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An INR-based definition of acute traumatic coagulopathy is associated with mortality, venous thromboembolism, and multiple organ failure after injury

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Abstract

Objective—Acute traumatic coagulopathy (ATC) is associated with adverse outcomes including death. Previous studies examining ATC's relationship with mortality are limited by inconsistent criteria for syndrome diagnosis, inadequate control of confounding and single-center designs. In this study, we validated the admission international normalized ratio (INR) as an independent risk factor for death and other adverse outcomes after trauma and compared two common INR-based definitions for ATC.

Design—Multicenter prospective observational study.

Setting—Nine level I trauma centers in the United States.

Patients—1,031 blunt trauma patients with hemorrhagic shock.

Interventions—None.

Measurements and Main Results—INR exhibited a positive adjusted association with all-cause in-hospital mortality, hemorrhagic shock-associated in-hospital mortality, venous thromboembolism, and multiple organ failure. ATC affected 50% of subjects if defined as an INR >1.2 and 21% of subjects if defined by INR >1.5. After adjustment for potential confounders, ATC defined as an INR >1.5 was significantly associated with all-cause death (OR 1.88, $p<0.001$), hemorrhagic shock-associated death (OR 2.44, $p=0.001$), venous thromboembolism (1.73, $p<0.001$), and multiple organ failure (OR 1.38, $p=0.02$). ATC defined as an INR >1.2 was not associated with an increased risk for the studied outcomes.

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Conclusions—Elevated INR on hospital admission is a risk factor for mortality and morbidity after severe trauma. Our results confirm this association in a prospectively-assembled multicenter cohort of severely injured patients. Defining ATC using an INR >1.5 but not an INR >1.2 identified a clinically-meaningful subset of trauma patients who, adjusting for confounding factors, suffered more adverse outcomes. Targeting future therapies for ATC to patients with an INR >1.5 may yield greater returns than using a lower INR threshold.

Keywords

Acute traumatic coagulopathy; Trauma; Hemorrhage; Multiple organ failure; Venous thromboembolism; International normalized ratio (INR)

Introduction

Traumatic injuries are a major cause of death and disability worldwide and the leading cause of death among children and young adults in the United States (1-3). Uncontrolled hemorrhage causes many of these deaths, particularly in the immediate post-injury phase (4, 5). Hemorrhage contributed to 42% of all deaths in a recent multicenter observational study of severely injured patients, including 67% of deaths within the first 24 hours and 81% of deaths within 6 hours of injury (6). Remediable factors that contribute to bleeding, such as coagulopathy, are therefore important therapeutic targets.

“Traditional” trauma-induced coagulopathy arises relatively late in the course of care (7). By contrast, acute traumatic coagulopathy (ATC) is an early-onset syndrome of post-injury coagulopathy characterized by endogeneously deranged clotting function present on admission to the emergency department (8, 9). Widely recognized only in the last decade, ATC affects 20-30% of severely injured patients and is associated with an increased risk of death and multiple organ failure (8-12).

The literature characterizing ATC as a distinct condition has several limitations. Many of the descriptions of ATC were conducted at a single center or were retrospective evaluations of registry data. Control for confounding in evaluating the association of ATC with outcomes was incomplete in most studies. Most importantly, there is no consensus regarding the laboratory definition of the condition. Studies to date use conventional coagulation tests (prothrombin time (PT) or international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, thrombin time and fibrinogen level) as well as non-standard modifications of these values (PT ratio, Quick's value, and PTT ratio) at varying thresholds and in varying combinations to define ATC (Table 1). Thromboelastography, a viscoelastic assay of clot formation and lysis in whole blood, may provide more rapid results and better simulate in vivo coagulation than conventional coagulation tests (13-15). However, aside from transfusion requirements, the literature linking one or more viscoelastic parameters to clinically-meaningful trauma outcomes is limited (16, 17). Problems of availability, reliability, complexity of interpretation and limited interchangeability of commercially-available systems further hinder thromboelastography's use to define ATC and, more generally, its routine use in trauma care (18, 19).

