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ORIGINAL ARTICLE

Hyperfibrinolysis: a crucial phenotypic abnormality of posttraumatic fibrinolytic dysfunction

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Abstract

Background: Traumatic fibrinolytic dysfunction is often categorized into 3 phenotypes based on the result of thromboelastography (TEG) lysis at 30 minutes (LY30): fibrinolysis shutdown, physiologic fibrinolysis, and hyperfibrinolysis. However, the molecular pathophysiology of fibrinolytic dysfunction and the association with clinical outcomes have not been fully evaluated.

Objectives: To assess whether posttraumatic fibrinolysis phenotypes identified by TEG correlate with levels of key fibrinolysis-related serum markers and with risk of mortality and hospital complications.

Methods: This is a secondary analysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial. Patients were stratified according to the degree of fibrinolysis upon arrival using TEG LY30 values: low LY30, <0.8%; normal LY30, 0.81% to 0.9%; and high LY30, ≥3%. Serial values of molecular markers (0-72 hours after admission) and clinical outcomes were compared between fibrinolysis groups.

Results: A total of 547 patients were included (low LY30, 320; normal LY30, 108; high LY30, 119). The high LY30 group had higher tissue plasminogen activator and plasmin-antiplasmin values upon hospital arrival than the low LY30 or normal LY30 groups ($P < .001$, respectively). There was no significant difference in levels of tissue plasminogen activator, plasmin-antiplasmin, and plasminogen activator inhibitor 1 between the low LY30 and normal LY30 groups. The high LY30 group was associated with an increased risk of 24-hour and 30-day mortality, while there was no significant difference in mortality between the low LY30 and normal LY30 groups.

Conclusion: Our results suggest that hyperfibrinolysis is the most common form of traumatic fibrinolytic dysfunction and is associated with worse outcome.

KEYWORDS
blood transfusion, hyperfibrinolysis, outcome, thromboelastography, trauma-induced coagulopathy

Essentials

- Data on fibrinolysis markers for identifying traumatic fibrinolytic dysfunction are scarce.
- We investigated fibrinolytic dysfunction and the association with clinical outcomes.
- Hyperfibrinolysis on hospital arrival was associated with increased risk of mortality.
- Hyperfibrinolysis as the true physiological state in traumatic fibrinolytic dysfunction.

1 | INTRODUCTION

Hemorrhage accounts for approximately 50% of all trauma deaths, and one of the primary goals in the management of patients with hemorrhagic shock is surgical and/or endovascular hemorrhagic control [1]. Additionally, it is reported that trauma-induced coagulopathy (TIC) is present upon arrival to the emergency department (ED) in approximately 40% of severely injured patients [2]. Viscoelastic hemostatic assays, such as thromboelastography (TEG), have been used to investigate the pathophysiology of TIC, and fibrinolytic dysfunction is considered a key component of TIC [3].

Previous studies proposed different fibrinolytic dysfunction phenotypes based on the results of the initial TEG on ED arrival as well as the early resuscitation period [4,5]. For example, traumatic fibrinolytic dysfunction is categorized into 3 groups based on the TEG lysis at 30 minutes (LY30) as follows: fibrinolysis shutdown, physiologic fibrinolysis, and hyperfibrinolysis [4]. The results in single- and multi-institutional studies suggest that fibrinolysis shutdown is the most common phenotypic abnormality observed on the initial TEG, whereas hyperfibrinolysis is associated with the greatest risk of mortality in trauma patients [4,6,7]. However, a recent study has suggested that fibrinolysis shutdown may not accurately represent TIC. Among the 3 different phenotypes, fibrinolysis shutdown may represent characteristics other than a coagulation disorder [8].

While TEG is a functional measure of coagulopathy, the molecular mechanisms underlying these functional phenotypes are not fully understood. In contrast to TEG data, there are scarce data on the utility of fibrinolysis-related serum markers in the pathophysiology of TIC [9,10]. Therefore, in the current study, we aimed to investigate the pathophysiology of traumatic fibrinolytic dysfunction by comparing the results between the fibrinolysis-related serum markers and TEG measurements. We hypothesized that hyperfibrinolysis represents a distinct phenotype that is associated with worse outcomes whereas fibrinolysis shutdown and physiologic fibrinolysis may be categorized into the same phenotype of fibrinolytic dysfunction.

