OBSERVATIONAL STUDY

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Thromboelastography-Guided Correction of Coagulopathy Before Tunneled Central Venous Access in Critically Ill Patients With Liver Disease: A Propensity Score-Matched Study

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IMPORTANCE: Optimal blood product transfusion strategies before tunneled central venous catheter (CVC) placement are required in critically ill coagulopathic patients with liver disease to reduce exposure to allogeneic blood products and mitigate bleeding and thrombotic complications.

OBJECTIVES: This study evaluated the safety and efficacy of a thromboelastography-guided transfusion strategy for the correction of coagulopathy in patients with liver disease compared with a conventional transfusion strategy (using international normalized ratio, platelet count, and fibrinogen) before tunneled CVC insertion.

DESIGN, SETTING, AND PARTICIPANTS: A retrospective propensity score-matched single-center cohort study was conducted at a quaternary care academic medical center involving 364 patients with liver disease (cirrhosis and acute liver failure) who underwent tunneled CVC insertion in the ICU. Patients were stratified into two groups based on whether they received blood product transfusions based on a thromboelastography-guided or conventional transfusion strategy.

MAIN OUTCOMES AND MEASURES: Primary outcomes that were evaluated included the volume, units and cost of blood products (fresh frozen plasma, cryoprecipitate, and platelets) when using a thromboelastography-guided or conventional approach to blood transfusions. Secondary outcomes included the frequency of procedure-related bleeding and thrombotic complications.

RESULTS: The total number of units/volume/cost of fresh frozen plasma (12 U/3,000 mL/$684 vs. 32 U/7,500 mL/$1,824 [$p = 0.019$]), cryoprecipitate (60 U/1,500 mL/$3,240 vs. 250 U/6,250 mL/$13,500 [$p < 0.001$]), and platelets (5 U/1,500 mL/$2,610 vs. 13 units/3,900 mL/$6,786 [$p = 0.046$]) transfused were significantly lower in the thromboelastography-guided transfusion group than in the conventional transfusion group. No differences in the frequency of bleeding/thrombotic events were observed between the two groups.

CONCLUSIONS AND RELEVANCE: A thromboelastography-guided transfusion strategy for correction of coagulopathy in critically ill patients with liver disease before tunneled CVC insertion, compared with a conventional transfusion strategy, reduces unnecessary exposure to allogeneic blood products and associated costs without increasing the risk for peri-procedural bleeding and thrombotic complications.

KEYWORDS: central venous catheters; critical illness; hemostasis; liver diseases; thromboelastography

Patients with liver dysfunction exhibit an imbalance of pro-coagulant and anti-coagulant clotting factors (1), which places them at risk for both bleeding and thrombotic complications (2). Critically ill patients with

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KEY POINTS

Question: We hypothesized that a thromboelastography-guided transfusion strategy in critically ill coagulopathic patients with liver disease before tunneled central venous catheter (CVC) insertion, compared with a conventional transfusion strategy, will lead to more judicious blood product transfusions.

Findings: This retrospective matched cohort study involving 364 critically ill patients with liver disease demonstrated that the total units of fresh frozen plasma/cryoprecipitate/platelets transfused before tunneled CVC insertion were significantly lower in the thromboelastography-guided transfusion group than in the conventional transfusion group.

Meanings: A thromboelastography-guided transfusion strategy before tunneled CVC placement in patients with liver disease represents a promising strategy to reduce unnecessary blood product transfusions.

liver disease, particularly those with prolonged hospitalizations, may require the placement of tunneled central venous catheters (CVCs), including tunneled hemodialysis catheters (TDCs), for a variety of purposes including vasoactive drug administration, parenteral nutrition, specific hepatic procedures such as trans-jugular liver biopsies, as well as kidney replacement therapy as a bridge to eventual liver transplantation (3). Procedure-related bleeding represents a significant complication associated with CVC insertion and a recent prospective, multicenter cohort study demonstrated that the frequency of bleeding complications with the placement of CVCs in patients with liver disease was approximately 6.7% (4). In contrast, in noncirrhotic patients, bleeding complications with insertion of CVCs are reported in less than 2% of cases (5). Furthermore, a randomized controlled trial (RCT) showed that in patients with severe thrombocytopenia, the bleeding risk with the use of tunneled catheters was higher as compared with nontunneled catheters (15.0% vs. 3.6%) (6). Consequently, critical care physicians often empirically transfuse blood products in patients with liver disease to correct coagulopathy before invasive procedures (7).

