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ORIGINAL ARTICLE

Prognostic capacity of hyperdense middle cerebral artery sign in anterior circulation acute ischaemic stroke patients receiving reperfusion therapy: a systematic review and meta-analysis

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Abstract

Pre-intervention CT imaging-based biomarkers, such as hyperdense middle cerebral artery sign (HMCAS) may have a role in acute ischaemic stroke prognostication. However, the clinical utility of HMCAS in settings of reperfusion therapy and the level of prognostic association is still unclear. This systematic review and meta-analysis investigated the association of HMCAS sign with clinical outcomes and its prognostic capacity in acute ischaemic stroke patients treated with reperfusion therapy. Prospective and retrospective studies from the following databases were retrieved from EMBASE, MEDLINE and Cochrane. Association of HMCAS with functional outcome, symptomatic intracerebral haemorrhage (sICH) and mortality were investigated. The random effect model was used to calculate the risk ratio (RR). Subgroup analyses were performed for subgroups of patients receiving thrombolysis (tPA), mechanical thrombectomy (EVT) and/or combined therapy (tPA + EVT). HMCAS significantly increased the rate of poor functional outcome by 1.43-fold in patients (RR 1.43; 95% CI 1.30–1.57; $p < 0.0001$) without any significant differences in sICH rates (RR 0.91; 95% CI 0.68–1.23; $p = 0.546$) and mortality (RR 1.34; 95% CI 0.72–2.51; $p = 354$) in patients with positive HMCAS as compared to negative HMCAS. In subgroup analyses, significant association between HMCAS and 90 days functional outcome was observed in patients receiving tPA (RR 1.53; 95% CI 1.40–1.67; $p < 0.0001$) or both therapies (RR 1.40; 95% CI 1.08–1.80; $p = 0.010$). This meta-analysis demonstrated that pre-treatment HMCAS increases risk of poor functional outcomes. However, its prognostic sensitivity and specificity in predicting long-term functional outcome, mortality and sICH after reperfusion therapy is poor.

Keywords HMCAS · Stroke · Endovascular therapy · Functional outcome · Symptomatic intracerebral haemorrhage · Mortality · Meta-analysis

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Abbreviations

HMCAS	Hyperdense middle cerebral artery
NCCT	Non-contrast computed tomography
AIS	Acute ischaemic stroke
EVT	Endovascular thrombectomy
tPA	Tissue-plasminogen activator
CTA	Computed tomography angiography
IV	Intravenous
CTP	Computed tomography perfusion
sICH	Symptomatic intracerebral haemorrhage
SITS-ISTR	Thrombolysis in Stroke International Stroke Thrombolysis Register
MCA	Middle cerebral artery
RR	Risk ratio

Introduction

Non-contrast computed tomography (NCCT) remains the primary imaging modality in acute ischaemic stroke (AIS) [1, 2]. Early recognition of AIS on imaging is important to decide the optimal therapeutic strategy [1, 2]. Hyperdense middle cerebral artery sign (HMCAS) is a focal and tubular hyper-density area often seen on NCCT in the middle cerebral artery (MCA) during the hyperacute phase [3, 4]. The prevalence of HMCAS is approximately 19–40% in acute MCA stroke patients [5, 6]. It has been shown to delineate the location of the occlusion and baseline stroke severity [3]. The wide availability of NCCT in comparison to advanced imaging modalities, such as computed tomography perfusion imaging (CTP) makes it easier to appreciate HMCAS in real-world settings [1, 7]. The HMCAS has also been used to investigate the morphological characteristics of the clot as a surrogate imaging biomarker [4, 5, 7].

The reperfusion strategies, using pharmacological or intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT), is currently the mainstay of acute ischaemic stroke treatment [8]. Despite the emerging role of HMCAS, its prognostic role in clinical settings, in settings of reperfusion therapy, needs further consideration. Indeed, the clot composition (such as the degree of clot density, relative composition of red blood cells (RBCs) [9]) in addition to other factors, such as time to reperfusion [10], baseline stroke severity [11], collateral status [12, 13], etc., are associated with the efficacy of the EVT [14, 15]. This study sought to investigate the association of HMCAS with clinical outcomes and its prognostic capacity in anterior circulation AIS patients receiving reperfusion therapy by performing a systematic review and meta-analysis.

Methods

Literature search: identification and selection of studies

Medline, Embase and Cochrane central register of controlled trials were used as the search engines. Articles were searched between January 2000 and August 2020. The search terms included: “hyperdense MCA sign” or “hyperdense artery sign” or “hyperdensity artery sign” or “HDMCA” or “HMCAS” in association with “stroke” or “anterior circulation” or “acute ischaemic stroke” and “Thrombectomy” or “Thrombolytic therapy” or “Tissue plasminogen activator” or “tPA” or “outcomes”. Additional limits were applied to exclude studies that were not in the English language and those that didn’t include human subjects. The full search term is available in the Supplementary Information (search strategy). The Preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist was adopted in this meta-analysis [16].

Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: (1) patients were aged 18 years or above; (2) patients had been diagnosed with AIS, (3) patients received endovascular therapy and/or mechanical thrombectomy; (4) studies with good methodological design and (5) studies with sufficient sample size, determined to be > 20 patients in each group. The exclusion criteria were: (1) animal studies; (2) duplicated publications; (3) full-text article not available; (4) systematic reviews, meta-analyses, letters and case reports or case series and (5) studies presented in the abstract form, with relevant data on HMCAS not available or no relevant post-reperfusion clinical outcome measured were excluded.

