The impact of leptomeningeal collaterals in acute ischemic stroke

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Systematic Review

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Abstract

Objectives: Leptomeningeal collaterals provide an alternate pathway to maintain cerebral blood flow in stroke to prevent ischemia, but their role in predicting outcome is still unclear. So, our study aims at assessing the significance of collateral blood flow (CBF) in acute stroke.

Methods: Electronic databases were searched under different MeSH terms from Jan 2000 to Feb 2019. Studies were included if there was available data on good and poor CBF in acute ischemic stroke (AIS). The clinical outcomes included were modified rankin scale (mRS), recanalization, mortality, and symptomatic intracranial hemorrhage (sICH) at 90 days. Data was analyzed using random-effect model.

Results: A total of 47 studies with 8,194 patients were included. Pooled meta-analysis revealed that there exist 2-fold higher likelihood of favorable clinical outcome ($mRS \leq 2$) at 90 days with good CBF compared with poor CBF (RR: 2.27; 95%CI: 1.94-2.65; $p < 0.00001$) irrespective of the thrombolytic therapy [RR with IVT: 2.90; 95%CI: 2.14-3.94; $p < 0.00001$, and RR with IAT/EVT: 1.99; 95% CI: 1.55-2.55; $p < 0.00001$]. Moreover, there exists 1-fold higher probability of successful recanalization with good CBF (RR: 1.31; 95% CI: 1.15-1.49; $p < 0.00001$). However, there was 54% and 64% lower risk of sICH and mortality respectively in patients with good CBF in AIS ($p < 0.00001$).

Conclusions: The relative risk of favorable clinical outcome is more in patients with good pretreatment CBF. This could be explained due to better chances of recanalization, combined with lesser risk of intracerebral hemorrhage in good CBF status.

Introduction

Reversing the trend of morbidity caused by ischemic stroke in our modern era has still proven difficult and; thus, poses a significant global burden¹. It is widely known that adequate blood flow to the brain by removing the clot forms the theoretical basis for management²⁻⁴. Therefore, thrombolytic therapies in the form of intravenous (IVT) or intra-arterial (IAT) aim for clot disruption, thus re-establishing the circulation⁵. The therapeutic implications of such interventions have been enhanced further by the presence of bypass vascular network channels, which provides an alternate pathway for cerebral blood flow to prevent permanent neurological damage²⁻⁴. Hence, these pial collaterals prolongs the time window for treatment after stroke and reduces the hemorrhagic transformation²⁻⁴. Thus, determination of collateral status before establishing any treatment is appealing because the coherence with adequate intervention can be improved. Consequently, there exists various ways to identify collateral circulation in the brain after acute ischemic stroke, although the effect of number of collaterals on clinical outcomes has not been assessed^{6,7}.

To determine whether good or poor collateral blood flow (CBF) has any impact on clinical outcome in AIS, we reviewed randomized controlled trials, case-control, prospective cohort and retrospective studies in adult patients receiving different thrombolytic therapies.

Methods

Study selection:

Randomized controlled trials, case-control studies, prospective cohort studies and retrospective studies studying the collateral status in patients with AIS who received IA/EVT± IV thrombolytic therapy. We excluded case series and case report studies from our systematic review. Articles were retrieved from January 2000 till February 2019. Various data bases were searched which included PubMed, Cochrane, EMBASE and Google Scholar. The MeSH headings included “collateral circulation”, “thrombolytic therapy”, and “stroke”. The reviewers were not incognizant with regards to the author’s name and institution, journals of publication, or study results. No language barriers were imposed. Eligibility assessment was performed independently by one reviewer (NF) in an unblinded manner. Disagreement between the reviewers was resolved by consensus. However, if still there was no agreement then third party (AS) would decide. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline⁸ for our meta-analysis.

Data abstraction:

Information was extracted from the studies included on: (1) baseline characteristics of studies (type of study, number of patients, mean age, NISS score, and inclusion criteria); (2) Collateral status (methodology, collateral definition, number of collaterals); (3) Thrombolytic therapies (types of therapies); (4) Clinical outcome in good versus poor CBF (mRS at 90 days, sICH, mortality, and recanalization). The definition of collateral scores and method of collateral scoring depended upon the included studies and are described in detail in Table 1. For the definition of our systematic review we defined good CBF as 50–100% collateral filling of the ischemic area while <50% collateral filling was defined as poor CBF.

The meta-analysis was performed using random-effect model by computing OR and 95% confidence interval for each study determining the outcome. The primary outcome was modified rankin scale mRS at 90 days (good clinical outcome = 0–2) in good CBF versus poor CBF in acute ischemic stroke. Secondary outcomes included mortality, recanalization and sICH.

Statistical analysis:

Review Manager Program version 5 as provided by Cochrane Library was used to perform Statistical analyses. The data from each study was extracted from the articles and placed in this software to perform a pooled meta-analysis and sub-group analysis.

Pooled meta-analysis on good versus poor CBF irrespective of type of treatment followed by dichotomization into IVT and IAT/EVT was evaluated using random-effect model. Subgroup analysis was performed with mortality, sICH, and recanalization. To assess the publication bias, funnel plot was also applied. The RR from separate studies were combined by the random-effects meta-analysis according to the Mantel-Haenszel method, which is also valid for paired RR. Heterogeneity between studies was assessed by the Breslow-Day χ^2 test and I² statistic.

