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Abstract

Background Fibrinogen (FIB) levels less than 150 mg/dL have been associated with increased rates of bleeding and lower survival in critically ill cirrhosis patients.

Objective We aimed to determine if treatment with cryoprecipitate (CRYO) for low FIB levels is associated with bleeding outcomes or survival.

Methods A total of 237 cirrhosis patients admitted to an intensive care unit at a tertiary care liver transplant center with initial FIB levels less than 150 mg/dL were retrospectively assessed for CRYO transfusion, bleeding events, and survival outcomes.

Results The mean MELD score was 27.2 (95% confidence interval [CI]: 26.0–28.3) and CLIF-C acute on chronic liver failure score was 53.4 (51.9–54.8). Ninety-nine (41.8%) were admitted for acute bleeding and the remainder were admitted for nonbleeding illnesses. FIB level on admission correlated strongly with disease severity. After adjusting for disease severity, FIB on admission was not an independent predictor of 30-day survival (hazard ratio [HR]: 0.99, 95% CI: 0.99–1.01, $p = 0.68$). CRYO transfusion increased FIB levels but had no independent effect on mortality or bleeding complications (HR: 1.10, 95% CI: 0.72–1.70, $p = 0.65$).

Conclusion In cirrhosis patients with critical illness, low FIB levels on presentation reflect severity of illness but are not independently associated with 30-day mortality. Treatment of low FIB with CRYO also does not affect survival or bleeding complications, suggesting FIB is an additional marker of severity of illness but is not itself a direct factor in the pathophysiology of bleeding in critically ill cirrhosis patients.

Keywords
- transfusion
- portal hypertension
- gastrointestinal bleeding
- disseminated intravascular coagulation
- international normalized ratio

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Introduction

Decompensated cirrhosis and its complications such as esophageal variceal bleeding, hepatic encephalopathy, and ascites are common causes for acute illness and critical care.[1] Although advances in care for patients with cirrhosis have led to decreased in-hospital mortality rates, hospitalizations and intensive care unit (ICU) admissions for complications of cirrhosis continue to rise.[2–4] Acute bleeding is one of the most common indications for ICU admission in patients with cirrhosis[2] and guidance for the management of portal hypertensive bleeding is established in societal guidelines.[5] Traditional markers of coagulation, such as platelet count and prothrombin time (PT)/international normalized ratio (INR), are routinely assessed in the management of critically ill cirrhosis patients with bleeding, but therapeutic interventions aimed at normalizing these markers have limited utility in the management of acute bleeding in this population.[6,7] There is scant evidence to suggest firm transfusion guidelines for these patients and critical care transfusion algorithms are frequently extrapolated from the literature for other patient populations, especially in the setting of acute bleeding.[8,9]

Fibrinogen (FIB) production and degradation in patients with decompensated cirrhosis remains poorly understood.[10] Early studies of fibrinolysis in cirrhosis demonstrated a correlation between low FIB levels and increased bleeding rates.[11–14] However, more recent studies have been unable to replicate findings suggesting a chronic hyperfibrinolytic state in decompensated cirrhosis.[15–18] Some authors propose that low levels of FIB and elevated D-dimer levels are more indicative of decreased hepatic production and/or clearance and thus reflect advancing hepatic synthetic dysfunction without direct involvement in the pathophysiology of bleeding.[17,19] While cryoprecipitate (CRYO), FIB concentrates, and sometimes fresh frozen plasma (FFP) are given to replete FIB clinically, it is not well established that decreased FIB is either causative or predictive of major or minor bleeding events in cirrhosis patients. Some researchers have found an association with low FIB levels and spontaneous bleeding risk in critical care patients[20] and in postvariceal ligation bleeding.[21] However, it is uncertain whether these bleeding events would have been prevented with prophylactic CRYO or FIB concentrate transfusions. The effect of CRYO transfusions for hypofibrinogenemia is not well studied in cirrhosis patients and no controlled trials on this topic have been published in this population.

The primary objective of this study is to compare critically ill patients with cirrhosis admitted to the medical ICU (MICU) with low baseline FIB levels who received CRYO transfusions to those who did not and assess the impact on survival and bleeding complications.

Methods

This is a retrospective parallel cohort study of adult patients with a previously established diagnosis of cirrhosis admitted to a MICU at a single liver transplant center between 2011 and 2018. Potential study subjects were initially screened through the use of administrative and billing databases. Because our institutional transfusion policy specifies a FIB level of less than 150 mg/dL as a potential indication for factor replacement therapy in patients with active bleeding, our subject screening criteria included all cirrhosis patients aged 18 years and older with critical care admission to an adult medical ICU and a FIB level on admission or arrival of less than 150 mg/dL. All patients meeting these criteria during the study time period were considered for inclusion into the study. Postoperative or trauma admissions, noncritical illness indications for ICU admission, and those patients with no FIB checked on admission were excluded. ►**Fig. 1** shows the study inclusion flowchart.