However, the indiscriminate transfusion of allogenic blood products to correct coagulopathy in patients with liver disease before tunneled CVC placement in an attempt to prevent bleeding complications may have an adverse impact on patient clinical outcomes. Certain consequences of blood transfusions, such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and allergic reactions, may complicate the clinical course of patients (8) with considerable financial impact on the healthcare system (9). The judicious use of blood product transfusions becomes even more significant in patients with liver disease since the dynamic nature of the coagulation state of patients with liver disease means that even minor physiologic insults can incite hemostatic pathology, leading to hemorrhagic and thrombotic complications (10). Although patients with liver disease frequently have thrombocytopenia as well as prolonged prothrombin time (PT), activated partial thromboplastin time (PTT), and international normalized ratio (INR), these traditional tests for hemostasis have not been shown to successfully predict bleeding risk in these patients (11) since they only represent the decreased prothrombotic clotting factors and do not necessarily depict the fragile equilibrium within the coagulation cascade (12).

Thromboelastography offers a more comprehensive assessment of a patient's coagulation status as it provides information on dynamics of clot development, stabilization, and eventual dissolution along with qualitative information regarding platelet function. Thromboelastography utilization has increased within the field of liver transplantation (13, 14) and has been recommended by the Society of Critical Care Medicine in their guidelines for the management of adult acute and acute-on-chronic liver failure in the ICU (15). This is because multiple RCTs have explored the use of thromboelastography for correcting coagulopathy in liver disease with a clear trend toward lower use of blood products in patients who were managed with thromboelastography (14, 16–19).

For instance, in a single-center RCT by Wang et al (14) involving 28 patients undergoing liver transplantation, patients in the thromboelastography group received half as much fresh frozen plasma (FFP) on average, and there was a trend toward less blood loss in the thromboelastography group demonstrating

that a thromboelastography-based transfusion strategy can be safe and potentially beneficial in a group of patients undergoing a major hemostatic challenge such as liver surgery. A larger RCT (16) involving 96 patients with cirrhosis and nonvariceal gastrointestinal bleeding also showed that patients in the thromboelastography arm received fewer of every type of blood product (FFP, cryoprecipitate, and platelets) than those in the conventional coagulation test arm. Furthermore, patients in the thromboelastography arm were significantly less likely to experience any transfusion-related complications, including TACO and TRALI ($p < 0.001$). Similarly, Rout et al (17) assessed the use of thromboelastography in patients with variceal hemorrhage and showed that patients randomized to the thromboelastography arm received fewer blood products, whereas the patients in the conventional transfusion group had an increased risk of rebleeding, potentially as a consequence of TACO with frequent blood transfusions causing increased portal venous pressures. In addition, other RCTs (18, 19) have demonstrated that in patients with cirrhosis and significant coagulopathy, a thromboelastography-guided transfusion strategy before invasive procedures (including central venous cannulation, paracentesis, percutaneous liver biopsies, endoscopic retrograde cholangiopancreatography, and endoscopic variceal banding) leads to a significantly lower utilization of blood products compared with a conventional transfusion strategy (guided by INR and platelet count), without an increase in bleeding complications.

Despite this growing body of literature, the implementation of thromboelastography-guided transfusion strategies in critically ill patients with liver disease has been hampered by the lack of consensus regarding the precise thresholds to be used to guide blood transfusions. Therefore, there is a distinct need to define optimal peri-procedural transfusion strategies in patients with liver disease in the ICU, to not only reduce exposure to allogenic blood products, but also mitigate bleeding/thrombotic complications related to the insertion of tunneled CVCs. The objective of our study was to assess the safety and efficacy of a pre-procedural thromboelastography-directed transfusion strategy for the correction of coagulopathy in patients with liver disease before the establishment of tunneled central venous access.

PATIENTS AND METHODS

Study Design and Outcomes

This was a retrospective propensity-matched single-center cohort study conducted at the Cleveland Clinic in Cleveland, OH. The study was conducted according to the guidelines of the 1975 Declaration of Helsinki and approved by the Institutional Review Board of the Cleveland Clinic (Reference Number 21-200) on June 3, 2021. The study protocol was titled "Thromboelastography guided correction of coagulopathy prior to tunneled central venous access in critically-ill patients with liver disease" and the protocol was exempted from the requirement for informed consent from patients since only de-identified data collected during hospital visits were included in the study.

