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Thromboelastography-Guided Therapy Enhances Patient Blood Management in Cirrhotic Patients: A Meta-analysis Based on Randomized Controlled Trials

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Abstract

Patients with cirrhosis often have abnormal hemostasis, with increased risk of hemorrhage and thrombosis. Thromboelastography provides a rapid assessment of the coagulation status and can guide product transfusions in adult patients with cirrhosis. This study aimed to determine whether the use of thromboelastography in adult patients with cirrhosis decreases blood product use and impacts adverse events or mortality compared with standard practice. A registered (PROSPERO CRD42020192458) systematic review and meta-analysis was conducted for randomized controlled trials (RCTs) comparing thromboelastography-guided hemostatic management versus standard practice (control). Co-primary outcomes were the number of transfused platelet units and fresh frozen plasma (FFP) units. Secondary outcomes were mortality, adverse events, utilization of individual blood products, blood loss or excessive bleeding events, hospital/intensive care unit stay, and liver transplant/intervention outcomes. The search identified 260 articles, with five RCTs included in the meta-analysis. Platelet use was five times lower with thromboelastography versus the control, with a relative risk of 0.17 (95% confidence interval [CI]: [0.03–0.90]; $p = 0.04$), but FFP use did not differ significantly. Thromboelastography was associated with less blood product ($p < 0.001$), FFP + platelets ($p < 0.001$), and cryoprecipitate ($p < 0.001$) use. No differences were reported in bleeding rates or longer term mortality between groups, with the thromboelastography group having lower mortality at 7 days versus the control (relative risk [95% CI] = 0.52 [0.30–0.91]; $p = 0.02$). Thromboelastography-guided therapy in patients with cirrhosis enhances patient blood management by reducing use of blood products without increasing complications.

Keywords
- thromboelastography
- cirrhosis
- blood products
- patient blood management

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With over 600 million individuals with chronic or acute blood loss and/or bleeding disorders worldwide, a recent policy brief by the World Health Organization (WHO) provides a call to action on the urgent need for effective patient blood management (PBM).[1] One of the core pillars outlined by the WHO relates to mitigation of blood loss and coagulation optimization.

Patients with cirrhosis present with hemostatic profiles characterized by both prohemorrhagic and prothrombotic tendencies in all pathways of coagulation: platelet number and function, anticoagulant and procoagulant factors and fibrinolysis. This can lead to both an increased risk of hemorrhage as well as thrombosis.[2–5] Effective PBM in terms of achieving hemostasis and preventing and treating thrombosis and bleeding are core elements of managing patients with decompensated cirrhosis.[4,6] However, there are limited data to guide the use of coagulation tests, especially in periprocedural risk assessment.[4] Standard coagulation tests such as international normalized ratio (INR)/prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not suitable for defining coagulation abnormalities, and, therefore, do not provide an accurate prediction of the risk of bleeding in patients with cirrhosis.[5,7,8] Thromboelastography provides a rapid assessment of hemostasis of a whole blood sample and can predict risk of thrombosis and bleeding.[9–11] The technology may be beneficial for patients with cirrhosis experiencing bleeding, thrombosis, or undergoing invasive procedures or surgery.[1,7,12,13] A recent prospective cohort study found that the thromboelastography marker of clot stability (maximum amplitude) could accurately distinguish between cirrhosis patients with major, life-threatening procedure-related bleeding and those who were not bleeding or had minor bleeding, whereas a low platelet count could not distinguish between any procedure-related bleeding (major or minor) and no bleeding.[14] Further, the potential utility of thromboelastography is emphasized by findings that liberal transfusion of allogeneic blood products such as packed red blood cells, plasma, and platelets is associated with increased mortality in patients with cirrhosis.[15–18]

The use of transfusion algorithms guided by technologies such as thromboelastography has been recommended by several associations and organizations for cardiovascular surgery, emergency bleeding, and organ transplant.[19–25] However, the American Gastroenterological Association (AGA) clinical practice update on coagulation in cirrhosis states that the role of technologies such as thromboelastography is yet to be fully established in this setting.[26] Conversely, the Society of Critical Care Medicine (SCCM) guidelines on the management of adults with acute and acute-on-chronic liver failure in the intensive care unit (ICU) support the use of thromboelastography over INR, platelet, and fibrinogen levels as a conditional recommendation based on low-quality evidence from a single study.[27] In addition, recent guidance from the SSC/ISTH (Scientific and Standardization Committee/International Society on Thrombosis and Haemostasis) on periprocedural hemostatic management in patients with cirrhosis states that PT/INR is inadequate in reflecting the rebalanced coagulation state seen in cirrhosis, and that thromboelastography may have utility in verifying that hemostasis is "normal" in cirrhosis patients.[28]

Thromboelastography is a commonly used technology to guide transfusion and coagulation management in patients undergoing liver transplantation.[29] However, until recently, there has been a lack of robust clinical trials investigating the utility of thromboelastography in guiding periprocedural PBM in cirrhosis patients.

This meta-analysis was, therefore, undertaken to determine whether the use of thromboelastography-guided therapy in adult patients with cirrhosis is beneficial in the optimization of PBM, considering blood product use, bleeding outcomes, and mortality compared with standard practice, i.e., standard coagulation testing. The primary outcomes investigated were the transfusion of platelet and fresh frozen plasma (FFP) units.

