tests were 2-sided, and the significance level was set at $p=0.05$. We calculated the diagnostic values for the SVS (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], accuracy rate) to predict a Red/Red-Black type thrombus. Statistical analysis was performed by using R statistical and computing software, Version 3.3.1 (<http://www.r-project.org/>) using the caret (<https://cran.r-project.org/web/packages/caret/index.html>) package.

RESULTS

Between May 2017 and July 2018, the clinical files of 277 patients with large vessel occlusions, treated by MT, and with an available photo of the retrieved clot were reviewed in the two centers. Of them, 139 were eligible to be included in the study. Reasons for exclusion were: absence either of MRI selection or of a SWI/gradient-recalled echo T2 (GRE T2) sequence before treatment (n=117) and poor clarity of the photos of the retrieved thrombi for macroscopic evaluation (n=21).

Among the 139 patients, 87 (62.6%) were included in Center 1 and 52 (37.4%) in Center 2. Median age was 70 (2-96) and sex ratio was 1.28 (78 men and 61 women). Characteristics of stroke and treatment were collected for each patient and 96 of them (69.1%) had a MCA occlusion versus 43 (30.9%) in other territories, baseline median NIHSS was 17 (2-27), 69 (49.6%) patients had a IV r-tPA injection before MT. The first line MT strategy was contact aspiration for 63 (45.3%) patients, stent-like retrievers for 16 (11.5%) and combined for 60 (43.2%) patients. After extensive research for each patient an underlying etiology (classified with TOAST classification), 71 (51.1%) were cardio-embolism and 68 (48.9%) other etiologies.

Baseline characteristics according to the SVS and TL-SVS are presented in Table. 1 and 2.

Overall, 117 (84.2%) patients had a SVS+ on MRI and 8 (5.8%) had TL-SVS. Inter-reader and intra-reader agreement for the SVS was 0.85 (95%CI, 0.81–0.87) and 0.92 (95% CI, 0.89 –0.93), respectively. Inter-reader and intra-reader agreement for the TL-SVS was 0.79 (95%CI, 0.76–0.83) and 0.83 (95% CI, 0.80–0.85), respectively.

According to the macroscopic evaluation on photos after treatment, patients were classified in 131 (94.2%) red/red-black thrombi and 8 (5.8%) white thrombi. The inter-reader agreement for graded thrombus color was excellent ($k = 0.83$ [95% CI 0.77 to 0.90]). Among the 8 white clots, the

etiological work-up found 2 endocarditis, 1 evolutive cancer, 1 atheroma, 2 emboli from cardiac origin and 2 unknown etiologies.

On multivariate analysis (Table. 3), only SVS was an independent predictor for red thrombus (Odd ratio 8.31, 95% CI 2.30 to 32, p value <0.001), while the center was not an independent predictor (Odd ratio 0.53, 95% CI 0.14 to 1.94, p value 0.10).

Concerning SVS diagnostic performances (Table. 4), the specificity was 0.58 (95% CI 0.28 to 0.85), the sensibility was 0.87 (95% CI 0.80 to 0.93), the NPV was 0.30 (95% 0.13 to 0.53), the PPV was 0.96 (95% CI 0.90 to 0.99) and accuracy was 0.85 (95% CI 0.78 to 0.90). For TL-SVS, the specificity was 0.92 (95% CI 0.62 to 1.00), the sensitivity was 0.06 (95% CI 0.03 to 0.12), the NPV was 0.09 (95 CI 0.04 to 0.15), the PPV was 0.89 (95% CI 0.52 to 1.00) and accuracy 0.14 (95% CI 0.09 to 0.21).

DISCUSSION

The main finding of our study is that the SVS provides a good prediction accuracy to differentiate the visual aspect at the moment of the withdrawal of the thrombus after MT for AIS. Interestingly, since its positive predictive value is almost perfect (0.96), in the presence of a SVS+ thrombus it is highly likely that this is a not a white, “atypical” thrombus.

