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A principal component analysis of coagulation after trauma

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Abstract

Background—Clotting factor abnormalities underlying acute traumatic coagulopathy are poorly understood, with application of traditional regression techniques confounded by collinearity. We hypothesized that principal components analysis (PCA), a pattern-finding and data reduction technique, would identify clinically predictive patterns in the complex clotting factor milieu after trauma.

Methods—Plasma was prospectively collected from 163 critically-injured trauma patients. Prothrombin, Factors V, VII, VIII, IX, X, D-dimer, activated and native Protein C, and antithrombin III levels were assayed, and subjected to non-linear PCA to identify principal components (PCs).

Results—Of 163 patients, 19.0% were coagulopathic on admission. PCA identified 3 significant PCs, accounting for 67.5% of overall variance. PC1 identified global clotting factor depletion; PC2 the activation of Protein C and fibrinolysis; and PC3 Factor VII elevation and VIII depletion. PC1 score correlated with penetrating injury and injury severity, predicting coagulopathy (OR 4.67, $p<0.001$) and mortality (OR 1.47, $p=0.032$). PC2 score correlated with injury severity, acidosis, and shock, and significantly predicted ventilator-associated pneumonia (OR 1.59, $p=0.008$), acute lung injury (OR 2.24, $p<0.001$), multiorgan failure (OR 1.83, $p=0.002$), and mortality (OR 1.62, $p=0.006$), but was not associated with INR- or PTT-based coagulopathy ($p>0.200$). PC3 did not significantly predict outcomes.

Conclusions—PCA identifies distinct patterns of coagulopathy: depletion coagulopathy predicts mortality and INR/PTT elevation, while fibrinolytic coagulopathy predicts infection, end-organ failure, and mortality, without detectable differences in INR or PTT. While depletion coagulopathy is intuitive, fibrinolytic coagulopathy may be a distinct but often overlapping entity with differential effects on outcomes.

Level of evidence—Prognostic study, Level III

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Keywords

Coagulopathy; principal components analysis; fibrinolysis

BACKGROUND

Hemorrhage remains the leading cause of potentially preventable death after trauma, complicated in up to a third of injured patients by coagulation abnormalities present on arrival to the emergency department.[1] Although well-studied, the importance of specific clotting factor abnormalities to the complex phenomenon of acute traumatic coagulopathy is poorly understood. Strong correlations between clotting factor levels pose a significant challenge to identifying the isolated importance of any individual factor. This collinearity makes standard regression techniques prone to unstable results, difficult to generalize, and at risk of identifying spurious statistical significance. Several mathematical techniques exist to more clearly describe the patterns that exist in such complex, correlated data sets, and to associate these patterns with binary outcomes; principal component analysis (PCA) is one such method.

PCA is a statistical pattern detection tool that distills a complex set of inter-correlations down to essential clusters of variables that move together as groups. To begin, a dataset of correlated variables is decomposed into a smaller set of uncorrelated synthetic multi-variables. A best-fit plane is described in this multivariate space, the axes of which are termed ‘principal components’ (PCs); the location of each individual data point in multivariate space can then be specifically described relevant to these PCs. In this sense, PCA can be thought of as a multivariate form of the Pearson correlation, in which the best-fit line is replaced by a best-fit multivariate plane. The dataset described here contains arrival clotting factor measurements in a panel of critically injured patients, in which many of the individual factor levels are highly correlated with each other. The application of PCA transforms each patient’s individual clotting factor measurements into a smaller set of PC ‘scores’, which can be interpreted as individual patient locations within multivariate outcome space. Furthermore, each PC can be broken down into ‘factor loadings’ that describe both the contribution of each individual clotting factor into the calculation of that PC score as well as each factor’s relationships with other factors. A detailed explanation of the rationale and methodology of PCA is available in the Supplemental Digital Content.

As an example, a PC controlled entirely by a single predictor would have a loading coefficient of +1.0 for the predictor in question, with all other predictor coefficients equal to zero; in contrast, a PC determined by mixed contributions from multiple factors would have loading coefficients spanning values from −1.0 to +1.0 for each contributing factor, corresponding to positive and inverse Pearson correlations. Intuitively, PCs describe the internal structure of a set of correlated measurements allowing patients to be grouped by global patterns of clotting factor perturbations as defined by high or low PC scores, and the clotting factor interrelationships that define each group can be described. For a set of highly interrelated predictors such as clotting factor measurements, PCA accommodates degrees of collinearity that would make standard regression approaches unstable.

Therefore, we hypothesized that PCA would identify clinically predictive patterns in the complex clotting factor milieu after trauma. In this study, we apply PCA to identify and examine the clotting factor relationships underlying these clinical patterns, and correlate these with outcomes in a panel of critically injured patients.