Data extraction

The title and abstracts were reviewed on Endnote first to rule out the articles mismatched to the eligibility criteria. The remaining articles were examined thoroughly to determine whether they should be included for the systematic review or meta-analysis according to the eligibility criteria. The screening was conducted independently by two authors. Disagreements were discussed and final decisions were reaches at by consensus. The data from each study/trial were extracted independently using a data extraction sheet to obtain the following information: (1) baseline demographics: author, country and year of publication; (2) study population: age of patients, sample

size, characteristics of acute stroke patients, presence or absence of HMCAS; (3) type and time window of the treatments and (4) outcome measures: functional outcome, sICH and mortality at 90 days.

Quality assessment of included studies

The methodological quality of each study was assessed independently by two researchers using the Newcastle Ottawa scale [17]. The scale evaluates the study quality based on the following evaluation criteria: Selection, comparability and outcomes. The total score for each study ranged from 0 to 9 points and using the nine items. National Institute of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies was also used for the quality assessment of the included studies. The total score for each study ranged from 0 to 14 points [18]. The risk of bias in results due to funding was evaluated, independently from the quality assessment, through the declaration of funding sources and conflicts of interest using the previously reported scoring test [19]. A score of 1–2 was considered to indicate a moderate potential for bias. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.

Statistical analysis

All statistical analyses were performed using STATA (Version 13.0, StataCorp LLC, College Station, Texas, USA). In this study, functional outcome, sICH and mortality were compared in patients with or without HMCAS. The Forest plots were generated to present the risk ratios (RR), 95% confidence intervals (CI), percentage weight and the heterogeneity between studies included in the meta-analysis. I^2 statistics and p values were used to assess the heterogeneity between the studies (25% = low, 50% = medium, 75% = high). The random effects model was used across all subgroup analyses. Subgroup analysis for patients receiving tissue plasminogen activator (tPA), mechanical thrombectomy (EVT) or both were also performed. The baseline characteristics of patients' populations were synthesized from all included studies. Where applicable, median and interquartile ranges were converted to mean and standard deviation using the method described by Wan et al. 2012 [20]. A (Begg's) funnel plot was used to visually detect the presence of publication bias in the meta-analysis. Asymmetry on either side of the funnel plot is indicative of the presence of publication bias. Sensitivity and specificity analysis were also used in the detection of prognostic performance in meta-analysis. p values < 0.05 were considered statistically significant (Fig. 1).

Results

Description of included studies

The total number of patients included in this study was 12,329, of which 7118 (57.7%) were male and 2724 patients (22.1%) were positive for HMCAS on pre-intervention NCCT. The mean age ± SD (range) of all included studies was 68.4 ± 15.6 years. The clinical characteristics are shown in Table 1. Definitions of poor functional outcome and sICH are varied across studies. The results of methodological quality, risk of bias and funding bias assessment of included studies are provided in Supplementary Information (Supplementary Tables 1, 2 and 3). Effect size analyses for functional outcome, sICH and mortality is also presented in Supplementary Information (Supplementary Figs. 1, 2 and 3).

Association of HMCAS with long-term functional outcome

Overall, 12 studies were included in the final meta-analysis of association of HMCAS with the functional outcome at 90 days comprising of 11, 894 patients [21–32]. A poor functional outcome was defined as a 90-days modified Rankin score (mRS) of 3–6 in 8 studies [21, 23–28, 30] and 2–6 in 4 studies [22, 29, 31, 32]. HMCAS significantly increased the risk of poor functional outcome by 1.43-fold (RR 1.43; 95% CI 1.30–1.57; $p < 0.0001$) (Fig. 2). Moderate heterogeneity was found between the studies ($I^2 = 55.1\%$, $p = 0.011$). No evidence of publication bias was observed by visual inspection of the funnel plot (Fig. 5). Significant association of HMCAS with functional outcome at 90 days was observed in patients receiving tPA (RR 1.53; 95% CI 1.40–1.67; $p < 0.0001$) or both therapies (RR 1.40; 95% CI 1.08–1.80; $p = 0.010$) (Fig. 2). No significant association of HMCAS with functional outcome at 90 days was observed in patients receiving EVT (RR 1.16; 95% CI 0.99–1.37; $p = 0.071$). The sensitivity and specificity of HMCAS stratified by reperfusion therapy are provided in Table 2.

Association of HMCAS with sICH

Ten studies consisting of 11,871 patients were included in the final meta-analysis of the association of HMCAS with sICH [22, 23, 25–30, 33, 34]. Most of the studies defined sICH according to SITS-MOST criteria. SITS-MOST criteria define sICH as local or remote PH2 (parenchymal haemorrhage) seen on CT at the 22–36 h combined with a neurological deterioration of 4 points on the baseline NIHSS or leading to death [23, 25, 28]. Other definitions of sICH used in these studies are described in Table 1.