2 | METHODS

2.1 | Study design and population

We performed secondary analysis of the data collected for the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial [11]. The PROPPR trial was a multicenter, randomized study designed to compare the effectiveness of 2 different ratios of blood products in severely injured patients [11]. We also excluded patients who did not have available TEG measurements upon arrival. Our study patients were stratified according to LY30 values on the TEG measurement upon arrival (low LY30 group, <0.8%; normal LY30 group, 0.81%–2.9%; and high LY30 group, ≥3%) [4]. Ethical approval for the current study was obtained from the Institutional Review Board of the University of Southern California.

2.2 | Data collection and testing

Patient demographics, injury severity and type, physiologic variables, and clinical outcomes were queried from the datasets from the PROPPR trial. Serum blood samples were collected at the time of ED arrival, then 2, 4, 6, 12, 24, 48, and 72 hours after admission and stored at −80 °C until further analysis. Tissue plasminogen activator (tPA; eBioscience), plasmin-antiplasmin (PAP; Abcam), and plasminogen activator inhibitor 1 (PAI-1; eBioscience) were measured by enzyme-linked immunosorbent assay. Whole blood was collected into citrated vacutainer tubes to use the TEG model 5000 (Haemonetics) in accordance with the company specifications.

2.3 | Study outcomes

The primary outcome of interest in this study was 24-hour and 30-day mortality, and the secondary outcome was total transfusion requirements during the hospital stay, cause of mortality, and hospital complications.

2.4 | Statistical analysis

Continuous variables were reported as medians with IQRs and categorical variables were reported as percentages. Univariable analysis was performed using Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Survival curves were estimated by the Kaplan–Meier method and compared between the study groups using the log-rank tests. A P value of <.05 was considered statistically significant. All data were analyzed using R for Windows version 4.3.1 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Patient characteristics

A total of 680 patients were included in the PROPPR trial. Of those, 547 patients met the criteria for the current study (low LY30 group, 320; normal LY30 group, 108; high LY30 group, 119; Figure 1). Table 1 summarizes patient characteristics. Patients in the high group were more likely to sustain blunt trauma (64.7%) compared with the low LY30 or normal LY30 groups (P = .039 and P < .001, respectively). Approximately one-third of the high LY30 patients had associated severe traumatic brain injury (TBI), and the median Glasgow Coma Scale score on admission was significantly lower than that in the other 2 groups (both P < .001). Similarly, the high LY30 group patients were more likely to sustain severe injuries defined by injury severity score ≥25. The high LY30 group had higher lactate values than the low LY30 or normal LY30 group (both P < .001).

3.2 | Fibrinolysis-related serum markers

Figure 2 shows serial values of the fibrinolysis-related markers from ED arrival to 72 hours after admission. The high LY30 group had higher tPA and PAP values upon arrival compared with the low LY30 or normal LY30 groups (both P < .001), while tPA and PAP values were not significantly different between the low LY30 and normal LY30 groups (P = .902 and P = .178, respectively). During the initial 24-hour period, tPA and PAP values were highest upon arrival to the ED in all 3 groups including the low LY30 and normal LY30 groups. PAI-1 values peaked over the initial 12 hours in all groups then downtrended between 12 and 72 hours after admission. There were no significant differences in PAI-1 values between the low LY30 and normal LY30 groups at any time points.

3.3 | Clinical outcomes

Figure 3 shows the Kaplan–Meier survival curve for each study group. The high LY30 group showed a lower probability of survival compared with the low LY30 and normal LY30 groups (both P < .001). However, there was no significant difference in the probability of survival between the low LY30 and normal LY30 groups (P = .8). Table 2 shows the transfusion requirements, 30-day mortality, cause of mortality, and hospital complications for each study group. The high LY30 group had a significantly higher transfusion requirement of red blood cells, plasma, and platelets compared with the low LY30 or normal LY30 groups (both P < .001). There was no significant difference observed in the transfusion requirements of plasma between the low LY30 and normal LY30 groups (P = .058). The low LY30 group had significantly higher transfusion requirements of red blood cells and platelets compared with the normal LY30 group (P = .039 and P = .030, respectively). The high LY30 group had significant higher 30-day mortality compared with the low LY30 and normal LY30 groups (both P < .001). When examining the cause of mortality, the high LY30 group was associated with a significantly increased risk of death due to hemorrhagic shock and TBI compared with the low LY30 and normal LY30 groups (both P < .001). There were no significant differences in the incidence of hospital complications among the 3 groups.

