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REVIEW ARTICLE

Value of thrombus imaging in predicting the outcomes of patients with large-vessel occlusive strokes after endovascular therapy

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Abstract

Background Acute ischemic stroke leads to serious long-term disability and high mortality, especially in patients with large-vessel occlusive strokes. Nowadays, endovascular therapy is considered as an alternative treatment for these patients. Several studies have used thrombus characteristics based on non-contrast computed tomography (NCCT) and computed tomography angiography (CTA) to predict prognosis in ischemic stroke. We conducted a systematic review to identify potential imaging predictive factors for successful recanalization and improved clinical outcome after endovascular therapy in patients with large-vessel occlusion (LVO) in anterior arterial circulation.

Methods The PubMed databases were searched for related studies reported between September 18, 2009, and September 18, 2019.

Results We selected 11 studies on revascularization and 12 studies on clinical outcome. Patients with thrombus of higher Hounsfield unit (HU), shorter length, higher clot burden score, and increased thrombus permeability may achieve higher recanalization and improved clinical outcome, but the matter is still under debate.

Conclusion Imaging of thrombus can be used as an aseessment tool to predict the outcomes and it needs further studies in the future.

Keywords Ischemic stroke · Thrombus imaging · Endovascular therapy · Recanalization · Clinical outcome

Introduction

Acute ischemic stroke leads to serious long-term disability and high mortality. More than 40% of ischemic strokes are caused by acute large-vessel occlusion. Patients with these strokes have a 3.5-fold increase in mortality at 6 months and a 67% reduction in favorable outcome [1]. Researchers have shown that improved clinical outcome was clearly associated with good recanalization. After pooling available data, Zangerle et al. showed favorable 90-day Rankin scores rate according to recanalization: complete recanalization, 58.3%; partial recanalization,10%; and without recanalization, 5.6% [2, 3].So revascularization is the key to the treatment.

The effectiveness and safety of intravenous thrombolysis (IVT) within 4.5 h after onset have been confirmed by several clinical trials [4, 5]. Despite this, several patients still have serious complications and poor prognosis. However, multiple randomized trials showed the efficacy of endovascular therapy over standard medical care since 2015 [6–9], which suggested that endovascular treatment might raise the possibilities of greater recanalization and improved clinical outcome.

Several studies have found associations between thrombus imaging characteristics and recanalization or clinical outcome. Understanding when endovascular treatment (EVT) could achieve complete recanalization and improved clinical outcome provides important information for us to select patients for endovascular therapy.

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Methods

Search strategy

We searched the PubMed database using the following keywords and terms: "ischemic stroke," "endovascular treatment," "thrombectomy," "thrombus," "clot," "computed tomography," "revascularization," "outcome," and "predictor," with different Boolean operators. Original articles published in English were selected between September 18, 2009, and September 18, 2019. We reviewed the titles and abstracts of the retrieved articles for eligibility and then read the full content of the articles for final eligibility. We also identify the relevant articles from references of each reviewed paper.

Inclusion and exclusion criteria

Inclusion criteria for the selection of articles to include in the review were the following: (1) patients were older than 18 years; (2) acute ischemic stroke was diagnosed within 24 h from last known well with large artery occlusion in the anterior circulation; (3) a visible and symptomatic thrombus was seen on baseline CT or CTA; (4) patients underwent endovascular therapy with or without prior intravenous alteplase; (5) successful recanalization and clinical outcome were reported; (6) reported the association with clinical outcome or successful revascularization for thrombus characteristics.

Study quality appraisal

Two tables were used to extract information from each article. The information included author(s), year of publication, subjects, imaging methods, measurement of thrombus characteristics, and findings. We propose a hypothesis that thrombus imaging could predict the successful revascularization and clinical outcomes of patients with large-vessel occlusive strokes in the anterior circulation after endovascular therapy.

Results

The PubMed databases were searched for studies reported between September 18, 2009, and September 18, 2019. A total of 17 studies meet inclusion criteria, which included 11 studies on revascularization and 12 studies on clinical outcome (Fig. 1).

Measurement of thrombus characteristics

Thrombus characteristics can be measured by various imaging modalities. Brain magnetic resonance imaging (MRI) is known as a powerful tool to identify thrombus by T1-hyperintense vessel sign (T1-HVS) and susceptibility vessel sign (SVS) on T2* MR imaging [10–12]. However, NCCT and CTA are more commonly used in routine stroke practice. In this review, we evaluate the relation between thrombus characteristics and outcomes based on NCCT or CTA.