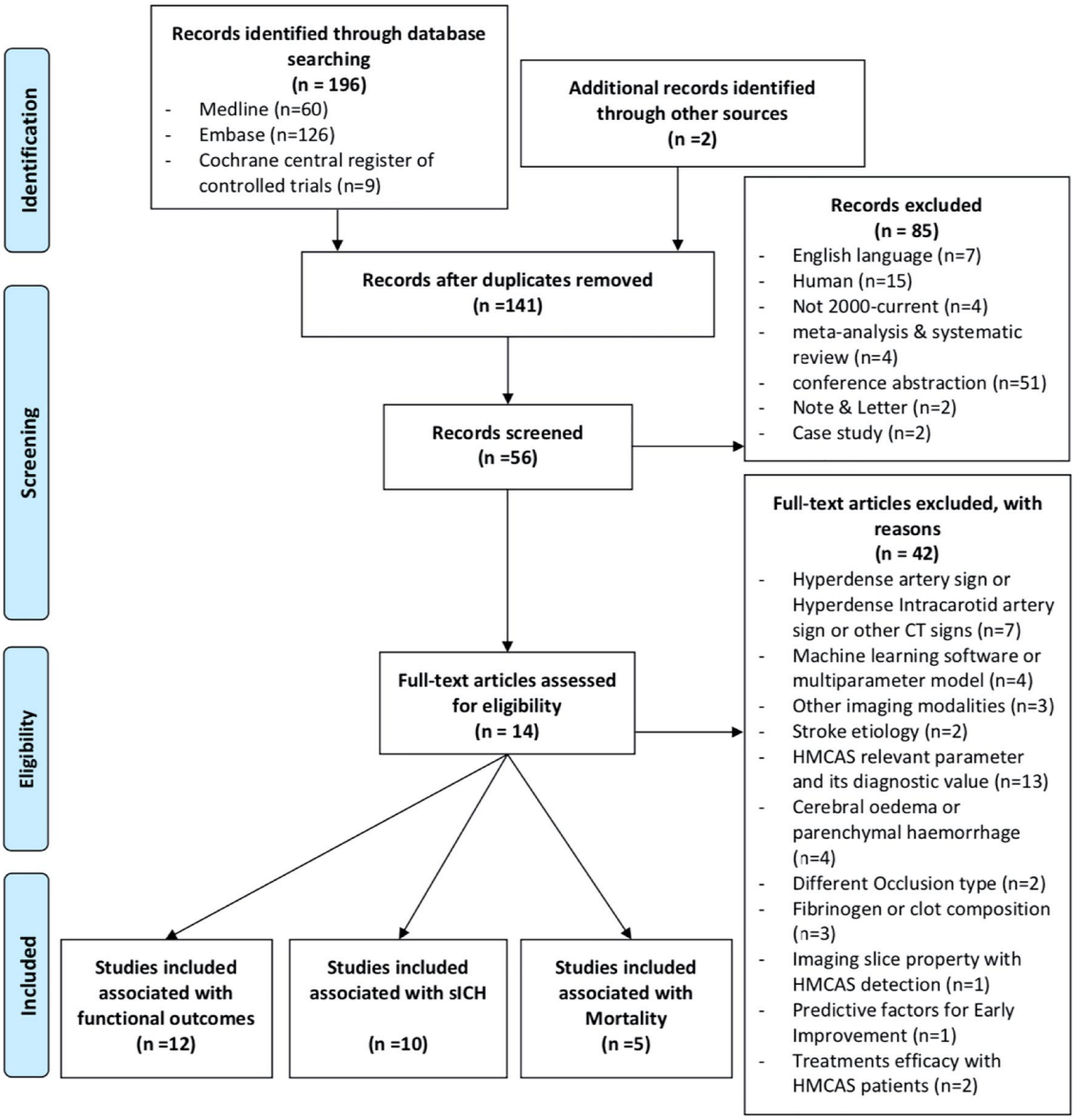


Fig. 1 The PRISMA flowchart showing the main characteristics of included studies

No significant association of HMCAS with sICH was observed (RR 0.91; 95% CI 0.68–1.23; $p = 0.546$; Fig. 3). Low heterogeneity was found between studies ($I^2 = 0.0\%$, $p = 0.705$). No evidence of publication bias was observed on the funnel plot (Fig. 5). For patients receiving tPA, the HMCAS was associated with decreased risk of sICH rates, though the association was not significant (RR 0.86; 95% CI 0.64–1.16; $p = 0.329$; Fig. 3). In EVT patients, HMCAS was associated with an increased risk of sICH, however it failed to reach statistical significance (RR 3.95; 95% CI 0.88–17.67; $p = 0.0.072$; Fig. 3). The sensitivity and specificity are shown for tPA and all included studies in Table 2.

Association of HMCAS with mortality

Five studies were included in the final analysis of association of HMCAS with mortality which comprised of 10,922 patients [21, 25, 26, 28, 33] (Table 1). HMCAS was not significantly associated with increased risk of mortality in patients with positive HMCAS as compared to negative HMCAS (RR 1.34; 95% CI 0.72–2.51; $p = 0.354$) (Fig. 4). The heterogeneity (I^2) was found to be high (88.0%, $p < 0.001$) across studies. There is no evidence of publication bias upon visual inspection of the funnel plot (Fig. 5). The association of HMCAS with mortality risk was not significant in patients who received thrombolysis (RR 1.26; 95% CI 0.61–2.62; $p = 0.531$) (Fig. 4). Meta-analysis on

Table 1 Baseline characteristics of included studies

Authors	Year	Region	Study type	Sample size	Baseline characteristics			Treatment	Outcome definition		
					Age, years (mean ± SD)	Sex Male %	Baseline NIHSS (mean ± SD)		Poor functional outcome	sICH	Mortality/survival
Kim et al. [26]	2017	South Korea	Retrospective	212	72 ± 10.4	50.5	13 ± 4.5	EVT	*	N/A	90-days mortality
Elofuke et al. [33]	2016	UK	Prospective	315	70 ± 11.5	58.1	15 ± 9.75	tPA	N/A	Symptomatic ICH is any ICH with worse NIHSS score at 24 h post thrombolysis	90-days survival
Ozdemir et al. [28]	2015	Turkey	Retrospective	252	65.3	53.6	14.4 ± 6	tPA	*	SITS-MOST definition	Mortality
Man et al. [27]	2015	USA	Retrospective	126	70.7 ± 13.7	47.6	16.2 ± 9.9	EVT	*	N/A	N/A
Topcuoglu et al. [31]	2015	Turkey	Retrospective	131	65.8 ± 13	50.5	15.8 ± 4.5	tPA + EVT	**	N/A	N/A
Li et al. [34]	2014	Melbourne, Australia	Retrospective	120	73.4 ± 14	58.3	12.5 ± 6	tPA	N/A	Symptomatic haemorrhage = sICH	N/A
Topcuoglu et al. [32]	2014	Turkey	Retrospective	105	63.3 ± 13.4	50.5	15.7 ± 4.6	tPA + EVT	**	N/A	N/A
Paliwal et al. [29]	2012	Singapore	Retrospective	226	58.7 ± 54.5	62.6	17.7 ± 20.9	tPA	**	N/A	N/A
Abul-Kasim et al. [21]	2010	Sweden	Retrospective	120	70 ± 12	55	12 ± 6	tPA	*	N/A	Death
Kharitonova et al. [25]	2009	International	Retrospective	10,023	69.4 ± 10.7	58.5	13 ± 9.6	tPA	*	SITS-MOST definition	Death
Aries et al. [23]	2009	Netherlands and Belgium	Prospective	384	68 ± 14	52	13 ± 8	tPA	*	SITS-MOST definition	N/A
Tartaglia et al. [30]	2008	UK and Canada	Retrospective	130	71.8 ± 12	51.5	13 ± 6	tPA	*	Occurrence of any severe bleeding complication	N/A
Agarwal et al. [22]	2004	USA	Retrospective	83	70.2 ± 15	57.8	14 ± 6	tPA	**	Haemorrhagic transformation of brain infarcts and were symptomatic	N/A
Barber et al. [24]	2000	North America	Prospective	102	68 ± 14	53.8	N/A	tPA	*	Haemorrhage had not been seen on a previous CT scan occurred with a decline in the neurological status	N/A