An ideal definition of ATC would identify a clinically-distinct subset of trauma patients using a laboratory test that is widely available, low cost, standardized globally and easily interpreted by practitioners. While the INR meets these laboratory criteria, it is unclear (1) whether INR as a single test measured on emergency department admission and reflective of extrinsic coagulation pathway abnormalities is independently associated with adverse outcomes and (2) which of the two most common INR-based ATC definitions — INR >1.2 (equivalent to PT, Quick's value or INR outside the normal range (9, 10, 20-24) or INR >1.5 (25-28) — is most clinically meaningful. To address these issues, we investigated the independent association of INR with mortality and morbidity in a prospective multicenter cohort of severely injured trauma patients. We then compared the adjusted association of ATC and adverse trauma outcomes resulting from these two candidate ATC definitions.

Materials and Methods

We obtained de-identified data from a multicenter prospective cohort study (Inflammation and the Host Response to Injury Consortium). Briefly, the study enrolled blunt trauma patients presenting to one of nine U.S. level I trauma centers from 2003-2010 who (1) exhibited shock within 60 minutes of emergency department (ED) arrival, defined as a base deficit ≥ 6 mEq/L or systolic blood pressure (SBP) <90 mmHg; (2) had any non-head abbreviated injury score (AIS) ≥ 2 ; and (3) required red blood cell transfusion within 12 hours. Exclusion criteria severe traumatic brain injury (AIS head ≥ 4 or score ≥ 3 for the motor component of the Glasgow Coma Scale [GCS] by 24 hours after injury); age <16 or >90 years; and complete cervical spine injury. Additional details regarding participating centers and the aims of this research study are provided at www.gluegrant.org. For the present study, we excluded patients who were not directly admitted to the participating trauma center from the field, who were on warfarin, or who received pre-hospital blood transfusions. The initial study was approved by the institutional review boards of each participating institution. Use of de-identified data for the current study was determined to be exempt from review by the University of Washington Institutional Review Board.

Clinical care was standardized across the participating hospitals (29-37). Trained research nurses abstracted data, with verification by independent abstraction and by central review. Subjects were monitored until discharge or post-injury day 28 for a range of post-trauma complications using standardized definitions (38). Acute respiratory distress syndrome (ARDS) was defined in accordance with the 1994 American-European Consensus Conference criteria as the acute onset of bilateral infiltrates on chest radiograph with $\text{PaO}_2/\text{FiO}_2$ ratio <200 and no evidence of left-sided heart failure (39). Venous thromboembolism (VTE) included pulmonary embolism (PE) or deep vein thrombosis (DVT). PE was diagnosed by angiography, CT scan, or moderate or high-probability ventilation/perfusion scan. DVT was identified in the extremities or pelvis on autopsy, venogram, or non-invasive vascular evaluation. Hypotension was defined as SBP <90 . Multiple organ failure (MOF) was defined as a Marshall multiple organ dysfunction score (40), excluding the neurologic component, of at least 6 at least 48 hours after injury (41).

Injury characteristics were defined using the International Classification of Diseases (9th revision) diagnosis codes recorded for each subject as previously described (42): femur

fracture (any 820.x and/or 821.x code); flail chest (807.4); pulmonary contusion (807.4, 807.13-19, and/or 861.x); pelvic fracture (any one of 808.x [except 808.2, stable pelvic fracture]); and spinal cord injury (any one of 806.x and/or 952.x). Massive transfusion was defined as receipt of 10 units of packed red blood cells (PRBCs) within 24 hours of ED admission.

We examined all-cause in-hospital mortality and hemorrhagic shock-associated in-hospital mortality as primary endpoints in this study. We evaluated the association of INR (modeled as a continuous variable) with these endpoints using multivariable logistic regression adjusted for potential confounders. We also examined the adjusted association of admission INR (as a continuous variable) and several secondary outcomes (MOF, ARDS, and VTE) using Cox proportional hazard analysis to account for the competing risk of mortality. Selection of adjustment variables for each model occurred *a priori* based on literature review (10-12, 42-47). Subjects with incomplete data for adjustment variables were excluded from the primary analyses but included in multiply imputed sensitivity analyses (see below). Validity of the proportional hazards assumption for each model was checked according to the method of Grambsch and Therneau (48).

We next examined the risk-adjusted association between ATC, modeled as one of two candidate dichotomous exposures, and the outcomes significantly associated with INR when it was modeled as a continuous variable. As a result, we evaluated two risk-adjusted models for each outcome, differing as to the ATC definition but otherwise containing the same covariates. We selected the two candidate ATC definitions, INR >1.2 or INR >1.5, based on the INR thresholds most frequently used in published literature to define ATC (9, 10, 20-28). We compared the fit of the two competing models for each outcome using the Akaike information criterion (49).

