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Cerebral small vessel disease modifies outcomes after minimally invasive surgery for intracerebral haemorrhage

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ABSTRACT

Background Minimally invasive surgery (MIS) for spontaneous supratentorial intracerebral haemorrhage (ICH) is controversial but may be beneficial if end-of-treatment (EOT) haematoma volume is reduced to ≤15 mL. We explored whether MRI findings of cerebral small vessel disease (CSVD) modify the effect of MIS on long-term outcomes.

Methods Prespecified blinded subgroup analysis of 288 subjects with qualified imaging sequences from the phase 3 Minimally Invasive Surgery Plus Alteplase for Intracerebral Haemorrhage Evacuation (MISTIE) trial. We tested for heterogeneity in the effects of MIS and MIS+EOT volume ≤15 mL on the trial's primary outcome of good versus poor function at 1 year by the presence of single CSVD features and CSVD scores using multivariable models.

Results Of 499 patients enrolled in MISTIE III, 288 patients had MRI, 149 (51.7%) randomised to MIS and 139 (48.3%) to standard medical care (SMC). Median (IQR) ICH volume was 42 (30–53) mL. In the full MRI cohort, there was no statistically significant heterogeneity in the effects of MIS versus SMC on 1-year outcomes by any specific CSVD feature or by CSVD scores (all $P_{interaction}$ >0.05). In 94 MIS patients with EOT ICH volume ≤15 mL, significant reduction in odds of poor outcome was found with cerebral amyloid angiopathy score <2 (OR, 0.14 (0.05–0.42); $P_{interaction}$=0.006), absence of lacunes (OR, 0.37 (0.18–0.80); $P_{interaction}$=0.02) and absence of severe white matter hyperintensities (WMHs) (OR, 0.22 (0.08–0.58); $P_{interaction}$=0.03).

Conclusions Following successful haematoma reduction by MIS, we found significantly lower odds of poor functional outcome with lower total burden of CSVD in addition to absence of lacunes and severe WMHs. CSVD features may have utility for prognostication and patient selection in clinical trials of MIS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Brain imaging biomarkers of cerebral small vessel disease (CSVD) are associated with an increased risk of recurrence of intracerebral haemorrhage (ICH) and with poor outcomes in predominantly lobar haemorrhages. It is not known whether functional outcomes vary by these brain imaging findings in patients undergoing surgical haematoma removal by minimally invasive surgery (MIS), where efficacy remains controversial and specific patient groups who may benefit have not been fully defined.

WHAT THIS STUDY ADDS

⇒ In this analysis of clinical trial data, the total burden of CVSD on brain MRI and especially that of severe white matter hyperintensities and lacunes significantly modified the effect of successful MIS on unfavourable outcome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ At this time, minimally invasive techniques cannot be recommended as routine care for patients with ICH. This study finds evidence that baseline CSVD affects long-term outcomes following successful MIS for ICH. This could lead to more efficient clinical trial selection criteria and help predict which patients are likely to have good versus poor outcomes.

INTRODUCTION

The pathophysiology of spontaneous intracerebral haemorrhage (ICH) reflects injury to small cerebral blood vessels.[1] The frequent use of MRI following ICH has resulted in characterisation of multiple markers for cerebral small vessel disease (CSVD),[2–8] identified as risk factors for both ICH[9] and cerebral amyloid angiopathy (CAA)[10] and for unfavourable outcome following ICH.[1 11] For example, presence of cerebral microbleeds (CMBs) and total burden of CSVD are associated with significantly lower odds of achieving functional independence[11] and several studies have identified correlations between severity of white matter hyperintensity (WMH) and poor outcome after ICH.[12–14] More recently, cumulative scores of CSVD such as the CSVD burden score[15] and the CAA score[16] have shown potential for risk stratification and predictive value for outcomes post-ICH.

ICH is the highest severity stroke subtype, with over 40% case-fatality at 30 days and less than one-third of survivors functionally independent after 12 months.[17 18] Large clinical trials are investigating ICH evacuation using

minimally invasive surgery (MIS), though none have been definitive in demonstrating improvement in functional outcome. Prediction of outcomes and selection of surgical candidates is challenging, as most clinically useful outcome scales focus on baseline characteristics and acute imaging findings without consideration of underlying cerebral pathology. Recommendations for patient selection criteria with the most opportunity to benefit from surgical evacuation are not supported by the current literature.

The phase 3 Minimally Invasive Surgery Plus Alteplase for Intracerebral Haemorrhage Evacuation (MISTIE III) trial[19] did not show a significant improvement in the primary outcome, modified Rankin Score (mRS) 0–3 at 1 year in favour of MIS. In a prespecified primary subgroup analysis, MIS patients achieving end-of-treatment (EOT) volume ≤15 mL demonstrated significant improvement in the primary outcome compared with standard medical care (SMC). Whether pre-existing specific CSVD lesions modify the effects of MIS on outcomes is unknown. To further explore these effects, we collected MRI scans performed on all MISTIE III participants at randomisation and conducted primary subgroup analyses of five components of CSVD: severe WMH, lacunar infarcts, CMBs ≥5, cortical superficial siderosis (cSS) and enlarged perivascular spaces (EPVS). We also analysed two previously reported cumulative CSVD scores[15 20] and a cumulative modified CSVD (mCSVD) score (one point per feature) to determine effect modification of CSVD burden on unfavourable outcome.

