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Effectiveness and safety of catheter-directed thrombolysis in conjunction with percutaneous mechanical thrombectomy for acute iliofemoral deep vein thrombosis: A meta-analysis

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ABSTRACT

Background: Patients with severe acute low iliofemoral deep vein thrombosis (DVT), such as phlegmasia cerulea dolens, benefit from catheter-directed thrombolysis (CDT). This meta-analysis investigated the effectiveness and safety of adjuvant percutaneous mechanical thrombectomy (PMT) during CDT compared with CDT alone in the treatment of acute iliofemoral DVT.

Methods: A meta-analysis was performed in accordance with the PRISMA guidelines. Medline, Embase, the Cochrane Library, China National Knowledge Internet, and Wanfang data were searched for studies on the management of acute iliofemoral DVT by means of CDT or CDT with adjuvant PMT. Randomized, controlled trials and nonrandomized studies were included. The primary outcomes were venous patency rate, major bleeding complications, and post-thrombotic syndrome occurrence within 2 years of the procedure. The secondary outcomes were thrombolytic time and volume, as well as the rates of thigh detumescence and iliac vein stenting.

Results: The meta-analysis included 20 eligible studies with a total of 1686 patients. The rates of venous patency (mean difference, 10.11; 95% confidence interval [CI], 5.59-14.62) and thigh detumescence (mean difference, 3.64; 95% CI, 1.10-6.18) of the adjuvant PMT group were higher than those of the CDT alone group. Compared with CDT alone, the adjuvant PMT group experienced fewer incidences of major bleeding complications (odds ratio, 0.45; 95% CI, 0.26-0.77) and occurrences of post-thrombotic syndrome within 2 years of the procedure (odds ratio, 0.55; 95% CI, 0.33-0.92). Furthermore, the duration of thrombolytic therapy was shorter, and the total dose of administered thrombolytics was lower with adjuvant PMT.

Conclusions: Adjuvant PMT during CDT is associated with improved clinical outcomes and a lower incidence of major bleeding complications. The studies investigated were, however, single-center cohort studies, and future randomized controlled trials are needed to substantiate these findings. (J Vasc Surg Venous Lymphat Disord 2023;11:843-53.)

Keywords: Deep vein thrombosis; Lower extremity; Thrombolysis; Thrombectomy; Meta-analysis

Therapeutic anticoagulation is the standard treatment for iliofemoral deep vein thrombosis (DVT).[1] For patients with severe symptoms, such as phlegmasia cerulea dolens owing to massive venous thrombosis, thrombolysis is associated with rapid and complete clot lysis, high rates of preserved venous valve function, and slightly lower rates of post-thrombotic syndrome (PTS).[2]

Thrombolytics can be administered systemically through a peripheral vein, locally or regionally through a vein close to the clot, or directly in the thrombus via a catheter inserted in the occluding thrombus. Catheter-directed thrombolysis (CDT) is thought to decrease the total administered dose by delivering the pharmacologic agent directly within the clot, which achieves complete clot lysis more frequently with fewer occurrences of PTS.[3] Implementation of thrombolysis into daily clinical practice is, however, limited owing to the risk induced by unwanted major bleeding.[3]

Endovascular techniques have been developed to further lower the risk of hemorrhage by means of percutaneous

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mechanical thrombectomy (PMT). These techniques remove the thrombus through aspiration via a catheter or disrupt the clot through mechanical rotation or rheolyses.[4] In rheologic thrombectomy, the thrombus is fragmented and macerated by pressurizing and pulsating saline with a high dose of thrombolytics. This creates a low-pressure zone (the Venturi-Bernoulli effect), which aids aspiration and removal of the thrombus.[5] Studies have suggested that PMT as an adjunct to CDT can improve procedural outcomes by decreasing the risk of major bleeding, decreasing rates of PTS, and preserving venous valve function.[4]

The objective of this meta-analysis was to investigate the effectiveness and safety of adjuvant PMT during CDT compared with CDT alone in the treatment of acute iliofemoral DVT.

METHODS

This meta-analysis and the corresponding search protocol have been registered in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO/, registration number: CRD42022293333).

Search strategy. A literature search was conducted in accordance with the PRISMA 2009 guideline. Medline, Embase, The Cochrane Library (2021, Issue 8), China National Knowledge Internet, and Wanfang Data were searched for studies on the management of acute iliofemoral DVT by means of CDT or CDT with adjuvant PMT published from January 2000 to August 2021. The full details of the search strategy are presented in Appendix 1 (online only). Additional studies were selected by screening the references of the included studies found by the search strategies, which were formulated with the help of a clinical librarian.

Study selection. Studies on the management of acute iliofemoral DVT were selected in which participants were allocated to CDT with adjuvant PMT (regardless of thrombus removal devices) or to CDT without PMT as the initial treatment for acute iliofemoral DVT. PMT was required to be performed prior to the start of CDT. Randomized controlled trials (RCT), nonrandomized prospective studies, and retrospective studies were eligible for inclusion. Acute iliofemoral DVT was defined as thrombus (the formation or presence of a blood clot) in the iliac and/or common femoral veins within the last 14 days. We excluded studies that had insufficient information about the primary or secondary outcomes, had fewer than five patients in total, or for which the full texts were unavailable. Conference abstracts, reviews, and case reports were excluded.

Outcomes measures. The primary outcomes were venous patency rate, major bleeding complications (bleeding of the digestive system, urinary system, and nervous system), and PTS occurrence within 2 years of the procedure (with a Villalta score of ≥ 5[6]). The venous patency rate was defined by the authors of the study and determined during the last angiography before the thrombolytic catheter removal. The follow-up for major bleeding complications was set until the end of the thrombolytic therapy.

Secondary outcomes were thrombolytic time and volume, and rates of thigh detumescence and iliac vein stenting. The thigh detumescence rate was defined as (thigh circumference difference before treatment − thigh circumference difference after treatment)/thigh circumference difference before treatment × 100%.[7]

Data collection and analyses. After the initial search and removal of duplicates, two authors (W.L. and A.Z.) screened the titles and abstracts independently for eligibility. Disagreements were resolved by discussion, and adjudication by a third reviewer (R.B.) was sought if consensus could not be reached. If an article was considered potentially relevant, the full text was assessed according to the predetermined inclusion and exclusion criteria by one author (W.L.). The extraction of data and assessment of methodological quality were conducted by one author (W.L.). The screening was performed in EndNote X9 (Thomson Reuters, New York, NY) and Rayyan (https://www.rayyan.ai; Cambridge, MA). Additional relevant publications were identified in two ways. First, references of the articles that were screened in whole were reviewed. Second, for each article found on Medline, the first 40 similar articles were screened for relevance after they were filtered on "best match."

