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THE HYPERFIBRINOLYTIC PHENOTYPE IS THE MOST LETHAL AND RESOURCE INTENSE PRESENTATION OF FIBRINOLYSIS IN MASSIVE TRANSFUSION PATIENTS

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Abstract

BACKGROUND—Among bleeding patients, we hypothesized that the hyperfibrinolytic (HF) phenotype would be associated with the highest mortality, while shutdown (SD) patients would have the greatest complication burden.

METHODS—Severely injured patients predicted to receive a massive transfusion at 12 level-1 trauma centers were randomized to one of two transfusion ratios as described in the PROPPR trial. Fibrinolysis phenotypes were determined based on admission clot lysis at 30 minutes (LY30): SD ≤0.8%, physiologic (PHYS) 0.9–2.9% and HF ≥3%. Univariate and multivariate analysis was performed. Logistic regression was used to adjust for age, gender, arrival physiology, shock, injury severity, center-effect and treatment arm.

RESULTS—Among the 680 patients randomized, 547(80%) had admission TEG values available to determine fibrinolytic phenotypes. Compared to SD and PHYS, HF patients had higher ISS (25 vs. 25. vs. 34), greater base deficit (−8 vs. − vs. −2) and were more uniformly hypocoagulable on admission by PT, PTT and TEG values; all p<0.001. HF patients also received more RBC, plasma and platelets (at 3, 6 and 24 hours), had fewer ICU, ventilator and hospital-free days, and had higher 24-hr and 30-d mortality. There were no differences in complications between the three

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phenotypes. Multivariate logistic regression demonstrated that HF on admission was associated with a 3-fold higher mortality (OR 3.06, 95% C.I. 1.57–5.95, p=0.001)

CONCLUSIONS—Previous data have shown that both the SD and HF phenotypes are associated with increased mortality and complications in the general trauma population. However, in a large cohort of bleeding patients, HF as confirmed to be a much more lethal and resource intense phenotype. These data suggest that further research into the understanding of SD and HF is warranted to improve outcomes in this patient population.

LEVEL OF EVIDENCE—II

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Keywords

Hemorrhage; Fibrinolysis; Hyperfibrinolysis; Complications

BACKGROUND

The Pragmatic, Randomized, Optimal Platelet and Plasma Ratio (PROPPR) trial was designed to address the effectiveness and safety of a 1:1:1 transfusion ratio to the 1:1:2 transfusion ratio for patients who were predicted to receive massive transfusion[1]. This study is seen as the logical progression of thought on how to best resuscitate the bleeding trauma patients. Since the start of the Global War on Terror in 2001, there has been a heightened focus and need to identify the best strategies and ratios for resuscitation for patients requiring massive transfusion.

In 2007 Borgman et al published data from a retrospective review of 246 combat casualties who received greater than 10 units red blood cells (RBCs) in a 24 hours period, breaking them down into low ratio, medium ratio, and high ratio plasma to RBCs[2]. Their review found that receiving massive transfusion in the high ratio plasma to RBCs (1:1.4) was independently associated with improved survival to hospital discharge by decreasing death from hemorrhage[3]. In 2011 Holcomb et al then published the PRospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study a prospective collection of data from ten US Level 1 trauma centers which identified that higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who were transfused at least three units of blood during the first 24 hours of admission[4].

Paralleling the advances in resuscitation strategy has been the implementation of viscoelastic testing, thrombelastography (TEG) and rotational thromboelastometry (ROTEM), as an adjunct test to facilitate resuscitation of massively transfused patients. The evaluation of the lysis of clot, quantified by the LY 30, has become an area of focus for research. Cotton et al in 2012 identified that an LY30> 3% was associated with significantly higher mortality and should be considered a therapeutic cutoff due to the abrupt doubling in mortality above that point[5]. Moore et al in 2016 stratified three distinct phenotypes of fibrinolysis at admission in a review of 2540 patients: (1) shutdown (SD) < 0.8%; (2) physiologic (PHYS) 0.9%–2.9%; and (3) hyperfibrinolysis (HF) >3%[6]. In their review they found that the shutdown

phenotype was the most common (46%) and was associated with an increased mortality (OR1.6, 95% CI 1.3–2.1, p = 0.0003).[7]

The purpose of our study is to evaluate the impact of the distinct fibrinolysis phenotypes in the severely injured trauma patients with major bleeding identified in the PROPPR trial. We hypothesized that the hyperfibrinolytic (HF) phenotype would be associated with the highest mortality, while shutdown (SD) patients would have the greatest complication burden.