METHODS

Study design

This represents a prespecified secondary data analysis from the multicentre, randomised, controlled trial, MISTIE III, which ran from 30 December 2013 to 4 September 2018. Ethics committees at each study site approved the parent trial protocol, and each participant or their legally authorised representative signed written informed consent before enrolment.[19] Additionally, the Johns Hopkins Medicine institutional review board approved this study.

Brain imaging protocol

The MRI analysis included participants with: (1) one of two study MRI scans obtained during hospital stay, at baseline, preferentially, otherwise, at 7–10 days after randomisation and (2) MRI with adequate quality sequences for assessment of CSVD markers, including T1, T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), T2-weighted gradient-recalled echo (GRE) or axial susceptibility-weighted imaging (SWI) and diffusion-weighted imaging sequences.

Imaging acquisition and analysis

Trained image readers blinded to outcomes used semi-automated CT planimetry to calculate ICH and intraventricular haemorrhage (IVH) volumes. Deep ICH required haematoma in included selective involvement of thalami, basal ganglia or both.[21] Lobar ICH required selective haematoma in cerebral cortex, underlying white matter or both. Parenchymal haematoma volume at 72 hours after final alteplase dose was designated EOT volume.

All MRI scans were performed on 1.5T to 3.0T scanners. We prespecified five CSVD features according to the Standards for Reporting Vascular changes in neuroimaging (STRIVE) consensus[6]: lacunar infarcts, WMHs, EPVS, CMBs and cSS. Definitions were as follows: lacunar infarct indicates a round or ovoid, subcortical or deep, fluid-filled cavity 3–15 mm in diameter, assessed on FLAIR; WMHs of presumed vascular origin, hyperintense on T2-weighted sequences and could appear isointense or hypointense on T1; EPVS, fluid-filled spaces that follow the typical course of a vessel as it penetrates grey or white matter; CMBs, round signal voids with associated blooming around 2–10 mm identified on T2-weighted GRE or SWI sequences; and cSS, a distinct pattern of hypointense blood-breakdown products on T2-weighted GRE or SWI images representing hemosiderin deposition limited to cortical sulci.[22]

All MRI images were independently reviewed by three expert investigators (YL, S-MC and HA) with blinding to other data; a fourth investigator (WCZ) adjudicated discordant findings. All analyses were performed on OsiriX MD (V.9.0.1). The mean inter-rater agreement was 0.82, based on 10% of randomly selected MRI scans.

We recorded presence and location (lobar or deep) of lacunar infarcts. CMBs were graded by a 5-point ordinal scale (0, 1, 2–4, 5–10 and >10 CMBs) and classified as lobar or deep and by total burden. WMH was assessed by Fazekas scale with a degree from 0 (no or single punctate lesion) to 3 (large confluent lesions).[23] Severe WMHs were defined as deep Fazekas score 2–3 or >3 in total. EPVS were evaluated at two locations, including basal ganglia and centrum semiovale, with rating of 0–4 (0, 1–10, 11–20, 21–40 and >40 EPVS). cSS were classified by occurrence and as focal (≤3 sulci) or disseminated (≥4 sulci).[22] All classifications were prespecified.

CSVD burden

We analysed CSVD severity using three grading tools: the original CSVD burden score,[15] the CAA score[20] and a mCSVD score. The original CSVD burden score and CAA score scores differ on criteria for number and location of CMBs and EPVS and use of lacunes (only included in CSVD score) and cSS (only included in CAA score). The mCSVD score combines features of both the original CSVD score and the CAA score as a 5-point ordinal score, with each domain contributing a single point: lacune (present vs absent), microbleed (≥5 total CMBs vs <5), severe EPVS in basal ganglia region (grade 3–4), severe WMHs (deep Fazekas score 2–3 or >3 in total) and cSS (present vs absent).

Outcomes

Functional status was evaluated by mRS at 365 days after symptom onset with independent adjudication at the University of Glasgow, Scotland, UK. mRS scores were dichotomised as favourable (mRS 0–3) and unfavourable (mRS 4–6) outcomes, as prespecified in the trial.

Statistical analysis

Data are reported as mean with corresponding SD, or as median with IQR, depending on normality of the distribution. Similarly, Wilcoxon rank-sum test or Student's t-test was used for continuous variables, and the χ^2 test for categorical variables.

We describe small vessel disease lesions by outcome group. We then investigated whether original CSVD burden score,[15] CAA score,[20] the mCSVD score and individual components thereof were associated with unfavourable outcome as expected.[12–14] We compared clinical characteristics between favourable and unfavourable outcome using univariable analysis with appropriate tests. Baseline variables with a predetermined significance of $p<0.1$ on univariable analysis were entered into logistic regression models. We evaluated heterogeneity of the effect of MIS on 1-year outcome between subgroups (SMC vs MIS, SMC vs ≤15 mL EOT volume and MIS with >15 vs ≤15 mL EOT volume) by including an interaction term between treatment group and each imaging feature (lacunes: presence vs absence; CMBs ≥5 vs <5; severe basal ganglia EPVS vs not severe; severe WMH vs not severe; CSS presence vs absence; CSVD burden score >1, CAA score >1 and mCSVD score >1 (vs <2 for all)), in regression models adjusted for age, Glasgow Coma Scale (GCS), baseline ICH volume, IVH present at baseline, lobar ICH, diabetes and admission systolic blood pressure. We performed separate regression models for each imaging feature. No adjustment was made for multiple comparisons as all analyses were considered exploratory.