Data were extracted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The information collected from the included studies contained general information (title, authors, publication date, population, and study design), basic features of the included patients (mean age, sex, interventions, sample size, and PMT devices), and outcomes, as mentioned elsewhere in this article.

Risk of bias and quality assessment. RCTs were assessed by a revised tool to assess risk of bias in randomized trials.[8] The Risk Of Bias In Non-randomized Studies of Interventions tool was performed to evaluate the risk of bias for nonrandomized studies. The appraisals throughout the various domains were visualized by means of a traffic light and summary plot (robvis visualization tool).[9] The Grading of Recommendations Assessment, Development, and Evaluation process was applied to grade the methodological quality of RCTs.[10] The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality for cohort studies.[11] The time to disease onset was deemed to be an essential confounding factor. Studies with a NOS score of less than 5 were considered of insufficient methodological quality and were excluded from the final pooled analyses.

Statistical analyses. Review Manager 5.3 software (The Cochrane Collaboration) and Stata 25.0 software

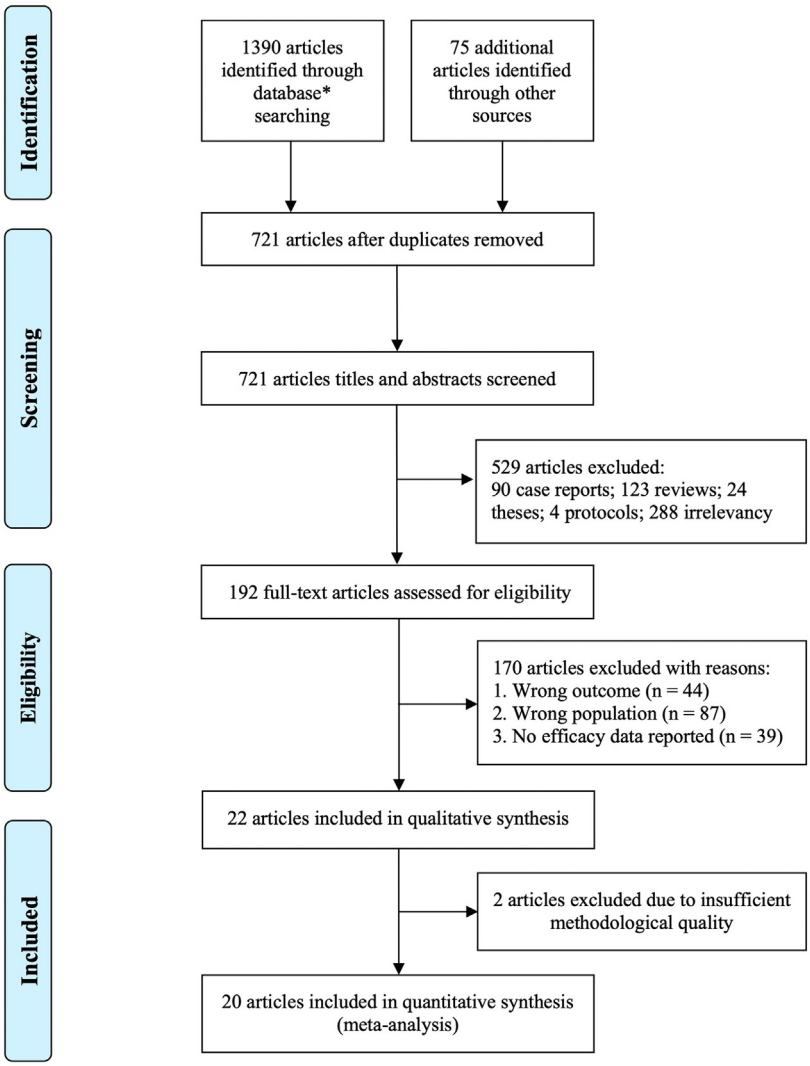


Fig 1. PRISMA flow diagram.

(StataCorp, College Station, TX) were used for statistical analyses. For binary data, the odds ratio (OR) was used, whereas for continuous data, the mean difference or standardized mean difference was used as the effect size, both with 95% confidence intervals (CIs). Random effect analysis was conducted for pooling of studies. Heterogeneity was investigated using the χ^2 or the Cochrane *Q* statistic and quantified by calculating I^2. If the *P* value was .1 or less, heterogeneity was deemed to exist. The I^2 value was used to measure the extent of heterogeneity, with 50% or higher considered as high heterogeneity.[12,13] A sensitivity analysis was conducted by serially removing studies to ascertain the effect of individual studies on pooled values. The Egger test and visual inspection of corresponding funnel plots were conducted to assess the significance of the publication bias and small study effects for outcome that included more than 10 studies.[14,15] We defined significant publication bias as a *P* value of less than .1. The trim-and-fill method was applied to estimate the effect sizes adjusted for publication bias on the interpretation of the results.[16]

RESULTS

The search resulted in 721 articles. After titles and abstracts were screened, 192 studies were included for full-text assessment, of which 170 were excluded based on the inclusion and exclusion criteria. Two of the remaining 22 studies were excluded owing to insufficient methodological quality (NOS score of <5), resulting in 20 studies