METHODS

Study Design

The PROPPR study was a pragmatic phase III, multicenter randomized trial that compared the effectiveness of two transfusion and resuscitation strategies for bleeding patients.[8] The study began August 2012 and concluded enrollment December 2013. Patients were randomized to receive platelets, plasma, and red blood cells (RBC) in a ratio of either 1:1:1 or 1:1:2 during the acute phase of resuscitation. The study was approved by the US Food and Drug Administration (FDA) (Investigational New Drug No. 14929), Health Canada, and the Department of Defense, as well as each individual site's institutional review boards. The PROPPR study used exception from informed consent (21 CFR 50.24), including community consultation with delayed patient or legally authorized representative content.

Study Population

The PROPPR study was conducted at 12 North American level-1 trauma centers, screening those patients who were severely injured and who met local criteria for highest-level trauma activation. To meet the study's intended focus on those injured patients who were bleeding at the time of arrival, research team personnel were notified simultaneously with trauma team activation and were present prior to patient arrival. Given the aim of rapidly enrolling those patients with severe hemorrhage, inclusion criteria were as follows: (1) highest-level trauma team activation, (2) estimated age of 15 years or older or weight of 50 kg or greater if age unknown, (3) patient received directly from the injury scene, (4) having received at least one unit of any blood component transfused prior to hospital arrival or within 1 hour of admission and (5) predicted by an Assessment of Blood Consumption (ABC) score of 2 or greater or by physician judgment of the need for a massive transfusion (defined as ≥10 U of RBCs within 24 hours)[9].

Viscoelastic Testing

Along with traditional coagulation testing, thrombelastography (TEG) was used to obtain information on coagulation factor function, platelet function, clotting strength, and fibrinolysis. All TEG specimens were run on a TEG thrombelastograph 5000 (Hemoscope Corporation, Niles, IL). Blood specimens for TEG were obtained as part of the usual blood samples acquired during the primary or secondary survey evaluation of all enrolled patients. TEG values collected include the following: R-value (reaction time), which is a representation of the time to the beginning of clot formation; alpha (α) angle which is the slope of the tracing that represents the rate of clot formation; maximal amplitude (mA) which is the greatest amplitude of the tracing and reflects platelet contribution to clot

strength; and LY30 which represents the percent amplitude reduction at 30 minutes after mA and reflects the degree of fibrinolysis.

Outcomes and Definitions

As with the primary paper and analysis, the co-primary outcomes of interest in this sub-analysis were 24-hour and 30-day mortality. Secondary outcomes included ICU-free days, ventilator-free days, hospital-free days, venous thromboembolic events (VTE), multiple-organ failure (MOF), sepsis, acute kidney injury (AKI), and acute lung injury (ALI). Venous thromboembolism events were defined as pulmonary embolism or deep-vein thrombosis identified on ultrasonography or computed tomography angiography of the chest. Multiple organ failure was defined by the Denver multiple organ failure scoring system[10]. Sepsis and ALI were defined in accordance with the guidelines of the American College of Chest Physicians and the Society of Critical Care Medicine[11]. AKI was defined in accordance with the guidelines of the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group[12]. Ventilator-free days were defined as days alive and free from the ventilator, calculated as (30-total ventilator days) = ventilator-free days. For those who died before 30 days and had no days free of the ventilator, this was recorded as “0.” Similarly, ICU-free days were defined as days alive and not admitted to the ICU (30-total ICU days = ICU-free days) and hospital-free days were defined as days alive and not admitted to the hospital (30-hospital days = hospital free days). Injury scores such as Glasgow Coma Scale (GCS), weighted Revised Trauma Score (w-RTS), and Injury Severity Score (ISS) were also collected and evaluated. The w-RTS incorporates the initial GCS, systolic blood pressure, and respiratory rate, using coded and weighted values that range from 4 (normal) to 0 (poor) for each of the physiological variables (yielding a high of 7.84 and a low of 0). The AIS is an anatomic injury scoring system that quantifies injuries in various body regions from a score of 1 (minor injury) to 6 (non-survivable). ISS is calculated by summing the squares of the three highest AIS scores in three different body regions (values range from 1–75).