Materials and Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[30] and registered in the PROSPERO database (CRD42020192458).

Systematic Literature Review

A systematic literature review was conducted in MEDLINE, Cochrane, and EMBASE databases to identify randomized controlled trials (RCTs) of adult patients (≥18 years) with cirrhosis in which thromboelastography was compared with standard practice, i.e., hemostatic management guided by standard coagulation tests including INR, PT, aPTT, and platelet count). Searches were performed in July 2020 and included terms for liver, cirrhosis, thromboelastography, and publication type; included publications were English language articles. A full list of the search terms used for MEDLINE, Cochrane, and EMBASE are provided in the **Supplementary Material** (Literature Search Terms [online only]). In addition, reference lists from identified meta-analyses were mined for further RCTs that fit the inclusion/exclusion criteria.

In the initial stage, titles and abstracts of identified articles were screened by two reviewers independently using predefined inclusion and exclusion criteria as shown in ►**Supplementary Table S1**, available in the online version only. Articles reporting studies in pediatric patients, nonhumans, patients without liver disease, or those using other devices or not reporting any of the predefined meta-analysis outcomes were excluded. All screening was performed using DistillerSR (Evidence Partners, Ontario, Canada) systematic review software, which collates user-inputted references for standardized review and screening. In a second screen, the full text of the selected publications was reviewed to confirm eligibility for inclusion by authors E.G.P. and G.G.-T., who had final decision on article inclusion. Data were extracted from identified RCTs evaluating clinical outcomes following the use of thromboelastography compared with standard practice (control).

All outcomes were prespecified in the PROSPERO protocol. Co-primary outcomes were the number of transfused platelet units and FFP units. Individual secondary outcomes were mortality, adverse events (AEs), utilization of individual blood products, platelets and FFP combined, blood loss or excessive bleeding events, hospital/ICU stay, liver transplant outcomes, and intervention outcomes. Where data were missing, attempts were made to contact authors for additional or supporting information. Assessment of bias was performed using version 2 of the Cochrane risk-of-bias tool for randomized trials, which assesses bias as low risk, some concerns, or high risk across five domains (randomization bias, deviation from intended intervention, missing outcome data, outcome measurement bias, and result reporting selection bias).[31]

Statistical Analysis

Meta-analysis methods were used to pool the results from the different studies to give a single estimate of the differences in outcome between treatments. All analyses were performed using the DerSimonian–Laird random-effects method, which is the most commonly used standard for meta-analysis with random effects, and assumes that treatment effects vary between studies according to a random distribution, regardless of heterogeneity between studies.[32] Heterogeneity was assessed based on the significance of the between-study heterogeneity, using I^2 statistics to describe the percentage of the variability in effect estimates due to heterogeneity (rather than sampling error) using the below calculation, with Q denoting the chi-squared statistic and df denoting degrees of freedom.

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Substantial heterogeneity was assumed if the I^2 value was >50%.

All outcomes analyzed were binary in nature; as a result, the pooled outcomes between thromboelastography and control groups were expressed as relative risks. Three of the five studies reported Kaplan–Meier survival curves, which were used to assess mortality, with focus on rates at 7 days. The 7-day time point was selected due to this being the timeframe within which patients would be expected to be treated for bleeding/rebleeding, and where thromboelastography may be used to guide the intervention. Later mortality (at 42 days) was also assessed. This time point was chosen as it was the most frequent longer term time point reported in the studies and was intermediate between other reported time points (28 and 90 days).

Results

Overview of Search Results and Patient Characteristics

The literature search identified a total of 260 articles. Following the title and abstract screen, 29 articles progressed to full-text review (►**Supplementary Fig. S1**, available in the online version only). Five articles met the predefined criteria and were included in the meta-analysis. The overall methodological quality of the studies was high to moderate; although, all five manuscripts were judged as having some concerns of bias (►**Supplementary Fig. S2**, available in the online version only).

All studies included in the analysis were RCTs comparing management with thromboelastography (TEG 5000 Analyzer [Haemonetics Corporation, Boston, MA] or MonoTEM-A [Framar Hemologix, Rome, Italy]) to standard practice. While the exact standard coagulation test algorithms varied slightly between studies, all of them included platelet count 50×10^9/L as the cut-off point for platelet transfusion requirements, and all except Wang et al used INR >1.8 as the cut-off for FFP transfusion (the algorithm used by Wang et al required red blood cell transfusions to maintain hemoglobin concentration of 8 g/dL, and FFP to maintain PT and aPTT at less than one and a half times the control). Four of the studies involved patients with cirrhosis[12,33–35] and one included patients undergoing liver transplantation due to cirrhosis.[36] The overall patient demographics for each of the five included studies were broadly comparable between the study and control groups (►**Table 1**). All patients included in the studies were adults, with the majority being male; no patients were treated with antiplatelet medication during the trials.

