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A principal component analysis of postinjury viscoelastic assays: clotting factor depletion versus fibrinolysis

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Abstract

Introduction—The mechanisms driving trauma-induced coagulopathy (TIC) remain to be defined and its therapy demands an orchestrated replacement of specific blood products. Thrombelastography (TEG) is a tool to guide the TIC multicomponent therapy. Principal component analysis (PCA) is a statistical approach that identifies variable clusters, thus, we hypothesize that PCA can identify specific combinations of TEG-generated values that reflect TIC mechanisms.

Methods—Adult trauma patients admitted from September 2010 to October 2013 for whom a massive transfusion protocol was activated were included. Rapid TEG values obtained within the first 6 hours postinjury were included in the PCA analysis. PCA components with an eigenvalue >1 were retained, and, within components, variable loadings (equivalent to correlation coefficients)>|60| were considered significant. Component scorings for each patient were calculated and clinical characteristics of patients with high and low scores were compared.

Results—Of 98 enrolled patients, 67% were male and 70% suffered blunt trauma. Median age was 41 years (IQR:28-55) and median Injury Severity Score was 31.5 (IQR: 24-43). PCA identified three principal components (PC) that together explained 93% of the overall variance. PC1 reflected global coagulopathy with depletion of platelets and fibrinogen whereas PC3 indicated hyperfibrinolysis. PC2 may represent endogenous anticoagulants such as the activation of protein C.

Conclusions—PCA suggests depletion coagulopathy is independent from fibrinolytic coagulopathy. Furthermore, the distribution of mortality suggests that low levels of fibrinolysis may be beneficial in a select group of injured patients. These data underscore the potential of risk

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for concurrent presumptive treatment for preserved depletion coagulopathy and possible fibrinolysis.

Introduction

Bleeding is the major cause of preventable death after trauma. Exacerbation of hemorrhage after severe injury is associated with trauma-induced coagulopathy (TIC). TIC was shown to be present in over 25% of severely injured patients on arrival to the emergency department[1] and was subsequently documented to occur at the time of ambulance arrival in the field.[2] These studies are consistent in indicating that abnormalities in prothrombin time/ international normalized ratio (PT/INR) and partial thromboplastin time (PTT), conventional laboratory assays used to identify TIC, are independent predictors of mortality after risk adjustment.[3] In an effort to replete the body with substrate for the coagulation cascade, plasma and platelets are presumptively administered in damage control resuscitation and massive transfusion protocols.[4-8] While the mechanisms of TIC are poorly understood, retrospective reviews suggest this early administration of plasma and platelets may lead to improved outcomes and survival.[4-8] However blood components are expensive and have been implicated in the pathogenesis of post injury acute lung injury.[9] Moreover, the role of presumptive antifibrinolytic therapy, remains controversial [10, 11]

The rapid onset of coagulopathy following severe injury prior to the confounding effects of resuscitation is well recognized, but the precise mechanisms remain unclear. The cell-based model of hemostasis indicates the complexity of TIC.[12, 13] Activation of protein C (APC) via thrombin binding to endothelial thrombomodulin has been proposed as central in the pathogenesis of TIC. While APC peptide cleavage inactivation of factors V and VIII is reasonably well established, the role of APC in enhancing fibrinolysis via degradation of plasminogen activator -1 (PAI-1) is not clear. Thrombelastography (TEG) offers unique insight into TIC as the viscoelastic profile components represent the relative contributions of the various elements of hemostasis as well as clot dissolution.