Results

A total of 2685 articles were reviewed from the above-mentioned electronic literature. 160 articles were retrieved and analyzed; ultimately 47 articles which met the inclusion criteria were included in our meta-analysis. Table 1 shows characteristics of included studies. Table 2 indicates the types of interventions and clinical outcomes. Table 3 identifies the results of all included studies.

A total of 8,194 patients were included in our meta-analysis with good and poor collaterals receiving either IVT, IAT or EVT for acute ischemic stroke. The median age of the included patients was 68 (54–78) with NIHSS score at the time of presentation as 15 (18–21).

Pooled analysis of all included studies^{3,9–54}: Patients with acute ischemic stroke with good CBF had a more than 2-fold higher likelihood of having good outcome (mRS 0–2 at 90 days) in comparison to patients with stroke having poor CBF (RR: 2.27; 95%CI: 1.94–2.65; $p < 0.00001$) as indicated in Figure 1 Panel A. Furthermore, patients with good pretreatment collaterals receiving intra venous thrombolysis showed around 3-fold higher risk of better outcome as compared to patients with poor collaterals (RR: 2.90; 95%CI: 2.14–3.94; $p < 0.00001$) as demonstrated in Figure 1 Panel B. In addition, patients with good collaterals who received thrombolysis either intrarterial or mechanical had approximately 2-fold higher risk of favorable outcome compared to patients with pre-treatment poor collaterals (RR: 1.99; 95% CI: 1.55–2.55; $p < 0.00001$) as shown in Figure 1 Panel C.

Further sub group analysis based upon the status of recanalization was performed based upon the pretreatment collaterals status, it was found that patients with good collaterals showed 1-fold higher likelihood of complete recanalization as compared to poor collaterals RR of Recanalization: 1.31; 95% CI: 1.15–1.49; $p < 0.00001$ (Figure 2)

Compared to poor collateral status, good pretreatment collaterals had 54% less relative risk of sICH at 90 days. The RR of sICH: 0.46; 95% CI: 0.35–0.60; $p < 0.00001$ (Figure 3)

Further sub group analysis was done comparing the collateral status with mortality. We found that patients with good collateral status has 64% less risk of mortality at 3-months compared to patients with poor collateral status irrespective of the type of thrombolysis. The RR of mortality: 0.36; 95%CI: 0.27–0.48; $p < 0.00001$ (Figure 4).

Statistical heterogeneity was further assessed using funnel plot, revealing asymmetrical distribution in the funnel plot. This could be due to publication bias, but we tried to minimize it by searching the unpublished literature as well. Though no study was included from the grey literature in our meta-analysis.

Discussion

Overall, there was a strong evidence of relationship between the collateral circulation and clinical outcomes in patients with AIS. This can be explained due to the fact that the expansion or reduction of penumbral tissue, immediately after the stroke, depends on collateral status⁵⁵.

Clinical outcomes:

In our meta-analysis, we demonstrated that the presence of good CBF was associated with increased likelihood of favorable clinical outcome, which validates the previous meta-analysis²⁴ (mRS at 3–6 months; $p < 0.0001$). In addition, further analysis showed that there was higher probability of predicting better neurological outcome with either IVT or IAT/EVT. Our results, however, are contradictory to recent trial of DEFUSE 3⁵⁴, which showed that good CBF does not predict the neurological status. Previous studies also revealed that IAT/EVT is efficient in clot-retrieval in stroke, combined with better neurological outcome^{59–61}

The degree of collateral circulation is essential to be determined prior to thrombolytic therapy. This status helps to determine the expansion of infarct, degree of reperfusion and efficacy of treatment. Although endovascular treatment is considered to be the treatment of choice for acute large-vessel occlusion, however, it was found that patients with poor collaterals had more odds of unfavorable clinical outcome (onset-to-puncture time: 300, 59% versus 300, 32%; OR, 0.24; $P .011$; puncture-to-reperfusion time: 60, 73% versus 60, 32%; OR, 0.21, $P .011$) as compared to those with good collaterals^{63–64}. Therefore, collateral circulation helps in minimizing the neurological damage by limiting the extent of infarction as it maintains the viability of the penumbral tissue.

Recanalization:

Our study suggests that recanalization was better achieved in patients with good pretreatment collateral status ($p < 0.00001$). This can be explained as collateral circulation sustain downstream perfusion and enhances ante grade perfusion to the distal arteries⁵⁷. Besides, it increases the delivery of thrombolytic agents to the clot itself from different sides, thus increasing the efficacy of treatment⁵⁷.

In previous literature, it was found that mechanical thrombectomy has higher rate of recanalization than IV treatment alone; like in a randomized trial EXTEND-IA, it was found that >90% recanalization was found in patients who received endovascular thrombectomy than those who received rt-PA⁵⁸. MR CLEAN⁶⁰ and ESCAPE trial⁵⁹ also demonstrated the same findings that there are low complications rate with endovascular treatment.

Mortality and sICH: Our meta-analysis revealed the there was reduction in mortality with good CBF than poor CBF ($p < 0.00001$). Though in previous study it was found that recanalization did not independently affect the mortality ($p > .15$)^{59–60}, thus collateral status plays indispensable role in decreasing the mortality as evident in previous studies⁶². Our study identified significant reduction in sICH in good CBF compared to poor CBF, this could be explained as collaterals limits the growth of infarct core before revascularization⁶². This ultimately helps in reducing the risk of hemorrhagic transformation.

