Prognostic Value of Clot Burden Score in Acute Ischemic Stroke after Reperfusion Therapies: A Systematic Review and Meta-Analysis

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Background and Aim: Clot burden score (CBS) was designed to weight the thrombus status in cerebral anterior circulation. We performed a systematic review and meta-analysis to investigate the prognostic value of CBS in acute ischemic stroke (AIS) patients undergoing reperfusion therapies. *Methods*: We searched relevant databases for eligible articles reporting CBS in AIS patients. The effect sizes of good functional outcome, recanalization, or hemorrhagic transformation (HT) were pooled with random-/fixed-effect models. Sensitivity analyses and heterogeneity tests were performed. *Results*: Fifteen eligible studies enrolling 3302 AIS patients undergoing reperfusion therapies were included. AIS patients with per 1-point increase CBS were associated with good functional outcome (pooled odds ratio [OR]: 1.15, 95% confidence interval [CI]: 1.09-1.20) and high rate of recanalization (pooled OR: 1.27, 95% CI: 1.14-1.40). Results from categorical groups indicated high CBS at baseline was associated with higher likelihood of good functional outcome (pooled OR: 1.59, 95% CI: 1.30-1.94) and superior recanalization rates (pooled OR: 2.53, 95% CI: 1.79-3.57). Further stratified analyses showed in intravenous thrombolysis (IVT) alone group, increasing CBS was associated with good functional outcome (continuous pooled OR: 1.18, 95% CI: 1.10-1.27; categorical pooled OR: 3.38, 95% CI: 2.01-5.69) or recanalization (categorical pooled OR: 4.13, 95% CI: 2.00-8.51), but not in endovascular therapy alone group. No significant association was found between CBS and HT. *Conclusions*: CBS could be a predictor for AIS after reperfusion therapies in functional outcome and successful recanalization particularly in patients receiving IVT alone; while CBS might not be a predictor for HT.

Key Words: Clot burden score—ischemic stroke—prognostic value—reperfusion therapy

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Introduction

Ischemic stroke is the leading cause of death and morbidity around the world.[1] Intravenous thrombolysis (IVT) and endovascular therapy (EVT) remain the most powerful intervention for in-time-window acute ischemic stroke (AIS) patients. In order to assess the efficacy and determine the best treatment timely, plenty of imaging indicators have been developed to screen patients eligible for IVT or EVT and predict the clinical outcome, including the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), early ischemic changes with hypoattenuation. However, these indicators are time-dependent in noncontrast computed tomography (CT) and they may be invisible in the early stage or in small infarct lesions. Moreover, several studies have shown no significant interaction between ASPECTS or CT leukoaraiosis and thrombolysis effect.[2,3] Due to the limitations, novel imaging indicators are necessary to be assessed.

Clot burden score (CBS), a CT angiography (CTA)-based grading system of thrombus burden on AIS patients, was firstly proposed by Puetz et al[4] It was developed to reflect the thrombus extent and location in the cerebral anterior circulation. Longer thrombus length and more proximal location gained lower scores in this 10-point scoring system, which was strongly related to successful recanalization and clinical outcome.[5] Therefore, CBS was accessible, not time-dependent, and it might be more predictive than other image indicators.[6]

Although several studies revealed the prognostic value of CBS in AIS patients with IVT or EVT, a comprehensive review with larger sample sizes and higher evident level was needed to assess the predictability of CBS. Moreover, uncertainty remained across published studies. Several studies reported that increasing CBS was associated with a higher likelihood of recanalization and improved neurological outcome at 90 days,[4,7-9] while another study found no relationship between CBS level and functional outcome or hemorrhagic transformation (HT) after AIS.[8,10-13] Thus, to review current evidence, we conducted a systematic review and meta-analysis to evaluate the prognostic value of CBS in AIS patients treated with reperfusion therapy.

Material and Methods

Our systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

Literature Search Strategy

We searched published studies up to February 2019 using the following databases: MEDLINE (PubMed), EMBASE, Web of Science, and Cochrane Library. Reference lists from identified articles and published reviews were hand-searched. We used the following keywords: "ischemic stroke" or "transient ischemic attacks (TIA)" and "clot burden score" or "CBS" and restricting to human species. We also screened the reference papers from retrieved articles. Detailed search strategy was also seen Data Supplement (Table S1).

Study Selection and Eligibility Criteria

We enrolled studies that met the following criteria: (1) patients with AIS or TIA older than 18 years old; (2) studies enrolled patients mainly undergoing reperfusion therapies, including EVT or IVT; (3) association of CBS and outcomes was reported; and (4) at least one of the following outcomes should be reported: modified Rankin scale score, recanalization, or HT.

We excluded those studies that (1) reported odds ratio (OR)/relative risk (RR)/hazard ratio without 95% confidence interval (CI) or lacked effect sizes; (2) effect sizes without any adjustment; (3) non-English language. Abstracts and titles were screened for potentially relevant studies by 2 independent reviewers (G.M. Li and H.P. Li). Divergences were resolved by discussion among all authors. Citation management and deduplication were performed in ENDNOTE X9.

Data Extraction and Methodological Quality Evaluation

Data were extracted by 2 independent investigators (G. M. Li and G.L. Wu) from the included studies and transcribed into a standardized data extraction template. The following information (if available) was extracted from included studies: authors; title; year of publication; region; study design; sample size; age; gender; National Institute of Health stroke scale at baseline; outcome and frequency of outcome; effect sizes and the corresponding 95% CI; and confounders. If studies reported multiple adjusted effect sizes from different model, the effect size with the most adjustment was used for further analyses. The outcome variables of interest were defined as good functional outcome (that was, modified Rankin scale $\leq$ 2), recanalization (mTICI $\leq$ 2a/3 by digital subtraction angiography or evaluated by CTA/MRA) and HT.

Quality Assessment

Study quality assessment was conducted by 2 independent investigators (G.L. Wu and Z.J. Qin) according to the Newcastle-Ottawa Quality Assessment Scale (NOS).[15] Assessment of NOS included selections of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest for case-control or cohort studies. The high-quality study was defined as a study with $\geq$7 awarded stars.