Principal components analysis (PCA), initially used in the social sciences, is a statistical approach for variable reduction. Multiple variables are unlikely to be independent of one another; i.e., a change in one is likely to be accompanied by a change in another. PCA assists in finding correlations between multiple variables and grouping them into uncorrelated components. In simple terms, PCA consists of an automated, systematic examination of correlations among measured variables, aimed at identifying underlying latent principal components (PC).[14, 15] The first PC is a line with the minimum possible distance from all the data points from several variables and explains the most variance; PC2 is a second line, perpendicular to the first line oriented in such a way as to explain the greatest amount of variation not explained by PC1. The process is repeated with subsequent individual components explaining lesser variance than the previous ones. The end result is that the original set of N variables is replaced by a smaller group of uncorrelated linear, weighted combinations of the original variables.[14, 15]

Recently, Kutcher et al.[16] employed PCA to analyze the potential mechanistic links in TIC using circulating levels of several coagulation factors. Their findings suggested three basic

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mechanistic pathways for TIC. However, platelet poor plasma studies do not replicate the cell-based model of coagulation. Thus, we hypothesize that a PCA of TEG-generated components would provide additional information on the independent mechanisms for the various phenotypes of TIC.

Methods

Trauma patients admitted to the Rocky Mountain Regional Trauma Center at Denver Health Medical Center (DHMC) from September 2010 to October 2013 for whom a massive transfusion protocol (MTP) was activated were included. Our institution's MTP is activated for SBP<90 and one of the following: penetrating torso injury, unstable pelvic fracture, or positive focused assessment with sonography for trauma or heuristic observation of the attending surgeon. DHMC is a state designated Level I trauma center verified by the American College of Surgeons Committee on Trauma. Inclusion criteria were: age older than 18 years, acute trauma sustained within 6 hours upon admission, and TEG values obtained within six hours postinjury. Patients with documented liver disease and known inherited defects of coagulation function were excluded.

Rapid TEG values were obtained within the first 6 hours postinjury. The distribution of elapsed time from injury to TEG was as follows: 15% in hour 1 postinjury, 38% in hour 2, 16% in hour 3, 12% in hour 4, 10% in hour 5, and 9% in hour 6. Overall, over 50% were obtained within 2 hours postinjury, and 70% within 3 hours. The numbers of packed red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate (CRYO), and platelet (PLT) units were recorded for the first 24 hours.

The TEG curve yields key parameters, each representing a functional component of coagulation. The activated clotting time, or ACT value, is the time to clot initiation and is representative of enzymatic clotting factor activation and initial thrombin generation. The angle is the rate of clot formation, which is governed by the effects of concentration of fibrinogen. K is the interval measured from the TEG-ACT to a fixed level of clot firmness or when the amplitude reaches 20 mm; this reflects thrombin's ability to cleave soluble fibrinogen and, hence, the kinetics of clot build-up. The maximum amplitude, or MA, measures the maximum clot strength, which includes the contributions of platelets and fibrin. LY30 is the amount of clot lysis at 30 minutes after MA and represents fibrinolysis. TEG also produces parameters related to the velocity of clotting, calculated from the first derivative of the TEG tracing. These variables, not typically used for clinical TEG interpretation, include maximum rate of thrombus generation (MRTG), time to maximum rate of thrombus generation (TMRTG), and total thrombus generation (TTG).

Adverse outcomes included ICU free days (IFD), ventilator free days (VFD), and mortality. IFD and VFD were determined according to the method proposed by Schoenfeld and Bernard.[17] Data collection and storage were in compliance with the Health Insurance Portability and Accountability Act regulations and have been approved by our Institutional Review Board.

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Statistical Analysis

Statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute, Cary, NC). Categorical variables were compared using the Chi-square test with Yates correction for continuity or the Fisher's exact test when expected cell values were < 5. Analysis of variance or t-tests were used for continuous variables with normal distributions (with appropriate modification when the assumption of equal variances did not hold) while continuous variables without a normal distribution were analyzed using the Kruskal-Wallis or Wilcoxon Tests. Due to multiple comparisons, $p<0.01$ was considered significant. Continuous data were expressed as mean ± standard error of the mean (SEM) or as median and interquartile range (IQR) and categorical data as percentages. PCA was performed using Proc Factor with Method=prin. Because TEG values are not normally distributed and have disparate variances, values were ranked before including them in the PCA. Components with an eigenvalue greater than 1 were retained, and, within components, variable loadings (equivalent to correlation coefficients, range -1 to +1) >|60| were considered significant. A component score was calculated for each patient using the weights of each of the variables for that particular component and was categorized into high and low scores using the median value.

