Safety and efficacy of endovascular thrombectomy in patients with severe cerebral venous thrombosis: A meta-analysis

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ABSTRACT

BACKGROUND: Cerebral venous thrombosis (CVT) is a rare thrombotic condition which is traditionally treated with anti-coagulation therapy. Subsets of patients with severe CVT have been treated with endovascular thrombectomy (EVT). Despite the high estimated mortality associated with severe CVT, there has been only one randomized control trial done regarding safety and efficacy of EVT in severe CVT compared to standard medical management. Evidence in this area is lacking.

OBJECTIVE: The aim of this systematic review is to analyze all existing literature and generate robust information regarding the role of EVT in the management of patients with severe CVT.

METHODS: This systematic review and meta-analysis followed PRISMA guideline. PubMed, Embase, Google Scholar, and CNKI were searched for eligible studies from 2007 to 2021. Safety and efficacy of EVT were evaluated by meta-analyzing recanalization status, the good functional outcome at follow-up, recurrent CVT, new hematoma. A pooled proportion with a 95% confidence interval was derived from a meta-analysis of various outcomes (CI).

RESULTS: A total of 33 studies comprising 610 patients treated with EVT were included for analysis which comprised one randomized control trial, one prospective study and 31 retrospective studies. Based on pooled data, 85% of patients had good functional outcome, 62% had complete recanalization, 5% had all-cause mortality, and 3% had catheter related complications. The efficacy outcomes in this analysis had a significant heterogeneity and a subgroup analysis was also done to explain these findings. The minimum time of follow up was 3 months and varied EVT techniques were used across the studies.

CONCLUSION: This meta-analysis suggests EVT may be safe and efficacious in treating patients with severe CVT.

REGISTRATION: Our protocol was registered with PROSPERO: International prospective register of systematic reviews with the registration number CRD42021254760.

KEYWORDS: Cerebral venous thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, CVST, endovascular thrombectomy, mechanical thrombectomy

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Introduction

Cerebral venous thrombosis (CVT) is a rare thrombotic condition caused by partial or complete occlusion of the major cerebral venous sinuses or smaller feeding cortical veins.[1] Young adults and females of childbearing age are more commonly affected, with an estimated prevalence of 1.3-1.6 cases per

100,000 people, accounting for .5-1% of all adult stroke cases. The mortality of CVT is recorded as 8-10%, while disability-related morbidity following CVT is estimated at 20%.[1,2] Although the clinical presentation varies according to the veins involved, CVT commonly presents with headache, visual changes, seizures, raised intracranial pressure, encephalopathy, and focal neurological signs.[1,2] Current guidelines from American Heart Association (AHA) and European Stroke Organization (ESO) recommend treating acute symptomatic CVT with either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) followed by an oral vitamin K antagonist (VKA) for 3-12 months to prevent a recurrence. The underlying cause should also be addressed.[3,4] Recently there has been an increasing interest in Direct oral anticoagulants (DOACs). In a recent meta-analysis by Lee et al. (2020), the efficacy of DOACs was comparable with VKA in terms of partial or full thrombus recanalization, excellent functional recovery with modified Rankin scale and had lower bleeding events.[5] Endovascular thrombectomy is an emerging treatment strategy in patients with CVT. As per AHA, endovascular thrombectomy (EVT) with or without thrombolysis is reserved for the patients who deteriorate despite anticoagulation treatment for CVT.[3] In contrast, the European Stroke Organization guideline does not provide a recommendation for or against this therapy.[4] Evidence in this area is lacking.

CVT severity is categorized according to one of several risk scores, including CVT grading scale (CVT-GS),[6] the International Study on Cerebral Vein and Dural Sinus Thrombosis Rating Scale (ISCVT-RS),[7] and Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT),[8] among others. Across all scoring systems, severe CVT generally consists of CVT with coma or severely decreased consciousness, >37 years, male sex, coma, mental status disorder, hemorrhage, anticoagulation failure, thrombosis of the deep cerebral venous system, central nervous system infection, and cancer.[6-8] Despite the high estimated mortality rate of 61.4% associated with severe CVT, there has been only one randomized control trial done regarding safety and efficacy of EVT in severe CVT compared to standard medical management, which has shown equivocal results.[9] In the International Study on Cerebral vein and Dural Sinus Thrombosis (ISCVT), 8% patients died either as a direct consequence of CVT or underlying condition despite treatment with anticoagulants.[7] Hence, patients with such risk factors may benefit from EVT compared to anticoagulation alone. However, comprehensive evidence regarding the added benefit of EVT for severe CVT is lacking. The aim of this systematic review is to analyze all existing literature and generate robust information regarding the role of EVT in the management of patients with severe CVT.

Methodology

We performed this systematic review and meta-analysis according to current standards and adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[10] Our protocol was registered with PROSPERO: International prospective register of systematic reviews with the registration number CRD42021254760.

Eligibility criteria

Original research studies published in any language meeting the following criteria were included: (a) the study recruited patients with CVT; (b) study patients were treated with EVT with or without thrombolysis; (c) the study reported at least one of the following outcomes: recanalization status (complete or partial), the good functional outcome at follow-up defined by the modified Rankin Scale (mRS) score ≤ 2, recurrent CVT, new hematoma or expansion of pre-existing hematoma, all-cause mortality and catheter-related complications; and (d) the study design included a randomized clinical trial (RCT), a prospective study, a retrospective study or a case series with more than 5 cases. Case series with fewer than five cases, case reports, reviews, opinion-based articles, and animal studies were excluded. However, conference abstracts were included if they provided the required information.

Search strategy and study Screening

PubMed, Embase, Google Scholar, and China National Knowledge Infrastructure (CNKI) were searched for potentially eligible studies published from January 2007 to April 2021. Boolean logic was used for conducting a database search, and Boolean search operators “AND” and “OR” were used to link search terms. Search strategy for PubMed search was as follows: ((“sinus thrombosis, intracranial"[MeSH Terms] OR “Cerebral Venous Thrombosis”[All Fields] OR “Cerebral Venous Sinus Thrombosis"[All Fields] OR “CVT”[All Fields] OR “CVST”[All Fields]) AND (“Endovascular Procedures”[MeSH Terms] OR “Thrombectomy”[MeSH Terms] OR “Embolectomy”[MeSH Terms] OR “Thrombolytic Therapy”[MeSH Terms] OR (“Mechanical Thrombectomy”[All Fields] OR “Endovascular Thrombectomy”[All Fields] OR “Intravenous Thrombolysis”[All Fields]))) AND ((english [Filter]) AND (2008:2021[pdat])). Similarly, search strategy for Embase search was as follows: (‘cerebral sinus thrombosis’/exp OR ‘cerebral sinus thrombosis’ OR ‘cerebral venous thrombosis’ OR ‘cvt’ OR ‘cvst’) AND (‘mechanical thrombectomy’ OR ‘percutaneous thrombectomy’ OR ‘intravenous thrombolysis’) AND (‘placebo’/exp OR placebo OR ‘randomized controlled trial’:jt OR ‘randomized’:au OR ‘observational’ OR “case series’). Our detailed search strategy is mentioned in the supplementary file. A search for foreign language and gray literature was conducted using Google Scholar and CNKI. The search was also broadened to include preprint servers and thesis repositories. There were no language restrictions. We scanned the reference list of each included study to identify further potential material of interest. All shortlisted studies were then imported to Mendeley library and

duplicates were removed appropriately. A subsequent manual check was done with the removal of the remaining duplicates where applicable. Citations were initially reviewed by title, keywords, and abstract by two reviewers (GN and SK) independently and subsequently verified with a third reviewer (MAC). Articles passing the initial screen were subsequently reviewed in full by two reviewers (GN and SK). We resolved differences in the final study selection between the two primary reviewers (GN and SK) by consultation with a third reviewer (MAC).