Stata V.14.0 (College Station, Texas, USA) and R software V.4.0.2 were used for all analyses. We determined area under the receiver-operating characteristic curve for each model to compare sensitivity and specificity of the three scores for CSVD. The optimal threshold of each score was calculated by Youden's Index. All analyses were two-tailed, and $p<0.05$ was deemed significant.

Data availability

Data can be requested from the corresponding author after submitting a proposal and completing a data access agreement.

RESULTS

MISTIE III enrolled 499 patients, of whom 288 patients (139 of 249 (48.3%) in SMC group and 149 of 250 (51.7%) in surgical group) had at least one MRI and full clinical data (figure 1). Patients without available MRI (n=211) were compared with those with MRI (online supplemental table 1). Hypertension and coronary artery

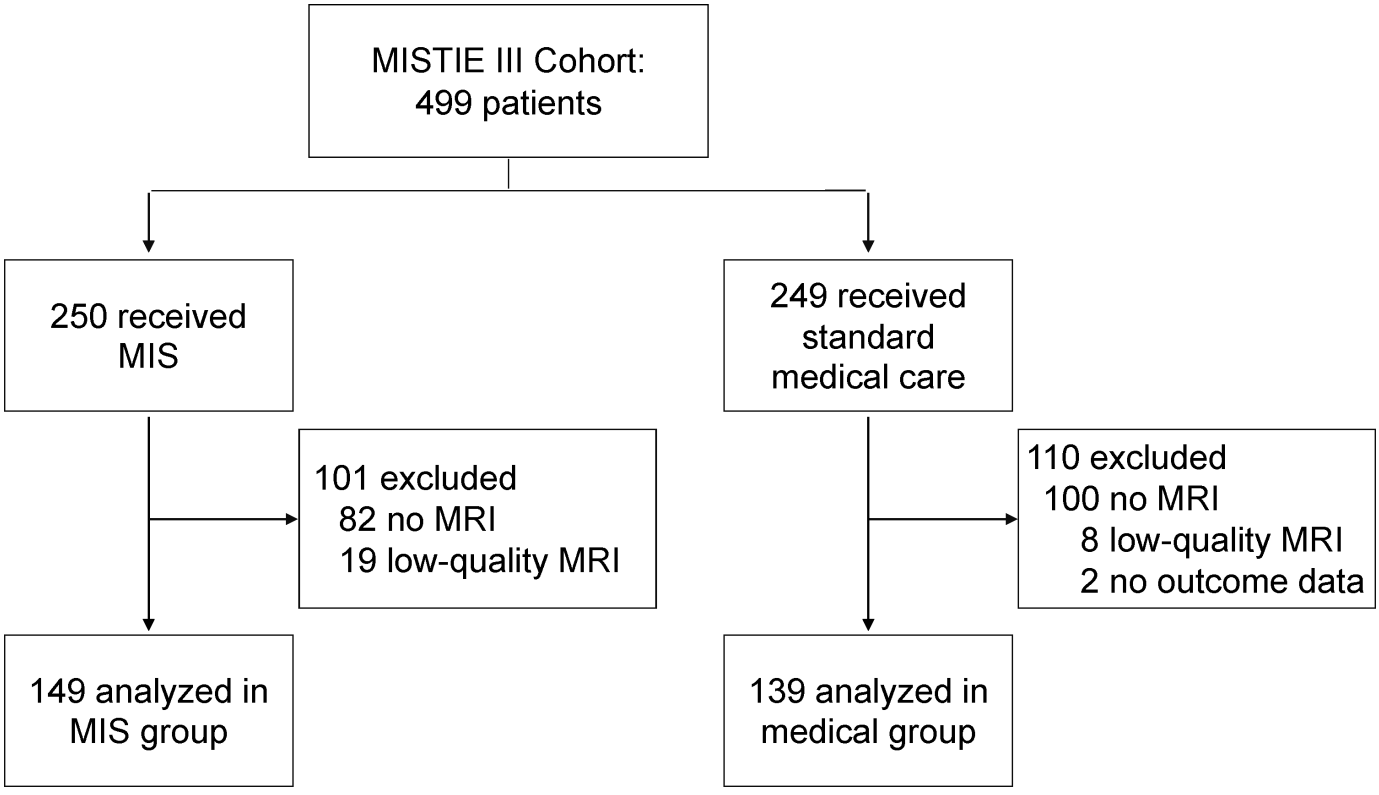

Figure 1 Flowchart of patients from MISTIE III trial. MIS, minimally invasive surgery; MISTIE III, phase III minimally invasive surgery plus alteplase for intracerebral haemorrhage evacuation.