Table 1 (continued)

Clinical outcomes								
Mortality/survival	Functional outcome result				sICH result		Mortality/survival	
	HMCAS		HMCAS−		HMCAS+ (*n*, %)	HMCAS− (*n*, %)	HMCAS+ (*n*, %)	HMCAS− (*n*, %)
	Poor (*n*, %)	Favourable (*n*, %)	Poor (*n*, %)	Favourable (*n*, %)				
90-days mortality	70 (59.3)	48 (40.7)	45 (47.9)	49 (52.1)	7 (5.9)	1 (1.1)	14 (11.9)	6 (6.4)
90-days survival	N/A				5 (6%)	13/222 (6%)	32 (15%)	28 (32%)
Mortality	49 (76.6)	15 (23.4)	83 (44.1)	105 (55.9)	5 (7.8%)	13 (6.9%)	16	25
N/A	59 (78.7)	16 (21.3)	36 (70)	15 (30)	4	1 (2)	N/A	
N/A	30 (76.9)	9 (23.1)	29 (48.3)	31 51.7)	N/A		N/A	
N/A	N/A				1 (3.1)	5 (6)	N/A	
N/A	29 (67.4)	14 (32.6)	34 (54.8)	28 (45.2)	N/A		N/A	
N/A	62 (56.9)	47 (43.1)	46 (39.3)	71 (60.7)	6	5	N/A	
Death	27 (69)	12 (31)	32 (40)	49 (60)	N/A		5 (13)	6 (7)
Death	1160 (69.3)	515/1675 (30.7)	3051 (44)	3889/6940 (56.0)	24 (1.3)	143 (1.8)	392/1675	898/6940
N/A	75 (72)	29 (28)	134 (48)	146 (52)	7 (7)	17 (6)	N/A	
N/A	40 (62.5)	24 (37.5)	36 (54.5)	30 (45.5)	7 (11)	8 (12)	N/A	
N/A	13 (86.7)	2 (13.3)	27 (52.9)	24 (47.1)	1	3	N/A	
N/A	7 (43.7)	9 (52.3)	43 (50)	43 (50)	N/A		N/A	

The new denominator is specified where the data are incomplete

HMCAS + patients with HMCAS, *HMCAS*– patients without HMCAS, *Poor* poor functional outcome at 90 days, *Favourable* favourable functional outcome at 90 days

