

Efficacy and safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis: a systematic review and meta-analysis

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Abstract

Background The role of anticoagulation in treating non-malignant portal vein (PV) thrombosis (PVT) in patients with liver cirrhosis remains unclear. In our meta-analysis, we aimed to evaluate the efficacy and safety of anticoagulation for the treatment of non-malignant PVT in these patients.

Methods We conducted a meta-analysis to estimate the effects of anticoagulation on non-malignant PVT in patients with liver cirrhosis. We assessed the rates of PV recanalization, variceal bleeding, and any bleeding.

Results We included 9 observational studies which involved 474 patients. The rate of PV recanalization was significantly higher in patients who received anticoagulation compared to those who did not: 65.2% vs. 25.2%; relative risk (RR) 2.31, 95% confidence interval (CI) 1.80-2.96; $P < 0.00001$. Variceal bleeding was significantly lower in patients who received anticoagulation: 0.1% vs. 18.5%; RR 0.15, 95%CI 0.04-0.55; $P = 0.004$. Any bleeding was similar between patients who received anticoagulation and those who did not: 10.3% vs. 22.7%; RR 0.43, 95%CI 0.09-1.99; $P = 0.28$.

Conclusions Anticoagulation use increased the rate of PV recanalization in cirrhotic patients with non-malignant PVT. Anticoagulation decreased the rate of variceal bleeding and did not increase the rate of any bleeding.

Keywords Warfarin, heparin, portal vein recanalization, bleeding

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Introduction

Liver cirrhosis is a clinical condition traditionally associated with bleeding risk (i.e., coagulopathy). This is due to multiple mechanisms, including prolonged bleeding time, increased

prothrombin time/international normalized ratio, decreased liver synthesis of clotting factors, thrombocytopenia, and hypofibrinolytic status [1]. In addition, liver cirrhosis is frequently complicated by esophageal varices, which further increases the risk of bleeding [2]. However, patients with liver cirrhosis are also at a high risk for venous thrombosis, especially portal vein (PV) thrombosis (PVT) [1]. Decreased levels of anticoagulant factors (protein C, protein S, and plasminogen), endothelial activation, disruption of the endothelial glycocalyx, and the generation of procoagulant microparticles all contribute to a prothrombotic status in cirrhotic patients [1]. Ultimately, the hemostatic balance in cirrhotic patients is fragile and may easily tend towards either a hypo- or a hypercoagulable status [1].

PVT is a frequent complication of liver cirrhosis, especially at the advanced stages [3]. Non-malignant PVT develops in 0.6-26% of patients with liver cirrhosis, depending on the severity of the cirrhosis, and the occurrence increases with cirrhosis progression [4]. Decreased PV velocity is determined to be the most important factor for development of PVT in patients with liver cirrhosis [5]. Anticoagulation has shown a proven benefit in the treatment of PVT in non-cirrhotic

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patients [6]. However, the role of anticoagulation in treating PVT in the setting of liver cirrhosis remains unclear because of the presumably greater risk of bleeding in cirrhotic patients [6].

We conducted a systematic review and meta-analysis of all published studies investigating the outcomes of anticoagulation in non-malignant PVT in cirrhotic patients compared with the outcomes of those who did not receive anticoagulation. The outcomes assessed were the efficacy of anticoagulation in achieving PV recanalization and the occurrence of variceal and any bleeding events.

Materials and methods

Data sources and search strategy

We performed a comprehensive search for published studies indexed in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to August 2019. We also performed a manual search for additional relevant studies using references of the included articles. The following were the main search terms: (“portal vein thrombosis” or “portal venous thrombosis”) and (“liver cirrhosis” or “hepatic cirrhosis”) and (“anticoagulation” or “anticoagulant”). Supplementary Table 1 describes the full search term used in PubMed. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies [7]. Two investigators (SG and AB) independently performed the search and shortlisted the studies for final review. Discrepancies were resolved by a third reviewer (KA). We assessed the quality of the included studies using the Newcastle-Ottawa Scale [8].

Inclusion and exclusion criteria

We included all available randomized controlled trials and cohort studies. Both full texts and abstracts were considered for the purpose of the manuscript. We excluded studies that included non-cirrhotic patients or malignant PVT. We also excluded single-arm studies, case reports, editorials, review articles, letters, guidelines and animal studies. No language limitation was applied.

Data extraction

The following data were extracted from the studies: study characteristics (author, publication year, study type, study design, and study population), type of anticoagulant used, number of patients in the anticoagulation group and control group, number of patients in whom PV recanalization was achieved (either partial or complete recanalization), and number of patients who developed bleeding (either variceal bleeding or any bleeding).