To assess the impact of low admission FIB levels and transfusion interventions targeting those low levels, FIB levels were analyzed as both continuous and dichotomized variables. However, to maintain consistency with published literature and for clarity, the final analysis is presented with subjects stratified into two primary groups: (1) those patients with initial FIB less than or equal to 100 mg/dL and (2) those with levels between 101 and 150 mg/dL.[20] The conclusions of the analysis were not different when FIB was considered as a continuous variable. A predetermined subgroup analysis was also planned in patients presenting with bleeding as the indication for critical care compared with those with other nonbleeding indications. Demographics, initial laboratory values, disease severity scales, and transfusion with CRYO due to low FIB levels were recorded by study personnel through standardized patient level clinical chart extraction. CRYO at the study institution is administered in dosages containing five pooled units per dose and there is no standardized dosing protocol for CRYO administration in cirrhosis patients. Response to CRYO administration was gauged by FIB levels measured no more than 24 hours after the administration of CRYO when available.

The primary outcome measure was 30-day all-cause mortality. Secondary outcomes included the incidence and etiology of major and minor bleeding complications after admission (distinct from those bleeding events that were indications for ICU admission) and 90-day mortality. Standardized definitions of bleeding events were utilized.[22–24] In summary, bleeding events were considered major events if they met at least one of the following criteria: bleeding directly contributing to mortality, bleeding causing hypovolemic shock, bleeding into a critical site (intracranial, epidural, pericardial, pleural, peritoneal, or retroperitoneal), bleeding requiring a surgical or procedural intervention to achieve hemostasis, bleeding requiring the transfusion of one or more units of packed red blood cells (PRBC), fresh hematemesis or nasogastric aspiration of greater than or equal to 100 mL of fresh blood more than 2 hours after the start of specific drug treatment or therapeutic endoscopy, or a 3 g/dL decrease or more in hemoglobin within 24 hours without transfusion. Minor bleeding events were defined as bleeding that did not meet any of the major bleeding criteria.

Because this was a retrospective cohort study, all patients meeting entry criteria during the study period were included

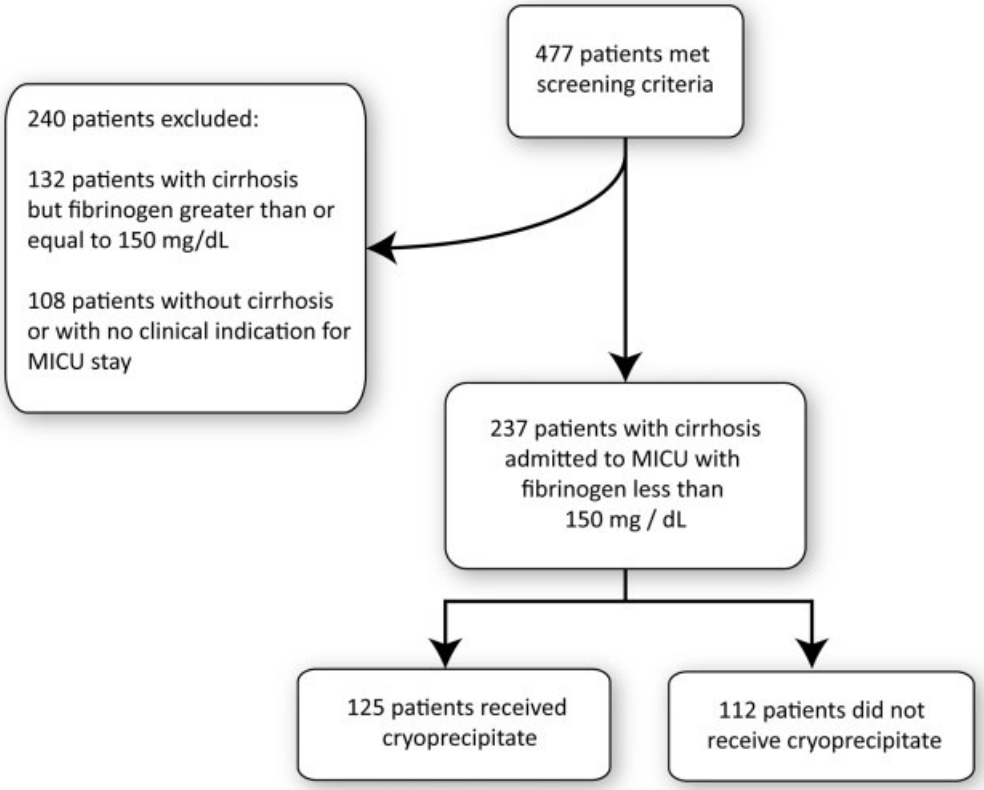

Fig. 1 Flowchart of study inclusion.

