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Raising the bar on fibrinogen: a retrospective assessment of critical hypofibrinogenemia in severely injured trauma patients

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ABSTRACT

Objectives Fibrinogen depletion may occur at higher levels than historically referenced. We evaluated hypofibrinogenemia and associated mortality and multiple organ failure (MOF) after severe injury.

Methods Retrospective investigation including 417 adult patients with Injury Severity Score (ISS) >15. Demographics and injury characteristics were collected. Fibrinogen within 30 minutes of admission was described: <150 mg/dL, 150 mg/dL to 200 mg/dL and >200 mg/dL. Primary outcome: 28-day mortality. Secondary outcomes: 28-day MOF and blood product transfusion. Multivariable logistic regression model evaluated association of fibrinogen categories on risk of death, after controlling for confounding variables. Results presented as OR and 95% CIs.

Results Fibrinogen <150 mg/dL: 4.8%, 150 mg/dL to 200 mg/dL: 18.2%, >200 mg/dL: 77.0%. 28-day mortality: 15.6%. Patients with <150 mg/dL fibrinogen had over fourfold increased 28-day mortality risk (OR: 4.9, 95% CI 1.53 to 15.7) after adjusting for age, ISS and admission Glasgow Coma Scale. Patients with lower fibrinogen were more likely to develop MOF (p=0.04) and receive larger red blood cell transfusion volumes at 3 hours and 24 hours (p<0.01).

Conclusions Fibrinogen <150 mg/dL is significantly associated with increased 28-day mortality. Patients with fibrinogen <150 mg/dL were more likely to develop MOF and required increased administration of blood products. The optimal threshold for critically low fibrinogen, the association with MOF and subsequent fibrinogen replacement requires further investigation.

Level of evidence Level III

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low fibrinogen (ie, <100 mg/dL) is associated with mortality and increased blood product transfusion in severely injured trauma patients; however, critical fibrinogen depletion that is associated with poor outcomes may occur at higher levels.

WHAT THIS STUDY ADDS

⇒ Admission fibrinogen <150 mg/dL was independently associated with more than twice the odds of death, after adjusting for age, injury severity and Glasgow Coma Scale score. Fibrinogen <150 mg/dL was also associated with an increased rate of multiple organ failure (MOF) and greater volumes of blood product transfusion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies are needed to determine if fibrinogen replacement to levels >150 mg/dL is associated with decreased mortality, MOF and blood product transfusion.

INTRODUCTION

Approximately one-quarter of severely injured trauma patients demonstrate an acute traumatic coagulopathy (ATC) at hospital admission.[1] This coagulopathy is associated with significantly greater resource utilization, including blood product administration, and an increased risk of mortality. Historically, ATC was identified by specific conventional coagulation tests (CCTs), such as partial thromboplastin time, and international normalized ratio (INR), with specific focus on coagulation factor depletion as the underlying etiology of post-traumatic coagulopathy.[1 2] As the mechanisms and complexity involved in ATC further evolved, a cell-based model of coagulation was developed and incorporated multiple pathways that control post-traumatic hemostasis and that may ultimately contribute to early disorders in coagulation, serve as markers of clinical outcome and provide targets for potential areas of therapeutic intervention.[3 4]

Fibrinogen is a serum protein that on activation by thrombin is converted to fibrin to form a mesh-work, which binds platelets and contributes to a hemostatic clot.[5] Fibrinogen levels were traditionally not included as part of the CCTs that defined ATC. Interestingly, fibrinogen is depleted earliest and most rapidly among the coagulation factors after hemorrhage.[6 7] Within the last decade, multiple investigations describe that admission fibrinogen levels are associated with increased mortality in severely injured trauma patients.[7–11] Inaba *et al*[9] reported that critically low fibrinogen (ie, <100 mg/dL) was the most significant predictor of in-hospital death. Similarly, Rourke *et al*[11] noted that decreased fibrinogen levels were an independent predictor of 24-hour and 28-day mortality. Low admission fibrinogen is also associated with worse injury severity, increasing depth of clinical shock and volume of prehospital crystalloid resuscitation.[8–11] Lastly, there are reports linking the need for massive transfusion to admission fibrinogen levels.[12]

Perhaps most striking is the level at which admission serum fibrinogen is considered clinically relevant and associated with adverse outcomes in severely injured patients. Historically, fibrinogen was not considered critically low until levels were <100 mg/dL.[6 13] Although hypofibrinogenemia is well recognized to correlate with mortality, less is known about the critical level at which it does so. More recent investigations suggest that critical fibrinogen levels occur at greater thresholds than previously thought, perhaps even as high as 229 mg/dL.[14] Additionally, the association with hypofibrinogenemia and multiple organ failure (MOF) has not been well established. Therefore, the purpose of the present investigation was to evaluate the association of admission fibrinogen levels on MOF and mortality in a severely injured cohort.