*mRS 3–6/3 months

**mRS2–6/3 months

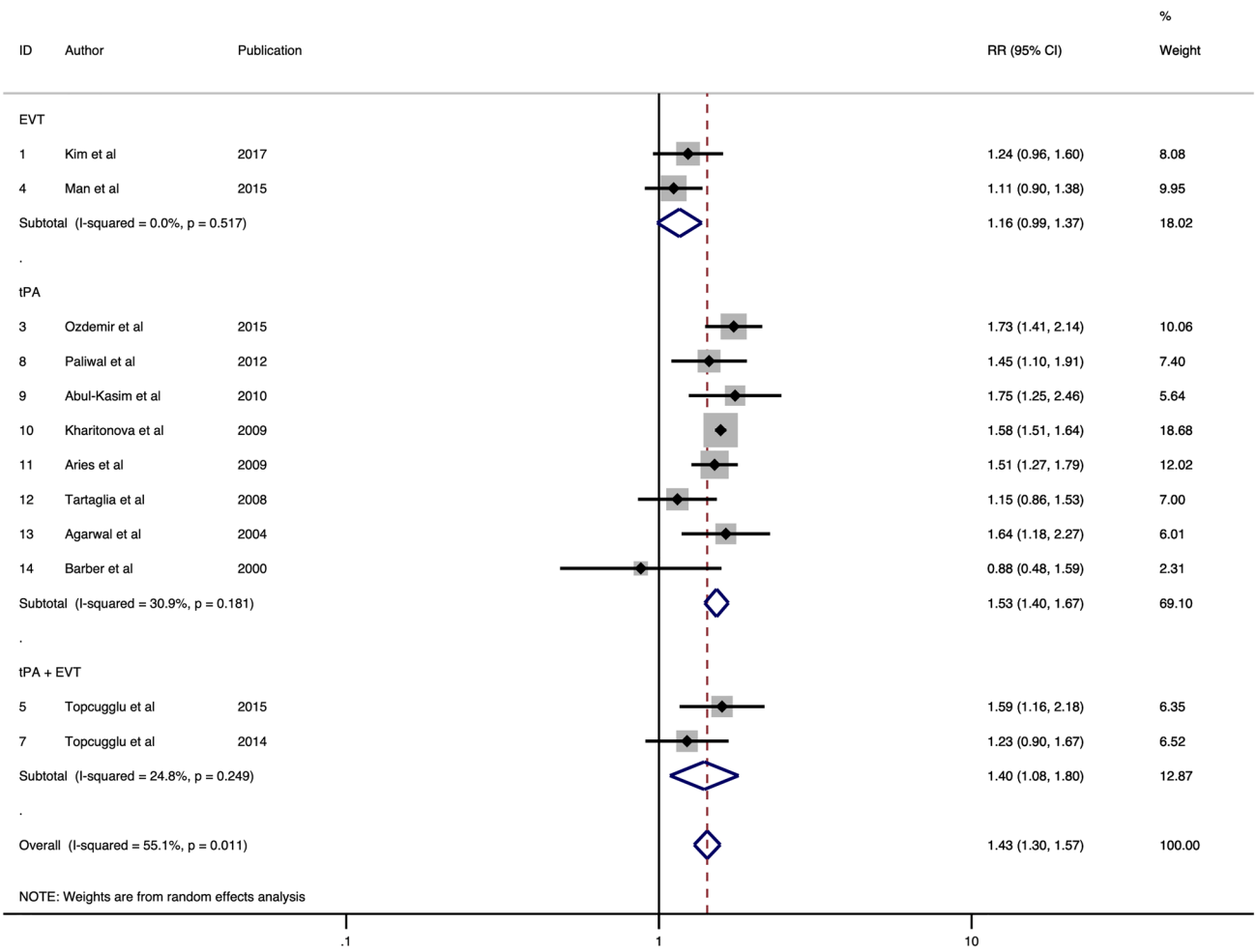


Fig. 2 Forest plot showing the association of the hyperdense middle cerebral artery sign with the risk of poor functional outcome in acute ischaemic stroke patients receiving thrombolysis or/and mechanical thrombectomy

association of HMCAS with mortality risk in EVT patients could not be done due to limited number of studies. The sensitivity and specificity stratified by treatment subgroups are provided in Table 2.

Discussion

This meta-analysis reports on the association of pre-treatment HMCAS with functional outcome, mortality and sICH in acute ischaemic stroke patients receiving reperfusion therapy. This meta-analysis revealed that HMCAS is associated with increased risk of poor functional outcome at 90 days, though its prognostic sensitivity is low. HMCAS is significantly associated with increased risk of poor functional outcomes at 90 days in patients treated with tPA or EVT + tPA, however the association failed to reach statistical significance in EVT subgroup. HMCAS was not significantly associated with risk of sICH or mortality at 90 days. Interestingly, HMCAS was associated with increased sICH risk following EVT, though the association didn't reach statistical significance. The meta-analyses on HDMCA and mortality risk in EVT patients could not be done due to lack of sufficient number of studies. Further studies are required to study the association of HMCAS with mortality and sICH risks following EVT.

Our analyses showed that patients with HMCAS on pre-treatment NCCT was 1.43 more likely to have a poor functional outcome at 90 days as compared to patients without HMCAS. There was no significant difference of sICH between HMCAS positive and HMCAS negative patients (RR 0.91). There was no significant association between HMCAS and risk of mortality at 90 days (RR 1.34). Our findings on risk ratios are consistent with the results of a recent systematic review and meta-analysis on association of HMCAS with functional outcomes (RR 1.56; 95% CI 1.50–1.62; $p = 0.25$) and sICH (RR 0.97; 95% CI 0.72–1.30; $p = 0.15$) [35]. However, the previous analyses

Table 2 Sensitivity and specificity of HMCAS in predicting functional outcome, sICH and mortality

Treatment	Poor functional outcome		sICH		Mortality	
	tPA	Total	tPA	Total	tPA	Total
Interstudy variation in sensitivity (ICC_SEN)	0.07 (0.00–0.14)	0.08 (0.01–0.15)	0.10 (0.00–0.22)	0.21 (0.02–0.40)	0.04 (0.00–0.11)	0.05 (0.00–0.13)
Interstudy variation in sensitivity (MED_SEN)	0.61 (0.57–0.70)	0.63 (0.58–0.69)	0.64 (0.57–0.76)	0.71 (0.62–0.83)	0.59 (0.54–0.70)	0.60 (0.55–0.70)
Interstudy variation in specificity (ICC_SPE)	0.11 (0.00–0.22)	0.14 (0.03–0.24)	0.06 (0.00–0.12)	0.10 (0.01–0.18)	0.24 (0.00–0.49)	0.22 (0.00–0.43)
Interstudy variation in specificity (MED_SPE)	0.65 (0.59–0.74)	0.67 (0.61–0.75)	0.61 (0.56–0.68)	0.64 (0.59–0.71)	0.72 (0.62–0.88)	0.71 (0.62–0.85)
AUROC	0.61 (0.57–0.65)	0.60 (0.56–0.64)	0.53 (0.48–0.57)	0.56 (0.52–0.61)	0.45 (0.40–0.49)	0.47 (0.43–0.52)
Heterogeneity (Chi-square)	138.749	331.478	42.649	88.019	124.699	162.541
Heterogeneity (*I*-square)	99 (98–99)	99 (99–100)	95 (92–99)	98 (96–99)	98 (97–99)	99 (98–99)
Sensitivity	0.38 (0.30–0.47)	0.43 (0.35–0.51)	0.29 (0.19–0.41)	0.39 (0.24–0.56)	0.39 (0.29–0.49)	0.42 (0.32–0.53)
Specificity	0.81 (0.72–0.87)	0.75 (0.66–0.82)	0.70 (0.62–0.76)	0.65 (0.56–0.73)	0.65 (0.40–0.83)	0.61 (0.40–0.79)
Positive Likelihood Ratio	1.9 (1.6–2.4)	1.7 (1.5–2.1)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	1.1 (0.7–1.7)	1.1 (0.8–1.5)
Negative Likelihood Ratio	0.77 (0.72–0.82)	0.76 (0.71–0.80)	1.02 (0.92–1.14)	0.94 (0.79–1.13)	0.95 (0.76–1.18)	0.95 (0.78–1.15)
Diagnostic Odds Ratio	3 (2–3)	2 (2–3)	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–2)