Co-primary Outcomes: Transfusion of Platelets and FFP

Four of the five studies reported data on the utilization of FFP and platelets in patients with cirrhosis; therefore, only these studies are included in the forest plots. Transfusion of FFP and platelets showed the highest heterogeneity between studies, with I^2 values >50% and a statistically significant heterogeneity ($p = 0.003$ and $p < 0.001$, respectively). Individual studies showed a significant difference in the use of platelets between groups (►**Table 2**). Meta-analysis of the pooled data demonstrates a statistically significant difference in the use of platelets between groups with platelet use five times lower with thromboelastography than with standard practice (relative risk [95% confidence interval, CI] = 0.17 [0.03–0.90]; $p = 0.04$) (►**Fig. 1A**). There was a trend towards lower use of FFP in the thromboelastography group, with each individual study showing lower FFP use (►**Table 2**), although this difference did not reach statistical significance. Pooled results suggested a reduced use of FFP with the use of thromboelastography compared with standard practice in patients with cirrhosis; however, this difference was likewise not significant (relative risk [95% CI] = 0.34 [0.10–1.16]; $p = 0.09$) (►**Fig. 1B**).

Secondary Outcomes

Secondary outcomes included safety outcomes such as mortality, AEs, blood loss, and utilization of individual blood products. Treatment effect for primary and secondary outcomes favored thromboelastography, as shown in ►**Fig. 2**.

Mortality

Mortality data were reported in all five studies; however, this was measured at various time points (from 5 days to 3 years),

Table 1 Patient characteristics in the five studies included in the meta-analysis

	De Pietri et al, 2016[12]	Kumar et al, 2020[33]	Rout et al, 2020[34]	Vuyyuru et al, 2020[35]	Wang et al, 2010[36]
Thromboelastography device	TEG 5000	TEG 5000	MonoTEM-A	MonoTEM-A	TEG 5000
Population	Patients with cirrhosis undergoing invasive procedures	Patients with cirrhosis with nonvariceal bleeding	Patients with cirrhosis with variceal bleeding	Patients with cirrhosis undergoing high-risk invasive liver procedures	Liver transplant patients
Total patients	60	96	60	58	28
Age, y					
Thromboelastography	57.8 (9.4)	48 [29–72]	42.1 (12.8)	35.1 (11.8)	58.6 (4.8)
Control	58.6 (12.1)	46 [29–67]	43.2 (11.1)	33.41 (12.9)	51.3 (12.5)
Male, *n* (%)					
Thromboelastography	16 (53.3)	36 (73.5)	22 (73.3)	22 (75.9)	7 (50.0)
Control	22 (73.3)	42 (89.4)	27 (90.0)	20 (68.9)	11 (85.7)
Ideal body weight, kg[a]					
Thromboelastography	63.7 (7.8)	67 [47–91]	61.2 (7.1)	63.5 (9.9)	BMI: 24.2 kg/m^2
Control	66.8 (7.8)	68 [45–102]	64.1 (5.0)	61.7 (10.7)	BMI: 24.2 kg/m^2
MELD score					
Thromboelastography	21.4 (9.9)	23 [11–40]	14.0 [8–26]	14 [12–23]	11.0 (4.2)
Control	20.5 (6.9)	21 [11–38]	16.5 [8–29]	13 [11–17]	11.6 (3.8)
Child–Pugh Class A, *n* (%)					
Thromboelastography	3 (10)	–	9 (30.0)	13 (14.8)	–
Control	5 (16.7)	–	9 (30.0)	20 (69.0)	–
Child–Pugh Class B, *n* (%)					
Thromboelastography	11 (36.7)	–	14 (46.7)	8 (27.6)	–
Control	5 (16.7)	–	11 (36.7)	5 (17.2)	–
Child–Pugh Class C, *n* (%)					
Thromboelastography	16 (53.3)	–	7 (23.3)	8 (27.6)	–
Control	20 (66.6)	–	10 (33.3)	4 (13.8)	–
Platelet count, 10^9/L					
Thromboelastography	56.5 (32.5)	40 [16–133]	46 [11–95]	47 [28.5–90.5]	–
Control	61.3 (41.9)	37 [19–119]	44 [13–118]	40 [30–60]	–
INR					
Thromboelastography	1.87 (0.55)	2.6 [1.15–4.12]	1.66 [1.05–3.39]	1.8 (0.6)	1.3 (0.2)
Control	2.01 (0.69)	2.5 [1.6– 4.62]	1.72 [1.04–2.77]	1.7 (0.7)	1.4 (0.4)
Albumin, g/dL					
Thromboelastography	2.9 (0.5)	2.5 [1.3–3.7]	3.0 (0.8)	3.6 (0.9)	–
Control	2.8 (0.4)	2.5 [1.4–3.7]	3.1 (0.6)	3.8 (0.8)	–
Creatinine, mg/dL					
Thromboelastography	1.46 (1.40)	0.99 [0.3–3.01]	0.7 [0.2–1.3]	0.7 [0.5–0.8]	–
Control	0.97 (0.46)	0.91 [0.25–2.5]	0.9 [0.3–1.4]	0.7 [0.5–0.8]	–
Total bilirubin, mg/dL					
Thromboelastography	8.5 (9.6)	3.1 [0.8–36.0]	1.5 [0.3–4.8]	2.1 [1.0–5.1]	4.6 (6.7)
Control	6.6 (6.3)	3.1 [0.8–39.9]	1.4 [0.3–4.8]	1.8 [1.0–2.9]	6.1 (6.9)
Ascites, *n* (%)	Grade ≥2	Grade ≥2	Any grade	Any grade	Any grade
Thromboelastography	19 (63.3)	30 (61.2)	19 (63.3)	6 (20.7)	–
Control	16 (53.3)	30 (63.9)	21 (70.0)	3 (10.3)	–

Abbreviations: BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease.
Note: Values are mean (SD) or median [IQR]. A dash indicates the demographic was not reported in the manuscript.
[a]To avoid interference of ascites or pleural effusion, the studies reported ideal body weight except for Wang et al. Ideal body weight was calculated using the Devine formula as follows: male ideal body weight = 50 kg + 2.3 kg per inch over 5 feet, and female ideal body weight = 45.5 kg + 2.3 kg per inch over 5 feet.