METHODS

This is a retrospective investigation from a single academic trauma center. Following approval by the Institutional Review Board (University of Maryland, Baltimore: HP-00078011), we searched the institution's trauma database over a 2-year period from October 1, 2015 to October 31, 2017. Due to the retrospective nature of the study, a waiver of informed consent was granted and therefore individual patient consent was not obtained. This study fulfilled Strengthening the Reporting of Observational studies in Epidemiology guidelines. Inclusion criteria were patients 18–89 years of age, Injury Severity Score (ISS) >15 and transferred from the scene of injury. In addition, included patients were also required to have a plasma fibrinogen level obtained within 30 minutes of admission. Patients who were transferred from an outside facility, sustained a cardiac arrest prior to arrival or who did not have a plasma fibrinogen level obtained within 30 minutes of presentation to the trauma center were excluded.

We collected patient demographics, injury characteristics, admission physiology data, admission Glasgow Coma Scale (GCS) score and CCTs. The admission Shock Index (SI) was calculated as the quotient of the admission heart rate over the admission systolic blood pressure (SBP) for each patient prior to blood transfusion. This value is a well-described marker for injury severity that is associated with increased transfusion requirements and mortality.[15] Volume of transfused packed red blood cells (PRBCs) was collected, and the total amount of each product was calculated at 1 hour, 3 hours and 24 hours after admission. The Critical Administration Threshold (CAT) was also calculated, indicating transfusion of ≥3 units PRBCs in 1 hour, which represents an early marker for massive transfusion.[16] At the time of data collection, our statewide trauma system did not use prehospital blood products. In addition, the time of each CCT was determined, and all CCT were obtained within 5 minutes of each other. These CCT laboratory values included platelet count, INR and plasma fibrinogen levels. Plasma fibrinogen was measured using the STA-Fibrinogen 5 assay (Diagnostica Stago, Parsippany, NJ, USA) and an STA Evolution device (Diagnostica Stago). Measurement was based on the Clauss method, where diluted plasma is treated with concentrated thrombin, and the clotting time is referenced against a calibrated curve to determine fibrinogen level.

The primary outcome was 28-day mortality. Secondary outcomes were 28-day MOF, CAT+ within 1 hour of admission, total PRBCs transfusion during the first 3 hours of admission and total 24-hour PRBCs transfused. MOF was defined by the Denver organ failure score.[17] This score is well validated in the trauma literature and consists of an evaluation of four organ systems (cardiac, pulmonary, hepatic and renal) on each day of intensive care unit (ICU) stay. The organ failure score for each system is calculated daily on a scale of 0 to 3, with the summation of scores for the four organ systems comprising the total organ failure score. MOF was considered present if the total daily sum of the worst scores from each organ system was >3, with the first event of MOF occurring at least 48 hours after admission to the ICU. Time from hospital admission until the first day on which MOF occurred was documented.

Statistical analysis

Descriptive statistics were used to evaluate the entire study population. Linear data were assessed for distribution. Symmetrically distributed data were described as the mean and SD, whereas asymmetrically distributed data were described by the median and IQR. Categorical data were described as frequency (n), percent (%). Univariate analysis was performed on the entire study population with 28-day mortality as the dependent variable. Categorical variables were assessed by the χ^2 test. Symmetrically distributed data were evaluated with the one-way analysis of variance test, and asymmetrically distributed variables were tested by the Kruskal-Wallis test.

The primary aim of this investigation was to evaluate the association of fibrinogen levels on 28-day mortality. Therefore, considering prior studies, admission plasma fibrinogen was categorized as <150 mg/dL, 150 mg/dL to 200 mg/dL and >200 mg/dL. Variables that demonstrated a p value <0.1 were selected for insertion into a multivariable logistic regression model in a forward stepwise method. The final multivariable model reports the OR and 95% CI for each predictor variable with 28-day mortality as the outcome event. Collinearity was assessed by the variance inflation factor. Model calibration was tested with the Pearson χ^2 goodness-of-fit test, and model discrimination was evaluated with the area under the receiver operator characteristic (AUROC) curve. Statistical analysis was performed with Stata software V.12.1 (Stata Corp), and significance was considered for a p value <0.05.

For the secondary outcomes, admission fibrinogen was considered by values <150 mg/dL, 150 mg/dL to 200 mg/dL and >200 mg/dL. Analysis was performed in a univariate manner with fibrinogen strata as the independent variable and 28-day MOF, CAT+ within 1 hour of admission, total PRBCs transfused during the first 3 hours of admission and total 24-hour PRBCs transfused as the dependent variables, respectively. Separate multivariable logistic regression analyses were performed for 28-day MOF and CAT+ within 1 hour. Based on prior literature,[18] the first model was adjusted for age and ISS, with fibrinogen strata as the independent variable and 28-day MOF as the dependent variable. The second model was adjusted for the following variables, based on prior data[19]: ISS, AIS head and admission SBP, with fibrinogen strata as the dependent variable and CAT+ within 1 hour as the dependent variable. There adjustment for multiple comparisons with the secondary outcomes; therefore, these results should be interpreted as exploratory.