Number of quadratics points is greater than number of observations for EVT and tPA + EVT treatment subgroups

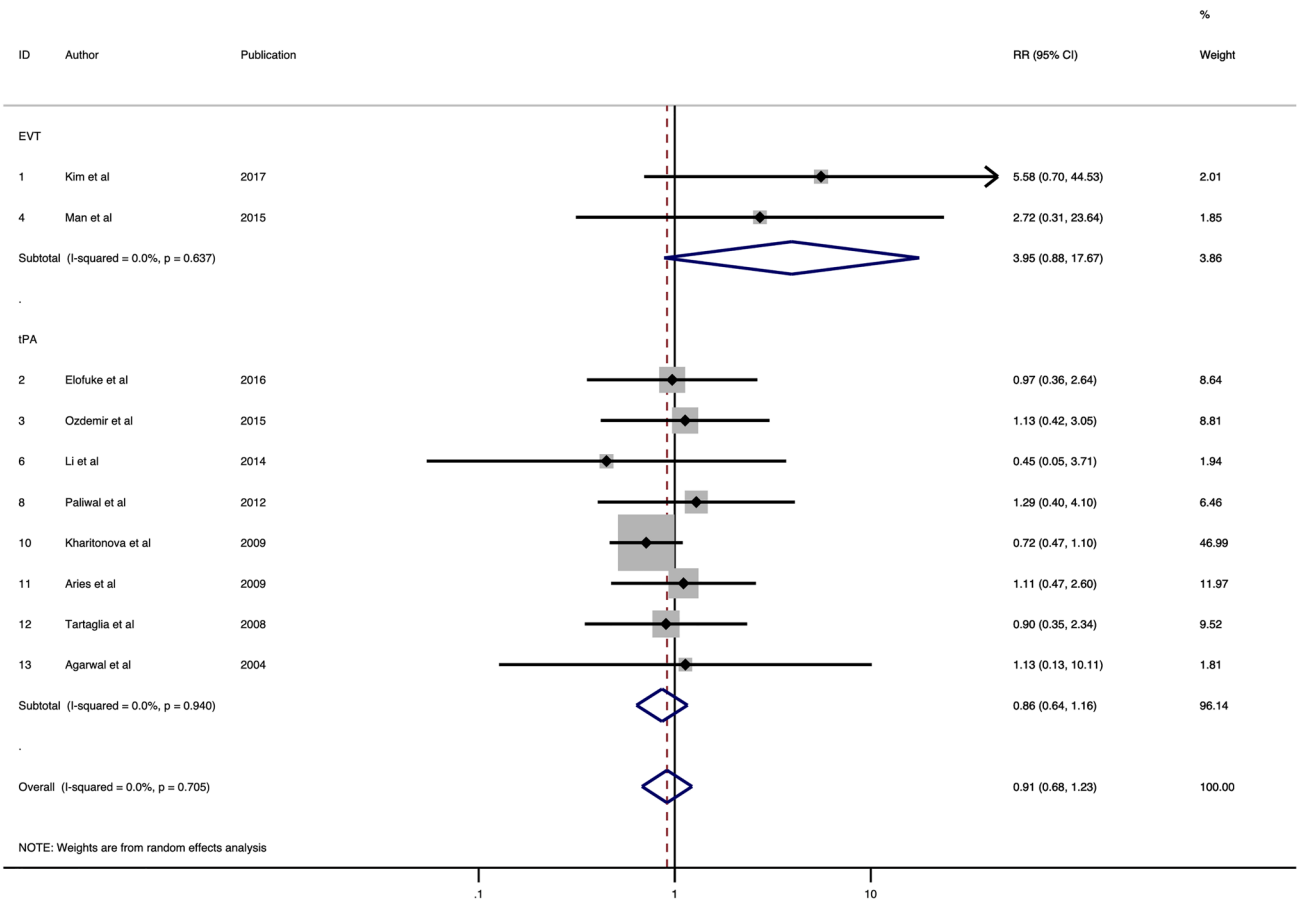


Fig. 3 Forest plot showing the association of the hyperdense middle cerebral artery sign with the risk of symptomatic intracerebral haemorrhage in acute ischaemic stroke patients receiving thrombolysis or/and mechanical thrombectomy