Data extraction

The final included studies were collated, and the two reviewers (GN and SK) used standardized data extraction formats to extract the data. After extraction, data were matched by reviewers before revisiting papers where disagreements arose. Any discrepancies were resolved through discussion with the third reviewer (MAC). In cases of ambiguity or missing information, we contacted corresponding authors of the studies in question to clarify necessary details. Duplicate studies were included only once in the final analysis, with the most comprehensive article being chosen. The extracted data included the following: first author, study design, site of study, year of publication, nationality of the patient, type of literature (published or gray), sample size, mean age of patients in the study, gender of patients in the study, the severity of CVT, EVT devices used, adjuvant therapy used, the timing of EVT, follow up duration and outcomes (recanalization status, good functional outcome at follow-up, recurrent CVT, new hematoma or expansion of pre-existing hematoma, all-cause mortality and catheter-related complications).

Regarding the aforementioned outcomes, recanalization status was defined as complete, partial, or no recanalization. Recanalization was determined for each sinus and was scored as complete (uninterrupted blood flow within the venous system disregarding some small residual thrombi adherent to the sinus wall) as seen in imaging, partial (more extensive thrombi with small interruptions of continuous blood flow or narrowing of the lumen), or absent (no recanalization, interrupted blood flow).[9] Good functional outcome at follow-up was defined as modified Rankin Scale (mRS) score ≤ 2. New or expansion of hematoma was diagnosed on post-procedure head CT in symptomatic patients, including those with decreased consciousness or complaint of headache, neck pain, or confusion. Recurrent CVT was defined as new episode of CVT during the follow-up period. All-cause mortality was defined as death of treated patient with any cause. Additionally, catheter-related complications noted among the included studies consisted of catheter-tip fracture, groin/retroperitoneal hematoma, sinus perforation, retroperitoneal hemorrhage, and formation of bilateral inguinal aneurysm.[11,12]

Statistical analysis

The safety and efficacy of EVT was evaluated by meta-analyzing the following outcomes: recanalization status, the good functional outcome at follow-up, recurrent CVT, new hematoma or expansion of pre-existing hematoma, all-cause mortality, and catheter-related complications. A meta-analysis of the proportion was performed for various outcomes and expressed as a pooled proportion with a 95% confidence interval (CI). Heterogeneity between the included studies was determined using the I^2 test. The presence of I^2 greater than 50% was considered an indicator of significant heterogeneity. If heterogeneity was determined, the Restricted Maximum Likelihood random-effects model was used for meta-analysis. If the I^2 value was less than 50%, a fixed-effect model was used. Forest plots with 95% CIs were created to show individual study results and weights as well as overall weighted mean estimates. Additionally, a sensitivity test was performed to examine the stability of the analysis. Subgroup analyses were also performed based on the type of literature, site of study, EVT devices used, adjunctive therapy, and age groups of patients. A P-value of < .05 was considered statistically significant. Statistical analysis was performed using the STATA software version 16 (StataCorp).

Risk of bias assessment

Two investigators (GN and SK) evaluated the quality of included studies in a consensus procedure. The Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used for the quality assessment of each study and described under three headings: selection,[4] comparability,[2] and exposure.[3] Studies with scores of five or more were considered qualified for inclusion, and studies with more than seven were considered high-quality studies.

The Cochrane risk of bias tool was used to evaluate the quality of the randomized controlled trials (RCTs). It includes seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was divided into low-risk, unknown, and high-risk.

Results

Search results and study characteristics

In total, 622 articles were identified after a thorough database search. After the exclusion of duplicates and those not meeting inclusion criteria, 33 studies were reviewed for data collection. Figure 1 shows the results of our literature search and selection. The characteristics of each included study discussed below are summarized in Table 1. The included studies were published from 2007 to 2021, and the study period spanned from 1999 to 2019. One of the included studies was a clinical trial,[9] one was a prospective observational study[13] and the rest were retrospective observational studies. Of the 33 studies, 26 were in the English language and 7 were exclusively in the Chinese language.[14-20] Seventeen studies were conducted in China,[9,11-29] 5 in the USA[30-34], 2 in Taiwan[12,35] and India,[36,37] two were multicenter studies (one conducted in USA and Netherlands[38] and other in

the Netherlands, China, and Portugal[9]), one study each was conducted in the UK[39], Hong Kong,[40] Netherlands,[13] Denmark[41] and Germany.[42]

The NOS score for observational studies ranged from 5 to 8. And for RCT by Coutinho et al there was high-risk of bias in 3 domains: allocation concealment, blinding of participants and personnel, blinding of outcome assessment.

Demographics, indications for EVT, follow-up duration and devices used

In 33 studies, the sample of CVT patients treated with EVT ranged from 6 to 52 among which 61.6% included females of age group 18-40 years. The majority of the included studies used EVT in severe CVT patients. The indication of EVT varied across the studies (Table 1), however, common indications were an anticoagulation failure, worsening neurological symptoms, coma, intracerebral hemorrhage, and cerebral edema, and raised intracranial pressure. Patients were followed up for a minimum of 3 months in most of the studies. Likewise, devices/procedure used varied among different studies which included rheolytic thrombectomy, balloon angioplasty, aspiration thrombectomy, coil thrombectomy, catheter fragmentation, local thrombolytic therapy, and stent retriever thrombectomy. All the patients included in our study, were treated with adjunctive anti-coagulation prior to EVT. The details of different EVT devices and adjunct therapy are tabulated in Table 1.

Modified Rankin Scale (mRS) score ≤ 2 for good functional outcome

Good functional outcome was measured at a range of follow-up intervals among the included studies, from 3 months to 62 months. However, the follow-up period for the majority of studies was 6 months. Thirty-one studies (n = 543) in our analysis reported good functional outcome events (n = 447) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on the random effect model (I^2 = 99.72%) showed that good functional outcomes occurred in 85% (95% CI: .81-.90) of CVT patients following EVT (Figure 2). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. . Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. No significant subgroup differences were found in the subgroup analysis.

Complete recanalization

In most of the included studies, evaluation of recanalization status was done post-procedure. Thirty-one studies (n = 531) in our

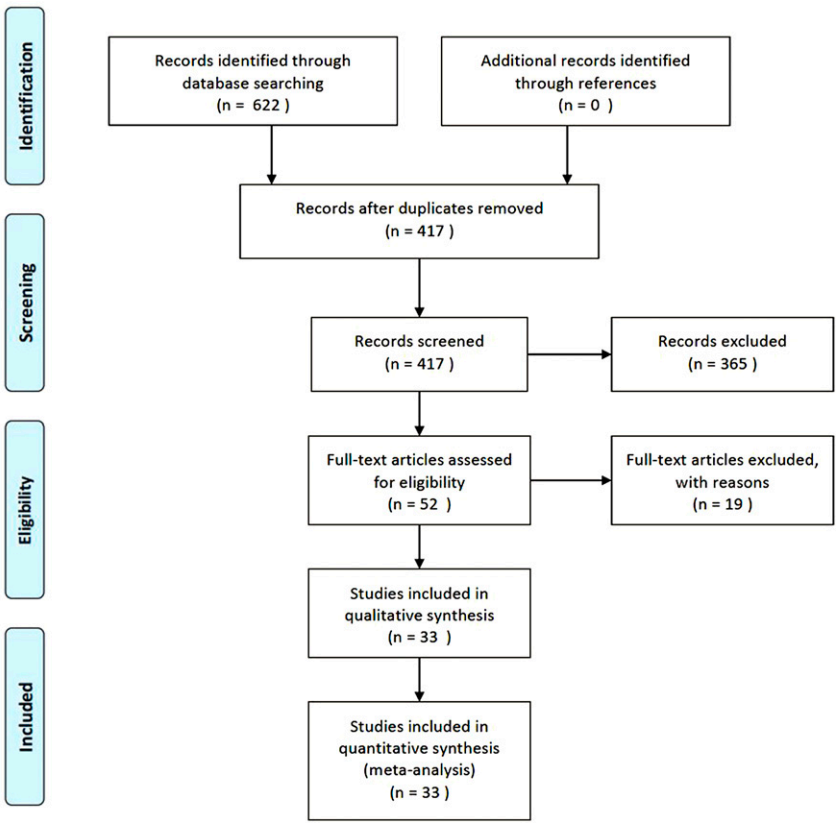

Figure 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review.

