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ORIGINAL ARTICLE

Viscoelastic Testing Prior to Non-surgical Procedures Reduces Blood Product Use Without Increasing Bleeding Risk in Cirrhosis

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Abstract

Background/Aims Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM) analyze hemostatic function in patients with coagulopathy. We sought to quantify the impact of TEG and ROTEM-guided transfusion algorithms on blood product utilization in patients with cirrhosis undergoing non-surgical procedures.

Methods We performed a systematic review and meta-analysis on the utility of viscoelastic testing prior to non-surgical procedures to determine their impact on pre-procedural blood product use and post-procedural bleeding events. Studies comparing TEG or ROTEM-guided transfusions with standard-of-care (SOC) prior to non-surgical procedures in adult patients with cirrhosis were included. Primary outcomes were fresh frozen plasma (FFP) and platelet transfusion and secondary outcomes of post-procedure bleeding, transfusion-related complications, and mortality; and were reported as standardized mean differences (SMD) and risk ratios (RR).

Results Six studies (five randomized controlled trials and one cohort study) involving 367 patients met inclusion criteria. Compared with SOC, TEG/ROTEM-guided transfusions led to an overall decreased number of patients who received FFP transfusions (SMD = −0.93, 95% CI [−1.54, −0.33], $p < 0.001$) and platelets transfusions (SMD = −1.50, CI [−1.85, −1.15], $p < 0.001$). Total amount of FFP (SMD−0.86, $p < 0.001$) and platelet (SMD = −0.99, $p < 0.001$) transfused in the TEG/ROTEM group were also lower. Decreased pre-procedure transfusion in the TEG/ROTEM group did not result in increased post-procedure bleeding (RR = 0.61, $p = 0.09$) or in mortality (RR = 0.91, $p = 0.93$).

Conclusion In patients with cirrhosis, TEG or ROTEM significantly reduces blood product utilization prior to non-surgical procedures, with no increase in post-procedure bleeding or mortality. TEG and ROTEM utilization can promote high-value care and improve transfusion stewardship in this population.

Keywords Thromboelastography · Liver disease · Transfusion · International normalized ratio · Platelets

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Abbreviations

INR	International normalized ratio
TEG	Thromboelastography
ROTEM	Rotational thromboelastometry
SOC	Standard-of-care
FFP	Fresh frozen plasma
MELD	Model for End-stage Liver Disease

Introduction

Regulation of hemostasis in patients with chronic liver disease is complex. Current understanding of the underlying physiology has shown a tenuous "rebalancing" of anticoagulant and procoagulant activity [1, 2]. Traditional coagulation tests such as international normalized ratio (INR) and platelet count do not accurately predict bleeding

risk in patients with cirrhosis [3, 4]. Reliance on results of these tests may lead to overutilization of prophylactic blood products in patients with cirrhosis undergoing procedures [5, 6]. Nevertheless, in clinical practice, patients with cirrhosis continue to be transfused with blood products prior to invasive procedures in order to "correct" their abnormal coagulation tests.

Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) provide real-time, point-of-care assessments of in vivo hemostatic activity and help clinicians determine the need for specific blood product replacement. These tests provide rapid assessments of clot formation, strength, and stability. These properties are best reflected by the r time and maximum amplitude in TEG, and clotting time and maximum clot formation in ROTEM. Once these devices measure the aforementioned hemostatic properties of a blood sample, a graphical depiction is developed through computer systems analysis which provides a visual aid in diagnosing platelet function, clot formation, and fibrinolysis. The r time in TEG and clotting time in ROTEM determine the time to first fibrin formation. The maximum amplitude in TEG and maximum clot formation in ROTEM provide a summation of platelet number and function, and factor VIII and fibrinogen concentration. Alpha angles in both ROTEM and TEG determine the rate of fibrin clot formation. Normal values and ranges depend on whether an activator (of clot formation) is added to the whole blood sample, and which type of activator is used [7]. Due to fundamental differences in operating methods and differences in activators used, information extracted by these two technologies cannot be interchanged [8].

Both TEG and ROTEM are routinely used to optimize coagulation management and to guide blood product utilization during liver transplantation [2, 9]. However, these tests are rarely used in patients with liver disease outside the operating room [7, 10]. Several studies suggested that TEG- or ROTEM-guided transfusion algorithms reduced blood product utilization compared with standard-of-care (SOC) algorithms based on INR and platelet thresholds in patients with cirrhosis undergoing invasive procedures, and all reported similar outcomes [11–16]. However, these studies have included small numbers of patients and the procedures involved a wide range of bleeding risks and varied transfusion cut-offs though these differences were small. Given the growing interest in using viscoelastic testing in the per-procedural setting outside the surgical setting in cirrhosis patients, we aimed to systematically review and complete a meta-analysis on the utility of TEG and ROTEM prior to invasive, non-surgical procedures in patients with cirrhosis to determine the impact of viscoelastic testing on pre-procedural blood product use and post-procedure bleeding events. Risk of bleeding associated with these procedures was defined according to AASLD guidelines [17]

Materials and Methods

We report this systematic review and meta-analysis according to the Preferred Reported Items for Systematic Review and Meta-Analyses Statement (PRISMA) [18]. The protocol for this systematic review and meta-analysis was registered in the Prospero database with reference number ID: CRD42020205760 on 9/23/2020 [19].