Table I. Basic features of included studies

	Country or region	Participants		Age, years		Sex (M/F)		Time to disease onset, days		Devices	Outcomes
		T1	T2	T1	T2	T1	T2	T1	T2		
Ding 2016[28]	Mainland China	12	14	50.2 ± 4.03	52.8 ± 5.15	7/5	6/8	/	/	AngioJet Solent	BDE
Feng 2021[18]	Mainland China	11	18	49.45 ± 3.64	52.22 ± 2.42	5/6	10/8	/	/	AngioJet[a]	ADEG
Gao 2019[27]	Mainland China	49	40	53.18 ± 11.3	51.70 ± 12.02	17/32	14/26	7.9 ± 2.92	9.13 ± 3.2	AngioJet Solent	ABDFG
Huang 2019[33]	Mainland China	21	31	51.18 ± 11.83	57.33 ± 15.67	9/12	15/16	5.81 ± 2.68	6 ± 2.89	AngioJet[a]	DEG
Kim 2006[4]	United states	14	23	53.0 ± 20.7	42.9 ± 13.2	7/7	9/14	/	/	AngioJet[a]	BDEG
Kuo 2016[20]	Taiwan	30	31	66.97 ± 18.9	64.48 ± 15.7	17/14	18/12	/	/	AngioJet[a]	ABDEFG
Liu 2016[21]	Mainland China	23	32	/	/	9/14	12/20	6.87 ± 4.39	5.82 ± 3.22	AngioJet[a]	ABDEF
Mao 2018[31]	Mainland China	18	20	53.34 ± 5.37	52.68 ± 5.24	7/11	10/10	6.78 ± 3.45	6.36 ± 3.28	AngioJet[a]	BDEG
Niu 2021[17]	Mainland China	27	27	57.53 ± 3.69	57.62 ± 3.87	14/13	15/12	7.75 ± 1.57	7.82 ± 1.53	AngioJet[a]	ABDEF
Park 2014[29]	South Korea	30	45	53.34 ± 5.38	52.68 ± 5.25	15/15	12/33	7.95 ± 5.45	6.16 ± 4.11	Trerotola	BDEG
Peng 2018[30]	Mainland China	12	30	50 ± 16	58 ± 11	5/7	11/19	/	/	AngioJet[a]	BCDEG
Qi 2021[23]	Mainland China	27	21	49 ± 12	52 ± 13	18/14	9/6	/	/	AngioJet[a]	ABEG
Song 2018[32]	Mainland China	25	25	48.5 ± 15	50.1 ± 14.2	10/15	12/13	5.4 ± 2.9	4.5 ± 3.0	AngioJet Solent	BCEG
Xu 2020[7]	Mainland China	186	238	53.5 (21-77)	57 (28-79)	91/95	112/126	2.5 ± 1.25	2.0 ± 1.85	AngioJet Solent	BCEFG
Yin 2018[25]	Mainland China	94	76	62 ± 14	59 ± 14	47/47	36/40	3.4 ± 1.6	3.7 ± 1.5	AngioJet[a]	BCDEG
Yu 2020[19]	Mainland China	38	31	60.3 ± 17.7	60.2 ± 16.7	20/18	15/16	12.3 ± 4.4	11.2 ± 6.1	Aspirex	BDEG
Zhang 2018[26]	Mainland China	16	16	64.4 ± 6.8	58.6 ± 7.5	8/8	10/6	4.7 ± 1.1	3.8 ± 0.9	AngioJet[a]	ABDEF
Zhang 2019[22]	Mainland China	30	30	62.1 ± 1.6	62.4 ± 1.5	15/15	17/13	8.3 ± 0.6	8.2 ± 0.7	AngioJet Solent	BDE
Zhao 2017[24]	Mainland China	82	80	61.43 ± 15.21	59.38 ± 15.21	37/45	34/46	7.16 ± 3.64	6.78 ± 3.85	AngioJet[a]	ABF
Zhao 2020[34]	Mainland China	67	46	55.61 ± 11.62	55.52 ± 11.64	31/36	20/26	8.48 ± 2.34	8.52 ± 2.28	AngioJet Solent	BDEF

A, Venous patency rate; *B*, major bleeding complications; *C*, post-thrombotic syndrome occurrence within 2 years of procedure; *D*, thrombolytic time; *E*, thrombolytic volume; *F*, thigh detumescence rate; *G*, iliac vein stenting rate; *T1*, adjuvant percutaneous mechanical thrombectomy during catheter-directed thrombolysis group; *T2*, catheter-directed thrombolysis group.
Values are number, mean ± standard deviation, or median (range).
[a]Catheter specifications not reported.

included in the meta-analysis. Fig 1 presents the review process.

All of the included studies were retrospective cohort studies, in which a total of 1686 patients were treated.[4,7,17-34] All the included patients underwent intervention had severe symptoms of lower extremity swelling or pain. Table I summarizes the basic features of included studies. Sample sizes ranged from 29 to 424. In total, 812 patients underwent adjuvant PMT during CDT, and 874 were treated with CDT alone. PMT was conducted in 18 studies using the AngioJet thrombectomy system (Boston Scientific, Marlborough, MA),

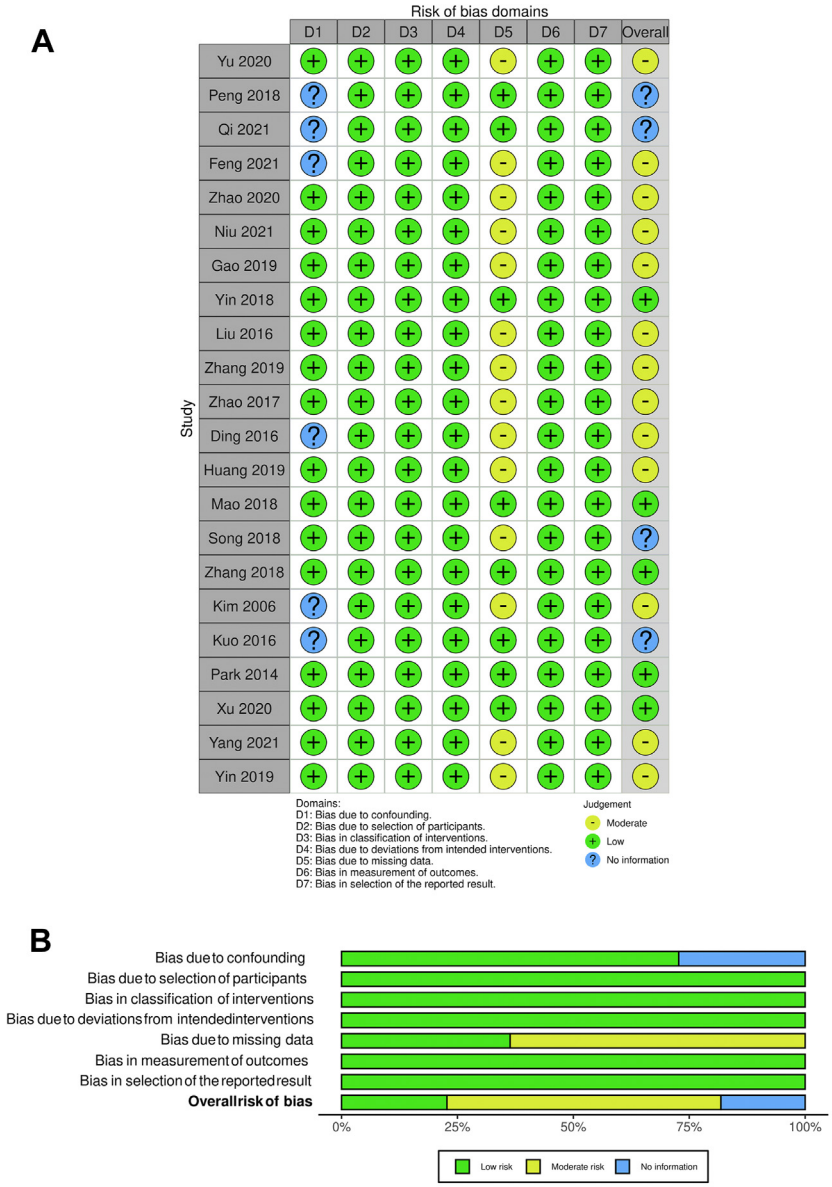


Fig 2. Risk of bias assessments of nonrandomized studies. **(A)** Traffic light plot shows the domain-level judgments for each individual study. **(B)** Summary plot depicts the distribution of risk of bias judgments within each bias domain.