Outcomes assessed

The primary outcome assessed in our meta-analysis was the efficacy of anticoagulation in achieving PV recanalization. Our secondary outcomes were the occurrence of variceal bleeding and any bleeding events.

Statistical analysis

We performed a meta-analysis of the included studies using Review Manager 5.3 (Cochrane Collaboration, Copenhagen, The Nordic Cochrane Centre) and Comprehensive Meta-Analysis (Biostat, Englewood, USA). A random-effects model was applied, considering the presumed heterogeneity due to the patient population, type of anticoagulation and patient setting involved. Higgins I^2 test was used to assess for heterogeneity [9]. I^2 values greater than 50% implied the presence of substantial heterogeneity. A P-value of <0.05 was considered statistically significant. Weighted pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Meta-regression was attempted to check if any variable had impacted our results.

Bias assessment

Bias assessment across studies was performed qualitatively, visualizing the funnel plot generated on review manager, as well as quantitatively, using Egger's regression analysis. A P-value was generated using the Egger analysis and a value of <0.05 was associated with significant publication bias. If bias was present, further statistics using the Fail-Safe N test and Duval and Tweedie's "Trim and Fill" test were used to ascertain the impact of the bias.

Results

A total of 542 papers were retrieved by our search strategy. Among these, 33 were eligible for systemic review. Subsequently, we excluded 10 papers because of irrelevant population, 3 because of irrelevant interventions, and 11 because they had no control group. Eventually, 9 papers met our inclusion criteria and were included in the study [3-5,10-15]. Fig. 1 shows the PRISMA flow diagram that illustrates how the final studies were selected. Table 1 shows the baseline characteristics of the studies included in the meta-analysis. We did not contact the authors of the studies.

All 9 studies were published between 2011 and 2019 and included patients with non-malignant PVT. As regards their study design, all 9 studies included were observational; 6 studies were retrospective and 3 were prospective. Of the 9 included papers, 5 were full-text publications and 4 were abstracts. The total number of patients included in these studies was 474; 256 received anticoagulation for non-malignant PVT while 218 did not. The mean age of the treated group was similar to the untreated group (54.5 vs. 53.9 years). The proportion of male

sex was 64.4% in the treated group compared to 48.8% in the untreated group. We assessed the quality of the included studies using the Newcastle-Ottawa Scale, shown in Supplementary Table 2. All studies scored ≥ 8 on the scale.

Primary outcome

Table 2 summarizes the primary and secondary outcomes of the individual studies included in the meta-analysis. The

Table 1 Baseline characteristics of the studies included in the meta-analysis

Author, year	Publication form	Study design	Anticoagulated patients and Controls (n)	Age (y)	Anticoagulant	Anticoagulation duration (m)	Follow up (m)	Indexes of LC severity
Chen, 2015 [3]	Full text	R	30 treated 36 controls	44.9 47.8	Warfarin	7.6	33	MELD: 9.9 CTP: 7.68 MELD: 8.9 CTP: 7.71
Chung, 2014 [10]	Full text	R	14 treated 14 controls	59.4 58.7	Warfarin	3.7	4	CTP: A(6), B(8), C(0) CTP: A(7), B(6), C(1)
Copaci, 2016 [11]	Abstract	P	50 treated 44 controls	NR	Sulodexidum	12	19	MELD: 14.6
Garcovich, 2011 [12]	Abstract	R	15 treated 15 controls	NR	LMWH	3-6	6	CTP: A and B
Noronha Ferreira, 2019 [4]	Full text	R	37 treated 43 controls	60 59	Warfarin & LMWH	10	25.5	MELD: 14 CTP: A(12), B(16), C(9) MELD: 16 CTP: A(9), B(18), C(16)
Risso, 2014 [13]	Abstract	R	50 treated 20 controls	NR	NR	NR	NR	NR
Scheiner, 2018 [14]	Full text	R	12 treated* 36 controls	52.9	LMWH or phenprocoumon	12	44.1	MELD: 13.6 CTP: A(14), B(19), C(18)
Senzolo, 2012 [5]	Full text	P	35 treated† 21 controls	55.5 52.3	LMWH	6	24	MELD: 12.6 CTP: A(11), B(16), C(8) MELD: 13.7 CTP: A(5), B(9), C(7)
Tiwari, 2018 [15]	Abstract	P	25 treated 20 controls	53.6	LMWH (9) or heparin (16)	NR	12	CTP: A(10), B(20), C(15)

