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ORIGINAL ARTICLE

Association between fibrinogen levels and prognosis in critically bleeding patients: exploration of the optimal therapeutic threshold

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Abstract

Background Severe bleeding is a leading cause of ICU admission and mortality. Fibrinogen plays a crucial role in prognosis, yet optimal thresholds and supplementation targets remain unclear.

Method Patients with major bleeding were extracted from the MIMIC-IV database. Restricted cubic splines (RCS) identified the optimal pre-treatment fibrinogen threshold, and propensity score matching adjusted for confounders. Multiple analytical methods, including multivariable regression and machine learning models, were applied. Post-treatment fibrinogen levels were stratified based on guideline recommendations, and Cox regression assessed survival outcomes.

Results Among 7,063 patients (6,666 survivors, 397 non-survivors), RCS analysis revealed a nonlinear relationship between pre-treatment fibrinogen and ICU mortality (P-non-linear < 0.001), with a threshold at 1.3 g/L. Patients with Fib > 1.3 g/L had a significant 28-day survival benefit (OR = 0.65, 95% CI: 0.48–0.87, p < 0.01). Post-treatment stratification showed that fibrinogen ≥ 1.3 g/L was associated with improved survival (p < 0.01). RCS analysis identified an optimal post-treatment target of 2.0–2.5 g/L.

Conclusion Fibrinogen levels are predictive of ICU outcomes in massive hemorrhage. A pre-treatment threshold of 1.3 g/L indicates poor prognosis, while post-treatment levels of 2.0–2.5 g/L may optimize survival.

Keywords Fibrinogen · Major bleeding · Intensive care Unit · Therapeutic target · Retrospective cohort analysis

Abbreviations

ICU	Intensive Care Unit
MIMIC-IV	Multiparameter Intelligent Monitoring in Intensive Care Database IV
RCS	Restricted Cubic Splines
PSM	Propensity Score Matching
IPW	Inverse Probability Weighting
HR	Hazard Ratio
CI	Confidence Interval
Fib	Fibrinogen
FFP	Fresh Frozen Plasma
PLT	Platelet
RBC	Red Blood Cells
BUN	Blood Urea Nitrogen
WBC	White Blood Cells
PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
INR	International Normalized Ratio
APSIII	Acute Physiology Score III
SAPSII	Simplified Acute Physiology Score II
OASIS	Oxford Acute Severity of Illness Score
LODS	Logistic Organ Dysfunction System
SOFA	Sequential Organ Failure Assessment
CHARLSON	Charlson Comorbidity Index
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CAD	Coronary Artery Disease
AFIB	Atrial Fibrillation

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CKD	Chronic Kidney Disease
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-Related Acute Lung Injury
VIF	Variance Inflation Factor
ANOVA	Analysis of Variance
SD	Standard Deviation
SSMD	Standardized Mean Differences
SQL	Structured Query Language
ISTH	International Society on Thrombosis and Haemostasis
PO2	Partial Pressure of Oxygen
PCO2	Partial Pressure of Carbon Dioxide
PH	Potential of Hydrogen (pH)
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALB	Albumin
TBIL	Total Bilirubin
APACHE III	Acute Physiology and Chronic Health Evaluation III (mentioned in Discussion)

Introduction

Bleeding is one of the major reasons for ICU admission and a frequently occurring critical condition among ICU patients, with an incidence reaching up to 50% in some ICUs, significantly increasing patient mortality [1, 2]. The key to managing patients with severe hemorrhage lies in timely and accurate etiological treatment, anti-shock and transfusion therapy, as well as effective coagulopathy management [3–5]. Coagulation factor deficiency is a major cause of coagulopathy in massive transfusion, as coagulation factors become diluted following volume replacement with crystalloids or colloids and the transfusion of red blood cell components. Fibrinogen, the final component of the coagulation cascade, binds to platelets and promotes their aggregation, playing a crucial role as both a key component and substrate in clot formation. Therefore, fibrinogen is essential for effective coagulation and platelet function [6]. In patients with massive hemorrhage, extensive consumption, dilution due to volume replacement, and whole blood loss lead to a rapid decline in plasma fibrinogen levels, making fibrinogen the first coagulation factor to reach critically low levels [7]. After 150% blood loss, fibrinogen levels may reach a critical threshold of 10 μg/L. Subsequently, with 200% blood loss, the activity of other unstable coagulation factors decreases to 25% [3]. Hypofibrinogenemia increases the risk of coagulopathy, leading to poor clinical outcomes in ICU patients [8]. Low fibrinogen levels upon admission are independently associated with higher in-hospital mortality [9], and fibrinogen treatment has been shown to improve survival rates [10]. However, for patients without congenital fibrinogen deficiency who develop relative fibrinogen deficiency due to trauma or major surgery, there is not enough evidence to establish a clear threshold for starting supplementation [11].

Current global research on fibrinogen supplementation primarily focuses on specific conditions such as trauma, postoperative bleeding after cardiac surgery, liver transplantation, and postpartum hemorrhage [12–14]. There is still a lack of clinical research on massive hemorrhage in ICU patients. Due to the high heterogeneity of ICU patients, transfusion strategies during bleeding episodes may be influenced by various concurrent treatment approaches, including methods for coagulation monitoring, blood product transfusion, and hemostatic drug administration. Consequently, significant global variation exists in the management of critical bleeding patients and the formulation of transfusion protocols in the ICU [15, 16]. Nevertheless, even disease-specific guidelines provide varying recommendations on the optimal fibrinogen levels to maintain in bleeding patients [4, 17, 18]. As a result, there is no consensus on the threshold for initiating fibrinogen supplementation or the target levels to achieve [4].

Although the European Society of Intensive Care Medicine published international guidelines specifically for ICU transfusion in 2021 [4], These guidelines provide some guidance for clinicians when performing coagulation resuscitation in patients with severe hemorrhage. However, the ICU transfusion guidelines released by the European Society of Intensive Care Medicine in 2021 are primarily based on low-quality evidence, including recommendations for fibrinogen infusion, for which there is currently no recommendation. Observational studies on trauma suggest that low fibrinogen levels are associated with increased mortality, while higher fibrinogen levels may be linked to both reduced mortality and increased thrombus formation [19]. Before recommending the early use of fibrinogen supplementation, more evidence is needed regarding both empirical and laboratory-based approaches. Studies have shown that increased plasma fibrinogen levels are associated with a higher risk of coronary artery disease and myocardial infarction. Iatrogenic hyperfibrinogenemia has also become a potential concern during treatment [20]. There is also considerable variation in doctors'understanding of fibrinogen use. Therefore, how to rationally supplement fibrinogen in patients with severe hemorrhage remains an area that requires further exploration. The aim of this study is to explore the relationship between fibrinogen levels and prognosis in patients with severe massive hemorrhage, and to investigate the threshold and target levels for initiating fibrinogen supplementation in these patients.

Methods.

Data source

Data was acquired from the Multi-parameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV) version 2.2 which enrolled more than 60,000 ICU stays between 2008 and 2019 [21]. The database was operated by the Beth Israel Deaconess Medical Center. We accomplish the course,Protecting Human Research Participants (certification number: 46538344), which is a National Institutes of Health web-based course. Our permission was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and the Beth Israel Deaconess Medical Center.