The primary objective of this study was to evaluate the effects of a thromboelastography-guided transfusion strategy in patients with liver disease before tunneled CVC insertion. Primary outcomes that were evaluated included the volume, units, and cost of blood products (FFP, cryoprecipitate, and platelets) when using a thromboelastography-guided or conventional approach to blood transfusions. The thromboelastography-guided transfusion strategy was defined as the following: reaction time of greater than 15 minutes (normal range: 4–10 min), alpha-angle of less than 45 degrees (normal range: 47–74 degrees), and/or maximum amplitude (MA) of less than 30 mm (normal range: 51–75 mm) received FFP at a dose of 10 mL/kg of ideal body weight, 10 units of cryoprecipitate, and/or one platelet apheresis transfusion (i.e., the equivalent of six or more units of platelets from whole blood, $3–6 \times 10^{11}$ platelets), respectively—which was similar to transfusion thresholds used for correction of thromboelastography parameters in patients undergoing liver transplantation (20). On the other hand, the conventional transfusion strategy was considered to be our own institutional algorithm defined as the following: patients with an INR greater than 2.0, fibrinogen level of less than 100 mg/dL, and/or platelet count of less than 20 K/L received FFP at a dose of 10 mL/kg of ideal body weight, 10 units of cryoprecipitate, and/or one platelet apheresis transfusion, respectively. This institutional algorithm approximates recommendations from the 2019 Society of Interventional Radiology consensus guidelines for low-bleeding-risk procedures in patients with an "inherently high risk for

bleeding" (correct INR to within range of 2.0–3.0 or less, consider platelet transfusion if platelet count is < 20×10^9/L) (21).

Secondary outcomes included the frequency of procedure-related bleeding complications and catheter-related thrombosis/occlusion. Procedure-related clinically significant bleeding was defined as any bleeding causing hemodynamic instability, requiring blood transfusions or minor interventions such as placement of sutures or prolonged external compression at the catheter exit-site for greater than 20 minutes within 24 hours of tunneled CVC insertion (22), whereas catheter-related thrombosis was recorded as any thrombotic or catheter occlusion event that occurred within 30 days of tunneled CVC insertion. Details regarding the adjudication of clinically significant procedure-related bleeding and thrombotic events are discussed in the "data acquisition" section of the methods.

Patient Population and Selection Criteria

We performed a retrospective chart review to identify all adult patients in the ICU with liver disease who underwent tunneled CVC placement, including TDC placement, between January 2020 and July 2021 at the Cleveland Clinic with thromboelastography-guided transfusion therapy before the procedure. To identify our control group of patients, we conducted a retrospective chart review of critically ill patients who underwent tunneled CVC insertion with pre-procedural transfusion therapy according to a conventional strategy between December 2014 and December 2020 at the Cleveland Clinic. Patients included in our analysis included those with acute liver failure, defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥ 1.5) in a patient without cirrhosis or preexisting liver disease, as well as patients with histologic or radiologic evidence of cirrhosis of any etiology, with or without evidence of decompensation, including variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, hepatorenal syndrome, or hepatopulmonary syndrome. Patients meeting the following criteria were excluded from the analysis: ongoing bleeding from a current peripheral or central venous access; previous or current thrombotic events defined as any documented blood clot in a vein or artery; and use of antiplatelet or oral anticoagulant therapy within 7 days of tunneled CVC placement, including aspirin, over-the-counter drugs containing aspirin, cilostazol, adenosine diphosphate receptor inhibitor (e.g., clopidogrel), glycoprotein IIb/IIIa inhibitors (e.g., tirofiban), warfarin (irrespective of pre-procedural INR), direct oral anticoagulants (e.g., apixaban and dabigatran), and use of parenteral anticoagulant therapy such as heparin and derivative substances within 24 hours of tunneled CVC placement.

Data Acquisition and Definitions of Variables

The Cleveland Clinic has used an electronic health record (EHR) for inpatient and outpatient care since 2001. Baseline data gathered from the EHR included age at the time of tunneled CVC placement, sex, race/ethnicity, etiology of liver disease, Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh score, and conventional coagulation parameters such as PT, PTT, INR, fibrinogen and platelet count, and thromboelastography measurements (reaction time, alpha-angle, and MA) before tunneled CVC placement.