Eligibility Criteria

We included randomized controlled trials (RCTs) and observational studies that evaluated the use of TEG or ROTEM compared to SOC in guiding transfusion of blood products including fresh frozen plasma (FFP) and platelets, prior to invasive, non-surgical procedures in patients with cirrhosis. Our study population included human subjects ≥ 18 years old with cirrhosis (based on clinical, laboratory, imaging or histological findings). Primary outcomes of interest included number of patients who received FFP or platelets and volume (mL) transfused. Secondary outcomes included post-procedure bleeding, transfusion-related complications, and mortality. We excluded studies that evaluated TEG or ROTEM prior to surgical procedures in patients with cirrhosis. Only full-text articles were included in our final analysis. The population of interest, intervention and comparison arms, as well as outcomes measured (PICO) are described in Supplementary Table 1.

Search Strategy

An experienced health sciences librarian conducted a systematic search of PubMed (NLM), EMBASE (Embase.com), CINAHL Complete (EBSCOhost), Scopus (Elsevier), Web of Science Core Collection (Thomson-Reuters), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (both Wiley), and ClinicalTrials.gov to identify articles up until February 1, 2021 related to the question whether viscoelastic testing reduces the need for blood products pre-procedurally in patients with cirrhosis.

Search terms included Medical Subject Headings (MeSH), and keywords (tagged as title/abstract) in PubMed, and translated to other databases using the Systematic Review Accelerator Polyglot tool and the searcher's discretion. Cited reference searching using six sentinel articles was conducted in Scopus to find articles that might have been missed because they were not indexed. To reduce bias, no filters were used. To reduce publication bias, both published (i.e., peer reviewed papers) as well as unpublished studies were considered in our initial search. To reduce language

bias, abstracts of articles in languages other than English were evaluated during the screening process. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, elaboration, and explanation [18].

A full description of the search strategy and complete list of search terms and limits used in each database are included in Supplementary Table 2. Citations were imported into EndNote X9 (Thomson Reuters, New York, NY) for deduplication.

Study Selection

Using a reference management system (EndNote X9, Clarivate Analytics), two reviewers (AS, JL) screened titles and abstracts independently for potential eligibility. Potentially eligible abstracts were then retrieved and screened in duplicate and discrepancies resolved by a third party (EBT). Only full-text articles were included in our final analysis. A total of 1447 eligible articles were identified. After 149 duplicates were removed, 1298 eligible records were screened. Of these, 1271 articles did not meet inclusion criteria by title and abstract alone, and the full-text articles of the remaining 27 titles were reviewed. Six studies (five RCT and one observational study) met inclusion criteria and were included in our final qualitative and quantitative synthesis. None of the included studies reported unpublished data. A PRISMA flowchart describing the exclusion criteria and the review process is shown in Fig. 1.

Data Extraction

The following variables were extracted from each study: study characteristics, patient characteristics and number of patients, severity of liver disease, SOC transfusion algorithm, and outcomes.