For purposes of analysis, patients were categorized according to their fibrinolysis phenotypes, as determined by their admission TEG LY30, as follows: hyperfibrinolysis (HF) was defined as LY30 >3%, fibrinolysis shutdown (SD) as LY30 of less than 0.8% and physiologic fibrinolysis (PHYS) as LY30 between 0.8% and 3%, based on the original description of the spectrum of post injury fibrinolysis defined by[13].

Statistical analysis

All analyses were performed using STATA Statistical software (version 12.1; StataCorp, College Station, TX). Continuous data are presented with the 25th and 75th percentile interquartile range (IQR) with comparisons between groups performed by use of the Kruskal-Wallis rank sum test. Categorical data were contrasted between fibrinolysis phenotypes with a Chi-square test. All statistical tests were 2-tailed.

Purposeful regression modeling was used to construct a multivariable logistic regression model. Variables were selected *a priori* based on clinical judgment and previous publications. Variables were entered into stepwise regression to identify statistically

significant variables. After this, variables with p <0.05 were entered into a multiple logistic regression model, developed to evaluate clinically and statistically significant variables with mortality as the outcome (dependent) variable; admission LY-30 phenotype was then added as the final independent variable to the model.

RESULTS

During the study period, 14,313 highest-level trauma activations occurred at the 12 sites, with 11,185 patients undergoing screening. Among these, 680 patients were enrolled and randomized (338 to the 1:1:1 group and 342 to the 1:1:2 group). Overall, 80% of patients were male and 64% were white, with a median age of 34 (24, 51). Mechanism of injury was blunt in 53%, with an overall median ISS of 26 (17, 41) and w-RTS of 6.81 (4.09, 7.84). For the study population, 24-hour and 30-day mortality were 14.7% and 24.1%, respectively.

Of the 680 enrolled, 547(80%) had admission TEG values available to determine fibrinolytic phenotypes. We evaluated the 133 patients for missingness patterns. There were no significant differences between those with missing admission TEG values and without missing values with respect to age, gender, race, mechanism of injury, arrival vital signs, injury severity or laboratory indicators of shock. There were also no differences in 24-hour or 30-day mortality between those with and without missing admission TEG values. The only significant finding was among sites where missingness ranged from as low as 4.8% per site to 59.7%.

The groups were described by admission phenotype and then analyzed; 333 (61%) patients had a SD profile, 95 (17%) patients had PHYS presentation and 119 (22%) had the HF phenotype. While there were no differences in age or gender, the PHYS presentation demonstrated a trend towards less White patients than that observed in the other phenotypes. (TABLE 1) While HF patients were more likely to have sustained blunt mechanism, those with PHYS phenotype were more likely to have had penetrating trauma. The HF phenotype had higher head AIS scores than the other phenotypes, while SD had lower abdominal AIS scores than the other phenotypes. Overall, however, the HF phenotype had higher ISS than both the SD and PHYS patients.

Consistent with their anatomic injury profile, the HF patients had lower admission GCS and worse w-RTS scores compared to the other two cohorts. (TABLE 2) The HF phenotype was also more profoundly coagulopathic by both admission TEG values and traditional coagulation testing. Not surprisingly, the HF group had greater laboratory evidence of shock on admission than the other two phenotypes.

In general, the HF phenotype was much more resource intensive and had higher mortality than the other two patient groups. (TABLE 3) HF patients received more RBC, plasma, and platelets than the SD and PHYS cohorts. The HF patients were also more likely to have received tranexamic acid than the other groups. HF patients had less ICU-free, ventilator-free, and hospital-free days. Both 24-hour and 30-day mortality were higher in the HF phenotype. (TABLE 4) There were no differences in complications between the three phenotypes.