4 | DISCUSSION

Previous studies proposed that traumatic fibrinolytic dysfunction can be classified into 3 phenotypes with different prognoses: fibrinolysis shutdown, physiologic fibrinolysis, and hyperfibrinolysis [4,6]. The current study using data from the PROPPR trial showed that there are no significant differences in the dynamics of the fibrinolysis-related markers including tPA, PAP, and PAI-1 between the

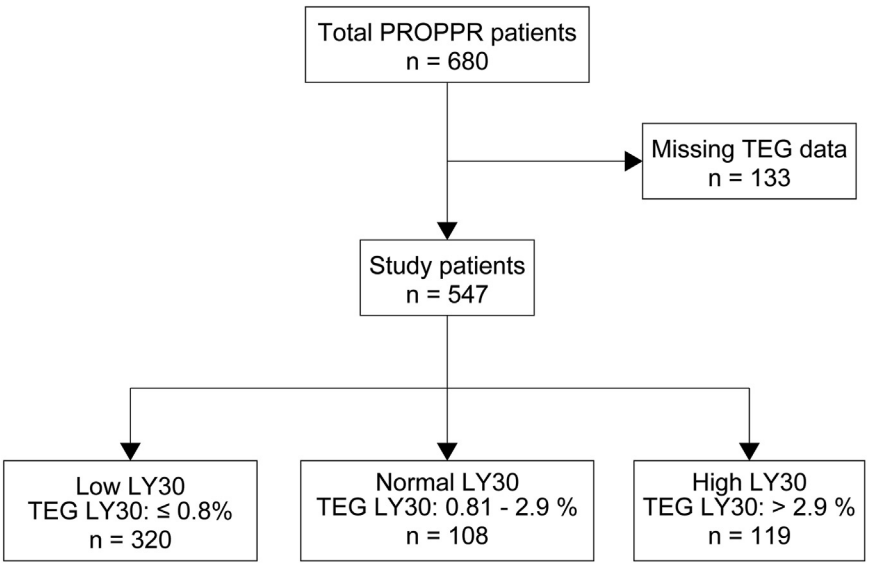

FIGURE 1 Flowchart describing study population. LY30, lysis at 30 minutes; PROPPR, Pragmatic, Randomized Optimal Platelet and Plasma Ratios; TEG, thromboelastography.

TABLE 1 Baseline characteristics of study patients.