Population selection

Patients were enrolled if they met the following criteria: (1) diagnosed with major bleeding according to ISTH defination [22]; (2) age ≥ 18 years; (3) stay in ICU for more than 24 h; (4) complete medical records and laboratory data; and (5) first stay was reserved if repetitively admitted into ICU. The study cohort flowchart is shown in Fig. 1. Defination of major bleeding according to ISTH: Symptomatic bleeding in critical areas (e.g., intracranial, retroperitoneal, pericardial), or Bleeding causing a hemoglobin drop of ≥ 2 g/dL (1.24 mmol/L) requiring transfusion of ≥ 2 units of red blood cells or whole blood.

Data extraction

We utilized Structured Query Language (SQL) to extract data from the Intensive Care Unit (ICU) patient records. These records included the patients'age, sex, race, weight, height, body mass index (BMI), various scoring systems (such as APSIII, SAPSII, OASIS, LODS, SOFA, and CHARLSON), use of mechanical ventilation, administration

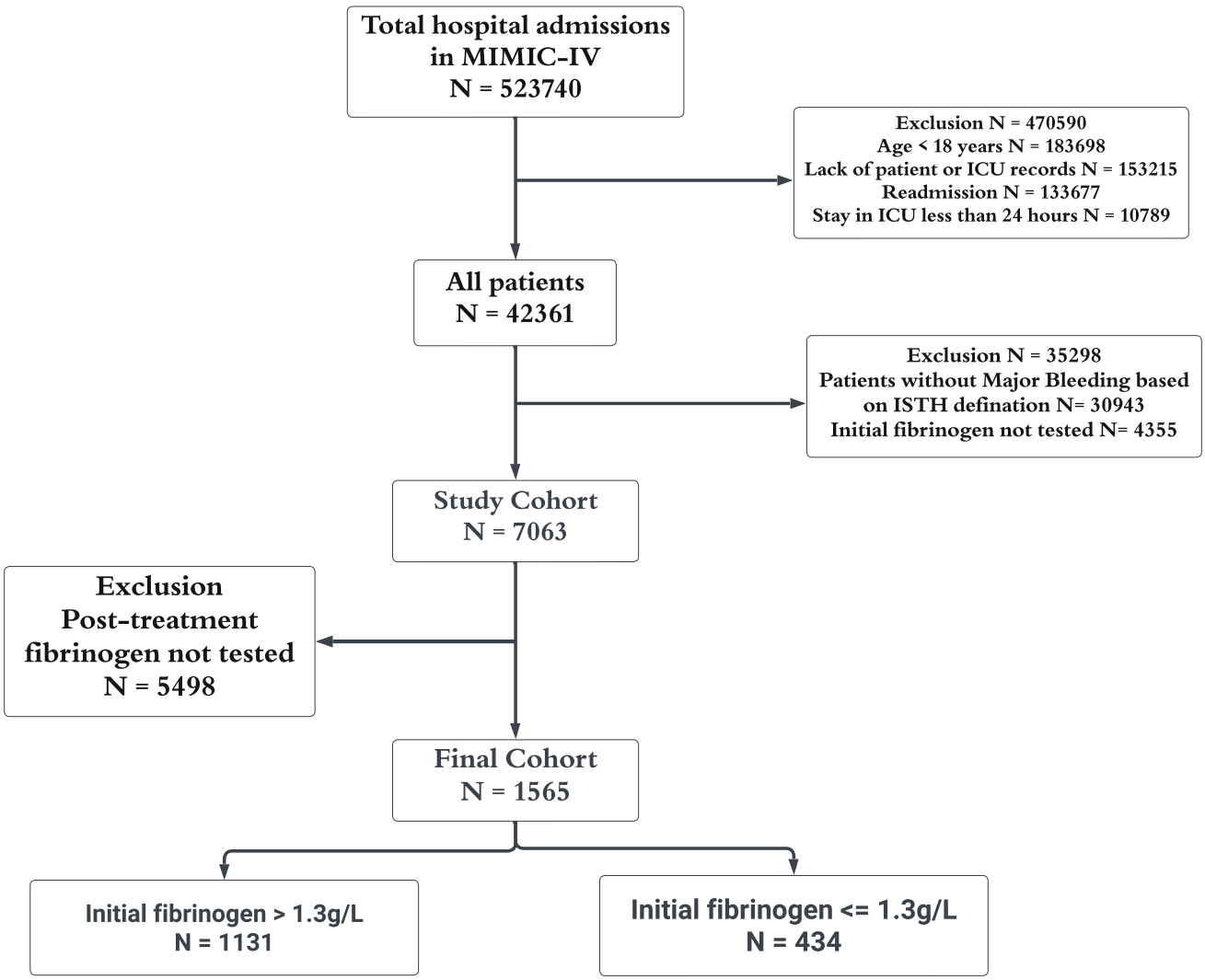

Fig. 1 Study Cohort Flowchart

of vasopressors and sedatives, presence of comorbidities (such as heart failure, atrial fibrillation, renal insufficiency, liver disease, chronic obstructive pulmonary disease, coronary artery disease, stroke, and malignancy), as well as laboratory tests performed within the first 24 h of admission (such as pH, partial pressure of oxygen, partial pressure of carbon dioxide, white blood cell count, red blood cell count, hemoglobin, platelet count, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, lactate, creatinine, prothrombin time, activated partial thromboplastin time, and international normalized ratio).

Pre-treatment fibrinogen level was defined as the worst fibrinogen value within the first 24 h of ICU admission, while post-treatment fibrinogen level was defined as the highest fibrinogen value recorded after the initial 24 h. These data are presented in Table 1. The primary outcome was 28-day survival, while secondary outcomes included ICU length of stay, total hospital length of stay, total red blood cell transfusion volume, total platelet transfusion volume, and total fresh frozen plasma transfusion volume. Except for fibrinogen, all laboratory parameters were collected only within the first 24 h of ICU admission. Variables with more than 20% missing data were excluded to minimize potential bias. For variables with less than 20% missing data, multiple imputation was performed to address missing values.

Statistical analysis

Continuous variables following a normal distribution were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequency (percentage). Group differences for normally distributed continuous variables were assessed using one-way analysis of variance (ANOVA) or Student's t-test, whereas the Kruskal–Wallis test was used for non-normally distributed continuous variables. Categorical variables were compared using the chi-square test.

Pre-treatment and post-treatment fibrinogen levels were analyzed as continuous variables using restricted cubic splines (RCS) to explore the dose–response relationship with the risk of major outcomes. Adjusted hazard ratios (HRs) were derived from fitted models, with the median fibrinogen level of all participants as the reference point. Separate RCS analyses were conducted to examine the association between fibrinogen levels (both pre- and post-treatment) and patient outcomes. Based on the inflection point (Fib = 1.3 g/L) identified from the RCS analysis, the study cohort was divided into a low fibrinogen group (Fib ≤ 1.3 g/L) and a high fibrinogen group (Fib > 1.3 g/L). Propensity score matching (PSM) was applied to adjust for confounding factors between groups.