Race/ethnicity was identified based on self-description as recorded in the EHR, and it was categorized as Caucasian, African American, Hispanic, Asian, or other (categorized as other when they were not classified as any of the aforementioned ethnicities or when race data were not available). The different etiologies of liver disease included acute liver failure, as defined in the previous section based on clinical practice guidelines from the American Association for the Study of Liver (23) and the European Association for the Study of the Liver (24), as well as cirrhosis related to hepatitis C, alcohol-associated liver disease, and metabolic dysfunction-associated steatotic liver disease. The MELD and Child-Turcotte-Pugh scores are two prognostic models that are useful for estimating disease severity and survival in patients with cirrhosis. Laboratory values including the serum bilirubin, serum creatinine, and INR were collected to calculate the MELD score, whereas the degrees of ascites, encephalopathy, and serum concentrations of albumin, bilirubin and INR were recorded to determine the Child-Turcotte-Pugh class/score.

The conventional coagulation parameters and thromboelastography measurements used to guide transfusion therapy that were collected from the EHR and were drawn within 24 hours before tunneled CVC insertion. Data on the number of units, total volume

and cost of blood products transfused before tunneled CVC insertion were also collected from the EHR. Blood products, including FFP, cryoprecipitate, and platelets, which were transfused within 8 hours before tunneled CVC placement, were considered part of the pre-procedural transfusion therapy for correction of underlying coagulopathy. Thromboelastography parameters were neither assessed after the transfusion of blood products in the pre-procedural period nor evaluated in the post-procedural period. The average costs of each unit of FFP, cryoprecipitate, and platelets were considered to be $57, $54, and $522, respectively, as reported by the 2017 National Blood Collection and Utilization Survey (25).

Data regarding procedure-related bleeding events occurring within 24 hours of tunneled CVC insertion were gathered from the EHR based on a standardized chart review template (**Supplemental Table S1**, http://links.lww.com/CCX/B284), which required the investigator to review the following elements of the EHR for each patient: 1) procedure nurse's post-procedure patient surveillance note (the procedure nurse involved with each tunneled CVC placement examined the patient post-procedurally within 12–24 hr and documented notable insertion site findings in the EHR including the presence of catheter exit-site bleeding/hematoma and requirement for any interventions such as sustained compression or suture placement to achieve hemostasis); 2) post-procedure hemoglobin/hematocrit levels and transfusion log to assess need for any transfusions within 24 hours of the procedure; 3) imaging studies and interventional radiology procedure notes to assess need for any elective operative interventions to achieve hemostasis; and 4) vital signs flowsheet if any bleeding events associated with the procedure were documented. After thorough assessment of the electronic patient records by two independent investigators based on the aforementioned standardized template, post-procedural bleeding events were adjudicated as clinically significant (grades 2–4) according to a standardized bleeding scale (**Table 1**) derived from the Common Terminology Criteria for Adverse Events (22), which was also previously used by Zeidler et al (26). Disagreements between reviewers were resolved by consensus and were reviewed by a third investigator. Grade 1 bleeding events were not considered clinically significant.

Similarly, details regarding catheter-related thrombosis occurring within 30 days of tunneled CVC insertion were obtained from the EHR as well. Thrombotic events were adjudicated as catheter-related thrombosis if one of the following criteria were met: 1) deep vein thrombosis diagnosed via vascular imaging (e.g., duplex ultrasonography, CT/MR venography) visualized in the central vein where the catheter is inserted; 2) inability to withdraw blood from or infuse into an indwelling catheter or inadequate blood flow rates for hemodialysis requiring alteplase administration into catheter lumens; and 3) removal of catheter with associated fibrin sheath noticed upon removal. Two independent investigators reviewed relevant components of the EHR based on a standardized template (**Supplemental Table S2**, http://links.lww.com/CCX/B284) to adjudicate clotting events as catheter-related thrombosis, with any disagreements between reviewers evaluated by a third investigator and resolved by consensus.

TABLE 1.
Standardized Bleeding Scale for Tunneled Central Venous Catheter-Related Bleeding

Bleeding Grade	Definition
Grade 0	No bleeding
Grade 1	Oozing; hematoma; bleeding that results in < 20 min of manual compression to stop
Grade 2	Bleeding that results in minor interventions to stop, such as prolonged manual compression (> 20 min)
Grade 3	Bleeding that results in radiologic or elective operative intervention or red-cell transfusion without hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability (hypotension, defined as a decrease of > 50 mm Hg or > 50% in either systolic or diastolic blood pressure), with associated tachycardia (heart rate increase, > 20% for 20 min) and resulting in increased red-cell transfusion or fatal bleeding