Table 2 Individual study results for the utilization of platelets and FFP

Study	Thromboelastography		Control		*p*-Value
	Number of patients (*n*) %	Units (U) or mL given	Number of patients (*n*) %	Units (U) or mL given	
Platelets					
De Pietri et al, 2016[12]	2 (6.7)	Low risk: 22 UHigh risk: 6 U	10 (33.3)	Low risk: 28 UHigh risk: 78 U	0.021
Kumar et al, 2020[33]	26 (53.1)	26 U 1 (0–1) U per patient	43 (91.5)	71 U 2 (0–3) U per patient	<0.001[a]
Rout et al, 2020[34]	0 (0.0)	N/A	16 (53.3)	3,150 mL[a]	<0.001
Vuyyuru et al, 2020[35]	2 (6.9)	–	21 (72.4)	–	<0.001
FFP					
De Pietri et al, 2016[12]	0 (0.0)	N/A	16 (53.3)	Low risk: 11,050 mL High risk: 4,000 mL	<0.0001
Kumar et al, 2020[33]	30 (61.2)	20,860 mL	45 (95.7)	40,300 mL	<0.001[b]
Rout et al, 2020[34]	1 (3.3)	1,345 mL	9 (30.0)	4,605 mL	0.012
Vuyyuru et al, 2020[35]	6 (20.7)	–	7 (24.1)	–	0.753
RBC					
De Pietri et al, 2016[12]	4 (13.3)	6 packs total	4 (13.3)	10 packs total	0.718
Kumar et al, 2020[33]	40 (80.6)	Median (range): 2 (0–7) packs	35 (74.5)	Median (range): 2 (0–10) packs	0.464

Abbreviations: FFP, fresh frozen plasma; N/A, not applicable; RBC, red blood cells.
[a]50 mL of platelets is approximately 1 unit. For FFP, 1 unit corresponds to around 200–300 mL.
[b]Patient transfused: 0.495; total mL transfused: <0.001; mL transfused per patient: <0.001.

making the pooling of data for analysis difficult (►**Table 3**). Three studies in patients with cirrhosis reported Kaplan–Meier survival curves. Analysis of these survival curves revealed that the relative risk of mortality in the thromboelastography group was significantly lower at 7 days when compared with the control group (relative risk [95% CI] = 0.52 [0.30–0.91]; $p = 0.02$) (►**Fig. 3**). No statistically significant difference in mortality between groups was found at any of the later time points reported by individual studies (►**Table 3**).

Utilization of Individual Blood Products

Individual blood products explored in the meta-analysis were any blood products, red blood cells, FFP and platelets combined, cryoprecipitate, and fibrinogen. Data on these outcomes were heterogeneously reported in the studies with data available from a single study (cryoprecipitate), two studies (any blood product, red blood cells), or three studies (FFP + platelets) with individual study data shown in ►**Table 2**. No studies reported data on fibrinogen use.

The pooled results suggested a statistically significant reduction in the use of any blood product ($n = 2$; relative risk [95% CI] = 0.24 [0.15–0.38]; $p \leq 0.001$), FFP and platelets combined ($n = 3$; relative risk [95% CI] = 0.48 [0.34–0.68]; $p \leq 0.001$), and cryoprecipitate ($n = 1$; relative risk [95% CI] = 0.64 [0.51–0.79]; $p \leq 0.001$) favoring thromboelastography. For red blood cells, no significant difference in utilization between the thromboelastography and control groups was observed ($n = 2$; relative risk [95% CI] = 1.09 [0.89–1.35]; $p = 0.41$).

Adverse Events

Of the five included studies, three included endpoints related to AEs. Of these, one study did not report any AEs occurring during the study and was excluded from this analysis. The other two studies each reported one AE in the control group and none in the thromboelastography group, with Rout et al reporting an adverse reaction in the form of urticaria[34] and De Pietri et al reporting an allergic reaction during FFP infusion.[12] Due to the low numbers of AEs, there was no heterogeneity between studies (0%) and no significant difference in the incidence of AEs between the thromboelastography and control groups was observed (relative risk [95% CI] = 0.33 [0.04–3.12]; $p = 0.34$).