Table 1. Key methodological characteristics of studies included in this meta-analysis.

SN	AUTHOR	STUDY PERIOD	STUDY DESIGN	STUDY SITE	TOTAL CVT PATIENTS	PATIENTS TREATED WITH EVT	SEVERITY OF CVT	INDICATION OF EVT	SEX(F/M) OF PATIENTS TREATED WITH EVT	MEAN/MEDIAN AGE OF PATIENTS TREATED WITH EVT	FOLLOW-UP	DEVICES USED FOR EVT	ADJUNCT THERAPY	NOS SCORE
1	Andersen 2020	2007-2018	Retrospective cohort	Denmark	28	28	Severe	Anticoagulation failure, altered mental status, worsening neurological symptoms	21/7	37.5 years(15-76)	3 and 6 months	AT, ST, CF, BA	LMWH, LTT	7
2	Chen 2017	2011-2015	Retrospective cohort	China	29	14	Severe	Anticoagulation failure, worsening neurological symptoms, cortical venous outflow stasis	NA	34 years(17-60 years)	3,6, and 12 months	ST	LMWH, LTT	7
3	Coutinho 2020	2011-2017	Clinical trial	Netherlands, China, Portugal	67	30	High risk	Altered mental status, coma, intracerebral hemorrhage, thrombosis of the deep venous system	23/7	42(33-50) years	6 and 12 months	RT, ST	LMWH, LTT	n/a
4	Dandapat 2019	2017-2018	Retrospective cohort	USA	16	16	Severe	Anticoagulation failure, altered mental status, worsening neurological symptoms	9/7	52.5 years	30 days	AT, CF and ST	LMWH	7
5	Dashti 2011	2009-2010	Retrospective cohort	USA	13	13	Severe	Anticoagulation failure, worsening neurological symptoms	7/6	45(17-73) years	7 months	RT	LMWH	6
6	Guo 2020	2010-2019	Retrospective cohort	China	56	14	Severe	Anticoagulation failure, worsening neurological symptoms	41/15	31(15-46 years)	6 months	ST, AT, BA	LMWH, LTT	7
7	Jankowitz 2012	2009-2012	Retrospective study	USA	27	6	Severe	Worsening neurological symptoms, cerebral edema, intracerebral hemorrhage on CT/MRI	5/1	1-25 years	7 months mean	AT	LMWH	7
8	Li 2013	2007-2010	Retrospective study	China	52	52	Severe	Anticoagulation failure, altered mental status, coma, worsening neurological symptoms, elevated intracranial pressure	22/30	33(10-77 years)	3,6 months	AT	LMWH, LTT	7

(Continued)

Table 1. Continued.

SN	AUTHOR	STUDY PERIOD	STUDY DESIGN	STUDY SITE	TOTAL CVT PATIENTS	PATIENTS TREATED WITH EVT	SEVERITY OF CVT	INDICATION OF EVT	SEX(F/M) OF PATIENTS TREATED WITH EVT	MEAN/MEDIAN AGE OF PATIENTS TREATED WITH EVT	FOLLOW-UP	DEVICES USED FOR EVT	ADJUNCT THERAPY	NOS SCORE
9	Li 2018	2002-2016	Retrospective study	China	17	17	High risk	Anticoagulation failure	11/6	37.6+-8.9 years(23-51 years)	3,6 months	ST	LMWH	6
10	Liao 2020	2005-2015	Retrospective study	Taiwan	30	14	Severe	Anticoagulation failure, altered mental status, worsening neurological symptoms, worsening seizures	8/6	47.50(29.75-54.25 years)	3 months	AT, BA, CF, ST	LMWH, LTT	8
11	Ma 2016	2013-2014	Retrospective study	China	23	23	Severe	Anticoagulation failure	13/10	17-65 years	6-14 months	ST	LMWH	7
12	Medhi 2020	2018-2019	Retrospective study	India	7	7	Severe	Anticoagulation failure, worsening neurological symptoms, worsening imaging	2/5	25-63 years	4 weeks, 3 months, 6 months	AT	LMWH	5
13	Mortimer 2013	1999-2013	Retrospective study	UK	9	9	Severe	Anticoagulation failure, worsening neurological symptoms, worsening imaging	6/3	18 months to 16 years	6-24 months	CF, BA, AT	LMWH, LTT	5
14	Mokin 2015	2010-2013	Retrospective study	USA	13	13	Severe	Anticoagulation failure, clot burden, worsening neurological symptoms	8/5	40 years	3 months	AT, ST	LTT	7
15	Qui 2021	2015-2019	Retrospective study	China	40	38	Severe	Anticoagulation failure, worsening neurological symptoms, altered mental status	17/23	37.9+-14.6(16-67) years	3-6 months	BA	LMWH, LTT	6
16	Shui 2014	2006-2012	Retrospective study	China	26	26	Severe	Anticoagulation failure, worsening neurological symptom	19/7	28.9 (18-46 years)	12-62 months (42.3 months mean)	BA	LMWH	6
17	Siddiqui 2014	1999-2012	Retrospective study	Netherlands and USA	63	34	Severe	Anticoagulation failure, Altered mental status, coma, cerebral edema, intracerebral hemorrhage, thrombosis of the deep venous system	26/8	35(12-57) years	3, 6 months	RT, AT, CT, BA	LMWH , LTT	8

(Continued)

Table 1. Continued.