Statistical Analysis

Patients were stratified into two groups based on whether they received blood product transfusions based on a thromboelastography-guided or conventional transfusion strategy. Descriptive statistics of patient characteristics were presented in mean and SD for continuous variables and frequencies and percentages for categorical variables. To address confounding and other sources of bias arising from the use of observational data, we performed propensity score matching to match patients who were transfused according to the thromboelastography-guided transfusion strategy to the control patients who were transfused based on a conventional transfusion strategy, using a 1:1 ratio without replacement according to the estimated propensity scores (27). A Love plot was used to visualize the differences before and after matching between the two groups. Matched patients, with 82 patients in each group, were considered for primary and secondary outcome analysis. Primary outcomes included number of units, total volume, and cost of FFP/platelets/cryoprecipitate transfused and secondary outcomes included bleeding complications, need for packed RBC transfusion for post-procedure bleeding, and catheter-related thrombosis/occlusion events. Continuous variables were compared using *t* test, whereas categorical variables were compared using Pearson's chi-square test or Fisher exact test as appropriate. The level of statistical significance was set at p value of less than 0.05 (two-tailed). All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Demographic and Clinical Characteristics

We identified a total of 364 patients with liver disease who underwent tunneled CVC insertion between December 1, 2014, and July 31, 2021, 89 of whom had blood products transfused before the procedure to correct their coagulopathy based on a thromboelastography-guided transfusion strategy and 275 of whom received blood products based on conventional coagulation parameters (INR, fibrinogen, and platelet count). The patients in the cohort had a mean age of 56.3 ± 15.9 years (interquartile range [IQR], 43–68 yr). A majority of the patients were male (n = 210; 57.7%). The study population comprised 75.8% Caucasian, 20.1% African-American, 2.5% Asian, and 1.6% Hispanic subjects. Fifty-six of the 89 tunneled CVCs inserted in patients in the thromboelastography-guided transfusion group and 52 of the 275 tunneled CVCs inserted in patients in the conventional transfusion group were TDCs placed for acute kidney failure requiring kidney replacement therapy. A detailed description of the baseline demographic and clinical characteristics of the overall cohort is provided in **Table 2**.

To control the observational bias between the two groups (patients who received thromboelastography-guided transfusion therapy vs. conventional transfusion therapy), propensity score matching was performed with a match ratio of 1:1. The standardized mean difference computed to assess the quality of matching, indicated a good overall balance of covariate distribution between the two groups, with a standardized mean difference under 0.013 for most variables. The baseline demographic and clinical characteristics of patients who received blood transfusions before tunneled CVC placement with a thromboelastography-guided transfusion strategy vs. a conventional transfusion strategy in the propensity score-matched sample are described in **Table 3**. The patients in the thromboelastography-guided transfusion strategy group had a mean age of 56.5 ± 11.1 years (IQR, 50–66 yr). A majority of the patients were male (n = 52; 58.4%). This group comprised 84.3% Caucasian, 9.0% African American, 6.7% Asian, and none of the patients identified as Hispanic. Overall, the thromboelastography-guided transfusion group was similar to the matched controls with respect to MELD and Child-Turcotte-Pugh scores, etiology of liver disease, and conventional coagulation parameters including INR, fibrinogen, and platelet count.

Blood Products Transfused With Thromboelastography-Guided Vs. Conventional Transfusion Strategy

The mean values for the thromboelastography coagulation parameters of reaction time, alpha-angle, and MA were 7.4 ± 2.8 minutes, 60.0 ± 10.2 degrees, and 50.1 ± 12.6 mm, respectively. Each unit of FFP, cryoprecipitate, and platelet apheresis transfusion corresponded to a total volume of 250, 25, and 300 mL,

TABLE 2.
Baseline Characteristics Pre-Matching, Overall, and Stratified by Transfusion Strategy