Our study has several limitations. Firstly, there is a possibility of selection and publication bias in our systematic review, since only two reviewers carried out this part of the process. They might therefore be more influenced by the positive trial results than by the negative ones. However, we tried to limit such bias using the following steps: a gray literature review, in which we reviewed the abstracts from several meetings in order to

capture any RCT that was presented as an abstract but not published because of a negative result. Second, in our meta-analysis there were different scales used to assess and define collateral circulation into good and poor CBF, therefore, resulting in a bias between two groups. Third, in our meta-analysis we didn't only restrict to anterior circulation stroke but also included posterior circulation stroke as well, this might have resulted in sampling bias. Fourth, there must be difference in ethnicity and co-morbidities, which might have led to sampling bias.

Conclusion

In conclusion, our meta-analysis points to a signal-of-efficacy of good CBF in the management of patients with acute ischemic stroke. However, further studies including randomized controlled trials are required to determine the effectiveness of thrombolytic therapy depending upon the collateral status.

Abbreviations

AIS: acute ischemic stroke; ASITN: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR); ASPECTS: Alberta Stroke Program Early CT score; CBF: Collateral Blood Flow; CTP: Computed Tomography Perfusion; CTA: Computed Tomography Angiography; CAOSD: Coronary Artery Septal Occlusion Defect; DSA: Digital subtraction Angiography; IV: Intravenous; ICA: Internal Carotid Artery; LMC: Leptomeningeal Collateral Grading; MRI: Magnetic Resonance Imaging; MCA: Middle Cerebral Artery; MRP: Magnetic Resonance Perfusion; mRS: modified rankin scale; NIHSS: National Institute of Health Stroke Scale; PROACT: Prolyse in Acute Cerebral Thromboembolism; rCBV: LVOS: Large vessel occlusion stroke; relative cerebral blood volume; RR: Relative Risk; sICH: symptomatic intracranial hemorrhage

Declarations

Competing interests: The authors declare no competing interests.

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Tables

Table 1: Baseline Characteristic of Various Studies

Trial or Study	Patients (n)	Age (Mean)	NIHSS score (Median)	Inclusion Criteria	Collateral Scoring	Collateral Score Definition
Lee et al 2000 ³	17	63	15	Acute middle cerebral artery (MCA) territory ischemic stroke within 3 hours after onset and were treated with IV recombinant tissue plasminogen activator (rt-PA).	CTP	MCA territory perfusion deficit
Kim DJ et al 2008 ⁴	13	60	13	Anterior and Posterior Circulation Ischemic Stroke	DSA	Graded as sufficient, moderate and poor
Miteff F et al ⁵ 2009	92	74	17	1. Anterior circulation stroke with IV thrombolysis within 6 hours of stroke 2. Repeat perfusion/infarct volume imaging at 24 hours	CTA	Good collaterals: entire MCA distal to occluded segment reconstituting with contrast Poor collaterals: distal MCA reconstituted partially
Lee et al 2009 ⁶	52	69	8	Acute middle cerebral artery (MCA) territory ischemic stroke within 3 hours after onset and were treated with IV recombinant tissue plasminogen activator (rt-PA).	FLAIR MRI	Distal hyperintense vessels on MRI slices
Lima F et al ⁷ 2010	741	69	13	Complete occlusion of the intracranial internal carotid artery (ICA) and/or the middle cerebral artery (MCA-M1 or M2 segments)	CTA	Leptomeningeal collateral pattern was graded as a three category less than contralateral unaffected side (score 1-2), equal to contralateral unaffected side (score 3) and greater than contralateral unaffected side (scores 4-5).
Angermaier et al 2011 ⁸	25	68	14	Anterior Circulation	CTA	Leptomeningeal collateral scoring

Ischemic Stroke						
Park et al 2011 ⁹	58	63	12	Anterior circulation stroke with IV tPA and baseline MRI	PWI	rCBV ratio by comparing the blood volume of the ischemic lesion with that of the corresponding unaffected contralateral region (i.e. ipsilateral divided by contralateral value).
Bang et al 2011 ¹⁰	222	65	17	Anterior Circulation Ischemic Stroke	DSA	ASITN collateral flow grading system
Choi et al 2011 ¹¹	55	64	15	Anterior Circulation Ischemic Stroke	DSA	Pial Collateral Score
Gallimanis et al 2012 ¹²	623	64	15	Anterior and Posterior Ischemic Stroke	DSA	Graded as none, poor or good
Souza et al 2012 ¹³	197	67	21	1. AIS with M1 and/or intracranial ICA occlusion 2.DWI and CTA within 9 hours from stroke onset	CTA	CS: 0= absent collaterals in >50% of an MCA M2 branch (superior or inferior division) territory; 1= diminished collaterals in >50% of an MCA M2 branch territory; 2= diminished collaterals in <50% of an MCA M2 branch territory; 3= collaterals equal to the contralateral hemisphere; and 4= increased collaterals
Rai et al 2012 ¹⁴	89	68	15	Anterior Circulation Ischemic Stroke	DSA	Graded as sufficient, moderate and poor
Calleja et al 2012 ¹⁵	54	73	10	1. Infarct core on cerebral blood volume (CBV) maps less than one-third of the MCA territory	CTP	Leptomeningeal collateral grading
Ichijo M et al 2012 ¹⁶	50	78	15	Acute proximal MCA occlusion patients who were treated with IV rtPA within 3	TOF-MRA	Presence or absence of circulation in the posterior cerebral artery circulation