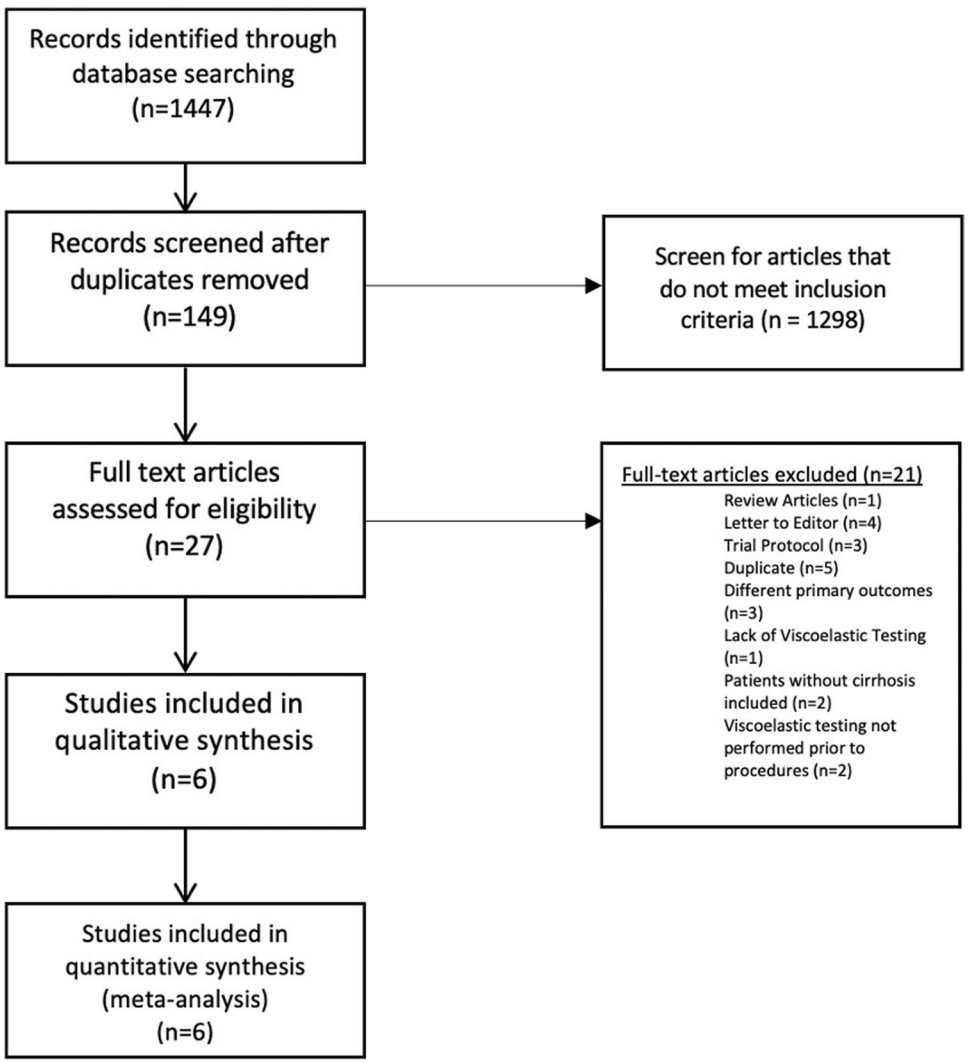

Fig. 1 Process of study selection

Statistical Analysis

Each study was analyzed separately to assess for differences in transfusions between groups. Primary outcomes included percent of patients transfused with either platelets or FFP and volume of platelets or FFP transfused in each arm. Secondary outcomes included transfusion-related adverse events, post-intervention bleeding (up to day 5), and mortality (4–6 weeks from procedure). Data were exported to STATA 16.1 (College Station, TX) for meta-analyses to provide a single estimate of pooled differences between treatment groups and effect size. Our meta-analyses were performed using a restricted maximum likelihood (REML) random-effects model [20]. Heterogeneity between studies was assessed using I^2. Treatment differences between groups for continuous and binary outcomes were calculated using standardized mean differences (SMD) and risk ratios (RR), respectively. A sensitivity analysis was not done due to the small number of studies and the small sample size, even among the high quality studies. Data unavailable from the publications were requested from the corresponding authors.

Results

Six studies (five RCTs and one observational study) involving a total of 367 patients (180 in TEG/ROTEM arm and 187 in SOC arm) met inclusion criteria (Table 2). All six studies were conducted as single-center studies, three in India, two in Italy, and one in Brazil. Four studies used TEG and two used ROTEM as the viscoelastic test. Both studies using ROTEM used the same device (ROTEM Delta, Tem Innovations GmbH, Munich, Germany) and had the same transfusion thresholds [11, 15]. Among the studies using TEG, two used a TEG5000 analyzer and two used a MonoTEM-A analyzer. Due to the inherent differences in the testing devices, transfusion thresholds differed between studies with different TEG devices in the intervention arm. Among the two studies that used the TEG5000 analyzer, De Pietri et al. used an r time > 40 min for FFP transfusion and maximum amplitude < 30 mm for platelet transfusion [12]. On the other hand, Kumar et al. used an r time > 10 min for FFP transfusion, maximum amplitude of < 55 mm for platelet transfusion, and an alpha angle of less than 45 degrees for cryoprecipitate transfusion [13]. Among the two studies that used MonoTEM-A, Rout et al. and Vuyurru et al. had similar transfusion thresholds for both platelet transfusion based on maximum amplitude and FFP transfusion based on r time [14, 16]. The thresholds for transfusion of FFP and platelets in the SOC arm were the same in all six studies (Table 1). Liver disease severity varied across the studies with median model for end-stage liver disease (MELD) scores ranging from 13 to 31 with similar MELD scores in the two arms in four studies and a trend toward higher MELD scores in the intervention arm compared with SOC arm in two studies [11, 15].

Two studies involved high-risk endoscopy procedures for control of non-variceal gastrointestinal bleeding [13] and banding for variceal bleeding [14]. One study involved mostly high-risk procedures including percutaneous liver biopsy (82.7% of procedures), transjugular intrahepatic portosystemic shunt placement, transarterial chemoembolization for hepatocellular carcinoma, and biliary sphincterotomy [16]. Two studies involved procedures with a range of bleeding risks including low-risk procedures such as paracentesis and thoracentesis as well as high-risk procedures such as percutaneous liver biopsy, radiofrequency ablation and transarterial chemoembolization for hepatocellular carcinoma [11, 12]. One study included only cardiovascular procedures, namely central venous catheterization with low bleeding risk [15]. Bleeding risks by procedure are listed in Supplementary Table 4.