Statistical Analysis

We conducted 3 main analyses: we investigated the associations between (1) CBS levels and good functional outcome, (2) CBS levels and successful recanalization, (3)

CBS levels and risk of HT, and (4) CBS levels and clinical outcomes in different reperfusion therapies groups.

Effect sizes and corresponding 95% CIs were pooled for the high versus low levels of CBS for each outcome. The reported effect sizes were classified into 2 types, categorical measures (top versus bottom; 2 groups, 3 groups, 4 groups divided by cut-off point) or continuous measures (per 1-point increase or decrease). For consistency of data synthesis, we converted the reported effect measures into 2 groups, categorical group (CBS > 6 versus CBS ≤ 6) and continuous group (per 1 point increase) using the method provided by Greenland and Longnecker.[16] We also adopted the method from Zhang et al to convert the relative ratio into odd ratio.[17] Studies were divided into 3 groups according to the reperfusion therapies, IVT alone group (mainly received IVT alone), EVT alone group (mainly received EVT), and mixed group (mainly received IVT or EVT).

Study heterogeneity was assessed using a Q test I^2 statistic.[18] We considered low, moderate, and high I^2 values to be 25%, 50%, and 75%, respectively. Random-effect model was applied to pool the data if I^2 exceeded 50%, otherwise, a fixed-effect model was used. Sensitivity analyses were also performed. Publishing bias was assessed by visual inspections of funnel plots. Begg's and Egger's test was also used to evaluate publication bias.[19] If the 2-side *P* value of Begg's and Egger's test was lower than .05, publication bias was considered statistically significant. Once the publication bias was detected, we used the fill−and−trim method to impute or fill artificial studies to achieve symmetry of the funnel plot and re-estimated the effect sizes.[20] All statistical analyses were performed with the STATA 14.0 (StataCorp, College Station, TX).

Result

Literature Research

The flow chart summarized the process of study selection (Fig 1). Initial databases searches yielded 689 articles after removal of duplicates. After screening titles and abstracts, 634 articles were excluded for case report, abstract articles, conference papers, or irrelevant to the current analysis. The full texts of 55 potentially relevant studies were retrieved for further identification. According to the inclusion or exclusion criteria, 40 studies were excluded for the following reasons: conference abstract (n = 13), without reported effect sizes or corresponding 95% CI (n = 10), association between CBS and reported outcome was unknown (n = 6), unknown prognostic value of CBS (n = 6), review articles (n = 2), derived from the same cohort or trial (n = 3). Finally, 15 eligible studies [4,6-9,11,13,21-28] met all the criteria based on the full text reviewed.

Study Characteristics

Descriptive data of 15 included studies were summarized in Table 1. The included studies were published between 2008 and 2019. Eight studies were prospective enrolled or ancillary analysis of randomized controlled trials whereas other 7 studies were retrospective. Four studies were performed in Canada, 2 in America, 3 in France, 2 in Netherlands, and 1 in Turkey, Finland, Korea, and German. The average NOS scores were 7.46 points from all included studies. Of them, 11 studies were high quality, whereas 4 studies were intermediate quality according to NOS scores.

Participant Characteristics

A total of 3302 subjects were identified, with an average age ranging from 63.2 to 73 years. The proportion of male subjects ranged from 36.5% to 61.0%. Baseline National Institute of Health stroke scale ranged from 7 to 18 points. Frequency of outcome ranged from 25.4% to 74% for good outcome, 42% to 85.3% for recanalization, and 6.5% to 47.2% for HT.

Prognostic Value of CBS for Good Functional Outcome

Seven studies showed that increasing CBS was associated with good functional outcome after AIS at 3 months in per 1-point increase (pooled OR: 1.15, 95% CI: 1.09-1.20, *P*= .237, I-square = 25.2%) (Fig 2). Also, compared with subjects in lower CBS group, higher CBS group was associated with good functional outcome after AIS at 3 months from 7 published studies (pooled OR: 2.46, 95% CI: 1.55-3.89, *P* = .002, I-square = 71.1%) (Fig 3). Since significant heterogeneity was detected in the categorical group, we performed a sensitivity analysis. After excluding 2 studies,[4,6] result from 5 studies indicated that higher CBS level was still associated with good functional outcome after AIS at 3 months (pooled OR: 1.59, 95% CI: 1.30-1.94, *P* = .130, I-square = 43.7%) (Fig 4). Begg's and Egger's test was found without statistical significance in continuous group (*P* > .05) while potential publication bias was detected in categorical group with a significant Egger's asymmetry test (*P* = .02). Thus the fill-and−trim method was applied and then 2 additional artificial studies were integrated into the meta−analysis to generate a symmetric funnel plot (Fig. S1). The fill-and−trimmed OR was 1.49 (95% CI, 1.03-2.15; *P* < .001) which indicated the result was stable in our study.

Prognostic Value of CBS for Recanalization

Based on 2 studies, increasing CBS was associated with success of recanalization after AIS in continuous group (pooled OR: 1.27, 95% CI: 1.14-1.40, *P* = .762, I-square = 0) (Fig 5) or in categorical group from 4 studies (pooled OR: 2.53, 95% CI: 1.79-3.57, *P* = .28, I-square = 21.7%) (Fig 6). Heterogeneity among these studies was not statistically significant. Publication bias was not detected by using Begg's and Egger's test in 4 included studies from the categorical group (*P* > .05).