				hours of symptom onset.		
Ramaiah et al 2014 ¹⁷	78	66	18	Acute ischemic stroke with intracranial ICA and/or MCA occlusions who received intra-arterial therapy.	CTA	Collateral statuses were divided into 4 categories: score 0 absence of contrast reaching the cortical surface of the affected hemisphere; score 1 contrast reaching the cortical surface but not the Sylvian fissure; score 2 contrast reaching the Sylvian fissure but opacifying 50% of hemisphere; score 3 contrast reaching the Sylvian fissure and opacifying 50% of the hemisphere.
Nambiar V et al 2014 ¹⁸	84	65.2	14	M1 segment MCA with or without intracranial ICA occlusions	CTA	Collateral status by use of the rLMC score (0–20) was trichotomized into 3 groups: good (17–20), intermediate (11–16), and poor (0 – 10)
Saarien et al 2014 ¹⁹	105	69	13	Anterior Circulation Ischemic Stroke with IV tPA and CTA	CTA	Leptomeningeal collateral circulation grading
Brunner et al 2014 ²⁰	246	74	14	NINDS protocol	CTA	Leptomeningeal collateral grading
Al-Ali et al 2014 ²¹	28	62	NA	Anterior Circulation Ischemic Stroke	DSA	Capillary Index Score
Marks MP et al DEFUSE 2014 ²²	60	63	18	1. Patients started endovascular treatment within 12 hours of ictus and 1.5 hours of the baseline MRI 2. ICA-M1 occlusion	CTA	Collateral score using a prior 5 point scale, from 0 (no collateral flow) to 4 (complete/rapid collaterals to entire ischemic territory).
Liebeskind	276	69	17	Anterior and	DSA	ASITN collateral

IMS-III et al 2014 ²³				Posterior Circulation Ischemic Stroke		flow grading
Liebeskind SWIFT et al 2014 ²⁴	119	67	18	Anterior and Posterior Circulation Ischemic Stroke	DSA	ASITN collateral flow grading
Mangiafico et al 2014 ²⁵	103	61	20	Anterior Circulation Ischemic Stroke	DSA	Collateral circulation score
Chen et al 2015 ²⁶	75	65	15	Anterior Circulation Ischemic Stroke	CTP	Collateral Flow Score
Sung SM et al 2015 ²⁷	35	61.5	16.87	Acute M1 occlusion	CTA	A score of zero indicated absent collateral supply to the occluded MCA territory. A score of 1 indicated collateral supply filling $\leq 50\%$ but >0% of the occluded MCA territory. A score of 2 was given for collateral supply filling >50% but <100% of the occluded MCA territory. A score of 3 was given for 100% collateral supply of the occluded MCA territory
Fanou et al 2015 ²⁸	395	72	14	Anterior Circulation Ischemic Stroke	CTA	Collateral Flow 0-3 Score 0-1 <50% ischemic territory Scores ≥ 2 indicates a good collateral status
Menon BK et al 2015 ²⁹	656	70		M1 MCA $\pm$ Intracranial ICA occlusion	CTA	Score 1: ACA-MCA and PCA-MCA pial arterial backfilling are each scored from 0–5 Score 2: 0-5 pial arterial backfilling in sylvian sulcus Score 3: 0-3 pial arterial backfilling in whole MCA ischemic territory

Kufner A et al 2015 ³⁰	62	71	11	IV-tPA within 4.5 hours of symptom onset, had MR imaging before and within 24 hours after treatment	FLAIR MRI	Hyperintense vessels on MRI sections
Hwang et al 2015 ³¹	207	68	17	Anterior Circulation Ischemic Stroke	DSA	ASITN collateral flow grading system
Singer et al 2015 (Singer OC) ENDOSTROKE ³²	148	71	20	Posterior Circulation Ischemic Stroke	DSA	ASITN collateral flow grading system
Singer et al 2015 ³³ ENDOSTROKE	160	72	15	Anterior Circulation Ischemic Stroke	DSA	ASITN collateral flow grading system
Zhang S et al 2016 ³⁴	80	69.	13	M1 ± internal carotid artery (ICA) occlusion	4D CTA	Collateral Grading Score
Seeters TV et al 2016 ³⁵	484	66.6	13	1. acute ischemic stroke of less than 9-h duration 2. confirmed occlusion in the M1 or M2 segment of the MCA on admission CTA	CTA	Poor leptomeningeal collateral status was defined as ≤50 % collateral filling of the perfusion territory of the affected MCA or MCA branch territory
Tan BYQ et al 2016 ³⁶	300	65.5	18	1. Anterior Ischemic Stroke (AIS) as proven by CTA	ASPECTS scoring	ASPECTS score≤5=poor collateral status and ASPECTS≥8 as good collaterals
Sheth sa et al 2016 ³⁷	117	68	19	Acute cerebral ischemia within the anterior circulation underwent conventional angiography	DSA	DSA assigns patients to grade 0 (no collaterals visible to the ischemic site), 1 (slow collaterals to the periphery of the ischemic site with persistence of some of the defect), 2 (rapid collaterals to the periphery of ischemic site with persistence of some of the defect)