This thrombus aspect, recently related to atypical etiologies of stroke (in particular infective endocarditis), represents its global and macroscopic structure. (7)

Of note, in this former work, the age of patients in the “white thrombi” group was significantly lower than in the “red thrombi” group. (7) Interestingly, studies have emphasized in AIS a “FPE paradox” with lower rate of first pass effect to achieve good recanalization with MT in younger patients compared to older patients. (19,20) Taken together, we can hypothesize that the “white” macroscopic structure of the thrombus, less uncommon in young patients and harder to extract with stent retrievers, is a potential explanation for the “FPE paradox”. Our present study that found a relation between the visual aspect at the moment of the withdrawal of the thrombus and the SVS is in line with this hypothesis since the absence of SVS have also been associated to less favorable outcome after MT with stent retrievers. (15,16)

We did not observe a strong relation between the visual macroscopic evaluation of the thrombi and the TL-SVS. The TL-SVS appears as a more specific biomarker of the high or very high content in red blood cells in the thrombus. Indeed, the clinical relevance in terms of interaction between the thrombus and the stent retriever struts does not seem as important as with the SVS. As previously published, the TL-SVS is maybe more interesting for the etiological work-up of AIS. (18,21)

Our study is the first to approach the visual aspect at withdrawal of the thrombus and the MRI signal in vivo. Of note, the strength of our study is to rely on a gross, macroscopic examination of the

thrombi retrieved just after the thrombectomy. Hence, we did not aim at challenging conventional histological analysis that has been extensively reported in this setting. Rather, we propose an original and complementary approach to assess thrombi retrieved from large vessel occlusions.

However, we acknowledge limitations since we have only analyzed thrombi that were actually retrieved and the study population was relatively small. Furthermore, since we gathered different first-line endovascular strategies (aspiration alone, stent retriever or combined), our work was not designed to study the rate of recanalization or clinical outcomes of patients included. Finally, although SVS identification is reliable and reproducible, with excellent inter-observer agreement, the acquisition of the sequences was performed on different MRI machines. This is a significant limitation, as it was previously reported in an in vitro study that the prevalence of the SVS varies significantly among different manufacturers. (22) Lastly, we were not able to record the length of the thrombus, however it would have been interesting to compare the thrombus burden of white and red/red-black thrombi.

CONCLUSION

The SVS on MRI at the acute phase of AIS provides a good prediction accuracy to anticipate the macroscopic visual aspect of the thrombus after MT. In the presence of a SVS+ thrombus it is highly likely that this is a not a white, “atypical” thrombus. Future studies should question how the macroscopic visual aspect of the thrombi could be related to the recanalization rate and to the clinical outcomes of treated patients.

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Figure 1.

Abbreviations : LVO : Large Vessel Occlusion, MRI : MagneticResonance Imaging, MT : mechanicalthrombectomy, AIS : Acute ischemic stroke

Figure 2.

A: A clot extracted from the patients, directly pictured. Macroscopic examination considered as a « white » clot

B: Corresponding MRI Time of flight confirming the a acute right MCA occlusion (white arrow)

C: Absence of SVS occlusion in the right MCA(white arrow)

Figure 3.

A: A clot extracted from the patients, directly pictured. Macroscopic examination considered as a « red » clot

B: Corresponding MRI Time of flight confirming the a acute left MCA occlusion (white arrow)