A hyperdense artery sign is often identified as thrombus on NCCT. The measurements on CTA are indirect and based on absence of contrast opacification. To some extent, the characteristics of the thrombus include the thrombus density, thrombus length, clot burden score, and thrombus permeability. Several studies evaluating imaging features of thrombi have assumed that thrombus density on CT can reflect the constituents of the clots [13, 14]. Thrombus permeability is often assessed by TAI (thrombus attenuation increase) and void fraction. The clot burden was measured by clot burden score (CBS), which was developed to quantify the extent of intracranial thrombus [15]. Details of imaging examinations and images analysis are presented in Table 1.

As shown in many previous trials, the thin-section NCCT is more reliable, sensitive, and accurate for the detection of thrombus when compared with standard NCCT [16–18]. In addition, the imaging information on CTA is approximate and only limited to the anterior circulation. Furthermore, it can also be affected by the collateral circulation and the elapsed time from contrast injection to imaging formation. Nowadays, multiphase four-dimensional CTA (4D-CTA) may provide a more accurate assessment of thrombus characteristics than single-phase CTA [19, 20].

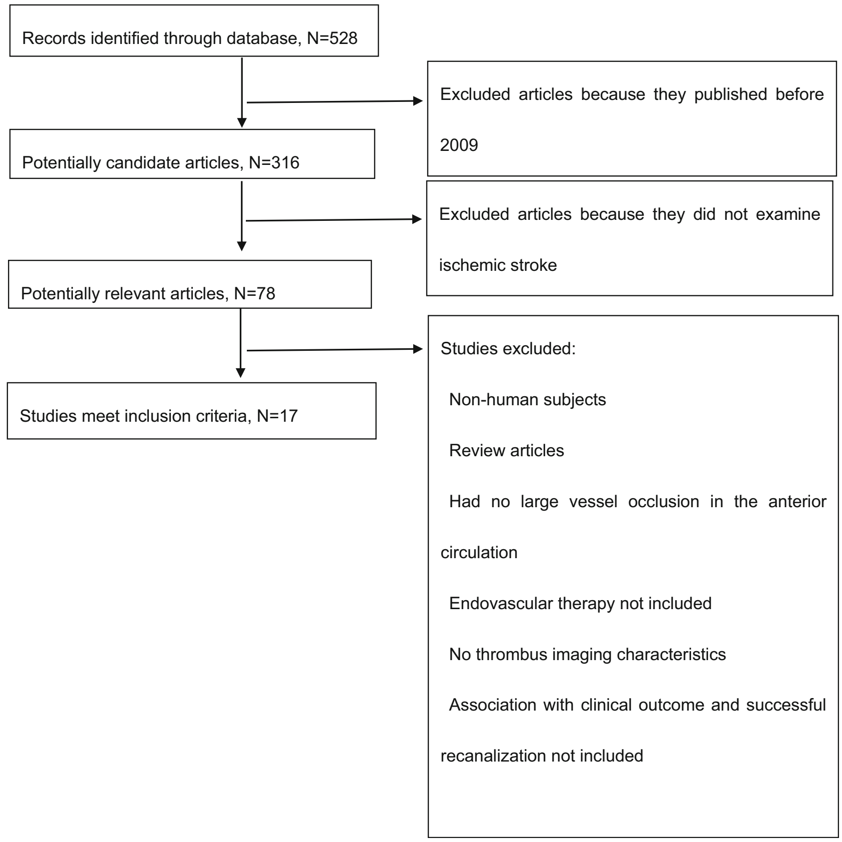
Association between successful revascularization and thrombus characteristics

The association between thrombus characteristics and successful recanalization after EVT has been investigated in Table 2. The results of the studies were not consistent.

Five studies were identified that assessed thrombus density as a predictive factor for successful revascularization after EVT. Only in the study conducted by Mokin et al. did they find that successful recanalization was achieved more frequently in patients with denser thrombi after EVT using the Solitaire stent retriever [21]. However, the other four studies agreed with the view that thrombus density had no influence on recanalization rate in endovascular treatment [22–25].

Five studies about the thrombus length were included in our review. In 2013, Shobha et al. evaluated the association between thrombus length and disappearance of the hyperdense middle cerebral artery sign (HMCAS). In the EVT group, they found that rate of disappearance of HMCAS was no difference from short (< 10 mm) to long length thrombus (> 20 mm) [26]. Since then, more and more researchers further investigated the association between thrombus length and recanalization situation defined as thrombolysis in cerebral infarction (TICI) score, modified TICI or extended TICI, although no significant association was found in these studies [21–23, 27].