in the analyses. The study team used standardized data collection forms and chart review techniques. The presence of cirrhosis was adjudicated by two study personnel and a patient was included in the study only if both team members agreed on the objective diagnosis of cirrhosis. Data management and statistical analyses were performed using SAS (version 9.4, Cary, North Carolina, United States). Chi-square and/or Fisher's exact test were used for categorical variables and Student's *t*-test or Wilcoxon's rank-sum for continuous variables as appropriate. Univariable time-based survival models with censoring at last follow-up or at the time of liver transplantation were analyzed using the Kaplan–Meier technique and multivariable models were constructed using the Cox proportional hazards technique utilizing a competing risks model with mortality and liver transplantation as competing outcomes. Multivariable survival models included an adjustment for statistical interaction between initial FIB levels and transfusion with CRYO. To better account for confounders between groups that received CRYO and those that did not, an inverse probability of treatment-weighted propensity score analysis modeling CRYO utilization was performed.[25] CLIF-C acute on chronic liver failure (ACLF) score and ICU admission for bleeding were included in the propensity score analysis. Because of the strong statistical association between CRYO administration and initial FIB level, it was statistically impossible to design a convergent and valid propensity score model incorporating FIB as a weighted variable based on the criteria of Stuart.[26] Therefore, the final propensity score model included the CLIF-C ACLF score as well as admission to the ICU for bleeding indications. The final proportional hazards survival model did, however, continue to adjust for the CRYO–FIB statistical interaction. Multivariable survival models included the CLIF-C ACLF score, bleeding as a criterion for ICU admission, initial FIB level, and transfusion with CRYO. The CLIF-C ACLF score is a multicomponent and validated measure of 28- and 90-day mortality in the cirrhosis population and is a more accurate disease severity measure for critically ill patients than Child–Turcotte–Pugh, MELD, or MELD-Na.[27,28] The components of the score include total bilirubin, creatinine, hepatic encephalopathy level, INR, vasopressor use, oxygen saturation and FiO_2, age, and white blood cell count. All statistical testing was two sided and the *p*-value level of significance was set at less than or equal to 0.05. Approval for retrospective review of medical records for research purposes was granted by the University of Virginia Institutional Review Board.

Results

Total Population and Initial Fibrinogen Levels

There were 237 subjects included in the analysis. ►**Table 1** shows the characteristics of the total population and the subgroup of subjects presenting with initial FIB level less than or equal to 100 mg/dL (low FIB group, mean: 74.6 mg/dL) and those with FIB from 101 to 150 mg/dL (high FIB group, mean: 125 mg/dL). Disease etiology was not different between groups ($p = 0.11$). The most common indication for ICU admission was for gastrointestinal (GI) bleeding followed

Table 1 Total population characteristics by admission fibrinogen level prior to any transfusion