Table 1 Baseline characteristics of participants in the MRI substudy

	Standard medical care (n=139)	MISTIE (n=149)	EOT volume ≤15 mL (n=94)
Sex, number (%)			
Male	85 (61)	89 (60)	56 (60)
Female	56 (39)	60 (40)	38 (40)
Age, median (IQR), years	62 (52–71)	62 (52–68)	63 (52–69)
Hypertension, number (%)	137 (99)	143 (96)	92 (98)
Diabetes, number (%)	45 (32)	45 (30)	27 (29)
Coronary artery disease, number (%)	17 (12)	23 (17)	13 (14)
Anticoagulant use, number (%)	4 (3)	15 (10)	4 (4)
Antiplatelet use, number (%)	52 (37)	44 (30)	28 (30)
Current smoker, number (%)	19 (14)	37 (25)	25 (27)
Alcohol abuse, number (%)	12 (9)	26 (17)	13 (14)
Baseline CT and clinical factors			
Diagnostic ICH volume, median (IQR), mL	40.5 (30.8–54.9)	42.2 (30.7–51.3)	36.8 (29.3–49.6)
Diagnostic IVH volume, median (IQR), mL	0 (0–1.8)	0 (0–1.6)	0 (0–1.1)
IVH present at diagnosis, number (%)	57 (41)	57 (38)	32 (34)
Lobar haematoma, number (%)	58 (42)	54 (36)	30 (32)
GCS at randomisation, median (IQR)	10 (8–13)	10 (8–13)	10 (8–13)
Systolic blood pressure, median (IQR), mm Hg	180 (160–202)	181 (155–208)	180 (149–213)
Diastolic blood pressure, median (IQR), mm Hg	98 (84–119)	98 (84–115)	98 (84–115)
Mean arterial pressure at first 24 hours, median (IQR)	92 (83–98)	92 (86–97)	93 (86–98)
Surgical group, number (%)	0	149 (100)	91 (97)
EOT CT ICH volume ≤15 mL, number (%)	3 (2)	91 (61)	94 (100)

EOT, end-of-treatment; GCS, glasgow coma scale; ICH, intracerebral haemorrhage; INR, international normalised ratio; IVH, intraventricular haemorrhage; MISTIE, minimally invasive surgery plus alteplase for intracerebral haemorrhage evacuation; PTT, partial thromboplastin time.

disease were more common in patients with MRI versus those without and prior ischaemic stroke was less common (96.5% vs 91.9%; p=0.03, 13.9% vs 6.6%; p=0.01 and 2.8% vs 6.2%; p=0.04, respectively). Among the included 288 patients, age, sex and ICH distributions were similar to the whole trial population. Median (IQR) ICH volume was 42 (30–53) mL. Table 1 compares treatment groups. Compared with the SMC group, patients randomised to MIS had more pre-admission use of anticoagulants (10% vs 3%), more alcohol abuse (25% vs 14%) and more smokers (17% vs 9%). Demographic and baseline clinical variables were otherwise similar between groups.

CSVD and long-term outcomes after MIS

Baseline MRI was performed at median 1 (1–6) day after ICH onset. Table 2 shows the results of radiographic analysis. Using modified Boston criteria,[22] 176 (61%) of 288 had 'possible CAA', and 43 (18%) of 194 met criteria for 'probable CAA'. Overall, CSVD markers were found more frequently in the unfavourable outcome group. All scores (CSVD, CAA and mCSVD) were significantly associated with unfavourable outcome on univariable testing. Optimal thresholds for predicting unfavourable outcome were >1 for all scores.

In the full cohort, presence of severe WMHs, CMBs≥5, cSS and all three scores (CSVD, CAA and mCSVD>1) were independently associated with increased odds for unfavourable outcome (figure 2). In the MIS group and successful MIS group (≤15 mL EOT volume), all CSVD features and scores >1 except severe EBVS in basal ganglia (MIS group) and cSS (≤15 mL EOT group) were significantly associated with increased odds for unfavourable outcome. In the SMC group, none of the CSVD markers or scores were associated with outcome.

Effect modification by CSVD

In the primary analysis (all MIS vs SMC), there was no significant heterogeneity in the effects of MIS on 1-year outcomes by any specific CSVD feature (figure 3). However, when comparing SMC with just those MIS patients with successful surgery (EOT volume ≤15 mL), we found significant beneficial effects of MIS with reduced odds of an unfavourable outcome with the following: absence of lacunes (OR, 0.37 (95% CI 0.18 to 0.80); $P_{interaction}$=0.02), absence of severe WMHs (OR, 0.22 (95% CI 0.08 to 0.58); $P_{interaction}$=0.03) and CAA score <2 (OR, 0.14 (95% CI 0.05 to 0.42); $P_{interaction}$=0.006). When comparing EOT ≤15 mL with EOT >15 mL in the MIS

Table 2 Comparison of cerebral small vessel disease (CSVD) features and CSVD burden scores between outcome groups

	Full cohort, number (%) (n=288)			
	Entire cohort (n=288)	Favourable outcome (n=127)	Unfavourable outcome (n=161)	P value
Presence of lacunes	26 (9)	8 (6)	18 (11)	0.21
Lobar lacunes	9 (3)	4 (3)	5 (3)	1.00
Deep lacunes	17 (6)	4 (3)	13 (8)	0.13
Presence of CMBs	118 (41)	45 (35)	73 (45)	0.09
Deep CMBs				0.06
0	214 (74)	102 (80)	112 (70)	
1	31 (11)	16 (13)	15 (9)	
2–4	20 (7)	6 (5)	14 (9)	
5–10	22 (8)	7 (6)	15 (9)	
>10	5 (2)	0 (0)	5 (3)	
Lobar CMBs				0.16
0	196 (68)	92 (72)	104 (65)	
1	31 (11)	16 (13)	15 (9)	
2–4	20 (7)	6 (5)	14 (9)	
5–10	30 (10)	11 (9)	19 (12)	
>10	11 (4)	2 (2)	9 (6)	
Total CMBs				0.19
0	170 (59)	82 (65)	88 (55)	
1	32 (11)	16 (13)	16 (10)	
2–4	25 (11)	10 (8)	15 (9)	
5–10	39 (14)	13 (10)	26 (16)	
>10	22 (8)	6 (5)	16 (10)	
CMBs≥5	61 (21)	19 (15)	42 (26)	0.03
Number of EPVS in BG				0.08
0	24 (8)	14 (11)	10 (6)	
1–10	98 (34)	50 (39)	48 (30)	
11–20	68 (24)	30 (24)	38 (24)	
21–40	74 (26)	26 (21)	48 (30)	
>40	24 (8)	7 (6)	17 (11)	
Number of EPVS in CSO				0.59
0	41 (14)	19 (15)	22 (14)	
1–10	61 (21)	27 (21)	34 (21)	
11–20	50 (17)	17 (13)	33 (21)	
21–40	74 (26)	36 (28)	38 (24)	
>40	62 (22)	28 (22)	34 (21)	
Severe EPVS in BG	166 (58)	63 (50)	103 (64)	0.02
Deep Fazekas score				<0.001
0	82 (29)	49 (39)	33 (21)	
1	129 (45)	62 (49)	67 (42)	
2	60 (21)	13 (10)	47 (29)	
3	17 (6)	3 (2)	14 (9)	
Periventricular Fazekas score				<0.001
0	6 (2)	6 (5)	0	

