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Validation of overestimation ratio and TL-SVS as imaging biomarker of cardioembolic stroke and time from onset to MRI

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Abstract

Objective We aimed to determine in the "THRACE" trial, the clinical and MRI technical parameters associated with the two-layered susceptibility vessel sign (TL-SVS) and the overestimation ratio (overR).

Materials and methods Patients with pre-treatment brain gradient echo (GRE) sequence and an etiological work-up were identified. Two readers reviewed TL-SVS, i.e., a SVS with a linear low-intense signal core surrounded by a higher intensity and measured the overR as the width of SVS divided by the width of the artery. Binomial and ordinal logistic regression respectively tested the association between TL-SVS and quartiles of overR with patient characteristics, cardioembolic stroke (CES), time from onset to imaging, and GRE sequence parameters (inter slice gap, slice thickness, echo time, flip angle, voxel size, and field strength).

Results Among 258 included patients, 102 patients were examined by 3 Tesla MRI and 156 by 1.5 Tesla MRI. Intra- and inter-reader agreements for quartiles of overR and TL-SVS were good to excellent. The median overR was 1.59 (IQR, 1.30 to 1.86). TL-SVS was present in 101 patients (39.2%, 95%CI, 33.1 to 45.1%). In multivariate analysis, only CES was associated with overR quartiles (OR, 1.83; 95%CI, 1.11 to 2.99), and every 60 min increase from onset to MRI time was associated with TL-SVS (OR, 1.72; 95%CI, 1.10 to 2.67). MRI technical parameters were statistically associated with neither overR nor TL-SVS.

Conclusion Independent of GRE sequence parameters, an increased overR was associated to CES, while the TL-SVS is independently related to a longer time from onset to MRI.

Key Points

- *An imaging biomarker would be useful to predict the etiology of stroke in order to adapt secondary prevention of stroke.*
- *The two-layered susceptibility vessel sign and the overestimation ratio are paramagnetic effect derived markers that vary according to the MRI machines and sequence parameters.*
- *Independent of sequence parameters, an increased overestimation ratio was associated to cardioembolic stroke, while the two-layered susceptibility vessel sign is independently related to a longer time from onset to MRI.*

Catherine Oppenheim and Olivier Naggara contributed equally to this work.

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Keywords Thrombosis · Embolism · Magnetic resonance imaging · Stroke · Biomarkers

Abbreviations

AIS-LVO	Acute ischemic stroke patients with large vessel occlusion
CES	Cardioembolic stroke
GRE	Gradient echo
overR	Overestimation ratio
SWI	Susceptibility-weighted imaging
THRACE	THRombectomie des Artères CErebrales
TL-SVS	Two-layered susceptibility vessel sign

Background

Unraveling the etiology in acute ischemic stroke patients with large vessel occlusion (AIS LVO) is important because it could potentially affect secondary stroke prevention strategies. In many AIS LVO, however, risk factors for both a large artery atherosclerotic and cardioembolic stroke (CES) are present. Furthermore, for up to 30% of strokes, the exact etiology remains uncertain [1]. Thanks to the endovascular retrieving, thrombi composition could potentially provide an important clue regarding stroke etiology. However, no clear association between thrombus composition and etiology was found in the literature [2–9]. Further understanding of the association between imaging characteristics of the thrombus and etiology could be useful to help determine stroke etiology. The susceptibility vessel sign (SVS) on gradient echo (GRE) is defined as a hypo intense signal exceeding the diameter of the contralateral artery at the site of the thrombus [10]. The SVS is seen in 50–85% of cases of AIS LVO, particularly in the case of a red blood cell-dominant thrombus, whereas a lack of SVS is indicative for a fibrin-dominant thrombus [11–17]. The SVS has been related to the stroke etiology with variable reliabilities [2, 15, 18–20]. Recently, two characteristics of the SVS, overestimation ratio (overR), a quantitative evaluation of the SVS, and the two-layered SVS (TL-SVS) were reported to predict CES [19–21]. Hence, both TL-SVS and high overR were described to exhibit an almost perfect specificity for CES [19, 20]. However, these studies were retrospective, monocentric, and used time-consuming susceptibility-weighted imaging or 3.0 Tesla systems. Furthermore, numerous technical parameters are involved in the paramagnetic effect on which these radio markers rely on [22]. As a consequence, the diagnostic accuracy of SVS-derived markers to predict thrombus composition varies according the MRI machines [11]. We hypothesized that the range of technical parameters used for the GRE sequence acquisition in the multicentric THRACE trial would interfere with the visualization of the TL-SVS or with the magnitude of the overR. Hence, we aimed to determine in the multicentric THRACE study [23] the independent clinical and technical factors related to the TL-SVS and to the overR.