RESULTS

Four hundred and seventeen patients fulfilled inclusion and exclusion criteria. The median age was 37 years (IQR: 26–54), median ISS was 26 (IQR: 21–33), median GCS score on arrival to the trauma center was 14 (IQR: 6–15) and the mean admission SI was 0.79 (SD: 0.41). The majority of patients were male (354 of 417, 84.9%), sustained a blunt mechanism of injury (298 of 417, 71.5%) and were transported to the trauma center by

Table 1 Demographic and injury characteristics by admission fibrinogen levels

	Fibrinogen <150 mg/dL (n=20)	Fibrinogen 150 mg/dL to 200 mg/dL (n=76)	Fibrinogen >200 mg/dL (n=321)	P value
Age, md (IQR)	25 (21.5–32.5)	30 (24.0–40.5)	43 (27–55)	<0.001
Blunt mechanism of injury, n (%)	5 (25)	45 (54.2)	238 (74.1)	0.03
Land transport, n (%)	8 (40)	46.0 (60.5)	189.0 (58.9)	0.23
Admission SI, mn (SD)	1.2 (1.03)	0.94 (0.46)	0.73 (0.29)	<0.001
Admission GCS, md (IQR)	3 (2-7)	14 (4–15)	14 (7–15)	<0.001
ISS, md (IQR)	34 (25–41)	27.0 (21.0–34.5)	26 (19–30)	0.001
Lactate (mmol/L), md (IQR)	6.1 (4.8–11.5)	5.2 (3.6–8.6)	3.5 (2.6–4.9)	<0.001
Platelets (×1000/µL), mn (SD)	178.6 (54.3)	223.2 (81.7)	240.4 (68.2)	0.003
INR, md (IQR)	1.8 (1.6–2.0)	1.2 (1.1–1.4)	1.1 (1.0–1.2)	0.001

Demographics and injury characteristics by admission fibrinogen <150, 150–200, and >200.
GCS, Glasgow Coma Scale; INR, international normalized ratio; ISS, Injury Severity Score; md, median; mn, mean; n (%), frequency, percent; SI, Shock Index.

ground (243 of 417, 58.3%). The mean admission fibrinogen was 262.3 mg/dL (SD: 87.6). The time from admission until the first fibrinogen value was obtained occurred at a mean of 12.0 minutes (SD: 6.0). Admission fibrinogen values were distributed among <150 mg/dL: 20 of 417 (4.8%), 150 mg/dL to 200 mg/dL: 76 of 417 (18.2%), and >200 mg/dL: 321 of 417 (77.0%). Patients in the lower admission fibrinogen strata (ie, <150 mg/dL and 150 mg/dL to 200 mg/dL) were significantly younger, had a greater admission SI, lower GCS, higher ISS, greater lactate and worse coagulation status, compared with patients with fibrinogen >200 mg/dL (table 1).

Primary outcome

Mortality occurred in 65 of 417 (15.6%) patients, and the cause of death was traumatic brain injury in 47 of 65 (72.3%), hemorrhage in 7 of 65 (10.8%), MOF in 6 of 65 (9.2%), respiratory failure in 1 of 65 (1.5%) and cardiogenic shock in 1 of 65 (1.5%). There were no differences in mechanism of injury, admission SI or admission lactate among patients who died (table 2). Results of an analysis from the patients that died due to traumatic brain injury (TBI) compared with other causes of death are presented in table 3.

Lower admission fibrinogen was associated with 28-day mortality (<150 mg/dL: 9 of 20, 45.0% vs 150 mg/dL to 200 mg/dL: 13 of 76, 17.1% vs >200 mg/dL: 44 of 321, 13.7%; p=0.001). Patients that died were also significantly older (53.5, IQR 31–72 vs 35, IQR 26–51; p=0.001), had a lower admission GCS score (4.5, IQR 3–9 vs 14, IQR 9–15; p=0.001) and greater ISS (30, IQR 25–35 vs 25, IQR 19–30; p=0.001). A multivariable logistic regression model demonstrated that admission fibrinogen <150 mg/dL, compared with 150 mg/dL to 200 mg/dL and >200 mg/dL, was an independent risk factor for 28-day mortality (OR: 4.9, 95% CI 1.53 to 15.7), after adjusting for age, ISS and admission GCS (table 4). There was no multicollinearity among variables, and the model did not demonstrate a lack of fit (p value >0.05). The AUROC for the multivariable model was 0.88.