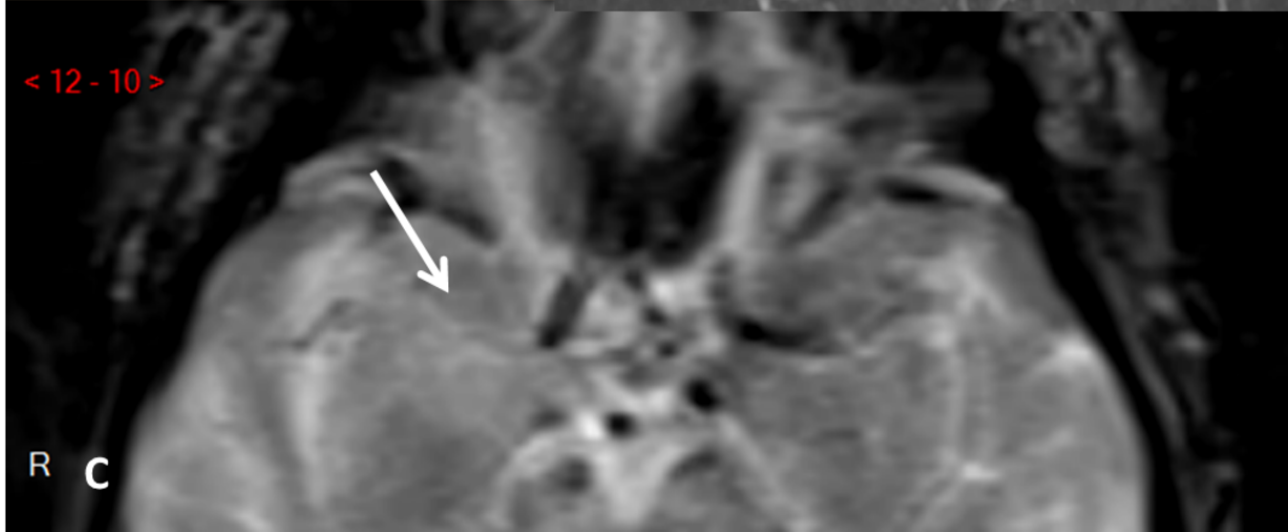
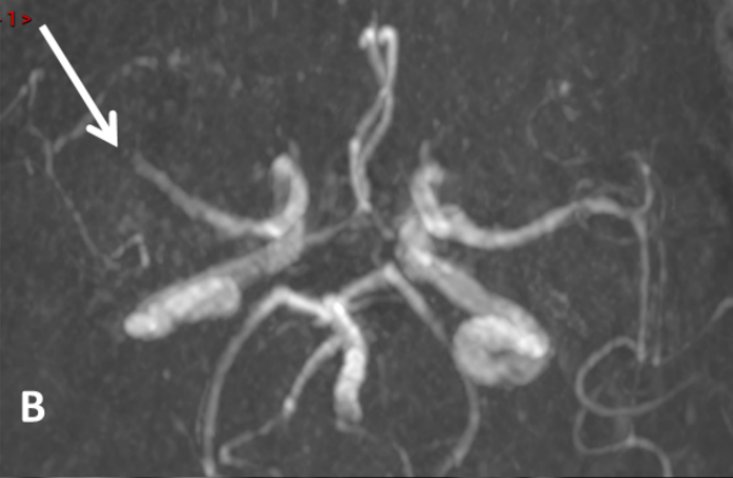
C: SVS occlusion in the left MCA (white arrow)