Materials and methods

THRACE study design

THRACE was a randomized controlled trial done in 26 centers in France. Study design and protocol were previously detailed [23]. Patients with acute ischemic stroke were eligible for inclusion if they were aged 18–80 years; had a US National Institutes of Health Stroke Scale score of 10–25; and had an occlusion of the intracranial internal carotid artery or the M1 segment of the middle cerebral artery on magnetic resonance angiography. Patients who had cervical internal carotid artery occlusion and sub occlusive stenosis were excluded. Patients were randomized (1:1) as soon as possible during intravenous thrombolysis to receive intravenous thrombolysis and mechanical thrombectomy or intravenous thrombolysis alone. Before randomization, written informed consent was obtained from all patients or their legal representatives. The study protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers.

Clinical and biological data

Clinical and biological data included age, gender, smoking rate, history of high blood pressure, diabetes mellitus, hypercholesterolemia, coronary artery disease, previous stroke, mean glycemia level at inclusion, topography of occlusion (M1 or ICA), and time from onset to imaging.

Stroke etiology was determined at the end of a complete etiological work-up by a stroke neurologist, according to Trial of Org 10172 in Acute Stroke Treatment classification [24].

Work-up for cardioembolic stroke

In THRACE trial, the recommended general work-up, according to the ESO Guidelines [25], included physiological parameters and routine blood tests, a 12-lead electrocardiography and continuous electrocardiography. In addition, a 24-h Holter electrocardiography monitoring was performed when arrhythmias were suspected and no other causes of stroke were found. The echocardiography was recommended when electrocardiography abnormalities or evidence of cardiac disease on history was reported or when no other identifiable causes of stroke were found.

Imaging data

In this prespecified post hoc analysis, we included patients with admission brain MRI with 2D GRE sequence. MRI acquisition parameters of the sequence were left to the discretion of the recruitment centers according to their routine practice without any standardization, but all the included patients were screened with a conventional GRE T2* (no echo planar acquisition). Hence, MRI and GRE sequence parameters recorded included slice thickness, inter slice gap, flip angle, echo time, field strength, and voxel acquisition size. Along with the GRE sequence, DWI, FLAIR, and TOF-MRA of the circle of Willis sequences were systematically performed.

Two readers, with 2 and 5 years of experience, blindly reviewed the TL-SVS images and performed the overR measurements. The second reader did this twice, 1 week apart, in order to analyze the intra-reader agreement. They searched for TL-SVS, i.e., an inhomogeneous susceptibility vessel sign with a linear low-intense signal core surrounded by a peripheral higher intensity signal [20]. The overR was manually measured according to the method previously described, i.e., overR = width of susceptibility vessel sign / width of large artery [21]. Note that the absence of the susceptibility vessel sign was considered as an overR = 1.

We excluded patients who were screened with a SWI instead of a GRE sequence because SWI was scarcely used in THRACE patients.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean (standard deviation) or median (interquartile range) for non-normal distribution. Normality of distributions was assessed graphically and by using the Shapiro-Wilk test. Main baseline clinical characteristics were described in included and non-included patients, and absolute standardized differences were calculated; values > 10% were interpreted as meaningful differences. Inter- and intra-reader agreements for TL-SVS and for quartiles of overR were assessed using unweighted Kappa for TL-SVS and weighted Kappa for the quartiles of overR with 95% confidence interval (CI).