Fig. 1 Flow of selected articles



The extant literature regarding the association between CBS and successful revascularization was reviewed. In the SWIFT PRIME trial, Mokin et al. found that the IVT plus stent retriever thrombectomy treatment was highly effective in achieving successful recanalization throughout the entire range of CBS values [28]. Most of the other studies also supported that CBS may have a smaller effect in endovascular treatment [21, 23, 29]. Contrary to these results, Treurniet et al. reported that a higher CBS was linked to a higher likelihood of recanalization [30]. Thus, the relationship between CBS and successful recanalization following endovascular treatment is still under debate.

Two studies on thrombus permeability were evaluated in this review. However, they had different opinions. On the one hand, Santos et al. found that patients with pervious thrombus were more likely to have successful recanalization [31]. On the other hand, Dutra et al. analyzed 408 patients with LVO in anterior arterial circulation and found successful reperfusion was associated with distal thrombi instead of thrombus permeability [23].

Association between clinical outcome and thrombus characteristics

The association between thrombus characteristics and clinical outcome after EVT has been investigated in Table 3.

Several studies have attempted to discover the association between clot density and clinical outcome. Spiotta and Dutra et al. found no significant associations between thrombus density and clinical outcomes [22, 23]. Similarly, Songsaeng et al. retrospectively evaluated the thrombus density on CT or CTA or CECT (contrast-enhanced CT) of 97 patients who underwent mechanical thrombectomy, and they found no difference among good, moderate, and poor clinical outcome [32]. Guzzardi et al. also agreed with the results [33]. However, when considering the relative thrombus density on CTA, Borst et al. observed that it was significantly associated with functional outcome with an adjusted common OR of 1.21 per 10% [34].

Evidence regarding thrombus length and clinical outcome is somewhat contradictory. On the one hand, Spiotta et al. retrospectively evaluated 141 patients who were given intra-arterial therapy (IAT) and found no significant associations between clot length and functional outcome at 90 days [22].On the other hand, Yoo et al. studied 108 patients in the THERAPY trial and discovered that longer symptomatic thrombi was associated with worse 90-day clinical outcome, although patients might have more benefits from aspiration thrombectomy than IVT alone [27]. There were many other studies on the length of the thrombus, but no consensus has been reached so far [23, 33, 35, 36].

Four studies that assessed clot burden score as a predictor for improved clinical outcome after EVT were identified. Three of these studies made a consensus that higher CBS was associated with improved outcome and might be used as a prognostic marker, especially for patients with a CBS ≥ 6, regardless of

Table 1 Methods to measure the thrombus characteristics

Characteristic	Imaging modality	Measurement method	Limitations
Length	NCCT	Pixel segmentation and Euclidean length measurement after reducing to skeleton using software	Limited in branched or curved arteries
	CTA	Based on absence of contrast opacification, used freehand curve function on maximum intensity projection (MIP) images after processing procedure	Indirect and the length can be overestimated
Clot burden score	CTA	A 10-point scoring system, two points were subtracted for the absence of contrast opacification in supraclinoid ICA, proximal M1 segment, or distal M1 segment, and 1 point was subtracted each for M2 branches, infraclinoid ICA, and A1 segment	Only limited to anterior circulation and is affected by the backflow from collateral circulation and the elapsed time from contrast injection to brain imaging
Density	NCCT/CTA	(1) Define the ROI (region of interest) before calculating density, then manually outlined the margin of clot in each section, and summed the values of HU in total sections; the value was further divided by the number of sections (2) Manually drawn small circles within the thrombus and then calculated mean values	Manual ROI placement may be subject to operator bias Composition may vary within the thrombus and the mean density of the thrombus could be less informative
Thrombus attenuation increase (TAI)	NCCT/CTA	subtract the mean density of the thrombus on NCCT from the mean density on CTA	Causing an underestimation because of hemodynamic restrictions, timing limitations, or pseudo-occlusions
Void fraction	NCCT/CTA	The ratio between the attenuation increase of the thrombus and the attenuation increase of the contralateral vessel segment	More time-consuming and less robust because additional manual measures in the contralateral artery are required

NCCT non-contrast computed tomography, *CTA* computed tomography angiography, *ICA* internal carotid artery

mechanical devices they used [23, 30, 37]. However, one literature has questioned the validity of CBS in clinical outcome and found that proportions of good clinical outcome were similar among the three groups divided by CBS values [28].