Continued

Table 2 Continued

	Full cohort, number (%) (n=288)			
	Entire cohort (n=288)	Favourable outcome (n=127)	Unfavourable outcome (n=161)	P value
1	133 (46)	79 (62)	54 (34)	
2	98 (34)	33 (26)	65 (40)	
3	51 (18)	9 (7)	42 (26)	
Total Fazekas score				<0.001
0	6 (2)	6 (5)	0	
1	64 (22)	36 (28)	28 (17)	
2	71 (25)	47 (37)	24 (15)	
3	65 (23)	22 (17)	43 (27)	
4	46 (16)	10 (8)	36 (22)	
5	19 (7)	3 (2)	16 (10)	
6	17 (6)	3 (2)	14 (9)	
Severe WMH	147 (51)	38 (30)	109 (68)	<0.001
Presence of cSS	38 (13)	9 (7)	27 (17)	0.02
Focal (≤3 sulci)	36 (13)	9 (18)	25 (16)	
Disseminated (≥4 sulci)	2 (1)	0	2 (1)	
CSVD score				<0.001
0	56 (19)	39 (31)	17 (11)	
1	80 (27)	42 (33)	38 (24)	
2	89 (31)	28 (22)	59 (37)	
3	57 (20)	16 (13)	41 (25)	
4	8 (3)	2 (1)	6 (3)	
CAA score				<0.001
0	98 (34)	66 (52)	32 (20)	
1	82 (29)	29 (23)	53 (33)	
2	53 (18)	20 (16)	33 (21)	
3	32 (11)	9 (7)	23 (14)	
4	21 (7)	3 (2)	18 (11)	
5	2 (1)	0	2 (1)	
6	0	0	0	
Modified CSVD score				<0.001
0	60 (21)	43 (34)	17 (11)	
1	91 (31)	46 (36)	44 (27)	
2	84 (29)	25 (20)	58 (36)	
3	41 (14)	11 (9)	30 (19)	
4	13 (5)	2 (1)	11 (7)	
5	1 (0)	0 (0)	1 (0)	

Severe EPVS=grade 3 (21–40) and 4 (>40).
BG, basal ganglia; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleeds; CSO, centrum semiovale; cSS, cortical superficial siderosis; CSVD, cerebral small vessel disease; EPVS, enlarged perivascular spaces; WMH, white matter hyperintensities.

group, we found significant effect modification for MIS with ≤15 mL EOT volume by CAA score <2 (OR, 0.10 (95% CI 0.03 to 0.37); $P_{interaction}$=0.002). Figure 4 shows mRS score distributions by CAA score 0–1 versus 2–6 in all cohorts. Odds of good outcome (mRS 0–3 vs 4–6) were significantly higher for patients with CAA score 0–1 (vs 2–6) in fully adjusted analyses for the full cohort, MIS group and group with EOT volume ≤15