We performed four sensitivity analyses for the association of INR with mortality outcomes. First, to determine whether the most severe INR derangements were skewing our analysis, we reestimated the logistic regression models after exclusion of subjects with admission INRs greater than two standard deviations above the mean. Second, to investigate whether the omission of cases with missing data introduced bias, we repeated our regression analyses after performing multiple imputation to account for missing data, employing chained equations to create 50 imputed data sets (50). Missing values for admission INR, base deficit, and temperature, body mass index, and pre-hospital GCS and intravenous fluid volume were imputed using predictive mean matching (51) from three nearest neighbors. Admission hypotension was imputed using logistic regression. Variables in the imputation models included the above missing variables, covariates from each logistic regression and Cox regression model, as well as outcome variables for all-cause and bleeding-associated mortality, ARDS, VTE, and MOF. The analyses of imputed data were repeated after excluding subjects with imputed INR data. Finally, since INR was recorded to two decimal place accuracy for some but not all subjects, a small fraction of subjects were differently classified using INR >1.2 versus INR >1.3 as the lower-threshold ATC definition. We therefore evaluated whether using an INR >1.3 rather than INR >1.2 for the lower-threshold ATC definition altered our findings.

Data analysis was performed using Stata version 13.1 (StataCorp LP, College Station, TX). For univariate analysis, continuous variables were compared using unpaired t-tests with unequal variance or Mann-Whitney tests as appropriate. Categorical variables were compared using chi-squared tests. Tests of significance in multivariable analysis employed the Wald test. Odds ratios (OR) and hazard ratios (HR) are reported with 95% confidence intervals based on robust standard errors clustered on center to allow for correlation within centers. A p value ≤ 0.05 was considered significant.

Results

Of 2,007 subjects entered in the Inflammation and Host Response to Injury database, 1,373 met inclusion criteria for the current study (Figure 1). Of those, 342 (25%) had missing data for one or more covariates in the pre-specified multivariable model for the primary outcomes. Initial ED temperature was the most frequent missing data element (222 subjects), followed by missing INR values and other covariate data elements (each representing approximately 5% or less of the eligible cohort). Demographic and other injury characteristics for the 1,031 subjects with complete data for the primary analysis are shown in Table 2. The majority (88.1%) of subjects were white and 14.0% were Hispanic. Most injuries resulted from motor vehicle collisions (52.9%), motorcycle collisions (15.9%) or pedestrians being struck by moving vehicles (15.7%). Overall, 153 (14.8%) subjects died, with 29% of deaths due in whole or part to hemorrhage (Table 3). Compared to subjects with complete data for the primary analysis, subjects with missing data were similar in age, prehospital blood pressure and GCS, admission INR, injury severity, and incidence of VTE and MOF (Table S1, Supplemental Digital Content 1). Subjects with missing data received less pre-hospital intravenous fluid, exhibited higher admission temperatures and base deficits, suffered more shock on ED arrival, and had a higher incidence of all-cause and hemorrhage-associated death, ARDS, and massive transfusion.

After adjustment for age, injury severity score, APACHE II score, time from injury to ED arrival, shock, temperature and base deficit on ED arrival, and pre-hospital GCS & IV fluid volume, INR was associated with significantly increased odds of all-cause mortality (Table 4). INR was also significantly associated with death caused primarily or in part by hemorrhagic shock (Table 4). Results were similar when we excluded subjects with admission INR values >2 standard deviations above the mean (INR >2.7 , representing the highest 2.5% of INR values) or repeated our analyses on multiply imputed data (Table S2, Supplemental Digital Content 2). The predicted probability of death increased more steeply at higher INRs (Figure 2). Increasing INR was also associated with a small but significantly increased risk of incident MOF and VTE but not ARDS (Table 4).