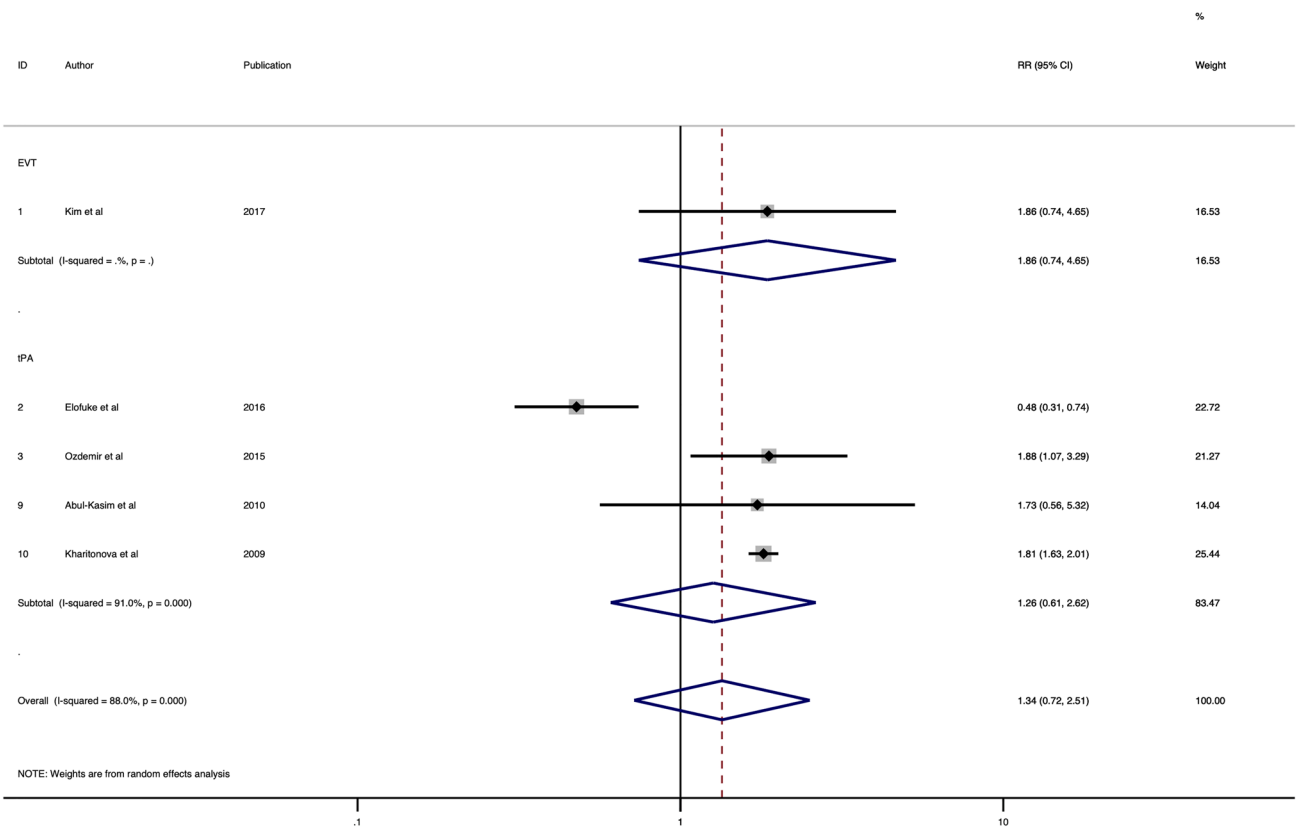


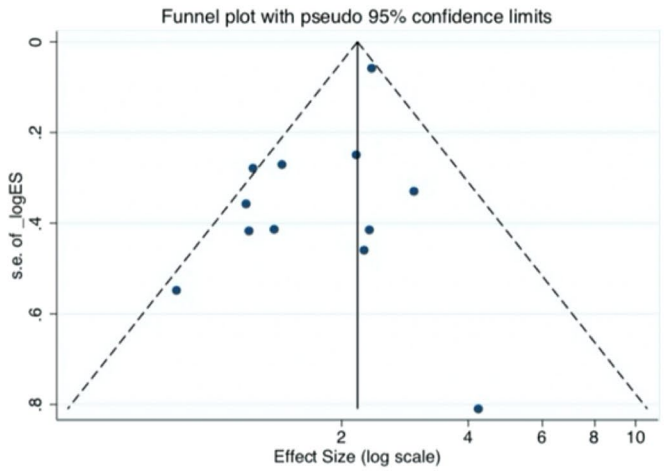
Fig. 4 Forest plot showing the association of the hyperdense middle cerebral artery sign with the risk of mortality in acute ischaemic stroke patients receiving reperfusion therapy

didn't stratify patients based on treatment type. Four studies on AIS patients receiving EVT and tPA were included in the current study [26, 27, 31, 32]. We found that patients with HMCAS receiving EVT (RR 1.1) were associated with lower rates of poor functional outcomes at 90 days as compared to patients receiving tPA (RR 1.53) and combined therapies (RR 1.40).

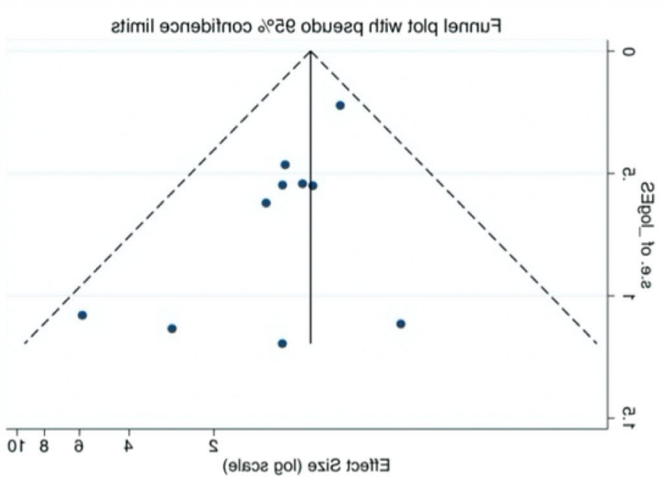
Sensitivity and specificity analyses on the association of HMCAS with clinical outcomes are reported elsewhere (Table 2). Overall, the prognostic sensitivity and specify of HMCAS is poor, with sensitivity lower than the specificity. The sensitivity of HMCAS in predicting a poor functional outcome was 0.43 (95% CI 0.35–0.51). In AIS patients receiving tPA, the sensitivity was 0.38 (95% CI 0.30–0.47). Similarly, the sensitivity of HMCAS in predicting sICH was 0.39 (95% CI 0.24–0.56) and 0.29 (95% CI 0.19–0.41) overall and in tPA subgroup, respectively. With regards to mortality, the sensitivity of HMCAS was 0.42 (95% CI 0.32–0.53) and 0.39 (95% CI 0.29–0.49) overall and in tPA subgroup, respectively. These findings demonstrate that HMCAS is not a robust prognostic biomarker in AIS patients receiving reperfusion therapy.