SN	AUTHOR	STUDY PERIOD	STUDY DESIGN	STUDY SITE	TOTAL CVT PATIENTS	PATIENTS TREATED WITH EVT	SEVERITY OF CVT	INDICATION OF EVT	SEX(F/M) OF PATIENTS TREATED WITH EVT	MEAN/MEDIAN AGE OF PATIENTS TREATED WITH EVT	FOLLOW-UP	DEVICES USED FOR EVT	ADJUNCT THERAPY	NOS SCORE
18	Stam 2008	2007	Prospective study	Netherlands	20	15	Severe	Altered mental status, coma, cerebral edema, intracerebral hemorrhage on CT/ MRI	16/4	32(12-57) years	3-6 months	RT	LMWH, LTT	7
19	Styczen 2019	2011-2018	Retrospective study	Germany	13	13	Severe	Altered mental status, coma, intracerebral hemorrhage, thrombosis of the deep venous system	10/3	34(15-57) years	9 days to six months (95 days median)	AT, ST	LMWH	7
20	Anand 2020	2018	Retrospective study (Master's Thesis)	India	23	22	Severe	Anticoagulation contraindication, worsening neurological symptoms, worsening imaging, cerebral edema, thrombosis of the deep venous system	11/11	30.5(18-70 years)	16 months median	BA	LMWH	NA
21	Tsai 2007	2003-2007	Retrospective study	Taiwan	25	15	Severe	Anticoagulation failure, worsening neurological symptoms, intracerebral hemorrhage on MRI/ CT	10/5	38(19-57) years	When clinically indicated (1-7 months)	BA	LMWH, LTT	5
22	Tsang 2018	2014-2018	Retrospective study	Hong Kong	6	6	Severe	Worsening neurological symptoms, intracerebral hemorrhage on MRI/ CT	3/3	49(29-71) years	3 months	AT	LMWH, LTT	5
23	Wang 2020	2013-2018	Retrospective study	China	29	8	Severe	Anticoagulation failure, worsening neurological symptoms, altered mental status, cortical venous outflow stasis	4/4	39(23-65) years	1-6 months	ST	LMWH, LTT	7
24	Zhang 2018	2013-2016	Retrospective study	China	23	9	Severe	Worsening neurological symptoms, coma, hemorrhage on MRI/ CT	4/5	39.2(23-65) years	4-28 months	ST, BA	LTT	7

(Continued)

Table 1. Continued.

SN	AUTHOR	STUDY PERIOD	STUDY DESIGN	STUDY SITE	TOTAL CVT PATIENTS	PATIENTS TREATED WITH EVT	SEVERITY OF CVT	INDICATION OF EVT	SEX(F/M) OF PATIENTS TREATED WITH EVT	MEAN/MEDIAN AGE OF PATIENTS TREATED WITH EVT	FOLLOW-UP	DEVICES USED FOR EVT	ADJUNCT THERAPY	NOS SCORE
25	Zhang 2008	2000-2006	Retrospective study	USA	6	6	High risk	Anticoagulation failure, worsening neurological symptoms, altered mental status, coma	5/1	28.5+-13.4(14 to 49)years	When clinically indicated (6-15 months)	RT	LTT	5
26	Zhen 2015	2009-2011	Retrospective study	China	8	8	Severe	Worsening neurological symptoms	6/2	27.5+-10.4(19-48) years	3-15 months	CF	LMWH, LTT	5
27	Hongrui 2018	2015-2016	Retrospective study (Master's Thesis)	China	77	37	High risk	Headache, Worsening neurological symptoms,coma	25/12	37 years (15.61 years)	6-24 months	BA, ST	LMWH	N/A
28	Li 2012	2009-2010	Retrospective study	China	23	23	Severe	Anticoagulation failure, coma, intracerebral hemorrhage on CT/MRI	13/10	31.5-13years	3,6,12months	CF	LMWH,LTT	6
29	Zhang 2018	2007-2017	Retrospective study (PhD Thesis)	China	172	36	High risk	Anticoagulation failure, coma, hemorrhage on MRI/CT, altered mental status	NA	39.1years(7-70)	6,12months	BA,ST,CF	LMWH	N/A
30	Qiu 2015	2008-2014	Retrospective study	China	12	12	Severe	Worsening neurological symptoms	8/4	37.2years(24-48years)	6-12mouths	CF,ST	LMWH	6
31	Shi 2015	2012-2015	Retrospective study	China	15	15	Severe	Intracerebral hemorrhage on CT/MRI	8/7	37.5+-18.5years	3months	ST	LMWH	6
32	Yang 2018	2007-2017	Retrospective study	China	20	20	Severe	Intracerebral hemorrhage on CT/MRI, venous siltation of the cerebral infarction, cerebral hernia	6/14	30.3+-10.6years(22-57)	3-12months	RT,BA,ST	LMWH	7
33	Zhang 2009	2000-2007	Retrospective study	China	11	11	Severe	Worsening neurological symptoms, anticoagulation failure	9/2	27.5+-10.4(14-49)	10-32months	RT,BA,ST	LMWH	6

Abbreviations: RT, Rheolytic thrombectomy; BA, Balloon angioplasty; AT, Aspiration Thrombectomy; CT, Coil thrombectomy; CF, Catheter Fragmentation; LTT, Local thrombolytic therapy; ST, Stent retriver Thrombectomy; CVT, cerebral venous thrombosis; EVT, endovascular thrombectomy; LMWH, low-molecular-weight heparin.

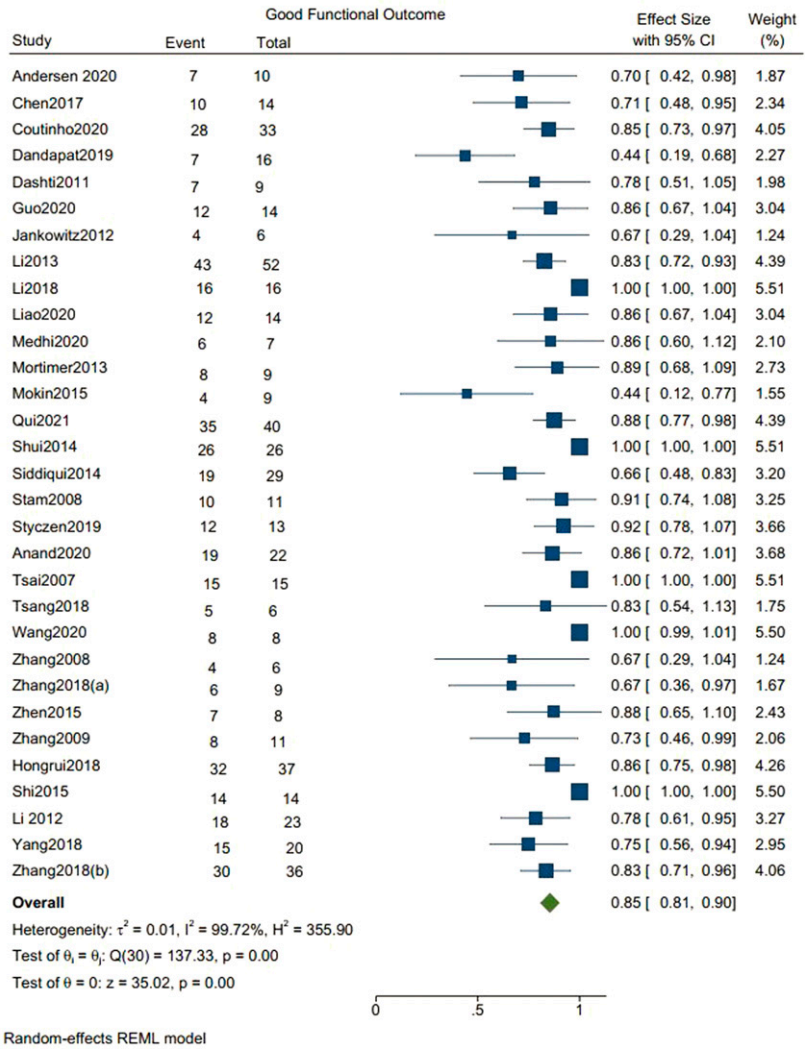

Figure 2. Forest plot with 95% CI for meta-analysis of proportion of cerebral venous thrombosis patients treated with endovascular thrombectomy achieving good functional outcome. The area of each square is proportional to the study's weight in the meta- analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

analysis reported complete recanalization events (n = 347) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on random effect model (I^2 = 99.95%) showed that complete recanalization occurred in 62% (95% CI: .53-.72) of CVT patients following EVT (Figure 3). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. The subgroup differences were significant for the study site (P = .001) and age groups (P = .011).