Admission INR was >1.2 in 519 subjects (50.3%) and >1.5 in 219 subjects (21.2%). In bivariate analyses, coagulopathy by either definition was associated with increased risk of all-cause mortality and death associated with hemorrhagic shock (Table 3). Massive transfusion, ARDS, VTE, and MOF were more common in coagulopathic subjects by either definition. The increased risks were more marked using the INR >1.5 threshold than the INR >1.2 threshold. For instance, 18.5% of subjects with INR >1.2 died in hospital compared to 11.1% with INR ≤ 1.2 (crude RR 1.66, 95% CI 1.23-2.25), whereas 26.5% of subjects with

INR >1.5 died compared to 11.7% with INR ≤1.5 (RR 2.26, 95% CI 1.69-3.03). Coagulopathic subjects also spent more time in the hospital, in the ICU and receiving mechanical ventilation.

We next used multivariable logistic regression to compare the adjusted association between mortality outcomes and ATC defined as INR >1.2 or INR >1.5 (Table 5). The adjusted risk of all cause death (OR 1.88, 95% CI 1.36-2.60) was significantly elevated in subjects with ATC as defined by INR >1.5 ($p<0.001$) compared to subjects without ATC (INR ≤1.5), but not when INR was dichotomized at 1.2 (OR 1.29, 95% CI 0.92-1.82, $p=0.14$). The Akaike information criterion was lower in the model using INR >1.5 (658) than the model dichotomizing INR as >1.2 versus ≤1.2 (663), indicating better model fit with the higher INR threshold.

The adjusted risk of death due to hemorrhagic shock was significantly elevated in subjects with ATC defined as INR >1.5 compared to those with an INR ≤1.5 (OR 2.44, 95% CI 1.43-4.18, $p=0.001$). The risk was not significantly different between subjects with an INR >1.2 compared to those with an INR ≤1.2 (OR 1.58, 95% CI 0.83-3.02, $p=0.16$). As observed for all-cause mortality, the AIC was lower for the model using ATC defined as an INR >1.5 (285) than for the model defining ATC as an INR >1.2 (289).

Excluding subjects with INR >2 standard deviations above the mean did not alter our findings regarding the association between candidate ATC definitions and all-cause or hemorrhage-associated death (Table S3, Supplemental Digital Content 3). Sensitivity analyses employing multiply imputed data (Table S4, Supplemental Digital Content 4) or using an INR ≤1.3 rather than an INR >1.2 for the low-threshold ATC definition (Table S5, Supplemental Digital Content 5) also yielded similar results.

In adjusted analyses, the presence of ATC was significantly associated with VTE when defined as INR >1.5 but not when defined as INR >1.2 (Table 5). For MOF, the magnitude of the adjusted association was similar for INR >1.5 and INR >1.2, but only the association with INR >1.5 was statistically significant.

We conducted an exploratory analysis of the adjusted risk of death or death due to hemorrhagic shock among individuals with mildly elevated admission INR (Table S6, Supplemental Digital Content 6). Admission INR was >1.2 and ≤1.5 in 30% ($N=300$). Compared to patients with INR ≤1.2, there was no increased risk of death (OR 1.01, 95% CI 0.7-1.44) or death due to hypovolemic shock (OR 1.20, 95% CI 0.59-2.45).

Discussion

In a well-described, multicenter cohort of patients with severe injuries, we confirmed that prolonged admission INR is a risk factor for all-cause and hemorrhage-associated mortality, venous thromboembolism, and multiple organ failure after adjustment for known and plausible confounders. Whereas INR >1.2 was not associated with trauma mortality or morbidity, ATC diagnosed using an admission INR >1.5 identified a subset of patients who, adjusting for other factors, were at increased risk of death, VTE, and MOF.

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Prolonged prothrombin time early after injury correlates strongly with ISS, shock and acidosis (11), raising the possibility that an abnormal prothrombin time (or a derivative) is simply a marker of overall injury severity instead of a biological mechanism for adverse outcomes. Many prior studies did not control confounding rigorously enough when examining the association of ATC with death and other outcomes to exclude this chance. Our carefully-controlled analysis of multicenter data provides evidence that an elevated admission INR is in fact an indicator of important abnormalities of the extrinsic coagulation pathway associated with these adverse outcomes.