For continuous outcome variables, standardized mean differences (SSMD) were calculated using paired t-tests to determine statistical significance, while McNemar's test was used for categorical outcomes. A series of sensitivity analyses were conducted to evaluate the robustness of the study findings and the impact of different causal inference models on our conclusions. Three causal inference models were applied in the sensitivity analysis: (1) a doubly robust model adjusting for all covariates, (2) an inverse probability weighting (IPW) model based on propensity scores, and (3) a multivariable logistic regression model. The estimated effect sizes and p-values from all models were reported and compared.

Patients were categorized into eight groups based on post-treatment fibrinogen levels: Group 1 (< 1.3 g/L), Group 2 (1.3–1.5 g/L), Group 3 (1.5–2.0 g/L), Group 4 (2.0–2.5 g/L), Group 5 (2.5–3.0 g/L), Group 6 (3.0–3.5 g/L), Group 7 (3.5–4.0 g/L), and Group 8 (> 4.0 g/L) [23]. Boruta analysis was performed to determine the importance of each variable in predicting patient outcomes and to select covariates for further modeling. To account for multicollinearity among covariates, the variance inflation factor (VIF) was calculated, with a VIF < 5 indicating that multicollinearity was unlikely to substantially affect the estimates. The selected covariates were then incorporated into a Cox proportional hazards regression model to estimate the association between each fibrinogen group and patient outcomes.

Results

Baseline characteristics of critically Ill ICU patients with severe bleeding

As shown in Table 1, a total of 7,063 ICU-admitted patients with bleeding were included in our study (Fig. 1), comprising 6,666 survivors and 397 non-survivors. Compared to the survivor group, non-survivors exhibited the following characteristics: a slightly younger mean age and a significantly higher proportion of females; a lower proportion of White patients and a higher proportion of other racial groups; lower body weight and height; significantly higher disease severity scores (APSIII, SAPSII, OASIS, LODS, SOFA, and Charlson); a higher prevalence of atrial fibrillation, liver disease, COPD, coronary artery disease, stroke, and malignancy; higher heart rate and respiratory rate, with no significant differences in systolic and diastolic blood pressure; significantly worse laboratory parameters, including pH, PO_2, white blood cell count, red blood cell count, hemoglobin, sodium, bicarbonate, chloride, blood urea nitrogen, lactate, and creatinine; prolonged PT, APTT, and INR; lower initial fibrinogen levels; and significantly longer ICU and total hospital length of stay.

Table 1 Baseline characteristics of study cohort

	Survivor ($N = 6666$)	Non_Survivor ($N = 397$)	p-value
Demographics			
Age (years)	66.13 (12.63)	66.03 (16.26)	0.304
Gender (Female)	2041 (30.62%)	179 (45.09%)	< 0.001
Race			
White	4834 (72.52%)	223 (56.17%)	< 0.001
Black	293 (4.40%)	30 (7.56%)	
Asian	170 (2.55%)	9 (2.27%)	
Other	1369 (20.54%)	135 (34.01%)	
Weight (kg)	86.26 (19.38)	82.78 (21.37)	< 0.001
Height (cm)	170.88 (10.27)	167.61 (10.90)	< 0.001
BMI (kg/m^2)	29.50 (5.97)	29.38 (6.39)	0.645
Severity Scores			
APSIII	39.87 (19.95)	79.28 (28.93)	< 0.001
SAPSII	38.48 (12.34)	56.65 (16.08)	< 0.001
OASIS	32.74 (7.51)	41.41 (8.89)	< 0.001
LODS	4.94 (2.56)	9.03 (3.13)	< 0.001
SOFA	5.69 (2.94)	10.91 (4.36)	< 0.001
CHARLSON	4.19 (2.29)	5.96 (3.01)	< 0.001
Interventions (1 st 24 h)			
Mechanical ventilation use	5428 (81.43%)	310 (78.09%)	0.112
Vasopressor use	5447 (81.71%)	311 (78.34%)	0.106
Sedative use	6354 (95.32%)	322 (81.11%)	< 0.001
Comorbidities			
HF	1417 (21.26%)	104 (26.20%)	< 0.05
AFIB	1447 (21.71%)	62 (15.62%)	< 0.01
Renal disease	958 (14.37%)	73 (18.39%)	< 0.05
Liver disease	214 (3.21%)	82 (20.65%)	< 0.001
COPD	602 (9.03%)	61 (15.37%)	< 0.001
CAD	4328 (64.93%)	122 (30.73%)	< 0.001
Stroke	450 (6.75%)	38 (9.57%)	< 0.05
Malignancy	593 (8.90%)	108 (27.20%)	< 0.001
Vital Signs (1 st 24 h)			
Temperature (°C)	36.26 (0.79)	36.16 (1.40)	0.269
Heart rate (bpm)	82.39 (14.26)	95.04 (21.33)	< 0.001
Respiratory rate (次/min)	15.82 (4.48)	20.69 (6.85)	< 0.001
SBP (mmHg)	113.84 (18.73)	114.02 (26.00)	0.537
DBP (mmHg)	60.53 (12.37)	63.57 (19.89)	< 0.05
MAP (mmHg)	78.31 (14.39)	77.92 (20.18)	0.08
Laboratory Tests (1 st 24 h)			
PH	7.39 (0.08)	7.29 (0.14)	< 0.001
PO2 (mmHg)	296.66 (109.03)	181.49 (121.96)	< 0.001
PCO2 (mmHg)	41.22 (7.65)	40.48 (13.01)	< 0.001
WBC ($\times 10^9$/L)	12.96 (7.68)	15.64 (14.42)	< 0.001
RBC ($\times 10^{12}$/L)	3.14 (0.62)	3.28 (0.93)	< 0.01
Hemoglobin (g/dL)	10.09 (2.22)	10.21 (2.69)	0.56
Platelet ($\times 10^9$/L)	150.01 (60.85)	155.75 (110.02)	< 0.01
Sodium (mmol/L)	135.90 (3.29)	137.56 (6.37)	< 0.001
Potassium (mmol/L)	4.62 (0.89)	4.53 (1.01)	< 0.001
Bicarbonate (mmol/L)	22.73 (2.80)	18.45 (5.32)	< 0.001
Chloride (mmol/L)	106.26 (5.68)	104.22 (7.75)	< 0.001

Table 1 (continued)

	Survivor (*N* = 6666)	Non_Survivor (*N* = 397)	*p*-value
BUN (mg/dL)	18.32 (10.94)	37.09 (28.56)	< 0.001
Lactate (mmol/L)	2.41 (1.36)	5.00 (3.94)	< 0.001
Creatinine (mg/dL)	1.01 (0.79)	1.91 (1.55)	< 0.001
PT (s)	16.24 (5.19)	22.61 (15.36)	< 0.001
APTT (s)	35.53 (18.96)	53.99 (33.90)	< 0.001
INR	1.48 (0.52)	2.12 (1.68)	< 0.001
Fibrinogen (g/L)	2.19 (0.94)	2.27 (1.72)	< 0.001
Fibrinogen treated* (mg/dL)	249.11 (128.01)	337.46 (210.45)	< 0.001
Outcomes			
Days in ICU	3.49 (5.20)	5.70 (5.10)	< 0.001
Days in hospital	8.36 (8.48)	7.20 (6.16)	< 0.001
RBC intake (mL)	647.59 (1539.10)	2066.40 (2922.24)	< 0.001
PLT intake (mL)	126.46 (434.02)	584.94 (1081.58)	< 0.001
FFP intake (mL)	226.08 (874.79)	1265.07 (2810.79)	< 0.001

Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Variables in bold have p-value < 0.05

Dose–response analysis of initial fibrinogen levels and 28-Day All-cause mortality

As shown in Fig. 2, after adjusting for age, sex, and race/ethnicity, the RCS analysis revealed a nonlinear relationship between initial fibrinogen levels and 28-day mortality (p-value < 0.05, p for nonlinearity < 0.01). A turning point was observed at a fibrinogen level of 1.3 g/L.

