Prehospital Prediction of Acute Coagulopathy of Trauma

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Abstract

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Abnormal clotting function afflicts up to 30% of severely-injured patients by the time they reach the emergency department and is associated with an increased risk of mortality, venous thromboembolism, and multiple organ failure. Prehospital identification of patients with acute coagulopathy of trauma (ACT), defined as an INR >1.5 on emergency department arrival, will facilitate study of the syndrome's mechanisms and targeted treatment. We developed a prehospital prediction model for ACT — the Prediction of Acute Coagulopathy of Trauma (PACT) score — using data from severely-injured trauma patients enrolled in a population-based, multicenter trauma registry. Construction of a parsimonious multivariable logistic regression model employed a best-subsets model selection approach and multiply imputed data to minimize bias. Predictors in the final model included elevated shock index, older age, prehospital cardiopulmonary resuscitation or endotracheal intubation, lower prehospital Glasgow Coma Score, and injury mechanism not related to driving or riding a motorcycle, bicycle or in a

motor vehicle. After internal validation of our model using bootstrap techniques, we externally validated the PACT score in a separate cohort of severely-injured, transfusion-requiring trauma patients admitted to the ICU of a level 1 trauma center. The PACT score demonstrated good discrimination (AUROC 0.80, 95% CI 0.72-0.88) and calibration (Hosmer-Lemeshow goodness-of-fit statistic p=0.37). At a threshold of ≥200, the PACT score's sensitivity and specificity for ACT were 73% and 72%, respectively. By comparison, a previously published prehospital ACT prediction score exhibited lower discrimination (AUROC 0.70, 95% CI 0.60-0.80, p=0.038 for comparison to PACT score) with evidence of inadequate calibration (Hosmer-Lemeshow goodness-of-fit statistic p=0.036). In summary, our prediction score uses routinely-available and objective prehospital data to identify patients at increased risk of ACT. The PACT score could facilitate subject selection for studies of ACT's targeted treatment.

INTRODUCTION

Traumatic injury caused over 110,000 U.S. deaths in 2011 and remains the leading killer of adults and children ages 1-44 years (1). Worldwide, trauma accounts for nearly 8% of deaths and 9% of disability-adjusted life years lost (2, 3). Uncontrolled hemorrhage is a major cause of trauma mortality, contributing to half of all injury-related deaths (4, 5).

Post-traumatic coagulopathy is a risk factor for hemorrhage after injury. Whereas "traditional" coagulopathy of trauma arises late after injury due to clotting factor dilution and consumption, acidosis, and hypothermia (6), acute coagulopathy of trauma (ACT) is an endogenous syndrome present on emergency department admission in up to 30% of severely-injured patients (7, 8). Defined as an international normalized ratio (INR) >1.5 on hospital admission, ACT is associated with an increased risk-adjusted probability of all-cause and hemorrhage-associated mortality after injury (9). ACT also indicates an increased risk of multiple organ failure and, paradoxically, venous thromboembolism (9).

Given the early occurrence of bleeding-related deaths, treatment to interrupt or attenuate ACT's adverse effects likely needs to begin quite rapidly after injury and potentially even in the prehospital setting. With available technology, diagnosis of ACT in this window is not possible: conventional coagulation tests are slow to return, but issues of validity, reliability, availability, and interpretation hinder use of point-of-care testing and viscoelastic measures (10-17). A simple, validated predictive index using data available by ED admission to identify patients at high risk for ACT would therefore advance research and clinical care by facilitating clinical trial enrollment, biological specimen collection and, ultimately, targeted ACT treatment.

The only out-of-hospital ACT prediction tool reported so far, the Coagulopathy of Severe Trauma (COAST) score, is based on vehicle entrapment, chest decompression by paramedics,

and prehospital assessment of blood pressure, temperature, and abdominal/pelvic content injury (18). Since the score was not externally validated after development in a single-center Australian cohort, its generalizability is uncertain (19). In particular, marked differences in U.S. ambulance crews' practice regarding chest decompression, injury pattern evaluation, and temperature measurement may pose obstacles to the COAST score's application in U.S. trauma settings.

In the current study, we developed and internally validated a prediction model for ACT using patient demographic information, injury characteristics, and clinical data available to providers before severely-injured patients' arrival in the emergency department. Using a separate cohort of severely-injured trauma patients, we then validated our score and compared its performance to that of the COAST score.

METHODS

Derivation cohort

To derive a multivariable model predicting ACT, we studied severely-injured non-pregnant patients age 18-89 years enrolled in the Oregon Trauma Registry from 2008-2012 (20). Oregon's 49 certified trauma facilities submit data to the registry, maintained by the Oregon Health Authority, on injured patients meeting ≥1 of the following criteria: intensive care unit (ICU) admission ≤24 hours from emergency department (ED) arrival; trauma team activation; surgical evaluation and treatment; prehospital trauma triage criteria met; and injury severity score (ISS) >8 (21). Patients dying before ED arrival, with isolated hip fracture after a ground-level fall, or not treated at a certified trauma center are excluded from the registry. We counted as severely injured patients dying prior to discharge or admitted directly from the ED to the ICU or surgery. We also included patients transferred from the initial ED to another trauma center's ED if they had an ISS >15 and were admitted from the receiving facility's ED directly to the ICU or to surgery. Exclusion criteria included missing admission INR; initial care outside the trauma system; pre-admission anticoagulant medication; blood transfusion during prehospital care; and no prehospital care. We also excluded patients with isolated burn or traumatic brain injury (no abbreviated injury score [AIS] ≥3 except for head) since coagulopathy in these conditions appears distinct from polytrauma-associated ACT (22, 23).