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Over the last decade, investigators have employed variable and sometimes complex laboratory criteria to define the syndrome of acute traumatic coagulopathy. ATC definitions based solely on prolonged prothrombin time or its derivatives, however, are increasingly common among studies utilizing conventional coagulation tests (Table 1). The lack of consensus on how to define ATC remains a barrier to the study and treatment of ATC as a distinct condition. We therefore compared the ability of two candidate INR-based definitions of ATC to identify injured patients at risk for adverse outcomes. Our data support diagnosing ATC when INR is >1.5 on ED admission. Strengths of this definition include its simplicity and generalizability, features which facilitate its application in both community hospitals and low-resource settings. An INR-based ATC definition offers advantages over definitions using the PT or PT ratio since (1) INR is directly reported by the laboratory and (2) INR corrects for variability in the prothrombin time ratio over time and between laboratories (52). While we were unable to evaluate definitions employing PTT, platelet count, or fibrinogen level, these parameters alone are insensitive for clinically significant coagulopathy and unlikely to markedly improve an INR-based definition (9, 26, 53-55). Viscoelastic assays' speed, ability to simulate in vivo clotting, and utility for mechanistic studies of acute coagulopathy make them attractive (14), but data linking specific functional abnormalities detected by these tests to trauma outcomes are too limited to base ATC diagnosis on this technology (56-58). An INR-based definition of ATC offers a reproducible, laboratory-based definition with low institutional and geographic variability, facilitating future clinical and translational research studies and ATC intervention trials.

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Defining ATC based on a single conventional coagulation test also has several potential problems. Logistically, the delay from collection to result may limit these tests utility in fast-paced trauma care (19). Application of point-of-care INR testing could overcome this obstacle, but this method has so far proven unsatisfactory in the trauma setting (19). More broadly, as a plasma-based test, INR reflects quantitative deficiencies in the "extrinsic" clotting pathway (factors V, VII, and X, prothrombin, and fibrinogen) under laboratory conditions rather than the cell-based clot formation that occurs in vivo (19). Some physiologically-important coagulation derangements present after trauma, such as hyperfibrinolysis, do not alter the PT/INR (59). The INR alone cannot distinguish between potential ATC mechanisms. Recent studies employing both conventional (60) and viscoelastic (28) measures suggest, however, that the PT/INR captures the most important type of coagulopathy for adverse trauma outcomes.

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The risk-adjusted association we observed between elevated admission INR and later hypercoagulability is superficially paradoxical. Potential mechanisms include delayed

initiation of VTE chemoprophylaxis (61), increased use of pro-coagulant therapies such as tranexamic acid in patients with ATC, or concurrent activation of anti- and procoagulant pathways, with the balance shifting over time from a predominantly hypocoagulable to a predominantly hypercoagulable state (62). Despite our attempts to adjust for known risk factors for post-traumatic VTE, the observed association could also result from residual confounding. Further studies are necessary to confirm this association and explore its mechanisms.

This study has several limitations. First, as with all observational studies, the observed association may not be causal. We made aggressive efforts to control for potential confounding factors in the studied relationships, but possibly omitted some relevant risk factors. Second, our results may not be generalizable to less severely injured trauma patients. We suspect, however, that ATC is more frequent and entails more severe ramifications in patients with severe injuries. Third, while standard operating procedures implemented across the participating institutions should have limited variations in care over time, changing transfusion strategies and other clinical practices may have altered the relationship of INR with outcomes across the study period. Fourth, the candidate INR-based definitions of ATC are not mutually exclusive and therefore cannot be directly compared. While it is possible that the risk we observed at INR >1.5 was driven by subjects with more severe INR derangements, sensitivity analyses eliminating subjects with the most severely deranged INRs did not alter our results. We cannot exclude the possibility that a larger study with increased power to detect a small increased risk would have resulted in significant associations between INR >1.2 and the studied outcomes. However, our exploratory analysis of subjects with mild INR elevations suggests that any increased risk of death detected among patients with INR >1.2 would in fact be driven by the increased risk experienced by patients with INR >1.5.

Finally, two groups of patients were excluded from our analysis. A substantial number of eligible subjects had missing covariate data, potentially influencing our multivariable analyses in an unpredictable fashion. Although repetition of our analyses using multiply imputed data did not alter our conclusions, we cannot exclude a “missing not at random” pattern of missing data despite our use of a broad panel of covariates for imputation (63). Our sensitivity analyses therefore reduce but do not eliminate the risk of bias due to missing data. Additionally, we excluded the 29% of the enrolled subjects who initially received care at another facility before transfer to the study center because INR values on arrival to the first treating ED were unavailable. Although this approach was similar to past ATC studies, transfer patients may differ from patients directly admitted to level 1 trauma centers in important ways. Future studies are required that clarify the implications of ATC in this important and fairly large subset of trauma patients.