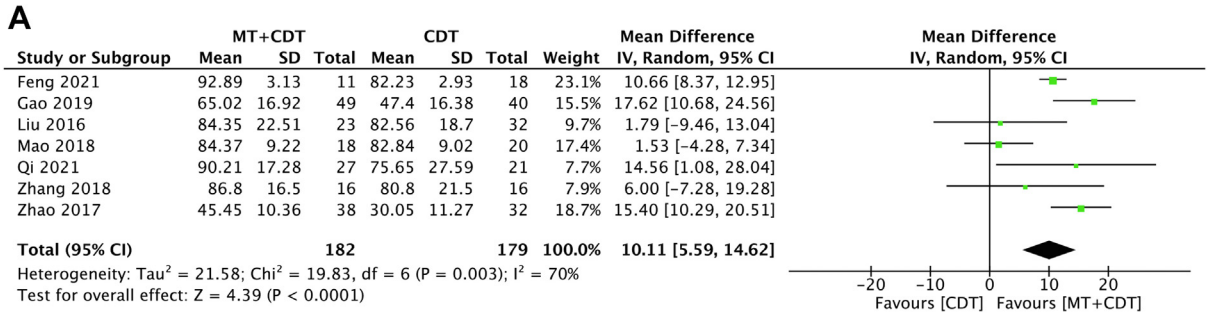
one used a 7F Arrow-Trerotola device (Arrow International, Reading, PA), and one used the Straub Aspirex device (Straub Medical, Wangs, Switzerland).

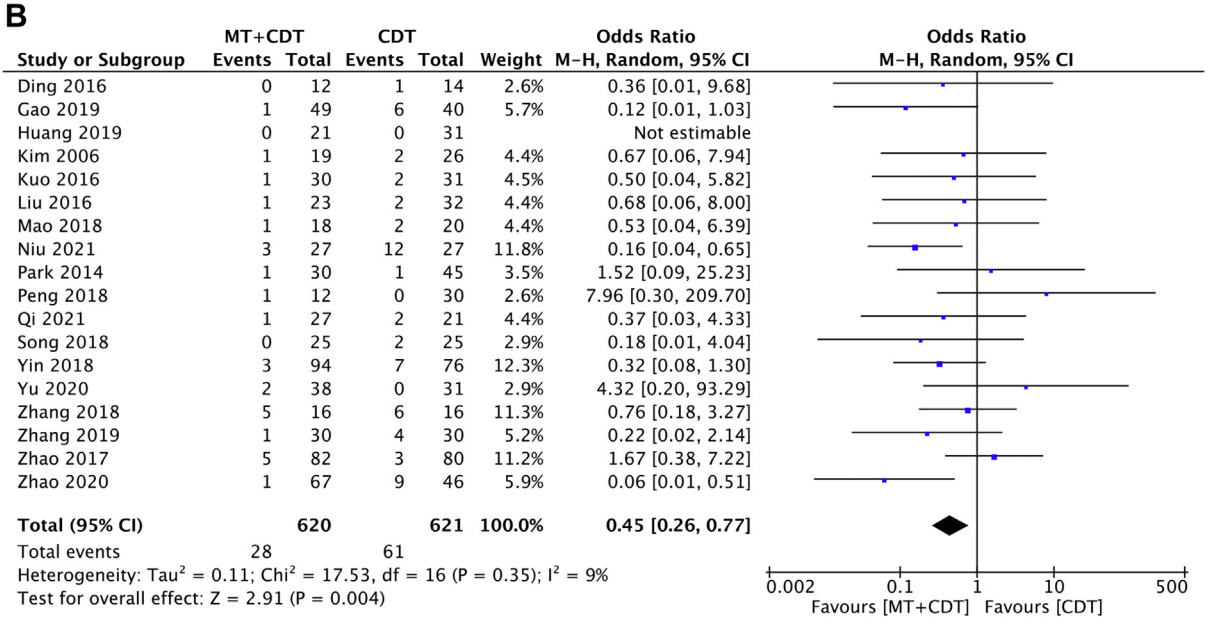
Risk of bias and qualify assessment

The results of the risk of bias assessment for the included studies are shown in Fig 2. Most of the studies showed moderate risk, and six studies had no information regarding the bias owing to confounding.[4,18,20,23,28,30] The Supplementary Table (online only) presents the NOS scores of included studies, in which two studies were excluded for the pooled analysis.

Primary outcomes

Venous patency rate. The venous patency rate was reported in seven studies.[18,21,23,24,26,27,31] All the studies calculated the venous patency rate based on the thrombotic score modified by Porter and Moneta[35] as (thrombotic score before treatment − thrombotic score after treatment)/thrombotic score before treatment × 100%. The score was calculated from 0 points (patent) to 3 points (occlusive thrombus throughout the length of the segment). The pooled mean difference was 10.11 (95% CI, 5.59-14.62; $P < .0001$). The meta-analysis indicated that the venous patency





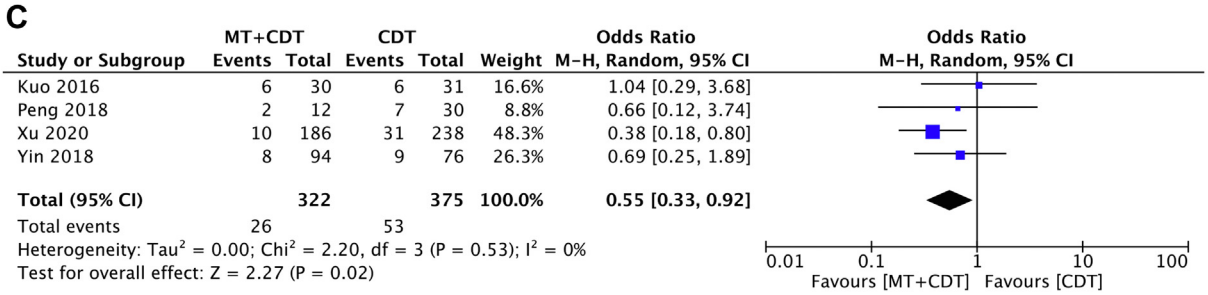


Fig 3. Forest plot and meta-analysis of venous patency rate **(A),** major bleeding complications **(B)**, and PTS occurrence within 2 years of the procedure **(C)**. *CDT*, catheter-directed thrombolysis; *CI*, confidence interval; *IV*, inverse variance; *M-H*, Mantel-Haenszel; *MT*, mechanical thrombectomy; *SD*, standard deviation.

rates were significantly higher after adjuvant PMT during CDT. Results of the χ^2 test demonstrated a heterogeneity among the studies ($P = .003$), and the I^2 statistic was 70% for the proportion of the variance that was attributable to study heterogeneity (Fig 3, *A*).