Table 2 Association between successful revascularization and thrombus characteristics

Ref. no	Authors (year)	Artery	Treatment modality	Study subjects	Imaging (CT thickness, mm)	Imaging characteristics	Association with successful revascularization
24	Yilmaz, 2013	MCA	Stent retrievers	70	NCCT (5.0), CTA	Density	No (50.1 ± 7.8 vs. 48.7 ± 8.2, P = 0.567) *
26	Shobha, 2013	M1	Not specified	35	NCCT (5.0)	Length	Yes (60% vs. 33% vs. 50%, P < 0.002) ✚
22	Spiotta, 2014	MCA	Penumbra aspiration system	122	CTA	Length Density	No (13.3 ± 10.0 vs.13.5 ± 7.6, P = 0.92) △ No (57.1 ± 16.3 vs. 68.7 ± 43.2, P = 0.22) *
21	Mokin, 2015	MCA, ICA	Solitaire stent retriever	41	NCCT (5.0), CTA	Density CBS Length	Yes (49.9 ± 7.6 vs. 43.8 ± 6.6, P = 0.01) * No (6.6 ± 1.1 vs. 6.6 ± 1.8, P = 0.87) ☆ No (12.2 ± 4.7 vs. 14.0 ± 6.0, P = 0.44) △
31	Santos, 2016	MCA, ICA	IVT, IAT	184	Thin-slice NCCT (< 2.5), CTA	TAI void fraction	Yes (OR 2.5; 95% CI, 1.3–4.8) Yes (OR 2.1; 95%CI, 1.1–4.1)
28	Mokin, 2017	MCA, ICA	Solitaire	69	CTA	CBS	No (6.5 ± 1.7 vs. 7.3 ± 1.3, P = 0.25) ☆
30	Treurniet,2016	MCA, ICA	Solitaire	499	CTA	CBS	Yes (model A, OR 1.25; 95% CI, 1.13–1.81; model B, OR 1.27; 95% CI, 1.14–1.41)
29	Angermailer, 2016	MCA, ICA	Stent retriever	63	NCCT (4.5), CTA	CBS	No (OR 1.3; 95% CI, 0.95–1.7)
27	Yoo, 2017	MCA, ICA	IAT	55	NCCT (5.0), CTA	Length	No (60% vs. 84.6% vs. 76.5%, P > 0.05) ▹
25	Jagani,2017	MCA	IAT	65	NCCT (5.0)	Density	No (49.2 ± 5.8 vs. 53.5 ± 17.1, P = 0.37) *
23	Dutra, 2019	Anterior arterial circulation	Stent retriever	356	Thin-slice NCCT (<2.5), CTA	CBS Length Density TAI	No (aOR 1.05; 95% CI, 0.97–1.14) No (aOR 0.97; 95% CI, 0.94–1.01) No (aOR 1.00; 95% CI, 0.98–1.02) No (aOR 0.99; 95% CI, 0.98–1.01)

NCCT non-contrast computed tomography, *CTA* computed tomography angiography, *MCA* middle cerebral artery, *ICA* internal carotid artery, *IVT* intravenous thrombolysis, *IAT* intra-arterial therapy, *CBS* clot burden score, *TAI* thrombus attenuation increase, *OR* odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval