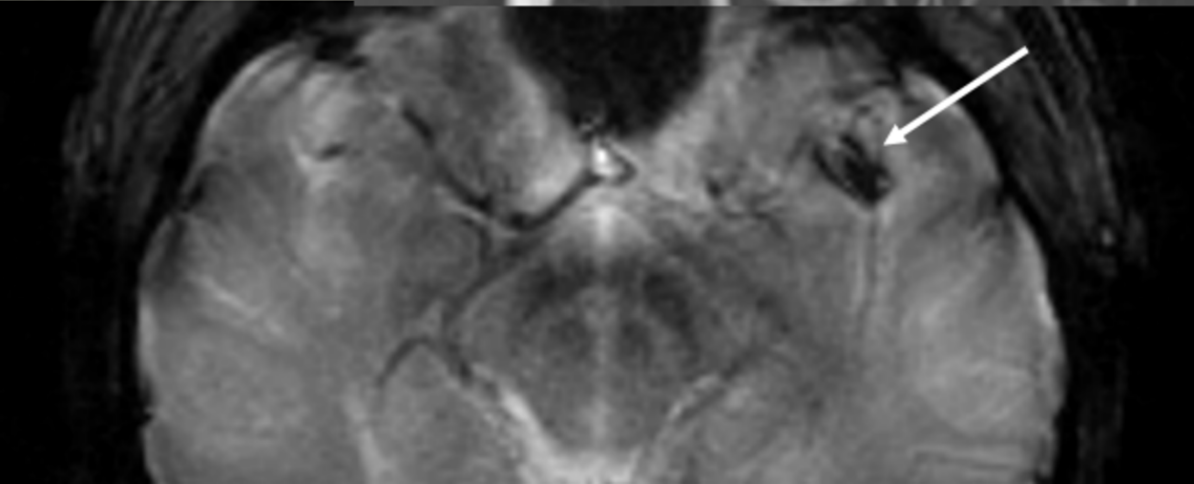
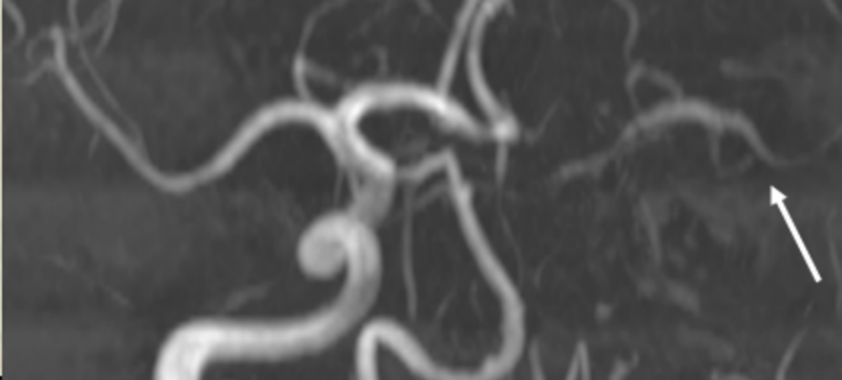
Figure 4.

A: A clot extracted from the patients, directly pictured. Macroscopic examination considered as a « red » clot

B: Corresponding MRI Time of flight confirming the acute terminaison of the right intern carotid occlusion (white arrow)

C: SVS occlusion in the right MCA (white arrow)





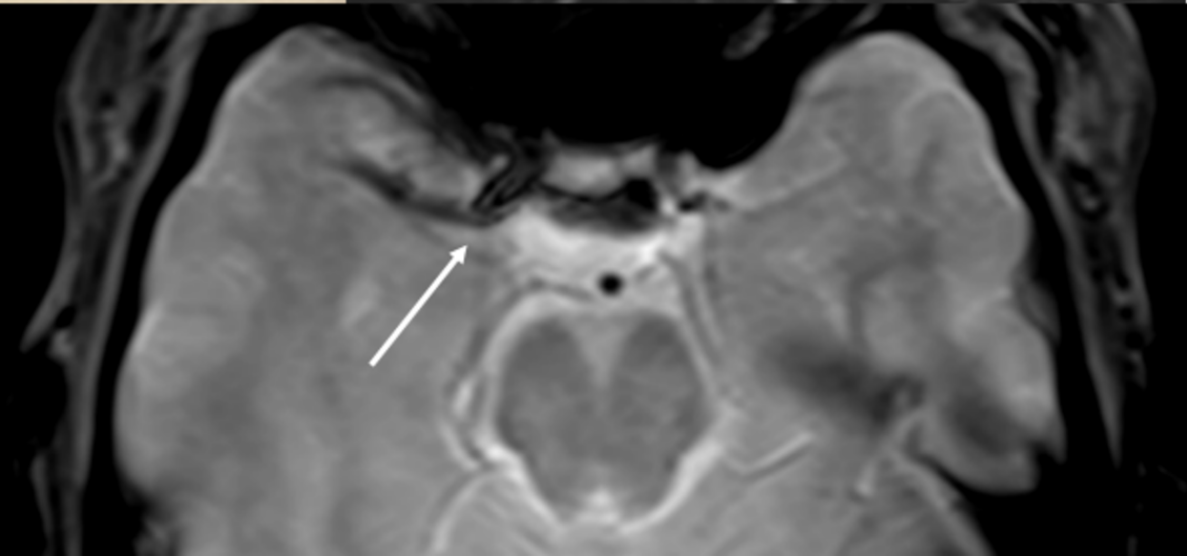
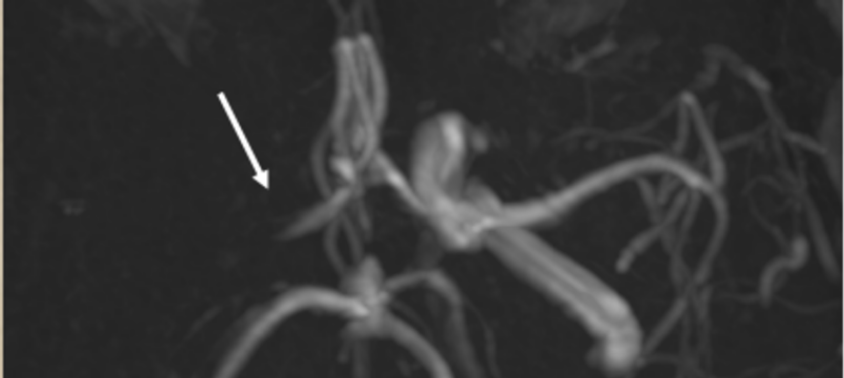