Conclusions

In this multicenter prospective cohort of severely injured trauma patients, we found that admission INR was associated with all-cause mortality, death due to bleeding, VTE, and MOF after controlling for other risk factors. An INR >1.5 but not an INR >1.2 identified a subset of trauma patients at increased risk for adverse outcomes. Defining ATC as an INR

>1.5 on ED admission provides a simple, generalizable, and clinically-meaningful laboratory definition of ATC. Future studies should investigate methods to rapidly identify patients meeting this INR-based definition of ATC and determine the efficacy of targeted therapy for treatment of this severe complication of trauma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Patient flow diagram. Some patients had >1 reason for ineligibility or were missing >1 data element. 1,031 patients with complete data were included in the primary analysis.

(Abbreviations: ED, emergency department; GCS, Glasgow Coma Scale)

Figure 2.

Probability of death as a function of INR on ED admission, adjusted for age, time from injury to ED arrival, injury severity score, APACHE II score, pre-hospital Glasgow Coma Scale, hypotension (systolic blood pressure <90), and pre-hospital IV fluid volume, and initial base deficit and temperature in the ED. Gray shaded area represents the 95% confidence interval.

Table 1
Definitions used in studies of acute traumatic coagulopathy prevalence in general trauma populations

Lead study author	Year	Components of acute coagulopathy definition ^a					Comment
		PT-based	PTT-based	Platelets	Fibrinogen (mg/dL)	Other	
Brohi (8)	2003	PT >18s	aPTT >60s	—	—	TT >15s	PT/PTT/TT >1.5× upper limit of normal
Macleod (9)	2003	PT >14s	PTT >34s	—	—	—	PT/PTT > upper limit of normal
Rugeri (64)	2007	INR >1.6	aPTT >60s	<100,000	<100	—	
Maegele (10)	2007	QV <70%	—	<100,000	—	—	
Niles (65)	2008	INR 1.5	—	—	—	—	
Hess (66)	2009	INR 1.5	aPTT 1.5	—	<100	—	
Frith (11)	2010	PT >1.2	—	—	—	—	
Mitra (25)	2011	INR >1.5	aPTT >60s	—	—	—	
Shaz (55)	2011	See comment	—	—	—	—	“PT greater than the normal range”
Davenport (19)	2011	PT >1.2	—	—	—	—	
Tauber (26)	2011	INR >1.5	aPTT >50s	<100,000	<150	—	
Floccard (67)	2012	—	—	—	—	DIC score 1	
Patregnani (68)	2012	INR 1.5	—	—	—	—	Pediatric patients
David (27)	2012	INR >1.5	aPTT >60s	<100,000	<150	—	
Mujuni (69)	2012	PT >18s	PTT >36s	—	—	—	
Hendrickson (20)	2012	PT >15.9s	PTT >42.1s	<185,000	<180	—	Pediatric patients
Cohen (12)	2013	INR 1.3	PTT 35s	—	—	—	
Cheddie (21)	2013	INR >1.2	—	—	—	—	
Whittaker (22)	2013	INR >1.2	—	—	—	—	Pediatric patients
Meyer (23)	2014	INR >1.2	—	—	—	—	
Matijevic (70)	2014	—	aPTT 35s	—	—	—	
Oshiro (71)	2014	PT >1.2	—	—	—	—	
Kutcher (72)	2014	INR 1.5	—	—	—	—	
Fröhlich (24)	2014	QV <70%	—	<100,000	—	—	
Chin (28)	2014	INR >1.5	—	—	—	—	

^a For studies employing >1 criterion, meeting any one or more of the listed criteria defined acute coagulopathy

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Abbreviations: PT, prothrombin time; INR, international normalized ratio; QV, Quick's value; PTt, prothrombin time ratio; PTT, partial thromboplastin time; aPTT, activated PTT; aPTTr, aPTT ratio; TT, thrombin time; s, seconds; DIC, disseminated intravascular coagulation