						and to only a portion of the ischemic territory), 3 (collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase), and 4 (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion).
Garcia-Tornel A et al 2016 ³⁸	108	69.6	17	Occlusion of the proximal segment of the middle cerebral artery (M1 MCA) or terminal intracranial carotid artery (TICA)	CTA	University of Calgary Collateral Grading (0-5)
Sallustio F et al 2016 ³⁹	135	69	18	Extracranial and intracranial arteries of patients with M1 segment middle cerebral artery (MCA) occlusion with or without internal carotid artery (ICA) occlusion.	CTA	Collateral status on CTA we adopted a scale from 0 to 3 derived from the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (0: no collaterals; 1: collaterals to the periphery of ischemia; 2: collaterals filling 50–100% of ischemic area; 3: collaterals filling 100% of ischemic area).
Gersing AS et al 2017 ⁴⁰	115	70.3		Patients undergoing Mechanical Thrombectomy in Middle cerebral artery occlusion (M1)	CTA	Regional Leptomeningeal collateral score 0 = no collaterals; 1 = less compared with the same region of the

						contralateral hemisphere; and 2 = equal or prominent collaterals compared with the same region of the contralateral hemisphere
Son JP et al 2017 ⁴¹	73	65	NA	(1) subjects who presented within 6 hours of symptom onset; (2) subjects who underwent serial brain MRI, including diffusion-weighted imaging (DWI), MRP, and MR angiography (MRA), at admission and at day 7; (3) subjects who had a NIH Stroke Scale (NIHSS) score of 4 or more points at admission; and (4) subjects with internal carotid artery and/or proximal MCA (M1 segment) occlusion associated with symptoms on admission MRA	MRP	NA
Nordmeyer H et al 2017 ⁴²	87	72.5	15	Acute ischemic stroke treated with mechanical thrombectomy	CTA	Tan score was used: A score of 0 indicated absent collateral supply of the occluded MCA territory in comparison to the contralateral side, while a score of 1 indicated collateral supply with a filling ≤ 50
Madelung CF et al 2017 ⁴³	187			MCA occlusion receiving thrombolytic therapy	CTA	1: Comparison to contralateral; 2: Percentage of collateral supply filling the occluded MCA territory; and 3: Extent of contrast visualized distal to the occlusion

Rebello LC et al 2017 ⁴⁴	122	54	17	Patients with (i) a past medical history or in-hospital diagnosis of AF or (ii) CASOD on conventional angiography and (iii) anterior circulation LVOS involving the intracranial internal carotid artery (ICA) and/or proximal middle cerebral artery (MCA) M1 and/or M2 segments who (d) underwent pre-intervention in-house computed tomography angiography (CTA) were included	CTA	0, absent collaterals in >50% of the affected territory; 1, diminished collaterals in >50% of the affected territory; 2, diminished collaterals in <50% of the affected territory; 3, collaterals equal to the contralateral side; and 4, increased collaterals
Dankbaar JW et al 2018 ⁴⁵	188	68.3	15	Occluded M1 segment (with or without extension in the intracranial ICA or M2 branches) on admission CTA	CTA	collateral filling in the affected hemisphere: 0 = absent; 1 = filling 50%; 2 = filling > 50–<100%; 3 = filling 100%
Kim BM et al 2018 ⁴⁶	554	67.3	14	Acute stroke due to occlusion of intra cranial ICA, MCA M1 or proximal M2	CTA	NA
Wang F et al 2018 ⁴⁷	270	71.26	14	Primary acute ischemic stroke with an onset of the first episode within the previous 4.5 h and (2) had an occlusion of the internal carotid artery (ICA) or of the proximal (M1) or distal (M2) segments of the middle cerebral artery (MCA)	CTA	NA
Park JS et al 2018 ⁴⁸	119	72.2	12	1. Acute Ischemic Stroke treated with EVT	CTA	Good collateral score LMC score: 17-20; Poor collateral score: 0-10

Havenon DA et al 2019 ⁴⁹	130	71	1. Endovascular therapy after acute ischemic stroke	CTA	Leptomeningeal Collateral Grading
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Abbreviations:

ASITN: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR); ASPECTS: Alberta Stroke Program Early CT score; CTP: Computed Tomography Perfusion; CTA: Computed Tomography Angiography; CAOSD: Coronary Artery Septal Occlusion Defect; DSA: Digital subtraction Angiography; IV: Intravenous; ICA: Internal Carotid Artery; LMC: Leptomeningeal Collateral Grading; MRI: Magnetic Resonance Imaging; MCA: Middle Cerebral Artery; MRP: Magnetic Resonance Perfusion; NIHSS: National Institute of Health Stroke Scale; PROACT: Prolyse in Acute Cerebral Thromboembolism; rCBV: LVOS: Large vessel occlusion stroke; relative cerebral blood volume