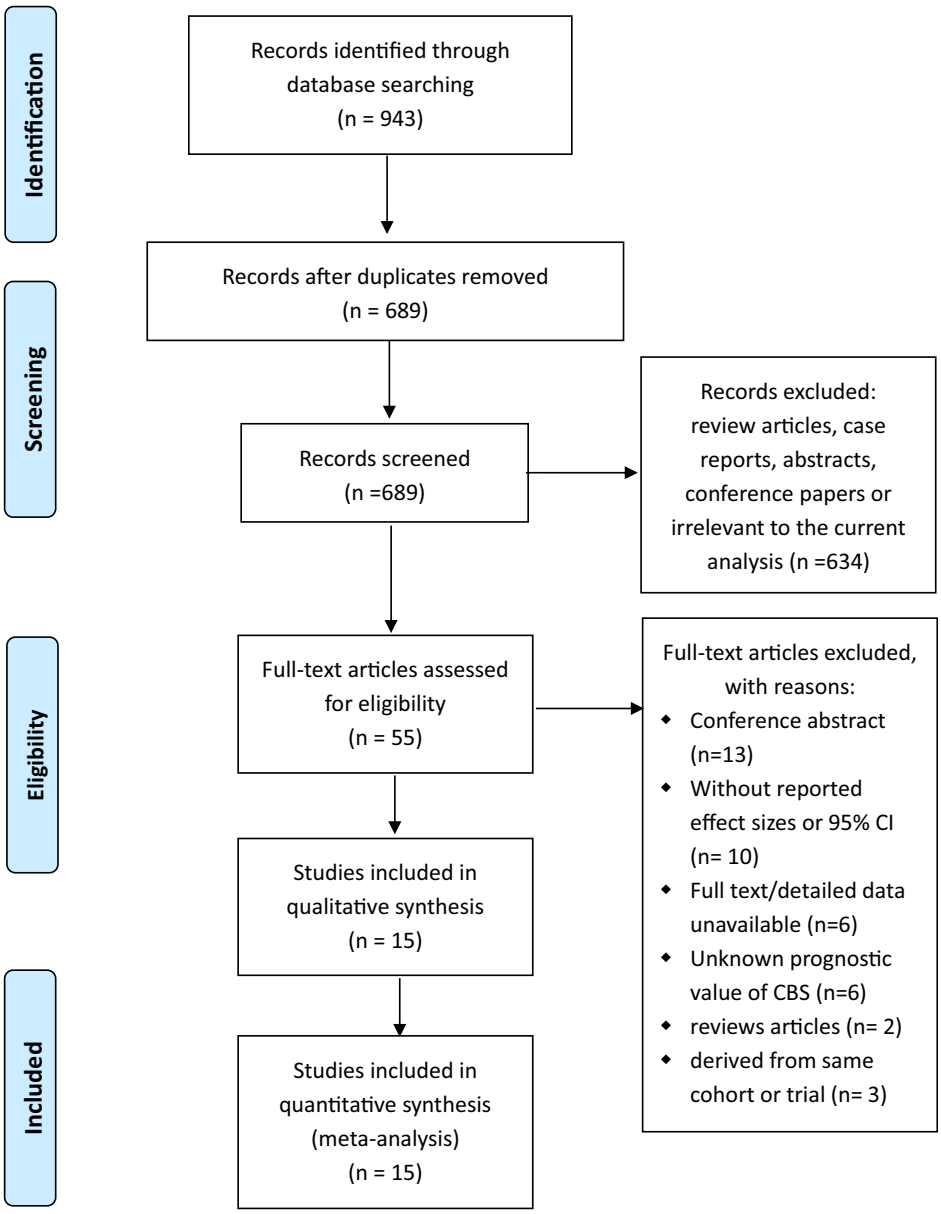

Figure 1. *Flowchart for study screening and selection.*

Prognostic Value of CBS for HT

Three results from 2 studies indicated no association between CBS level and HT after AIS in continuous group (pooled OR: 1.02, 95% CI: .88-1.17, $P = .028$, I-square = 72.0%) (Fig 7) or in categorical group from 2 studies (pooled OR: 1.07, 95% CI: .47-2.41, $P = .092$, I-square = 64.8%) (Fig 8). Statistically significant heterogeneity was observed in both groups. Sensitivity analysis and publication bias were unable to perform since only 2 studies in this subgroup meta-analysis.

Prognostic Value of CBS in IVT Alone or EVT Alone

For good functional outcome, in patients receiving IVT alone, increasing CBS was associated with good functional outcome in continuous group (pooled OR: 1.18, 95% CI: 1.10-1.27, $P = .13$, I-square = 46.5%) (Fig. S2) or in categorical group (pooled OR: 3.38, 95% CI: 2.01-5.69, $P = .58$, I-square = 0%) (Fig. S3). In patients receiving EVT alone, one study[28] reported higher CBS was not associated with good functional outcome in continuous group (OR: .94, 95% CI: .79-1.12, $P = .73$) or in categorical group from 4 studies (pooled OR: 1.75, 95% CI: .80-3.81, $P = .009$, I-square = 74.0%) (Fig. S4).

For recanalization, in IVT alone group, 2 studies demonstrated success of recanalization in favor of high CBS in categorical group (pooled OR: 4.13, 95% CI: 2.00-8.51, $P = .53$, I-square = 0%) (Fig. S5). In EVT alone group, no association was found in continuous group from 1 study[21] (OR: 1.18, 95% CI: .74-1.87, $P = .49$) while positive

Table 1. *Baseline characteristics of included studies*

Author	Year	Study design	Region	Reperfusion therapy (n, %)	Sample size	Male (%)	Age, y	NIHSS	CBS comparisons	GOF (%)	Rec (%)	HT (%)	NOS
Angermaier A.	2016	RE	Germany	EVT	63	36.5	73*	13	Per 1 score increase		66.7	6.5	8
Dehkharghani S.	2015	PRO-RE	USA	IVT or EVT	62	41.9	70*	15	Per 1 score increase	34.0			6
Krishnan P.	2015	RE	Canada	IVT (219, 80.2%)	273	52.3	71.68	DNR	Per 1 score increase	35.8		38.8	6
Legrand L.	2013	PRO-RE	France	IVT	184	57.0	69*	15	CBS > 6	56.0	42.0		9
Puetz V.	2008	PRO-RE	Canada	IVT or IAT (131, 49.8%)	263	52.1	73*	10	CBS ≤ 5 vs 10	45.2			7
Sillanpaa N.	2012	RE	Finland	EVT	83	51.8	71*	7	CBS > 6	74.0			9
Tan I.Y.	2009	RE	Canada	IVT (60, 70.5%)	85	42.0	70	16	Per 1 score increase and CBS > 6	43.5	43.5		6
Topcuoglu M.A.	2014	RE	Turkey	IVT or EVT	105	50.4	63.3	DNR	Per 1 score increase	40.0			7
Treurniet K.M.	2016	RCT	Netherlands	IVT or EVT	499	58.3	64.2	17	Per 1 score increase and CBS > 6	25.4	53.0		9
Alexander D. Horsch	2016	PRO	Netherlands	IVT or IAT	545	61.0	68*	8	Per 1 score increase			10	7
Jung-Soo Park	2018	RE	Korea	IVT or EVT	119	50.4	72.9	14	CBS > 6	31.9			7
François Zhu	2018	RCT	France	EVT	231	53.7	69.3	18	CBS > 6	52.0	85.3	47.4	9
Armin Eilaghi	2013	PRO	Canada	IVT (89, 78%)	114	50.9	69	13	Per 1 score increase	DNR			6
Fanou E.M.	2015	RE	USA	IVT (273, 69.1%)	395	49.9	72	14	CBS > 6		55.7	20.5	7
Imad Derraz	2019	RCT	France	IVT or EVT	281	52.3	63.2	18	Per 1 score increase and CBS > 6	51.2			9