Impact of TEG/ROTEM on FFP and Platelets Transfusion

All six studies showed significantly less FFP, and platelets transfused when TEG/ROTEM was utilized in a transfusion algorithm prior to an invasive non-surgical procedure compared with SOC (Table 2) [11–16]. Compared with SOC, TEG/ROTEM guided-transfusions led to an overall decreased number of patients who received FFP transfusions (SMD = −0.93, 95% CI[−1.54, −0.33], $p < 0.001$) ($I^2 = 71.72\%$, $p < 0.001$) and platelets transfusions (SMD = −1.50, CI[−1.85, −1.15], $p < 0.001$) ($I^2 = 0\%$, $p = 0.42$) (Fig. 2), and a lower total amount of FFP (SMD−0.86, 95% CI[−1.21, −0.50]), $p < 0.001$) ($I^2 = 8.95\%$, $p = 0.36$) and platelet (SMD = −0.99, 95% CI[−1.44, −0.53], $p < 0.001$) ($I^2 = 36.35\%$, $p = 0.23$) transfused (Supplementary Fig. 2). Kumar et al. included patients who received platelets, FFP as well as cryoprecipitate, and showed statistically significant decreases in transfusions compared to SOC. As this study included transfusions of three types of blood products for each patient, we included all patients in our analyses of FFP and platelet transfusion [13]. Only one other study analyzed differences in cryoprecipitate transfusion with no differences between the two arms [15]. The number of patients who received FFP and platelet transfusions across the studies is detailed in Table 2. In addition, our meta-analysis was performed in only a subgroup of studies based on availability of data for each particular outcome. For example, three studies included in our review [11, 15, 16] did not include total amount in mL of blood product transfused in their data and analysis on this particular outcome was excluded.

Table 1 Study characteristics

Study design	Country	Author	Timeline	Intervention	SOC (Transfusion threshold)	Procedure Type	MELD intervention vs. SOC	Outcomes measured (Blood product use)	Outcomes measured (Post-Procedural bleeding with definitions)	Outcomes measured (Mortality)
RCT	Italy	De Pietri [12]	2011–2014	TEG	INR > 1.8 PLT ≤ 50	Varied Low and High risk	21 vs. 20	Total FFP, PLT transfusion	Post-Procedural Bleeding Event (WHO score)	Yes (90-day)
RCT	India	Kumar [13]	2016–2018	TEG	INR > 1.8 PLT ≤ 50	EGD for non-variceal bleeding (high risk)	23 vs. 21	FFP Transfusion	Major Bleeding Event (Re-Bleeding from Esophageal Varices)	Yes (6-weeks)
RCT	Brazil	Rocha [15]	2014–2016	ROTEM vs. SOC vs. Restrictive (INR > 5.0, PLT ≤ 25)	INR > 1.5 PLT ≤ 50	CVC (low risk)	31 vs. 24	Transfusion of any blood product prior to CVC insertion	Major Bleeding Events (ISTH, WHO score)	Yes (4 weeks)
RCT	India	Rout [14]	2017	TEG	INR > 1.8 PLT ≤ 50	EGD for varices (high risk)	14 vs. 16.5	Total FFP, PLT Transfusion	Major Bleeding Event (Re-Bleeding from Esophageal Varices)	Yes (6 weeks)
RCT	India	Vuyurru [16]	2017–2019	TEG	INR > 1.8 PLT ≤ 50	Varied High risk	14 vs. 13	Total FFP, PLT Transfusion	Bleeding events (Common Terminology Criteria for Adverse Events (CTCEA) from Grade 1–5 along with Hemoglobin reduction/clinical parameters)	Yes (4 weeks)
RS	Italy	Debernardi [11]	N/A	ROTEM	INR > 1.8 PLT ≤ 50	Varied Low and High Risk	20.6 vs. 14	PLT, FFP Transfusion	Post-Procedural Hemorrhagic Events (Hematoma, Hematemesis with reduction in Hemoglobin levels at least 1 g/dL)	N/A

RCT: Randomized Control Trial, *RS*: Retrospective Study, *TEG*: Thromboelastography, *ROTEM*: Rotational Thromboelastometry, *SOC*: Standard-of-Care, *MELD*: Model for end-stage liver disease, *CVC*: Central venous catheterization, *FFP*: Fresh Frozen Plasma, *INR*: International normalized ratio, *PLT*: Platelets; N/A: not available

Table 2 Number of patients who received blood products in the intervention and standard-of-care groups

Study	Intervention/SOC	Platelet transfused	FFP transfused	Both PLT/FFP Transfused
De Pietri	TEG, $n=30$	2 (6.7)	0 (0)	3 (10)
	SOC, $n=30$	10 (33.3)	16 (53.3)	4 (13.3)
Kumar	TEG, $n=40$	13 (26.5)	13 (26.5)	7 (14.3)
	SOC, $n=47$	41 (87.2)	41 (87.2)	0 (0)
Rocha	TEG, $n=19$	0 (0)	8 (42.1)	N/A
	SOC, $n=19$	8 (42.1)	13 (68.4)	N/A
Rout	TEG, $n=30$	0 (0)	1 (3.3)	3 (10)
	SOC, $n=30$	16 (53.3)	9 (30)	5 (16.7)
Vuyurru	TEG, $n=29$	2 (6.9)	6 (20.7)	1 (3.4)
	SOC, n-29	21 (72.4)	7 (24.1)	1 (3.4)
Debernardi	ROTEM, $n=32$	9 (28)	12 (37.5)	N/A
	SOC, $n=32$	25 (78)	18 (56)	N/A