A multivariate logistic regression was then created using variables chosen a priori and developed through a stepwise regression. Given the difference in missingness by site, enrollment site was added to the model. Stepwise regression generated age, gender, arrival physiology, shock, injury severity, and treatment arm as significant variables (enrollment sites were not significant). To this, was added the fibrinolytic phenotypes. This model demonstrated that HF on admission was associated with a 3-fold higher 30-day mortality. (TABLE 5) When this model was repeated for 24-hour mortality, HF also carried a 3-fold higher mortality compared to the other two phenotypes (OR 2.95, 95% C.I. 1.473–5.925; p=0.002).

DISCUSSION

In our large cohort of bleeding patients, HF is confirmed to be a much more lethal and resource intense phenotype. All three cohorts of patients were similar in terms of baseline characteristics and demographics, however the HF group had a significantly higher ISS at admission. This parallels the findings of Cotton et al in 2012 where the HF group in their retrospective review had a higher admission ISS than the non-HF group (ISS 25 vs ISS 16)[14]. Conclusions from that review cited the amount of prehospital crystalloid administered as a reason for the presence of HF on admission. However, in this study the HF group received less pre-randomization crystalloid (HF 1.0, PHYS 1.1, and SD 1.7) not statistically significant, pointing to the underlying pathophysiology, rather than amount of prehospital crystalloid as the reason for the difference.

Moore et al identified the SD phenotype to be associated with increased mortality and resource utilization in their retrospective review; our data, however, suggests that the HF phenotype is the group that requires the greatest amount of interventions and hospital resources[15]. The HF phenotype had fewer ICU free days, vent free days, and hospital free days. The HF phenotype also required significantly larger volume of transfused red cells, plasma and platelets. The HF phenotype did not, however, have a greater burden of post injury complications including VTE, MOF, Sepsis, Infection, AKI, or ALI.

Recent research has focused on the underlying molecular mechanisms for hyperfibrinolysis. The data from Chapman et al in 2016 suggests that overwhelming TPA release, not the degradation of Plasminogen Activation Inhibitor 1 (PAI-1), as the underlying cause of HF[16]. This determination was made based on findings from a novel TPA-challenged TEG and serves as a basis for further research. Lustenberger et al postulated that the depletion of Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) and its activated form (TAFIa) is responsible for HF and subsequent development of trauma-induced coagulopathy (TIC)[17]. While the purpose of this study was not to identify the molecular etiologies of HF, it is important to pursue the causes of HF in order to prevent the excess morbidity and mortality it causes. Not addressed in this study is the influence of the endothelium on the coagulation cascade and fibrinolysis. Research by Johansson et al involving biomarkers reflecting endothelial damage (syndecan-1, thrombomodulin, and sE-selectin) were shown to be independent predictors of mortality in a group of 424 trauma patients[18]. Identifying these by-products and coming up with novel treatment paradigms addressing them will hopefully decrease the morbidity and mortality of HF, but will require future research endeavors.

In our subgroup analysis we found that the administration of tranexamic acid (TXA) occurred in all three of the fibrinolytic phenotypes. We found, however, that 19.5% of the SD, 15.8% of the PHYS, and 27.7% of the HF phenotypes received TXA during our study. There was no significant difference in the incidence of prothrombotic complications in each of the subgroups. The difference in utilization of TXA may be secondary to the established practice patterns at individual institutions and that supported in the literature. Both Cotton et al and Chapman et al identified an LY-30 ≥3% as the threshold for starting TXA for patients requiring massive transfusion (when the patient was within three hours of injury)[19,20]. Further research is necessary to identify whether or not strict adherence to TEG based algorithms for patients with LY30 > 3% requiring massive transfusion will reduce mortality and complications associated with hemorrhage.

There are several obvious limitations to our study. While our sample size is large, 547 total patients, it is less than the total number of patients enrolled in the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study which analyzed 905 patient who received three total units of blood products within 24 hours[21]. Although we enrolled fewer patients, our study population is overall a more highly injured group of patients who all required MTP. All of our TEGs were run as standard TEGs, not as a rapid TEG (r-TEG). There is some research that may suggest that the addition of tissue factor (used in r_TEG but not standard TEG) may create different overall TEG when comparing the same sample run as a TEG vs r-TEG[22]. We do not feel, however, that this affected our results as our distribution of hyperfibrinolysis phenotypes directly parallels that of Moore et al in 2016 of 2540 patients whose TEG's were run as r-TEG, not standard TEG[23]. Finally, we were only able to include 547 (80%) of the 680 enrolled patients in the study, as 20% who fell-out did not have admission TEG. Extensive reviews of these patients at the time of data collection and analysis for the publication of the index article showed these patients to be random fall-outs, and not likely to skew the subsequent data one way or another.