Primary outcome and sensitivity studies

As shown in Table 2, The doubly robust analysis demonstrated a significant beneficial effect of Fibrinogen Level in terms of the 28-day mortality. The adjusted odds ratio was 0.65 (95% CI 0.42–0.99, p < 0.001). For the sensitivity analysis, as summarized in Table 3, all four estimation models led to the same conclusion: patients who had high fibrinogen levels had lower 28-day mortality.

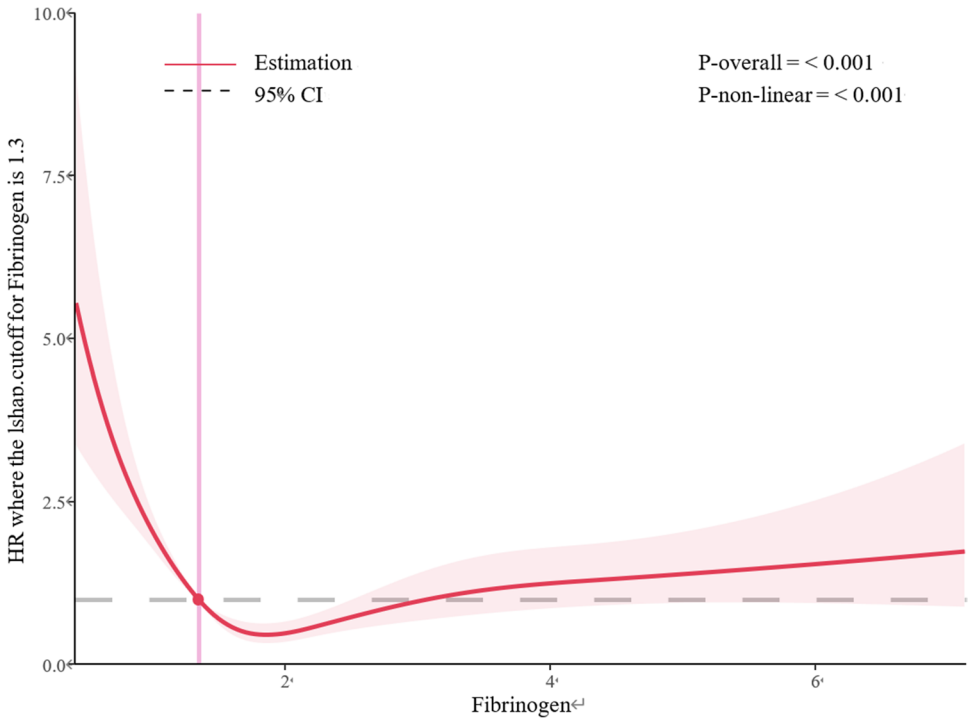

Fig. 2 RCS curve for the Pre-Treatment Fibrinogen Levels in 28-day mortality. RCS, Restricted cubic splines; HR, hazard ratio; CI, confidence interval

Table 2 Primary outcome with different models for cohort

	p-value	Result
Multivariate logistic model adjusted with all covariates [OR (95% CI)]	< 0.05	0.59 (0.39, 0.89)
Propensity score IPTW [OR (95% CI)]	< 0.01	0.65 (0.48, 0.87)
Doubly robust estimation with all covariates [OR (95% CI)]	< 0.05	0.65 (0.42, 0.99)
Doubly robust estimation with unbalanced covariates [OR (95% CI)]	< 0.05	0.63 (0.41, 0.96)

Statistical analyses of different models with p-value < 0.05 were displayed in bold

OR Odds Ratio, *CI* Confidence Interval

Clinical characteristics of the low and high fibrinogen groups

The cohort was divided into a high fibrinogen group (Fib > 1.3 g/L, n = 1,131) and a low fibrinogen group (Fib ≤ 1.3 g/L, n = 434). Propensity score matching was applied to adjust for confounding factors between the two groups, with the contribution of each covariate to the matching process shown in Appendix Fig. 1. A summary of the characteristics of the low and high fibrinogen groups before and after matching is presented in Table 3.

Clinical differences in patients with high and low fibrinogen levels

In our study cohort, patients in the high fibrinogen group exhibited significant differences upon hospital admission. Specifically, they had lower disease severity scores: APSIII (51.73 ± 25.80 vs. 65.19 ± 30.62), SAPSII (43.38 ± 15.75 vs. 47.76 ± 16.19), OASIS (35.25 ± 8.87 vs. 37.50 ± 8.39), LODS (6.32 ± 3.15 vs. 7.89 ± 3.22), and SOFA (7.47 ± 3.92 vs. 9.94 ± 4.28). Additionally, within the first 24 h of hospitalization, patients with higher fibrinogen levels had lower rates of mechanical ventilation (82.76% vs. 86.18%) and vasopressor use (73.03% vs. 79.26%).

As shown in Table 4, significant differences were observed between the high fibrinogen group (Fib > 1.3 g/L) and the low fibrinogen group (Fib ≤ 1.3 g/L). Patients in the high fibrinogen group had notable differences in ICU length of stay, total hospital stay, and transfusion requirements, including RBC, PLT, and FFP consumption (p < 0.001).

Dose–response analysis of post-treatment fibrinogen levels and 28-day all-cause mortality

A total of 1,565 patients with available post-treatment fibrinogen levels were included in the subsequent analysis. As shown in Fig. 3, after adjusting for age, sex, and race, the RCS analysis demonstrated an independent linear association between post-treatment fibrinogen levels and 28-day mortality (p < 0.001, p for nonlinearity < 0.01). A turning point was identified at a fibrinogen level of 2.3 g/L.

Exploration of the optimal therapeutic threshold for hypofibrinogenemia

The Boruta algorithm was employed to identify variables significantly associated with 28-day all-cause mortality (see Appendix Fig. 2). Multicollinearity among covariates was assessed using the variance inflation factor (VIF), with VIF < 5 indicating that multicollinearity is unlikely to affect estimation (see Appendix Fig. 3). The final model included the following covariates:"Creatinine,""Lactate,""BUN,""Chloride,""Bicarbonate,""Sodium,""Platelet,""WBC,""PCO2,""PO2,""PH,""SBP,""Respiratory_rate,""Heart_rate,""Temperature,""Liver,""Renal,""Sedative_use,""Mechanical_ventilation_use,""CHARLSON,""SOFA,"and"OASIS."