Abbreviations: CBS, clot burden score; EVT, endovascular treatment; GOF, good functional outcome; HT, hemorrhagic transformation; IAT, intra-arterial treatment; IVT, intravenous thrombolysis; NOS, Newcastle-Ottawa quality assessment scale scores; PRO, prospective; PRO-RE, prospective enrolled, retrospectively analysis; RCT, ancillary analysis of randomized controlled trial; RE, retrospective; Rec, recanalization.

*Expressed in median.

association was found in categorical group from 1 study[13] (RR: 1.09, 95% CI: 1.01-1.18, $P = .018$).

For HT, in patients receiving IVT alone, only 1 study[8] reported possible negative association between CBS and HT in continuous group (OR: .91, 95% CI: .84-.99, $P = .03$) while another 1 study[27] indicated no association in categorical group (OR: .67, 95% CI: .30-1.45, $P = .30$). Also, in patients receiving EVT alone, CBS was not associated with HT in categorical group[13] (RR: 1.25, 95% CI: .93-1.67, $P = .14$).

Discussion

To the best of our knowledge, this was the first systematic review and meta-analysis of the evidence for an association between CBS and clinical outcome of AIS. Our study demonstrated the prognostic value of CBS for good functional outcome and successful recanalization for AIS patients undergoing reperfusion therapy. However, we found no association between CBS and HT.

Obvious heterogeneity in categorical group for good functional outcome might be introduced from 2 studies due to odd ratio was transformed[4] or with small sample sizes.[6] After excluding these studies, no heterogeneity was found and higher CBS was still significantly associated with good functional outcome (pooled OR: 1.59, 95% CI: 1.30-1.94, $P = .130$, I-square = 43.7%).

CBS was a comprehensive scoring system reflecting the thrombus status, including (1) the extent of the thrombus and (2) the cerebral arteries segments involved by the thrombus. Those 2 thrombus factors were strongly related to clinical outcome of AIS. For thrombus length, shorter thrombus was associated with successful recanalization[5,29] and was more likely to achieve better outcome in recanalization therapy.[30] In contrary, more extensive thrombus might cause occlusion and larger infarction size. For that thrombus longer than 8 mm or 9 mm, IVT had nearly no response to recanalization.[31,32] As for thrombus location, more distal thrombus achieved better outcome than in proximal internal carotid artery.[33-37] Patients with AIS achieved good outcome from 77% to 82% in middle cerebral arteries M2 segment while from 17% to 29% in proximal internal carotid artery or internal carotid artery. Distal thrombus was more likely to respond to reperfusion therapy.[38]

Moreover, several studies had illustrated that patients with higher thrombus burden were associated with a higher likelihood of larger infarct size,[4,13,22,24] higher baseline neurological deficit,[6] longer duration of EVT,[39] which led to poor functional outcome and failing to recanalization. Impact of thrombus status on AIS clinical outcome was multifaceted. From the above, CBS could be a reliable predictor of prognosis in patients with AIS undergoing reperfusion therapy.

In addition, our meta-analysis suggested no relationship between CBS and HT. As far as we knew, few studies had revealed the association between thrombus status and HT. HT was more likely to develop in AIS patients with previous antiplatelet use or history of hypertension.[40] In Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials study,[41] compared to control group, EVT was not associated with increasing risk of HT in different CBS groups. The authors also found no association between CBS and time between onset and imaging which was considered as a risk factor for HT.[42] Although 1 study[4] reported patients with higher CBS was less likely to develop HT (45% versus 18% CBS ≤ 5 versus CBS > 5), it should be noticed that these findings were unadjusted for potential key variables related to HT. In our meta-analysis, heterogeneity was detected across enrolled studies in this subgroup and it could be explained by small sample sizes and different reperfusion therapies.

Interestingly, the predictive value of CBS was failed to be demonstrated in AIS patients receiving EVT alone. Predictability of CBS was probably less powerful in AIS patients receiving EVT. Similar to our results, several studies[43-45] found no significant relationship between thrombus length and successful reperfusion with EVT. Derraz et al[28] also found that T2*-CBS was not statistically significant in EVT alone group but significant for IVT alone group. Those results indicated that higher clot burden might not influence the efficacy of EVT whereas patients with lower CBS gained poorer functional outcome and less successful recanalization. Clinical decisions on IVT should be more carefully made once evidence of higher clot burden was found. However, due to limited enrolled studies and different generation thrombectomy devices in EVT alone group, the heterogeneity was high across studies. The results should be generated carefully and further analyses on predictive value of CBS in EVT were essential to conduct.