Partial Recanalization

Thirty studies (n = 503) in our analysis reported partial recanalization events (n = 162) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on random effect model (I^2=91.63%) showed that partial recanalization occurred in 37% (95% CI: .27-.46) of CVT patients following EVT (Figure 4). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. . Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. The subgroup differences were significant for the study site (P < .001) and age groups (P < .001).

New or Expansion of hematoma

In most of the studies, new or expansion of hematoma was diagnosed on post-procedure head CT in symptomatic patients, including those with decreased consciousness or complaints of headache, neck pain, or confusion.[35,43] In these cases, time frame of original and repeat CT scans were variable, as they depended on each patient's variable onset of hematoma symptoms.

Table 2. Subgroup analysis of various outcomes based on type of literature, study site, type of devices, adjunctive therapy and age group.

SUBGROUPS		RESULTS	COMPLETE RECANALIZATION	PARTIAL RECANALIZATION	FUNCTIONAL OUTCOME MRS (0 TO 2)	MORTALITY OR DEATH	NEW OR EXPANSION OF ICH	RECURRENT CVT	CATHETER RELATED COMPLICATIONS
Literature type	Published	No. of studies	28	27	28	29	28	26	28
		Effect size	65%, 95% C.I. = .55-.75	34%, 95% C.I. = .24-.44	85%, 95% C.I. = .78-.93	6%, 95% C.I. = .04-.08	.04, 95% C.I. = .03-.06	2%, 95% C.I. = .01-.04	3%, 95% C.I. = .01-.04
		Heterogeneity	I^2 = 99.95%	I^2 = 90.64%	I^2 = 99.79%	I^2 = 3.63%	I^2 = 31.62%	I^2 = 0%	I^2 = 0%
	Grey	No. of studies	3	3	3	3	3	2	2
		Effect size	44%, 95%C.I. = .06-.82	56%, 95%C.I. = .19-.94	85%, 95%C.I. = .78-.93	2%, 95%C.I. = −.009 to .043	.02, 95%C.I. = -.01-.04	2%, 95%C.I. = -.02-.05	2%, 95%C.I. = - .02-.05
		Heterogeneity	I^2 = 93.99%	I^2 = 93.99%	I^2 = 0%	I^2 = 0%	I^2 = 0%	I^2 = 0%	I^2 = 0%
Study site	China	No. of studies	17	17	16	17	17	14	15
		Effect size	77%,95% C.I. = .67-.87	22%,95% C.I. = .13-.32	89%,95% C.I. = .84-.95	3%,95% C.I. = .02-.05	.03,95% C.I. = .01-.04	2%,95% C.I. = .00-.03	2%,95% C.I. = .00-.03
		Heterogeneity	I^2 = 99.94%	I^2 = 88.67%	I^2 = 99.72%	I^2 = 0%	I^2 = 29.62%	I^2 = 0%	I^2 = 0%
	Others	No. of studies	14	12	15	15	14	14	15
		Effect size	47%, 95% C.I. = .32-.61	55%, 95% C.I. = .42-.68	80%, 95% C.I. = .72-.89	9%, 95% C.I. = .05-.13	.06, 95% C.I. = .03-.10	3%, 95% C.I. = .01-.06	6%, 95% C.I. = .03-.09
		Heterogeneity	I^2 = 90.70%	I^2 = 74.43%	I^2 = 75.80%	I^2 = 4.29%	I^2 = 20.41%	I^2 = 0%	I^2 = 0%
Adjunctive therapy	EVT alone	No. of studies	12	12	12	13	13	10	12
		Effect size	63%, 95% C.I. = .43-.83	36%, 95% C.I. = .17-.54	85%, 95% C.I. = .77-.94	4%, 95% C.I. = .01-.06	.03, 95% C.I. = .01-.05	2%, 95% C.I. = .00-.04	2%, 95% C.I. = .01-.04
		Heterogeneity	I^2 = 99.99%	I^2 = 96.73%	I^2 = 99.90%	I^2 = 0%	I^2 = 55.37%	I^2 = 0%	I^2 = 0%
	EVT + Thrombolysis	No. of studies	14	14	13	13	14	12	13
		Effect size	66%, 95%C.I. = .56-.76	31%, 95%C.I. = .21-.41	85%, 95%C.I. = .78-.92	5%, 95%C.I. = .02-.08	.05, 95%C.I. = .02-.07	2%, 95%C.I. = .00-.05	2%, 95%C.I. = .00-.04
		Heterogeneity	I^2 = 61.55%	I^2 = 65.66%	I^2 = 58.10%	I^2 = 30.19%	I^2 = .27%	I^2 = 0%	I^2 = 0%
	Mixed	No. of studies	5	4	6	6	4	6	5
		Effect size	55%, 95% C.I. = .32-.76	53%, 95% C.I. = .27-.78	85%, 95% C.I. = .73-.97	10%, 95% C.I. = .04-.16	.04, 95% C.I. = -.01-.09	2%, 95% C.I. = -.01-.05	6%, 95% C.I. = .01-.12
		Heterogeneity	I^2 = 77.31%	I^2 = 73.10%	I^2 = 76.98%	I^2 = 14.13%	I^2 = 0%	I^2 = 0%	I^2 = 0%

(Continued)

Table 2. Continued.

SUBGROUPS		RESULTS	COMPLETE RECANALIZATION	PARTIAL RECANALIZATION	FUNCTIONAL OUTCOME MRS (0 TO 2)	MORTALITY OR DEATH	NEW OR EXPANSION OF ICH	RECURRENT CVT	CATHETER RELATED COMPLICATIONS
Age groups	<18 years	No. of studies	1	1	1	1	1	1	1
		Effect size	33%, 95% C.I. = .03-.64	67%, 95% C.I. = .36-.98	89%, 95% C.I. = .68-1.09	11%, 95% C.I. = -.09-.32	.22, 95% C.I. = -.05-.49	6%, 95% C.I. = -.11-.23	2%, 95% C.I. = -.05-.49
		Heterogeneity	I^2 = NA	I^2 = NA	I^2 = NA	I^2 = NA	I^2 = NA	I^2 = NA	I^2 = NA
	18-40 years	No. of studies	24	24	24	25	24	21	23
		Effect size	69%, 95% C.I. = .59-79	29%, 95% C.I. = .20-.39	88%, 95% C.I. = .83-.93	4%, 95% C.I. = .02-06	.03, 95% C.I. = .02-.05	2%, 95% C.I. = .01-.04	2%, 95% C.I. = .01-.04
		Heterogeneity	I^2 = 99.95%	I^2 = 90.67%	I^2 = 99.72%	I^2 = 22.95%	I^2 = 43.59%	I^2 = 0%	I^2 = 0%
	>40 years	No. of studies	6	5	6	6	6	6	6
		Effect size	41%, 95% CI = .20-.61	68%, 95% CI = .52-.84	72%, 95% CI = .57-.88	8%, 95% CI = .03-.14	.04, 95% CI = .00-.08	3%, 95% CI = −.01-.06	5%, 95% CI = −.01-.10
		Heterogeneity	I^2 = 79.54%	I^2 = 49.76%	I^2 = 65.79%	I^2 = 0%	I^2 = 0%	I^2 = 0%	I^2 = 0%