Major bleeding complications. Major bleeding complications were reported in 18 studies,[4,17,19-34] including 28 cases in the group with adjuvant PMT during the CDT (n = 620) and 61 in the group with CDT alone (n = 621). The pooled major bleeding rate was 4.5% with adjuvant PMT and 9.8% with CDT alone. The pooled OR was 0.45 (95% CI, 0.26-0.77; $P = .004$). The meta-analysis showed significantly fewer major bleeding complications when adjuvant PMT during CDT was used in treating acute

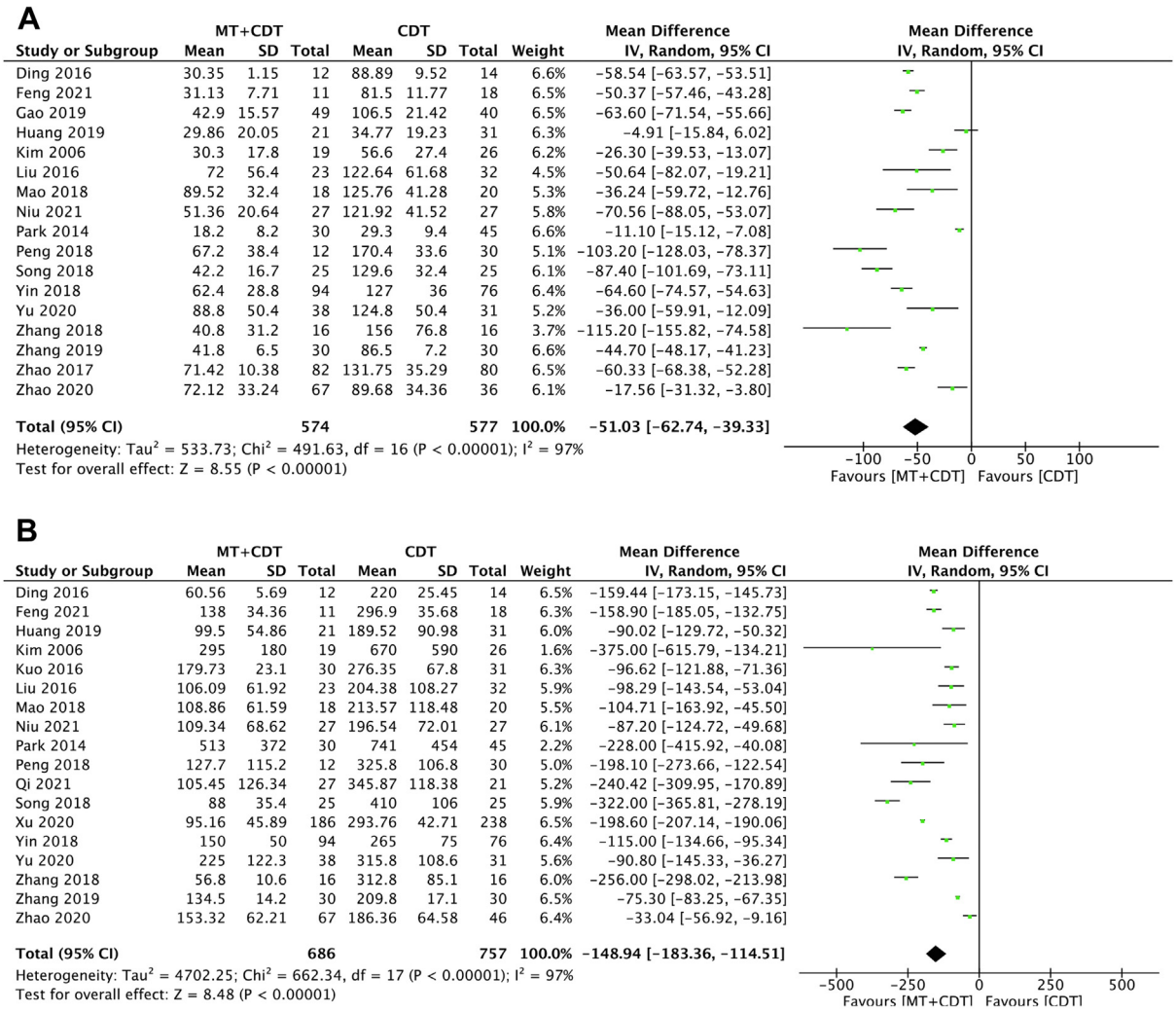


Fig 4. Forest plot and meta-analysis of thrombolytic time **(A)** and thrombolytic volume **(B)**. *CDT,* catheter-directed thrombolysis; *CI,* confidence interval; *IV,* inverse variance; *M-H,* Mantel-Haenszel; *MT,* mechanical thrombectomy; *SD,* standard deviation.

iliofemoral DVT. The χ^2 test showed a *P* value of .35, indicating insufficient evidence of heterogeneity among the studies, with an I^2 statistic of 9% (Fig 3, *B*).

PTS occurrence within 2 years of the procedure. Four studies[7,20,25,30] compared the PTS occurrence within 2 years of the procedure between the two groups (26 of 322 in the adjuvant PMT during the CDT group vs 53 of 375 in the CDT group). The pooled OR was 0.55 (95% CI, 0.33-0.92; $P = .020$). Analysis results reported a significantly lower PTS occurrence within 2 years of the procedure in the adjuvant PMT during CDT group than in the CDT group for acute iliofemoral DVT. The χ^2 test result showed inadequate evidence of heterogeneity, with 0% for the I^2 statistic (Fig 3, *C*).

Secondary outcomes

Thrombolytic time and volume. Thrombolytic time was reported in 17 studies,[4,17-19,21,22,24-34] and thrombolytic volume was compared in 18 studies,[4,7,17-23,25,26,28-34] in which all of the thrombolytic agents were urokinase. All volume and time units were converted to 10,000 international units and hours, respectively. The pooled mean difference was −51.03 (95% CI, −62.74 to −39.33; $P < .0001$) in thrombolytic time and −148.94 (95% CI, −183.36 to −114.51; $P < .0001$) in thrombolytic volume. The results reported significantly shorter thrombolytic time and smaller thrombolytic volume in patients with CDT with adjuvant PMT than in patients with CDT alone. For both thrombolytic time and thrombolytic volume, the χ^2 test indicates heterogeneity among the studies (both *P* values < .001), with high proportions of the total observed variances reflecting substantial heterogeneity (I^2 values of 97% and 96%, respectively) (Fig 4, A and B).