Transferred versus non-transferred patients

Overall, 24.5% of patients included in the study were transferred from an outside hospital. Transferred and non-transferred patients did not differ regarding demographic characteristics (age: 38 years (25-52) vs. 51 years (32-56), p=0.1132; male sex: 69% vs. 63%, p=0.56) or injury severity [ISS: 37 (28-44) vs. 29 (24-41), p=0.14]. Blunt injuries were more frequent among transferred patients (92% vs. 64%, p=0.009). No differences in intravenous fluid (IVF) and transfusion rates at 6 hours were detected [IVF: 7L (5-9) vs. 8.6L (6-10), p=0.09; RBC: 8U (4-12) vs. 9U (6-16), p=0.29; FFP: 3U (0-6) vs. 4U (2-8), p=0.06; CRYO: 0U (0-1) vs. 0U (0-2) p=0.34; PLT: 0U (0-1) vs. 1U (0-2), p=0.18]. Mortality was also similar between the two groups (25% vs. 28%, p=0.75).

Results

Of the 98 patients included in this study, 92 (94%) patients had complete data necessary for the PCA. Of these, 67% (n=66) were male, 70% (n=69) due to blunt injury mechanisms. The median age was 41 years (IQR: 28-55), and median body mass index 26.2 kg/m2 (IQR: 23.5-31.4). The median ISS was 31.5 (IQR: 24-43). In the emergency department (ED), median systolic blood pressure was 92 mmHg (IQR: 78-114) and median heart rate was 111 beats per minute (IQR: 96-130). These patients arrived relatively acidotic with a median pH of 7.20 (IQR: 7.09-7.30). Fifty-one percent had an INR within the first 6 hours>1.5. The overall mortality rate was 28% (n=27).

PCA produced three distinguishable components, which accounted for 93% of the variance shown in Table 1. Also seen in Table 1, variables with significant loading for Principal Component (PC) 1 included K, angle, MA, MRTG, and TTG. For PC2, ACT and TMRTG were variables with significant loading. For PC3, LY30 was the only significant variable.

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Comparing patients with high versus low PC1 scores, there was no difference in age, sex, or injury mechanism (Table 2). High PC1 scores represented patients with a greater injury severity than patients with low PC1 scores. In regards to components of coagulation, patients with high PC1 scores had significantly lower platelet counts and fibrinogen levels ($p=0.0001$, $p<0.0001$, respectively). Patients with high PC1 scores also had a significantly higher INR and PTT ($p=0.0135$ and $p=0.0035$, respectively). Overall, patients with high PC1 scores required greater volumes of blood products than patients with low PC1 scores. Specifically, patients with high PC1 scores were given more RBC, FFP, CRYO, and PLT within the first 6 hours compared to patients with low PC1 scores ($p<0.0001$, $p<0.0001$, $p=0.0002$, $p=0.0001$, respectively). This pattern continued at 12 and 24 hours post injury. Patients with high PC1 scores were more likely to have a significantly higher CRYO: RBC and PLT: RBC ratios at 6 hours ($p=0.0011$, $p=0.0048$, respectively). High PC1 scores were associated with significantly worse VFD and IFD ($p=0.0015$, $p=0.0022$, respectively) and higher mortality, although the latter association was non-significant ($p=0.05$). With the exception of male sex, and ED heart rate, none of the measured variables showed a significant association with PC2 scores (Table 3).

The PC 3 score was most significantly loaded by LY30, and all patients with low PC3 scores had an LY30=0. Patients with high PC3 scores had significantly lower blood pressure than patients with low PC3 scores ($p=0.0074$), and required more RBC than patients with low PC3 score, although this difference did not reach significance ($p=0.0213$) (Table 4).