Implications for Clinical Practice

Several imaging indicators had been developed to predict the clinical outcome in AIS. Barreto et al reported a 5-point scoring tool which also reflected the thrombus extent and was related to clinical outcome.[46] Limitations of this thrombus grade included, (1) evaluated by invasive DSA, (2) had not been widely validated, and (3) did not take the thrombus location into account. Another imaging indicator, the Boston Acute Stroke Imaging Scale, which we had been previously using to study the predictive value of AIS,[47] addressed the location of thrombus. However, the Boston Acute Stroke Imaging Scale was unable to reflect the thrombus extent and the sensitivities and specificities for detecting good clinical outcome were lower than CBS.[6] In additional, ASPECT had been well studied that it was reliable to predict outcome among ischemic stroke patients. Nevertheless, that hypodensities on noncontrast CT in early stage or with multiple small

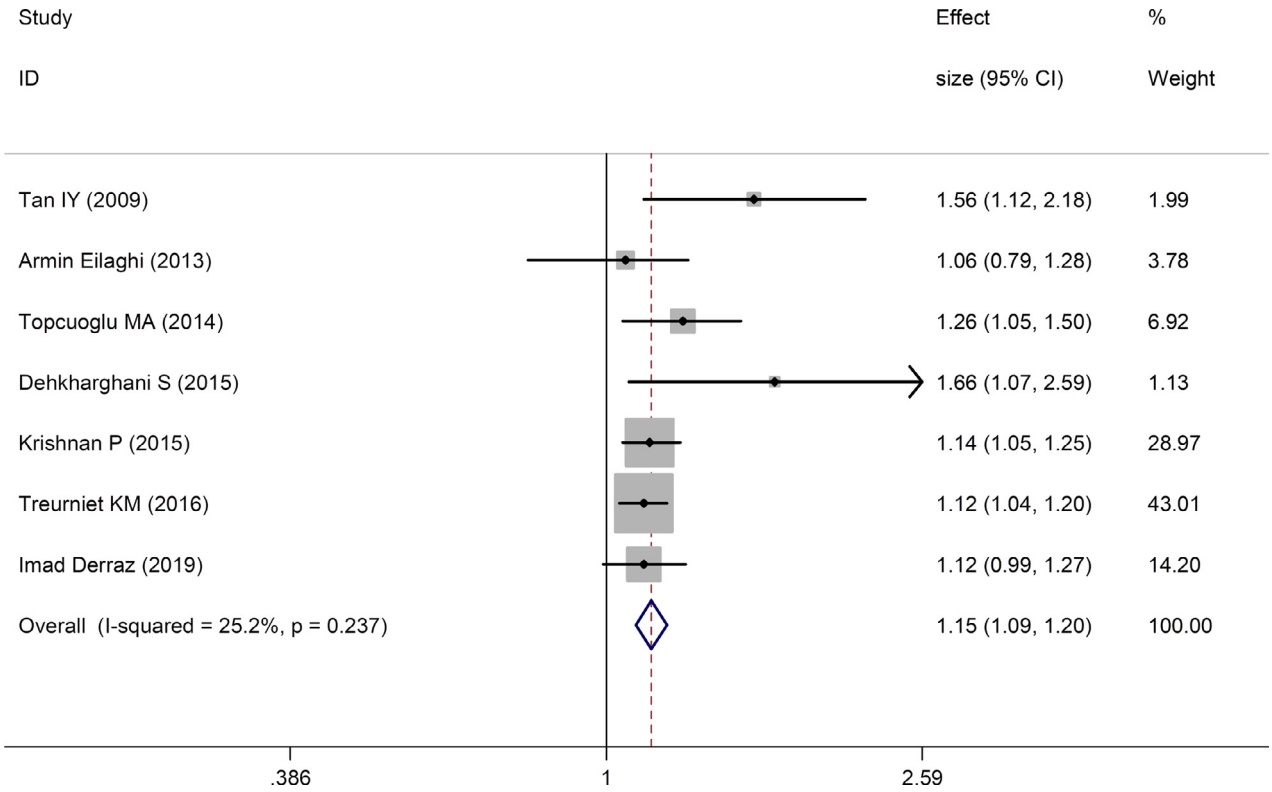

Figure 2. *Forest plot of association between continuous CBS and good functional outcome.*

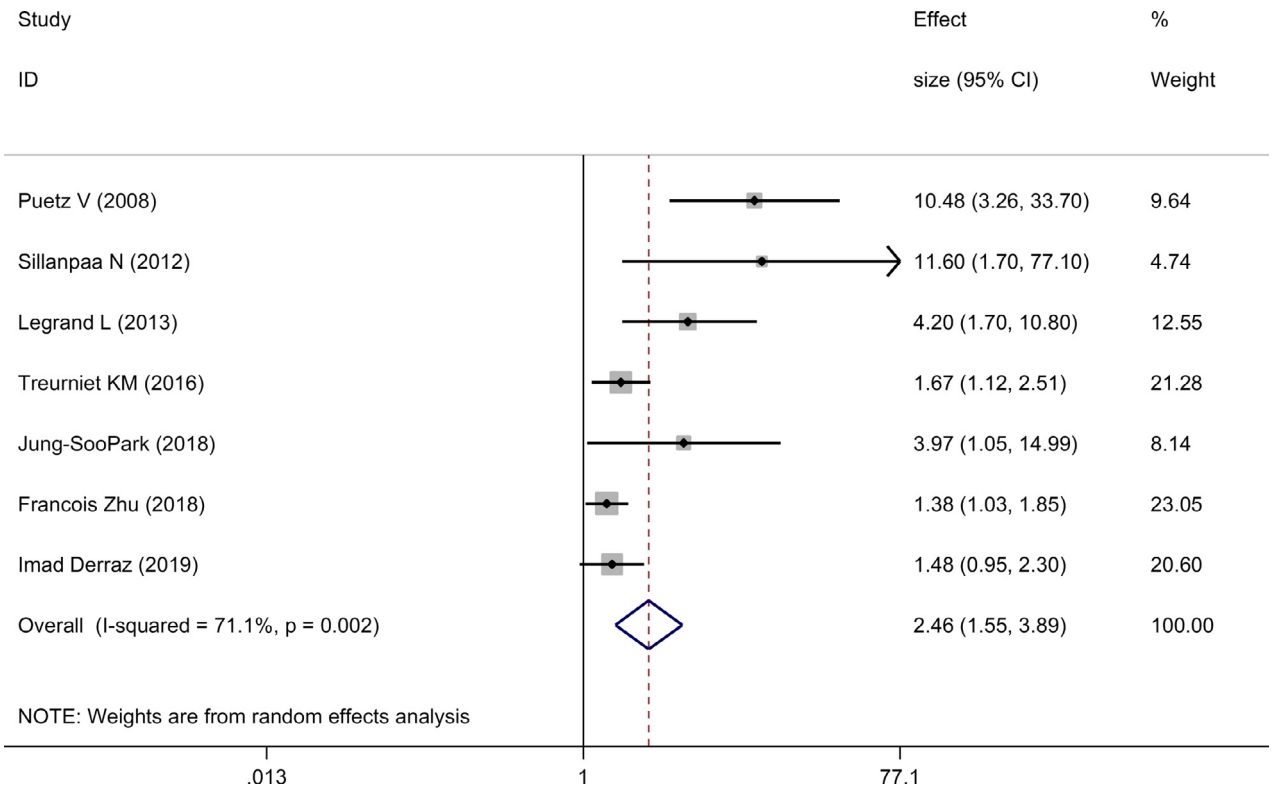

Figure 3. *Forest plot of association between categorical CBS and good functional outcome.*