Serious transfusion-related reactions were reported in one study in patients with cirrhosis and nonvariceal bleeding.[33] A significant reduction in serious transfusion-related reactions was observed following the use of thromboelastography compared with standard practice during 42 days of follow-up, including a significant reduction in transfusion-related acute lung injury (TRALI; 6 patients [12.2%] in the thromboelastography group and 23 patients [48.9%] in the control group, $p \leq 0.001$). While there is a low incidence of TRALI overall in bleeding patients, the likelihood of

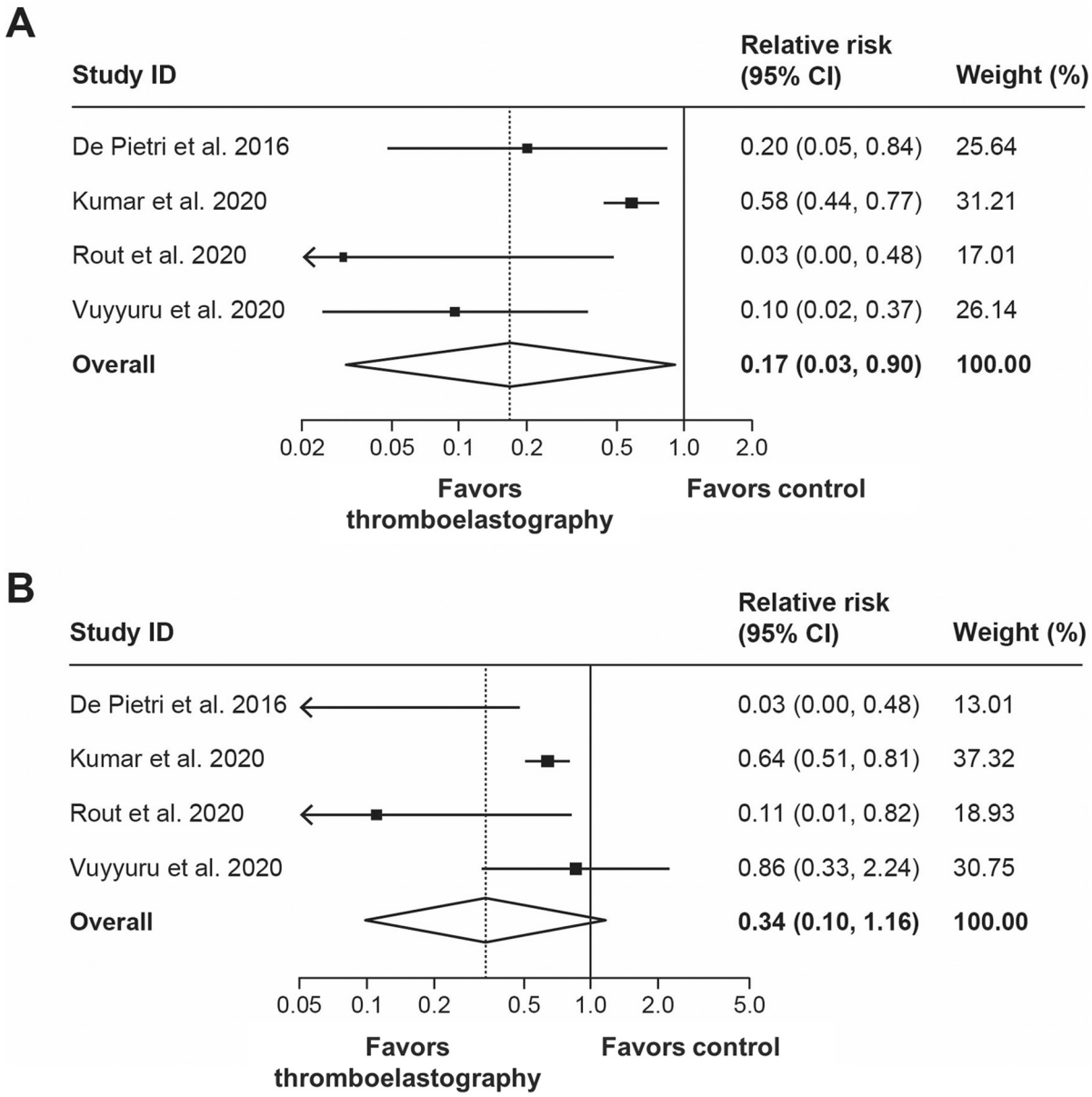

Fig. 1 Individual study results and pooled differences for (**A**) utilization of platelets and (**B**) utilization of FFP. Weight determined by the DerSimonian-Laird random-effects method with studies weighted inversely to the standard error of the risk ratios. CI, confidence interval; FFP, fresh frozen plasma.

developing TRALI is higher in patients with end-stage liver disease.[37] In this population with severe cirrhosis it is therefore a useful safety outcome to compare. In all other categories, including transfusion-associated circulatory overload and acute respiratory distress syndrome, lower rates of transfusion-related reactions were observed with thromboelastography versus standard practice; however, these differences were not statistically significant.

Additional Outcome Measures

Additional prespecified outcome measures included analysis of bleeding events and length of ICU/hospital stay. Four studies in cirrhosis patients reported data on blood loss or excessive bleeding; however, because the definitions of bleeding events were not generally comparable between studies, results were not included in the meta-analysis. Additional data provided by the authors of two studies[33,34] were used instead, with meta-analysis demonstrating that there was no significant difference in either bleeding up to Day 5 or rebleeding after Day 5 (►**Supplementary Fig. S3**, available in the online version only).