Discussion

In this study, we examine variables of rapid TEG to seek combinations that reflect coagulation mechanisms. High PC1 scores represent a global depletion hypocoagulable state in which there is increased time to clot, slower incorporation of fibrin, and decreased clot strength, identified by a delay in fibrinogen conversion by thrombin (K), initiation of fibrin crosslinking (angle), and ultimately, reduction in clot strength (MA). K represents initial clot kinetics and thrombin's ability to cleave fibrinogen. The angle represents the speed of clot strengthening, influenced by the conversion of fibrinogen to fibrin. It is dependent on the functional fibrinogen level and is affected by the rate of thrombus generation, and, thus, is related to MRTG. MA represents the platelet integration into the fibrin mesh. The amount of thrombus generated (TTG) is associated with the initiation of clot formation. Overall, this score appears to indicate global coagulation related to the enzymatic and platelet components of hemostasis. Having a high PC1 score indicated greater coagulopathy and patients with high PC1 scores were more likely to require blood transfusions and have adverse outcomes than patient with low PC1 scores.

For PC2, we conjecture that the significance of ACT and TMRTG represents a unique parameter of endogenous anticoagulants, such as activation of protein C. Recent studies have found TMRTG correlated with thrombin antithrombin (TAT) levels, indicating that TMRTG may be a marker of thrombin generation.[18] Based on previous studies with TMRTG,[19] we would expect a high PC2 score to be associated with hypocoagulability and worse outcomes. Yet, we found no difference in outcomes or transfusion requirements between high and low PC2 scores. Interestingly, Kutcher et al. found a third component in

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their model that was significant loaded with Factor VIII. PC2 may represent another unique phenotype of TIC, which may be due to signals from the endothelium that contributes to thrombin generation. This finding requires further investigation.

The third PC represents hyperfibrinolysis, based on LY30 as a measure of fibrinolysis. A high PC3 score signifies hyperfibrinolysis. Half of the patients had no evidence of fibrinolysis yet a mortality rate over 25%. This is contrary to the notion that patients with any or hyper fibrinolysis are a greater risk of mortality. This supports our previous observation and hypothesis that patients with no evidence of fibrinolysis, or fibrinolysis shutdown, is associated with organ failure, and patients with significant fibrinolysis, or hyperfibrinolysis, is associated with poor outcomes related to exsanguination.[18] On the contrary, patients with evidence of low fibrinolysis, or physiologic fibrinolysis, are able to lyse clot to perfuse vital organs without exsanguination.

The role of the platelets in coagulation is reflected in PC1. In our PCA, lower platelet counts were associated with low PC1 scores and more blood component transfusions. However, neither median was within the range that most would consider being thrombocytopenic.[20-25] Thrombocytopenia has been shown to be associated with increased mortality, multiple organ failure, and poor clinical outcomes in critically ill patients across various specialties.[20,21,23,25] The mechanism underlying thrombocytopenia is not known. A previous study from our group showed that thrombocytopenia in trauma patients is an independent risk factor for multiple organ failure and mortality.[25] This PCA supports the conclusion that low platelets are associated with more blood component transfusion and mortality.

Our PCA using TEG variables confirms the conclusion of Kutcher et al.[16] that global depletion coagulopathy is a separate pathological manifestation of TIC from hyperfibrinolysis. Similar to the San Francisco group, we observed three independent components of coagulopathy despite using different coagulation variables and instruments. Our study used TEG, which can provide information about the clotting process, from initial thrombin activation to fibrinolysis. We have found that TEG provides the cell-based model of coagulation, broken down into three critical steps (initiation, amplification, and propagation) and have used it to guide resuscitation of severe trauma patients.[26] Based on these components, it may be possible to identify groups of patients who share characteristics or phenotypes that can guide therapy.

Collectively, this study and others strongly suggest independent mechanisms driving global depletion coagulopathy versus hyperfibrinolysis. A corollary is that empiric treatment of both may not result in the best outcome. Specifically, our recent clinical study[27] suggests that low grade fibrinolysis is protective in a subgroup of patients. We are currently pursuing proteomics and metabolomics in attempts to discern this better at a signaling level.