Oregon trauma facilities employ one trauma registrar per 750 annual trauma cases and provide them annual training. Hospitals actively solicit missing data from in-transferring facilities and prehospital providers. Unique trauma registry identifiers allow patient data linkage across phases of care. Biannual site visits by the state accrediting organization include review of

trauma registry data and procedures. The University of Washington and Oregon Health Authority Institutional Review Boards approved use of Oregon Trauma Registry data.

Validation cohort

For model validation, we performed a secondary analysis of data from a prospective cohort study (Age of Transfused Blood and Lung Injury After Trauma Study) conducted at Harborview Medical Center, a level 1 trauma center in Seattle, WA (24, 25). Blunt trauma patients age ≥18 presenting to the ED from March 2010 to December 2013 were eligible for enrollment if admitted to the ICU from the ED (directly or via surgery) and transfused ≥1 units of red blood cells within 24 hours of injury. Study exclusion criteria included isolated traumatic brain injury (radiologic evidence of brain injury and no non-brain injury), transfusion within 6 months prior to admission, acute respiratory distress syndrome on admission, patient in police custody, pregnancy, and expected survival <24 hours. Subjects on warfarin, with no prehospital medical care, or missing initial INR values were excluded from the model validation cohort.

Study subjects were followed from initial ED admission to death or hospital discharge. Trained research staff unaware of coagulopathy status collected data on patient characteristics, prehospital care, referring hospital care, clinical procedures, complications, and outcomes. Independent re-abstraction of 11% of records demonstrated excellent inter-rater reliability with κ 0.90 (95% CI 0.77-1.00) for ≥1 high-risk injury indicators and κ 0.93 (95% CI 0.80-1.00) for the performance of ≥1 prehospital procedures. An experienced database manager confirmed the validity of manually abstracted variables and reconciled results with linked, separately abstracted data in the hospital's trauma registry. The University of Washington Institutional Review Board approved the original study and granted exempt status to the current secondary analysis.

Predictor and outcome definitions

ACT was defined as an INR >1.5 on initial measurement in the first ED (9). Potential ACT predictors were identified *a priori* and included patient and injury characteristics as well as clinical and management data available prior to hospital arrival. Vital signs are the first-recorded values from the prehospital setting and initial ED. Consistent with previous reports (26, 27), we observed ≤1 point difference between Glasgow Coma Scores (GCS) measured in the prehospital setting and ED for, respectively, 84% and 89% of derivation and validation cohort subjects not intubated before ED arrival. We therefore substituted the GCS measured in the ED for missing prehospital values if the subject was not intubated prehospital. Given its inverse association with ACT risk, GCS was analyzed as the difference between the measured GCS and a normal GCS of 15 to provide a positive coefficient in the prediction model. Shock index, calculated as the first prehospital heart rate divided by the first prehospital systolic blood pressure, was considered elevated if ≥1 (28, 29). Out-of-hospital treatments obtained from documentation by prehospital and ED providers included cardiopulmonary resuscitation, chest decompression ("flutter" valve or needle or tube thoracostomy), and endotracheal intubation or other invasive airway (i.e. laryngeal mask airway). Injury severity indicators, also based on provider documentation, included death of another person on scene, ejection or need for extrication from vehicle ("entrapment"), and rollover motor vehicle accident (30). ISS and AIS values were used as markers of global and regional injury severity (31).

COAST scores (Table 1) were calculated as previously described (18). Since prehospital providers in the United States do not systematically document abdominal/pelvic content injury (32), we applied a definition — abdominal/pelvic AIS ≥1 — used for a sensitivity analysis in the COAST score's original description (18, 33). Similarly, since U.S. prehospital providers do

not systematically record temperature for trauma patients (32), we employed the first ED temperature in place of the prehospital value (34).

Table 1: Coagulopathy of Severe Trauma (COAST) score[a]

Variable	Value	Score
Entrapment	Yes	1
Systolic blood pressure	<100 mmHg	1
	<90 mmHg	2
Temperature	<35˚C	1
	<32˚C	2
Chest decompression	Yes	1
Abdominal or pelvic content injury	Yes	1
Highest total possible		7

[a] Reprinted from Mitra *et al*. (*Resuscitation* , 2011; 82: 1208-1213) with permission from Elsevier Ltd.

Missing data

To minimize bias due to missing data in the derivation and validation cohorts, we performed multiple imputation based on chained equations to create 50 imputed data sets (35-38). Missing values were imputed using predictive mean matching from three nearest neighbors for continuous variables (39) and logistic regression for binary variables. Imputation model variables (Table 2) included missing and non-missing candidate predictors, hospital and coagulopathy outcomes, and other patient characteristics correlated with missing variables (40).