Thigh detumescence rate. Eight studies reported the thigh detumescence rate.[7,17,21,24,26,27,31,34] The analysis based on the eight studies showed a favorable thigh

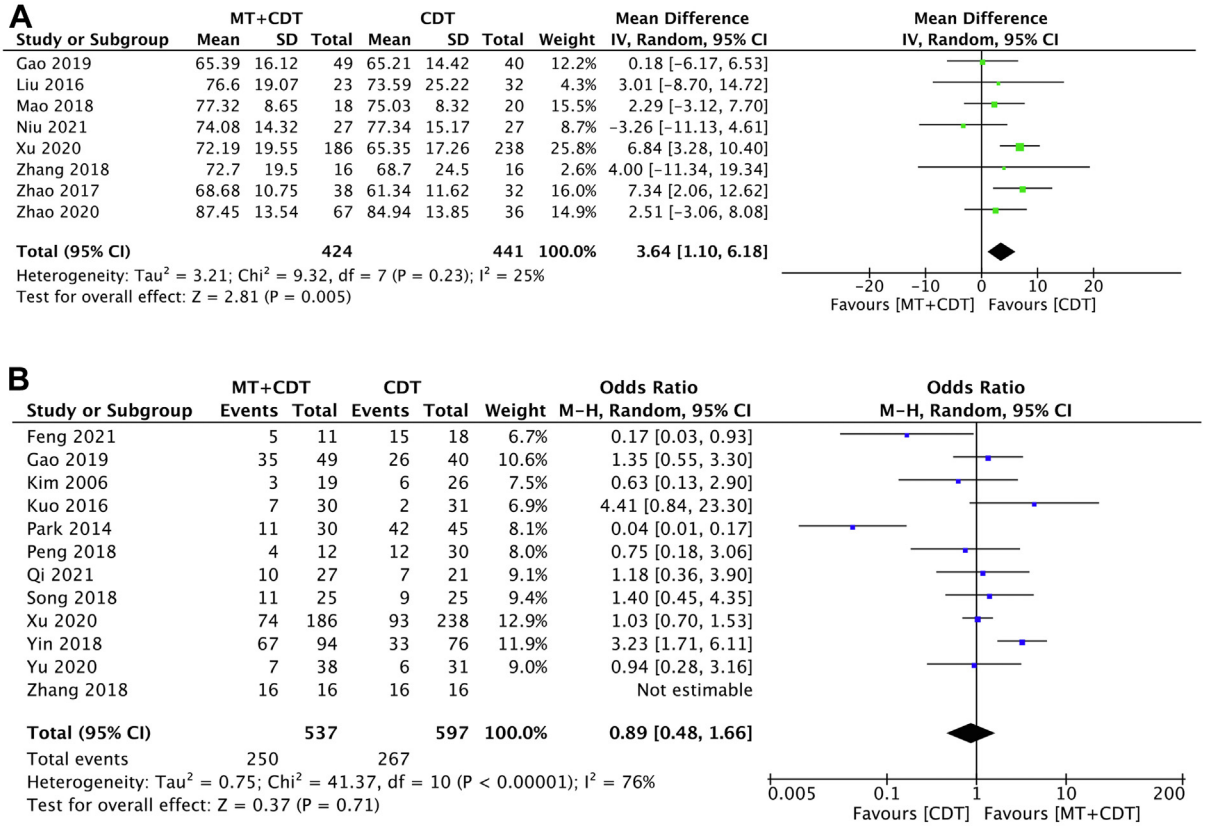


Fig 5. Forest plot and meta-analysis of thigh detumescence rate **(A)** and iliac vein stenting rate **(B)**. *CDT,* catheter-directed thrombolysis; *CI,* confidence interval; *IV,* inverse variance; *M-H,* Mantel-Haenszel; *MT,* mechanical thrombectomy; *SD,* standard deviation.

detumescence rate with adjuvant PMT during CDT, and the difference was statistically significant. The pooled mean difference was 3.64 (95% CI, 1.10-6.18; $P = .005$). The χ^2 test showed a P value of .23, indicating insufficient evidence of heterogeneity among the studies. The I^2 statistic indicated that the proportion of the observed variance reflecting differences in the true effect sizes was 25% (Fig 5, *A*).

Iliac vein stenting rate. The iliac vein stenting rate was covered in 12 studies[4,7,18-20,23,25-27,29,30,32] (250 of 537 in the group with adjuvant PMT during the CDT vs 267 of 597 in the group with CDT alone). The pooled OR was 1.06 (95% CI, 0.83-1.36; $P = .71$). The analysis demonstrated no significant difference in the iliac vein stenting rate between the two groups in the treatment of acute iliofemoral DVT. Sufficient evidence of heterogeneity among the studies was suggested by the χ^2 test ($P < .0001$), with 76% for the I^2 statistic (Fig 5, *B*).

PUBLICATIONS BIAS

Funnel plots of outcomes (included >10 studies) are presented in Fig 6. No publication bias (Egger's test for asymmetry, $P < .1$) was evident for thrombolytic volume, iliac vein stenting rate, and major bleeding complications; however, both the funnel plot and the Egger's test suggested publication bias with regard to thrombolytic time. Two missing studies could be filled in the trim-and-fill method (Table II), and the further analysis demonstrated that this publication bias did not impact the estimates (eg, the results of the trim-and-fill did not significantly alter the effect direction).

DISCUSSION

This systematic review is the first to address the value of adjuvant PMT during CDT in treating acute iliofemoral DVT. The results demonstrate that the rates of venous patency and thigh detumescence of adjuvant PMT during CDT are higher than those of CDT alone, indicating better clot reduction. Adjuvant PMT during CDT is also associated with reduced duration of thrombolytic therapy, dose of thrombolytic agents, and postprocedure major bleeding complications. Moreover, the PTS occurrence within 2 years of the procedure is lower when PMT and CDT are combined.