Table 2
Characteristics of study subjects overall and by coagulopathy categories

Subject demographics ^a	Overall (N=1031)	Low INR threshold			High INR threshold		
		INR 1.2 (N=512)	INR >1.2 (N=519)	p	INR 1.5 (N=812)	INR >1.5 (N=219)	p
Age (years)	41 (18)	44 (17)	38 (18)	<0.001	43 (17)	37 (19)	<0.001
Male sex	687 (66.7%)	334 (65%)	353 (68%)	0.34	539 (66.4%)	148 (67.6%)	0.74
Pre-hospital vital signs & resuscitation							
Pre-hospital hypotension (SBP <90) ^b	489 (49.2%)	196 (40.1%)	293 (58.0%)	<0.001	357 (45.7%)	132 (62.0%)	<0.001
Highest heart rate ^b	115 (26)	112 (25)	119 (26)	<0.001	113 (25)	123 (27)	<0.001
First GCS (median [IQR])	13 (6-15)	14 (8-15)	12 (5-15)	<0.001	14 (7-15)	11 (3-14)	<0.001
IV fluid volume (L, median [IQR])	1.0 (0.4-2.0)	0.7 (0.2-1.4)	1.6 (0.75-2.6)	<0.001	0.9 (0.3-1.7)	2.0 (1.1-3.3)	<0.001
Minutes from injury to ED arrival	64 (39)	59 (38)	69 (39)	<0.001	61 (37)	74 (42)	<0.001
Initial ED data							
Hypotension on arrival (SBP <90)	236 (22.9%)	113 (22.1%)	123 (23.7%)	0.53	184 (22.7%)	52 (23.7%)	0.74
Heart rate	111 (27)	109 (27)	113 (28)	0.011	109 (27)	116 (29)	0.005
Temperature (Celsius)	35.6 (1.2)	35.9 (1.1)	35.3 (1.2)	<0.001	35.7 (1.1)	35.0 (1.3)	<0.001
GCS (median [IQR])	8 (3-15)	14 (3-15)	3 (3-14)	<0.001	11 (3-15)	3 (3-10)	<0.001
Hemoglobin (g/dL)	11.2 (2.6)	12.3 (2.2)	10.2 (2.5)	<0.001	11.8 (2.3)	9.3 (2.5)	<0.001
First base deficit (mEq/L)	8.2 (4.6)	7.7 (4.3)	8.8 (4.8)	<0.001	7.8 (4.3)	10.0 (5.2)	<0.001
Injury severity score	33 (14)	30 (13)	36 (14)	<0.001	31 (13)	38 (15)	<0.001
APACHE II score	29 (7)	27 (7)	30 (7)	<0.001	28 (7)	32 (6)	<0.001
Body mass index ^b	28 (7)	29 (7)	27 (6)	<0.001	29 (7)	26 (5)	<0.001
Pulmonary contusion	402 (39.0%)	185 (36.1%)	217 (41.8%)	0.06	298 (36.7%)	104 (47.5%)	0.004
Flail chest	74 (7.2%)	33 (6.5%)	41 (7.9%)	0.37	53 (6.5%)	21 (9.6%)	0.12
Multiple fractures	571 (55.4%)	278 (54.3%)	293 (56.5%)	0.49	441 (54.3%)	130 (59.4%)	0.18
Femur fracture	320 (31.0%)	146 (28.5%)	174 (33.5%)	0.08	239 (29.4%)	81 (47.0%)	0.032

^aContinuous variables reported as mean (SD) unless indicated. Categorical data are presented as N (%).

^bNumber of subjects with missing data for the variable: pre-hospital hypotension: 37; pre-hospital hypotension: 401 body mass index: 27.

Abbreviations: SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ED, emergency department; INR, international normalized ratio; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; IQR, interquartile ratio.