	All patients (*n* = 547)	Low LY30 (*n* = 320)	Normal LY30 (*n* = 108)	High LY30 (*n* = 119)
Demographics				
Age (y)	34 (25 to 51)	34 (26 to 52)	35 (23 to 47)	34 (24 to 55)
Male	443 (81.0)	260 (81.3)	91 (84.3)	92 (77.3)
White	358 (65.5)	214 (67.2)	64 (66.9)	80 (59.3)
ISS ≥25	323 (59.1)	183 (57.2)	54 (50.0)	86 (72.3)[a,b]
Blunt trauma	287 (52.5)	170 (53.1)[c]	40 (37.0)	77 (64.7)[a,b]
Mechanism of injury				
MVC	151 (27.6)	90 (28.1)	24 (22.2)	37 (31.1)
AVP	53 (9.7)	32 (10.0)[c]	3 (2.8)	18 (15.1)[b]
Fall	28 (5.1)	19 (5.9)	4 (3.7)	5 (4.2)
GSW	202 (36.9)	120 (37.5)	52 (48.1)	30 (25.2)[a,b]
Stabbing	56 (10.2)	30 (9.4)	14 (13.0)	12 (10.1)
Injury data				
Head injury (AIS ≥3)	127 (23.2)	68 (21.3)	18 (16.7)	41 (34.5)[a,b]
Chest injury (AIS ≥3)	333 (60.9)	195 (60.9)	59 (54.6)	79 (66.4)
Admission vital signs				
SBP (mmHg)	100 (80 to 125)	100 (80 to 123)	106 (82 to 125)	100 (78 to 130)
GCS	14 (3 to 15)	14 (3 to 15)[c]	15 (11 to 15)	7 (3 to 15)[a,b]
Laboratory parameters on arrival				
pH	7.24 (7.12 to 7.31)	7.24 (7.15 to 7.31)[c]	7.27 (7.18 to 7.34)	7.12 (6.97 to 7.24)[a,b]
BE (mmol/L)	−8 (−12.2 to −4)	−7.9 (−12 to −4)[c]	−6.5 (−10 to −2.7)	−12 (−18 to −6.7)[a,b]
Lactate (mmol/L)	6.2 (3.6 to 9.3)	5.7 (3.5 to 8)	5 (3.4 to 8.2)	9.1 (5.2 to 12.4)[a,b]
Hb (g/dL)	11.7 (10.2 to 13.3)	11.6 (10.2 to 13.4)	12.1 (10.7 to 13.4)	11.3 (9.8 to 13.0)[b]
Fibrinogen (mg/dL)	199 (141 to 253)	196 (132 to 242)[c]	239 (203 to 290)	171 (147 to 222)[b]
Platelet (×103/mL^3)	211 (164 to 259)	215 (164 to 263)	217 (188 to 263)	191 (144 to 242)[a,b]
Time course				
Time from EMS call to specimen collection (min)	64 (43 to 92)	72 (47 to 102)[c]	52 (40 to 71)	56 (39 to 81)[a]
Time from specimen collection to TEG (min)	41 (29 to 72)	41 (31 to 73)	38 (16 to 72)	42 (30 to 68)

Values are reported as median (IQR) or *n* (%).

AIS, abbreviated injury score; AVP, automobile vs pedestrian; BE, base excess; EMS, emergency medical services; GCS, Glasgow coma scale; GSW, gunshot wound; Hb, hemoglobin; ISS, injury severity score; LY30, lysis at 30 minutes; MVC, motor vehicle collision; SBP, systolic blood pressure; TEG, thromboelastography.

[a]$P < .05$, compared between the high LY30 and low LY30 groups.

[b]$P < .05$, compared between the high LY30 and normal LY30 groups.

[c]$P < .05$, compared between the low LY30 and normal LY30 groups.

fibrinolysis shutdown and physiological fibrinolysis phenotypes as categorized by TEG LY30 values on hospital arrival. In the PROPPR dataset, patients who presented with hyperfibrinolysis more commonly experienced significantly higher mortality, whereas there were no differences in survival between the fibrinolysis shutdown and physiologic fibrinolysis phenotypes in severely injured patients requiring blood transfusion. Notably, the dynamics of tPA, PAP, and PAI-1 levels in the PROPPR dataset suggest that the fibrinolytic cascade is also activated by the time of arrival to the hospital in the nonhyperfibrinolysis phenotypes (ie, fibrinolysis shutdown and physiologic fibrinolysis). This may indicate that all severely injured patients requiring blood transfusion are in a state of hyperfibrinolysis to some extent during the very early postinjury phase. Despite this, tPA and PAP levels were significantly higher in the high LY30 group, which had significantly higher mortality than the other groups. We believe that these findings highlight the importance of identifying hyperfibrinolysis earlier in the management of trauma patients requiring massive blood transfusion.