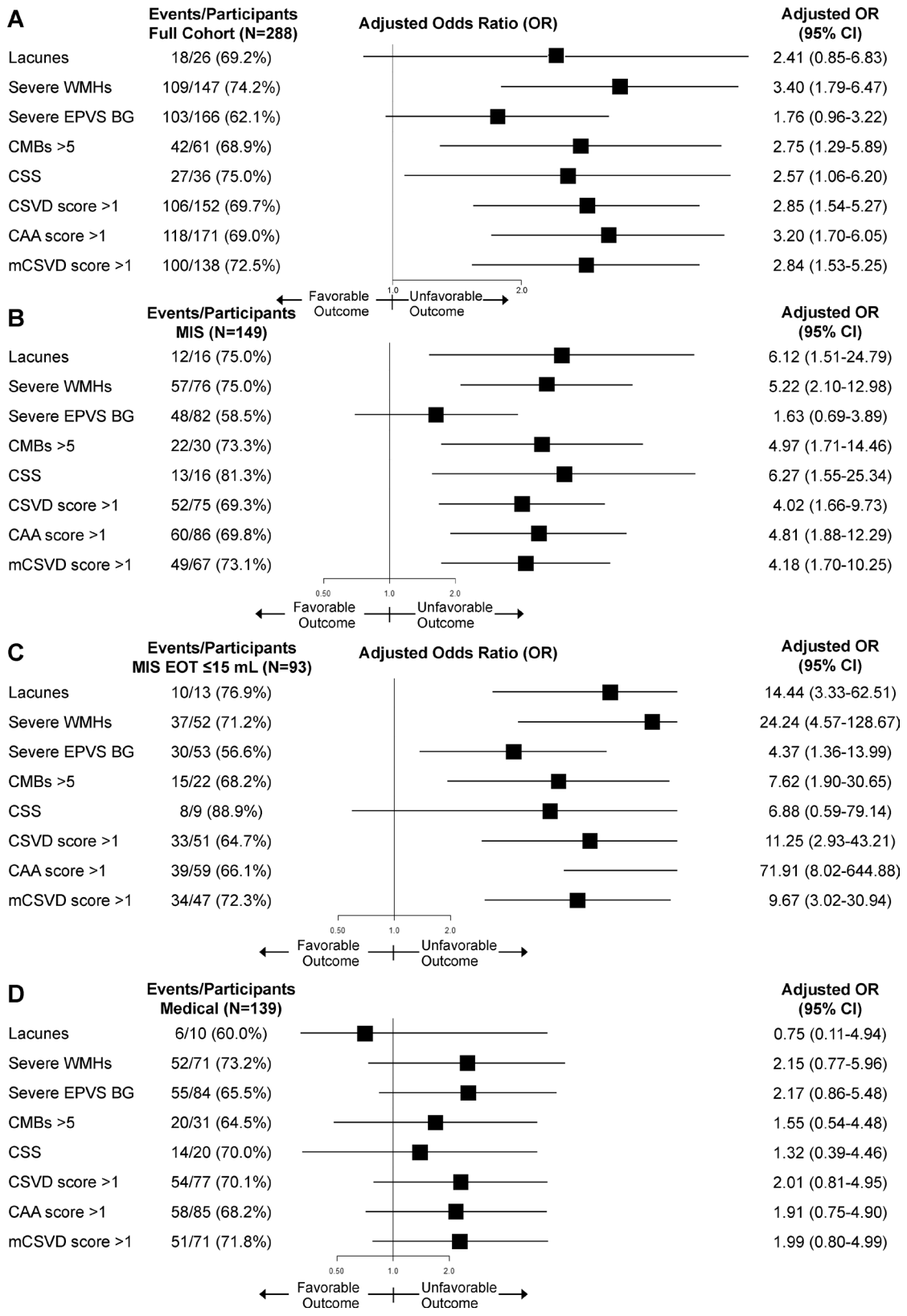

Figure 2 Prespecified adjusted subgroup analyses of odds of poor functional outcome at 1 year by brain MRI features for (A) full cohort, (B) MIS, (C) EOT volume ≤15 mL and (D) standard medical care (medical) group. All analyses were adjusted for age, admission GCS, diagnostic ICH volume, IVH present at diagnosis, lobar ICH location, diabetes and admission systolic blood pressure. BG, basal ganglia; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSS, cortical superficial siderosis; CSVD, cerebral small vessel disease; EOT, end-of-treatment; EPVS, enlarged perivascular spaces; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mCSVD, modified CSVD; MIS, minimally invasive surgery.