Main analysis of association of clinical and MRI technical parameters with overR was done after categorization of overR into quartiles due to non-normal distribution. We firstly investigated the association of clinical and MRI technical parameters with overR quartiles and TV-SVS using generalized linear mixed models (logistic for TV-SVS and ordinal for overR quartiles) including centers as random effect. As a sensitivity analyses, we assessed the association of clinical and MRI technical parameters with overR treated as continuous variables using non-parametric tests (Mann-Whitney *U* test or Spearman's rank correlation coefficient). For overR quartiles and TV-SVS, a multivariable generalized linear mixed model was performed by including clinical and MRI technical parameters with a p value < 0.20 in center-adjusted analyses. Statistical testing was conducted at the level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute).

Results

Among 412 patients included in the THRACE trial (between June 2010 and February 2015), 301 were MRI-based selection for revascularization treatment. Of these 301 patients, 43 patients were excluded due to poor imaging quality ($n = 9$), absence of GRE sequence ($n = 5$), or no information on Trial of Org 10172 in Acute Stroke Treatment classification ($n = 29$) (Fig. 1). Main baseline characteristics of included and non-included patients are reported in supplemental Table 1. Included patients were older, less often current smokers, and have more often hypertension, hypercholesterolemia, and history of stroke than excluded patients (absolute standardized difference > 10%). Of the 258 included patients, 102 patients were examined by 3 Tesla MRI and 156 by 1.5 Tesla MRI. Inter-reader agreement for quartiles of overR and TL-SVS was 0.79 (95% CI, 0.74–0.83) and 0.87 (95% CI, 0.80–0.93), respectively. Intra-reader agreement for quartiles of overR and TL-SVS was 0.82 (95% CI, 0.79–0.85) and 0.90 (95% CI, 0.85–0.95), respectively.

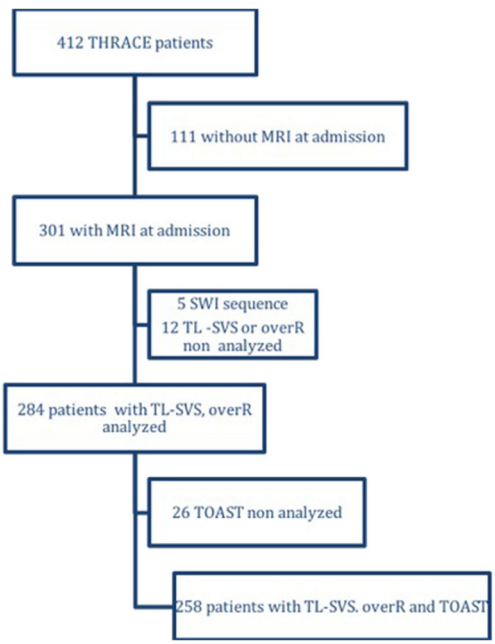

Fig. 1 Inclusion Flowchart. THRACE, THRombectomie des Artères CErebrales; SWI, susceptibility-weighted imaging; TL-SVS, two-layered susceptibility vessel sign; overR, overestimation ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment

Table 1 Univariate associations of overestimation ratio with clinical and MRI technical parameters