Characteristics	Overall (*n* = 364)	Thromboelastography-Guided Transfusion Strategy (*n* = 89)	Conventional Transfusion Strategy (*n* = 275)
Age, mean ± SD	56.3 ± 15.9	56.5 ± 11.1	56.2 ± 17.2
Male, *n* (%)	210 (57.7)	52 (58.4)	158 (57.5)
Caucasian, *n* (%)	276 (75.8)	75 (84.3)	201 (73.1)
Model for End-Stage Liver Disease score, mean ± SD	30.8 ± 6.0	31.8 ± 6.8	30.5 ± 5.8
Child-Turcotte-Pugh score, mean ± SD	10.2 ± 2.0	11.1 ± 2.0	10.0 ± 2.0
Etiology of liver disease, *n* (%)			
Metabolic dysfunction-associated steatotic liver disease-related cirrhosis	98 (26.9)	25 (28.1)	73 (26.5)
Alcohol-related cirrhosis	163 (44.8)	45 (50.6)	118 (42.9)
Other (including acute liver failure and hepatitis C virus-related cirrhosis)	103 (28.3)	19 (21.3)	84 (30.6)
Conventional coagulation parameters before tunneled CVC insertion, mean ± SD			
International normalized ratio	1.9 ± 0.7	1.9 ± 0.5	1.9 ± 0.7
Fibrinogen, mg/dL	179.2 ± 103.6	159.9 ± 112.5	185.4 ± 99.9
Platelet count, K/uL	77.9 ± 47.7	76.2 ± 47.5	78.4 ± 47.8
Thromboelastography parameters before tunneled CVC insertion, mean ± SD			
Reaction time, min	7.4 ± 2.8	7.4 ± 2.8	NA
α-angle, degrees	60.0 ± 10.2	60.0 ± 10.2	NA
Maximum amplitude, mm	50.1 ± 12.6	50.1 ± 12.6	NA

CVC = central venous catheter, NA = not available.

respectively. The total number of units of FFP (12 vs. 32 [$p = 0.019$]), cryoprecipitate (60 vs. 250 [$p < 0.001$]), and platelets (5 vs. 13 [$p = 0.046$]) transfused were significantly lower in the thromboelastography-guided transfusion group than in the conventional transfusion group. Therefore, the total volume/cost of transfusions of FFP (3,000 mL/$684 vs. 7,500 mL/$1,824 [$p = 0.019$]), cryoprecipitate (1,500 mL/$3,240 vs. 6,250 mL/$13,500 [$p < 0.001$]), and platelets (1,500 mL/$2,610 vs. 3,900 mL/$6,786 [$p = 0.046$]) in the thromboelastography-guided transfusion group was significantly lower than in the conventional transfusion group (**Table 4**).

Supplemental Table S3 (http://links.lww.com/CCX/B284) depicts the proportion of patients in the two groups who met transfusion criteria based on thromboelastography and conventional parameters. Fewer than 90% of patients in the thromboelastography-guided transfusion group met transfusion criteria based on reaction time, alpha-angle, and MA, respectively. By comparison, higher proportions of patients in the thromboelastography-guided transfusion group would have satisfied transfusion criteria based on conventional coagulation parameters (INR [39.0%], fibrinogen [34.1%], and platelet count [15.9%]). Similarly, a larger percentage of patients in the conventional transfusion group met transfusion criteria based on INR (34.1%), fibrinogen (36.6%), and platelet count (18.3%).

Catheter-Related Complications With Thromboelastography-Guided Vs. Conventional Transfusion Strategy

There was no statistically significant difference in the frequency of clinically significant bleeding events observed between the thromboelastography-guided

TABLE 3.
Baseline Characteristics Post-Matching, Overall, and Stratified by Transfusion Strategy

Characteristics	Overall (n = 164)	Thromboelastography-Guided Transfusion Strategy (n = 82)	Conventional Transfusion Strategy (n = 82)	p[c]
Age, mean ± SD	56.4 ± 14.3	57.0 ± 11.0	55.8 ± 17.0	0.59[a]
Male, *n* (%)	96 (58.5)	49 (59.8)	47 (57.3)	0.75[b]
Caucasian, *n* (%)	136 (82.9)	68 (82.9)	68 (82.9)	0.99[b]
Model for End-Stage Liver Disease score, mean ± SD	31.7 ± 6.2	31.3 ± 6.7	32.0 ± 5.7	0.46[a]
Child-Turcotte-Pugh score, mean ± SD	10.9 ± 2.0	10.9 ± 1.9	10.8 ± 2.0	0.81[a]
Etiology of liver disease, *n* (%)				0.86[b]
Metabolic dysfunction-associated steatotic liver disease-related cirrhosis	53 (32.3)	25 (30.5)	28 (34.1)	
Alcohol-related cirrhosis	75 (45.7)	38 (46.3)	37 (45.1)	
Other (including acute liver failure and hepatitis C virus-related cirrhosis)	36 (22.0)	19 (23.2)	17 (20.7)	
Conventional coagulation parameters before tunneled central venous catheter insertion, mean ± SD				
International normalized ratio	1.9 ± 0.61	1.9 ± 0.55	1.8 ± 0.67	0.27[a]
Fibrinogen, mg/dL	164.9 ± 107.2	162.9 ± 116.0	167.0 ± 98.4	0.80[a]
Platelet count, K/uL	76.3 ± 48.6	75.6 ± 47.5	76.9 ± 49.9	0.87[a]

[a]Analysis of variance test.
[b]Pearson's χ^2 test.
[c]$p < 0.05$ will be considered statistically significant.

transfusion group (n = 2; [2.4%]) and the conventional transfusion group (n = 2; [2.4%]) within 24 hours of tunneled CVC insertion (p = 0.99). None of the patients in either group had catheter-related thrombosis/occlusion within 30 days of insertion.