* Initially, 51 patients were enrolled. 3 patients died early during follow up and were excluded from further analysis. 12 patients were treated with long-term anticoagulation (≥ 9 months) and 36 patients received no anticoagulation or short-term anticoagulation

† Two patients were excluded after enrollment

CTP, Child-Turcotte-Pugh; LC, liver cirrhosis; LMWH, low molecular weight heparin; MELD, model for end-stage liver disease; m, month; NR, not reported; P, prospective; R, retrospective; y, year

Table 2 Primary and secondary outcomes of the individual studies included in the meta-analysis

Study	PVT recanalization, n (%)		Variceal bleeding, n (%)		Any bleeding, n (%)	
	Anticoagulation	No anticoagulation	Anticoagulation	No anticoagulation	Anticoagulation	No anticoagulation
Chen, 2015 [3]	15 (68.2%)	4 (25.0%)	NR	NR	8 (36.4%)	0 (0.0%)
Chung, 2014 [10]	11 (78.6%)	5 (35.7%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (14.3%)
Copaci, 2016 [11]	31 (62.0%)	12 (27.3%)	NR	NR	NR	NR
Garcovich, 2011 [12]	7 (46.7%)	5 (33.3%)	NR	NR	NR	NR
Noronha Ferreira, 2019 [4]	18 (51.4%)	6 (18.8%)	0 (0.0%)	4 (12.5%)	0 (0.0%)	4 (12.5%)
Risso, 2014 [13]	37 (74.0%)	8 (40.0%)	NR	NR	NR	NR
Scheiner, 2018 [14]	7 (58.3%)	10 (27.8%)	0 (0.0%)	9 (25.0%)	0 (0.0%)	16 (44.4%)
Senzolo, 2012 [5]	21 (63.6%)	1 (4.8%)	1 (3.0%)	5 (23.8%)	4 (12.1%)	5 (23.8%)
Tiwari, 2018 [15]	20 (80.0%)	4 (20.0%)	NR	NR	NR	NR