METHODS

Plasma was collected from 163 critically injured trauma patients on arrival to the emergency department of an urban Level I trauma center from 2/2005 to 10/2010 as part of an on-going clinical study.[2] Consecutive patients triggering activation of the highest level of a two-tiered triage system during the study period were prospectively enrolled under a waiver of consent; patients aged <18 years old, those with >5% body surface area burns, those who received >2 liters of intravenous fluid prior to arrival, and those transferred from another institution were excluded. Patients were retrospectively excluded if informed consent was unobtainable or declined. Admission blood samples were collected via initial placement of a 16g or larger peripheral IV into 3.2% (0.109M) sodium citrate, and processed within 3h of being drawn; sample collection methodology is described in detail elsewhere.[2] Activity levels of Factors II, V, VII, VIII, IX, and X, antithrombin III and Protein C, as well as antigen D-dimer levels were assayed using a Stago Compact Functional Coagulation Analyzer (Diagnostica Stago; Parsippany, NJ). Activated Protein C was assayed using an established ELISA method reported elsewhere.[3] Demographics, laboratory and resuscitation data, and outcomes were collected in parallel. Injury was assessed by injury severity score (ISS).[4] Acute lung injury was based on the American-European consensus definition.[5] Multiorgan failure (MOF) was defined as a multiple organ dysfunction score of >3 using established Denver criteria.[6] The study was approved by the University of California Committee on Human Research.

Non-linear PCA was performed using SPSS categories CAT-PCA (IBM; Chicago, IL); specific details are available in the Supplemental Digital Content Methods. Possible nonlinear correlations among coagulation factors were accounted for in the input stage, resulting in an output of continuous, linear PC scores and PC loadings[7]; see Supplemental Digital Content Figure 1. All measured factor levels were included as predictors: prothrombin, Factors V, VII, VIII, IX, and X, D-dimer, activated Protein C, Protein C, and antithrombin III. PCs were considered significant for eigenvalues greater than or equal to 1.0 (see Supplemental Digital Content Figure 2); factor loadings were considered significant for coefficients greater than or equal to 0.3. Continuous PC scores were calculated for each patient along each PC axis, and differences between the highest and lowest quartile of patients for each significant PC were examined using standard univariate statistics. The predictive capacities of independent PC scores were evaluated using unadjusted logistic regression for the binary outcomes of mortality, multiorgan failure, acute lung injury, and ventilator-associated pneumonia (VAP), and for standard definitions of coagulopathy determined by admission international normalized ratio (INR) and partial thromboplastin time (PTT).

Data are presented as mean ± standard deviation, median (interquartile range [IQR]), or percentage; univariate comparisons were made using Student's *t*-test for normally distributed data, Wilcoxon rank-sum testing for skewed data, and Fisher's exact test for proportions. Missing predictor data was imputed using multiple imputation; results were similar to those obtained using only complete data as well as using a dataset completed with population means (data not shown). An alpha of 0.05 was considered significant. All analysis was performed by the authors using SPSS Categories (IBM; Chicago, IL) and Stata version 12 (StataCorp; College Station, TX).

RESULTS

Our 163-patient study population had mean age 41.3±19.3y and mean injury severity score 23.2±5.4; there was 31.0% penetrating and 61.2% brain injury. Of 163 patients, 22 (19.0%) were coagulopathic on arrival as defined by INR ≤1.3, and 56 (34.4%) were coagulopathic as defined by PTT ≤30. Non-linear PCA identified 7 independent PCs, together accounting

for 92.0% of the variance present in the data. PCs 1, 2, and 3 were considered significant (eigenvalues greater than 1.0); these together accounted for 67.5% of total variance. Eigenvalues, percentage of variance explained, and the factor loading matrix for all individual clotting factors for the three significant PCs are shown in **Table 1**. Factor loadings were considered significant for loading coefficients greater than or equal to 0.3.

PC1 accounted for 43.9% of overall variance, including significant negative factor loading on (analogous to inverse Pearson correlation with) prothrombin, Factors V, VII, VIII, IX, X, Protein C, and antithrombin III (**Table 1**). To identify patient-level characteristics associated with high PC1 scores, patients with the highest quartile of PC1 score were compared to those in the lowest quartile (**Table 2**). Patients in the highest quartile of PC1 score had significantly more common penetrating injury (34.2% vs. 12.5%, p=0.035) and more severe injury (mean ISS 32.2 vs. 23.8, p=0.011) compared to those in the lowest quartile. High PC1 patients also had significantly elevated admission INR (median 1.2 vs. 1.0, p<0.001) and PTT (median 32.6 vs. 27.0 sec, p<0.001), as well as lower admission platelet count (mean 245 vs. 311 $*10^3$/uL, p<0.001). High PC1 patients also had significantly higher transfusion requirements for red blood cells (median 5 vs. 0 units, p<0.001), plasma (median 2 vs. 0 units, p<0.001), and platelets (median 0 [IQR 0-2] vs. 0 [0] units, p=0.003), and significantly higher mechanical ventilation requirements (median 6.5 vs. 17.5 ventilator-free days, p=0.016). Expressed in terms of odds ratios, each unit increase in PC1 score was associated with a 4.68-fold higher incidence of INR-based coagulopathy (p<0.001), a 3.35-fold higher incidence of PTT-based coagulopathy (p<0.001), and 1.48-fold higher mortality (p=0.032).