DISCUSSION

In summary, our propensity score-matched retrospective cohort analysis demonstrated that the implementation of a thromboelastography-guided transfusion strategy in patients with liver disease before tunneled CVC placement lead to the transfusion of significantly fewer units and lower volume of blood products with a significantly lower cost of blood transfusions, than with a conventional transfusion strategy (involving INR, fibrinogen, and platelet count), without increasing the frequency of catheter-related bleeding and thrombotic complications.

The implementation of a thromboelastography-guided transfusion strategy in critically ill patients with liver disease has been limited and practice management guidelines such as those from the American Gastroenterological Association (28) have stopped short of recommending thromboelastography over conventional coagulation parameters for management of coagulopathy in patients with cirrhosis before procedures owing to the lack of prospective data to define precise thresholds to guide pre-procedural blood transfusions. Nonetheless, several RCTs (14, 16–19) have demonstrated that thromboelastography-guided transfusion strategies in patients with liver disease as opposed to transfusion based on conventional coagulation parameters are associated with fewer blood product transfusions and lower frequency of TACO/TRALI without increasing the frequency of bleeding complications. For instance, the study by De Pietri et al (18) explored the utilization of thromboelastography to guide blood product administration before a variety of

TABLE 4.
Study Outcomes Post-Matching, Overall, and Stratified by Transfusion Strategy

Study Outcomes	Overall ($n = 164$)	Thromboelastography-Guided Transfusion Strategy ($n = 82$)	Conventional Transfusion Strategy ($n = 82$)	p[c]
Number of units of FFP, *n* (%)	Total = 44	Total = 12	Total = 32	0.019[a]
0	147 (89.6)	78 (95.1)	69 (84.1)	
2	7 (4.3)	0 (0.0)	7 (8.5)	
3	10 (6.1)	4 (4.9)	6 (7.3)	
Volume of FFP (mL)	10,500	3,000	7,500	0.019[a]
Cost of FFP ($)	2,508	684	1,824	0.019[a]
Number of units of cryoprecipitate, *n* (%)	Total = 310	Total = 60	Total = 250	< 0.001[a]
0	133 (81.1)	76 (92.7)	57 (69.5)	
10	31 (18.9)	6 (7.3)	25 (30.5)	
Volume of cryoprecipitate (mL)	7,750	1,500	6,250	< 0.001[a]
Cost of cryoprecipitate ($)	16,740	3,240	13,500	< 0.001[a]
Number of units of platelets, *n* (%)	Total = 18	Total = 5	Total = 13	0.046[a]
0	146 (89.0)	77 (93.9)	69 (84.1)	
1	18 (11.0)	5 (6.1)	13 (15.9)	
Volume of platelets (mL)	5,400	1,500	3,900	0.046[a]
Cost of platelets ($)	9,396	2,610	6,786	0.046[a]
Frequency of bleeding within 24 hr of tunneled CVC insertion, *n* (%)	4 (2.4)	2 (2.4)	2 (2.4)	0.99[b]
Number of units of packed RBCs transfused for bleeding events, *n* (%)	3	1	2	0.99[b]
Frequency of catheter thrombosis or occlusion within 30 d of tunneled CVC insertion, *n* (%)	0 (0)	0 (0)	0 (0)	0.99[b]

CVC = central venous catheter, FFP = fresh frozen plasma.
[a]Pearson's χ^2 test.
[b]Fisher exact test.
[c]$p < 0.05$ considered statistically significant.

procedures, including those associated with low risk of peri-procedural bleeding such as central vein cannulation, as well as those with a higher risk of bleeding such as liver biopsy and endoscopic retrograde cholangiopancreatography. All patients in the conventional coagulation test group received blood products, whereas 93% of patients in the thromboelastography group did not receive any blood products at all, illustrating again that using conventional coagulation tests leads to over-utilization of blood products. Consequently, the Society of Critical Care Medicine has recommended using thromboelastography over measuring INR/platelets/fibrinogen in critically ill patients with acute liver failure or acute on chronic liver failure undergoing procedures (15).