Model development

A multivariable ACT prediction model was constructed from the prehospital variables — identified *a priori* and defined as above — in three steps: candidate predictor modeling, selection of a parsimonious final predictor set, and coefficient estimation. To minimize predictive optimism and bias in the final predictive model, we sought a final ratio of at least ten outcome events to one candidate predictor entered in the model selection algorithm (38, 41-43). To achieve this ratio, we (1) discarded variables with p value >0.25 in bivariable analyses or missingness >25%; (2) "forced" a variable based on the first prehospital systolic blood pressure into the final prediction model given its strong epidemiologic association with ACT and

Table 2: Missing and non-missing variables employed in imputation equations

	Derivation cohort (N=1829)			Validation cohort (N=285)		
		Imputation model			Imputation model	
	Missing N (%)	Imputed	Non-missing covariate	Missing N (%)	Imputed	Non-missing covariate
Age	0		X	0		X
Sex	2 (0.1)	X		0		X
Race	37 (3.3)	X		0		X
Hispanic ethnicity	37 (3.3)	X		8 (1.8)	X	
Transfer status	0		X	0		X
Time from injury to ED arrival	315 (17.2)	X		0		X
Year	0		X	0		X
Mechanism of injury	0		X	0		X
Pre-hospital vital signs						
First systolic blood pressure	295 (16.1)	X		31 (10.9)	X	
First heart rate	195 (10.7)	X		35 (12.3)	X	
First respiratory rate	403 (22.0)	X		62 (21.8)	X	
First Glasgow Coma Score	355 (19.4)	X		68 (23.9)	X	
Lowest systolic blood pressure[a]	—	—	—	31 (10.9)	X	
Pre-hospital interventions						
Cardiopulmonary resuscitation	0		X	0		X
Chest decompression	0		X	0		X
Intubation	0		X	0		X
IV fluid[a]	—	—	—	43 (15.1)	X	
First measured ED vital signs						
Systolic blood pressure	12 (0.7)	X		4 (1.4)	X	
Heart rate	10 (0.5)	X		0		X
Temperature	283 (15.5)	X		25 (8.8)	X	
Injury severity score	48 (2.6)	X		15 (5.3)	X	
Maximum abdominal AIS	48 (2.6)	X		15 (5.3)	X	
Admission INR	0		X	0		X
Acute coagulopathy of trauma	0		X	0		X
Death before discharge	0		X	0		X
Hospital length of stay	2 (0.1)	X		0		X

[a] Variable unavailable for development cohort.

Abbreviations: AIS, abbreviated injury score; ED, emergency department; INR, international normalized ratio

evidence for a causal mechanism underlying this association (44); (3) dropped predictors (such as paramedic assessment of injury anatomy) at risk for significant subjectivity (45); (4) merged candidate predictors (prehospital systolic blood pressure and heart rate combined into shock index) when feasible (29, 38, 46); and (5) collapsed categories of candidate predictors (injury mechanism, shock index) when feasible and supported by bivariable analysis (19). Graphical

analysis based on locally weighted scatterplot smoothing (LOWESS) plots did not reveal significant non-linearity in the associations between candidate predictors and admission INR. Continuous candidate predictors were therefore evaluated without transformation.

We adapted the "majority rules" approach to model selection previously described by Vergouwe *et al* (47). Within each imputed dataset, we evaluated all possible combinations of predictor variables using a best-subsets approach and a leaps-and-bounds algorithm adapted for logistic regression (48-50). The selected model had the lowest Akaike information criterion, a likelihood-based measure of model fit that penalizes larger models to reduce overfitting (51). The final prediction model included predictors selected in 50% or more of the imputation-derived models (Figure 1). Coefficients for the final prediction model were obtained by combining estimated regression coefficients from the 50 imputed datasets using Rubin's rules (52). The raw prediction model was simplified by rounding each coefficient to one decimal place and multiplying by 100 to create the Prediction of Acute Coagulopathy of Trauma (PACT) score.

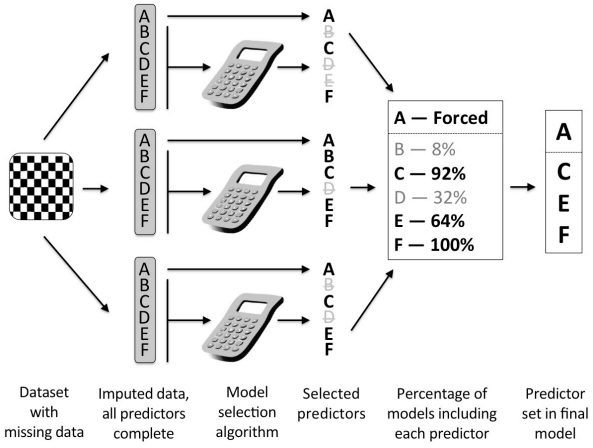

Figure 1. Schematic of "majority rules" model selection algorithm.