TABLE 2: TYPES THROMBOLYTIC THERAPIES AND CLINICAL OUTCOME

Trial or Study	Therapies	Good versus Poor Collaterals	Clinical Outcome	Recanalization	sICH
Lee et al 2000 ³	IVT: 17	9: 4	NA	NA	NA
Kim DJ et al 2008 ⁹	EVT	6: 3	-mRS at 90 days -sICH	NA	NA
Miteff F et al ¹⁰ 2009	IVT: 60 EVT: 32	51: 41	-mRS at 90 days -absolute infarct expansion	Thrombolysis in Cerebral Infarction: Grade 1: Minimal perfusion 2: Partial perfusion 2a: <2/3 rd filling 2b: complete filling but slow rate 3: Complete perfusion	NA
Lee et al 2009 ¹¹	IVT: 52	20/14	NA	NA	NA
Lima F et al ¹² 2010	IVT: 8 EVT: 9 Combined: 13	55:96:45	-mRS at 30 days	NA	NA
Angermaier et al 2011 ¹³	EVT	15: 10	-sICH	NA	NA
Park et al 2011 ¹⁴	IVT: 36 EVT: 22	37: 21	- Recanalization -sICH	An improvement in the TIMI grade from the baseline to arterial obstruction by ≥ 2 points	Any sign of hemorrhage on follow-up CT or MRI scans associated with clinical deterioration of 4 points on the NIHSS
Bang et al 2011 ¹⁵	EVT	144: 78	-sICH	NA	Signs of hemorrhage on follow-up CT or MRI scans

					associated with clinical deterioration of 4 points on the NIHSS
Choi et al 2011 ¹⁶	EVT	29: 26	-mRS at 90 days -sICH	NA	NA
Gallimanis et al 2012 ¹⁷	EVT	316: 69	-mRS at 90 days -sICH	NA	NA
Souza et al 2012 ¹⁸	IVT: 49 EVT: 82 No Reperfusion Therapy 66/197	22/197 CS=0, 40/197 CS=1, 67/197 CS=2, 42/197 CS=3, 26/197 CS=4.	-mRS at 90 days -Mortality	NA	NA
Rai et al 2012 ¹⁹	EVT	62: 27	-mRS at 90 days -mortality	NA	NA
Calleja et al 2012 ²⁰	IVT: 40 EVT: 13	34:53	-mRS at 90 days -mortality -Sich -TICI	Thrombolysis in Cerebral Infarction	NA
Ichijo M et al 2012 ²¹	IVT: 54	37: 17	NA	NA	NA
Ramaiah et al 2014 ²²	IVT: 50	20: 30	NA	NA	NA
Nambiar V et al 2014 ²³	52.6% IV tpa Good Collaterals 55.9% Intermediate collaterals 48.4% poor collaterals	19:34:31	mRS at 90 days -infarct expansion -TICI	Successful recanalization on final angiogram	N/A
Saarien et al 2014 ²⁴	IVT: 105	47: 58	-mRS at 90 days	NA	NA
Brunner et al 2014 ²⁵	IVT: 246	171: 41	-sICH	NA	NA

Al-Ali et al 2014 ²⁶	IVT: 15/55:18/58	29:31	-Clinical outcome at 90 days -TICI reperfusion	TICI 2B partial reperfusion of >50% of occluded artery	N/A
Marks MP et al DEFUSE 2014 ²⁷	EVT: 28	13: 15	-mRS at 90 days	NA	NA
Liebeskind IMS-III et al 2014 ²⁸	EVT	96: 180	-mRS at 90 days -sICH -mortality	NA	NANA
Liebeskind SWIFT et al 2014 ²⁹	EVT	35: 71	-mRS at 90 days -mortality	NA	NA
Mangiafico et al 2014 ³⁰	EVT	65: 37	-mRS at 90 days -sICH -mortality	NA	NA
Chen et al 2015 ³¹	EVT	25: 50	-mRS at 90 days -sICH -mortality	NA	NA
Sung SM et al 2015 ³²	IVT: 20	11:19	-mRS at 90 days -TICI -sICH	Thrombolysis in Cerebral Infarction (TICI) scale (graded as 0 for absent perfusion, 1 for minimal distal per- fusion, 2 for partial perfusion, and 3 for complete perfusion).	Any intracranial hemorrhage associated with ≥ 4 point's increase on the NIHSS.
Fanou et al 2015 ³³	NA	310:85	-mRS at 90 days -TICI	Thrombolysis in MI score, in which a score of ≥ 2 equals a	NA

				good collateral status	
Menon BK et al 2015 ³⁴	IVT:59 EVT: 126	NA	-mRS at 90 days	NA	NA
Kufner A et al 2015 ³⁵	IVT: 62	30/31	-TICI 2b-3	NA	NA
Hwang et al 2015 ³⁶	EVT	131: 76	-mRS at 90 days -sICH -mortality	NA	NA
Singer et al 2015 (Singer OC) ENDOSTROKE ³⁷	EVT	41: 83	-mRS at 90 days	NA	NA
Singer et al 2015 ³⁸ ENDOSTROKE	EVT	78: 82	-mRS at 90 days	NA	NA
Zhang S et al 2016 ³⁹	IVT	23/41	-mRS at 90 days -TICI 2b-3 -mortality at 90 days	NA	NA
Seeters TV et al 2016 ⁴⁰	IVT/EVT/Combined	342:142	-mRS at 90 days	NA	NA
Tan BYQ et al 2016 ⁴¹	IVT	143: 97	-mRS -sICH -Mortality	NA	NA
Sheth sa et al 2016 ⁴²	Good Collateral: IV Tpa:21; IA tPA:7; Thrombectomy:41 Poor Collateral: IV tPA:22; IA-Tpa:9; Thrombectomy:55	54:66	-mRS at 90 days -Sich -TICI	N/A	Hemorrhagic transformation was categorized as hemorrhagic infarctions or parenchymal hematomas
Garcia-Tornel A et al	IVT: 56 EVT: 82	63:45	mRS at 90 days	Early clinical improvement or	Symptomatic intracranial hemorrhage