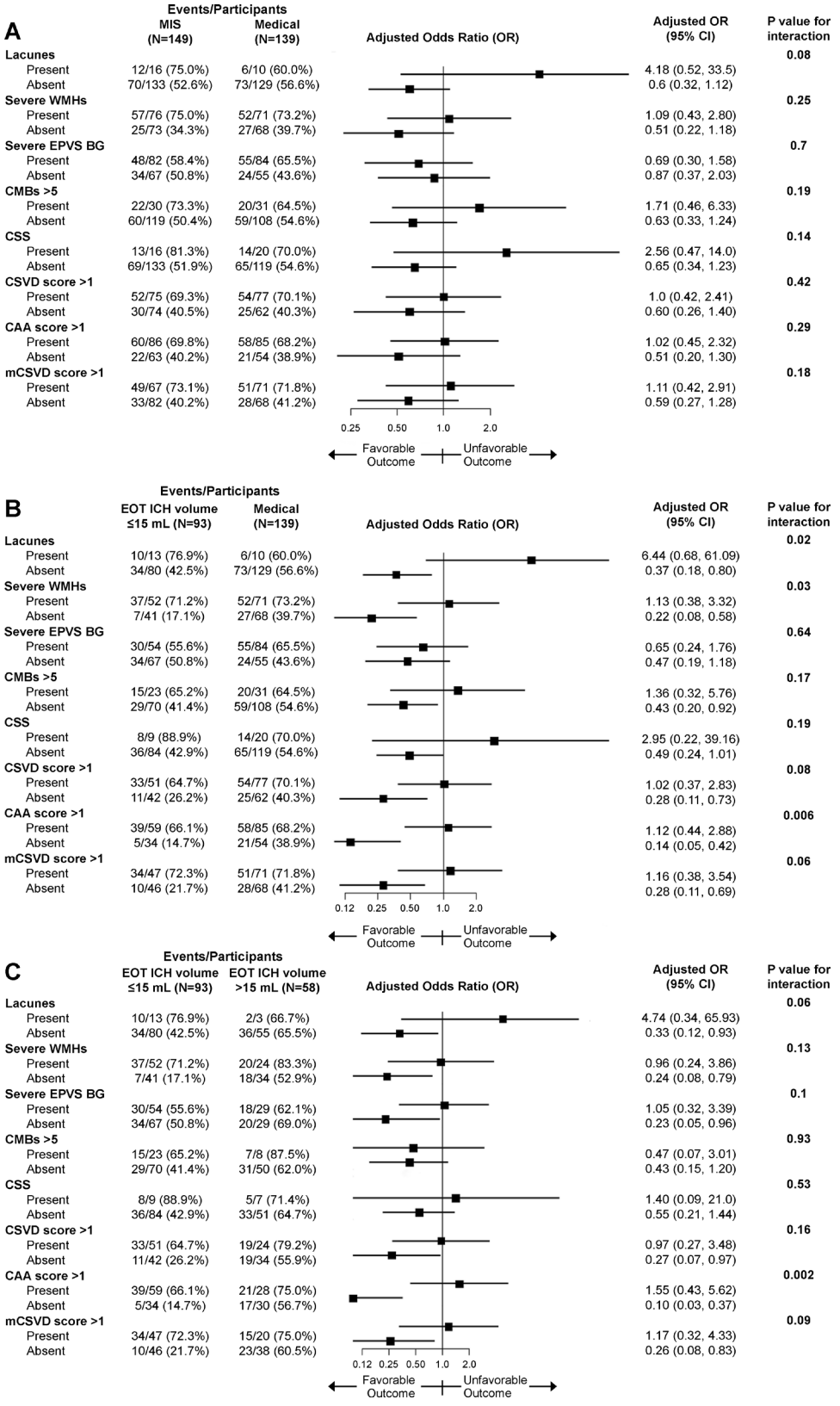

Figure 3 Pre-specified adjusted subgroup analysis of the odds of poor functional outcome at 1 year by brain MRI features comparing (A) MIS versus SMC, (B) EOT volume≤15 mL versus SMC and (C) EOT volume≤15 mL versus EOT volume>15 mL. All analyses were adjusted for age, admission GCS, diagnostic ICH volume, IVH present at diagnosis, lobar ICH location, diabetes and admission systolic blood pressure. BG, basal ganglia; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSS, cortical superficial siderosis; CSVD, cerebral small vessel disease; EOT, end-of-treatment; EPVS, enlarged perivascular spaces; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mCSVD, modified CSVD; MIS, minimally invasive surgery.

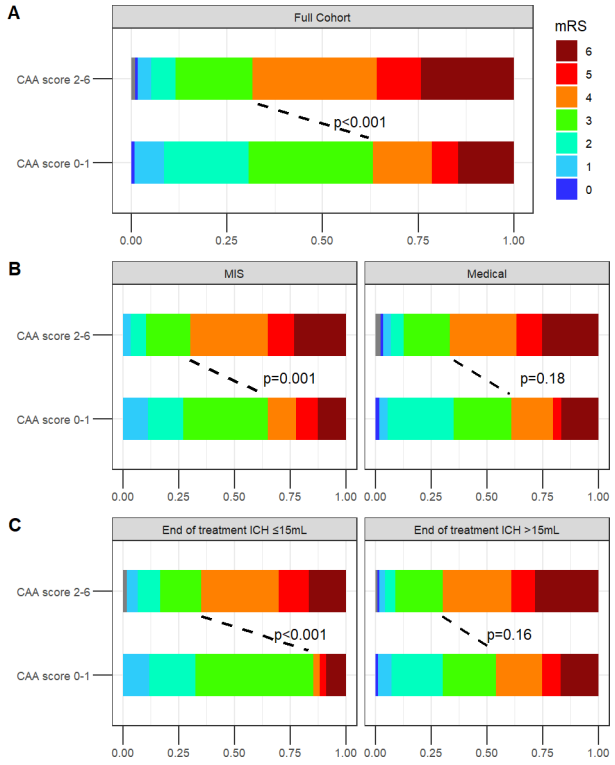

Figure 4 mRS score distribution by CAA score 0–1 versus 2–6 in (A) full MRI cohort (n=288), (B) MIS (n=149) versus medical (n=139) groups and (C) EOT volume≤15 mL (n=94) versus>15 mL (n=194). mRS scores range from 0 (no disability) to 6 (death). P values are for odds of mRS 0–3 versus 4–6 for CAA score 0–1 versus 2–6 in analyses adjusted for age, admission GCS, diagnostic ICH volume, IVH present at diagnosis, lobar ICH location, diabetes and admission systolic blood pressure. CAA, cerebral amyloid angiopathy; CSVD, cerebral small vessel disease; EOT, end-of-treatment; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mCSVD, modified CSVD; MIS, minimally invasive surgery; mRS modified Rankin Score.

mL, but not for the SMC group and group with EOT volume>15 mL.

DISCUSSION

This was an exploratory MRI subgroup analysis of MISTIE III, in which the absence of SVD imaging markers, specifically lacunes, severe WMHs and high CSVD burden defined by CAA score >1 modified the effect of successful MIS on functional outcome. When all surgical outcomes were considered together, however (including subjects with EOT volume >15 mL), effect modification by MRI features of CSVD on 1-year functional outcomes was not observed.