Only one study in patients with cirrhosis and nonvariceal bleeding presented data on length of ICU/hospital stay[33]; therefore, this outcome was not included in the meta-analysis. Total ICU length of stay during the first admission was significantly shorter with thromboelastography compared with the control ($p = 0.012$). In addition, a higher number of patients were discharged from hospital following first admission with thromboelastography versus control (69.4 vs. 48.9%); however, there was no significant difference in the longer time points of total ICU length of stay up to 42 days and total hospital length of stay up to 42 days. The study did

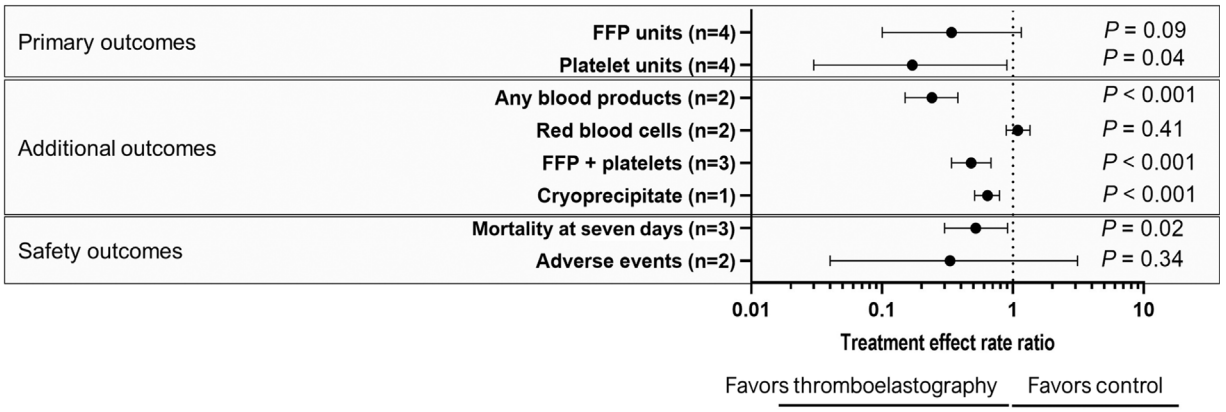

Fig. 2 Treatment effect for primary and secondary outcomes. Summary of treatment effects for primary, secondary, and safety outcomes, where *n* =number of studies reporting results. Only two studies reported any adverse events occurring, with both reporting one in the control group and none in the viscoelastic testing group. One study, which recorded adverse events but did not report any adverse events occurring, was excluded from the meta-analysis. FFP, fresh frozen plasma.

not report on any factors that might have explained the differences between discharge levels during first admission, and so the generalizability of this result is uncertain. Because there were no consistent ICU/hospital stay outcomes reported, a meta-analysis could not be performed.

Discussion

Effective PBM can help to preserve the patient's own blood and reduce transfusion requirements, which is crucial since transfusion in itself is independently associated with adverse outcomes.[1] Nevertheless, it is important that the efficacy of specific PBM strategies be confirmed through the generation and collation of high-quality evidence in specific populations and settings. The meta-analysis presented here, through the inclusion of high-quality RCT data alone, supports that thromboelastography-guided therapy in patients with cirrhosis who are bleeding or undergoing surgical interventions/liver transplant enhances PBM by significantly reducing transfusions of platelets, all blood products, and combined FFP and platelets compared with standard coagulation test-guided therapy. Although a trend towards lower use of FFP alone was observed, it did not reach statistical significance. Nevertheless, the benefit to the patient of thromboelastography-guided therapy is supported by lower early (7-day) mortality versus the control groups and the absence of an increased risk of bleeding, with one study suggesting a significant reduction in transfusion-related reactions in patients with advanced cirrhosis. These data may be useful in expanding on current clinical guidelines for the use of thromboelastography in this setting.

The 2019 AGA clinical practice update on coagulation in cirrhosis states that thromboelastography "may eventually have a role in the evaluation of clotting in patients with cirrhosis, but currently lacks validated target levels."[26] Conversely, the 2020 SCCM guidelines for the management of critically ill adults with acute and acute-on-chronic liver failure who are undergoing procedures provide conditional guidance for the use of thromboelastography in preference to measuring INR, platelet, and fibrinogen.[27] Furthermore, recent guidance on periprocedural hemostatic management in patients with cirrhosis by SSC and ISTH cites a potential role for thromboelastography in this area.[28]

Data included in our meta-analysis represent recent RCTs in patients with cirrhosis, most of which have not been included in recent guidelines. Recommendations from the SCCM guideline,[27] and other recent clinical recommendations in patients with acute-on-chronic liver failure,[38] that thromboelastography should guide the evaluation of coagulation pathways and hyperfibrinolysis are based on an older single RCT of 60 patients with cirrhosis scheduled to undergo

Table 3 Mortality rate and time points reported across all five studies

Study	Time point (following surgery/intervention)	Mortality in VET group, *n* (%)	Mortality in control group, *n* (%)
De Pietri et al, 2016[12]	90 days	8 (26.6)	7 (23.3)
Kumar et al, 2020[33]	5 days	11 (22.4)	14 (29.8)
	42 days	27 (55.1)	31 (66.0)
Rout et al, 2020[34]	6 weeks	4 (13.3)	8 (26.7)
Vuyyuru et al, 2020[35]	28 days	0 (0.0)	1 (3.4)
Wang et al, 2010[36]	3 years	12 (85.8)	11 (78.6)

Abbreviation: VET, viscoelastic test.