Secondary outcomes

MOF occurred in 28 of 417 (6.7%) patients, and the median time to organ failure was 5.5 days (IQR 3.0–7.5). As previously described, MOF was the cause of death in 6 of 65 (9.2%) patients. Admission fibrinogen was significantly associated with 28-day MOF (<150 mg/dL: 4 of 20, 20.0% vs 150 mg/dL to 200 mg/dL: 6 of 76, 7.9% vs >200 mg/dL: 18 of 321, 5.6%; p=0.04). In a multivariable logistic regression model, only fibrinogen <150 mg/dL was significantly associated with 28-day MOF (OR: 4.02, 95% CI 1.09 to 14.88), after adjusting for age (OR: 1.02, 95% CI 1.00 to 1.04) and ISS (OR: 1.04, 95% CI 1.01 to 1.07). There was no evidence of collinearity in the model, and the AUROC was 0.71. There was a significant difference among admission fibrinogen strata in the frequency of patients that

Table 2 Study population by 28-day mortality

	Died (n=65)	Alive (n=352)	P value
Age, md (IQR)	53.5 (31.0–72.0)	35 (26–51)	<0.01
Male, n (%)	61 (93.8)	293 (83.2)	0.03
Land transport, n (%)	32 (49.2)	142 (40.3)	0.18
Blunt mechanism of injury, n (%)	52 (80.0)	246 (69.9)	0.1
Admission SI, mn (SD)	0.87 (0.7)	0.79 (0.4)	0.22
GCS, md (IQR)	4 (3-8)	14 (9–15)	<0.01
ISS, md (IQR)	30 (25–35)	26 (19–30)	<0.01
Lactate (mmol/dL), md (IQR)	3.5 (2.2–7.0)	3.9 (2.8–5.7)	0.55
Fibrinogen			<0.01
<150 mg/dL, n (%)	9 (13.8)	11 (3.1)	
150 mg/dL to 200 mg/dL, n (%)	13 (20.0)	63 (17.9)	
>200 mg/dL, n (%)	43 (66.2)	278 (79.0)	

GCS, Glasgow Coma Scale; ISS, Injury Severity Score; md, median; mn, mean; MOF, multiple organ failure; n (%), frequency, percent; SI, Shock Index.

Table 3 Demographic, injury and coagulation data by death due to TBI

	Death due to TBI (n=48)	Non-TBI related death (n=17)	P value
Age, md (IQR)	55.5 (36.0–73.0)	35.0 (27.0–55.0)	0.09
Male, n (%)	2 (4.2)	2 (11.8)	0.27
Blunt Mechanism of Injury, n (%)	40 (83.3)	12 (70.6)	0.26
Land Transport, n (%)	22 (52.1)	7 (41.2)	0.44
Admission SI, md (IQR)	0.53 (0.4–0.95)	1.04 (0.82–1.16)	0.01
ISS, md (IQR)	29.0 (25.0–33.5)	35.0 (30.0–50.0)	0.02
Lactate (mmol/dL), md (IQR)	3.3 (2.0–5.5)	8.4 (3.1–11.8)	0.01
Platelets (×1000/µL), mn (SD)	213.3 (75.4)	194.6 (83.1)	0.4
INR, md (IQR)	1.2 (1.1–1.6)	1.2 (1.1–1.6)	0.88
Fibrinogen, n (%)			0.15
<150 mg/dL	34 (70.8)	9 (52.9)	
150–200 mg/dL	9 (18.8)	4 (23.5)	
>200 mg/dL	5 (10.4)	4 (23.5)	

INR, international normalized ratio; ISS, Injury Severity Score; md, median; mn, mean; n (%), frequency, percent; SI, Shock Index; TBI, traumatic brain injury.

Table 4 Multivariable logistic regression assessing risk of 28-day mortality

	OR	95% CI	P value
Age	1.06	1.04 to 1.08	<0.001
ISS	1.04	1.01 to 1.07	0.001
GCS	0.80	0.75 to 0.86	<0.001
Fibrinogen			
>200 mg/dL	Reference		
150 mg/dL to 200 mg/dL	1.80	0.77 to 4.24	0.32
<150 mg/dL	4.91	1.53 to 15.7	0.02

Multivariable logistic regression model for risk of 28-day mortality.
GCS, Glasgow Coma Scale; ISS, Injury Severity Score.

achieved CAT+ status within the first hour of hospital admission (<150 mg/dL: 12 of 20, 60.0% vs 150 mg/dL to 200 mg/dL: 28 of 76, 36.8% vs >200 mg/dL: 37 of 321, 11.5%; p<0.01). In a separate multivariable model, after controlling for admission SBP (OR: 0.97, 95% CI 0.96 to 0.98), head AIS (OR: 0.82, 95% CI 0.69 to 0.97) and ISS (OR: 1.03, 95% CI 1.01 to 1.06), both fibrinogen <200 mg/dL (OR 2.89, 95% CI 1.5 to 5.53) and fibrinogen <150 mg/dL (OR: 7.14, 95% CI 2.21 to 23.05) were significantly associated with CAT+ within 1 hour of admission. There was also no evidence of collinearity and the AUROC was 0.84. Patients with lower admission fibrinogen also received significantly more PRBCs within the first 3 hours and 24 hours after admission (table 5).