PC2 accounted for 13.4% of overall variance, including significant positive factor loading on (analogous to positive Pearson correlation with) Factor VIII, D-dimer, and activated Protein C levels (**Table 1**). Similarly to above, patients in the highest PC2 quartile were again compared to those in the lowest (**Table 3**). High PC2 patients had more severe injury (mean ISS 37.3 vs. 23.0, p<0.001), acidosis (mean pH 7.27 vs. 7.23, p=0.032), and base deficit (mean −8.4 vs. −5.5, p=0.029). High PC2 patients received less prehospital intravenous fluid (median 0 vs. 500mL), consistent with expedited transport. Despite these differences in injury and shock severity, admission INR and PTT did not differ significantly by PC2 quartile (p=0.440 and p=0.756, respectively), although admission platelet count was higher in the high PC2 population (mean 288 vs. 238 $*10^3$/uL, p=0.015). High PC2 patients had significantly higher transfusion requirements for red blood cells (median 6 vs. 0 units, p<0.001), plasma (median 4 vs. 0 units, p<0.001), and platelets (median 0 [IQR 0-2] vs. 0 [0], p=0.002). In terms of outcomes, high PC2 patients had prolonged ICU (median 12 vs. 4.5 days, p=0.003) and total hospital stays (median 22.5 vs. 8.5 days, p=0.004), and significantly higher mechanical ventilation requirements (median 2 vs. 22 ventilator-free days, p=0.002). The incidences of ventilator-associated pneumonia (55.0% vs. 29.8%, p=0.028), acute lung injury (73.5% vs. 26.7%, p<0.001), multiorgan failure (32.5% vs. 4.2%, p<0.001), and mortality (37.5% vs. 16.7%, p=0.031) were all markedly higher in the high PC2 population. Expressed in terms of odds ratios, PC2 score was not associated with significant increases in the incidence of either INR- or PTT-based coagulopathy (p=0.220 and p=0.340, respectively); however, each unit increase in PC2 score was associated with a 1.59-fold higher incidence of ventilator-associated pneumonia, a 2.24-fold higher incidence of acute lung injury, a 1.83-fold higher incidence of multiorgan failure (p=0.002), and 1.62-fold higher mortality (p=0.006).

PC3 accounted for 10.1% of overall variance, including significant positive factor loading with Factor VII and activated Protein C, and significant negative loading with Factor VIII (**Table 1**). Patients in the highest PC3 quartile had significantly better Glasgow Coma Scores (median 9 vs. 6, p=0.034) and lower admission PTT (median 26.6 vs. 28.8 sec,

p<0.001); high PC3 patients also had a lower incidence of acute lung injury (40.0% vs. 67.6%, p=0.033; **Table 4**). Unit increases in PC3 were associated with a 1.44-fold increase in the incidence of PTT-based coagulopathy (p=0.041); however, PC3 scores were not significantly associated with other measured outcomes (all other p>0.05).

In order to graphically assess inter-relationships between principal components and their relationship to outcomes, scatter plots were generated representing each patient in multivariate space by PC1 and PC2 score (Figure 1). Visually, the majority of patients with a prolonged INR and PTT are seen to have an elevated PC1 score; these are equally balanced between high and low PC2 scores (Figure 1a and 1b). In comparison, the majority of patients with multiorgan failure and mortality are seen to have an elevated PC2 score; these are equally balanced between high and low PC1 scores (Figure 1c and 1d). Odds ratio data for all binary outcomes assessed are summarized in Table 5.

DISCUSSION

Here we describe the use of PCA to interrogate the data structure of clotting factor levels in a panel of 163 critically-injured trauma patients. Three significant uncorrelated multivariate components were identified, together explaining 67.5% of the total variance in observed clotting factor measurements. PC1 accounted for 43.2% of overall variance, and consisted of significant negative loading coefficients for all procoagulant clotting factors, as well as the anticoagulants Protein C and antithrombin III. Intuitively, PC1 identifies global clotting factor depletion, and its patient-level values are associated with increased incidences of admission coagulopathy as well as mortality. PC2 accounted for 13.4% of variance, consisting principally of significant positive factor loading on D-dimer and activated Protein C levels. Intuitively, PC2 identifies a fibrinolytic component to the clotting factor milieu; interestingly, this component *is not* significantly associated with admission coagulopathy by INR or PTT-based definitions, but *is* significantly associated with ventilator-associated pneumonia, acute lung injury, multiorgan failure, and mortality. PC3 accounted for 10.1% of variance, consisting principally of significant negative loading on Factor VIII, with smaller contributions from Factor VII and activated Protein C. Intuitively, PC3 may account for an element of coagulopathy associated with consumption-driven depletion of Factor VIII; PC3 was associated only with admission PTT-based coagulopathy.