Evaluation of model performance

We estimated model optimism in the multiply-imputed derivation cohort using bootstrap techniques (53, 54). After sampling with replacement for 1,000 iterations, we performed the previously-described model selection procedure on each bootstrap sample and compared model discrimination in the bootstrapped versus original derivation cohort. The average difference for

the 1,000 bootstrap samples is an estimate of the deterioration in model discrimination attributable to sampling bias. To formally test generalizability, we evaluated the discrimination and calibration of the PACT and COAST scores when applied to the validation cohort.

Statistical analysis

To maximize study power and model generalizability, we included all eligible subjects in both cohorts. Bivariable analyses employed unpaired t-tests with unequal variance or Mann-Whitney tests for continuous variables and chi-square or Fisher's exact tests for categorical variables as appropriate. Regression coefficients are reported with robust standard errors. Model discrimination was measured using the area under the receiver operating characteristic curve (AUROC), which is reported with 95% confidence intervals and compared using the method of Delong *et al* (55). Model calibration was evaluated (1) graphically by plotting the observed versus predicted ACT probabilities across equal quantiles of predicted ACT probability and (2) using the Hosmer-Lemeshow goodness-of-fit statistic (56). A p value >0.1 for this statistic indicates no significant divergence of observed from predicted probabilities (57). Since the 7-point COAST score cannot be divided into >7 quantiles, the primary PACT score calibration analysis also used 7 quantiles of predicted risk. For other tests, a p value ≤0.05 was considered significant. We used Stata version 13.1 (StataCorp LP, College Station, TX) for all analyses and adhere to published guidelines for reporting multivariable prediction models (58).

We performed two sensitivity analyses. We tested whether an alternate ACT definition adding partial thromboplastin time (PTT) >60 seconds to INR >1.5 altered our results. We also reevaluated our model's calibration using deciles of ACT risk predicted by the PACT score.

RESULTS

A total of 1,829 patients enrolled in the Oregon Trauma Registry between 2008 and 2012 met criteria for inclusion in the model derivation cohort (Figure 2). ACT was present in 108 (5.9%). Coagulopathic patients were more severely injured, less likely to be injured while operating or riding in a motor vehicle, motorcycle or bicycle, more likely to undergo prehospital interventions and had lower prehospital systolic blood pressure and GCS (Table 3). Compared to the derivation cohort, the 285 subjects meeting criteria for inclusion in the validation cohort (Figure 3) were more severely injured, displayed greater physiologic derangements, and were more likely to be intubated prehospital (Table 4). In-hospital mortality was 49% for subjects with ACT compared to 7% for subjects without ACT ($p<0.001$) in the derivation cohort and 24% vs 7% ($p=0.001$) in the validation cohort.

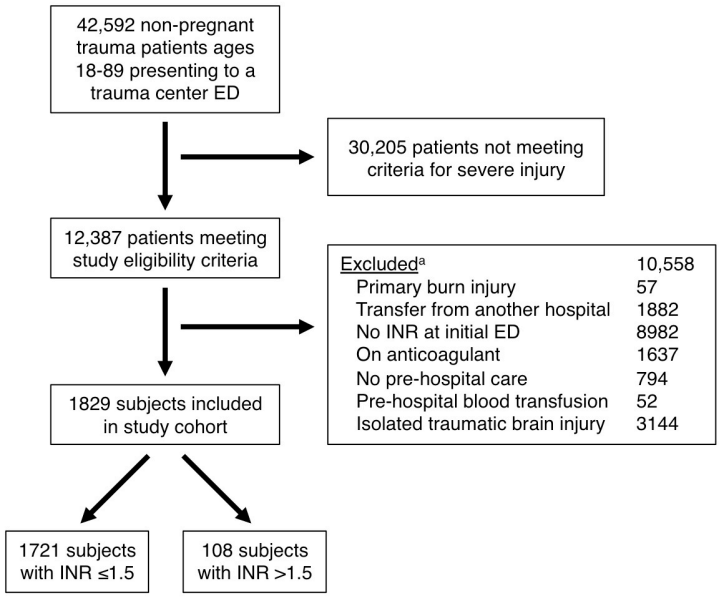

Figure 2. Patient enrollment flow diagram for derivation cohort. Some patients had >1 reason for exclusion.

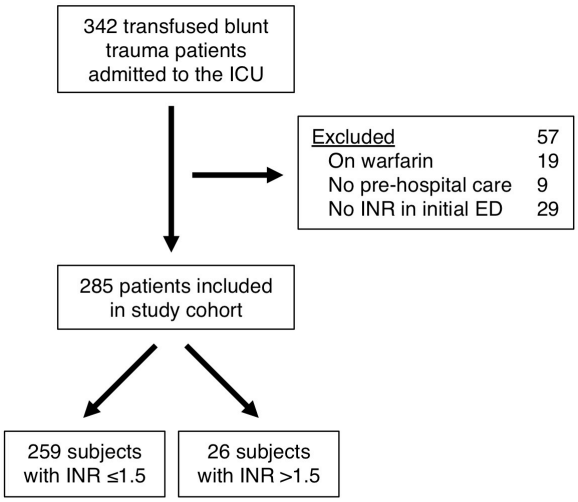

Figure 3. Patient enrollment flow diagram for validation cohort.