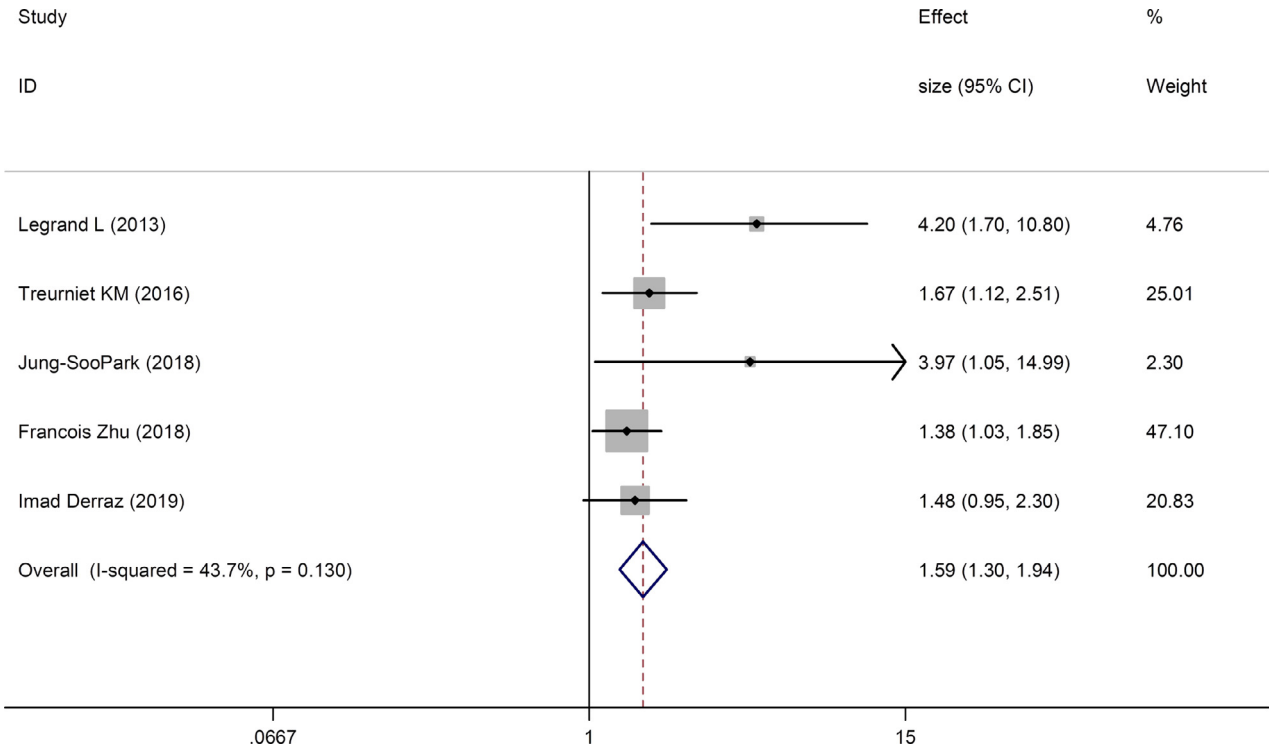

Figure 4. *Forest plot of association between categorical CBS and good functional outcome after excluding 2 studies.*

infarct lesions [48] might be invisible caused us to underestimate the severity of ischemic stroke and make inaccurate clinical decisions.

CBS was a rapid and CTA-based scoring system reflecting both thrombus extent and location with well predictive value for AIS patients. To date, CTA was widely available in many regions and provided a rapid and more precise assessment of variables. Therefore, CBS was easy and timely assessed. Moreover, Evaluation of CBS was not time-dependent and thus it could be well assessed in an early stage. Thus, CBS could be an important complement factor to help predict the likelihood of recovery