Admission values	Total population ($n = 237$)	Low fibrinogen ($\leq$100 mg/dL) on presentation ($n = 94$)	High fibrinogen (101–150 mg/dL) on presentation ($n = 143$)	Low vs. high *p*-value
Patient characteristics				
Age, y	53.9 (52.4–55.4)	52.7 (50.2–55.1)	54.7 (52.9–56.6)	0.18
Female gender	87 (36.7%)	34 (36.2%)	53 (37.1%)	0.89
Etiology of cirrhosis				0.11
Alcohol	95 (40.1%)	33 (35.1%)	62 (43.4%)	
Viral	76 (32.1%)	38 (40.4%)	38 (26.6%)	
Nonalcoholic steatohepatitis	48 (20.3%)	15 (16.0%)	33 (23.1%)	
Other	18 (7.6%)	8 (8.5%)	10 (7.0%)	
Indication for ICU admission				0.03
GI bleeding	82 (34.6%)	26 (27.7%)	56 (39.2%)	
Sepsis	61 (25.7%)	20 (21.3%)	41 (28.7%)	
Altered mental status	45 (19.0%)	24 (25.5%)	21 (14.7%)	
Respiratory failure	16 (6.8%)	9 (9.6%)	7 (4.9%)	
Uremia	14 (5.9%)	9 (9.6%)	5 (3.5%)	
Other	19 (8.0%)	6 (6.4%)	13 (9.1%)	
Severity of illness and initial laboratory indicators				
MELD score	27.2 (26.0–28.3)	31.3 (29.6–33.0)	24.4 (23.1–25.8)	<0.01
Child–Turcotte–Pugh score	10.5 (10.2–10.7)	11.2 (10.9–11.6)	10.0 (9.6–10.3)	<0.01
CLIF-C ACLF score	53.4 (51.9–54.8)	55.6 (53.2–58.0)	52.0 (50.2–53.7)	0.01
SOFA score	9.50 (9.02–9.99)	10.2 (9.42–10.9)	9.07 (8.43–9.71)	0.03
Fibrinogen, mg/dL	105 (102–109)	74.6 (71.2–78.1)	125 (123–128)	<0.01
INR	2.57 (2.41–2.74)	3.22 (2.89–3.56)	2.15 (2.01–2.29)	<0.01
Total bilirubin, mg/dL	9.86 (8.41–11.3)	11.4 (9.25–13.5)	8.87 (6.90–10.8)	0.10
Creatinine, mg/dL	1.85 (1.66–2.04)	1.94 (1.65–2.24)	1.79 (1.54–2.04)	0.44
White blood count, k/μL	11.4 (10.3–12.4)	11.9 (9.94–13.8)	22.0 (9.77–12.3)	0.44
Platelet count, k/μL	79 (73–85)	73 (63–82)	83 (76–91)	0.08
Vasopressor requirement	93 (39.2%)	36 (38.3%)	57 (39.9%)	0.81
Mechanical ventilation requirement	107 (45.2%)	39 (41.5%)	68 (47.6%)	0.36
Renal replacement therapy requirement	29 (12.2%)	11 (11.7%)	18 (12.6%)	0.84
Intervention, bleeding events, and survival				
Cryoprecipitate given	125 (52.7%)	75 (79.8%)	50 (35.0%)	<0.01
Fresh frozen plasma given	48 (20.3%)	24 (25.5%)	24 (16.8%)	0.10
Any bleeding complication after FIB level checked	117 (49.4%)	50 (53.2%)	67 (46.9%)	0.34
Major bleeding event after FIB checked	102 (43.0%)	43 (45.7%)	59 (41.3%)	0.50
Survival/transplanted within 30 days	101/22 (51.9%)	27/10 (39.4%)	74/12 (60.1%)	<0.01
Survival/transplanted within 90 days	67/22 (37.6%)	16/10 (27.7%)	51/12 (44.0%)	0.03

Abbreviations: FIB, fibrinogen; INR, international normalized ratio.
Note: Continuous variables are presented as mean (95% confidence interval) and categorical variables are presented as *n* (column percentage).

by sepsis, altered mental status, primary respiratory failure, and uremia. Subjects with high FIB levels presented more often with GI bleeding or sepsis, while those with low FIB presented with respiratory failure or uremia ($p = 0.02$). Low FIB levels correlated strongly with higher disease severity measures and subjects with low FIB had higher initial MELD score (31.3 in low FIB vs. 24.4 in high FIB, $p < 0.01$), CTP score (11.2 vs. 10.0, $p < 0.01$), CLIF-C ACLF score (55.6 vs. 52.0, $p = 0.01$), and SOFA score (10.2 vs. 9.07, $p = 0.03$). Similarly, INR was more elevated in those presenting with low FIB (3.22 vs. 2.15, $p < 0.01$). Subjects with low FIB levels on presentation were much more likely to receive CRYO transfusion (79.8% in low FIB vs. 35.0% in high FIB subjects, $p < 0.01$) independent of the presence of bleeding ($p = 0.13$). The use of FFP transfusion was not different between groups ($p = 0.10$). There was no difference between groups in initial platelet count (73 k/μL in low FIB group vs. 83 in high FIB, $p = 0.08$) and no difference in PRBC transfusions ($p = 0.12$). Despite the difference in FIB levels at presentation, there was no correlation between low FIB and major bleeding complications (45.7% in low FIB vs. 41.3% in high FIB, $p = 0.50$) during the ICU stay. There was a strong correlation with initial FIB level and 30-day survival or survival to transplantation within 30 days. Subjects with low FIB on presentation had a 39.4% 30-day unadjusted survival (or transplant within 30 days) compared with 60.1% in those with high FIB ($p < 0.01$). A similar significant trend was seen in 90-day unadjusted survival. MELD, CLIF-C ACLF score, and CTP score all showed expected correlations with 30-day survival.