	Overestimation ratio (quartiles)					
	< 25th ($n = 64$)	25th to 49th ($n = 65$)	50th to 74th ($n = 65$)	≥ 75th ($n = 64$)	OR (95%CI)[a]	p
Overestimation ratio, median (range)	1.00 (1.00 to 1.29)	1.46 (1.30 to 1.58)	1.74 (1.59 to 1.85)	2.08 (1.86 to 2.90)		
Demographics and clinical						
Age, years, median (IQR)	66 (49 to 73)	67 (51 to 76)	64 (50 to 73)	71 (59 to 75)	1.13 (0.97 to 1.33)[b]	0.11
Men	34 (53.1)	36 (55.4)	32 (49.2)	35 (54.7)	0.99 (0.63 to 1.54)	0.95
Current smoking	20 (33.3)	10 (17.2)	17 (27.4)	12 (20.7)	0.74 (0.43 to 1.26)	0.26
Hypertension	36 (56.2)	29 (45.3)	27 (42.2)	38 (59.4)	1.05 (0.67 to 1.64)	0.82
Hypercholesterolemia	29 (52.7)	36 (63.2)	23 (37.1)	34 (61.8)	0.99 (0.61 to 1.58)	0.96
Diabetes	9 (14.1)	3 (4.6)	4 (6.3)	8 (12.7)	0.93 (0.43 to 1.98)	0.85
History of CAD	6 (9.8)	7 (11.1)	8 (12.9)	11 (17.7)	1.59 (0.81 to 3.12)	0.18
History of stroke	5 (7.8)	5 (7.9)	3 (4.8)	4 (6.4)	0.78 (0.32 to 1.90)	0.59
Admission glycemia, mg/dl[a], median (IQR)	110 (99 to 124)	122 (104 to 137)	117 (101 to 136)	119 (103 to 144)	1.14 (0.65 to 1.99)[c]	0.65
MCA occlusion	54 (84.4)	59 (90.8)	55 (84.6)	49 (76.6)	0.62 (0.33 to 1.14)	0.12
Cardioembolic stroke	15 (23.4)	31 (47.7)	26 (40.0)	34 (53.1)	1.95 (1.24 to 3.07)	0.004
MRI parameters						
Time from onset to MRI, min, median (IQR)	111 (42)	113 (38)	113 (36)	117 (31)	1.16 (0.81 to 1.67)[d]	0.41
3 Tesla	28 (43.8)	27 (41.5)	23 (35.4)	24 (37.5)	0.81 (0.51 to 1.28)	0.36
Voxel size, μm, mean (SD)	3.9 (1.2)	4.2 (1.2)	4.0 (0.9)	4.1 (1.0)	1.02 (0.83 to 1.25)	0.84
Flip angle, degree					1.10(0.78 to 1.54)[f]	0.57[f]
< 20	28 (43.7)	24 (36.9)	28 (43.1)	21 (32.8)	1.00 (ref.)	–
20	30 (46.9)	30 (46.2)	29 (44.6)	37 (57.8)	1.30 (0.81 to 2.09)	0.23
> 20	6 (9.4)	11 (16.9)	8 (12.3)	6 (9.4)	1.06 (0.51 to 2.20)	0.89
Echo time, ms,median (IQR)	17 (15 to 20)	18 (16 to 23)	18 (15 to 23)	20 (16 to 25)	1.04 (0.88 to 1.23)[e]	0.62
Inter slice gap, mm					0.97 (0.75 to 1.26)[f]	0.82[f]
0.0	24 (38.1)	25 (39.1)	22 (33.9)	25 (40.3)	1.00 (ref.)	–
0.0 to 0.9	17 (27.0)	17 (26.5)	13 (20.0)	20 (32.3)	1.07 (0.60 to 1.87)	0.83
≥ 1.0	22 (34.9)	22 (34.4)	30 (46.1)	17 (27.4)	0.94 (0.56 to 1.58)	0.82
Slice thickness, mm					1.36 (0.81 to 2.26)[f]	0.24[f]
< 5.0	8 (12.5)	11 (16.9)	6 (9.2)	6 (9.4)	1.00 (ref.)	–
5.0	53 (82.8)	50 (76.9)	53 (81.6)	53 (82.8)	1.33 (0.67 to 2.63)	0.41
> 5.0	3 (4.7)	4 (6.2)	6 (9.2)	5 (7.8)	1.85 (0.64 to 5.30)	0.25