Limitations

The small sample of this study limits its findings. PCA generally requires large samples to produce stable components that can be validated in a separate dataset. Another limitation of this study was that we used rapid TEG values obtained during the first 6 hours postinjury. In

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this population of severely injured trauma patients, several interventions may have occurred within this period. This may have affected the TEG values; however, the median IVF fluids received before the TEG was performed was 1625 mL (IQR: 500-2300), the median RBC was 2 units (IQR: 0-3), and median FFP was 0 (IQR: 0-1). It has been shown that RBC contains negligible amounts of coagulation factors and platelets and does not correct coagulopathy.[28] Although 25% of the patients were transfers from other regional hospitals, all were admitted to DHMC within 6 hours of injury and did not differ substantially from those who were admittedly primarily to our center. No differences in the proportion of transfers were detected for high and low PC1 and PC2 scores. We did observe that a greater percentage of patients with low PC3 scores were transferred compared to the group with high PC3 scores. We suspect that patients who were likely to survive the transfer were more likely to have lower LY30 values. Patients who had high LY30 values (resulting in high PC3 scores) may have had significant hemodynamic instability and early mortality from exsanguination. As a result, these patients were likely not transferred, which may contribute to our inability to detect differences in outcomes between high and low PC3 scores. Finally, the study was limited to one institution and the results may not be generalizable to other institutions.

Conclusion

Trauma induced coagulopathy is a complex process, whose mechanism is not fully understood. Our principal component analysis suggests primary mechanisms for coagulopathy from depleted factors and platelets are distinct from hyperfibrinolysis and underscore the potential of risk for concurrent presumptive treatment for preserved depletion coagulopathy and possible fibrinolysis. Based on these summary variables, we may be able to identify phenotypes of postinjury coagulopathy.

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Table 1

Composition of Principal Components (PC)

	PC 1	PC 2	PC 3
Eigenvalue	5.1	1.4	1.0
% Variance	63%	17%	13%
r-TEG activated clotting time	−30	90 *	6
r-TEG K	−95 *	15	−4
r-TEG angle	92 *	−26	5
r-TEG maximum amplitude	95 *	−15	−10
r-TEG % lysis at 30 minutes	−4	0	99 *
r-TEG time to maximal rate of thrombus generation	−13	95 *	−5
r-TEG maximal rate of thrombus generation	94 *	−23	3
r-TEG total thrombus generation	94 *	−14	−16

r-TEG: rapid thrombelastogram

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Table 2

PC1 Characteristics

	Low PC1		High PC1		P-value
Demographics					
Male, % (n)	61% (28)		74% (34)		0.1821*
Blunt, % (n)	65% (30)		74% (34)		0.3648*
Transfers, % (n)	28% (13)		20 % (9)		0.3282*
	Median	IQR	Median	IQR	Wilcoxon Test P-Value
Age, years	43	28 - 54	41	29 - 55	0.8487
BMI, kg/m2	28.7	24.9 - 34.2	24.9	22.0 - 29.8	0.011
Injury Severity	Median	IQR	Median	IQR	
ISS	25	17 - 38	35	26 - 48	0.0016
ED GCS	14	3 - 15	5.5	3 - 14	0.0381
ED SBP, mmHg	100	80 - 120.5	88	66 - 105	0.0283
ED HR, beats per minute	116.5	102 - 134	104	85 - 130	0.0345
ED pH	7.2	7.13 - 7.28	7.23	7.13 - 7.34	0.311
ED Base Deficit	−12	−15 - −10	−11	−16 - −8	0.3669
ED Hemoglobin, g/dL	11.9	10.5 - 13.9	12.4	9.0 - 13.4	0.3965
Coagulation Measures	Median	IQR	Median	IQR	
Platelet Count, k/uL	273	210 - 338	181	119 - 250	<.0001
Partial Thromboplastin Time, seconds	32.05	26.9 - 42.5	42	32 - 60.6	0.0035
International Normalized Ratio	1.36	1.16 - 1.67	1.69	1.28 - 2.4	0.0135
Fibrinogen Level, mg/dL	157.5	132 - 190	113	80 - 135	<.0001
D-Dimer, ug/mL	9.7	2.1 - 20.0	12.6	4.9 - 20.0	0.2298
Transfusion and Fluids at 6 Hours	Median	IQR	Median	IQR	
Total IV fluids, mL	8225	6300 - 10100	8650	5913 - 10300	0.5879
RBC, units	7	4 - 10	13.5	8 - 27	<.0001
FFP, units	3	0 - 4	6	4 - 12	<.0001
CRYO, units	0	0 - 0	1	0 - 2	0.0002
PLT, units	0	0 - 1	1	0 - 2	0.0001
FFP:RBC	0.37	0.00 - 0.71	0.50	0.33 - 0.62	0.0921
CRYO:RBC	0.00	0.00 - 0.00	0.07	0.00 - 0.12	0.0011
PLT:RBC	0.00	0.00 - 0.10	0.08	0.00 - 0.13	0.0048
Outcomes	Median	IQR	Median	IQR	
Ventilator free days	21	11 - 26	9.5	0 - 21	0.0015
ICU free days	16	7 - 23	5	0 - 19	0.0022