Depletion coagulopathy

The global procoagulant depletion phenotype described by PC1 matches the clinical intuition that patients with overwhelming tissue injury and acute hemorrhage frequently present with coagulopathy resulting from clotting factor consumption. The early recognition of this ‘vicious cycle’ of self-perpetuating consumptive coagulopathy is a mainstay of trauma resuscitation,[8] with recent studies extending these clinical observations to confirm the association of specific clotting factor deficits to poor outcomes after injury.[9] The global procoagulant depletion phenotype reflected by PC1 and its association with both coagulopathy and mortality reflect the clinical intuition that clotting factor depletion must be anticipated and treated early in order to minimize its deleterious effects; precisely this insight has driven recent trends in plasma-based hemostatic resuscitation therapy for critically injured patients.[10,11]

Fibrinolytic coagulopathy

The fibrinolytic phenotype described by PC2 is significantly associated with multiple functional outcomes, but is interestingly *not* associated with standard admission laboratory values such as INR or PTT. This subtlety supports the hypothesis that injury-induced activation of endogenous anticoagulants and other systemic effectors, as opposed to

consumptive depletion of procoagulant factors alone, plays a critical role in the pathophysiology of acute traumatic coagulopathy. Recent work suggests several candidate biochemical pathways that may mediate dysfunctional coagulation after trauma independently of clotting factor depletion, including catecholamine-mediated degradation of the endothelial glycocalyx[12,13] and activation of the Protein C system.[2,3] While activated Protein C mediates receptor-independent proteolysis of activated Factors Va and VIIIa as well as derepression of fibrinolysis,[2] it may also play an additional receptor-dependent role in potentiating the systemic inflammatory response.[3] Kerschen *et al.* recently showed that a recombinant form of activated Protein C with targeted mutation leading to <10% anticoagulant activity is equivalent to native protein in reducing mortality in sepsis models in mice.[14] A prospective study of clotting factor levels in 71 injured patients identified a significant negative correlation between severity of systemic hypoperfusion after injury and the activity of several procoagulant factors, but found that decreased Factor V activity may occur via a consumption-independent mechanism such as Protein C-mediated cleavage.[15]

This identification of PC2 as a fibrinolytic component is also consistent with a growing recognition of the importance of hyperfibrinolysis to acute traumatic coagulopathy. Hyperfibrinolysis is estimate to occur from 3% to 20% of significantly-injured patients, with mortality spanning 38.5% to 100%.[16] At the biochemical level, the presence of hyperfibrinolysis is associated with significantly elevated levels of D-dimer and activated Protein C.[17] Recent intriguing data suggest that the use of plasminogen-targeted antifibrinolytics such as tranexamic acid (TXA) may provide the missing pharmacologic treatment for the hyperfibrinolytic component of acute traumatic coagulopathy.[18,19] Taken together, these results suggest that aggressive clotting factor repletion by empiric plasma-based therapies may inadequately treat the fibrinolytic component of acute traumatic coagulopathy, and that targeted therapies are a promising area of active investigation.

Study limitations

As with other single-center prospective studies examining the relationship between admission clotting factor studies and outcomes, several limitations are important to interpretation of this data. Although our sample size is modest, highly-cited work in PCA suggests that 5-10 samples for each predictor included is adequate for robust results,[20,21] which our 163-patient panel well exceeds for our 10-predictor model. Importantly, this analysis does not provide for strict causal interpretation; neither PCs themselves nor the individual patient PC scores provided by PCA are directly clinically interpretable. Furthermore, the PCA model itself is not generalizable or portable, but is only applicable to the dataset from which it is derived; PC scores cannot be derived for novel patients outside of the dataset presented here. For this exploratory analysis, we included all classical clotting factor measurements available; however, other relevant physiological measures (such as pH or temperature) and clotting cascade elements (such as calcium and fibrinogen) were not uniformly available. Thus the final PCA model may be sensitive to predictor selection. Cognates to common predictor selection strategies for regression analysis (such as forward/backward and information criteria-based selection) are not well-established for the construction of PCA models, and will require detailed sensitivity analyses to validate. Overall, however, the purpose of the current study was not to construct a comprehensive predictive model, but instead to interrogate the clotting cascade for clinically compelling patterns. We suggest that these patterns identify unique groups of patients that would otherwise go undetected based on standard clinical characteristics alone, and that the further analysis of these groups may identify novel molecular markers and potential therapeutic targets.