Values are no./no. total (%) unless otherwise as indicated

CAD coronary artery disease, *CI* confidence interval, *IQR* interquartile range, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *OR* odds ratio, *SD* standard deviation

[a] Common OR for quartile increase in overestimation ratio (calculated using mixed ordinal logistic regression models including center as random effect)

[b] OR per 10-year increase

[c] OR per 100 mg/dl increase

[d] OR per 60-min increase

[e] OR per 10-min increase

[f] OR calculated by treating the variable as an ordinal categorical variable

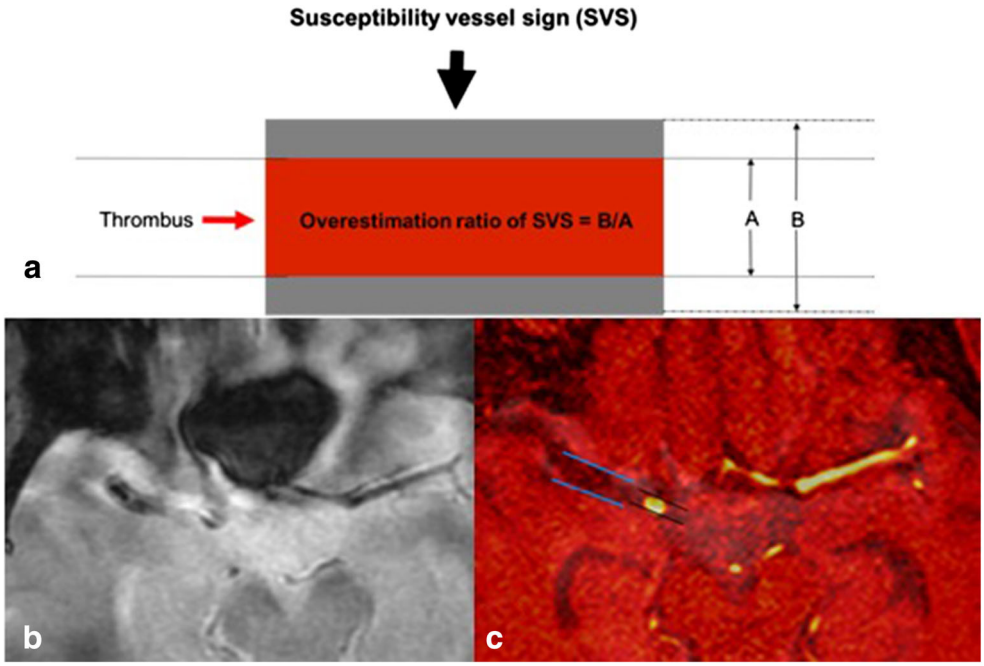

Fig. 2 Overestimation ratio measurement. **a** Illustration of overestimation ratio measurement. **b**, **c** Susceptibility vessel sign (SVS) and overestimation ratio of SVS. A 69-year-old man with right middle cerebral artery occlusion whose overestimation ratio of SVS was 2.21 was found of cardiogenic embolism. The sequences of magnetic resonance imaging from (**b**), T2*-weighted gradient echo (GRE) images showing SVS (arrowheads) and (**c**), the coregistered images of TOF-MRA and T2*-GRE image

Table 2 Univariate associations of the two-layered susceptibility vessel sign with clinical and MRI technical parameters