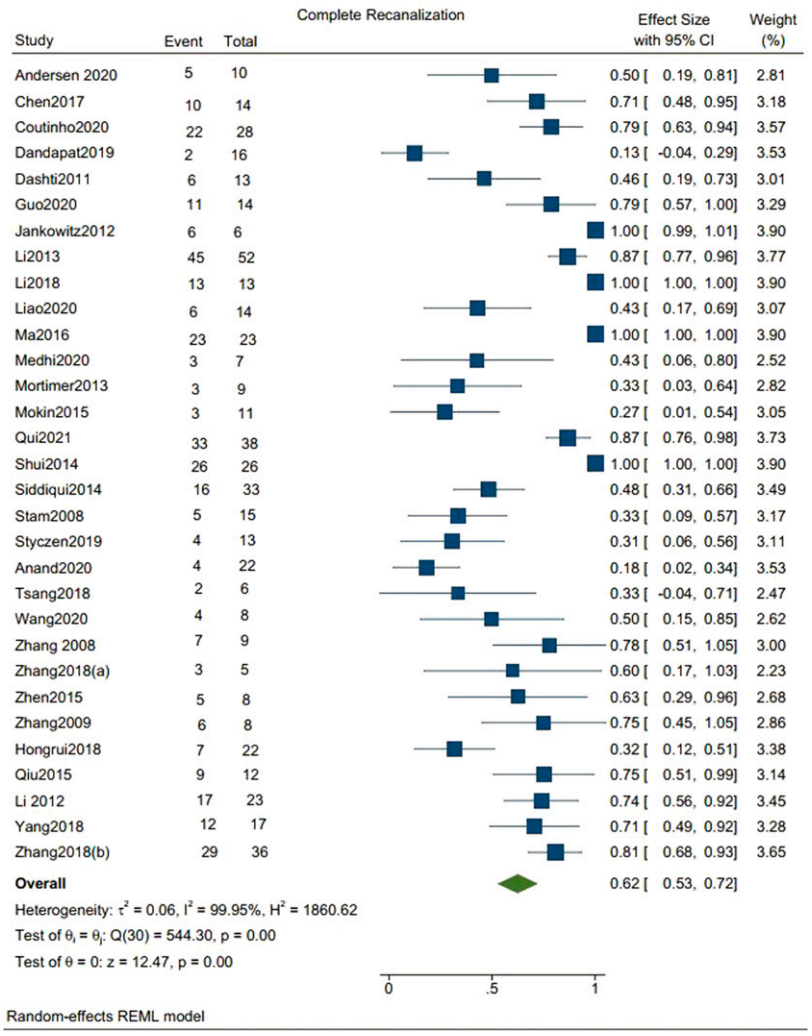

Figure 3. Forest plot with 95% CI for meta-analysis of proportion of cerebral venous thrombosis patients treated with endovascular thrombectomy achieving complete recanalization. The area of each square is proportional to the study's weight in the meta- analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

Thirty-one studies (n = 551) in our analysis reported new hematoma or expansion of hematoma (n = 41) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on fixed effect model (I^2 = 30.45%) showed that new or expansion of hematoma occurred in 4% (95% CI: .02-.05) CVT patients following EVT (Figure 5). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. The subgroup difference was significant for only the study site (P = .044).

All-cause mortality

All-cause mortality was measured at a range of follow-up intervals among the included studies, from 3 months to 62 months. However, the follow-up period for the majority of studies was 6 months. Thirty-two studies (n=584) in our analysis reported all-cause mortality events (n = 50) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on the fixed effect model (I^2 = 18.24%) showed that all-cause mortality occurred in 5% (95% CI: .03-.06) of CVT patients following EVT (Figure 6). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. The subgroup differences were significant for literature type (P = .007) and study site (P = .006).

Recurrent CVT

In most of the included studies, occurrence of new episode of CVT during the follow-up period was defined as recurrent CVT. It was measured at a range of follow-up intervals among the included studies, from 3 months to 62 months. However, the follow-up period for the majority of studies was 6 months.

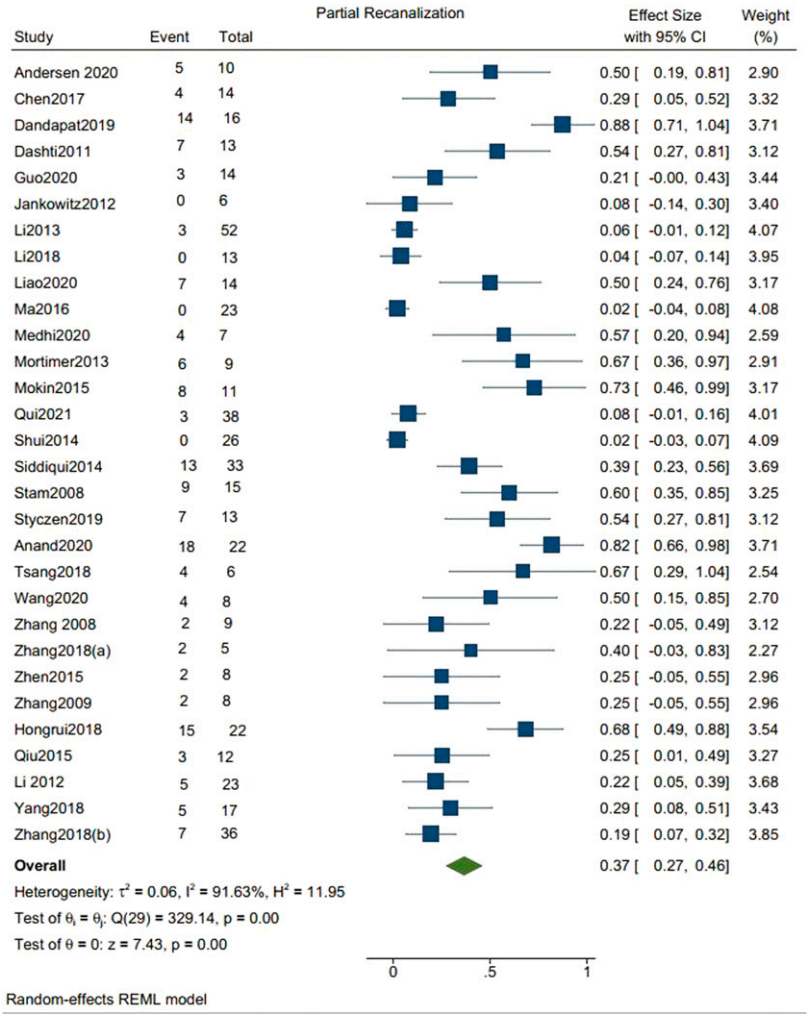

Figure 4. Forest plot with 95% CI for meta-analysis of proportion of cerebral venous thrombosis patients treated with endovascular thrombectomy achieving partial. The area of each square is proportional to the study's weight in the meta- analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

Twenty-eight studies (n = 499) in our analysis reported recurrent CVT events (n = 9) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on the fixed effect model (I^2 = 0%) showed that recurrent CVT occurred in 2% (95% CI: .01-.04) of CVT patients following EVT (supplementary Figure 1). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. No significant subgroup differences were found in the analysis.

Catheter-related complications

Catheter related complications were reported during and after endovascular procedure. In most of the included studies, catheter-related complications noted among the included studies consisted of catheter-tip fracture, groin/retroperitoneal hematoma, sinus perforation, retroperitoneal hemorrhage, and formation of bilateral inguinal aneurysm. Thirty studies (n = 516) in our analysis reported catheter-related complication events (n = 13) after mechanical thrombectomy in CVT patients. The meta-analysis of proportion based on the fixed effect model (I^2 = 0%) showed that catheter-related complications occurred in 3% (95% CI: .01-.04) of CVT patients following EVT (supplementary Figure 2). Sensitivity test performed by sequentially excluding one study at a time and recalculating the summary effect size showed stable overall effect size. Subgroup analysis based on literature type, study site, adjunctive therapy, and age group is shown in Table 2. The subgroup difference was significant for only the study site (P = .023).