Based on recommendations from different guidelines, post-treatment fibrinogen levels were categorized into eight groups: Group 1 (< 1.3 g/L), Group 2 (1.3–1.5 g/L), Group 3 (1.5–2.0 g/L), Group 4 (2.0–2.5 g/L), Group 5 (2.5–3.0 g/L), Group 6 (3.0–3.5 g/L), Group 7 (3.5–4.0 g/L), and Group 8 (> 4.0 g/L). Group 1 was set as the reference group, and the selected covariates were incorporated into a Cox proportional hazards regression model. The results, presented in Table 5, indicate significant survival benefits across all groups compared to Group 1. Kaplan-Meier analysis demonstrated significantly divergent survival trajectories, with Group 1 showing rapid deterioration and sustained low levels, while higher fibrinogen groups exhibited progressively attenuated mortality risks (log-rank $p < 0.0001$) (see Fig. 4)

Discussion

This study is the first to investigate the relationship between initial ICU fibrinogen levels and prognosis in critically ill patients with major hemorrhage, revealing a nonlinear association. Lower initial fibrinogen levels were associated with worse outcomes, with patients having fibrinogen levels below 1.3 g/L experiencing poorer prognoses. Furthermore, post-treatment fibrinogen levels greater than 2.3 g/L, particularly within the range of 2.0–2.5 g/L, were associated with the most favorable outcomes, suggesting this as an optimal therapeutic target. These findings may facilitate early

Table 3 Baseline characteristics before and after propensity score matching of two cohorts

	Before Matching				After Matching			
	Fib > 1.3 (N = 1131)	Fib < = 1.3 (N = 434)	p-value	SMD	Fib > 1.3 (N = 204)	Fib < = 1.3 (N = 204)	p-value	SMD
Demographics								
Age (years)	63.57 (15.17)	60.09 (16.65)	< 0.001	0.219	61.25 (16.51)	61.27 (15.58)	0.981	0.001
Gender (Female)	413 (36.52%)	168 (38.71%)	0.456	0.045	77 (37.75%)	69 (33.82%)	0.47	0.082
Race								
White	756 (66.84%)	261 (60.14%)	< 0.05	0.148	122 (59.80%)	133 (65.20%)	0.566	0.08
Black	78 (6.90%)	33 (7.60%)			19 (9.31%)	15 (7.35%)		
Asian	46 (4.07%)	16 (3.69%)			10 (4.90%)	6 (2.94%)		
Other	251 (22.19%)	124 (28.57%)			53 (25.98%)	50 (24.51%)		
Weight (kg)	85.02 (20.47)	81.37 (20.29)	< 0.001	0.179	81.41 (19.70)	84.57 (20.74)	0.162	0.156
Height (cm)	170.55 (10.56)	169.53 (11.01)	0.102	0.094	169.68 (10.91)	170.80 (10.60)	0.375	0.105
BMI (kg/m^2)	29.17 (6.33)	28.19 (5.90)	< 0.01	0.161	28.22 (5.66)	28.87 (6.05)	0.37	0.112
Severity Scores								
APSIII	51.73 (25.80)	65.19 (30.62)	< 0.001	0.476	65.63 (28.53)	55.66 (25.04)	< 0.001	0.372
SAPSII	43.38 (15.75)	47.76 (16.19)	< 0.001	0.274	48.82 (16.36)	43.55 (14.35)	< 0.001	0.343
OASIS	35.25 (8.87)	37.50 (8.39)	< 0.001	0.26	38.23 (8.87)	35.26 (7.50)	< 0.001	0.363
LODS	6.32 (3.15)	7.89 (3.22)	< 0.001	0.492	7.84 (3.12)	6.89 (2.82)	< 0.01	0.322
SOFA	7.47 (3.92)	9.94 (4.28)	< 0.001	0.602	10.20 (4.03)	8.46 (3.74)	< 0.001	0.448
CHARLSON	4.68 (2.82)	4.47 (2.63)	0.253	0.079	4.97 (2.90)	4.61 (2.61)	0.195	0.13
Interventions (1 st 24 h)								
Mechanical ventilation use	936 (82.76%)	374 (86.18%)	0.118	0.094	180 (88.24%)	168 (82.35%)	0.124	0.167
Vasopressor use	826 (73.03%)	344 (79.26%)	< 0.05	0.147	156 (76.47%)	152 (74.51%)	0.73	0.046
Sedative use	1001 (88.51%)	377 (86.87%)	0.419	0.05	185 (90.69%)	172 (84.31%)	0.072	0.194
Comorbidities								
HF	259 (22.90%)	64 (14.75%)	< 0.001	0.21	43 (21.08%)	35 (17.16%)	0.378	0.1
AFIB	192 (16.98%)	81 (18.66%)	0.476	0.044	29 (14.22%)	37 (18.14%)	0.347	0.107
Renal disease	177 (15.65%)	51 (11.75%)	0.061	0.114	30 (14.71%)	28 (13.73%)	0.887	0.028
Liver disease	103 (9.11%)	102 (23.50%)	< 0.001	0.397	48 (23.53%)	34 (16.67%)	0.108	0.172
COPD	112 (9.90%)	29 (6.68%)	0.058	0.117	14 (6.86%)	14 (6.86%)	1	< 0.001
CAD	469 (41.47%)	116 (26.73%)	< 0.001	0.315	64 (31.37%)	64 (31.37%)	1	< 0.001
Stroke	91 (8.05%)	37 (8.53%)	0.836	0.017	14 (6.86%)	21 (10.29%)	0.289	0.123
Malignancy	252 (22.28%)	80 (18.43%)	0.11	0.096	51 (25.00%)	43 (21.08%)	0.411	0.093
Vital Signs (1 st 24 h)								
Temperature (°C)	36.46 (1.02)	36.16 (1.31)	< 0.001	0.252	36.19 (1.30)	36.40 (1.06)	0.153	0.177
Heart rate (bpm)	90.39 (19.44)	90.99 (20.07)	0.423	0.03	92.90 (19.75)	88.29 (17.11)	< 0.05	0.25
Respiratory rate (次/min)	18.16 (6.50)	18.24 (5.84)	0.23	0.013	19.33 (6.53)	17.79 (5.53)	< 0.05	0.255
SBP (mmHg)	116.23 (23.36)	113.89 (22.22)	0.107	0.103	113.36 (23.72)	115.07 (21.40)	0.566	0.076
DBP (mmHg)	63.18 (16.35)	63.23 (16.90)	0.976	0.003	61.26 (16.08)	63.73 (15.98)	0.122	0.154
MAP (mmHg)	80.11 (18.79)	78.71 (17.71)	0.204	0.077	78.00 (17.80)	79.43 (16.99)	0.402	0.082
Laboratory Tests (1 st 24 h)								
PH	7.35 (0.10)	7.30 (0.14)	< 0.001	0.408	7.30 (0.13)	7.35 (0.10)	< 0.001	0.395
PO2 (mmHg)	241.85 (128.31)	236.36 (131.61)	0.412	0.042	226.02 (132.03)	243.75 (130.60)	0.162	0.135
PCO2 (mmHg)	41.63 (10.22)	42.39 (12.56)	0.918	0.067	41.29 (12.27)	41.30 (9.35)	0.582	0.001
WBC ($\times 10^9$/L)	14.06 (10.51)	12.79 (7.25)	< 0.05	0.142	12.70 (9.16)	13.85 (7.28)	< 0.01	0.14

Table 3 (Continued)