	Two-layered susceptibility vessel sign			
	No ($n = 157$)	Yes ($n = 101$)	OR (95%CI)[a]	p
Demographics and clinical				
Age, years, median (IQR)	66 (51 to 74)	68 (57 to 74)	1.08 (0.89 to 1.30)[b]	0.42
Men	82 (52.2)	55 (54.5)	0.86 (0.51 to 1.44)	0.56
Current smoking	40 (27.0)	19 (21.1)	0.73 (0.38 to 1.40)	0.34
Hypertension	78 (50.3)	52 (51.5)	1.03 (0.61 to 1.72)	0.91
Hypercholesterolemia	73 (52.9)	49 (53.9)	1.03 (0.59 to 1.78)	0.93
Diabetes	17 (10.8)	7 (7.1)	0.65 (0.25 to 1.65)	0.36
History of CAD	18 (11.9)	14 (14.4)	1.27 (0.59 to 2.72)	0.54
History of stroke	8 (5.2)	9 (9.1)	1.81 (0.66 to 4.94)	0.25
Admission glycemia, g/l[a], median (IQR)	117 (100 to 141)	114 (104 to 135)	0.61 (0.27 to 1.34)[c]	0.21
MCA occlusion	136 (86.6)	81 (80.2)	0.62 (0.31 to 1.24)	0.18
Cardioembolic stroke	59 (37.6)	47 (46.5)	1.63 (0.96 to 2.75)	0.07
MRI parameters				
Time from onset to MRI, min, median (IQR)	109 (39)	121 (32)	1.74 (1.13 to 2.68)[d]	0.012
3 Tesla	55 (35.0)	47 (46.5)	1.57 (0.88 to 2.80)	0.13
Voxel size, μm, mean (SD)	4.1 (1.1)	4.0 (1.0)	0.93 (0.71 to 1.21)	0.58
Flip angle, degree			0.88 (0.57 to 1.34) [f]	0.55[f]
< 20	62 (39.5)	39 (38.6)	1.00 (ref.)	–
20	71 (45.2)	55 (54.5)	1.33 (0.73 to 2.43)	0.35
> 20	24 (15.3)	7 (6.9)	0.50 (0.18 to 1.38)	0.18
Echo time, ms, median (IQR)	18 (16 to 23)	18 (16 to 23)	0.89 (0.68 to 1.17)[e]	0.39
Inter slice gap, mm			0.78 (0.56 to 1.09)[f]	0.14[f]
0.0	51 (33.3)	45 (44.5)	1.00 (ref.)	–
0.0 to 0.9	42 (27.5)	25 (24.8)	0.61 (0.31 to 1.19)	0.15
≥ 1.0	60 (39.2)	31 (30.7)	0.74 (0.35 to 1.58)	0.43
Slice thickness, mm			1.40 (0.72 to 2.71)[f]	0.31[f]
< 5.0	22 (14.0)	9 (9.9)	1.00 (ref.)	–
5.0	123 (78.4)	86 (85.2)	1.65 (0.69 to 3.91)	0.25
> 5.0	12 (7.6)	6 (5.9)	1.60 (0.40 to 6.37)	0.50

Values are n(%) unless otherwise as indicated

CAD coronary artery disease, *CI* confidence interval, *IQR* interquartile range, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *OR* odds ratio, *SD* standard deviation

[a] OR of two-layered susceptibility vessel sign (calculated using mixed logistic regression models including center as random effect)

[b] OR per 10-year increase

[c] OR per 100 mg/dl increase

[d] OR per 60-min increase

[e] OR per 10-min increase

[f] OR calculated by treating the variable as an ordinal categorical variable

Table 3 Multivariate analysis of clinical and MRI technical parameters associated with overestimation ratio and two-layered susceptibility vessel sign

	OR (95%CI)	*p*
Model 1 (overestimation ratio)		
Age per 10 increase	1.06 (0.89 to 1.26)	0.50
History of CAD	1.34 (0.87 to 2.66)	0.40
MCA occlusion	0.66 (0.35 to 1.22)	0.18
Cardioembolic stroke	1.83 (1.11 to 2.99)	0.016
Model 2 (two-layered susceptibility vessel sign)		
MCA occlusion	0.63 (0.30 to 1.30)	0.21
Cardioembolic stroke	1.65 (0.96 to 2.85)	0.071
Onset to MRI time per 60 min increase	1.72 (1.10 to 2.67)	0.017
3 Tesla	1.33 (0.85 to 2.08)	0.20
Inter slice gap per 1-mm increase[a]	0.86 (0.59 to 1.27)	0.45