NR, not reported; PVT, portal vein thrombosis

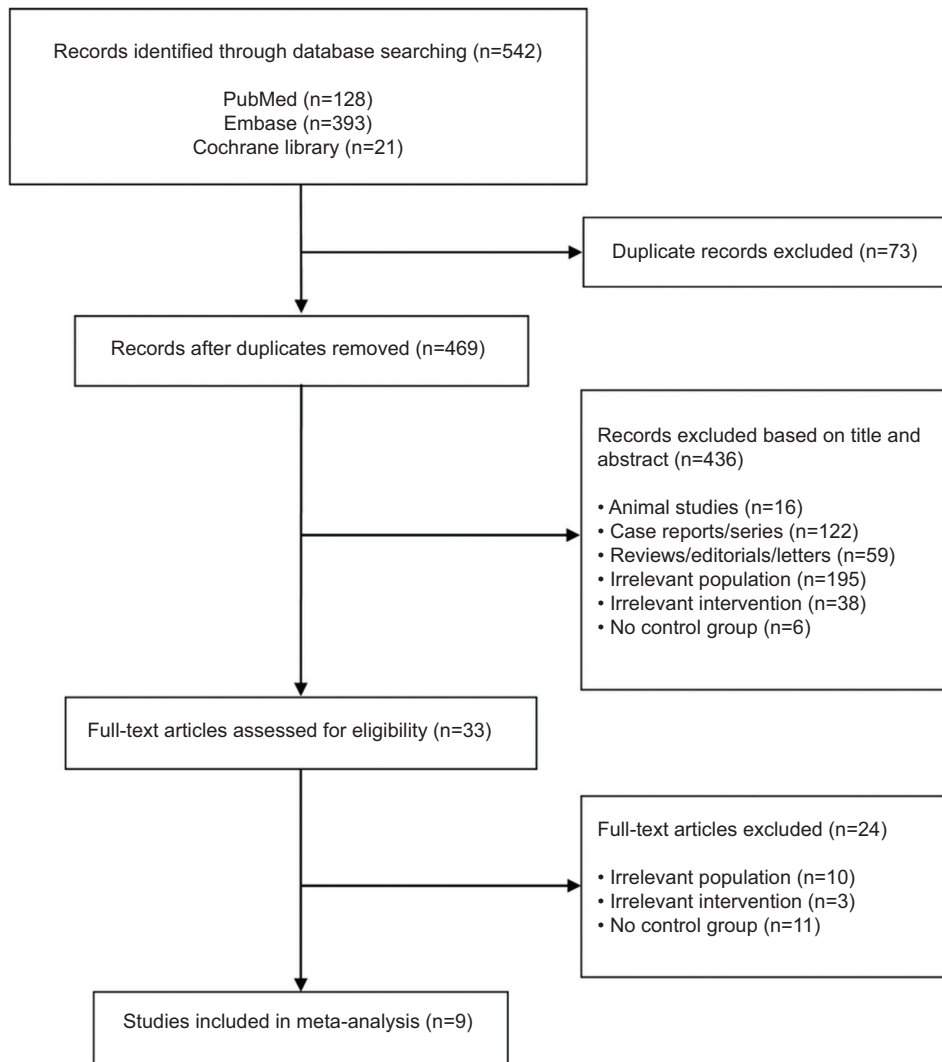


Figure 1 PRISMA flow diagram for selection of studies

rate of PV recanalization in patients with non-malignant PVT was significantly higher in the anticoagulated group compared to the untreated group (65.2% vs. 25.2%; RR 2.31, 95%CI 1.80-2.96; $P<0.00001$; $I^2=0\%$) (Fig. 2). Meta-regression of all studies evaluating PV recanalization did not reveal any significant moderating effect of publication year ($P=0.46$), study design ($P=0.63$) or publication type ($P=0.76$) (Supplementary Fig. 1, 2). Similarly, meta-regression of the studies that reported the severity and etiology of liver cirrhosis did not show the model for end-stage liver disease score ($P=0.56$) or etiology ($P=0.88$) as moderators of PV recanalization (Supplementary Fig. 3, 4).

Secondary outcomes

The risk of variceal bleeding was reported in 4 studies. These studies included a total of 197 patients, of whom 94 received anticoagulation and 103 did not. The risk of variceal

bleeding was significantly lower in the anticoagulated group than in the untreated group (0.1% vs. 18.5%; RR 0.15, 95%CI 0.04-0.55; $P=0.004$; $I^2=0\%$) (Fig. 3A). The risk of any bleeding was reported in 5 studies. These studies included 235 patients, of whom 116 received anticoagulation and 119 did not. The difference in the risk for any bleeding in both groups was not statistically significant (10.3% vs. 22.7%; RR 0.43, 95%CI 0.09-1.99; $P=0.28$; $I^2=52\%$) (Fig. 3B).

Subgroup analysis

We conducted a subgroup analysis that included studies in which the anticoagulant used was low molecular weight heparin (LMWH). It showed that PV recanalization was significantly higher in the anticoagulated group compared to the control group (64.2% vs 22.0%; RR 2.76, 95%CI 1.41-5.41; $P=0.003$; $I^2=54\%$) (Fig. 4A). We conducted another

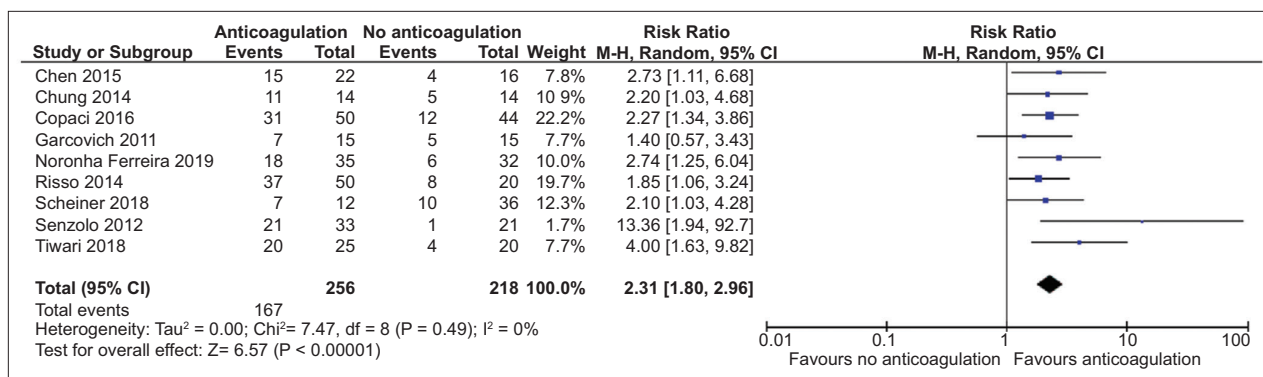


Figure 2 Meta-analysis of studies that investigated the efficacy of anticoagulation in achieving portal vein recanalization in non-malignant portal vein thrombosis in patients with liver cirrhosis