DISCUSSION

In the current study, we described the phenotype of hypofibrinogenemia as younger, more severely injured patients, presenting with a higher lactate and who were more coagulopathic. Admission fibrinogen <150 mg/dL was associated with a greater risk of 28-day mortality, compared with 150 mg/dL to 200 mg/dL or >200 mg/dL. Patients with an admission fibrinogen <150 mg/dL and 150 mg/dL to 200 mg/dL, compared with >200 mg/dL, were more likely to receive greater amounts of PRBCs in the first few hours after hospital admission and achieve CAT+ status within 1 hour, which reflect a valuable marker to identify patients that receive a massive resuscitation, are at greater risk of death and require intense resource utilization. These patients represent an important population that may benefit from early, and potentially prehospital, blood product transfusion.[20–22] An interesting observation was that admission fibrinogen was associated with an increased incidence of MOF. This is particularly relevant given recent discussion regarding hypofibrinogenemia and endothelial glycocalyx damage after severe injury.[23] There is documented evidence that endothelial glycocalyx degradation is associated with increased MOF.[23] Although our observation is strictly hypothesis generating, this should encourage future investigations to study the implications of admission fibrinogen on subsequent post-traumatic MOF.

Fibrinogen exists in plasma as a serum protein that is cleaved by thrombin and subsequently polymerized to form strands of fibrin.[5 6 24] These fibrin strands serve as the framework on which platelets attach and are activated via glycoprotein IIb/IIIa receptors, further contributing to platelet activity, thrombin generation and clot amplification.[3 6] Therefore, fibrinogen is crucial to functional hemostasis after injury. The reported physiologic range of fibrinogen is between 1.5 and 4.0 g/L (eg, 150 mg/dL to 400 mg/dL)[3–5]; however, the serum concentration decreases rapidly during active bleeding and reaches critically low levels more quickly than other clotting factors, despite the fact it is an acute phase reactant protein. Additional processes involved with traumatic coagulopathy, such as endothelial glycocalyx degradation, autoheparinization, protein C activation and hyperfibrinolysis contribute to impaired and pathologic fibrinogen utilization after severe injury.[3 5] Iatrogenic causes are also responsible for rapid depletion of fibrinogen during hemorrhage such as excessive crystalloid resuscitation that dilutes serum coagulation factor concentrations and further exacerbates trauma- induced coagulopathy.[5 6 11] Similarly, blood product resuscitation may also contribute to further decreases in fibrinogen levels, as red cells, plasma and platelets are typically not sufficient to replace hypofibrinogenemia.[6 25]

Hypofibrinogenemia is an established marker of adverse outcomes; however, the precise threshold and quantitative fibrinogen level associated with clinical outcomes has not been clearly defined. Rourke *et al*[11] described that for every 1 mg/dL increase in fibrinogen, the risk of 28-day mortality decreased by 22%. The American Society of Anesthesiologists (ASA) Practice Guidelines for Perioperative Blood Management suggest that clinically relevant thresholds of hypofibrinogenemia exist at 80 mg/dL to 100 mg/dL and recommend that fibrinogen replacement rarely is indicated at levels <150 mg/dL.[13] Recent European guidelines suggest critical levels of fibrinogen are less than 150 mg/dL in bleeding patients; however, data to support this threshold are based on limited evidence.[26] The results of the current study demonstrate that admission fibrinogen <150 mg/dL is associated with a significantly increased risk of 28-day mortality, after adjusting for age, injury severity and admission GCS. It is important to acknowledge that our study population size may not have been large enough to detect differences in mortality at other fibrinogen thresholds, such as 150 mg/dL to 200 mg/dL. Hagemo *et al* observed in a multicenter study of 1133 trauma patients that a threshold for admission fibrinogen of 229 mg/dL was associated with a significant increase in mortality, suggesting that the critical value for low fibrinogen be reassessed.[14] Future studies would benefit from larger, multicenter populations to potentially identify an optimal cut-off at which fibrinogen is associated with worse clinical outcomes in trauma patients. Nonetheless, the results of our investigation provide further evidence that warrants reassessment of the presently suggested thresholds for critical levels of hypofibrinogenemia that are recommended by the ASA[13] and American College