CAD coronary artery disease, *CI* confidence interval, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *OR* odds ratio

[a] Multivariable generalized linear mixed model (logistic or ordinal) including clinical and MRI technical parameters with a *p* value < 0.20 in center-adjusted analyses

Overestimation ratio (Fig. 2)

Distribution of overR was not normal, with 17.1% ($n = 44$) of patients having a value of 1.0. The median overR was 1.59 (IQR, 1.30 to 1.86). Main clinical and MRI technical parameters are described according to overR quartiles in Table 1. In center-adjusted analyses, increase in overR quartiles was only significantly associated with CES (common OR, 1.95%; 95%CI, 1.24 to 3.07). None of MRI technical parameters were associated with overR quartiles. Similar results were found when overR was analyzed as continuous variables using non-parametric tests, except a significant weak correlation with echo time ($r = 0.13$, $p = 0.036$; supplemental Table 2). In multivariate analysis including variables associated with center-adjusted $p < 0.20$, CES remained associated with overR quartiles (Table 3).

Two-layered susceptibility vessel sign (Fig. 3)

TL-SVS was present in 101 patients (39.2%, 95%CI, 33.1 to 45.1%). As shown in Table 2, after adjustment for center, only time from onset to MRI was associated with TL-SVS, with an OR per 60 min increase of 1.74 (95%CI, 1.13 to 2.68). A non-significant association was found with CES (OR, 1.63; 95%CI, 0.96 to 2.75). Similarly than overR, none of MRI technical parameters were associated with TL-SVS. In multivariate analysis including variables associated with center-adjusted $p < 0.20$, increase in time from onset to MRI remained associated with TL-SVS (Table 3).

Discussion

The main finding of our work is that, independent of GRE sequence parameters, an increase overR is associated to CES, while the TL-SVS is independently related to a longer time from onset to MRI.

Studies on human thrombi retrieved from AIS LVO patients have revealed varying compositions [3, 6, 8, 9], but published articles failed to found a reliable and reproducible association between the thrombi histology, imaging characteristics, and stroke etiology [2]. Indeed, there is inherent bias in assessing histologic characteristics of thrombi retrieved in vivo in relation to the imaging or to the stroke etiology: IVT is administrated before histological analysis and only the thrombi retrieved are available for analysis, which might bias the analysis [26, 27]. Hence, the imaging characteristics of thrombi could provide a relevant shortcut towards the stroke etiology "by

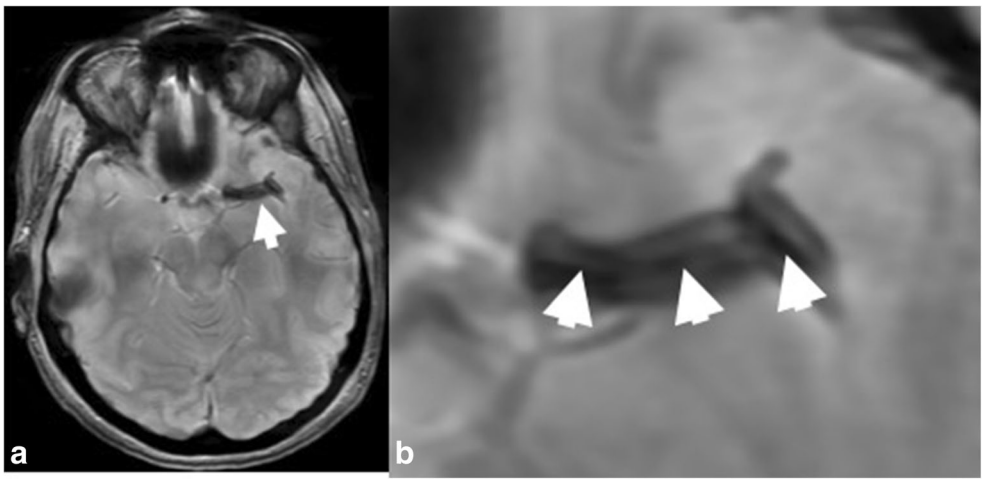

Fig. 3 **a**, **b** Two-layered susceptibility vessel sign (TL-SVS). A 62-year-old man with left middle cerebral artery (MCA) occlusion because of cardioembolism. 1.5-Tesla (T)-T2*-weighted gradient echo (GRE) imaging scan (white arrow) showing a two-layered SVS with a low-intense signal core (arrowheads) surrounded by a higher intensity signal