MISTIE III was the first surgical trial for ICH that defined thresholds for potential benefit from clot volume reduction; this study is the first to investigate whether MIS impact on functional outcome varies by CSVD imaging lesions. The finding that these features modify the effect of successful surgery but not MIS without significant volume reduction or standard non-surgical care is consistent with the importance of maximal haematoma reduction as a prerequisite for good outcome.[24]

MRI features associated with long-term outcomes

MRI features of greatest individual significance in the surgical group were lacunes and WMHs. Lacunes and WMHs are ischaemic markers correlated with severity of hypertension and independently associated with cognitive decline in the elderly,[6 25] suggesting that the extent of chronic vascular dysfunction may be an important baseline condition, limiting good outcomes in ICH patients even after successful MIS. Additionally, these markers could be prerequisites for additional events that contribute to poor recovery and are correlated with white matter lesions, such as poststroke depression,[26] cognitive impairment[27 28] and new ischaemic strokes.[27 29] In ischaemic stroke patients undergoing endovascular treatment (EVT), a higher burden of white matter lesions was correlated with worse outcomes, despite achieving benefit from EVT, whether or not successful reperfusion was achieved.[30] Because MIS remains of uncertain effectiveness for improving functional outcomes,[31] we cannot recommend consideration of WMHs, lacunes or CAA score as selection criteria for MIS from this exploratory analysis. However, data on CSVD features could help to select appropriate patients for clinical trials who are most likely to benefit. If these findings are confirmed in larger clinical trial populations for MIS, one implication is that the CAA score and particularly findings of lacunes and severe WMHs may portend a significantly lower odds of good functional outcome even with successful surgical evacuation. These findings are not likely to differentiate outcomes between CAA and hypertensive SVD-related ICH due to significant overlap of relevant MRI findings in this study. Patients in the MISTIE-3 trial had predominantly deep hypertensive ICH and yet a not insignificant proportion (18%) of patients met modified Boston criteria for CAA.

The association between WMH severity and long-term unfavourable outcomes, as in prior studies,[32 33] is confounded by lobar haemorrhages being larger and occurring in older patients in MISTIE III. With a predominance of deep haemorrhages in MISTIE III, however, hypertension-associated severe WMH likely contributed to the significance of this finding, which was not observed in a smaller study of older subjects with mostly lobar ICH and less hypertension.[11]

Utility of CSVD scores

We evaluated two established small vessel disease burden scores, the CSVD burden score and the CAA score.[15 20] Both scores had good predictive strength for unfavourable outcome in the surgical group, with CAA score performing best as a significant effect modifier in the MIS EOT ≤15 mL group. We then evaluated a clinically modified set of criteria including lacunes, CMBs, EPVS, WMHs and cSS in our mCSVD score, which had similar

prediction value to the other two scores for unfavourable outcome but was a weaker effect modifier of the effect of successful MIS on unfavourable outcome compared with the CAA score. The relative superiority of the CAA score in modifying the effects of successful MIS may be due to the threshold applied and small number of lacunes observed (not included in CAA score), where most patients without CAA >1 did not have poor outcomes in the successful MIS group. Because CMBs might be difficult to observe adjacent to a hematoma, we chose five as our CMB threshold, as used in other studies.[34] EPVS location was another modification based on a stronger relationship with unfavourable outcome for severe basal ganglia, but not centrum semiovale EPVS. Although most studies report cSS on 3T MRI, we found cSS on 1.5T MRI and therefore added cSS based on a significant association with unfavourable outcome in univariate analysis. Since categorical classification of cSS could require higher resolution capabilities, we employed presence or absence.

Limitations

With regards to strengths, this study included a large well-adjudicated clinical trial cohort with long-term outcomes and use of standardised CSVD visual methodology by trained reviewers blinded to clinical information. Early withdrawal of active life support was an exclusion criterion for the trial and did not impact our findings. Potential weaknesses are found in the specific elements of study design and lack of generalisability where MISTIE III was very selective in terms of patients screened (over 19 thousand with 499 enrolled) and while results are difficult to generalise to ICH populations in general, they are relevant for similar trial settings and for patients with large supratentorial ICH. The trial was well represented for baseline clinical factors, including deep ICH in two-thirds of subjects, a population which along with high clinical severity has been studied less frequently in large ICH cohorts with MRI. This trial was conducted in tertiary care academic medical centres and may not reflect the full spectrum of clinical care delivered in community settings. The study relied on high-quality MRI scans (with 50 cases excluded, mostly due to low-quality images or lack of SWI or GRE sequences) and was limited by relatively low acquisition of MRI due to high clinical severity of this ICH population. Some bias in comorbidities was detected in acquisition of MRI, although baseline ICH volume, GCS and outcomes were not different between patients with and without MRI.

Limitations inherent to all studies evaluating MRI for CSVD are those related to challenges to obtaining MRI in critically ill patients, adjudication practices, use of SWI in place of GRE (known to be more sensitive for CMB detection) and constant evolution in techniques for evaluating CSVD. Further direction may include volumetric analysis of WMH and diffusion tensor imaging analysis to quantify extent and integrity of white matter tracts. Validating the sensitivity of CT findings of CSVD such as using von Swieten score may obviate need for acute MRI in this population.[14]

Interpretation

In this MISTIE III substudy, we demonstrate associations of lower burden of CSVD features on MRI, in particular, absence of severe WMHs and lacunes with lower odds of poor clinical outcomes in patients attaining successful hematoma volume reduction for large ICH. This is the first study to evaluate use of MRI to target surgical therapy to those with the greatest opportunity to benefit. Future trials of MIS for ICH could evaluate whether specific MRI features of CSVD or cumulative burden scores are useful in guiding surgical treatment strategies.

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