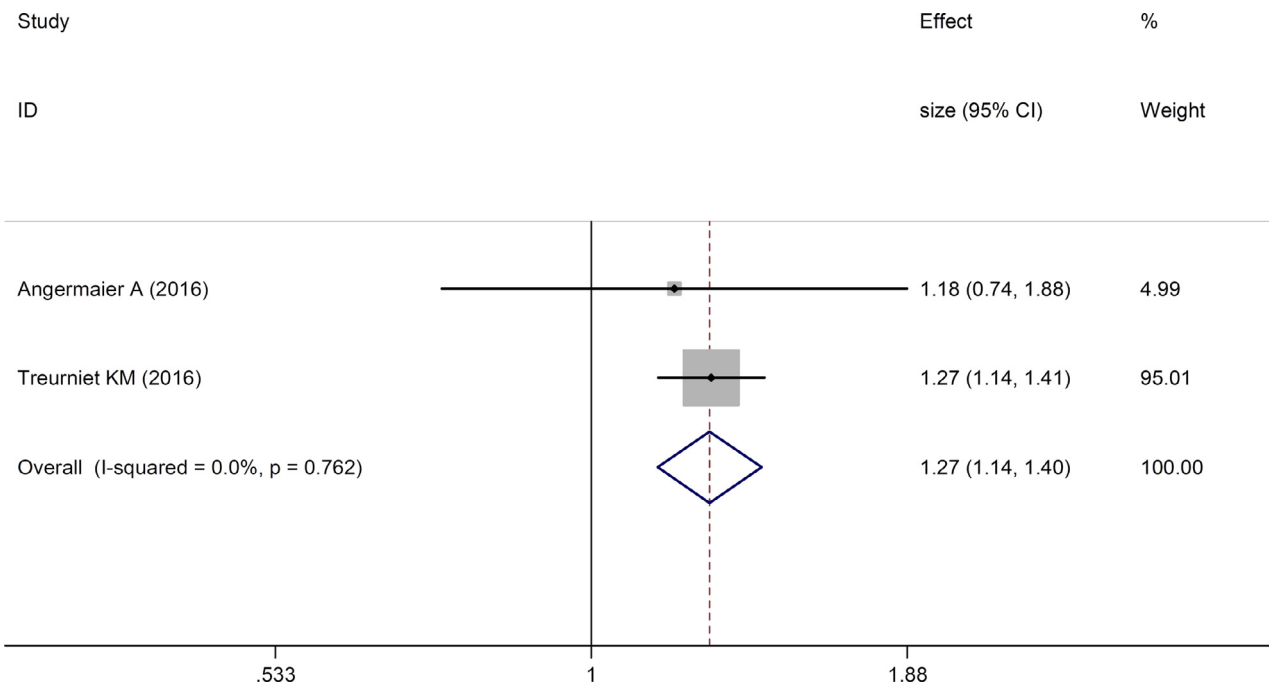

Figure 5. *Forest plot of association between continuous CBS and recanalization.*

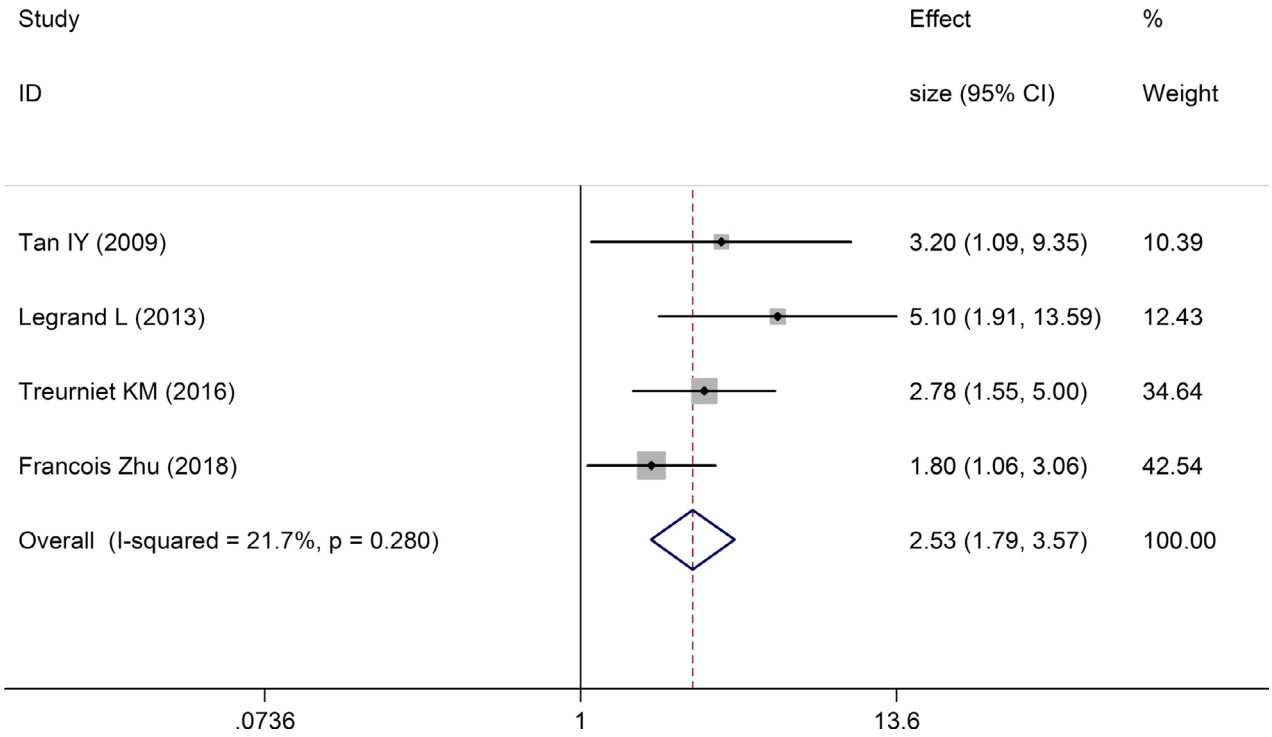

Figure 6. *Forest plot of association between categorical CBS and recanalization*

from ischemic stroke and guide physicians to make the best reperfusion strategy. Lower CBS allowed patient selection for more aggressive recanalization strategies. In Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials study,[41] patients in lower CBS group (CBS 0-4) gained better outcome from EVT than those in higher CBS group from 8 to 10 (adjusted cOR, 2.3 versus 1.6). Greater benefits were achieved from endovascular therapies among AIS patients with greater thrombus burden. As for HT, we should take more attention to other potential risk factors for HT rather than CBS. Level of CBS might not cause HT from our studies.