Table 3: Demographic, injury and clinical characteristics of subjects included in the derivation cohort by coagulopathy status

	INR ≤1.5 (N=1721)	INR >1.5 (N=108)	p
Age	44.5 (18.4)	47.5 (21.0)	0.14
Male sex	1248 (72.6)	79 (73.1)	0.93
Race			0.20
Black	56 (3.3)	4 (3.8)	
White	1381 (81.9)	80 (75.4)	
Other	249 (14.8)	22 (20.8)	
Hispanic	174 (10.3)	13 (12.3)	0.52
Minutes from injury to ED arrival	51 (39-69)	49 (34-67)	0.21
Mechanism of injury			0.003
Motor vehicle accident	577 (33.5)	29 (26.9)	
Motorcycle accident	170 (9.9)	5 (4.6)	
Bicycle accident	77 (4.5)	1 (0.9)	
Pedestrian struck	102 (5.9)	14 (13.0)	
Fall	571 (33.2)	47 (43.5)	
Other	224 (13.0)	12 (11.1)	
Injury severity indicators			
Ejection from vehicle	65 (3.8)	4 (3.7)	0.97
Extrication	113 (6.6)	8 (7.4)	0.73
Rollover motor vehicle accident	136 (7.9)	8 (7.4)	0.85
First measured pre-hospital vital signs			
Systolic blood pressure	132 (27)	119 (28)	<0.001
Heart rate	94 (22)	95 (31)	0.79
Respiratory rate	20 (5.3)	21 6.9)	0.28
GCS	15 (13-15)	14 (9-15)	<0.001
Pre-hospital interventions			
Cardiopulmonary resuscitation	25 (1.5)	15 (13.9)	<0.001
Chest decompression	24 (1.4)	5 (3.6)	0.025
Intubation	263 (15.3)	42 (38.9)	<0.001
Initial ED temperature (C)	36.4 (0.98)	35.6 (2.04)	0.002
Injury severity score	17.4 (11.8)	26.0 (13.7)	<0.001
Death before discharge	122 (7.1)	53 (49.1)	<0.001
Hospital length of stay (days)	6 (2-12)	6 (1-19)	0.36

Values reported as median (SD), N (%) or median (IQR).

Abbreviations: ACT, acute coagulopathy of trauma; ED, emergency department; GCS, Glasgow Coma Score; INR, international normalized ratio.

In addition to the binary variable for shock index ≥1 that was forced into the prediction model, seven candidate predictors were entered into the model selection algorithm based on bivariable associations with ACT: age; time from injury to ED arrival; GCS; a binary variable indicating the subject's injury mechanism did not involve driving or riding in a motor vehicle, motorcycle or bicycle; prehospital cardiopulmonary resuscitation; prehospital endotracheal intubation or other advanced airway placement; and prehospital chest decompression by needle or tube thoracostomy. Variables selected algorithmically in >50% of imputed datasets and therefore included in the final ACT prediction model were age, prehospital CPR and intubation, GCS, and injury mechanism not motor vehicle, motorcycle or bicycle accident in addition to the required prehospital shock index variable (Table 5). Within the

derivation cohort, the model's AUROC was 0.75 (95% CI 0.69-0.80). After conversion to a score, the AUROC was essentially unchanged (0.74, 95% CI 0.69-0.79). The Hosmer-Lemeshow goodness-of-fit test demonstrated no evidence for inadequate model fit (p=0.92). Internal validation using bootstrap methods estimated the optimism contained in the PACT score's AUROC as 0.03 (95% CI -0.04–0.09), resulting in an optimism-adjusted AUROC for our ACT prediction score of 0.72 (95% CI 0.66-0.78). An interactive PACT score calculator is available online at www.pactscore.com.

Table 4: Demographic, injury, and resuscitation characteristics of derivation and validation cohorts

	Derivation cohort (N=1829)	Validation cohort (N=285)
Age	44.6 (21.0)	48.2 (19.0)
Male sex	1327 (72.6)	204 (71.6)
Non-white race	331 (18.5)	40 (14.0)
Hispanic	187 (10.4)	18 (6.4)
Minutes from injury to ED arrival	51 (39-69)	56 (40-86)
Blunt injury	1612 (88.1)	285 (100)
Mechanism of injury		
Motor vehicle accident	606 (33.1)	104 (36.5)
Motorcycle accident	175 (9.6)	50 (17.6)
Bicycle accident	78 (4.3)	10 (3.5)
Pedestrian struck	116 (6.3)	51 (17.9)
Fall	618 (33.8)	44 (15.4)
Other	236 (12.9)	26 (9.1)
First recorded pre-hospital vital signs		
Systolic blood pressure	131 (28)	116 (37)
Heart rate	94 (23)	99 (26)
Respiratory rate	20 (5.4)	19 (7.6)
First recorded non-intubated GCS	15 (13-15)	14 (8-15)
Pre-hospital interventions		
Cardiopulmonary resuscitation	40 (2.2)	9 (3.2)
Chest decompression	29 (1.6)	8 (2.8)
Intubation	305 (16.7)	145 (50.9)
Initial ED temperature	36.3 (1.07)	35.9 (1.23)
Injury severity score	17.9 (12.1)	32.3 (15.1)
Admission INR	1.19 (0.77)	1.25 (0.26)
Acute coagulopathy of trauma	108 (5.9)	26 (9.1)
Death before discharge	175 (9.6)	37 (13.0)