PMT is able to accelerate clot dissolution by means of aspiration, thereby further improving the thigh detumescence and venous patency.[36] After the use of PMT, the residual thrombus burden is decreased, and the lytic exposure is reduced or completely avoided.[37] A previous meta-analysis of 17 studies demonstrated that PMT

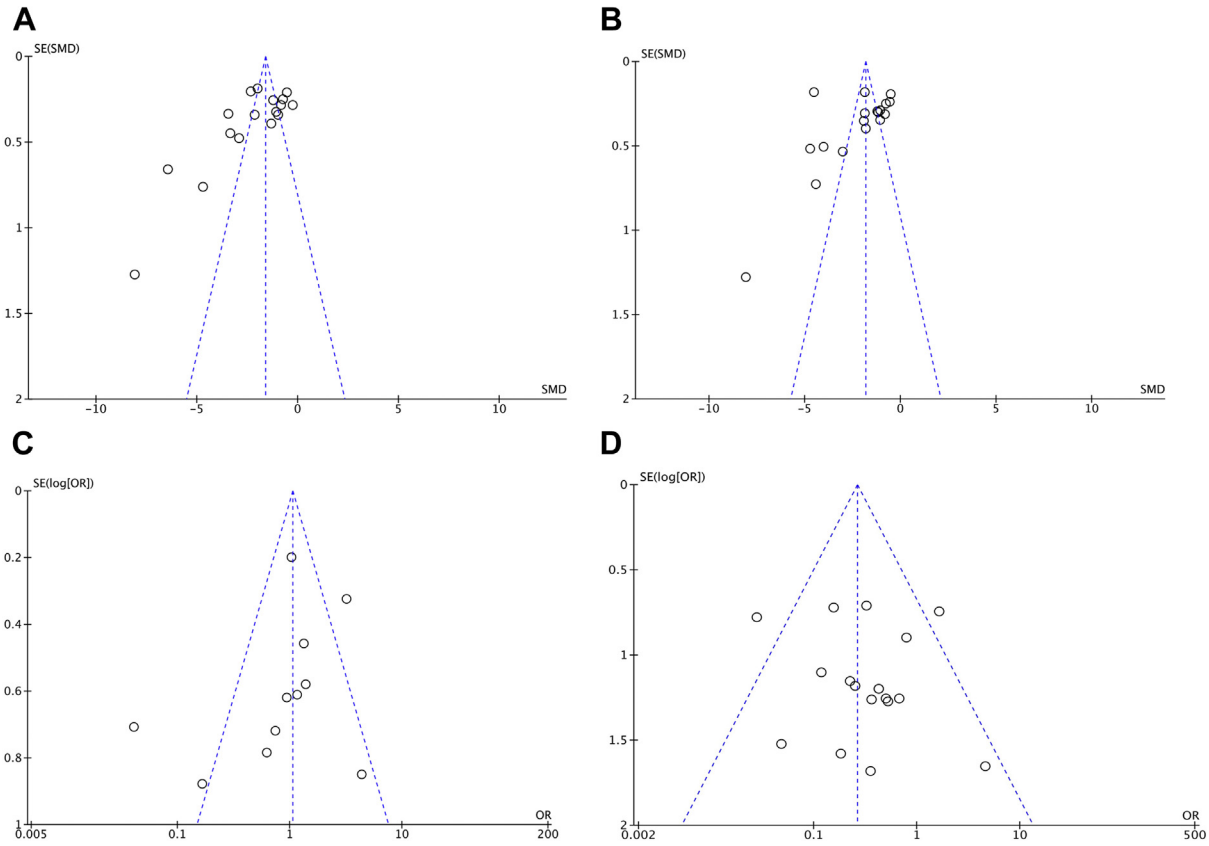


Fig 6. Funnel plots with pseudo 95% confidence limits (the ordinate is the standard effect size standard error [*SE*]), and the abscissa is each effect size) shows **(A)** thrombolytic time, **(B)** thrombolytic volume, **(C)** iliac vein stenting rate, and **(D)** major bleeding complications.

resulted in a higher primary patency rate at 6 months than CDT alone.[38] In addition, another meta-analysis reported that PMT, with or without CDT, was able to reduce the thrombolytic drug dose and shorten the procedural time compared with CDT alone.[39] These two systematic reviews, however, did not provide direct evidence for adjuvant PMT during CDT.

Bleeding complications have been a significant risk consistently associated with thrombolysis therapy,[40] and the pooled major bleeding rate was only 4.5% with adjuvant PMT therapy in this study. Given the relatively short catheter insertion time, we hypothesized that adjutant PMT decreased the thrombolytic time and volume and may, therefore, lead to a lower incidence of major

Table II. Assessment for publication bias

Variables	Thrombolytic time	Major bleeding complications	Thrombolytic volume	Iliac vein stenting rate
Studies, No.	17	18	18	12
Egger regression test				
Slope	0.058	−1.761	−1.052	0.598
P value for bias	0.015	0.589[a]	0.371[a]	0.354[a]
Nonadjusted OR or MD (95% CI)[b]	−2.20 (−2.79 to −1.61)	0.31 (0.17 to 0.55)	−2.23 (−2.93 to −1.52)	0.89 (0.48 to 1.66)
Adjusted OR or MD (95% CI)[c]	−2.58 (−3.31 to −1.86)	NR	NR	NR
Studies adjusted, n	2	NR	NR	NR

CI, Confidence interval; *MD*, mean difference; *NR*, did not perform owing to a *P* value for bias of >.1 in the Egger's test; *OR*, odds ratio.
NR: did not perform owing to *P*-value for bias >.1 in the Egger's test.
[a]No publication bias was evident.
[b]Effect size derived from pooled analysis of studies.
[c]Effect size after adjustment for publication bias by means of the trim-and-fill method.

bleeding than CDT alone. A previous meta analysis[41] of 16 studies demonstrated that PMT decreased the bleeding events compared with CDT; however, the study did not analyze the effect of adjuvant PMT during CDT. Overall, the adjuvant PMT emerges as a potentially faster[37] and safe alternative,[42] and the hypothesis requires further investigation.

PTS is one of the most serious complications of iliofemoral DVT. Removing clots by means of adjuvant PMT is recommended in preventing PTS and venous reflux based on the potential efficacy.[42] In our meta-analysis, the occurrence of PTS was lower within the 2-year period after thrombolytic therapy with adjuvant PMT. As for the long-term outcome, a retrospective study with 79 patients by Hager et al[43] compared the long-term PTS events after PMT and CDT in treating acute iliofemoral DVT. After 48 months of follow-up and comparison, no significant difference was found in PTS events between the groups ($P > .05$). Despite the limited number of reports regarding the long-term outcome of PTS after PMT, we hypothesize that this effect may be maintained owing to the promising results of the venous patency rate and PTS events in 2 years.