Discussion

Based on the cumulative data of 610 patients treated with EVT for CVT from 33 studies that were analyzed, EVT was

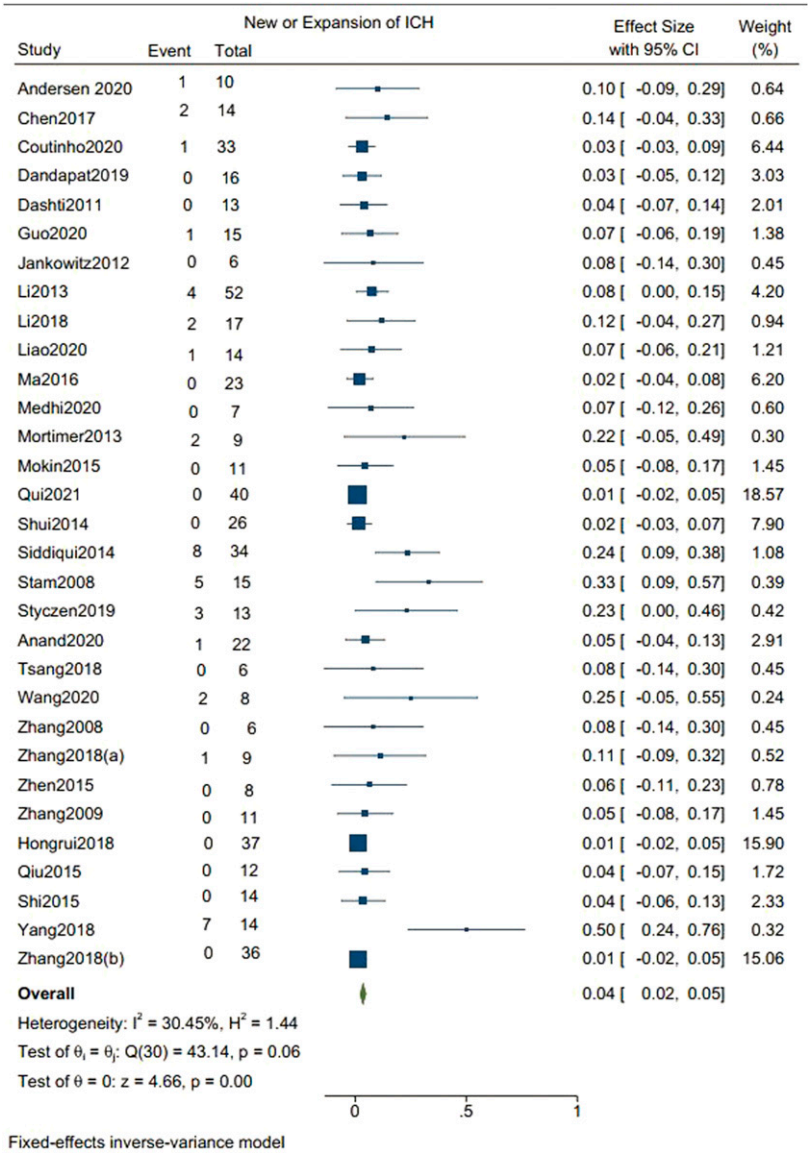

Figure 5. Forest plot with 95% CI for meta-analysis of proportion of cerebral venous thrombosis patients treated with endovascular thrombectomy developing new or expanding intracerebral hemorrhage. The area of each square is proportional to the study's weight in the meta- analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

considered in patients with anticoagulation failure, altered mental status, worsening neurological symptoms, cortical venous outflow stasis, intracerebral hemorrhage, deep venous thrombosis, cerebral edema, elevated intracranial pressure, worsening seizures, higher clot burden, worsening neuroimaging, or coma. Therefore, in our study, patients undergoing EVT represent a subset of patients with CVT who were expected to have poor prognosis as determined by previous studies.

Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial is the only published randomized controlled trial (RCT) evaluating the role of EVT as it compares to standard anticoagulation. The TO-ACT trial studied 67 patients with severe CVT with 33 cases in EVT group and 34 cases in standard medical therapy (control) group. Among EVT vs control group, mRS 0-1 at 12 months was 67% vs 68%, mortality was 12% vs 3%, and symptomatic intra-cranial hemorrhage was 3% vs 9%, respectively, none of which were statistically different. However, the control group had longer hospital stay and greater number of seizures (30% vs 3%, p .006). For mechanical thrombectomy, microcatheters, balloon angioplasty devices, rheolytic catheters, and stent retrievers were used at the discretion of the interventionalist.[9]

In our meta-analysis, good functional outcome at follow-up was observed in 85% of CVT patients following EVT, which was higher than that observed in the TO-ACT trial (67%).[9] Likewise, all-cause mortality occurred in 5% of patients after EVT, which was lower than the TO-ACT trial (12%).[9]

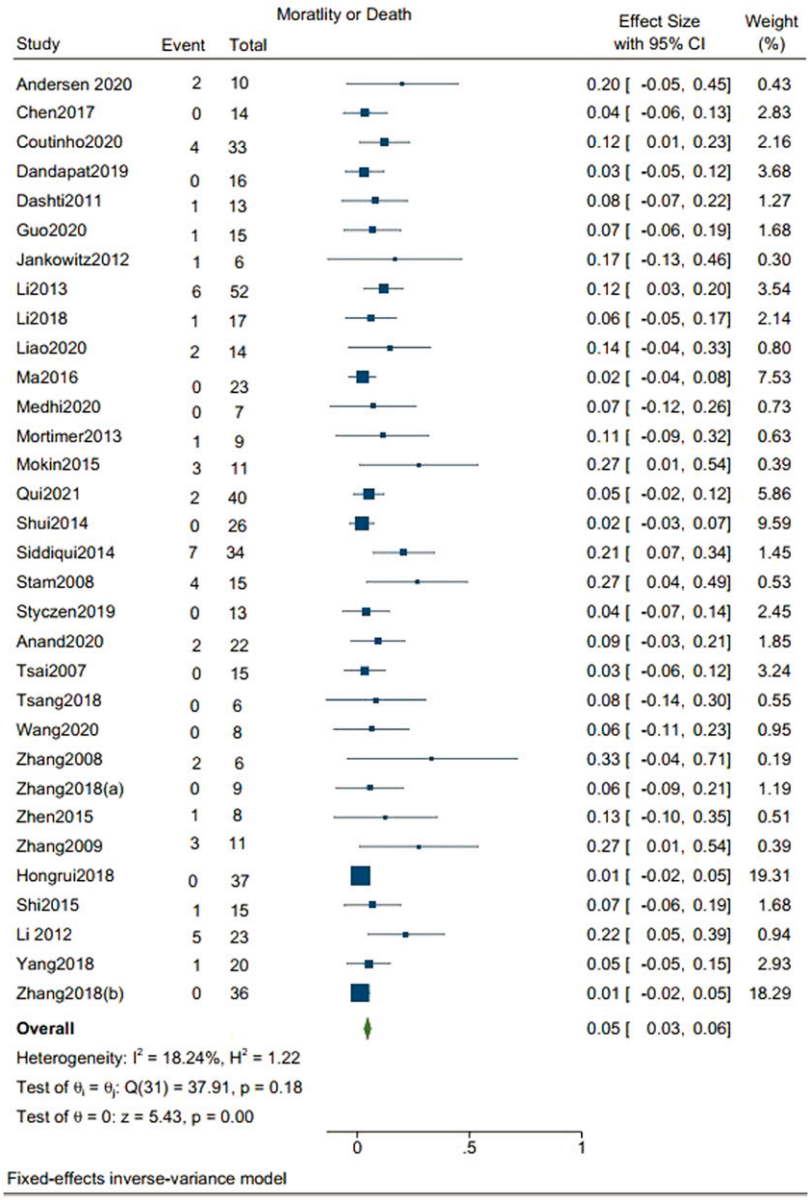

Figure 6. Forest plot with 95% CI for meta-analysis of proportion of cerebral venous thrombosis patients treated with endovascular thrombectomy who died. The area of each square is proportional to the study's weight in the meta- analysis, while the diamond shows the pooled result. The horizontal lines through the square illustrate the length of the confidence interval. The width of the diamond serves the same purpose. The overall meta-analyzed measure of effect is an imaginary vertical line passing through the diamond.