CONCLUSION

Previous data have shown that both the SD and HF phenotypes are associated with increased mortality and complications in the general trauma population. However, in a large cohort of bleeding patients, HF as confirmed to be a much more lethal and resource intense phenotype. These data suggest that further research into the understanding of SD and HF is warranted to improve outcomes in this patient population.

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TABLE 1

Demographics and baseline variables by LYSIS phenotype

	SD (n=333)	PHYS (n=95)	HF (n=119)	p-value
Median age	34 (25, 52)	35 (22, 46)	34 (24, 55)	0.575
Male gender	81%	84%	77%	0.424
White race	67%	57%*	67%	0.060
Blunt mechanism	52%*	40%*	65%	0.001
Median head AIS	0 (0, 2)*	0 (0, 0)*	0 (0, 4)	0.005
Median chest AIS	3 (0, 4)*	3 (0, 4)	3 (0, 4)	0.397
Median abdomen AIS	2 (0, 4)*	3 (2, 4)	3 (0, 4)	0.009
Median extremity AIS	2 (0, 3)	2 (0, 3)	2 (0, 3)	0.847
Median ISS	25 (17, 38)*	25 (16, 34)*	34 (22, 45)	0.001

SD: shutdown, 0–0.8% LY-30; PHYS: physiologic, 0.9–2.9% LY-30; HF: hyperfibrinolysis, ≥3% LY-30; AIS: abbreviated injury scale; ISS: injury severity score; Medians are presented as 25^{th} and 75^{th} interquartile range

TABLE 2

Arrival physiology and laboratory data

	SD (n=333)	PHYS (n=95)	HF (n=119)	p-value
Median arrival SBP	100 (80, 123)	107 (82, 125)	100 (77, 130)	0.918
Median arrival HR	113 (93, 132)*	117 (94, 135)	120 (102, 136)	0.329
Median arrival temp	36.2 (35.7, 36.6)	36.4 (36.1, 36.8)	36.0 (35.5, 36.66)	0.875
Median arrival GCS	14 (3, 15)*	14 (11, 15)*	7 (3, 15)	<0.001
Median arrival w-RTS	6.37 (4.09, 7.55)	7.55 (6.08, 7.84)	5.96 (4.09, 7.55)	<0.001
Median arrival Hgb	11.7 (10.2, 13.4)	12.2 (10.7, 13.4)	11.3 (9.8, 13.0)	0.545
Median arrival PT	15.4 (14.3, 17.2)*	15.3 (14.4, 17.1)*	17.5 (15.7, 20.6)	0.007
Median arrival PTT	28.2 (25.0, 34.6)*	28.1 (25.8, 31.5)*	34.9 (30.0, 53.0)	<0.001
Median arrival Fibr	196 (132, 242)	258 (211, 290)*	171 (147, 222)	0.042
Median arrival r-value	3.8 (2.9, 4.5)	3.2 (2.5, 3.9)	4.3 (3.3, 5.5)	0.616
Median arrival k-time	1.5 (1.2, 2.0)	1.2 (1.1, 1.5)	1.7 (1.3, 2.3)	0.112
Median arrival angle	70 (64, 74)	74 (70, 76)	67 (58, 72)	<0.001
Median arrival mA	61 (56, 66)	62 (58, 66)	52 (37, 62)	<0.001
Median arrival LY-30	0.0 (0.0, 0.2)	1.6 (1.1, 2.0)	14.0 (5.6, 52.8)	<0.001
Median arrival lactate	5.6 (3.5, 8.1)	5.0 (3.4, 8.2)	9.1 (5.2, 12.4)	<0.001
Median arrival base	−8.0 (−2, −4)*	−6 (−10, −2)*	−12 (−18, −7)	<0.001