Values reported as median (SD), N (%) or median (IQR).
Abbreviations: ACT, acute coagulopathy of trauma; ED, emergency department; GCS, Glasgow Coma Score; INR, international normalized ratio.

Application of the final PACT score to the more severely injured independent validation cohort demonstrated good discrimination, with an AUROC of 0.80 (95% CI 0.72-0.88). Performance was superior to the COAST score (Figure 4), which demonstrated an AUROC of 0.70 (95% CI 0.60-0.80, p=0.038 for comparison). A sensitivity analysis including a PTT >60 seconds in the definition of ACT yielded similar results (AUROC 0.79 vs 0.71, p=0.048). In

Table 5: Results of majority rules model selection, coefficients of prediction model for acute coagulopathy of trauma and points assigned for Prediction of Acute Coagulopathy of Trauma (PACT) score

Variable	Models containing candidate predictor	In final prediction model?	Regression coefficient	SE	Value	Points per unit
First prehospital shock index ≥1	Forced into model	Yes	0.925	0.261	Yes	90
Age	100%	Yes	0.0119	0.005	Age, rounded to nearest decade	1
Mechanism of injury *not* motor vehicle, motorcycle, or bicycle accident	100%	Yes	0.559	0.225	Yes	60
Number of GCS points below 15	98%	Yes	0.0735	0.034	15 – GCS	7
Prehospital CPR	100%	Yes	1.069	0.468	Yes	110
Prehospital intubation or advanced airway	64%	Yes	0.487	0.333	Yes	50
Prehospital chest decompression	2%	No	—	—	—	—
Time from injury to emergency department	6%	No	—	—	—	—
Constant	N/A	Yes	-4.288	0.341	—	—

Abbreviations: CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Score; N/A, not applicable

contrast to the COAST score ($\chi_{df=5}$=11.25, p=0.036), the Hosmer-Lemeshow goodness-of-fit statistic for the PACT score demonstrated no statistical evidence of inadequate calibration ($\chi_{df=5}$=5.51, p=0.37). Graphical evaluation of each score suggested good calibration of the PACT score but an inconsistent association between observed and predicted ACT risk at higher COAST score

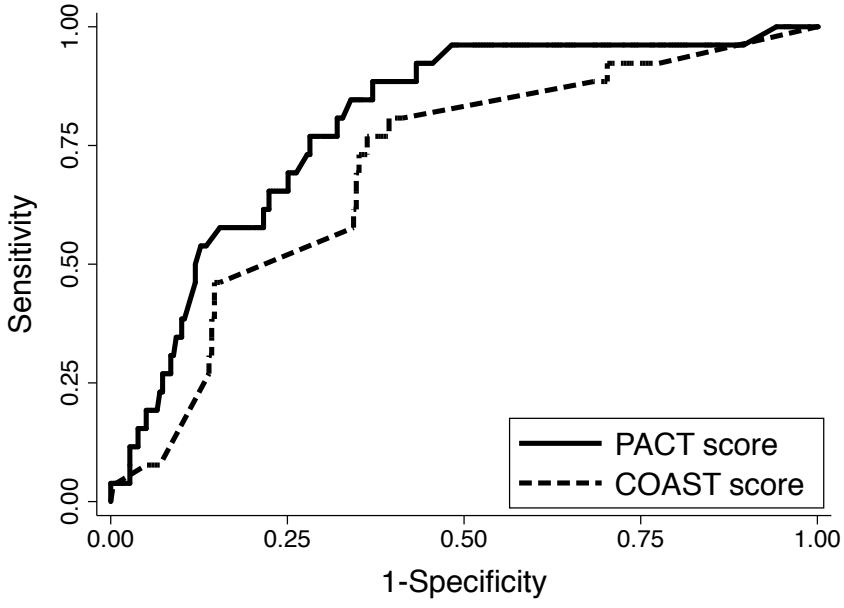

Figure 4. Comparison of the ability of the PACT (AUROC 0.79 [0.70-0.87]) and COAST scores (AUROC 0.68 [0.58-0.79]) to discriminate acute coagulopathy of trauma in the ATLAS cohort (p=0.041).

values (Figure 5). A sensitivity analysis dividing the PACT score into deciles rather than 7 quantiles of predicted risk did not alter these conclusions ($\chi_{df=8}$=7.93, p=0.44).