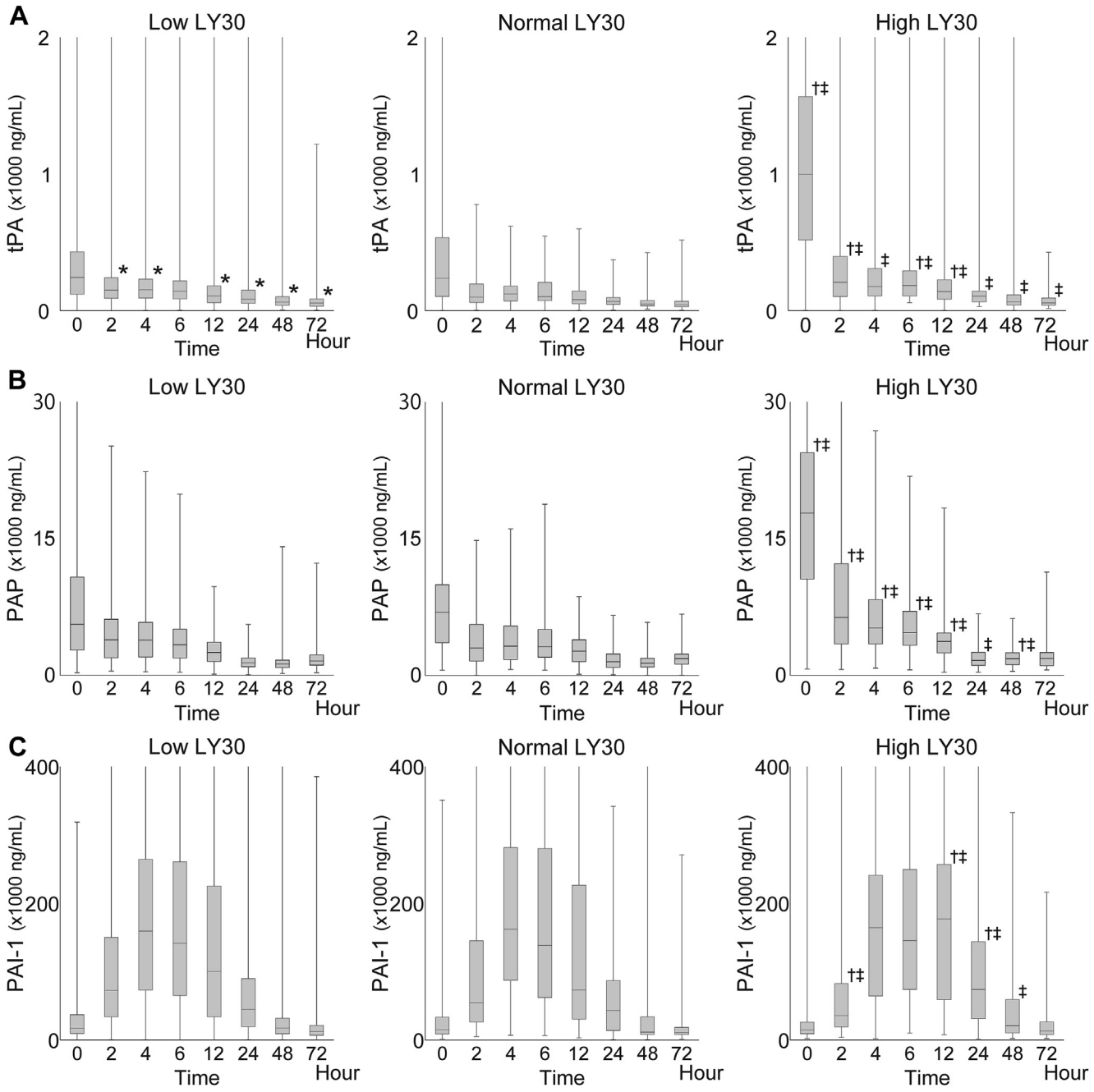

FIGURE 2 The level of fibrinolysis-related markers. (A) Tissue plasminogen activator (tPA; ×1000 ng/mL). (B) Plasmin-antiplasmin (PAP; ×1000 ng/mL). (C) Plasminogen activator inhibitor (PAI-1; ×1000 ng/mL). *$P < .05$, compared between the low lysis at 30 minutes (LY30) and normal LY30 groups. †$P < .05$, compared between the high LY30 and low LY30 groups. ‡$P < .05$, compared between the high LY30 and normal LY30 groups.