CI, confidence interval

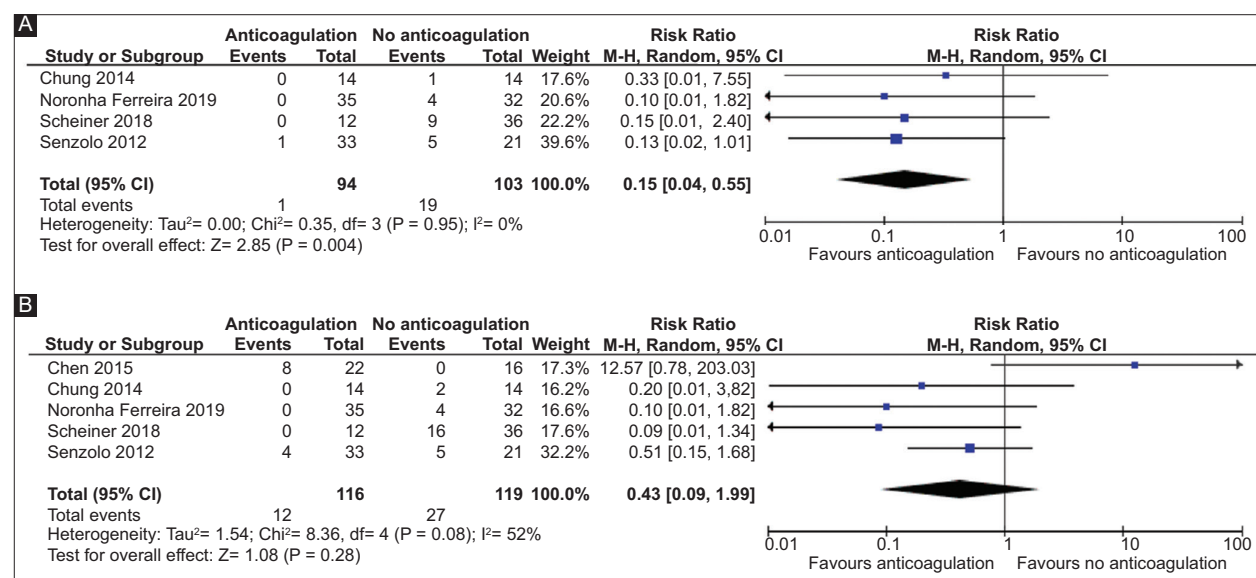


Figure 3 Meta-analysis of studies that investigated the safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis. (a) Occurrence of variceal bleeding. (b) Occurrence of any bleeding

CI, confidence interval

subgroup analysis that included studies in which the anticoagulant used was warfarin. It also showed that PV recanalization was significantly higher in the anticoagulated group (72.2% vs. 30.0%; RR 2.41, 95%CI 1.35-4.28; P=0.003; I²=0%) (Fig. 4B).

Bias assessment

There was visible gross asymmetry observed in the funnel blot, suggesting publication bias (Supplementary Fig. 5A). A significant trend towards positive reporting of any anticoagulation did appear to exist (Egger’s test P=0.05). The outcomes of our study did not change after implementing further statistics as mentioned previously (Supplementary Fig. 5B).

Discussion

This study was a systematic review and meta-analysis of published studies that assessed the effect of anticoagulation in patients with non-malignant PVT and liver cirrhosis, while excluding studies that included PVTs related to malignancy. We demonstrated that patients who received anticoagulation had a significantly higher rate of PV recanalization compared with those who did not receive anticoagulation (65.2% vs. 25.2%, respectively). Interestingly, our study showed that anticoagulation is associated with a lower incidence of variceal bleeding and any other bleeding events. This is consistent with a previous meta-analysis performed by Loffredo *et al*, which demonstrated that anticoagulant use is associated with a lower risk of variceal bleeding [16]. This finding can be explained by a decrease