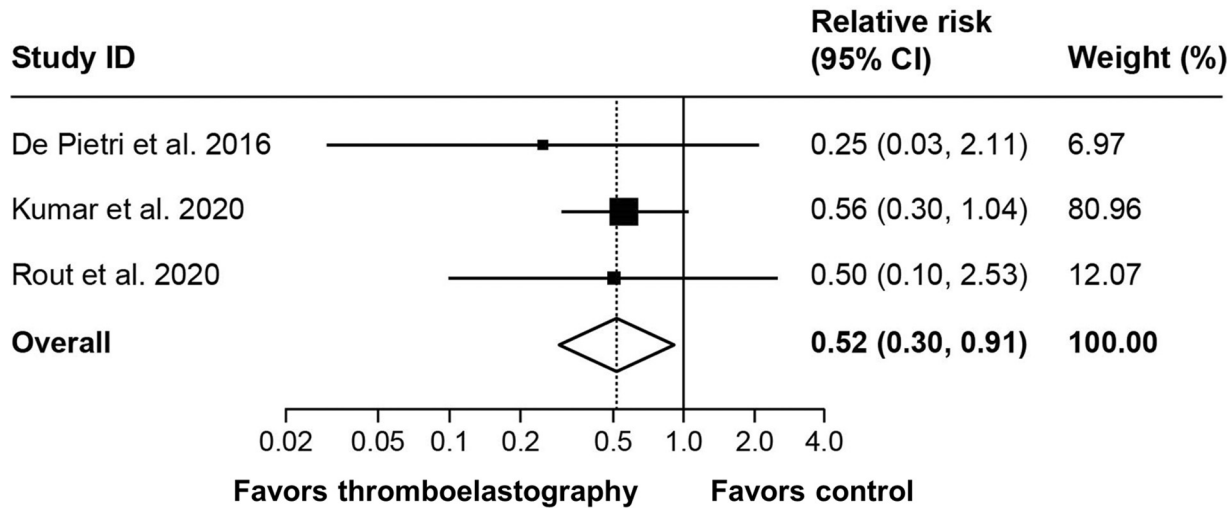

Fig. 3 Individual study results and pooled differences for mortality at day 7. CI, confidence interval.

an invasive procedure published by De Pietri et al.[12] Further, RCT evidence presented in relation to thromboelastography was limited to two studies captured in our meta-analysis (De Pietri et al[12] and Vuyyuru et al[35]) in the recent SSC/ISTH guidance.[28] The other studies included in our meta-analysis are not cited in these guidelines; therefore, our meta-analysis extends the evidence base used for these guidelines.

While this meta-analysis reported on the use of thromboelastography specifically based on RCTs, our findings are broadly consistent with those of a recently published meta-analysis by Tangcheewinsirikul et al comparing the use of viscoelastic tests (VETs) with standard coagulation tests in managing perioperative bleeding of cirrhotic patients,[39] as well as those of a recent meta-analysis by Kovalic et al of thromboelastography or rotational thromboelastometry that included retrospective and non-randomized trials in addition to RCTs.[40] Tangcheewinsirikul et al identified and included the same five studies on thromboelastography included in the present report,[12,33–36] and as the authors investigated the use of VET in general, two further studies concerning rotational thromboelastometry (ROTEM, Tem Innovations GmbH, Munich, Germany) were included.[41,42]

The decrease in platelet and cryoprecipitate transfusion associated with the use of thromboelastography observed in this study was confirmed by Tangcheewinsirikul et al, who observed similar results with the use of VET, including no effect on red blood cell transfusion. However, while the decrease in FFP use did not reach significance in the present study, Tangcheewinsirikul et al reported a significant effect of VET on this endpoint. The pooled rate of FFP transfusion was 48% significantly lower in the VET group (relative risk [95% CI] = 0.52; [0.35–0.77]; $p = 0.001$; $I^2 = 56\%$).[39] Similarly, Kovalic et al reported a significant reduction in the number of patients requiring platelet and FFP transfusions with thromboelastography/thromboelastometry compared with laboratory test-guided therapy, with a pooled odds ratio of 0.29 (95% CI: 0.12–0.74; $p = 0.009$) and 0.19 (95% CI: 0.12–0.31; $p < 0.00001$), respectively.[40] A significant decrease in the total number of bleeding events and intraoperative bleeding events during liver transplantation with thromboelastography/thromboelastometry versus standard practice of laboratory test-based care was also observed, but there was no significant difference in mortality between groups.[40]

Although thromboelastography has been the most frequently used technology in liver cirrhosis RCTs, as shown by recent meta-analyses of viscoelastic testing,[39,43] RCT evidence is also emerging for rotational thromboelastometry. Studies in other therapeutic areas have demonstrated correlation between parameters and clinical outcomes between viscoelastic testing devices,[44–46] and so it would be expected that studies in cirrhosis with comparable study designs conducted with other technologies would show similar results to those using thromboelastography. Nevertheless, since most of the available RCT data relate to thromboelastography, further studies with rotational thromboelastometry and other technologies are warranted.