Table 5 Admission fibrinogen levels and secondary outcomes

	Fibrinogen <150 mg/dL (n=20)	Fibrinogen 150 mg/dL to 200 mg/dL (n=76)	Fibrinogen >200 mg/dL (n=321)	P value
MOF, n (%)	4 (20)	6 (7.9)	18 (5.6)	0.04
CAT+ in first hour, n (%)	12 (60.0)	28 (36.8)	37 (11.5)	<0.01
Total PRBCs in first 3 hours, md (IQR)	11.5 (4.5–16.5)	3.0 (0.0–8.0)	0.0 (0.0–3.0)	<0.01
Total 24-hour PRBCs, md (IQR)	14.5 (5.0–29.5)	5.0 (0.0–9.5)	0.0 (0.0–3.0)	<0.01

CAT, critical administration threshold; md, median; mn, mean; MOF, multiple organ failure; n (%), frequency, percent; PRBCs, packed red blood cells.

of Surgeons Committee on Trauma in severely injured trauma patients.[27]

Perhaps more interesting from the present study is that fibrinogen levels were associated with MOF. A potential explanation for this finding may in part be associated with the endothelial dysfunction that occurs after traumatic injury and coagulopathy.[23] Endothelial glycocalyx damage is associated with the release of tissue plasminogen activator, dissolution of fibrin strands and subsequent hypofibrinogenemia.[28] In addition, destruction of the glycocalyx is also associated with increased levels of systemic syndecan-1, which correlates with organ dysfunction.[29] It has been observed in vitro that fibrinogen stabilizes syndecan-1 on the endothelial cell membrane to restore endothelial cell barrier integrity.[30] Additionally, in a mouse model of hemorrhagic shock, fibrinogen decreased microRNA-19b, a pathologic microRNA that contributes to endothelial cell dysfunction.[31] Barry *et al*[32] demonstrated in a similar mouse model of hemorrhagic shock that resuscitation with cryoprecipitate preserved endothelial cell function and reduced vascular permeability. There is also human data suggesting that fibrinogen may mitigate the development of MOF. The Reversal of Trauma-Induced Coagulopathy using First Line Coagulation Factor Concentrates or Fresh Frozen Plasma trial randomized severely injured patients to early fibrinogen or factor concentrate compared with fresh frozen plasma resuscitation and found that patients receiving fibrinogen had a significantly lower odds of developing MOF.[20] Due to the smaller sample size of our population, we are unable to comment on the effect of fibrinogen replacement via cryoprecipitate or to perform an adjusted analysis with MOF as an outcome. We selected the Denver MOF score because this is a validated scoring system in trauma patients with greater specificity for identifying prolonged mechanical ventilation, ICU length of stay and mortality.[17 33 34] However, other scoring systems, such as the Sequential Organ Failure Assessment and Multiple Organ Dysfunction Score, are also described in the tr

There are a number of additional limitations to this investigation. Due to the retrospective nature, we are unable to determine if low admission fibrinogen is the cause of the observed increased mortality. We also evaluate quantitative fibrinogen levels and were unable to investigate qualitative studies, such as functional fibrinogen. Furthermore, although we adjusted for clinically relevant confounding variables, there may be factors associated with death that we may have not captured in our analysis. For example, our trauma registry was not able to provide data on prehospital crystalloid content or volume. Clinical practice in our statewide trauma system is limited to prehospital crystalloid, and there is no administration of colloid; however, the precise effect of prehospital resuscitation volume in our cohort is unknown. We were also unable to obtain consistent temperature and serum pH values on admission for each patient. Hypothermia and acidemia are variables that may affect fibrin polymerization and function in bleeding patients.[6] Serum ionized calcium levels were not immediately obtained in every patient. Hypocalcemia affects hemostatic clot function and is associated with increased mortality.[35] The cause of death in a majority of patients in our cohort was due to TBI. Although TBI is associated with an inherent coagulopathy,[36] the results from this investigation may not be applicable to all trauma patients. It is possible that low fibrinogen is simply a specific marker of injury severity in patients with severe TBI that is not captured by other traditional measures of coagulopathy, such as INR.[37]

We were also unable to determine from the present study if fibrinogen supplementation in patients with hypofibrinogenemia results in decreased 28-day mortality. In the USA and UK, cryoprecipitate is used to treat acquired hypofibrinogenemia, with pooled units providing approximately 2g to 3g of fibrinogen, whereas fibrinogen concentrate is primarily used and approved for trauma patients in Europe.[38] A previous retrospective study observed that fibrinogen supplementation with higher ratios of cryoprecipitate: PRBCs in patients receiving a massive resuscitation was associated with decreased mortality in a combat support hospital[21]; however, there is limited prospective data on fibrinogen replacement and mortality in trauma patients. Results of the Early Cryoprecipitate for Major Hemorrhage in Trauma (CRYOSTAT-2) trial should be available in the near future, which compares early (within 90 minutes of arrival) high-dose cryoprecipitate to standard of care massive transfusion and the effect on mortality.[22] There is also current development of cryoprecipitate with a longer shelf-life that would allow for more readily available product in emergency settings. Our data collection also occurred prior to implementation of whole blood administration at our institution, and we are unable to draw conclusions on the association of whole blood transfusion in patients with low fibrinogen. We did not administer prehospital blood products in our statewide trauma system, and it is conceivable that earlier transfusion of fibrinogen containing blood products may impact the severity of hypofibrinogenemia at hospital arrival.[39–41] Although the current study does not address fibrinogen repletion, it does highlight the gap in current knowledge as to whether low fibrinogen is a biomarker of severe injury or a target for intervention.