Setting the PACT score cutoff at ≥200 maximized sensitivity and specificity at 73.1% and 72.3%, respectively (Table 6). Applying this threshold to the validation cohort, 187 of 194 patients (96.4%) with a PACT score <200 were correctly identified as not having coagulopathy. Among those with a positive PACT score, 19 of 89 (20.9%) had coagulopathy. At the COAST score's recommended threshold of ≥3, sensitivity was 26.9% and specificity was 86.1% with 36 of 43 positive results (84.7%) being false positives (Table 7).

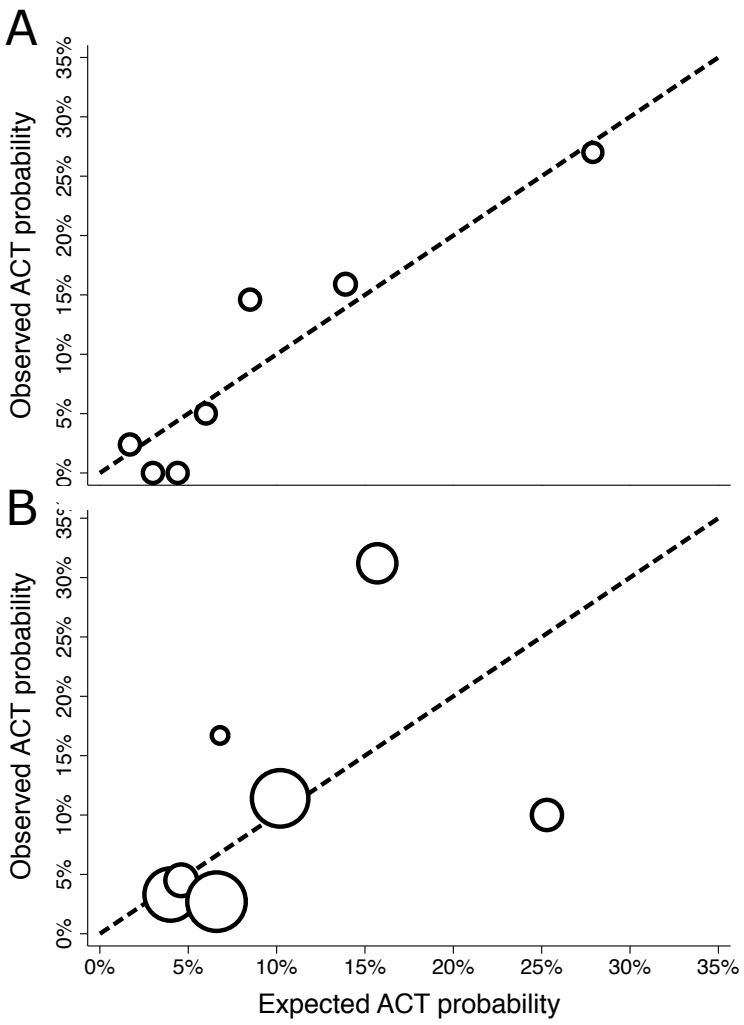

Figure 5. Calibration in the validation cohort for observed ACT risk versus probability of ACT predicted by the (A) PACT and (B) COAST scores. Circle sizes, proportional to the number of subjects represented, indicate 1/7th quantiles of predicted risk (PACT) or actual score (COAST) value.

Table 6: Operating characteristics for selected thresholds of the Prediction of Acute Coagulopathy of Trauma (PACT) score

	≥50	≥100	≥150	≥200	≥250	≥300
Patients						
True positive	25	25	25	19	12	4
False positive	232	198	127	72	31	10
True negative	27	61	132	187	228	249
False negative	1	1	1	7	14	22
Operating characteristics						
Sensitivity (%)	96.2	96.2	96.2	73.1	46.2	15.4
Specificity (%)	10.4	23.6	51.0	72.3	88.0	96.1
Positive likelihood ratio	1.07	1.26	1.96	2.63	3.86	3.98
Negative likelihood ratio	0.37	0.16	0.08	0.37	0.61	0.88

Table 7: Operating characteristics of the Coagulopathy of Severe Trauma (COAST) score

	≥1	≥2	≥3	≥4	≥5
Patients					
True positive	23	15	7	1	0
False positive	177	89	36	2	0
True negative	82	170	223	257	259
False negative	3	11	19	25	26
Operating characteristics					
Sensitivity (%)	88.5	57.7	26.9	3.9	0
Specificity (%)	31.7	65.6	86.1	99.3	100
Positive likelihood ratio	1.29	1.68	1.94	4.98	—
Negative likelihood ratio	0.36	0.64	0.85	0.97	1

DISCUSSION

We developed and externally validated a model for predicting ACT prior to ED arrival in victims of severe trauma. The PACT score incorporates a small number of objective and easily measured data elements routinely available to prehospital providers. Our ACT prediction score exhibited good discrimination and calibration when its performance was tested in an independent trauma cohort and performed better in both domains than the only previously published ACT prediction model.

The benefits of out-of-hospital identification, expedited triage, and receiving hospital notification are well recognized in trauma and other conditions — including stroke and myocardial infarction — for which time to treatment affects outcomes (30, 59-61). Given the time course of exsanguination-related mortality, the best time to intervene in ACT appears likely to be within minutes of injury (13). We created the PACT score in answer to calls for improved identification of patients at high ACT risk within this window of opportunity (62, 63).