Table 1. Basic descriptive statistics for SVS + or SVS – patients

	SVS – (n = 22)	SVS + (n = 117)	P value
Female sex	7 (31.82%)	54 (46.15%)	0.25
Age - median (IQR)	66.00 (59.25 – 73.50)	71.00 (60.00 – 82.00)	0.61
Center 1	10 (45.45%)	44 (65.81%)	0.093
Red clot type	17 (77.27%)	114 (97.44%)	0.003
Baseline NIHSS- median (IQR)	16.00 (13.50 – 19.50)	17.00 (11.00-20.00)	0.35
MCA location of occlusions	15 (68.18%)	81 (69.23%)	1.0
IV tPA use	9 (40.91%)	60 (51.28%)	0.49
First Line MT strategy			0.50
-Aspiration	8 (36.6%)	55 (47.01%)	
-Combined	12 (54.55%)	48 (41.03%)	
-Stent	2 (9.09%)	14 (11.97%)	
Final reperfusion TIC1 ≥2B	20 (90.91%)	100 (85.47%)	0.74
NIHSS day one - median (IQR)	14.00 (5.25 – 20.75)	8.00 (2.00-19.00)	0.65
Any ICH			0.36
-No	14 (63.64%)	56 (47.86%)	
-Yes	7 (31.82%)	49 (41.88%)	
Functional independence at 3 months			0.95
-No	10 (45.45%)	50 (42.74%)	
-Yes	11 (50.00%)	60 (51.28%)	
CE stroke etiology	9 (40.91%)	62 (52.99%)	0.36

Abbreviations : SVS : susceptibility vessel sign, NIHSS : National Institutes of Health Stroke Scale, MCA: Middle cerebral artery, IV tPA : Intravenous recombinant tissue plasminogen activator, MT : mechanical thrombectomy, TIC1 : thrombolysis in cerebral infarction scale, ICH : intracerebral hemorrhage, CE : cardioembolism

Table 2. Basic descriptive statistics for TLSVS + or TLSVS - patients

	TLSVS – (n = 131)	TLSVS + (n = 8)	P value
Female sex	59 (45.04%)	2 (25%)	0.47
Age - median (IQR)	70.00 (58.50 – 82.00)	69.50 (66.75 – 72.25)	0.23
Center 1	82 (62.60%)	5 (62.50%)	1.0
Red clot type	123 (93.89%)	8 (100%)	1.0
Baseline NIHSS- median (IQR)	17 (11.00-20.00)	17.50 (12.00 – 24.00)	0.056
MCA location of occlusions	91 (69.47%)	5 (62.50%)	0.70
IV tPA use	63 (48.09%)	6 (75.00%)	0.17
First Line MT strategy			0.56
-Aspiration	59 (45.04%)	4 (50.00%)	
-Combined	56 (42.75%)	4 (50.00%)	
-Stent	16 (12.21%)	0 (0.00%)	
Final recanalization TIC1 ≥2B	114 (87.02%)	6 (75.00%)	0.30
NIHSS day one - median (IQR)	8.00 (3.00 – 19.00)	16.00 (1.00 – 42.00)	0.005
Any ICH			0.66
-No	65 (49.62%)	5 (62.50%)	
-Yes	54 (41.22%)	2 (25.00 %)	
Functional independence at 3 months			0.59
-No	56 (42.75%)	4 (50.00%)	
-Yes	68 (51.91%)	3 (37.50%)	
CE stroke etiology	67 (51.15%)	4 (50.00%)	1.0