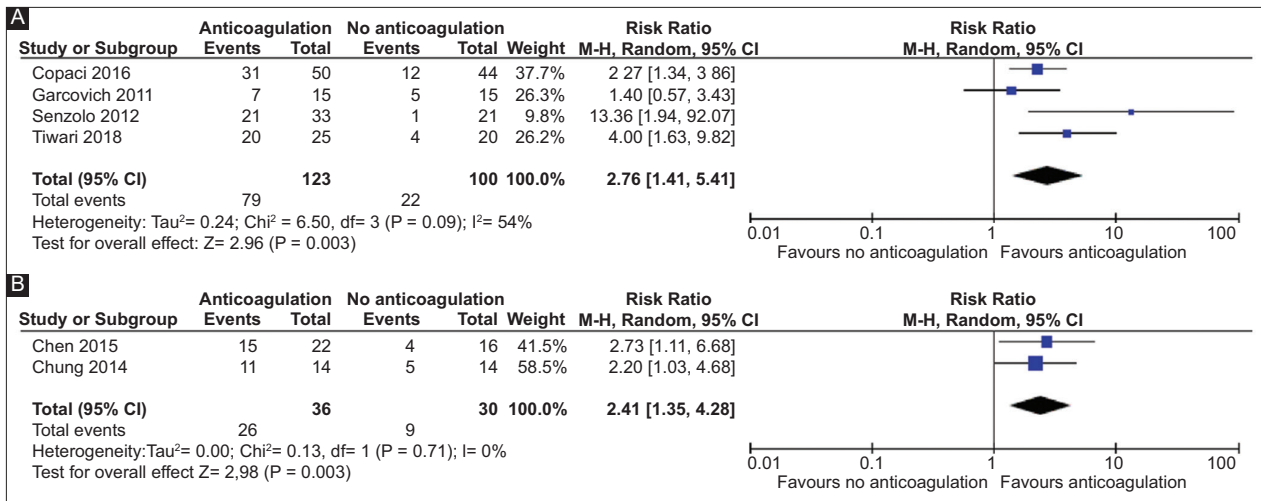


Figure 4 Subgroup analysis of studies that investigated the efficacy of anticoagulation in achieving portal vein recanalization in non-malignant portal vein thrombosis in patients with liver cirrhosis, based on anticoagulant drug used. (a) Studies that used heparin or low molecular weight heparin. (b) Studies that used warfarin
CI, confidence interval

in portal and intrahepatic vascular resistance that ultimately prevents variceal rupture and bleeding [14,16]. However, we recommend endoscopic screening for varices and initiation of primary or secondary prophylactic measures of variceal bleeding before starting anticoagulation treatment in those patients [17].

PVT is a common sequela of liver cirrhosis and its occurrence increases with cirrhosis progression [3]. A recent study reported that patients with advanced liver cirrhosis have an annual PVT incidence of about 10-15% [18]. Reduced PV velocity is considered the main contributor to the development of PVT in cirrhotic patients [5].

Anticoagulation provides a proven benefit in the treatment of PVT in non-cirrhotic patients [18]. However, the role of anticoagulation in treating PVT in the setting of liver cirrhosis remains unclear, because the data supporting starting anticoagulation are based mainly on retrospective small cohort studies and there is a lack of randomized controlled trials [18]. Although some studies have reported that spontaneous recanalization of PV can occur in up to 40% of cases, several studies have reported that the use of anticoagulation in cirrhotic patients achieves significant recanalization compared to those who did not receive anticoagulation [19,20]. A study by Francoz *et al* showed that no patients achieved recanalization in the group without anticoagulation, while 42% achieved recanalization in the anticoagulation group [20]. Therefore, based on our study findings, we recommend that cirrhotic patients with non-malignant PVT should be treated with anticoagulation to avoid thrombus extension into the mesenteric veins, which can lead to complications including intestinal infarction [21].

Patients with liver cirrhosis can develop malignant PVT (caused by hepatocellular carcinoma) or non-malignant PVT (caused by venous stasis and portal hypertension) [22]. To date, only 2 meta-analyses have investigated the efficacy and safety of anticoagulation in the treatment of PVT in cirrhotic patients [16,23]. Both meta-analyses included malignant and non-malignant PVT. Given the fact that malignant and non-malignant PVT are inherently different, we applied stricter

exclusion criteria and excluded studies that included patients with malignant PVT. Further, newer studies have been reported, and we provide an updated meta-analysis based on recent publications. Our meta-analysis results are similar to those from a recent meta-analysis by Loffredo *et al* which showed that the rate of PV recanalization was significantly higher (71% vs. 42%) in patients receiving anticoagulation, without major bleeding events or increased variceal bleeding [16].