Stratification of trauma patients according to ACT risk using the PACT score could aid study of the condition's mechanisms and facilitate interventional trials of its treatment. Enrolling patients at high ACT risk would foster efficient resource use, reduce heterogeneity, and enrich cohorts with the subjects most likely to benefit from a particular treatment, thereby increasing study power. For instance, an important recent study testing 1:1:1 versus 2:1:1 transfusion strategies for red blood cells, plasma and platelets failed to show a benefit for its primary end point, all-cause mortality, after enrolling patients based on their risk of massive transfusion (64). One wonders if targeting patients at high risk of coagulopathy rather than massive transfusion — overlapping but not synonymous categories — might have yielded a positive result.

The PACT score demonstrated good ability to discriminate patients with ACT. Discrimination, measured by the AUC, was in fact better in the validation cohort compared to the derivation cohort, suggesting the PACT score has better predictive accuracy for sicker trauma patients. This score cannot, however, diagnose ACT with perfect accuracy. The appropriate PACT score cutoff will, moreover, depend on the specific application. One ACT authority has suggested that a useful ACT prediction model should have at least 90% sensitivity with specificity out-performing physician intuition (62). For our model, a score ≥161 is associated with 92% sensitivity and 57% specificity. Alternatively, for a theoretical study recruiting patients with high ACT risk from the validation cohort, a PACT score ≥250 would enroll 43 patients of whom 28% would have ACT. Lowering the threshold to ≥200 would enroll 91 subjects, 21% with ACT. Both thresholds compare favorably with the COAST score at its recommended threshold, which would enroll 27 subjects with a 19% probability of ACT.

Patients with ACT experienced substantially increased mortality in both study cohorts. This is consistent with previous studies showing ACT to be an independent risk factor for all-cause and hemorrhage-associated mortality (8, 9, 65). As a whole, variables in our model indicate greater injury relative to physiologic reserve, in line with prior research correlating ACT prevalence with injury severity and hypoperfusion (7, 66). However, this study was not designed to evaluate for independent relationships between ACT and "risk factors" and our results should not be interpreted as evidence of causal associations between the studied predictors and ACT.

The strengths of our study include use of a truly independent cohort for external model validation, maintenance of an adequate ratio of events per variable during model selection, and use of a model selection algorithm balancing variables' predictive utility against the risk of overfitting. In contrast to complete case analysis, which would have limited our effective sample

size and introduced bias into model development and evaluation (38, 67, 68), our approach to missing data, multiple imputation, avoided excluding patients with missing predictor values and has been widely recommended in recent literature on predictive models (38, 58, 67, 68). Nevertheless, we cannot exclude the possibility of residual bias. Excluding patients with missing data for the study outcome, admission INR, could also have introduced bias.

The COAST score's calculation required several approximations to accommodate differences between the Australian derivation dataset and our datasets. We estimated prehospital temperature using ED measurements, an extrapolation previously shown to be valid (34). Instead of using prehospital providers' subjective determination of abdominal or pelvic injury, a variable that was also not available for our cohorts, we used the abdominal AIS score as was done for a sensitivity analysis in the score's original description (18, 33). These modifications may nevertheless have unfairly penalized the COAST score in comparisons with the PACT score. A sensitivity analysis substituting the ACT definition employed by Mitra *et al.* — INR >1.5 or PTT >60 seconds — did not alter the results for our comparison of the COAST and PACT scores.

Our study has several additional limitations. We defined ACT as an INR >1.5 on hospital admission, a validated definition (9) which may nevertheless not capture all mechanisms — including hyperfibrinolysis — relevant to the syndrome's impact on trauma outcomes. As noted previously, however, our results were unchanged after adding a measure of intrinsic coagulation pathway function to our extrinsic pathway-focused definition. Moreover, this increasingly common ACT definition does identify a subset of severe trauma patients who, controlling for other factors, suffer increased risk of all-cause and hemorrhage-associated mortality (9). In parallel with past studies (18), we focused on severely-injured subjects. However, severe injury may not be easily recognizable to prehospital providers or on ED admission, and may result in

application of the PACT score to patients on whom it has not been tested. The model derivation cohort was much less severely injured and, as a result, had less physiologic derangement and lower mortality than the validation cohort. This would be expected more rigorously test generalizability compared to evaluation in a similarly injured cohort. The fact that the PACT score actually performed better in the validation cohort suggests that our model is most accurate in very severe injuries. Finally, the incidence of ACT in the validation cohort was lower than expected, resulting in a lower than optimal effective sample size for model validation (69).

CONCLUSIONS

We report derivation and external validation of a prediction model that employs objective data elements routinely collected by pre-hospital providers to identify patients at increased risk of ACT. The PACT score exhibited improved discrimination and calibration relative to a previously reported ACT prediction model. Application of the PACT score during study recruitment could aid research into ACT treatment by enriching enrolled cohorts with the patients most likely to benefit from treatments targeting coagulopathy.

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