TEG: Thromboelastography, *ROTEM*: Rotational Thromboelastometry, *SOC*: Standard-of-Care, *FFP*: Fresh Frozen Plasma, *PLT*: Platelets; *N/A*: not available

Bleeding Events Post-Procedure

Post-procedure bleeding was reported in five studies (Supplementary Table 5). Bleeding events were rare, regardless of the transfusion strategy used. Two studies encountered no bleeding events in the intervention arm compared to 1 of 30 and 2 of 19 in the SOC arms [12, 15]. Three studies showed fewer bleeding events in the TEG/ROTEM arms compared to SOC arms [11, 13, 14]. Pooled analysis showed no significant increase in bleeding events in the intervention arm (RR = 0.61 (log RR = −0.49) 95%CI [−1.08, 0.09], $p=0.09$) ($I^2=0\%$, $p=0.78$). Patients in the study by Kumar et al. inherently had an increased risk of post-procedure bleeding as they presented with non-variceal GI bleeding; however, there was no significant increase in bleeding events in the TEG arm compared with the SOC arm despite significantly decreased transfusions in the TEG arm [13].

Transfusion-Related Adverse Events

Four studies reported transfusion-related adverse events including allergic reactions, urticaria, transfusion-related acute lung injury, transfusion-associated circulatory overload, and acute respiratory distress syndrome (Supplementary Table 3) [12–15]. On meta-analysis, the patients in the SOC group were more likely to have transfusion-related adverse events than the TEG/ROTEM arm (RR = 1.84 (log RR = −0.87) 95% CI [−1.31, −0.43], $p<0.001$) ($I^2=0\%$, $p=0.93$). Adverse events were overall rare across studies and the majority of adverse events (79.92%) came from one study [13]. The patients in that study did not have higher MELD compared to other studies included in our analysis, but majority of the patients were transfused with all three blood products; platelets, FFP, and cryoprecipitate. Among those that had adverse events in this study, serious transfusion-related reactions were significantly less in the TEG group (30.6%) compared with SOC (74.5%). Transfusion-related acute lung injury and acute respiratory distress syndrome were also significantly less frequent in the TEG group (12.2%) compared with the SOC group (48.9%).

Mortality

Mortality was explored in five RCT's (Supplementary Table 5). Two studies evaluated 4-week mortality and two evaluated 6-week mortality. De Pietri et al. evaluated 90-day mortality, and because this has different implications compared to 4–6 week mortality, this study was not included in our mortality analysis. Of the four studies analyzed, mortality in the TEG/ROTEM group was similar to the SOC group (RR = 0.91, (log RR −0.09) 95% CI [−1.02, 0.82], $p=0.84$) ($I^2=69.12\%$, $p=0.05$).

Methodological Quality, Risk of Bias Assessment, and Publication Bias

We used a Cochrane Risk of Bias 2 tool (RoB 2) to assess the methodological quality of the five RCTs. For each trial, we judged articles as having high, unclear, or low risk of bias for the following domains: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. If one domain was classified as high risk of bias, the overall risk of bias was regarded as high. If at least one of the domains was classified as unclear without any domain regarded as high risk, the overall risk of bias was classified as unclear. The overall methodological quality of the