In conclusion, we observed that traditional thresholds of hypofibrinogenemia are inadequate to define critical levels of fibrinogen in severely injured patients. The current data suggest that the association with hypofibrinogenemia and mortality may occur at <150 mg/dL. We have also shown an important association between hypofibrinogenemia and MOF. This may suggest that the effect of low fibrinogen levels extends beyond its effect on bleeding. Early identification of patients with hypofibrinogenemia may represent an important clinical target for specific early and targeted blood product transfusion, such as cryoprecipitate, fibrinogen concentrate or whole blood. Larger clinical studies that evaluate the full spectrum of trauma care and patient outcomes are necessary to identify the true impact of hypofibrinogenemia in the severely injured trauma population, which is necessary to guide replacement strategies and improve outcomes.

Contributors JR: study concept and design, data collection and interpretation, article preparation, study and manuscript guarantor. BTF: study design, data collection and interpretation, and manuscript interpretation. JHC: study concept and design, data collection and interpretation, and article interpretation. TS: study concept, data interpretation and article interpretation. RK: study concept and design, data interpretation and article preparation.

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REFERENCES

1 Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma* 2003;54:1127–30.
2 Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, *et al*. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011;39:2652–8.
3 Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. *Br J Anaesth* 2016;117:iii31–43.
4 Winearls J, Reade M, Miles H, Bulmer A, Campbell D, Görlinger K, Fraser JF. Targeted coagulation management in severe trauma: the controversies and the evidence. *Anesth Analg* 2016;123:910–24.
5 Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg* 2012;114:261–74.
6 Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. *Br J Anaesth* 2010;105:116–21.
7 Hayakawa M, Gando S, Ono Y, Wada T, Yanagida Y, Sawamura A. Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma: a retrospective observational study. *Semin Thromb Hemost* 2015;41:035–42.
8 Bouzat P, Ageron F-X, Charbit J, Bobbia X, Deras P, Nugues JBD, Escudier E, Marcotte G, Leone M, David J-S. Modelling the association between fibrinogen concentration on admission and mortality in patients with massive transfusion after severe trauma: an analysis of a large regional database. *Scand J Trauma Resusc Emerg Med* 2018;26:55.
9 Inaba K, Karamanos E, Lustenberger T, Schöchl H, Shulman I, Nelson J, Rhee P, Talving P, Lam L, Demetriades D. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg* 2013;216:290–7.
10 McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. *Injury* 2017;48:1074–81.
11 Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012;10:1342–51.
12 Schöchl H, Cotton B, Inaba K, Nienaber U, Fischer H, Voelckel W, Solomon C. Fibtem provides early prediction of massive transfusion in trauma. *Crit Care* 2011;15:R265.
13 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American society of anesthesiologists task force on perioperative blood management*. *Anesthesiology* 2015;122:241–75.
14 Hagemo JS, Stanworth S, Juffermans NP, Brohi K, Cohen M, Johansson PI, Røislien J, Eken T, Næss PA, Gaarder C. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. *Crit Care* 2014;18:R52.
15 Cannon CM, Braxton CC, Kling-Smith M, Mahnken JD, Carlton E, Moncure M. Utility of the shock index in predicting mortality in traumatically injured patients. *J Trauma* 2009;67:1426–30.
16 Meyer DE, Cotton BA, Fox EE, Stein D, Holcomb JB, Cohen M, Inaba K, Rahbar E. A comparison of resuscitation intensity and critical administration threshold in predicting early mortality among bleeding patients: a multicenter validation in 680 major transfusion patients. *J Trauma Acute Care Surg* 2018;85:691–6.
17 Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. *Shock* 2009;31:438–47.
18 Richards JE, Scalea TM, Mazzeffi MA, Rock P, Galvagno SM. Does lactate affect the association of early hyperglycemia and multiple organ failure in severely injured blunt trauma patients? *Anesth Analg* 2018;126:904–10.
19 Meizoso JP, Moore EE, Pieracci FM, Saberi RA, Ghasabyan A, Chandler J, Namias N, Sauaia A. Role of fibrinogen in trauma-induced coagulopathy. *J Am Coll Surg* 2022;234:465–73.