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	Low PC1	High PC1	P-value
Mortality, % (n)	15% (7)	33% (15)	0.0505*

PC: principal component; IQR: interquartile range; BMI: body mass index; ISS: Injury Severity Score; ED: emergency department; GCS: Glasgow Coma Scale; SBP: systolic blood pressure; HR: heart rate; RBC: red blood cell; FFP: fresh frozen plasma; CRYO: cryoprecipitate; PLT: platelet; ICU: intensive care unit

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Table 3

PC2 Characteristics

	Low PC2		High PC2		P-value
Demographics					
Male, % (n)	78% (36)		57% (26)		0.0261*
Blunt, % (n)	74% (34)		65% (30)		0.3648*
Transfers, % (n)	24% (11)		24% (11)		1*
	Median	IQR	Median	IQR	Wilcoxon Test P-Value
Age, years	45	31 - 55	38	24 - 53	0.2308
BMI, kg/m2	26.2	24.7 - 32.0	26.5	21.9 - 31.4	0.2788
Injury Severity	Median	IQR	Median	IQR	
ISS	34.5	25 - 43	27.5	20 - 38	0.273
ED GCS	12.5	3 - 15	11	3 - 15	0.8862
ED SBP, mmHg	92.0	78.0 - 110.0	94.0	80.0 - 118.0	0.6899
ED HR, beats per minute	104.5	89.0 - 120.0	118.0	100.0 - 138.0	0.0094
ED pH	7.24	7.15 - 7.32	7.20	7.08 - 7.29	0.5358
ED Base Deficit	−11	−12.9 - −8	−14.5	−18 - −10	0.0388
ED Hemoglobin, g/dL	12.1	9.6 - 13.6	12.2	10.4 - 13.4	0.9529
Coagulation Measures	Median	IQR	Median	IQR	
Platelet Count, k/uL	211	146 - 254	263	174 - 332	0.0951
Partial Thromboplastin Time, seconds	35.1	28.1 - 47.3	39.4	27.7 - 52.4	0.3035
International Normalized Ratio	1.53	1.22 - 1.94	1.5	1.22 - 2.07	0.8517
Fibrinogen Level, mg/dL	143	117 - 172	131	90 - 152	0.0966
D-Dimer, ug/mL	11.8	4.0 - 20.0	9.7	2.4 - 20.0	1
Transfusion and Fluids at 6 Hours	Median	IQR	Median	IQR	
Total IV fluids, mL	9330	7000 - 10383	7035	5495 - 9700	0.0207
RBC, units	10	5 - 16	8	6 - 15	0.8335
FFP, units	4	2 - 6	4	2 - 8	1
CRYO, units	0	0 - 1	0	0 - 2	0.4581
PLT, units	1	0 - 2	0.5	0 - 2	0.5766
FFP:RBC	0.37	0.24 - 0.60	0.49	0.29 - 0.71	0.2856
CRYO:RBC	0.00	0.00 - 0.11	0.00	0.00 - 0.12	0.3728
PLT:RBC	0.06	0.00 - 0.12	0.02	0.00 - 0.12	0.6811
Outcomes	Median	IQR	Median	IQR	
Ventilator free days	15	0 - 23	15.5	0 - 24	0.8849
ICU free days	13	0 - 20	13.5	0 - 21	0.6436