	Before Matching				After Matching			
	Fib > 1.3 (N = 1131)	Fib < = 1.3 (N = 434)	p-value	SMD	Fib > 1.3 (N = 204)	Fib < = 1.3 (N = 204)	p-value	SMD
RBC ($\times 10^{12}$/L)	3.26 (0.82)	3.10 (0.86)	< 0.001	0.2	3.12 (0.91)	3.25 (0.78)	0.054	0.153
Hemoglobin (g/dL)	10.24 (2.43)	10.12 (2.60)	0.483	0.048	9.89 (2.69)	10.47 (2.41)	< 0.05	0.228
Platelet ($\times 10^{9}$/L)	153.79 (84.09)	116.44 (74.23)	< 0.001	0.471	115.85 (72.79)	141.87 (86.31)	< 0.001	0.327
Sodium (mmol/L)	136.83 (4.59)	137.16 (5.36)	0.099	0.066	136.94 (4.92)	136.50 (4.81)	0.467	0.089
Potassium (mmol/L)	4.51 (0.84)	4.55 (1.00)	0.979	0.045	4.53 (0.88)	4.46 (0.84)	0.402	0.087
Bicarbonate (mmol/L)	21.38 (4.14)	20.01 (4.96)	< 0.001	0.301	19.73 (4.67)	21.17 (4.05)	< 0.01	0.331
Chloride (mmol/L)	105.49 (6.08)	105.97 (6.95)	0.066	0.074	105.09 (5.98)	105.14 (6.29)	0.598	0.007
BUN (mg/dL)	23.15 (18.62)	24.77 (21.56)	0.131	0.08	25.91 (21.04)	24.72 (20.91)	0.468	0.057
Lactate (mmol/L)	3.17 (2.52)	4.64 (3.35)	< 0.001	0.498	5.07 (3.51)	3.39 (2.25)	< 0.001	0.573
Creatinine (mg/dL)	1.27 (1.12)	1.48 (1.36)	< 0.001	0.173	1.45 (1.19)	1.40 (1.45)	0.067	0.035
PT (s)	17.53 (9.63)	23.27 (14.48)	< 0.001	0.467	20.33 (14.81)	22.27 (14.57)	< 0.05	0.132
APTT (s)	41.41 (26.39)	57.36 (34.29)	< 0.001	0.522	46.32 (27.19)	51.57 (34.35)	0.224	0.17
INR	1.61 (1.01)	2.16 (1.41)	< 0.001	0.45	1.91 (1.76)	2.07 (1.41)	< 0.05	0.1
Fibrinogen (g/L)	2.37 (1.17)	0.98 (0.23)	< 0.001	1.66	2.13 (1.08)	1.01 (0.23)	< 0.001	1.45
Fibrinogen treated* (mg/dL)	3.80 (1.98)	2.91 (1.81)	< 0.001	0.467	3.53 (1.83)	2.91 (1.79)	< 0.001	0.342
Outcomes								
Days in ICU	6.46 (8.06)	8.13 (8.97)	< 0.001	0.197	7.53 (7.87)	8.08 (8.55)	0.744	0.068
Days in hospital	13.25 (13.14)	14.33 (14.30)	0.365	0.079	14.73 (12.87)	14.09 (13.40)	0.55	0.049
RBC intake (mL)	1707.18 (2294.85)	3366.44 (4001.52)	< 0.001	0.509	2653.79 (3120.10)	2871.79 (3615.00)	0.732	0.065
PLT intake (mL)	401.24 (777.35)	879.44 (1208.64)	< 0.001	0.471	739.77 (1049.06)	670.10 (968.26)	0.802	0.069
FFP intake (mL)	747.42 (1473.22)	1919.13 (3098.47)	< 0.001	0.483	1524.93 (2339.12)	1678.26 (3574.17)	0.617	0.051

Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Variables in bold have p-value < 0.05

identification of patients requiring intervention, enabling timely measures to improve prognosis.

Fibrinogen, a serum glycoprotein, plays a crucial role as a coagulation factor and is also involved in the inflammatory response, including the regulation of macrophage adhesion and the activation of cytokine and chemokine production [24]. Currently, many physicians have yet to fully recognize the critical role of fibrinogen in acute hemorrhage. Moreover, in many healthcare institutions, fibrinogen is not routinely monitored during treatment [25, 26]. However, there currently is a lack of awareness among physicians regarding the significance of fibrinogen during acute bleeding and, at many centers, fibrinogen is even not monitored routinely during treatment [27]. In criticallly sepsis patients, The elevated level of fibrinogen hints at better overall survival in critically ill patients with sepsis. Decreased levels of fibrinogen may be of little value in identifying patients with a high risk of death [28]. Our findings revealed that the initial fibrinogen level was independently and non-linearly associated with 28-day mortality. As fibrinogen levels decreased (p-value < 0.05, p for nonlinearity < 0.01), mortality significantly increased. A turning point was observed at a fibrinogen level of 1.3 g/L. Below this threshold, mortality sharply increased as fibrinogen levels declined, with a steep curve. Conversely, when fibrinogen levels exceeded 1.3 g/L, the impact on mortality was less pronounced, and the curve flattened.

Hypofibrinogenemia is a crucial predictor of poor prognosis in critically ill patients with hemorrhage, potentially due to several reasons. First, fibrinogen is a key protein in the coagulation process, as it is converted by thrombin into fibrin to form clots and prevent bleeding. When fibrinogen levels are low, hemostasis is compromised, increasing the risk of hemorrhage and leading to worse clinical outcomes. Second, low fibrinogen levels may indicate a greater extent of bleeding. Studies have shown that fibrinogen levels are closely related to bleeding risk, with hypofibrinogenemic patients exhibiting higher bleeding tendencies and more severe clinical manifestations. Additionally, fibrinogen plays a role in the inflammatory response. In our study, patients with low fibrinogen levels had significantly worse APACHE III, SAPS II, OASIS, LODS, and SOFA scores compared

Table 4 Secondary outcome analysis with propensity score matched cohorts

	Before Matching				After Matching			
	Fib > 1.3 (N = 1131)	Fib < = 1.3 (N = 434)	p-value	SMD	Fib > 1.3 (N = 204)	Fib < = 1.3 (N = 204)	p-value	SMD
Secondary Outcomes								
Days in ICU	6.46 (8.06)	8.13 (8.97)	< 0.001	0.197	7.53 (7.87)	8.08 (8.55)	0.744	0.068
Days in hospital	13.25 (13.14)	14.33 (14.30)	0.365	0.079	14.73 (12.87)	14.09 (13.40)	0.55	0.049
RBC intake (mL)	1707.18 (2294.85)	3366.44 (4001.52)	< 0.001	0.509	2653.79 (3120.10)	2871.79 (3615.00)	0.732	0.065
PLT intake (mL)	401.24 (777.35)	879.44 (1208.64)	< 0.001	0.471	739.77 (1049.06)	670.10 (968.26)	0.802	0.069
FFP intake (mL)	747.42 (1473.22)	1919.13 (3098.47)	< 0.001	0.483	1524.93 (2339.12)	1678.26 (3574.17)	0.617	0.051

Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Variables in bold have p-value < 0.05

to those with higher fibrinogen levels.Based on our findings, a decline in initial plasma fibrinogen levels serves as a valuable prognostic threshold for critically ill hemorrhagic patients, with 1.3 g/L potentially being a key predictive cutoff. Other studies have also supported the prognostic significance of fibrinogen levels in various diseases. For instance, one study found that in heart failure patients, plasma fibrinogen levels followed a U-shaped relationship with the risk of rehospitalization within six months, with the highest risk observed at a fibrinogen level of 2.4 g/L. Another study indicated that elevated fibrinogen levels were associated with poor prognosis in patients with liposarcoma. These findings further validate the prognostic value of fibrinogen levels across different diseases.Future research should explore the relationship between fibrinogen levels and inflammatory markers, as well as the potential for combining fibrinogen with other biomarkers to enhance prognostic accuracy.