Bleeding Subgroup

Because of the differences in transfusion management strategies in patients requiring critical care due to bleeding compared with those admitted with other medical issues, a predefined subgroup analysis was performed analyzing low FIB ($n = 28$, mean FIB: 76 mg/dL) versus high FIB ($n = 71$, mean FIB: 124 mg/dL) populations in those patients presenting with bleeding. The majority of bleeding events were due to esophageal or gastric varices (51%), nonvariceal upper GI sources (28%), and hemoperitoneum or abdominal wall hematoma after paracentesis (10%). There were no statistical differences in original source of bleeding between low and high FIB groups ($p = 0.44$). The bleeding subgroup was similar to the total population in that low FIB correlated with higher disease severity as measured by MELD (28.6 in low FIB group and 21.2 in high FIB group, $p < 0.01$), CTP score (11.0 vs. 9.4, $p < 0.01$), and CLIF-C ACLF score (54.1 vs. 49.0, $p = 0.04$, $p = 0.04$). There was no difference between groups in initial platelet count (83 k/μL in low FIB group vs. 91 in high FIB group, $p = 0.44$) or presenting hemoglobin values (7.5 vs. 8.0 g/dL, $p = 0.31$). Patients presenting with low FIB received transfusion of PRBC more often than those with high FIB (75 vs. 52%, $p = 0.04$). Predictably, based on the institutional protocols, subjects with low FIB on presentation with bleeding received CRYO more frequently (89%) than those with high FIB (46%), $p < 0.01$. There was no difference in the use of FFP between the groups ($p = 0.11$). There were more nonmajor bleeding complications after initial hemostasis in the low FIB group (89% in the low FIB group vs. 59% in the high FIB group, $p < 0.01$) but no difference in major rebleeding complications ($p = 0.40$). Unadjusted survival showed a similar trend to the total population and low FIB correlated with lower survival at 30 and 90 days. Unadjusted 30-day survival (or transplant within 30 days) was highest in the subgroup presenting with bleeding and a high FIB level compared with all other populations ($p < 0.01$; ►**Fig. 2**), while subjects with bleeding and a low FIB level had similar 30-day survival compared with the nonbleeding population.

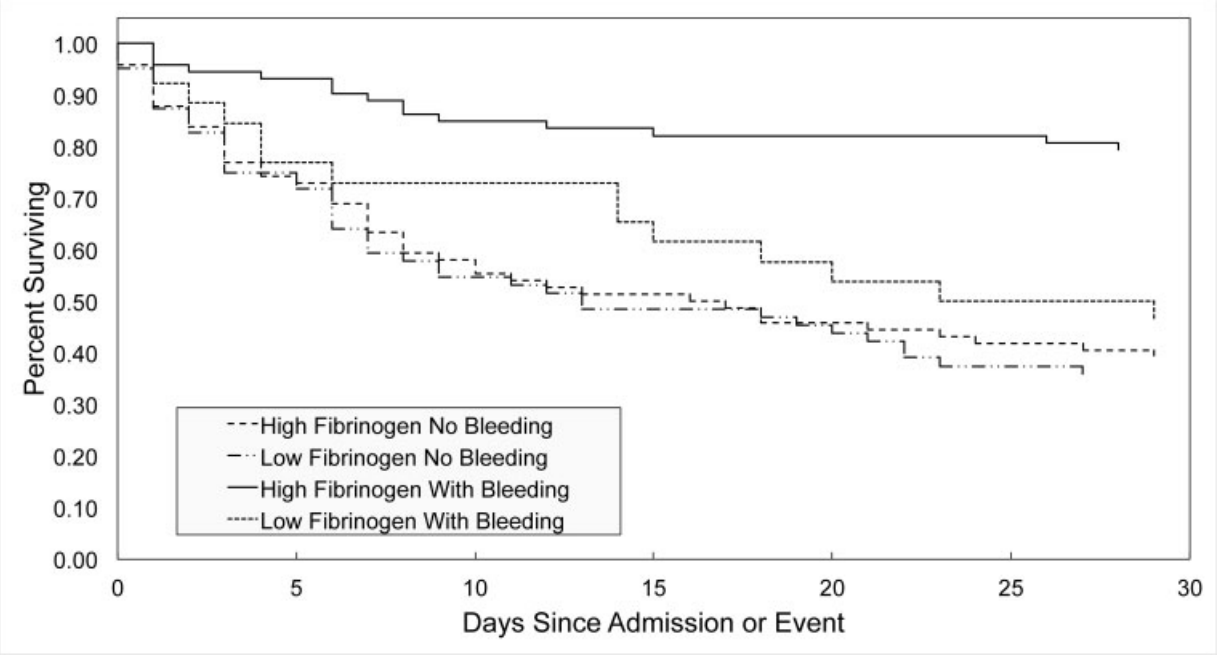

Fig. 2 Unadjusted survival at 30 days by presentation fibrinogen level prior to any transfusion and bleeding as an indication for intensive care unit admission. High fibrinogen with bleeding (top) compared with all others, $p < 0.01$.