Summary

Taken together, these results suggest that PCA accurately identifies patterns embedded in the complex milieu of the coagulation cascade in injured patients. The independent consumptive and fibrinolytic components identified here show robust correlation with patient-level outcomes, and match prevailing clinical intuition regarding drivers of acute traumatic coagulopathy. In particular, the fibrinolytic phenotype is associated with markedly poor outcomes but *not* with abnormalities in INR or PTT, highlighting the inadequacy of these measures in describing the complexity of traumatic coagulopathy and the need for validated markers of abnormal fibrinolysis after trauma. Whereas standard regression techniques are problematic for investigating the role of clotting factors in isolation, PCA is well-suited to address just such highly collinear systems of predictors as patterns. The pattern-finding capability demonstrated here holds promise for elucidating critical mechanisms underlying the pathophysiology of acute traumatic coagulopathy. Further development of data-driven analytical methods such as PCA may ultimately provide critical insights to drive advances in clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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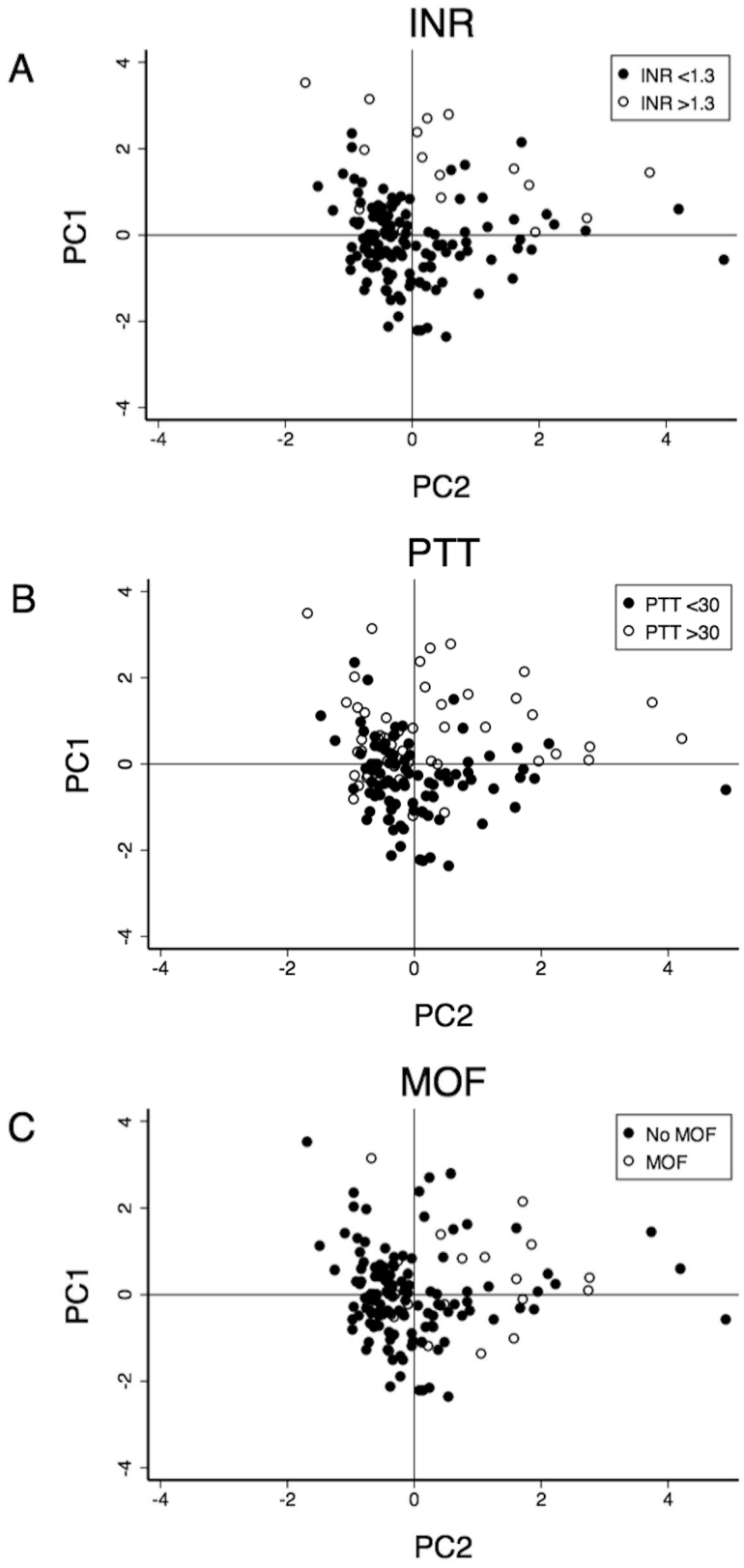
REFERENCES

1. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma. Oct; 2008 65(4):748–754. [PubMed: 18849786]
2. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg. May; 2007 245(5):812–818. [PubMed: 17457176]
3. Cohen MJ, Call M, Nelson M, et al. Critical Role of Activated Protein C in Early Coagulopathy and Later Organ Failure, Infection and Death in Trauma Patients. Ann Surg. Dec 1.2011
4. Baker SP, O'Neill B, Haddon W Jr. Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. Mar; 1974 14(3):187–196. [PubMed: 4814394]
5. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. American journal of respiratory and critical care medicine. Mar; 1994 149(3 Pt 1):818–824. [PubMed: 7509706]
6. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. May; 2009 31(5):438–447. [PubMed: 18838942]
7. Linting M, Meulman JJ, Groenen PJ, van der Koojj AJ. Nonlinear principal components analysis: introduction and application. Psychological methods. Sep; 2007 12(3):336–358. [PubMed: 17784798]
8. Kashuk JL, Moore EE, Millikan JS, Moore JB. Major abdominal vascular trauma- -a unified approach. J Trauma. Aug; 1982 22(8):672–679. [PubMed: 6980992]
9. Rizoli SB, Scarpelini S, Callum J, et al. Clotting factor deficiency in early trauma-associated coagulopathy. J Trauma. Nov; 2011 71(5 Suppl 1):S427–434. [PubMed: 22071999]
10. Duchesne JC, Holcomb JB. Damage control resuscitation: addressing trauma-induced coagulopathy. Br J Hosp Med (Lond). Jan; 2009 70(1):22–25. [PubMed: 19357573]

11. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. Sep; 2008 248(3):447–458. [PubMed: 18791365]
12. Johansson PI, Sorensen AM, Perner A, et al. High sCD40L levels Early After Trauma are Associated with Enhanced Shock, Sympathoadrenal Activation, Tissue and Endothelial Damage, Coagulopathy and Mortality. Journal of thrombosis and haemostasis : JTH. Dec 12.2011
13. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. Ann Surg. Aug; 2011 254(2): 194–200. [PubMed: 21772125]
14. Kerschen EJ, Fernandez JA, Cooley BC, et al. Endotoxemia and sepsis mortality reduction by non-anticoagulant activated protein C. The Journal of experimental medicine. Oct 1; 2007 204(10): 2439–2448. [PubMed: 17893198]
15. Jansen JO, Scarpelini S, Pinto R, Tien HC, Callum J, Rizoli SB. Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma. Nov; 2011 71(5 Suppl 1):S435–440. [PubMed: 22072000]
16. Schochl H, Voelckel W, Maegele M, Solomon C. Trauma-associated hyperfibrinolysis. Hamostaseologie. Jan; 2012 32(1):22–27. [PubMed: 22009115]
17. Kutcher ME, Cripps MW, McCreery RC, et al. Criteria for empiric treatment of hyperfibrinolysis after trauma. The journal of trauma and acute care surgery. Jul; 2012 73(1):87–93. [PubMed: 22743377]
18. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. Oct 17.2011
19. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. Jul; 2010 376(9734):23–32. [PubMed: 20554319]
20. Nunnally, JO. Psychometric Theory. McGraw-Hill; NY: 1978.
21. Tabachnik, BG.; Fidell, LS. Using Multivariate Statistics. 5th ed. Pearson Education; Boston: 2007.



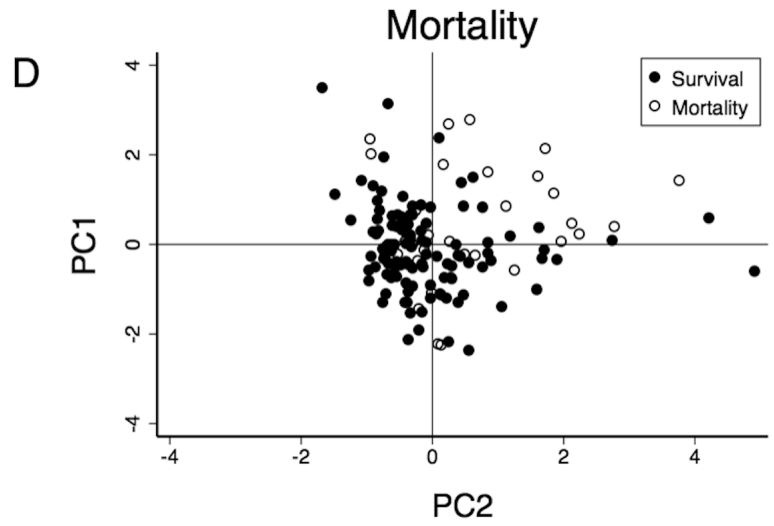


Figure 1.