However, these subsets of patients should not be compared to patients with less severe CVT manifestations treated with DOAC or standard anticoagulation treatment. Previous study has suggested that, among patients with less severe CVT treated with DOAC vs standard anticoagulation treatment, good functional outcome was seen in 91.52% vs 86.91% of patients, respectively, and all-cause mortality was seen in 1.36% and 1.28% of patients, respectively.[44]

Our meta-analysis also found that after EVT, 62% of CVT patients experienced complete recanalization, which was lower than the TO-ACT trial (79% for superior sagittal sinus and 96% for straight sinus, both at 6 months follow-up).[9] However, this rate was higher compared to that observed in standard LMWH/warfarin treatment (49%) and direct oral anticoagulants (DOACs) treatment (59%),[44,45] as EVT employs direct clot removal from the involved vein by clot manipulation and also increases the surface of thrombus exposed to anticoagulants and thrombolytics. However, not all studies included in our analysis mentioned the types and proportion of EVT techniques used.

The new or expansion of hematoma occurred in 4% of CVT patients following EVT, which was slightly higher than the TO-ACT trial (3%).[9] However, this rate was lower than that of minor hemorrhage seen in patients treated with DOACs (5.06%) and standard anticoagulation therapy (5.03%).[44] Recurrent CVT occurred in 2% of CVT patients following EVT, which was similar to that observed in DOACs treatment

(1.03%) and standard anticoagulation (1.06%).[44] Overall, catheter-related complications occurred in 3% of CVT patients after EVT, which was lower than the TO-ACT trial (9% venous system perforation during EVT).[9] This rate is similar to the rate of procedural complications during coiling in intracranial aneurysms (5.87%)[46] and lower than that seen during mechanical thrombectomy (~15%) for acute ischemic stroke.[47,48] Hence, the procedure can be considered safe and should be considered in patients with severe symptoms at experienced centers. Overall differences between this meta-analysis and the TO-ACT trial regarding complete recanalization, intracranial hemorrhage, and catheter-related complications might be explained either by variations in EVT technique, use and duration of thrombolytics, type of thrombolytics and follow up duration or experience of the physician.

In subgroup analysis, subgroup differences were present on study site, literature type, and age group of included patients. Literature type differences may be explained by the small number of studies (n = 3) included in the grey literature subgroup. Similarly, differences between age groups may be explained by the small number of studies included in the < 18 years subgroup (n = 1) and the >40 years subgroup (n = 6). Furthermore, CVT is more common in females of reproductive age (18-40 years). Hormonal factors contribute to CVT in this group and also grant a better prognosis.[49] Compared to hormone-related factors, non-hormonal factors like coagulopathy and infection are more likely to be the cause of CVT in males of all ages and females ages <18 years and >40 years. Perhaps the differences in etiology are responsible for relatively poor outcomes seen in ages <18 years and >40 years. The reason for subgroup differences based on study site remains unclear, as anticoagulant choices before EVT and devices used for EVT were largely consistent across all studies, regardless of location. Further investigation is necessary for determining whether these differences may be explained by variables between study sites, such as time to endovascular intervention, the experience of the physician, number of EVT attempts, EVT technique, quality of defining criteria for complete recanalization, baseline health of CVT patients, or other factors.

While RCT is the most definite way to answer whether EVT with anticoagulation is superior to standard anticoagulation, there are challenges in performing such trials. The TO-ACT trial was the only RCT performed at the time of our meta-analysis; however, its control group data could not be synthesized in our meta-analysis as other included studies lacked the necessary control arm. The TO-ACT trial was underpowered and was prematurely stopped for futility. Hence, the possibility of small treatment effect in some patients cannot be excluded, especially in the subgroup of patients with coma where the number enrolled patients were very low.[9] The utility of EVT seems reasonable in patients with deteriorating symptoms despite standard anticoagulation and in patients at high risk of poor outcome discussed earlier. Yet, there is no consensus on the recommendation, nor any standard scoring systems to aid clinicians in deciding who exactly would benefit from EVT.

Interestingly, a small subset of patients has CVT involving deep venous system which has three times higher mortality rate due to increased rates of infarction and venous parenchymal hemorrhage. Due to rarity of the condition there is no consensus on its treatment. Only Stam et al (2008) included in our analysis mentioned 11 patients with deep vein thrombosis, accounting for almost 50% of total patients with CVT.[13] However, other studies do not mention this. In a study by Yeo et al (2020) anticoagulation was suggested as an effective strategy for deep vein thrombosis except for in cases of intracranial hemorrhage at presentation which were deemed to have poorer outcomes.[50] Majority of cases in a study by Stam et al (2008) underwent EVT despite involvement of deep veins as they presented with altered mental status, coma, cerebral edema, intracerebral hemorrhage on CT/MRI.[13] The propensity to consider EVT is based on severity of CVT rather than the deep venous involvement. The authors recommend similar strategy for patients presenting with deep venous involvement.

The strength of our study lies in the inclusion of multi-center studies across the world without limitations to EVT techniques and literature types. Most included studies were designed to be retrospective, which allowed us to capture long-term outcomes after EVT. Yet, it should be noted that some studies included in the present meta-analysis date back to 1999, at which time EVT techniques were less advanced than they are today. With this, both the outcome measures and the rate of adverse events could be impacted by the time period and length of the study. Further, methodological quality was accessed by rigorous sub-group analysis, which strengthens this meta-analysis, despite the lack of control group.

In our study, most of the patients underwent EVT only after a trial of anticoagulation. Given the clinical scenario of worsening neurological condition and anticoagulation failure, it would raise an ethical dilemma not to intervene in such patients, provided the possible benefit of EVT in these patients. Thus, head-to-head comparison with further RCTs comparing EVT to standard anti-coagulation may not be possible, given current guidelines and evidence from prior studies. This is one of the major limitations of our study. Second, there is substantial heterogeneity in our analysis and therefore our findings should be interpreted with caution. Subgroup analysis was done where feasible to generate strong conclusion. Third, different thrombectomy devices and techniques were used for EVT and our study did not metaanalzye if one device was better than the others due to lack of sufficient data from individual studies.

Conclusion

Among patients who underwent EVT for severe CVT, overall 85% had good functional outcome, 62% had complete recanalization, 37% had incomplete recanalization, 4% had new hematoma or expansion of hematoma, 5% had all-cause mortality and 3% had catheter related complications. Despite substantial heterogeneity, our results suggest that EVT can be considered as a safe and efficacious salvage therapy for patients with severe CVT. Further prospective, comparative trials will be necessary to assess the outcome of EVT as per EVT techniques, use of

thrombolytics, baseline characteristics of patients, etiology of CVT and time of intervention.

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