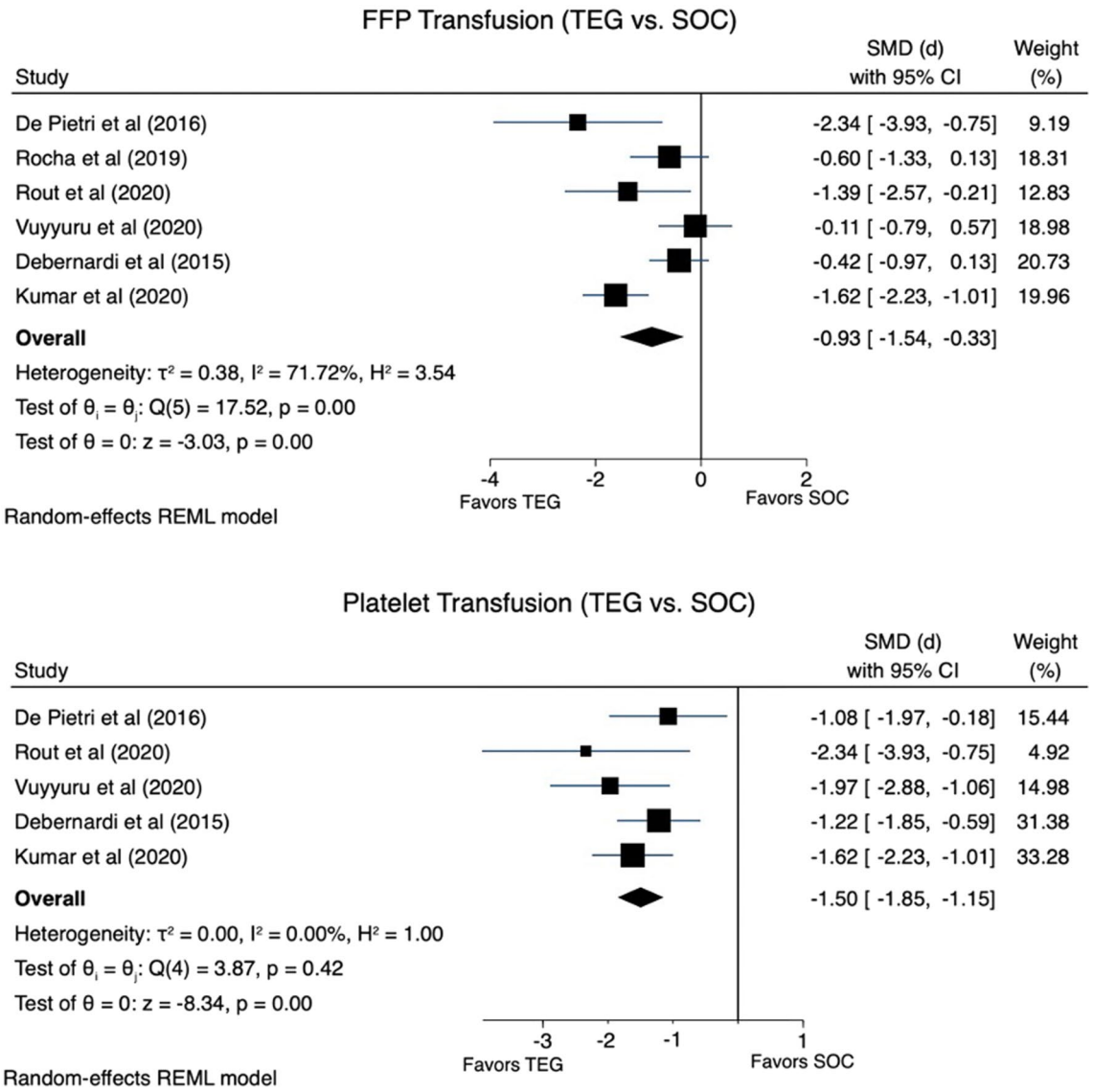

Fig. 2 Forest plots of primary outcomes of FFP and PLT transfusion, Key: FFP: Fresh Frozen Plasma, PLT: Platelets, TEG: Thromboelastography

studies was moderate (Supplementary Table 3). Among the five RCTs, only one had overall low risk of bias [13]. Random sequence generation was adequately reported in all five RCTs, allocation concealment in four studies, [13–16] and blinding of group allocation, personnel, and outcome measures in three studies [12, 13, 15]. For the sole retrospective study analyzed, we utilized the Newcastle–Ottawa scale and generated a score of 7 out of 9 with regard to quality for this non-randomized study with points deducted primarily for follow-up length and adequacy [11, 21]. Of note, two out of the five RCT's included in our analysis were not blinded. These two studies and the sixth study which was observational are prone to bias, especially in the setting of relatively small sample sizes [14, 16].

A funnel plot for asymmetry and Egger's test for publication bias is shown in Supplementary Fig. 1A and B though we recognize given the small number of studies in our review, this is significantly underpowered.

Discussion

Coagulation in Cirrhosis and the Role of Viscoelastic Testing

Patients with cirrhosis have low platelet count due to decreased thrombopoietin and hypersplenism, and elevated INR primarily due to impaired synthesis and clearance of

pre-vitamin K activated coagulation and clotting factors among other reasons [22–24] They are frequently perceived to have increased risk of bleeding, and prophylactic transfusion of platelets and FFP is often given to these patients to correct the abnormal platelet count and INR test results prior to invasive procedures. However, cirrhosis is also associated with thrombosis and a "rebalanced" hemostatic system with changes in both pro-coagulant and anti-coagulant properties [1] This "rebalanced" system leads to an increased risk of thrombosis including deep venous thrombosis, portal venous thrombosis, and pulmonary embolism together with an increased risk of spontaneous and procedure-related bleeding. This state of coagulation makes clinical decision making on bleeding risk challenging in this patient population. Real-time assessment of hemostatic activity with viscoelastic testing helps take into account not just number of platelets and concentration of clotting factors but their function and other components of the hemostatic system such as fibrinolysis, providing more accurate information on the balance between pro- and anti- coagulation to guide the need and type of blood products in patients with cirrhosis undergoing surgery or other invasive procedures.

Viscoelastic testing such as TEG and ROTEM are widely used during liver transplantation surgery and have been shown to decrease overall blood product utilization without increasing bleeding events and improves management of hemostasis [2, 9, 25–27]. However, TEG and ROTEM are seldom used outside of liver transplantation surgery, and hepatology practice continues to be burdened by an overuse of blood products [28]. Blood transfusion stewardship has major benefits including improved patient safety, decreased hospital expenditures, and appropriate resource allocation [29]. This systematic review and meta-analysis demonstrates that patients with cirrhosis monitored by viscoelastic testing—TEG or ROTEM—prior to non-surgical procedures received less blood products including FFP and platelets, without increased risk of bleeding, and possibly decreased transfusion-related adverse events.