Plots of patient scores within multivariate principal component space, by binary outcomes. Representative two-dimensional (PC1-PC2 space) plots provided. (a) International normalized ratio (INR) ≤ 1.3, (b) partial thromboplastin time (PTT) ≤ 30, (c) multiorgan failure, and (d) mortality. Markers indicate outcome status (filled circles = absence, hollow circles = presence).

Table 1

Composition of principal components.

	PC1	PC2	PC3
Eigenvalue	4.39	1.35	1.01
Percent variance	43.91	13.45	10.12
Prothrombin	−0.86	−0.04	0.11
Factor V	−0..78	0.01	−0.11
Factor VII	−0..62	0.01	0.47
Factor VIII	−0..35	0.34	−0.73
Factori IX	−0.69	0.07	0.03
Factor X	−0.88	−0.01	0.20
D-dimer	0.25	0.80	0.00
aPC	0.20	0.74	0.39
Protein C	−0.80	0.11	−0.05
AT III	−0.74	0.16	−0.17

Heatmap: 

Principal component eigenvalues, percentage of variance accounted for, and factor loading magnitudes. Positive loading (analogous to a positive Pearson correlation) is indicated in shades of red, with negative correlation (analogous to inverse Pearson correlation) indicated in shades of blue. The magnitude of the loading for each factors is shown in text, and considered significant for values of >0.30.

Table 2

Patient characteristics by first principal component (PC1).

	Low PC1 (N = 40)	High PC1 (N = 41)	P-value
PC score	−1.16 ± 0.52	1.29 ± 0.78	-
Age	39.8 ± 14.2	42.1 ± 19.9	0.564
BMI	28.5 ± 5.5	27.5 ± 5.9	0.466
Penetrating injury	12.5%	34.2%	0.035
ISS	23.8 ± 12.8	32.2 ± 16.2	0.011
GCS	7 (4.5 - 12)	7 (3 - 14)	0.782
Temperature	35.4 ± 0.9	35.3 ± 1.1	0.690
Prehospital IVF	200 (0 - 600)	0 (0 - 150)	0.118
pH	7.29 ± 0.11	7.26 ± 0.12	0.143
Base deficit	−5.8 ± 4.5	−8.1 ± 6.7	0.089
INR	1.0 (1.0 - 1.1)	1.2 (1.1 - 1.4)	<0.001
PTT	27.0 (24.9 - 28.1)	32.6 (27.5 - 38.5)	<0.001
Platelet count	311 ± 85	245 ± 84	<0.001
RBC / 24h	0 (0 - 0)	5 (1 - 14)	<0.001
FFP / 24h	0 (0 - 0)	2 (0 - 9)	<0.001
Platelets / 24h	0 (0 - 0)	0 (0 - 2)	0.003
Hospital days	14 (6.5 - 29)	14 (6 - 30)	0.769
ICU days	9 (3 - 16)	9 (3 - 21)	0.861
Ventilator-free days	17.5 (1.5 - 26)	6.5 (0 - 22.5)	0.016
VAP	42.5%	39.0%	0.823
Acute lung injury	38.2%	51.4%	0.341
Multiorgan failure	17.5%	17.1%	1.000
Mortality	17.5%	31.7%	0.198

Data from the lowest ('Low PC1') and highest ('High PC1') patient quartiles are presented as mean ± standard deviation or median (interquartile range). BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, IVF = intravenous fluid, INR = international normalized ratio, PTT = partial thromboplastin time, RBC = red blood cell units, FFP = fresh frozen plasma units, ICU = intensive care unit.

* $p < 0.05$ by Student's *t*, Mann-Whitney, or Fisher's exact testing.

Table 3

Patient characteristics by second principal component (PC2).