* Recanalization vs. nonrecanalization, HU

△ Recanalization vs. nonrecanalization, mm

☆ Recanalization vs. nonrecanalization

✚ Thrombus length < 10 mm vs. 10–19 mm vs. 20 mm

▹ ≤ 11.1 mm vs. 11.3–17.7 mm vs. ≥ 18.0 mm

Table 3 Association between clinical outcome and thrombus characteristics

Ref. no	Authors (year)	Artery	Treatment modality	Study subjects	Imaging (CT thickness, mm)	Imaging characteristics	Association with favorable clinical outcome
22	Spiotta, 2014	MCA	Penumbra aspiration system	122	CTA	Length Density	No (12.8 ± 7.7 vs.14.6 ± 11.2, P = 0.30) △ No (57.6 ± 14.0 vs.62.6 ± 33.2, P = 0.34) ☆
36	Lobsien, 2015	MCA	IVT IVT-MT	59 28	Thin-slice NCCT (1.0), CTA	Length	No (OR 5.307; 95% CI, 0.485–58.085)
31	Santos, 2016	ICA, MCA	IVT, IAT	184	Thin-slice NCCT (< 2.5), CTA	TAI void fraction	Yes (OR 3.2; 95% CI, 1.7–6.4) Yes (OR 3.3; 95%CI, 1.7–6.3)
28	Mokin, 2017	MCA, ICA	Solitaire	69	CTA	CBS	No (60.9% vs. 42.9% vs. 73.9%, P = 0.52) *
30	Treurniet,2016	MCA, ICA	Solitaire	499	CTA	CBS	Yes (model A, aOR 1.11; 95% CI, 1.04–1.18; model B, aOR 1.12; 95% CI, 1.04–1.20)
35	Jadhav, 2017	MCA, ICA	Not specified	50	NCCT, CTA	Length	No (OR 2.38; 95% CI, 0.42–13.4; P = 0.32)
27	Yoo, 2017	MCA, ICA	IVT IAT	53 55	NCCT (5.0), CTA	Length	Yes (OR 1.24; 95% CI, 1.04–1.52; P = 0.02) ✚
34	Borst, 2017	Anterior arterial circulation	IAT Medical treatment	78 121	Thin-slice NCCT (< 2.5), CTA	Density	Yes (aOR 1.21; 95% CI, 1.02–1.43; P = 0.029) ▹
37	Park, 2018	ICA terminus	Penumbra aspiration catheter	119	NCCT (4.5), CTA	CBS	Yes (OR 3.97; 95%CI, 1.05–14.99; P = .042)
33	Guzzardi, 2018	Anterior arterial circulation	ADAPT IVT + ADAPT	8 22	NCCT (2.0), CTA	Length Density	Yes (40% vs. 79%, P = 0.05) ▲ No [1.37 (1.25–1.54) vs. 1.43 (1.29–1.62), P = 0.06] ▼
32	Songsaeng, 2019	Anterior arterial circulation	Not specified	97	NCCT (1.25 or 1.5), CTA, CECT	Density	No (NCCT, 58.4 ± 7.0 vs. 60.4 ± 9.0 vs. 58.0 ± 7.5, P = 0.485; CTA, 58.5 ± 10.6 vs. 63.8 ± 8.8 vs. 59.8 ± 10.2, P = 0.203; CECT 60.7 ± 1.8 vs. 61.7 ± 10.5 vs. 57.9 ± 8.4, P = 0.441) ★
23	Dutra, 2019	Anterior arterial circulation	Stent retriever	356	Thin-slice NCCT (< 2.5), CTA	CBS Length Density TAI	Yes (aOR 1.15; 95% CI, 1.07–1.24) Yes (aOR 0.96; 95% CI, 0.94–0.99) No (aOR 1.01; 95% CI, 0.98–1.02) Yes (aOR 1.01; 95% CI, 1.00–1.02)

NCCT non-contrast computed tomography, *CTA* computed tomography angiography, *CECT* contrast-enhanced computed tomography, *MCA* middle cerebral artery, *ICA* internal carotid artery, *IVT* intravenous thrombolysis, *IAT* intra-arterial therapy, *IVT-MT* mechanical thrombectomy plus additional intravenous thrombolysis, *ADAPT* a direct aspiration first pass technique, *CBS* clot burden score, *TAI* thrombus attenuation increase, *OR* odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval, *density* clot density ratio

*Clot burden score 0–5 vs. 6–7 vs. 8–9

△ mRS score of 0–2 at 90 days vs. score of 3–6, mm

☆ Score of 0–2 at 90 days vs. score of 3–6,HU;

✚ Worse outcome with per 5-mm thrombus length increment

▹ Relative density calculated by dividing the mean Hounsfield unit of the thrombus by the mean Hounsfield unit of the contralateral vessel segment

★ mRS 0–2 vs. 3–4 vs. > 4

▲ Thrombus length »10 mm vs. <10 mm

▼ mRS ≤ 2 vs. mRS > 2, clot density (Hounsfield units) corrected by contralateral

Only two studies about the thrombus permeability were included in our review. Santos et al. observed that a pervious thrombus defined as TAI ≥ 10.9 HU and void fraction ≥ 6.5% was more likely to have improved functional outcome [31]. Likewise, Dutra et al. found that a pervious thrombus was strongly associated with better clinical outcome, which also validated the finding [23].

A new challenge: calcified cerebral emboli

Calcified cerebral emboli (CCE) area rarely reported cause of LVO in acute stroke, but it may be recurrent and devastating [38]. In previous literature, it was observed in 1.1–3% of patients obtaining a NCCT of head [39–42]. The most common site that calcified emboli located was middle cerebral artery, followed by anterior and posterior cerebral arteries. In addition, the embolus attenuation usually ranged from 79 to 435 HU on NCCT [41]. However, up to 27% of cases were overlooked or misinterpreted because emboli were often small (2–3 mm) [41]. There were even some pitfalls, such as false patency, reported in the literature with the use of CTA [43, 44]. So, when CT shows hyperdense emboli but CTA does not observe LVO, we should be cautious about false patency sign and consider alternative imaging modalities.