pass" of the histological examination. Two recent retrospective studies using 3.0T systems analyzed separately diagnostic accuracies of TL-SVS and overR for CES prediction. Authors found a specificity of 97% and 91%, respectively, of TL-SVS and an overR cutoff of 2.01 for predicting CES [19–21]. In our study, we have been able to precisely record the relevant GRE sequence parameters in order to analyze their weight in the presence of the TL-SVS and the overR. Indeed, the SVS effects (TL-SVS and overR) are due to the presence of a paramagnetic blood clot that induces local magnetic field heterogeneities, proportional to the static magnetic field (B0). As a consequence, the diagnostic accuracy of SVS to predict thrombus composition varies according the MRI machines [11]. We demonstrated that, in real world conditions including brain MRI performed in 26 different centers on either 1.5 or 3.0T MR unit, using less-than-a-minute GRE sequence, contrary to the TL-SVS, the overR remains associated with CES.

Furthermore, we showed a significant and independent relation between time from onset to imaging and the TL-SVS. As a clot ages, the hemoglobin passes through several forms (oxyhemoglobin, deoxyhemoglobin, and methemoglobin) prior to red cell lysis and breakdowns into ferritin and hemosiderin [28, 29]. Many patients with wake-up or unknown time of onset stroke are excluded from recanalization treatment. If DWI-FLAIR mismatch is a crucial imaging biomarker in the management of such patients, its interpretation is often difficult [30] and may benefit of an additional biomarker to date the occlusion.

The present prospective study is the largest to date that has evaluated the TL-SVS and the overR in the context of stroke. We acknowledge limitations, including that THRACE was not a trial designed to specifically investigate stroke etiology. However, work-ups were performed in referral comprehensive stroke centers that ensure for high quality and extensive etiological work-up, gating with the guidelines [25]. Second, no information was registered on anticoagulation regimen, the use of antiplatelet or the platelet count before imaging, all factors that may have influenced the thrombus composition, and thus the paramagnetic effects in it [31, 32]. Third, 111/412 patients were excluded since an admission brain CT was performed rather than MRI. In addition, 17/301 patients with admission MRI were excluded from analysis for technical reasons (low imaging quality or no GRE-T2*). However, included and excluded patient groups were similar for demographical and clinical baseline characteristics (supplemental Table 1). Fourth, the application of our results is exclusively restricted to patients screened with MRI. Further studies must validate new computed tomography imaging biomarkers of CES. Last, bandwidth, another technical parameter that may also influence susceptibility radio marker evaluation, has not been recorded.

Conclusion

Independent of GRE sequence parameters, an increase overR is associated to CES, while the TL-SVS is independently related to a longer time from onset to MRI. These results, from the largest serie to date, could be useful for the comprehensive use of these radio markers in clinical practice.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hubert Desal, head of the Department of Neuroradiology, University Hospital of Nantes France.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry J. Labreuche from the Centre Hospitalier Regional Universitaire de Lille, Biostatistics, Lille, Hauts-de-France, France, kindly provided statistical advice for this manuscript.

Informed consent Before randomization, written informed consent was obtained from all patients or their legal representatives.

Ethical approval The study protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers.

Methodology
- Prospective
- Diagnostic or prognostic study
- Multicenter study

Disclaimer The trial steering committee attests to the integrity of the trial, the fidelity of this report to the study protocol, and the completeness and accuracy of the reported data.

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