	Low PC2 (N = 48)	High PC2 (N = 40)	P-value
PC score	−0.79 ± 0.21	1.38 ± 1.09	-
Age	43.7 ± 16.1	44.5 ± 20.7	0.831
BMI	26.1 ± 5.0	27.8 ± 4.7	0.114
Penetrating injury	14.6%	17.5%	0.775
ISS	23.0 ± 15.3	37.3 ± 16.6	<0.001
GCS	7 (3 - 9)	8 (4 - 14)	0.122
Temperature	35.6 ± 0.8	35.5 ± 0.9	0.526
Prehospital IVF	500 (125 - 775)	0 (0 - 0)	0.001
pH	7.32 ± 0.10	7.27 ± 0.12	0.032
Base deficit	−5.5 ± 5.3	−8.4 ± 5.6	0.029
INR	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)	0.440
PTT	29.4 (26.2 - 32.4)	28.8 (25.6 - 37.5)	0.756
Platelet count	238 ± 71	288 ± 107	0.015
RBC / 24h	0 (0 - 3)	6 (1 - 14)	<0.001
FFP / 24h	0 (0 - 3)	4 (0 - 12)	<0.001
Platelets / 24h	0 (0 - 0)	0 (0 - 2)	0.002
Hospital days	8.5 (3 - 23)	22.5 (9.5 - 40.5)	0.004
ICU days	4.5 (2 - 12.5)	12 (6 - 22)	0.003
Ventilator-free days	22 (0 - 26)	2 (0 - 19)	0.002
VAP	29.8%	55.0%	0.028
Acute lung injury	26.7%	73.5%	<0.001
Multiorgan failure	4.2%	32.5%	<0.001
Mortality	16.7%	37.5%	0.031

Data from the lowest ('Low PC2') and highest ('High PC2') patient quartiles are presented as mean ± standard deviation or median (interquartile range). BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, IVF = intravenous fluid, INR = international normalized ratio, PTT = partial thromboplastin time, RBC = red blood cell units, FFP = fresh frozen plasma units, ICU = intensive care unit.

* $p < 0.05$ by Student's *t*, Mann-Whitney, or Fisher's exact testing.

Table 4

Patient characteristics by third principal component (PC3).

	Low PC3 (N = 41)	High PC3 (N = 40)	P-value
PC score	−1.19 ± 0.63	1.22 ± 0.74	-
Age	43.4 ± 18.7	41.0 ± 18.7	0.567
BMI	27.3 ± 5.8	28.2 ± 5.8	0.550
Penetrating injury	17.1%	32.5%	0.128
ISS	27.9 ± 15.2	26.4 ± 11.9	0.644
GCS	6 (3 - 9)	9 (4 - 15)	0.034
Temperature	35.7 ± 0.7	35.5 ± 1.0	0.395
Prehospital IVF	0 (0 - 450)	0 (0 - 300)	0.953
pH	7.31 ± 0.10	7.28 ± 0.17	0.429
Base deficit	−6.1 ± 4.9	−7.0 ± 7.1	0.560
INR	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)	0.654
PTT	28.8 (27.0 - 34.3)	26.6 (23.8 - 29.8)	<0.001
Platelet count	276 ± 99	292 ± 81	0.435
RBC / 24h	0 (0 - 6.5)	1.5 (0 - 5.5)	0.829
FFP / 24h	0 (0 - 4.5)	0 (0 - 3.5)	0.730
Platelets / 24h	0 (0 - 1)	0 (0 - 0)	0.325
Hospital days	11 (5 - 25)	14.5 (6.5 - 28)	0.192
ICU days	8 (3 - 18)	6 (3 - 15.5)	0.940
Ventilator-free days	8 (0 - 24)	20.5 (1 - 26)	0.084
VAP	48.8%	32.5%	0.176
Acute lung injury	67.6%	40.0%	0.033
Multiorgan failure	19.5%	10.0%	0.349
Mortality	34.1%	17.5%	0.128

Data from the lowest ('Low PC3') and highest ('High PC3') patient quartiles are presented as mean ± standard deviation or median (interquartile range). BMI = body mass index, ISS = injury severity score, GCS = Glasgow coma score, IVF = intravenous fluid, INR = international normalized ratio, PTT = partial thromboplastin time, RBC = red blood cell units, FFP = fresh frozen plasma units, ICU = intensive care unit.

* $p < 0.05$ by Student's *t*, Mann-Whitney, or Fisher's exact testing.

Table 5

Principal component scores as predictors of outcomes.

		PC1	PC2	PC3
Odds ratio	Mortality	1.48 (1.03-2.12) AUC: 0.616	1.62 (1.15-2.29) AUC: 0.669	-
	Multiorgan failure	-	1.83 (1.25-2.68) AUC: 0.750	-
	Acute lung injury	-	2.24 95% CI: AUC:	-
	VAP	-	1.59 (1.13-2.24) AUC: 0.628	-
	INR ≥1.3	4.68 (2.37-7.66) AUC: 0.844	-	-
	PTT ≥30	3.35 (2.06-5.45) AUC: 0.769	-	1.44 (1.02-2.04) AUC: 0.593

Significant odds ratios derived from continuous principal component scores in univariate, unadjusted logistic regression models. 95% confidence intervals and area under the receiver operator characteristic curve (‘AUC’) are given for all significant predictors. Nonsignificant (Wald test p-values greater than 0.05) odds ratios marked as ‘-‘. VAP: ventilator-associated pneumonia, INR: international normalized ratio, PTT: activated partial thromboplastin time.