2016 ⁴³			-infarct expansion -TICI -sICH	deterioration was defined by a decrease or an increase of ≥ 4 points from baseline on the NIHSS at 24 h	(sICH) in cases with a 4-point increase in the NIHSS score.
Sallustio F et al 2016 ⁴⁴	IVT: 51.6:66.6	75:60	mRS at 90 days -TICI -sICH	NA	Symptomatic intracranial hemorrhage (sICH) in cases with a 4-point increase in the NIHSS score.
Gersing AS et al 2017 ⁴⁵	IVT: 83 EVT: 115	75:40	-NIHSS -mRS at 90 days -TICI 2b-3	NA	NA
Son JP et al 2017 ⁴⁶	IVT: 4 EVT: 19 Combined: 41	23:14	-Infarct volume -TICI 2b-3	NA	NA
Nordmeyer H et al 2017 ⁴⁷	IVT: 29 EVT: 87	37: 14	-sICH -mRS -mortality at follow up -TICI 2b-3	TICI 2b-3 was considered as complete recanalization	Any intracranial hemorrhage observed on control NCCT associated with an increase of 4 points or more on NIHSS score
Madelung CF et al 2017 ⁴⁸	IVT: 126 EVT: 5 Combined: 56	NA	NA	NA	NA
Rebello LC et al 2017 ⁴⁹	IVT: 44 EVT: 97	94: 28	-Infarct growth -mRS at 90 days -mortality at 90 days TICI 2b-3	NA	NA
Dankbaar JW et al 2018 ⁵⁰	NA	138: 50	NA	NA	NA
Kim BM et al	EVT	468: 86	-mRS 90 days	NA	NA

2018 ⁵¹			-TICI 2b-3		
Wang F et al 2018 ⁵²	IVT, EVT and Combined	185: 85	-mRS at 90 days	NA	NA
			-mortality at 90 days		
			-sICH		
Park JS et al 2018 ⁵³	IVT, EVT and Combined	33: 57	-TICI 2b-3	NA	NA
			-sICH		
			-mRS		
			-mortality at 90 days		
Havenon DA et al 2019 ⁵⁴	IVT: 8	97:33	-Infarct volume	>90% reduction in the region of perfusion delay (Tmax of >6 seconds)	≥4 point worsening of immediate pre deterioration NIH
	EVT: 130		-mRS at 90 days		
			-Mortality at 90 days	between baseline and 24 hours and complete recanalization on	Stroke Scale neurological status versus post deterioration and associated
				the 24-hour CT or magnetic resonance angiogram.	with brain hemorrhage

Abbreviations: EVT: Endovascular Thrombolysis; IVT: Intravenous thrombolysis; mRS: modified rankin scale; NA: Not applicable; NCCT: Non contrast CT scan; NIHSS: National Institute of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; sICH: symptomatic intracerebral hemorrhage

TABLE 3: RESULTS OF ALL STUDIES

Trial or Study	Modified rankin scale (0-2) Good v/s Poor Collaterals	TICI 2b-3 Good v/s Poor collaterals	Infarct Volume Expansion (ml) Good v/s Poor Collaterals	Mortality Good v/s poor collaterals	sICH Good v/s poor
Lee 2000	9/9: 1/4	NA	NA	NA	1/13: 0/4
Kim et al 2008	4/6: 2/3	NA	NA	NA	1/6: 0/3
Miteff F et al 2009	24/51: 3/41	N/A	4:42	NA	NA
Lee 2009	NA	15/20: 10/14	NA	NA	NA
Lima F et al 2010	IVT:25/82 IA thrombolysis 7/82 72/82:10/82	NA	NA	7/55:14/45	NA
Angermaier et al 2011	NA	NA	NA	NA	2/15: 0/10
Park et al 2011	NA	30/35: 7/23	NA	NA	0/37: 3/21
Bang et al 2011					22/144: 20/78
Choi et al 2011	20/29: 5/26	NA	NA	NA	3/29: 12/26
Gallimanis et al 2012	163/316	NA	NA	NA	5/190: 28/420
Souza et al 2012	No Treatment: 45/175:8/22 IVT:30/175:13/22 IAT±IV: 75/175:1/22	NA	NA	45/175:11/22	NA
Rai et al 2012	38/62: 6/27	NA	NA	9/62: 14/27	NA
Ramaiah et al 2014	24/34:23/53 IVT:22/34:18/53 IAT:2/34:11/53	25/34:35/53	NA	2/34:11/53	4/34:13/53
Calleja et al 2013	24/37: 2/17	22/37: 5/15	NA	NA	1/37: 1/17
Ichijo et al 2013	15/20: 11/30	12/12: 7/14	NA	NA	NA
Nambiar V et al. 2013	N/A	23/53:9/31	42.1:37.6:90.9	8/53:24/31	N/A