It remains controversial whether fibrinolysis shutdown, defined by a certain LY30 cutoff on TEG, is a distinct phenotype of fibrinolytic dysfunction [12,13]. It is important to note that there are several technical differences in the measurement of LY30 and fibrinolysis-related serum markers, which can lead to significant discrepancies in the assessment of fibrinolytic dysfunction. Fibrinolysis-related markers such as tPA, PAP, and PAI-1 are measured as a specific protein in plasma, and the results provide quantitative values at a specific time point. In contrast, using a whole blood specimen, TEG results provide a functional evaluation of coagulation and fibrinolysis dynamics [14]. Conversely, as one of the values determined by TEG, LY30 represents the functional balance between clot formation and clot dissolution and does not exclusively evaluate fibrinolysis. A previous study showed that LY30 was also associated with abnormal fibrinogen consumption and platelet dysfunction [8]. Another study showed that TEG does not always detect coagulopathy, even when

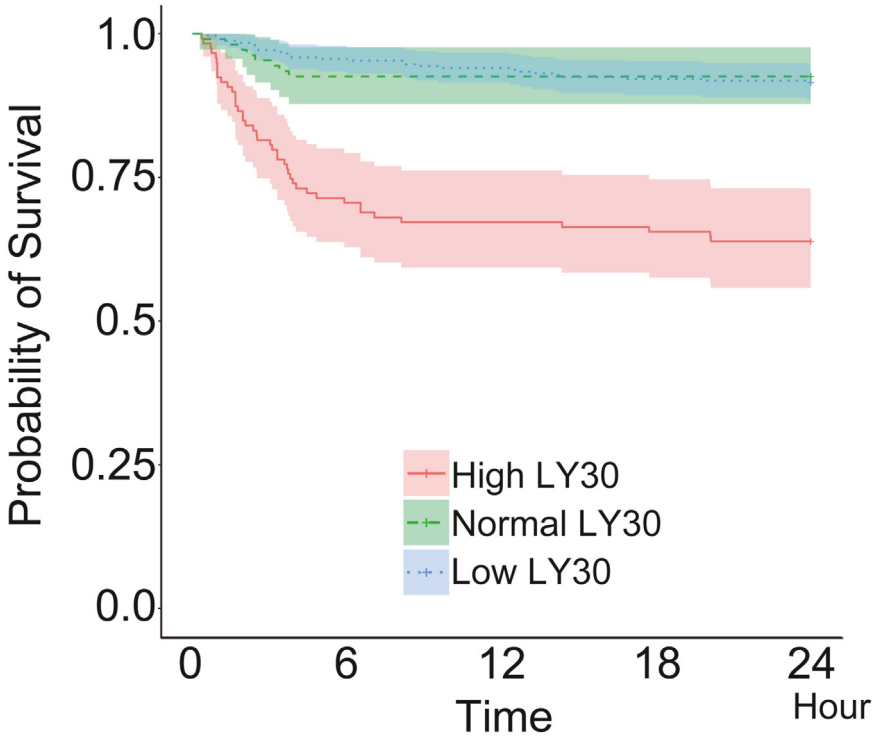

FIGURE 3 Kaplan–Meier survival curve. LY30, lysis at 30 minutes.

PAP complex levels exceed the normal range [15]. It is essential to utilize fibrinolysis-related markers in TEG assessment for understanding the pathophysiology of TIC.

We did not observe a difference in either plasma fibrinolysis-related markers or clinical outcomes between the low LY30 and normal LY30 groups, suggesting that TEG LY30 phenotypes may not correspond to distinct clinical and molecular phenotypes. In the current study, both the low LY30 and normal LY30 groups exhibited activated fibrinolysis upon arrival, followed by suppressed fibrinolysis suggested by an increased PAI-1 level. Even in the high LY30 group,

TABLE 2 Clinical outcomes.

	All patients (*n* = 547)	Low LY30 (*n* = 320)	Normal LY30 (*n* = 108)	High LY30 (*n* = 119)
Transfusion requirements				
Packed red blood cells	9 (5-16)	9 (5-14)	7 (4-12)[a]	15 (9-24)[b,c]
Plasma	6 (3-12)	6 (3-10)	4 (2-9)	11 (5-17)[b,c]
Platelets	6 (6-18)	6 (6-12)	6 (0-12)[a]	12 (6-24)[b,c]
Mortality (30 d)	130 (23.4)	55 (17.2)	14 (13.0)	61 (51.3)[b,c]
Cause of mortality				
Hemorrhagic shock	65 (11.9)	21 (6.6)	7 (6.5)	37 (31.1)[b,c]
Traumatic brain injury	51 (9.3)	25 (7.8)	4 (3.7)	22 (18.5)[b,c]
Multiple organ failure	14 (2.6)	7 (2.2)	2 (1.9)	5 (4.2)
Hospital complications				
Acute kidney injury	105 (25.4)	64 (24.2)	21 (22.6)	20 (36.4)
Deep vein thrombosis	33 (8.0)	21 (7.9)	9 (9.7)	3 (5.5)
Pulmonary embolism	32 (7.8)	22 (8.3)	5 (5.4)	5 (9.1)

Values are reported as median (IQR) or *n* (%).