Central Findings

Our work illustrates that across the studies analyzed, there was a significant decrease in both FFP and platelet transfusions in patients who underwent viscoelastic testing prior to non-surgical procedures compared to those who did not. The latter patients, managed per SOC, received FFP or platelet transfusion based on pre-determined threshold for INR or platelet count. In the TEG/ROTEM arm, 14.4% (26/180) patients and 22.2% (40/180) patients required platelets and FFP transfusions, respectively, compared with 64.7% (121/187) and 55.6% (104/187) in the SOC arm. Our findings extend to not only number of patients who received transfusions but also the amount of FFP and platelets transfused per patient.

These findings are consistent with the current literature on the benefits of viscoelastic testing in cirrhosis patients undergoing cardiac surgery and liver transplantation [25, 30–33]. Current guidelines by the American Gastroenterological Association and American Association for the Study of Liver Diseases do not recommend routine prophylactic transfusions for low-risk non-surgical procedures in patients with cirrhosis and concur that there may be a future role for global tests of clot formation such as ROTEM and TEG to evaluate pre-procedure hemostatic activity [4, 17].

Our analysis showed no significant increase in bleeding events in the TEG/ROTEM arm, despite decreased prophylactic transfusions. The rarity of bleeding events, regardless of transfusion strategy utilized, further supports that transfusions for arbitrary coagulation marker thresholds may not be necessary and may not prevent the rare bleeding due to direct vessel puncture rather than the patient's state of hemostasis or traditional markers of coagulation [34]. In addition, there were fewer transfusion-related adverse events including acute lung injury in the TEG/ROTEM group, though a majority of the adverse events were from one study [13]. Our study did not show a difference in mortality between groups, a finding also seen with recent reviews and meta-analyses that evaluated mortality as an outcome in cardiac and liver surgery patients comparing viscoelastic testing and SOC, though not all patients in these studies had cirrhosis [31, 35].

Contextual Factors

Our study extends the literature with a systematic review and meta-analysis covering both TEG and ROTEM, focusing exclusively on non-surgical procedures in patients in cirrhosis. A recent review evaluating the impact of viscoelastic testing in cirrhosis included studies on patients undergoing liver transplantation [36]. There are several limitations to our study. First, our study combined results of four studies that used two different TEG analyzers and two studies that used ROTEM and had similar but not identical cut-offs for transfusion in the viscoelastic testing arm. Thus, firm recommendations cannot be made on cut-offs in TEG/ROTEM regarding when to transfuse. As seen in these differences, there remains a relative lack of standardization in viscoelastic testing practice with regard to transfusion parameters. However, all of these viscoelastic tests measured the same coagulation parameters: time to first fibrin formation, rate of fibrin clot formation, and summation of platelet, factor function, and fibrinogen. In addition, we acknowledge that SOC arms in some studies included in our analysis transfused patients in excess of modern guidance. Regardless, there were significantly fewer transfusions overall in the viscoelastic testing arm. Second, a variety of procedures were

performed across the studies though all were non-surgical and the bleeding risks of the procedures in the intervention and SOC arms in each study were balanced [13, 15]. Third, studies included in our analysis were small and though appropriately powered to detect significant differences in transfusion, were not powered to examine secondary outcomes of transfusion-related adverse events. These studies also excluded certain confounding factors that have been shown to increase risk of bleeding in patients with cirrhosis, including acute kidney injury and sepsis [17]. Fourth, we did not conduct a cost analysis though the cost savings in transfusions are expected to more than balance the cost of the TEG or ROTEM tests. Fifth, there are inherent limitations with viscoelastic testing itself. Viscoelastic testing does not fully reflect in vivo hemostasis given the lack of measurement of the protein C pathway and interactions with von Willebrand factor. Sixth, the patients across all studies were decompensated and our findings may not be extrapolated to patients with compensated cirrhosis. Seventh, there remains a relative lack of standardization in viscoelastic testing practice and in transfusion parameters. As noted in our review, there were slightly varied transfusion parameters in the viscoelastic testing arm, similar to varied transfusion practice differences seen in the SOC arm. Finally, we limited our study selection to include only full text, published articles given the need for comprehensive results and detailed methodology, omitting abstracts that may have met inclusion criteria otherwise.

Conclusion

Our systematic review showed that viscoelastic testing using TEG or ROTEM improved transfusion stewardship in cirrhosis patients undergoing non-surgical procedures. However, TEG and ROTEM are not widely available, and performance of the tests and interpretation of the results require training. Confirmation of the benefits of viscoelastic tests in non-surgical settings in large, randomized trials with stratification for bleeding risk may promote widespread adoption of these tests as high-value care in patients with cirrhosis. Until this has been accomplished and its efficacy confirmed, these tests should be limited to liver centers experienced in the use of these tests.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-021-07376-6.

Author's contribution All authors AS, JL, CS, EBT, ASL, approve the final version of the submitted manuscript.

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Declarations

Conflict of interest AS, JL, CS and ASL report no conflicts of interest. Elliot Tapper reports grant funding from Gilead and Bausch, consulted for Kaleido, Axcella, Novo Nordisk, Novartis and Allergan, and has served on advisory boards for Bausch and Mallinckrodt.