Our retrospective cohort study adds to a growing body of literature that suggests thromboelastography-guided transfusion strategies reduce transfusion of blood products compared with the standard of care based on conventional coagulation parameters without

increasing bleeding or thrombotic complications in the peri-procedural setting. However, our study fills a gap in the existing literature since the aforementioned RCTs did not address transfusion strategies or procedure related bleeding risk in patients undergoing tunneled CVC placement and did not involve critically ill liver disease patients, including those with kidney dysfunction. This is crucial since concomitant kidney disease has been associated with deleterious effects on global hemostatic profiles in patients with decompensated cirrhosis (29).

In the above referenced RCTs that have investigated the utilization of thromboelastography in patients with liver disease, patients with acute/chronic kidney failure (17) and those requiring kidney replacement therapy (16, 18) were excluded. In contrast, in our patient cohort, 56 of the 89 tunneled CVCs (62.9%) inserted in patients in the thromboelastography-guided transfusion group and 52 of the 275 tunneled CVCs (18.9%) inserted in patients in the conventional transfusion group were TDCs, which demonstrates that a considerable proportion of patients had concomitant kidney failure requiring kidney replacement therapy. Acute and chronic kidney disease are commonly encountered in patients with decompensated cirrhosis (30, 31) and acute liver failure (32) and have been associated with further increased risk of bleeding (33) and thrombosis (34) in patients with liver disease. For example, a retrospective chart review study (33) analyzing patients with decompensated cirrhosis undergoing paracentesis (considered a low bleeding risk procedure by the 2019 Society of Interventional Radiology guidelines [21] similar to central vein cannulation), demonstrated that acute kidney injury before paracentesis was an independent predictor of post-paracentesis bleeding (odds ratio, 4.3; 95% CI, 1.3–13.5; $p = 0.01$), independent of coagulation parameters (platelets, INR), and severity of liver disease (MELD). This highlights that the inclusion of patients with kidney failure in our study was critical, since we were able to demonstrate how a thromboelastography-guided transfusion strategy can be used to minimize unnecessary blood product transfusions in this most vulnerable population with concomitant liver and kidney dysfunction—those with a greater risk of peri-procedural bleeding and those more likely to have adverse outcomes with transfusion-related complications (35).

Furthermore, even though prior studies (18, 36) have investigated the use of thromboelastography-guided transfusion protocols and other restrictive strategies in cirrhosis patients undergoing nontunneled CVC placement and have shown a reduction in transfusions before CVC, our study specifically focused on tunneled CVCs, including TDCs. This is especially important because many cirrhosis patients may eventually develop hemodialysis dependent kidney dysfunction and require durable hemodialysis vascular access as a bridge to liver transplantation.

Our analysis also demonstrated that the total cost of blood product transfusions in the thromboelastography-guided transfusion group was significantly lower than in the conventional transfusion group as a result of transfusion avoidance. Although there are conflicting data regarding the cost-effectiveness of thromboelastography across different systematic analyses in various patient populations, such as those with trauma-induced coagulopathy and those undergoing liver and cardiac surgery (37–39), one study showed that, in patients undergoing liver transplantation, a thromboelastography-based hemostatic management approach compared with the standard of care, lead to significant cost savings associated not only with transfusion avoidance but also with length of ICU stay and reoperation for bleeding (40).

Our study was limited by its retrospective design, which increased the potential for introduction of selection bias, impacting the applicability of the results in terms of the optimal thresholds to be used to guide blood transfusions in the general population, including patients with compensated cirrhosis. This was especially evident in our patient population given a significant proportion of the patients in the control group received cryoprecipitate transfusions (30.5%), indicating a degree of selection bias for very critically ill patients after propensity score matching. Furthermore, the adjudication of post-procedural clinically significant bleeding and thrombotic events may have been potentially skewed in certain cases (e.g., packed RBCs documented in EHR as transfused following tunneled CVC insertion but may have been transfused for another clinical indication per physician discretion)—we tried to attenuate this limitation with the utilization of standardized chart review templates.

CONCLUSIONS

In conclusion, using a thromboelastography-guided transfusion strategy, rather than one involving conventional coagulation parameters, to direct blood transfusions and hemostatic factor repletion before tunneled CVC placement in patients with liver disease may represent a promising approach to potentially reduce unnecessary exposure to allogeneic blood products and associated costs, without increasing the risk for periprocedural bleeding and thrombotic complications.

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