Table 2 Population characteristics by cryoprecipitate administered

Admission values	Did *not* receive cryoprecipitate transfusion ($n = 112$)	Received cryoprecipitate transfusion ($n = 125$)	*p*-Value
Patient characteristics			
Age, y	55.3 (53.4–57.3)	52.7 (50.5–54.8)	0.07
Female gender	46 (41.1%)	41 (32.8%)	0.22
Indication for ICU admission: bleeding	41 (36.6%)	58 (46.4%)	0.13
Severity of illness and initial laboratory indicators			
MELD score	24.5 (22.9–26.0)	30.0 (28.0–31.1)	<0.01
Child–Turcotte–Pugh score	9.8 (9.5–10.2)	11.0 (10.7–11.3)	<0.01
CLIF-C ACLF score	51.2 (49.0–53.4)	55.3 (53.5–57.1)	<0.01
SOFA score	9.0 (8.3–9.7)	10.0 (9.3–10.6)	0.05
Fibrinogen prior to any transfusion, mg/dL	119 (114–124)	93 (88–97)	<0.01
INR	2.17 (2.02–2.32)	2.94 (2.66–3.21)	<0.01
Total bilirubin, mg/dL	8.7 (6.5–11.0)	10.9 (9.0–12.8)	0.14
Creatinine, mg/dL	1.85 (1.53–2.16)	1.86 (1.63–2.08)	0.96
White blood count, k/cu mL	10.0 (8.5–11.4)	12.6 (11.1–14.2)	0.01
Platelet count, k/μL	79 (71–87)	79 (70–87)	0.92
Vasopressor requirement	40 (35.7%)	53 (42.4%)	0.29
Mechanical ventilation requirement	47 (42.0%)	60 (48.0%)	0.35
Renal replacement therapy requirement	17 (15.2%)	12 (9.6%)	0.23
Intervention, bleeding events, and survival			
Any bleeding complication after admission	43 (38.4%)	74 (59.2%)	<0.01
Major bleeding event after admission	34 (30.4%)	68 (54.4%)	<0.01
Survival/transplant within 30 days	54/12 (58.9%)	47/10 (45.6%)	0.12
Survival/transplant within 90 days	40/12 (46.4%)	27/10 (29.6%)	0.03

Note: Continuous variables are presented as mean (95% confidence interval) and categorical variables are presented as *n* (column percentage).

Subjects Receiving Cryoprecipitate Transfusion

To investigate the effect of CRYO transfusion on outcome, characteristics of the population receiving CRYO transfusion ($n = 125$) were compared with those who did not receive CRYO ($n = 112$; ►**Table 2**). The patients who received CRYO transfusions had higher disease severity measures including MELD (29.6 in those transfused vs. 24.5 in not transfused, $p < 0.01$), CTP score (11.0 vs. 9.8, $p < 0.01$), CLIF-C ACLF score (55.3 vs. 51.2, $p < 0.01$), INR (2.94 vs. 2.17, $p < 0.01$), and lower baseline FIB level (93 vs. 119, $p < 0.01$). There was no difference in initial platelet count between groups ($p = 0.92$); however, subjects receiving CRYO transfusion were more likely to receive at least one unit of PRBC (29.5% in those not receiving CRYO vs. 56.8% in those receiving CRYO, $p > 0.01$) despite having equal starting hemoglobin values ($p = 0.18$). Patients who received CRYO transfusion had more total ($p < 0.01$) and major ($p < 0.01$) bleeding events after admission. There was numerically lower unadjusted 30-day survival (or transplant within 30 days) in those patients receiving CRYO transfusion (45.6%) compared with those who did not (58.9%), $p = 0.12$, but the unadjusted difference was statistically significant at 90 days ($p = 0.03$).

This was a retrospective noninterventional study and real-time patient management was determined by the clinical team caring for the patient. The indication for CRYO administration in an individual patient was not always documented clearly, but active or recent bleeding was the most common recorded indication for CRYO use. Of all patients receiving CRYO, 22% had esophageal or gastric variceal bleeding, 22% had nonvariceal GI bleeding, and 14% had bleeding from a non-GI source. When bleeding was not the primary indication for transfusion, the remainder of the CRYO-administered group received transfusion for concern of a consumptive coagulopathy (36%) and/or treatment of an abnormal FIB level or for prophylaxis prior to invasive procedures (6%). The mean number of pooled CRYO doses (five pooled units per dose) administered was 2.3 (median: 1, range: 20, IQR: 1.0). Of 125 patients, 108 (86%) patients administered CRYO had at least one follow-up FIB level assessed within 24 hours of CRYO dosing. The mean FIB level increased by 27.8 mg/dL (SD:

28.2) per patient after transfusion from a mean starting level of 92.6 mg/dL (SD: 25.9) to a mean follow-up value of 119.0 mg/dL (SD: 30.7). The target threshold for level of FIB posttransfusion of CRYO was not specified in the clinical records in most subjects. Typically, the clinical aim at our institution is FIB greater than 100 to 120 in the setting of CRYO transfusion, although this is variably practiced. Of the patients who had a repeat FIB level checked after transfusion of CRYO in this study, 70.4% reached a threshold of greater than 100 mg/dL. FFP was used more often in patients who also received CRYO (30 vs. 10%, $p < 0.01$) and the mean number of FFP units administered was 2.5 (median: 1.5, range: 9.0, IQR: 2.5) with a mean drop in INR of 0.95 (SD: 1.86) after FFP administration from a mean starting value of 3.5 (SD: 2.2).

Adjusted Survival Analysis

Because of the clear correlation between severity of illness and initial FIB level, a multivariable time-dependent competing risks survival analysis was performed in both the total population and the predefined subpopulation presenting with bleeding (►**Table 3**). In the total population, CLIF-C ACLF score (HR: 1.053 per unit change, $p < 0.01$) and admission to the ICU for bleeding (HR: 0.416, $p < 0.01$) were the only statistically significant independent predictors of 30-day mortality. With adjustment for disease severity and indication, initial FIB level (HR: 0.999 per unit change, $p = 0.68$) and transfusion with CRYO (HR: 1.104, $p = 0.65$) were not independent predictors of mortality. In the subgroup of patients presenting with bleeding, CLIF-C ACLF score (HR: 1.045 per unit change, $p = 0.03$) was again independently associated with 30-day mortality. Again, in this bleeding population, neither initial FIB level (HR: 0.991 per unit change, $p = 0.21$) nor CRYO transfusion (HR: 1.500, $p = 0.44$) were independent predictors of mortality in this subgroup.

Discussion

Fibrinogen is a soluble glycoprotein that forms the scaffolding of a blood clot when converted to the active form of fibrin by the enzyme thrombin. It is a critical building block of an active clot and physiologically important for lasting control of bleeding after primary hemostasis has been achieved.[7] As with many of the prohemostatic clotting proteins, FIB is produced in the liver and the protein synthetic dysfunction related to cirrhosis affects both the quantity and quality of the FIB available to the patient with chronic liver disease.[29] The role of low FIB levels in the hemostatic capacity of patients with cirrhosis remains poorly understood. Although low FIB levels and delayed FIB to fibrin conversion due to posttranslational modifications in the FIB molecule have been suggested to contribute to bleeding,[30] there are also studies suggesting that the fibrin clot of patients with cirrhosis actually have prothrombotic properties despite decreased FIB plasma levels.[29] Low plasma FIB levels may thus be more indicative of decreased hepatic production rather than directly involved in the pathophysiology of bleeding. In addition, although early studies of fibrinolysis in cirrhosis demonstrated a correlation between hyperfibrinolysis and increased bleeding rates,[11–14] more recent studies have been unable to replicate a chronic hyperfibrinolytic state in decompensated cirrhosis and in fact suggest a hypofibrinolytic state especially in critically ill patients.[31]

Typical laboratory measures of hemostasis in cirrhosis indicate a steady-state deficiency of prohemostatic proteins that worsens as the course of liver disease progresses. However, the preserved ability of patients with liver cirrhosis to form adequate clots and achieve hemostasis has been demonstrated despite lower than normal levels of prohemostatic proteins including FIB.[17,32] It is not clear in patients with cirrhosis whether low FIB levels are merely a sign of progressive protein synthetic dysfunction (similar to the

Table 3 Multivariable analysis of factors associated with 30-day mortality in the total population and in patients admitted to the ICU for bleeding

Variable	Hazard ratio (HR)	95% CI of HR	Parameter estimate	Standard error	*p*-Value
Total population					
CLIF-C ACLF score (per unit change)	1.053	1.033–1.074	0.052	0.010	<0.01
Admission to ICU for bleeding	0.416	0.269–0.645	−0.876	0.222	<0.01
Initial fibrinogen level prior to any transfusion (per unit change)	0.999	0.992–1.006	−0.001	0.004	0.68
Transfusion with cryoprecipitate	1.104	0.717–1.699	0.099	0.220	0.65
Population admitted to ICU for bleeding					
CLIF-C ACLF score (per unit change)	1.045	1.005–1.086	0.044	0.020	0.03
Initial fibrinogen level (per unit change)	0.991	0.976–1.005	−0.009	0.007	0.21
Transfusion with cryoprecipitate	1.500	0.532–4.227	0.405	0.529	0.44

Note: Components of CLIF-C ACLF score include total bilirubin, creatinine, hepatic encephalopathy level, international normalized ratio, vasopressor use, oxygen saturation and FiO_2, age, and white blood cell count (see text). Hazard ratios for continuous variables indicate a change in hazard per unit change in the variable.