20 Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, Gruber G, Schmid S, Friesenecker B, Lorenz IH, *et al*. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematol* 2017;4:e258–71.
21 Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, Hess JR, Dubick MA, Simon CD, Beekley AC, *et al*. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma* 2008;64:S79–85.
22 Marsden M, Benger J, Brohi K, Curry N, Foley C, Green L, Lucas J, Rossetto A, Stanworth S, Thomas H, *et al*. Coagulopathy, cryoprecipitate and cryostat-2: realising the potential of a nationwide trauma system for a national clinical trial. *Br J Anaesth* 2019;122:164–9.
23 Johansson PI, Henriksen HH, Stensballe J, Gybel-Brask M, Cardenas JC, Baer LA, Cotton BA, Holcomb JB, Wade CE, Ostrowski SR. Traumatic endotheliopathy: a prospective observational study of 424 severely injured patients. *Ann Surg* 2017;265:597–603.
24 Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. *Transfusion* 2014;54:1389–405.
25 Khan S, Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, Curry N, Stanworth S, Gaarder C, Brohi K. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. *Intensive Care Med* 2015;41:239–47.
26 Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina R, Maegele M, Nardi G, Riddez L, *et al*. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019;23:98.
27 American college of surgeons. *Massive transfusion in trauma*, 2014. https://www.facs.org/-/media/files/quality-programs/trauma/tqip/transfusion_guildelines.ashx.
28 Chignalia AZ, Yetimakman F, Christiaans SC, Unal S, Bayrakci B, Wagener BM, Russell RT, Kerby JD, Pittet J-F, Dull RO. The glycocalyx and trauma: a review. *Shock* 2016;45:338–48.
29 Kozar RA, Pati S. Syndecan-1 restitution by plasma after hemorrhagic shock. *J Trauma Acute Care Surg* 2015;78:S83–6.
30 Wu F, Chipman A, Pati S, Miyasawa B, Corash L, Kozar RA. Resuscitative strategies to modulate the Endotheliopathy of trauma: from cell to patient. *Shock* 2020;53:575–84.
31 Chipman AM, Wu F, Kozar RA. Fibrinogen inhibits microRNA-19b, a novel mechanism for repair of haemorrhagic shock-induced endothelial cell dysfunction. *Blood Transfus* 2021;19:420–7.
32 Barry M, Trivedi A, Miyazawa BY, Vivona LR, Khakoo M, Zhang H, Pathipati P, Bagri A, Gatmaitan MG, Kozar R, *et al*. Cryoprecipitate attenuates the endotheliopathy of trauma in mice subjected to hemorrhagic shock and trauma. *J Trauma Acute Care Surg* 2021;90:1022–31.
33 Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, Maier RV, Burlew CC. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. *J Trauma Acute Care Surg* 2014;76:582–92.
34 Fröhlich M, Wafaisade A, Mansuri A, Koenen P, Probst C, Maegele M, Bouillon B, Sakka SG. Which score should be used for posttraumatic multiple organ failure? - Comparison of the MODS, Denver- and SOFA- Scores. *Scand J Trauma Resusc Emerg Med* 2016;24:130.
35 Moore HB, Tessmer MT, Moore EE, Sperry JL, Cohen MJ, Chapman MP, Pusateri AE, Guyette FX, Brown JB, Neal MD, *et al*. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. *J Trauma Acute Care Surg* 2020;88:588–96.
36 Cucher D, Harmon L, Myer B, Ngyuen A, Rankin T, Cook A, Hu C, Tesoriero R, Scalea T, Stein D. Critical traumatic brain injury is associated with worse coagulopathy. *J Trauma Acute Care Surg* 2021;91:331–5.
37 Maegele M, Schöchl H, Menovsky T, Maréchal H, Marklund N, Buki A, Stanworth S. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol* 2017;16:630–47.
38 Cushing MM, Haas T, Karkouti K, Callum J. Which is the preferred blood product for fibrinogen replacement in the bleeding patient with acquired hypofibrinogenemia-cryoprecipitate or fibrinogen concentrate? *Transfusion* 2020;60 Suppl 3:S17–23.
39 Curry N, Foley C, Wong H, Mora A, Curnow E, Zarankaite A, Hodge R, Hopkins V, Deary A, Ray J, *et al*. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Crit Care* 2018;22:164.
40 Curry N, Rourke C, Davenport R, Beer S, Pankhurst L, Deary A, Thomas H, Llewelyn C, Green L, Doughty H, *et al*. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. *Br J Anaesth* 2015;115:76–83.
41 Ziegler B, Bachler M, Haberfellner H, Niederwanger C, Innerhofer P, Hell T, Kaufmann M, Maegele M, Martinowitz U, Nebl C, *et al*. Efficacy of prehospital administration of fibrinogen concentrate in trauma patients bleeding or presumed to bleed (FIinTIC): a multicentre, double-blind, placebo-controlled, randomised pilot study. *Eur J Anaesthesiol* 2021;38:348–57.