Although the outcomes of adjuvant PMT seem promising, many factors regarding the use of adjuvant PMT, however, remain unknown. For instance, the safety and effectiveness of the adjuvant PMT for the treatment of nonacute iliofemoral DVT is unknown; hence, studies are required to access the maximal acceptable timing of PMT from DVT symptom onset and the effectiveness of PMT in thrombus of different ages, especially chronic thrombus. Moreover, PMT devices using high-velocity spray, such as the AngioJet, may cause hematuria and even acute kidney injury, given the destruction of red blood cells leading to hemolysis.[44] Thus, further studies are needed to determine the factors, such as treatment time and duration of hematuria, for the optimal use of adjuvant PMT to avoid acute kidney injury.[45]

This study has several limitations. First, there were no RCTs in this study, which may have led to selection bias, reporting bias, and overestimation of the effect seizes. Another limitation was that most of the included studies used the AngioJet thrombectomy system; however, this study did not analyze the results for different PMT devices or catheter specifications, resulting in inconsistent outcome comparisons, such as thrombolytic time and lytic usage. The results are, therefore, potentially not generalizable; hence, further studies are needed to determine the outcomes after the use of other PMT devices. Finally, although ultrasound-accelerated CDT, such as the EkoSonic Endovascular System, is considered a promising mechanical thrombolysis device, such an approach is not included because the topic of the study focused on adjuvant mechanical thrombectomy instead of thrombolysis.

In conclusion, the use of adjuvant PMT with CDT improves the rates of venous patency and thigh detumescence, with shorter thrombolytic time, compared with CDT alone. Moreover, the adjuvant PMT shows a smaller thrombolytic volume, fewer major bleeding complications, and fewer PTS events in the short-term after the procedure. Although this study demonstrated that adjuvant PMT during CDT treatment remains effective, safe, and feasible, treatment protocols are based on nonrandomized retrospective data. Therefore, further randomized studies with a larger sample size are needed to validate these findings.

AUTHOR CONTRIBUTIONS

Conception and design: WL, RB
Analysis and interpretation: WL, CZ, MM, JV, HD, RB
Data collection: WL, AZ, RB
Writing the article: WL, RB
Critical revision of the article: WL, AZ, CZ, MM, JV, HD, RB
Final approval of the article: WL, AZ, CZ, MM, JV, HD, RB
Statistical analysis: WL, MM, RB
Obtained funding: Not applicable
Overall responsibility: RB

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Additional material for this article may be found online at www.jvsvenous.org.

APPENDIX 1. SEARCH STRATEGY

MEDLINE*

Results 343 references. ("Venous thrombosis"[Mesh] OR phlebothrombosis[tiab] OR vein thrombos*[tiab] OR venous thrombos*[tiab]) AND ("Lower Extremity"[Mesh] OR lower[tiab] OR iliofemoral[tiab]) AND ("Thrombectomy"[Mesh] OR thrombectom*[tiab] OR angiojet[tiab] OR "Mechanical Thrombolysis"[Mesh] OR clot disruption [tiab]) AND ("Thrombolytic therapy"[Mesh] OR thrombolys*[tiab] OR fibrinolytic[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

Embase

Results: 549 references. ('lower extremity deep vein thrombosis'/exp OR 'deep vein thrombosis'/de OR (phlebothrombosis OR 'vein thrombos*' OR 'venous thrombos*'):ab,ti,de) AND ('lower limb'/exp OR 'lower extremity deep vein thrombosis'/exp OR (lower OR iliofemoral):ab,ti,de) AND ('thrombectomy'/exp OR 'thrombectomy catheter'/exp OR (thrombectom* OR angiojet OR 'clot disruption'):ab,ti,de) AND ('fibrinolytic therapy'/exp OR (thrombolys* OR fibrinolytic):ab,ti,de) NOT (('animal'/exp NOT 'human'/exp) OR 'conference abstract'/it)

Cochrane Library

Results: 27 references, of which 1 cochrane review. ([mh "Venous thrombosis"] OR phlebothrombosis:ti,ab OR ("vein" NEXT thrombos*):ti,ab OR ("venous" NEXT thrombos*):ti,ab) AND ([mh "Lower Extremity"] OR lower:ti,ab OR iliofemoral:ti,ab) AND ([mh Thrombectomy] OR thrombectom*:ti,ab OR angiojet:ti,ab OR [mh "Mechanical Thrombolysis"] OR "clot disruption":ti,ab) AND ([mh "Thrombolytic therapy"] OR thrombolys*:ti,ab OR fibrinolytic:ti,ab)

*: the search string was translated into Chinese for searching in China National Knowledge Internet (271 references) and Wanfang Data (201 references).

Supplementary Table (online only). Detailed quality assessment by the Newcastle-Ottawa Scale (NOS)

	Selection				Comparability	Outcome			
Studies	A	B	C	D	E	F	G	H	Scores
Ding[28] 2016	1	1	1	1	0	1	0	0	5
Feng 2021[18]	1	1	1	1	0	1	0	0	5
Gao 2019[27]	1	1	1	1	1	1	0	0	6
Huang 2019[33]	1	1	1	1	1	1	0	0	6
Kim 2006[4]	1	1	1	1	1	1	1	0	7
Kuo 2016[2]	1	1	1	1	2	1	1	1	9
Liu 2016[21]	1	1	1	1	2	1	1	1	9
Mao 2018[31]	1	1	1	1	2	1	1	1	9
Niu 2021[17]	1	1	1	1	1	1	0	0	6
Park 2014[29]	1	1	1	1	2	1	1	1	9
Peng 2018[3]	1	1	1	1	1	1	1	1	8
Qi 2021[23]	1	1	1	1	1	1	1	1	8
Song 2018[32]	1	1	1	1	2	1	0	0	7
Xu 2020[7]	1	1	1	1	2	1	1	1	9
Yang 2021[a]	1	1	1	1	0	0	0	0	4
Yin 2018[25]	1	1	1	1	2	1	1	1	9
Yin 2019[a]	1	1	1	1	0	0	0	0	4
Yu 2020[19]	1	1	1	1	1	1	1	0	7
Zhang 2018[26]	1	1	1	1	2	1	1	1	9
Zhang 2019[22]	1	1	1	1	1	1	0	0	6
Zhao 2017[24]	1	1	1	1	2	1	0	0	7
Zhao 2020[34]	1	1	1	1	2	1	1	1	9

A, Representativeness of the exposed cohort; *B*, Newcastle-Ottawa Scale selection of the non exposed cohort; *C*, ascertainment of exposure; *D*, demonstration that outcome of interest was not present at start of study; *E*, comparability of cohorts on the basis of the design or analysis (sex/age/time to disease onset/); *F*, assessment of outcome; *G*, was follow-up long enough for outcomes to occur (>6 months); *H*, adequacy of follow up of cohorts (>80%).
[a]Studies with fewer than 5 points representing a high risk of bias were excluded.