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	Low PC2	High PC2	P-value
Mortality, % (n)	22% (10)	26% (12)	0.625*

PC: principal component; IQR: interquartile range; BMI: body mass index; ISS: Injury Severity Score; ED: emergency department; GCS: Glasgow Coma Scale; SBP: systolic blood pressure; HR: heart rate; RBC: red blood cell; FFP: fresh frozen plasma; CRYO: cryoprecipitate; PLT: platelet; ICU: intensive care unit

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Table 4

PC3 Characteristics

	Low PC3		High PC3		P-value
Demographics					
Male, % (n)	65% (30)		70% (32)		0.6565*
Blunt, % (n)	76% (35)		63% (29)		0.174*
Transfers, % (n)	37% (17)		11% (5)		0.0034*
	Median	IQR	Median	IQR	Wilcoxon Test P-Value
Age, years	42	30 - 55	40	25 - 55	0.5569
BMI, kg/m2	27.0	23.5 - 31.4	26.2	24.1 - 30.0	0.5638
Injury Severity	Median	IQR	Median	IQR	
ISS	33	22 - 43	26.5	25 - 38	0.4784
ED GCS	9	3 - 15	13	3 - 15	0.35
ED SBP, mmHg	100	86 - 130	84	65 - 107	0.0074
ED HR, beats per minute	114	96 - 136	108	96 - 121	0.3839
ED pH	7.24	7.14 - 7.32	7.21	7.13 - 7.29	0.6413
ED Base Deficit	−11	−15 - −8	−12.5	−16 - −10	0.1977
ED Hemoglobin, g/dL	12.4	10.45 - 13.9	11.7	9 - 13.3	0.3167
Coagulation Measures	Median	IQR	Median	IQR	
Platelet Count, k/uL	216	153 - 291	233	162 - 308	0.7703
Partial Thromboplastin Time, seconds	36.8	28.1 - 47.4	35.75	27.9 - 49.2	0.9658
International Normalized Ratio	1.47	1.20 - 1.97	1.55	1.23 - 2.01	0.6544
Fibrinogen Level, mg/dL	138.5	99 - 165	133	98 - 161	0.8711
D-Dimer, ug/mL	18.5	4.5 - 20.0	8.2	2.6 - 19.6	0.0727
Transfusion and Fluids at 6 Hours	Median	IQR	Median	IQR	
Total IV fluids, mL	7222.5	6200 - 10000	9330	6317 - 10383	0.1432
RBC, units	8	4 - 12	10	7 - 17	0.0213
FFP, units	3.5	1 - 8	5	3 - 9	0.0578
CRYO, units	0	0 - 2	0	0 - 2	0.6632
PLT, units	1	0 - 1	1	0 - 2	0.4063
FFP:RBC	0.49	0.20 - 0.64	0.40	0.29 - 0.62	0.7601
CRYO:RBC	0.00	0.00 - 0.12	0.00	0.00 - 0.07	0.2837
PLT:RBC	0.06	0.00 - 0.12	0.06	0.00 - 0.12	0.9603
Outcomes	Median	IQR	Median	IQR	
Ventilator free days	15	0 - 23	18	0 - 24	0.6381
ICU free days	12.5	0 - 20	14	0 - 21	0.7323

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	Low PC3	High PC3	P-value
Mortality, % (n)	26% (12)	22% (10)	0.625*

PC: principal component; IQR: interquartile range; BMI: body mass index; ISS: Injury Severity Score; ED: emergency department; GCS: Glasgow Coma Scale; SBP: systolic blood pressure; HR: heart rate; RBC: red blood cell; FFP: fresh frozen plasma; CRYO: cryoprecipitate; PLT: platelet; ICU: intensive care unit

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