INR) or are in fact a rate-limiting component in clotting failure and an independent bleeding risk factor that could be reversed with transfusion. Because of this uncertainty and the lack of detailed scientific understanding of the FIB system in cirrhosis, transfusion protocols in patients with cirrhosis are extrapolated from noncirrhosis populations which have little pathophysiology in common with the critically ill cirrhosis patient.[9]

In the setting of our local institutional transfusion guidance (not specific to cirrhosis patients) suggesting consideration of transfusion with CRYO for FIB level less than 200 mg/dL in all patients presenting with bleeding or less than 150 mg/dL in all other critically ill patients, we undertook this retrospective study to determine if low FIB in the cirrhosis population was associated with bleeding complications and whether attempted increase of FIB with CRYO transfusion improved bleeding or survival. We found in this study that low FIB correlates well with validated disease severity indices and is indeed a marker of more severe liver disease but is not an independent risk factor for death or major bleeding complications in the critically ill cirrhosis population. This was true both in patients presenting with acute bleeding and those admitted to the ICU for nonbleeding indications. The effect of initial FIB levels on 30-day mortality was weakest in the group presenting with acute bleeding. It is well documented that GI bleeding, especially due to esophageal varices, is a favorable prognostic factor in cirrhosis patients admitted to an ICU.[33] In our study, as in others, it is clear that in the course of these bleeding events, many other prognostic factors prevailed over the role of low FIB. These other prognostic factors are strongly represented in our study by the CLIF-C ACLF score. Our findings suggest that FIB is a marker of disease severity and not an independent risk factor for death or bleeding, as correction of low FIB level with CRYO should not directly address underlying hepatic dysfunction. This notion is also supported by the finding in this study that CRYO transfusion showed no independent influence on death or bleeding complications despite increases in FIB levels after transfusion.

There are several limitations to our study and the retrospective nature of the data collection and analyses are the most obvious. We have attempted to control for confounders using validated disease severity indices, predefined subgroup analyses, and adequate sample size, but a prospective randomized study, especially in the population presenting with bleeding, would generate gold standard data. There are no randomized trials on the topic of low FIB in patients with cirrhosis and no studies published on the effect of CRYO transfusion on bleeding and survival in critically ill cirrhosis patients. Our retrospective study along with other published cross-sectional studies on this topic could yield useful planning and sample size information. We also did not have routine viscoelastic testing and other detailed hemostatic test results in a large enough portion of the population to better define true disease states such as disseminated intravascular coagulation or another consumptive process. Also, FIB concentrates were not available during this study period for cirrhosis patients in the United States; so, all factor replacement was achieved through CRYO. It is possible that more specific repletion of FIB with concentrates could be a more effective therapy, but there is no definitive evidence that FIB concentrates are clearly superior to CRYO for FIB replacement. Finally, despite a sample size of more than 230 patients, it is possible that we found no associations with FIB and CRYO on survival due to type 2 error.

In summary, we found that low FIB levels on presentation in critically ill patients with cirrhosis reflect disease severity and do not directly influence survival or bleeding complications. In addition, FIB level is not independent of other proven disease severity indicators in the cirrhosis population. This finding is independent of indication for admission to the ICU or initial presentation with bleeding. Transfusion with CRYO does not affect bleeding complications or outcomes. Further studies, particularly randomized controlled trials in the bleeding cirrhosis population, could help clarify the utility of CRYO as a resuscitative measure.

What is known about this topic?

- Hypofibrinogenemia is a common finding of uncertain significance in critically ill cirrhosis patients.
- No studies have evaluated the impact of transfusion for the correction of low fibrinogen levels in this population.

What does this paper add?

- Fibrinogen level reflects disease severity of critically ill cirrhosis patients but is not an independent predictor of death or bleeding.
- Cryoprecipitate transfusion does not affect bleeding or survival in this population.

Author Contributions

I.M.B.: aided in design and research plan and preformed data collection, manuscript writing, and editing; J.P.E.D., M.J.S., N. M.I.: aided in design, research plan, analysis, and editing manuscript; A.S., S.B.K., C.E.L., J.P.A.: data collection and validation; T.L.: aided in analysis and research design, critical review, and writing of manuscript; P.G.N.: conceptualization of project, study design, data collection/validation, analysis, writing of manuscript, and final editorial approval.

Conflict of Interest

None declared.

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