Only small samples were reported in the previous literature. Raghib et al. compared the clinical outcome of 11 patients with calcified cerebral emboli who underwent acute treatment (4 patients with EVT) and suggested it should be given to EVT preferentially [42]. Two case reports showed successful recanalization of calcified embolisms after mechanical treatment [45, 46], which indirectly confirmed the result. However, in contrast with the findings, two studies using mechanical aspiration thrombectomy or stent retriever thrombectomy reported that EVT might be less effective for calcified thromboemboli than the other types of clots due to hardness of the calcified plaque [39, 40].

There is little data available on the efficacy or safety of EVT in patients with CCE, and we lack therapeutic experience. Moreover, despite the low incidence of brain calcification, there are still many cases of misdiagnosis. It is somewhat challenging to make diagnosis and provide optimal treatment. It still needs large samples and more randomized studies in the future.

Discussion

Several studies evaluating imaging features of thrombi have assumed that thrombus density on CT can reflect the constituents of the clots. Kirchhof et al. found that "red thrombus" had higher HU than "white thrombus" [14]. Furthermore, a hyperdense artery sign is commonly associated with RBC-rich thrombi [13]. Animal models of femoral artery thrombosis and embolic stroke have shown that thrombolysis was more effective in patients with erythrocyte-rich clots [47, 48]. Nam et al. found that thrombus resolution increased by 18% per 10-HU increase [49], and Niesten et al. noted that a cutoffs of absolute HU < 56.5 and relative HU < 1.38 were the predictive values for persistent occlusion [50, 51]. However, as the results in our review, thrombus density has largely been shown to be irrelevant in successful revascularization and favorable clinical outcome for patients with EVT.

Riedel et al. observed that increasing thrombus length was a strong predictor for lower recanalization rate after IV-tPA treatment, especially for patients with thrombus length longer than 8 mm [52]. In addition, Rohan et al. found an optimal cutoff of 12 mm with sensitivity 0.67 and specificity 0.7 to predict recanalization for patients presented with M1 segment occlusion [53]. However, Behrens et al. conducted the first research to analyze the impact of thrombus length on recanalization for patients treated with bridging thrombolysis and determined that clots longer than 16 mm were unlikely to have complete recanalization, suggesting a cutoff length somewhat higher than previously reported [54]. After that, more and more researchers further investigated the association between thrombus length and recanalization after EVT. Although the results of the previous studies were inconsistent, the predictability of thrombus length for successful recanalization seems more remarkable in IVT treatment than in endovascular treatment.

Despite thrombus length, clot burden score may affect the response to reperfusion treatment. Puetz et al. supported that CBS not only was associated with the final infarction size but also was closely linked to the hemorrhagic transformation rate and clinical outcomes [15]. The following research further stated that higher CBS (>6 points) was the useful marker predicting higher recanalization rates and smaller infarct volumes for patients treated with intravenous recombinant tissue plasminogen [55]. In a post hoc analysis of the IMS-III trial, the author found significant difference in recanalization rates between the IAT and IVT groups for higher thrombus burden, which implied a higher efficacy of IAT relative to IVT for lower CBS [56]. It seemed that CBS might have a smaller effect in endovascular treatment than in intravenous recombinant tissue plasminogen treatment. In our review, relationship between CBS and successful recanalization or clinical outcome following endovascular treatment is still under debate.

In our review, we evaluated the thrombus permeability measured by TAI or void fraction. Although the cutoff values for dichotomizing perviousness were various, they suggested that patients with impermeable thrombi recanalize less commonly and more slowly, which lead to worse outcome and may require mechanical means. There is a few research about the association between thrombus permeability and successful revascularization or clinical outcome, so studies are still need to further verify.

Conclusions

Patients with large-vessel occlusive strokes have variable clinical responses to endovascular therapy. Imaging of thrombus can be used as an assessment tool to predict the outcomes. Patients with thrombus of higher HU, shorter length, higher clot burden score, and increased thrombus permeability may achieve higher recanalization and improved clinical outcome. However, controversial results have been provided in our review, which suggested the matter is still under debate and it needs further studies in the future.

Compliance with ethical standards

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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

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