During the coagulation process, adequate plasma levels of fibrinogen are crucial for the formation of stable blood clots. Fibrinogen molecules are cleaved by thrombin into fibrin monomers, which subsequently form a fibrin network that enmeshes platelets. In cases of major bleeding, fibrinogen reaches critically low plasma concentrations earlier than other coagulation factors [29].The normal range of plasma fibrinogen concentration is approximately 2 to 4.5 g/L. However, the minimum critical fibrinogen concentration required to maintain hemostasis remains a subject of debate. If depleted, the supplementation of fibrinogen is key for the

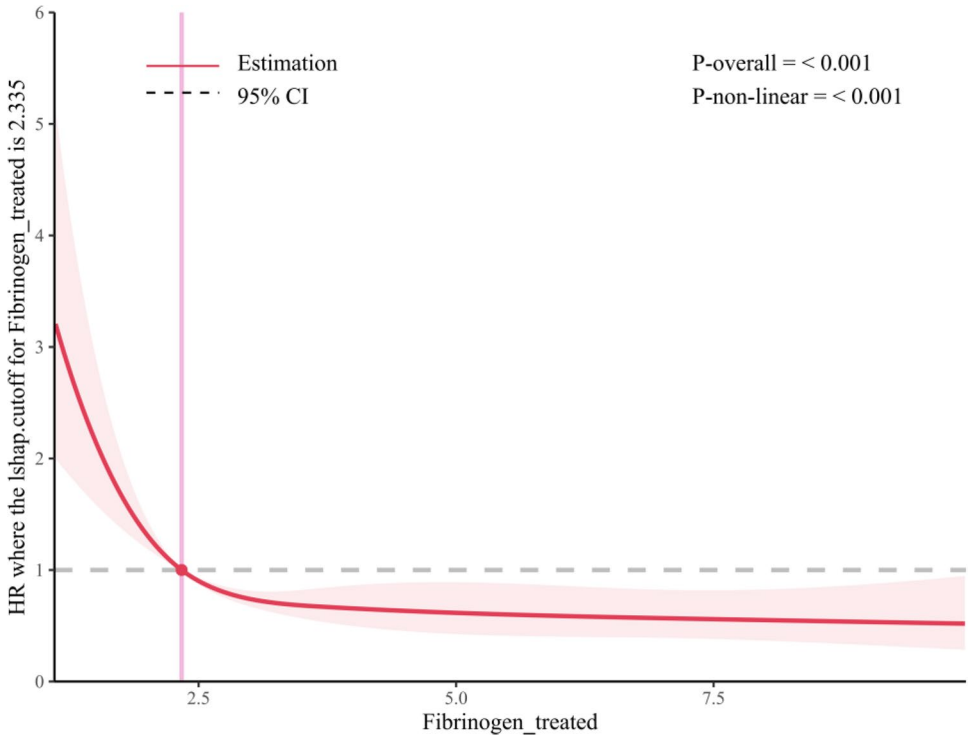

Fig. 3 RCS curve for the Post-Treatment Fibrinogen Levels in 28-day mortality. RCS, Restricted cubic splines; HR, hazard ratio; CI, confidence interval

Table 5 Multivariable Cox Proportional Hazards Analysis

Group	HR	95% CI	p-value
1	Ref		
2	0.28	0.12—0.66	< 0.001
3	0.22	0.11—0.43	< 0.001
4	0.15	0.07—0.29	< 0.001
5	0.10	0.05—0.21	< 0.001
6	0.11	0.05—0.24	< 0.001
7	0.13	0.06—0.31	< 0.001
8	0.10	0.05—0.2	< 0.001

Group1:Fibrinogen_treated < 1.3 g/L; Group2:Fibrinogen_treated 1.3 g/L ~ 1.5 g/L;

Group3:Fibrinogen_treated 1.5 g/L ~ 2.0 g/L; Group4: Fibrinogen_treated 2.0 g/L ~ 2.5 g/L;

Group5:Fibrinogen_treated 2.5 g/L ~ 3.0 g/L; Group6:Fibrinogen_treated 3.0 g/L ~ 3.5 g/L;

Group7:Fibrinogen_treated 3.5 g/L ~ 4.0 g/L; Group8:Fibrinogen_treated > 4.0 g/L

rescue and maintenance of hemostatic function; however, the threshold at which such intervention should be triggered is currently poorly define. Viscoelastic studies have shown that clot strength increases linearly with fibrinogen concentration suggesting that irrespective of the baseline plasma level,fibrinogen supplementation will always increase clot strength [30].In vitro viscoelastic analysis of whole blood has shown that clot strength increases linearly until fibrinogen concentration reaches 3.0 g/L, with a minimum threshold of 2.0 g/L required to maintain optimal clot formation rates. A systematic review found that preoperative fibrinogen levels serve as a negative predictor of postoperative bleeding, recommending a critical preoperative plasma fibrinogen infusion threshold of 2.5 g/L [31]. A secondary analysis based on the Zero-Plasma Trial found that in cardiac surgery, maintaining fibrinogen levels above 2.87 g/L was associated with improved patient outcomes [32]. However, there is still a lack of clinical research on a broader ICU population, leading to no consensus on the optimal threshold and target fibrinogen levels for supplementation in critically ill patients with major bleeding [33]. Our study found that, after adjusting for age, sex, and race, RCS curve analysis demonstrated an independent linear association between post-treatment fibrinogen levels and 28-day mortality, with a turning point at 2.335 g/L. The proposed supplementation threshold and target value fill the gap in fibrinogen supplementation for critically ill patients with major bleeding, providing more broadly applicable guidance for fibrinogen supplementation in a wider ICU bleeding population.

Guidelines demonstrate significant heterogeneity in recommended fibrinogen supplementation thresholds for hemorrhagic patients [23]. Currently, most clinical guidelines recommend a target range for fibrinogen supplementation rather than an absolute fixed value.Guidelines from the American Society of Anesthesiologists Task Force on Peri-operative Blood Management recommend fibrinogen supplementation for patients with bleeding and a plasma fibrinogen level below 0.8 to 1 g/L [34]. However, more recent European guidelines recommend threshold levels of 1.5 to 2 g/L relating to perioperative bleeding and trauma