Saarien et al 2014	41/57: 13/47	NA	NA	NA	NA
Brunner et al 2014	NA	NA	NA	NA	10/205: 6/41
Al-Ali et al 2014	8/13: 1/15	NA	NA	NA	NA
Marks MP et al. 2014	NA	10/15:5/7	NA	NA	NA
Sung SM et al 2014	9/30	7/11:11/19	N/A	N/A	2/30
Liebeskind IMS-III et al 2014	50/96: 54/180	NA	NA	11/96: 40/180	6/96: 11/180
Liebeskind SWIFT et al 2014	20/35: 14/71	NA	NA	3/35: 27/71	NA
Mangiafico et al 2014	22/65: 4/37	NA	NA	12/65: 13/37	7/66: 6/37
Chen et al 2015	21/25: 9/50	NA	NA	3/25: 8/50	3/25: 12/50
Fanou et al 2015	NA	19/310:26/85	NA	NA	NA
Menon BK et al 2015	IVT CCS1: 42/59:17/59 CCS 2: 52/59:7/59 CCS 3: 43/59:16/59 EVT CCS1: 88/126:38/126 CCS 2: 107/126: 19/126 CCS 3: 92/126: 34/126	NA	NA	NA	NA
Kufner 2015	NA	16/30: 23/31	NA	NA	NA
Hwang et al 2015	82/131: 35/76	NA	NA	13/131: 11/76	6/131: 4/76
Singer et al 2015	20/41: 25/83	NA	NA	NA	NA

ENDOSTROKE					
Singer et al 2015	38/78: 24/82	NA	NA	NA	NA
ENDOSTROKE					
Zhang S et al 2016 (Zhang S)	15/23: 4/41	11/23: 16/41	16.1/52.8	0/23: 10/41	0/23: 6/41
Van Seeters T et al 2016	194/342:39/142	NA	NA	NA	NA
Tan BYQ et al 2016	77/143: 24/97	65/99: 49/73	NA	15/143:25/97	12/143: 18/97
Sheth sa ET AL 2016	NA	27/51:27/66	73:13	NA	20/51:41/66
Garcia-Tornel A et al 2016	40/65:12/27	49/63:32/45	17:98	NA	2/3:4/9
Sallustio F et al 2016	N/A	55/75:33/60	N/A	6/75:27/60	5/75:22/60
Gersing AS et al 2017 (Gersing AS)	53/75: 23/40	34/75: 21/40	NA	NA	NA
Son JP et al 2017 (Son JP)	NA	10/23: 5/14	4.5/52	NA	NA
Nordmeyer H et al 2017 (Nordmeyer H)	19/37: 2/14	34/37: 12/14	NA	0/37: 12/14	NA
Madelung CF et al 2017 (Madelung CF)	40/55: 10/44	NA	NA	NA	NA
Rebello LC et al 2017 (Rebello LC)	49/87: 7/24	81: 19	30.1±49.4: 34.7±62.8	13/87: 4/24	NA
Dankbaar JW et al 2018 (Dankbaar JW)	65/138:10/50	NA	NA	NA	NA
Kim BM et al 2018 (Kim BM)	303/468: 5/86	NA	NA	20/468: 31/86	25/468: 20/86
Wang F et al 2018 (Wang F)	112/185: 27/85	NA	NA	17/185: 30/85	29/185: 27/85
Park JS et al 2018 (Park JS)	21/33: 7/57	24/33: 34/57	NA	2/33: 16/57	2/33: 14/57
Havenon DA et al 2019 (Havenon AD)	29/97: 13/33	42/97: 12/33	26.9: 65.7	18/97: 8/33	5/97: 12/33

Figures

A

B

C

Figure 1

Pooled analysis of all included studies. A. Patients with acute ischemic stroke with good CBF had a more than 2-fold higher likelihood of having good outcome (mRS 0-2 at 90 days) in comparison to patients with stroke having poor CBF (RR: 2.27 ; 95%CI: 1.94-2.65; $p < 0.00001$). B. Patients with good pretreatment collaterals receiving intra venous thrombolysis showed around 3-fold higher risk of better outcome as compared to patients with poor collaterals (RR: 2.90; 95%CI: 2.14-3.94; $p < 0.00001$). C. Patients with good collaterals who received thrombolysis either intrarterial or mechanical had approximately 2-fold higher risk of favorable outcome compared to patients with pre-treatment poor collaterals (RR: 1.99; 95% CI: 1.55-2.55; $p < 0.00001$)

Figure 2

Patients with good collaterals showed 1-fold higher likelihood of complete recanalization as compared to poor collaterals RR of Recanalization: 1.31; 95% CI: 1.15-1.49; p<0.00001

Figure 3

Compared to poor collateral status, good pretreatment collaterals had 54% less relative risk of sICH at 90 days. The RR of sICH: 0.46; 95% CI: 0.35-0.60; p<0.00001

Figure 4

Patients with good collateral status has 64% less risk of mortality at 3-months compared to patients with poor collateral status irrespective of the type of thrombolysis. The RR of mortality: 0.36; 95%CI: 0.27-0.48; $p < 0.00001$