Future research should be directed on the combined use of HMCAS with other baseline characteristics or biomarkers. For example, other imaging biomarker considerations, such as arterial collateral status are important in determining the prognosis of AIS patient [36–39]. Although, HMCAS might not be the initial preference in predicting clinical outcome in the tertiary care settings, it may be relatively easy to appreciate in an emergency setting and could reduce the time and complexity of acute stroke workflow [5, 22]. This suggests a potential prognostic use of HMCAS in low-resourced settings where only NCCT imaging is available. This is also applicable in telestroke services where a neurologist can provide remote reperfusion treatments to AIS patients, especially in the Coronavirus disease (COVID-19) settings when minimizing viral exposure to healthcare workers is of public health concern [40].

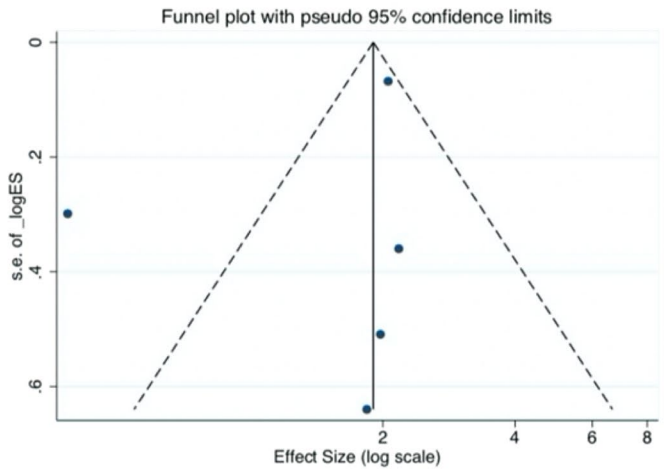
There are several limitations to this study. The heterogeneity in the patient population due to varying patients' selection criteria across several studies was one of the limitations. However, the use of random-effect modelling should mitigate the risk and limitations of heterogeneity in this meta-analysis. Secondly, the CT slice thickness was not uniform across all studies. Varying slice thickness on NCCT imaging affect the accuracy of HMCAS identification by the reporting radiologist. Thin-sliced NCCT is recommended to provide more sensitive and reliable detection of MCA clots [41, 42].



(A) Poor functional outcome at 90 days



(B) Symptomatic intracerebral hemorrhage



(C) Mortality

Fig. 5 Funnel plots showing studies on association of HMCAS with **A** functional outcome at 90 days, **B** sICH and **C** mortality

Another limitation of this study was a relatively small sample size. There were only 4 articles identified with patients receiving EVT or combined therapies. Therefore, subgroup analysis for the association of HMCAS and mortality in EVT patients could not be performed. Short term clinical outcomes at 24 h was considered in this meta-analysis; however, short term outcomes were defined differently across studies, including early neurological deterioration [23], neurological improvement at 24 h [28], dramatic neurological improvement at 24 h [28], rapid neurological improvement [34] and early dramatic recovery [31, 32]. Overall, the HMCAS positive patients were more likely to be associated with increasing rates of early neurological deterioration [23] (39% vs 28%) and lower rates of neurological improvement [28, 31, 32, 34] as compared to HMCAS negative patients. Similarly, only 3 articles, with varying angiographic assessment criteria: mTICI [26, 27], TCD monitoring (TIBI) [28], were included to study the association of HMCAS with angiographic recanalization. This was not sufficient to conduct a meta-analysis. One study included 10,023 patients from the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register (SITS-ISTR) which would skew the results [25]. The risk ratio would deviate towards this study's result since it accounted for more than half of the cumulative weights in the meta-analysis. Furthermore, we did not report on the association of location (proximal vs distal) [27, 34, 43] and attenuation (persistence vs disappearance) [29, 44] of HMCAS which may be of prognostic significance. It is suggested that proximal M1 and full-length M1 are more likely to have a lower rate of long-term favourable functional outcome [27, 43]. Paliwal et al. suggested that persistence of HMCAS can be an early prognostic factor of poor functional outcome (OR 3.352; 95% CI 1.991–11.333; $p = 0.039$) [29]. Kharitonova et al. reported that the disappearance of HMCAS was associated with twice the rates of good functional outcome relative to the persistent HMCAS [44]. Therefore, further studies are required to delineate the accurate relationship between HMCAS and clinical outcomes following AIS across various treatment subgroups. Moreover, the interaction of HMCAS with good and poor collaterals [39] and their role in mediating outcomes following reperfusion therapy is an another potential area of further research. Notably, the role of clot composition, including imaging features, such as clot density or clot perviousness, has been of increasing clinical interest as they may be useful in guiding treatment selection [9, 15]. For example, it is postulated that a very dense artery, would be composed of RBC and thus amenable to aspiration with EVT; and less to IVT using alteplase for example [9]. The pathologic correlations of actual EVT-retrieved clot features with the preintervention non-invasive imaging features, such as HMCAS on NCCT or blooming artefact on MRI are also of pathophysiological significance [14, 45, 46].

Conclusions

This meta-analysis demonstrated that though HMCAS is associated with increased risk of poor functional outcomes, its sensitivity in predicting long-term functional outcome, mortality and sICH after reperfusion therapy is poor. Future studies to delineate the prognostic role of HMCAS in EVT patients are recommended. Moreover, the role of clot composition or clot density in guiding selection of optimal reperfusion therapy or EVT device warrant further research.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Information, further inquiries can be directed to the corresponding author.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-021-01720-3.

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Author contributions SB conceived the study, contributed to the planning, draft and revision of the manuscript; supervision of the students. SB encouraged CS to investigate and supervised the findings of this work. CS and SB wrote the first draft of this paper. All authors contributed to the revision of the manuscript. All authors approved the final draft of the manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

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