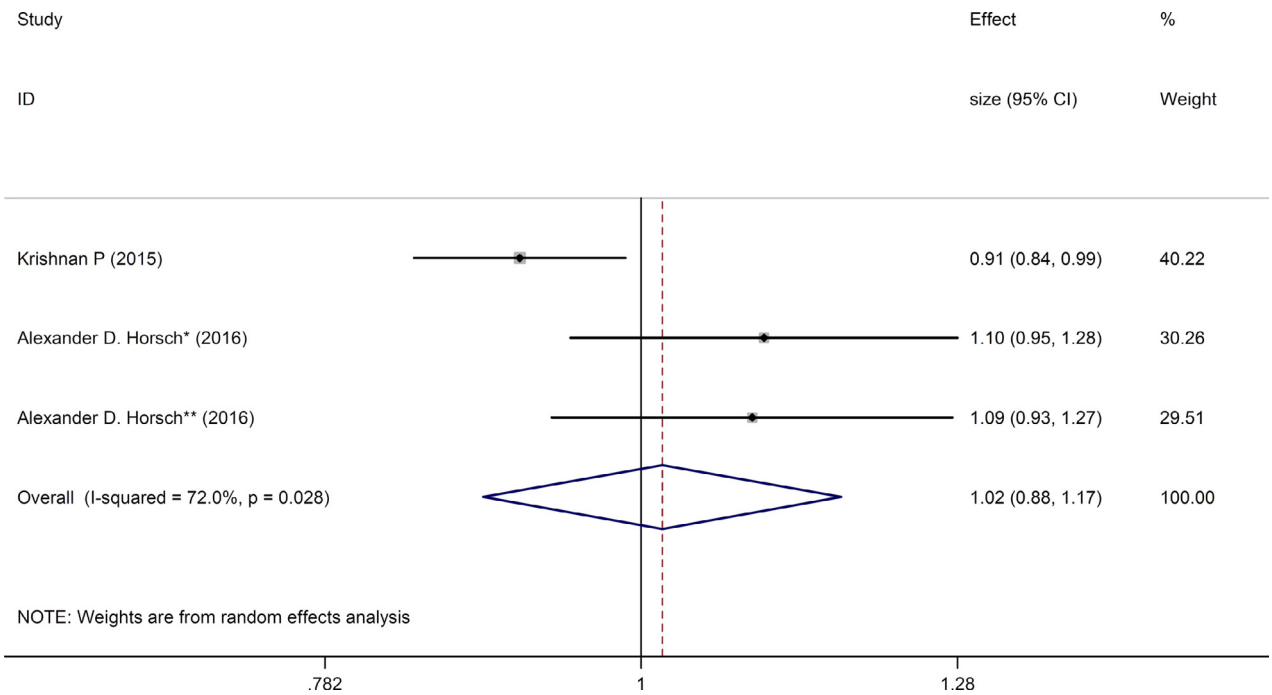

Figure 7. *Forest plot of association between continuous CBS and HT.*

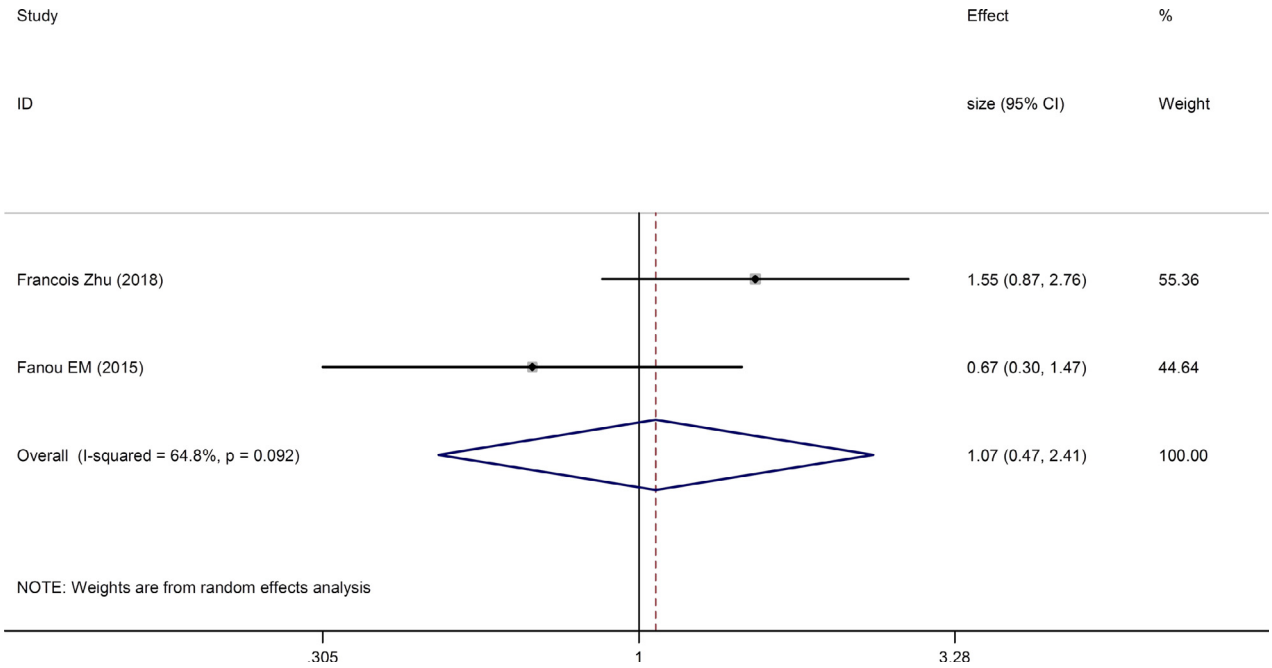

Figure 8. *Forest plot of association between categorical CBS and HT.*

Limitations

The result of our study must be interpreted with caution because of several limitations. First, in our review, assessment of CBS was different and mostly evaluated based on CTA while 3 studies were on MRA.[9,13,28] According to previous reports regarding thrombus burden assessment, the contrast agents used in CTA might not reach the distal end of the thrombus in poor collateral status.[49] In MRA, thrombus was assessed on susceptibility vessel sign which was highly depended on clot composition and age. Thrombus in time-of-flight MRA might not be fully visible.[50] Thus, assessment of clot burden might be overestimated with CTA and underestimated with MRA. Although the disparity of assessment on CBS existed between MRA and CTA in theory and could introduce heterogeneity to our study, Legrand et al found that the CBS interobserver ratings on T2* sequences were reliable with CTA.[9] Thus, as a prognostic indicator, both assessments of CBS were reliable for AIS patients. Second, interventions were varied across the included studies. To explore the difference, subgroup analysis stratified by interventions or not should have been performed. However, due to the limited results, comprehensive subgroup analysis was infeasible in our study. Third, all enrolled studies were observational and 7 of them were retrospective. That might also reduce the validity of our study.

Conclusions

Our systematic review and meta-analysis had revealed the potential prognostic value of CBS in functional outcome and recanalization on AIS patients undergoing reperfusion therapies particularly in patients receiving IVT alone; while CBS might not be a predictor for HT after reperfusion therapies.

Disclosure Statement: The authors declare no conflicts of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.07.009.

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