Subgroup analysis showed that treatment with heparin/LMWH was effective in PV recanalization, with an RR of 2.76 (95%CI 1.41-5.41; P=0.003). Similarly, warfarin (used in 66 patients) had similar effectiveness in PV recanalization, with an RR of 2.41 (95%CI 1.35-4.28; P=0.003). The role of direct oral anticoagulants (DOACs) in patients with cirrhosis is still unknown, because most studies that evaluated their efficacy have excluded patients with liver disease [21]. However, Intagliata *et al* performed a first clinical study assessing the use of DOACs in patients with cirrhosis [24]. In that retrospective study, bleeding events did not differ significantly between patients who received DOACs compared with patients who received traditional anticoagulation (warfarin or LMWH) [21,24]. Therefore, it would be interesting to assess the impact of DOACs in cirrhotic patients with non-malignant PVT.

There are certain limitations to our meta-analysis. First, the studies included had a small sample size. Our meta-analysis only included 9 studies with a total of 474 patients. Second, because the literature lacks randomized controlled trials, our analysis only included observational studies. Future research should involve randomized controlled trials that report high quality evidence with large sample sizes to confirm our results. Third, only one study reported the subjects' survival rates. Long follow-up studies are needed to assess the long-term efficacy and the potential mortality benefit of anticoagulation use. Fourth, we could not assess the quality of the abstracts included in the analysis, which might affect the validity of our conclusion.

Despite the limitations, our updated meta-analysis recruited studies using stringent inclusion and exclusion criteria. The included observational studies were of high quality based on Newcastle-Ottawa scoring. Our results were consistent across all subgroup analyses and are in line with previous reported meta-analyses. We further attempted a meta-regression analysis based on publication year, publication type, study design, and severity and etiology of cirrhosis, which did not significantly alter our primary outcome.

In conclusion, our study supports anticoagulation use in patients with non-malignant PVT and cirrhosis, since it is associated with a high rate of PV recanalization without any obvious increase in bleeding risk. Despite the inspiring outcome in our meta-analysis, we emphasize that all the existing evidence is of low quality in the absence of randomized controlled trials. Accordingly, it is imperative to perform a randomized controlled study to validate the efficacy and safety of anticoagulation in the treatment of non-malignant PVT in the setting of liver cirrhosis. Future studies should also investigate the optimal duration of anticoagulation. Ultimately, treatment of PVT with anticoagulation should be considered on a case-by-case basis to maximize patient benefits and limit the risk of bleeding.

Summary Box

What is already known:

- Anticoagulation is the mainstay treatment for portal vein thrombosis (PVT) in non-cirrhotic patients
- Liver cirrhosis is associated with hypercoagulability and coagulopathy
- Previous meta-analyses have investigated the role of anticoagulation for PVT in cirrhotic patients, but have not made the distinction between malignant and non-malignant PVT

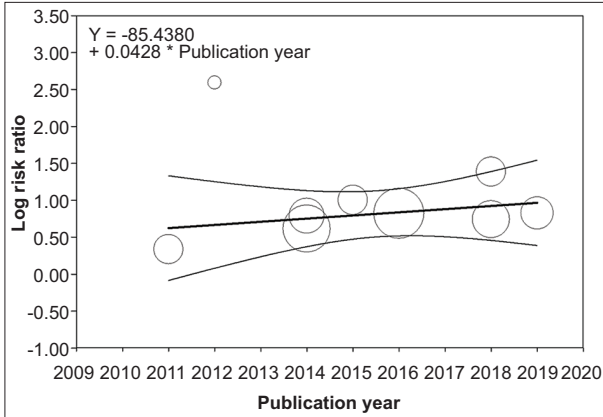
What the new findings are:

- Anticoagulation is effective in achieving portal vein recanalization in non-malignant PVT in cirrhotic patients
- In this population, anticoagulation does not increase the risk of any bleeding, and may even lower the risk of variceal bleeding
- Portal vein recanalization in this population can be achieved regardless of whether low molecular weight heparin or warfarin is used