Recent prospective studies in patients with liver disease have shown strong correlations between some thromboelastography parameters and the patient's coagulation profile.[47,48] The reduced use of allogeneic blood products has been shown to decrease the risk of complications associated with transfusion and may also reduce indirect and direct costs.[49,50] In a prospective observational trial, rotational thromboelastometry used to guide transfusion prior to invasive procedures in patients with cirrhosis reduced the use of platelets by 64%, with no significant effect on FFP transfusion.[51]

Blood management strategies to reduce the use of blood products have been shown to improve outcomes, such as morbidity, mortality, hospital stay, etc., in a variety of clinical settings.[52–56] Data from this meta-analysis suggest that the use of thromboelastography can similarly reduce blood product use and improve outcomes in patients with cirrhosis.

In the current meta-analysis, mortality at 7 days was significantly reduced in patients managed using

thromboelastography, while there was no statistically significant difference at the later time point (42 days). This appears to align with the concept that early period mortality in cirrhosis is more likely driven by rebleeding than later-period mortality. Of note, Tangcheewinsirikul et al. showed no effect on mortality; however, the authors investigated overall mortality rates instead of rates at a specific time point,[39] which may reflect the lack of an effect at later time points.

When comparing blood loss between individual studies in patients with cirrhosis, there was no significant difference between thromboelastography and standard practice in the management of patients with bleeding at Day 5 or post-Day 5 rebleeding. However, the results of one study[34] demonstrated a significant reduction in nonvariceal bleeding among patients managed with thromboelastography compared with the control. In this study, the authors report a significant reduction in rebleeding at Day 42 ($p = 0.012$; hazard ratio [95% CI]: 0.224 [0.062–0.805]) with thromboelastography compared with the control group.[34] Intraoperative massive transfusion is common in patients undergoing liver transplantation; the use of thromboelastography to determine the risk of hemorrhage can significantly reduce the use of unnecessary blood products.[57,58] In addition, assessment of fibrinolysis by thromboelastography in liver transplant recipients resulted in accurate prediction of early allograft dysfunction.[59]

Use of thromboelastography-guided treatment was associated with a significant reduction in the rate of serious transfusion-related reactions, particularly TRALI, compared with standard practice in one study.[33] As previously discussed, the reported TRALI rates in this study were higher than those generally reported in the literature, which is likely related to the disease state itself (i.e., end-stage liver disease). Data from the same study also demonstrated significantly shorter ICU stays; however, further data are needed to confirm these findings, as it was not clear from the paper whether there were any other factors in level of care that could explain the hospital discharge times. Furthermore, although the differences in reporting on AEs in the studies included in this meta-analysis meant no significant differences were found between the two treatment groups, when individual studies are directly compared, thromboelastography-guided management tended to be associated with a lower incidence of AEs.[12,34] In line with this, transfusion-related AEs were significantly reduced by VET-guided therapy in the meta-analysis by Tangcheewinsirikul et al.[39]

Together these data provide evidence that thromboelastography may be beneficial for monitoring and guiding treatment in patients with cirrhosis. It has been suggested that VET should be considered as an adjunct to conventional coagulation testing in order to provide a robust assessment of coagulation in patients undergoing liver surgery.[58,60]

However, it is important to note some limitations to this systematic review and meta-analysis. The present analysis was prospectively planned to be restricted to RCTs utilizing thromboelastography, and RCTs reporting data on the use of TEG 5000 and MonoTEM-A only were included in the analysis; therefore, the results cannot be assumed to be directly transferable to other devices. As thromboelastography has been introduced long before other viscoelastic technologies, and as it is to this day in many geographies the most commonly used VET to guide transfusion in patients with cirrhosis, it is overrepresented in the literature. The large majority of peer-reviewed studies, particularly RCTs, were conducted using thromboelastography and our searches identified only two RCTs[40,41] using rotational thromboelastometry with the ROTEM device. However, despite this, it is encouraging that the data presented herein are corroborated by other meta-analyses of RCTs and/or nonrandomized observational studies that included the limited data on rotational thromboelastometry, suggesting these findings may be applicable across comparable VET platforms.[39,40,43,61–64] With the publication of RCTs using a wider range of devices, the evidence landscape will evolve and warrant further analyses on this topic.

Further, in the present analysis, relatively few studies ($n = 5$) were identified that met the high RCT standard and specifically examined patients with cirrhosis, and data within these studies were reported heterogeneously. Consequently, meta-analyses for several outcomes are limited to a small number of studies. In particular, the finding in relation to the significant reduction in the use of cryoprecipitate for thromboelastography versus standard practice control was based on only one study reporting use of cryoprecipitate and should be interpreted with caution. Given that cryoprecipitate, along with fibrinogen, may be transfused when patient fibrinogen levels drop below 1 g/L, we expected this outcome measure might have been captured more regularly in studies. However, current guidelines suggest there are limited data for efficacy of cryoprecipitate in the liver setting,[28] which may explain why the majority of the studies did not report it as an outcome.

Conclusion

Our analysis suggests that the use of thromboelastography-guided therapy in patients with cirrhosis enhances PBM via decreasing the use of blood products, particularly platelets, without increasing the risk of bleeding while reducing early mortality. However, further studies, in particular RCTs, are needed and clear, evidence-based diagnostic and monitoring protocols and algorithms would help to support implementation of thromboelastography in specific clinical settings where patients with cirrhosis are at risk of bleeding complications.

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Conflict of Interest
J.H. and J.D.D are employees of Haemonetics Corporation. The remaining authors declare no further competing interests.

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