SD: shutdown, 0–0.8% LY-30; PHYS: physiologic, 0.9–2.9% LY-30; HF: hyperfibrinolysis, ≥3% LY-30; SBP: systolic blood pressure in mmHg; HR: heart rate in beats per minute; GCS: Glasgow coma scale; w-RTS: weighted revised trauma score; Hgb: hemoglobin; PT: prothrombin time in seconds; PTT: partial thromboplastin time in seconds; Fibr: fibrinogen; r-value: reaction time value in minutes; k-time: clot kinetics time in minutes; mA: maximal amplitude in millimeters; LY-30: percent lysis at 30 minutes from achieving 20mm deviation; Medians are presented as 25^{th} and 75^{th} interquartile range

TABLE 3

Resuscitation, transfusion and hemostatic data

	SD (n=333)	PHYS (n=95)	HF (n=119)	p-value
Median pre-random blood	2 (1, 3)	2 (1, 3)*	2 (2, 3)	0.001
Median pre-random IVF	1.7 (0.5, 3.0)*	1.1 (0.3, 2.5)	1.0 (0.1, 2.4)	0.060
Median RBC 0–60 min	4 (2, 6)	4 (3, 6)	6 (3, 8)	<0.001
Median plasma 0–60 min	2 (0, 3)	2 (0, 3)	3 (1, 5)	<0.001
Resuscitation Intensity	4 (2, 6)	4 (2, 6)	6 (4, 8)	<0.001
Median 24 hr RBC	9 (5, 14)*	7 (4, 12)*	15 (9, 24)	<0.001
Median 24 hr plasma	6 (3, 10)*	4 (2, 10)*	11 (4, 17)	<0.001
Median 24 hr platelets	6 (6, 12)*	6 (0, 12)*	12 (6, 24)	<0.001
Median 24 hr cryo	0 (0, 0)	0 (0, 0)	0 (0, 10)	0.263
Median 24 hr crystalloid	6 (4, 10)	7 (4, 10)	6 (3, 10)	0.732
Median 24 hr colloid	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.288
Received TXA	19.5%	15.8%*	27.7%	0.038
Early TXA	10.2%	5.3%*	13.5%	0.019
Late TXA	9.3%	10.5%	14.2%	0.127

SD: shutdown, 0–0.8% LY-30; PHYS: physiologic, 0.9–2.9% LY-30; HF: hyperfibrinolysis, ≥3% LY-30; IVF: intravenous crystalloid fluids; RBC: red blood cells; cryo: cryoprecipitate; TXA: tranexamic acid; Medians are presented as 25^{th} and 75^{th} interquartile range.

TABLE 4

Outcomes

	SD (n=333)	PHYS (n=95)	HF (n=119)	p-value
24-hour mortality	9%	5%	35%	<0.001
30-day mortality	17%	13%	54%	<0.001
Median ICU-free days	6 (1, 12)	7 (3, 11)	0 (0, 5)	<0.001
Median vent-free days	8 (2, 16)	10 (5, 17)	0 (0, 7)	<0.001
Median hosp-free days	4 (0, 17)	11 (0, 19)	0 (0, 10)	<0.001
VTE	20%	18%	20%	0.900
MOF	5%	2%	9%	0.056
Sepsis	30%	29%	23%	0.421
Infection	29%	38%	27%	0.177
AKI	23%	23%	27%	0.728
ALI	15%	9%	18%	0.180

SD: shutdown, 0–0.8% LY-30; PHYS: physiologic, 0.9–2.9% LY-30; HF: hyperfibrinolysis, ≥3% LY-30; ICU: intensive care unit; VTE: venous thromboembolic event; MOF: multiple organ failure; AKI: acute kidney injury; ALI: acute lung injury; medians are presented as 25^{th} and 75^{th} interquartile range

Table 5

Multivariate logistic regression model for 30-day mortality

	Odds ratio	95% C.I.	p-value
Age	1.03	1.020–1.054	<0.001
Male gender	1.30	0.631–2.680	0.475
w-RTS	0.62	0.523–0.733	<0.001
ISS	1.05	1.031–1.079	<0.001
Admission base value	0.92	0.880–0.967	0.001
Hyperfibrinolytic phenotype	3.06	1.578–5.949	0.001

95% C.I.: 95% confidence interval; w-RTS: weighted revised trauma score; ISS: injury severity score