Abbreviations : TLSVS : Two-Layered Susceptibility Vessel Sign ,NIHSS : National Institutes of Health Stroke Scale, MCA: Middle cerebral artery, IV tPA : Intravenous recombinant tissue plasminogen activator, MT : mechanical thrombectomy, TIC1 : thrombolysis in cerebral infarction scale, ICH : intracerebral hemorrhage, CE : cardioembolism

Table 3. Logistic regression for predictors of Red clot type

univariate analysis	OR	95%CI lower-bound	95%CI upper-bound	p value
Age	1,02	0,98	1,05	0,35
Female sex	1,10	0,33	3,89	0,88
Baseline NIHSS	1,02	0,92	1,12	0,71
Center 1	0,36	0,10	1,20	0,10
Final recanalization TIC1 \geq 2B	1,36	0,38	4,52	0,62
IV tPA use	1,02	0,30	3,41	0,98
MCA location of occlusions	1,51	0,80	3,35	0,26
TL-SVS	0,75	0,12	14,61	0,80
SVS	9,54	2,73	35,83	<0,0001
multivariate analysis	OR	95%CI lower-bound	95%CI upper-bound	p value
Center 1	0,53	0,14	1,94	0,10
SVS	8,31	2,30	32,00	<0,001

Abbreviations: SVS : susceptibility vessel sign, TLSVS : Two-Layered Susceptibility Vessel Sign NIHSS : National Institutes of Health Stroke Scale, IV tPA : Intravenous recombinant tissue plasminogen activator, MCA: Middle cerebral artery, TIC1 : thrombolysis in cerebral infarction scale.

Table 4. SVS and TLSVS diagnostic performances for the prediction of Red clot type

SVS diagnostic performances	Value	95%CI lower-bound	95%CI upper-bound
specificity	0,58	0,28	0,85
sensibility	0,87	0,80	0,93
npv	0,30	0,13	0,53
ppv	0,96	0,90	0,99
Accuracy	0,85	0,78	0,90
TLSVS diagnostic performances	Value	95%CI lower-bound	95%CI upper-bound
specificity	0,92	0,62	1,00
sensibility	0,06	0,03	0,12
npv	0,09	0,04	0,15
ppv	0,89	0,52	1,00
Accuracy	0,14	0,09	0,21

Abbreviations : SVS : susceptibility vessel sign, TLSVS : Two-Layered Susceptibility Vessel Sign, NPV: negative predictive value, PPV: Positive predictive value

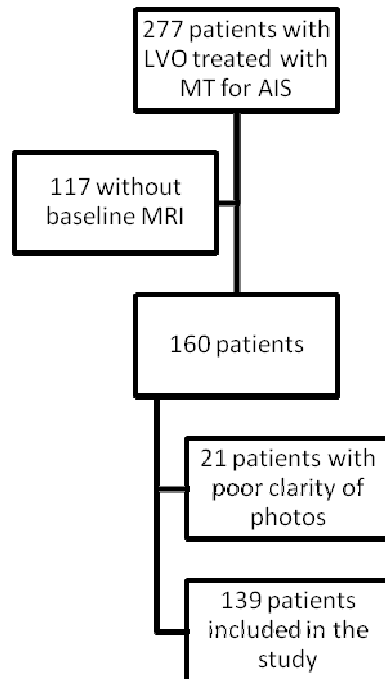


Figure 1.

Abbreviations : LVO : Large Vessel Occlusion, MRI : Magnetic Resonance Imaging, MT : mechanical thrombectomy, AIS : Acute ischemic stroke