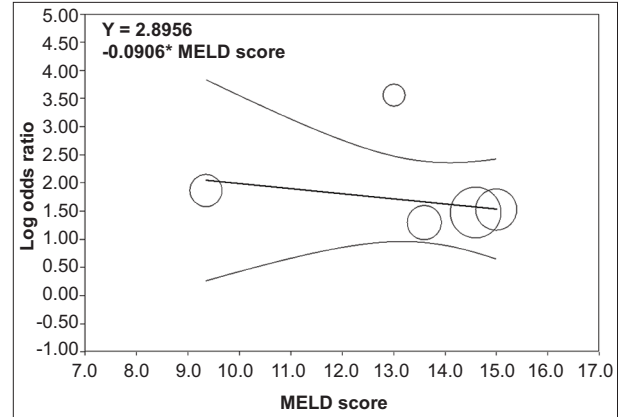
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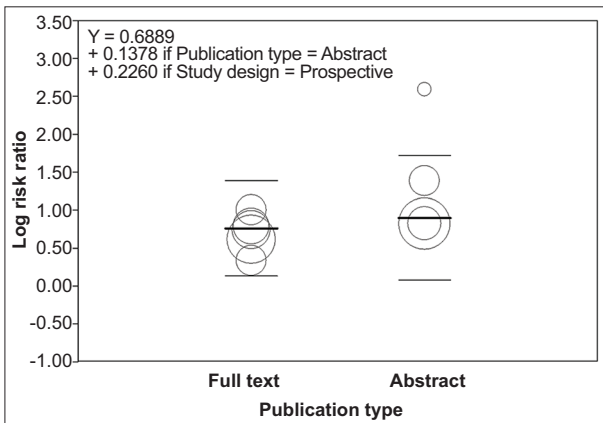
Supplementary material



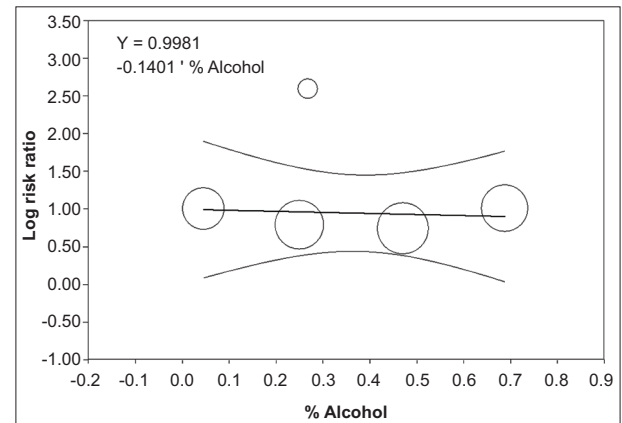
Supplementary Figure 1 Regression of log risk ratio on publication year. Meta-regression model did not demonstrate significant moderating effect of year of publication ($P=0.46$). (Note: bubbles represent study, size of the bubble represents study weight, central thick line represents meta-regression line, curved upper and lower lines represent 95% confidence interval)



Supplementary Figure 3 Regression of log odds ratio on model for end-stage liver disease (MELD) score. Meta-regression model did not demonstrate significant moderating effect based on MELD score ($P=0.56$). (Note: bubbles represent study, size of the bubble represents study weight, central thick line represents meta-regression line, curved upper and lower lines represent 95% confidence interval)



Supplementary Figure 2 Regression of log risk ratio on publication type. Meta-regression model did not demonstrate significant moderating effect based on study design ($P=0.63$) and publication type ($P=0.76$). (Note: bubbles represent a study, size of the bubble represents study weight, central thick line represents meta-regression line, upper and lower thin lines represent 95% confidence interval)



Supplementary Figure 4 Regression of log risk ratio on the percentage of alcoholic cirrhosis as the etiology of liver cirrhosis. Meta-regression model did not demonstrate significant moderating effect based on the percentage of alcoholic cirrhosis as the etiology of liver cirrhosis ($P=0.88$). (Note: bubbles represent study, size of the bubble represents study weight, central thick line represents meta-regression line, curved upper and lower lines represent 95% confidence interval)

Supplementary Table 2 Quality assessment of the studies using the Newcastle-Ottawa Scale

Criteria	Condition	Chen 2015	Chung 2014	Noronha Ferreira 2019	Scheiner 2018	Senzolo 2012
Selection						
Representativeness of exposed cohort	Patients diagnosed with non-malignant portal vein thrombosis who underwent anticoagulation	*	*	*	*	*
Selection of non-exposed cohort	Patients diagnosed with non-malignant portal vein thrombosis who did undergo anticoagulation	*	*	*	*	*
Ascertainment of exposure?	Secure records	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Yes	*	*	*	*	*
Comparability						
Study controls for baseline imbalances?	Age and severity of liver cirrhosis	**	**	**	*	**
Outcome						
Assessment of outcome	Confirmation by ultrasound	*	*	*	*	*
Was follow up long enough for outcomes to occur	6 months	*	-	*	*	*
Adequacy of follow up of cohorts	Complete follow up or less than 10% lost to follow up	*	-	*	*	*

A study can be awarded a star (*) for a criterion if it satisfies the condition for that criterion. A study can be awarded 2 stars (**) in the comparability item if it controls for both age and severity of liver cirrhosis