Table 3
Clinical outcomes overall and by coagulopathy category

Outcome ^a	Overall (N=1031)	Low INR threshold			High INR threshold		
		INR 1.2 (N=512)	INR >1.2 (N=519)	p	INR 1.5 (N=812)	INR >1.5 (N=219)	p
In-hospital mortality	153 (14.8%)	57 (11.1%)	96 (18.5%)	0.001	95 (11.7%)	58 (26.5%)	<0.001
Death due to hemorrhagic shock							
Overall	45 (4.4%)	14 (2.7%)	31 (6.0%)	0.011	23 (2.8%)	22 (10.1%)	<0.001
Among in-hospital deaths (N=204)	45 (29.4%)	14 (24.6%)	31 (32.3%)	0.31	23 (24.2%)	22 (37.9%)	0.071
Massive transfusion	254 (24.6%)	87 (17.0%)	167 (32.2%)	<0.001	155 (19.1%)	99 (45.2%)	<0.001
Acute respiratory distress syndrome	290 (28.1%)	129 (25.2%)	161 (31.0%)	0.038	213 (26.2%)	77 (35.2%)	0.009
Venous thromboembolism	87 (8.4%)	38 (7.4%)	49 (9.4%)	0.24	59 (7.3%)	28 (12.8%)	0.009
Multiple organ failure	310 (30.1%)	133 (26.0%)	177 (34.1%)	0.004	231 (28.5%)	79 (35.1%)	0.029
Hospital length of stay ^c	22 (14-33)	21 (12-32)	23 (15-34)	0.003	21 (13-32)	24 (18-38)	0.003
ICU day ^{s,b,c}	10 (5-10)	9 (4-18)	11 (6-18)	0.011	10 (5-18)	14 (7-19)	<0.001
Ventilator day ^{s,b,c}	7 (3-14)	6 (2-14)	7 (4-14)	0.003	6 (2-13)	8 (4-14)	0.001

^aContinuous variables reported as median (interquartile range). Categorical data are presented as N (%).

^bNumber of subjects with missing data for the variable: hospital days, 2; ICU days, 1; ICU ventilator days, 3.

^cRestricted to subjects who survived to hospital discharge (N=878)

Table 4
Adjusted association of admission INR with adverse trauma outcomes

Subject outcome	OR	p
All-cause mortality ^b	1.71 (1.61-1.83)	<0.001
Death due to hemorrhagic shock ^b	1.70 (1.25-2.32)	<0.001
	HR	p
Multiple organ failure ^c	1.26 (1.14-1.38)	<0.001
Venous thromboembolism ^d	1.25 (1.17-1.35)	<0.001
Acute respiratory distress syndrome ^e	1.03 (0.85-1.27)	0.78

^a Odds ratio (OR) or hazard ratio (HR) reported with 95% confidence intervals.

^b Adjusted for age, injury severity score, APACHE II score, time to ED arrival, shock, temperature and base deficit on ED arrival, and pre-hospital Glasgow Coma Scale & IV fluid volume.

^c Cox proportional hazards regression adjusted for age, sex, injury severity score, APACHE II score, time to ED arrival, shock and base deficit on ED arrival, and body mass index.

^d Cox proportional hazards regression adjusted for age, injury severity score, admission Glasgow Coma Scale, femur and pelvic fractures, and spinal cord injury.

^e Cox proportional hazards regression adjusted for age, injury severity score, APACHE II score, pre-hospital IV fluid volume, and the presence of pulmonary contusion and flail chest.

Table 5
Risk of mortality and morbidity after trauma by coagulopathy category after adjustment for confounding factors using logistic regression or Cox survival analysis

Subject outcome	INR >1.2 (N=519/1031)		INR >1.5 (N=219/1031)	
	OR	p	OR	p
All-cause mortality ^b	1.29 (0.92-1.82)	0.14	1.88 (1.36-2.60)	<0.001
Death due to hemorrhagic shock ^b	1.58 (0.83-3.02)	0.16	2.44 (1.43-4.18)	0.001
	HR	p	HR	p
Multiple organ failure ^c	1.20 (0.94-1.53)	0.14	1.23 (1.01-1.50)	0.041
Venous thromboembolism ^d	1.17 (0.73-1.87)	0.51	1.85 (1.52-2.25)	<0.001

^a Odds ratio (OR) or hazard ratio (HR) reported with 95% confidence intervals.

^b Adjusted for age, injury severity score, APACHE II score, time to ED arrival, shock, temperature and base deficit on ED arrival, and pre-hospital Glasgow Coma Scale & IV fluid volume.

^c Cox proportional hazards regression adjusted for age, sex, injury severity score, APACHE II score, time to ED arrival, shock and base deficit on ED arrival, and body mass index.

^d Cox proportional hazards regression adjusted for age, injury severity score, admission Glasgow Coma Scale, femur and pelvic fractures, and spinal cord injury.