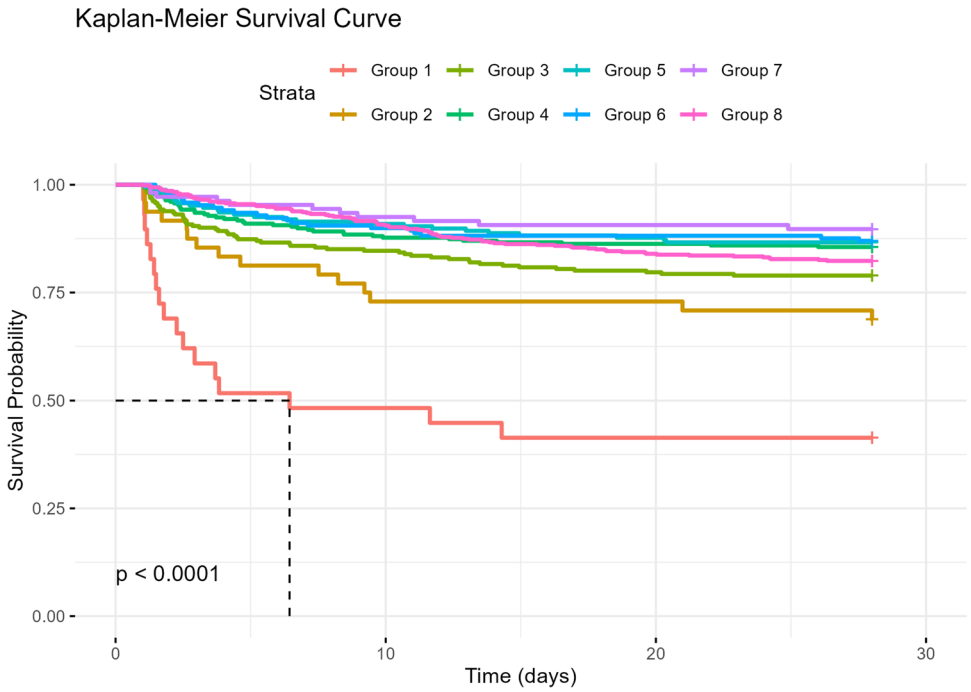

Fig. 4 Kaplan–Meier Survival Curves by Post-Treatment Fibrinogen Groups. Group1:Fibrinogen_treated < 1.3 g/L; Group2:Fibrinogen_treated 1.3 g/L ~ 1.5 g/L;Group3:Fibrinogen_treated 1.5 g/L ~ 2.0 g/L; Group4: Fibrinogen_treated 2.0 g/L ~ 2.5 g/L;Group5:Fibrinogen_treated 2.5 g/L ~ 3.0 g/L; Group6:Fibrinogen_treated 3.0 g/L ~ 3.5 g/L;Group7:Fibrinogen_treated 3.5 g/L ~ 4.0 g/L; Group8:Fibrinogen_treated > 4.0 g/L

[4, 35, 36]. For peripartum patients, fibrinogen levels should reach 5–6 g/L. If fibrinogen levels fall below 2 g/L, the risk of postpartum hemorrhage is 100% [37, 38]. Based on the general consensus of clinical guidelines, we categorized the optimal threshold range into eight groups for further analysis. We included patients with an initial fibrinogen level < 1.3 g/L (and those with post-treatment fibrinogen levels available, totaling 1,565 cases) to re-evaluate the optimal target level for replacement therapy.

The results showed that all groups exhibited significant survival improvement compared to Group 1(fibrinogen level less than 1.3 g/L). However, pairwise comparisons revealed no significant differences between groups beyond Group 4 (fibrinogen level 2.0–2.5 g/L), whereas significant differences were observed between groups before Group 4. This suggests that within a certain range, increasing fibrinogen levels is associated with improved survival, but beyond the level of 2.0–2.5 g/L, this trend is no longer significant. This finding provides critical clinical guidance, indicating that fibrinogen levels should be maintained within an appropriate range during treatment to optimize patient outcomes.

Current guidelines demonstrate significant heterogeneity in fibrinogen supplementation thresholds for hemorrhagic patients, largely due to evidence derived from specialized clinical contexts where thresholds are tailored to disease-specific pathophysiology [23]. Critically ill patients with major hemorrhage frequently present multisystem pathologies, rendering conventional single-disease thresholds inadequate. Notably, achieving post-treatment levels of 2.0–2.5 g/L correlated with optimal prognosis, surpassing current disease-specific targets. These thresholds reflect critical care-specific pathophysiology: synergistic fibrinogen depletion from systemic inflammation/endothelial injury and hemodilution from resuscitation necessitated higher concentrations to compensate for platelet dysfunction and coagulation factor imbalances. Targeting 2.0–2.5 g/L might address multifactorial hemostatic demands.

While our study employed robust statistical methods including restricted cubic splines for dose–response analysis, propensity score matching to address baseline confounding, and sensitivity analyses with doubly robust estimator, these approaches remain constrained by the inherent limitations of observational designs. Notably, residual confounding from unmeasured variables and time-varying factors could not be fully eliminated. Other methods such as the target trial emulation (TTE) framework might also strengthen causal inference by explicitly defining hypothetical trials in priori [39]. Future prospective studies adopting TTE principles could utilize advanced causal inference techniques to rigorously analyze the temporal relationships between fibrinogen levels, concurrent interventions, and clinical outcomes in critical hemorrhage settings [40].

Our study has several limitations that warrant consideration. First, the retrospective observational design, despite employing propensity score matching and multivariable adjustment, inherently carries risks of residual confounding due to unmeasured variables and selection biases inherent to electronic health record-derived cohorts. Second, while we rigorously applied the ISTH criteria for major bleeding identification, potential misclassification bias may persist from diagnostic coding inaccuracies or incomplete documentation within the database. Thirdly, while we choose the post-treatment fibrinogen level as the target of therapy, other confounding factors might also influence level of fibrinogen, which is dificult to exclude in a retrospective study. Lastly, the single-center nature of our cohort may limit the generalizability of findings to diverse clinical settings. These constraints underscore the necessity for further prospective multicenter cohorts or randomized controlled trials to validate the external applicability of our conclusions regarding fibrinogen supplementation thresholds.

Conclusion

This study, based on the MIMIC-IV database, deeply explores the relationship between fibrinogen levels and prognosis in critically ill bleeding patients. Our findings are as follows: 1) Initial fibrinogen levels are an independent risk factor for poor prognosis in critically ill bleeding patients; 2) Initial fibrinogen levels are nonlinearly associated with ICU mortality, with a turning point at 1.3 g/L, which may represent the optimal threshold for predicting prognosis in critically ill bleeding patients. After treatment: 1) For critically ill bleeding patients with hypofibrinogenemia, increasing fibrinogen levels contributes to improved prognosis; 2) We found a significant nonlinear relationship between post-treatment fibrinogen levels and 28-day mortality, with a turning point at 2.335 g/L; 3) A fibrinogen target range of 2.0–2.5 g/L may be the potential optimal target for fibrinogen supplementation in patients with severe bleeding.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00068-025-02886-8.

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Author contributions Ren Bingkui contributed to the conception and design of the study. Zhang Yuping performed data extraction, data analysis, and results visualization. Ren Bingkui and Zhang Yuping contributed equally to this paper and should be considered as co-first authors.Chen Siying, Dai Jinglong, and Chong Junci were responsible

for manuscript drafting. Chang Zhigang provided critical revisions for intellectual content, supervised the manuscript review and editing, and acquired funding for the research.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Access to the MIMIC-IV database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC), respectively. This research utilized de-identified, publicly available data from the MIMIC-IV repository; therefore, the requirement for ethical review and written informed consent was formally waived by the overseeing ethics committees.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

Clinical trial number Not applicable.

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