References

1. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood.* 2010;116:878–885.
2. Blasi A, Beltran J, Pereira A, Martinez-Palli G, Torrents A, Balust J et al. An assessment of thromboelastometry to monitor blood coagulation and guide transfusion support in liver transplantation. *Transfusion.* 2012;52:1989–1998.
3. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol.* 2013;11:1064–1074.
4. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology. 2019;157:34-43 e1.
5. Intagliata NM, Henry ZH, Shah N, Lisman T, Caldwell SH, Northup PG. Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. *Liver Int.* 2014;34:26–32.
6. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol. 2006;101:1524–8; quiz 680.
7. Davis JPE, Northup PG, Caldwell SH, Intagliata NM. Viscoelastic Testing in Liver Disease. *Ann Hepatol.* 2018;17:205–213.
8. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol.* 2014;89:228–232.
9. Coakley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. *J Cardiothorac Vasc Anesth.* 2006;20:548–553.
10. Fatourou EM, Tsochatzis EA. Transfusion strategies in patients with cirrhosis: less is more. *Liver Int.* 2016;36:503–504.
11. Debernardi Venon W, Ponzo P, Sacco M, Mengozzi G, Raso S, Valpreda A et al. Usefulness of thromboelastometry in predicting the risk of bleeding in cirrhotics who undergo invasive procedures. *Eur J Gastroenterol Hepatol.* 2015;27:1313–1319.
12. De Pietri L, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. *Hepatology.* 2016;63:566–573.
13. Kumar M, Ahmad J, Maiwall R, Choudhury A, Bajpai M, Mitra LG et al. Thromboelastography-Guided Blood Component Use in Patients With Cirrhosis With Nonvariceal Bleeding: A Randomized Controlled Trial. *Hepatology.* 2020;71:235–246.
14. Rout G, Shalimar, Gunjan D, Mahapatra SJ, Kedia S, Garg PK, et al. Thromboelastography-guided Blood Product Transfusion in Cirrhosis Patients With Variceal Bleeding: A Randomized Controlled Trial. J Clin Gastroenterol. 2020;54:255–62.
15. Rocha LL, Neto AS, Pessoa CMS, Almeida MD, Juffermans NP, Crochemore T et al. Comparison of three transfusion protocols prior to central venous catheterization in patients with

cirrhosis: A randomized controlled trial. *J Thromb Haemost.* 2020;18:560–570.
16. Vuyyuru SK, Singh AD, Gamanagatti SR, Rout G, Gunjan D, Shalimar. A Randomized Control Trial of Thromboelastography-Guided Transfusion in Cirrhosis for High-Risk Invasive Liver-Related Procedures. Dig Dis Sci. 2020;65:2104–11.
17. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2020.
18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.
19. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev.* 2012;1:2.
20. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods.* 2019;10:83–98.
21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25:603–605.
22. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med.* 2011;365:147–156.
23. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology.* 2005;41:553–558.
24. Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology.* 2009;137:2105–2111.
25. Kang Y. Thromboelastography in liver transplantation. *Semin Thromb Hemost.* 1995;21:34–44.
26. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesth Analg.* 1985;64:888–896.
27. Wang SC, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. *Transplant Proc.* 2010;42:2590–2593.
28. Rahimi RS, O'Leary JG. Transfusing common sense instead of blood products into coagulation testing in patients with cirrhosis: Overtreatment not equal safety. *Hepatology.* 2016;63:368–370.
29. Desai AP, Mohan P, Nokes B, Sheth D, Knapp S, Boustani M et al. Increasing Economic Burden in Hospitalized Patients With Cirrhosis: Analysis of a National Database. *Clin Transl Gastroenterol.* 2019;10:e00062.
30. Meco M, Montisci A, Giustiniano E, Greco M, Pappalardo F, Mammana L et al. Viscoelastic Blood Tests Use in Adult Cardiac Surgery: Meta-Analysis, Meta-Regression, and Trial Sequential Analysis. *J Cardiothorac Vasc Anesth.* 2020;34:119–127.
31. Dias JD, Sauaia A, Achneck HE, Hartmann J, Moore EE. Thromboelastography-guided therapy improves patient blood management and certain clinical outcomes in elective cardiac and liver surgery and emergency resuscitation: A systematic review and analysis. *J Thromb Haemost.* 2019;17:984–994.
32. Hawkins RB, Raymond SL, Hartjes T, Efron PA, Larson SD, Andreoni KA et al. Review: The Perioperative Use of Thromboelastography for Liver Transplant Patients. *Transplant Proc.* 2018;50:3552–3558.
33. Mallett SV, Chowdary P, Burroughs AK. Clinical utility of viscoelastic tests of coagulation in patients with liver disease. *Liver Int.* 2013;33:961–974.
34. Shen L, Tabaie S, Ivascu N. Viscoelastic testing inside and beyond the operating room. *J Thorac Dis.* 2017;9:S299–S308.
35. Li C, Zhao Q, Yang K, Jiang L, Yu J. Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. *J Thorac Dis.* 2019;11:1170–1181.
36. Wei H, Child LJ. Clinical utility of viscoelastic testing in chronic liver disease: A systematic review. *World J Hepatol.* 2020;12:1115–1127.