LY30, lysis at 30 minutes.

[a]$P < .05$, compared between the low LY30 and normal LY30 groups.

[b]$P < .05$, compared between the high LY30 and low LY30 groups.

[c]$P < .05$, compared between the high LY30 and normal LY30 groups.

increased PAI-1 levels during the first 12 hours after admission, suggesting decreased fibrinolysis activity, was observed. These findings align with a previous study by Cardenas et al. [10] in which all patients exhibited drastic increase in PAP complex suggestive of activated fibrinolysis. It is thus suspected that low LY30 values on TEG reflect a coagulopathic state with moderate fibrinolysis and associated fibrinogen consumption rather than shutdown of enzymatic fibrinolysis. While others suggest that patients with fibrinolysis shutdown demonstrated tPA resistance, we believe that fibrinolysis is activated during the early postinjury phase even in the fibrinolysis shutdown and the physiologic fibrinolysis groups given the finding of increased PAP levels [16]. These phenomena are consistent with previous reports describing the physiologic response to trauma including the transition from early disseminated intravascular coagulation with tPA induced hyperfibrinolysis to PAI-1-induced suppression of fibrinolysis [17]. Previous studies indicated that patients who presented with fibrinolysis shutdown on TEG experienced higher mortality than those with evidence of fibrinolysis shutdown on TEG [4,6]. These studies included data before the era of modern resuscitation strategies in trauma, whereas all the PROPPR trial patients received a liberal transfusion therapy with a 1:1:1 or 1:1:2 ratio of platelets, plasma, and red blood cells [11]. Additionally, the implementation of balanced resuscitation, which includes limited used of crystalloid for resuscitation, might have influenced changes in mortality [18].

4.1 | Limitations

There are several limitations to the current study. First, this study is a secondary analysis of the PROPPR trial that aimed to enroll severely injured patients requiring blood transfusion. Therefore, the study findings may not be applicable to trauma patients with different injury profiles (eg, isolated TBI). Second, we were not able to assess the association between specific types of organ injuries and fibrinolysis dysfunction. Previous studies showed that TBI was more commonly associated with the incidence of TIC [19]. While we observed significant differences in the severity of injuries between the study groups, due to lack of data on the organ injury scale in the PROPPR database, the impact of injured organs on the incidence of traumatic fibrinolytic dysfunction remains unknown.

5 | CONCLUSION

Our results suggest that 2 TEG-based fibrinolytic phenotypes, fibrinolysis shutdown and physiologic fibrinolysis, exhibited similar dynamics at the level of fibrinolysis-related markers and mortality. Patients with hyperfibrinolysis had significantly higher levels of tPA and PAP on arrival than the other 2 groups and had significantly worse mortality at 30 days. These findings suggest that hyperfibrinolysis, which may occur in part due to elevated plasma tPA and PAP levels, is the most clinically relevant phenotype of fibrinolytic dysfunction in severely injured trauma patients.

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AUTHOR CONTRIBUTIONS

K.T. and K.Y. conceived and designed this study, interpreted the data, and drafted the manuscript. All authors critically revised the report, commented on the drafts of the manuscript, and approved the final report.

RELATIONSHIP DISCLOSURE

J.B.H. is on the board of directors of Decisio Health, CCJ Medical Devices, QinFlow, Hemostatics, Zibrio and Oxyband. He receives research grant support from the DoD, DARPA, NIH and CSL focused on hemorrhage control and resuscitation. He consults with WFIRM and Aspen Medical, is the coinventor of the Junctional Emergency Tourniquet Tool and receives royalties from UT Health. All other authors deny any potential conflicts of interest. The other authors have no Conflicts of Interest to declare.

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