Title page:

Early identification of Trauma-Induced Coagulopathy: development and validation of a multivariable risk prediction model.

Running head:

Early Prediction of Trauma-Induced Coagulopathy

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Introduction

Trauma is a global public health problem and a leading source of the world's burden of disease. [1-3] A critical complication following trauma haemorrhage is the early development of deranged coagulation.[4] Patients that develop trauma-induced coagulopathy (TIC) have worse outcomes, with significantly higher rates of organ dysfunction, sepsis and mortality. [4-6] Furthermore, this patient group place considerable demand on hospital resources with greater blood transfusion and ventilator requirements, and longer critical care and hospital length of stay. [7, 8]

Early and aggressive resuscitation strategies that directly target TIC are associated with improved outcomes. [9-14] These "damage control" strategies include early empiric transfusion of whole blood or balanced ratios of blood products (1:1:1 for units of plasma to platelets to red blood cells) [14, 15], permissive hypotension [16], rapid haemorrhage control with abbreviated surgical procedures[10], and early administration of plasma [17], cryoprecipitate [18] and tranexamic acid [9]. While these interventions improve survival in patients at risk of TIC, they may cause significant harm and waste precious resources if used in the majority of injured patients with normal coagulation. [19-21] Early identification of TIC is, therefore, key to effective initiation of damage control interventions.[22] [23] However, rapid identification of at-risk patients can be challenging. Conventional coagulation tests have limited accuracy in trauma, and results are not available in a clinically useful timeframe to guide therapy. [24, 25] Existing prediction models are also not accurate enough to reliably inform treatment decisions.[26] Viscoelastic haemostatic assays are better able to diagnose TIC and can provide results within a few minutes of blood draw [24, 27], but these complex devices are expensive, problematic for use in an emergency setting, and are unlikely to be routinely available worldwide. Current practice, therefore, relies on clinical judgement, which although rapid, is prone to error in the emergency setting [28, 29]; or blind, unguided protocols, which preclude the tailoring of decisions to individual patient needs.

Advances in machine learning, together with the availability of high-quality patient datasets, provide the opportunity to develop robust risk prediction algorithms that could be used to support early and tailored therapeutic decisions.[30, 31] Accordingly, this study aimed to develop and validate a prediction

model that can provide clinicians with an early and accurate estimate of an injured patient's risk of developing clinically relevant TIC.

Methods

Study design

We developed a multivariable risk prediction model using a supervised machine learning method that combined domain knowledge and data from patients enrolled in the Activation of Coagulation & Inflammation in Trauma (ACIT) study. The development cohort comprised data from consecutive patients enrolled in the ACIT study between January 2007 and October 2011 at the Royal London Hospital. Performance was validated in new patients enrolled into the ACIT study following completion of model development (November 2011 to January 2014) at the Royal London Hospital (Temporal validation cohort) and two independent centres (External validation cohort): John Radcliffe Hospital, Oxford, UK, and the Cologne-Merheim Medical Centre, Cologne, Germany. The study is reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[32]

Sources of information

Domain knowledge

Domain knowledge on the causal mechanisms of TIC was identified by an electronic search of the MEDLINE and Embase databases using a combination of the terms “trauma” and “coagulopathy”. Relevant original studies, review articles, and clinical guidelines were considered. The reference lists of relevant articles were reviewed to identify additional publications. A structured framework is used to organise and present the evidence and knowledge that underpins each part of the model. [33]

Cohort study

ACIT is a multi-national, prospective cohort study designed to identify the mechanisms by which the body’s coagulation pathways are activated immediately following injury.[34] Adult patients (>15 years) presenting directly to participating Major Trauma Centres, who meet local criteria for trauma team activation, are included. Exclusion criteria include: arrival in the emergency department > 2 hours after injury; prehospital administration of > 2000ml intravenous fluid; and burns covering > 5% of body surface area. Patients are retrospectively excluded if they decline consent, take anticoagulation

medication, have moderate or severe liver disease, or a bleeding diathesis. The study was reviewed and approved by the National Research Ethics Committee of participating countries and written informed consent was obtained for all participants.

Data collection

Data were collected prospectively on patient demographics, injury characteristics, admission vital signs, treatment administered, and outcome. Blood samples were collected immediately on hospital arrival and used for standard laboratory coagulation tests, rotational thromboelastometry (ROTEM, TEM Innovations, Munich Germany), and blood gas analysis. Injuries were classified according to the 2005 Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) by certified coders.[35] All patients were followed-up daily until hospital discharge or death.

Prediction outcome

The model was designed to predict the risk of developing clinically relevant TIC. As standard coagulation tests have limitations in diagnosing TIC [24, 26], a systematic approach was used to classify each patient's coagulation status into normal or TIC. First, all patients were classified according to the clinically accepted laboratory definition of TIC, an admission Prothrombin Time ratio (PTr) > 1.2. [36] Second, all patients were independently clustered into normal or abnormal coagulation, based on the their clinical, laboratory, and thromboelastometry profile, using an expectation-maximisation (EM) algorithm.[37] Third, cases where laboratory and machine-learning methods agreed were assigned the corresponding coagulation state as their final classification. Finally, cases where the two methods disagreed, or the PTr sample had haemolysed, underwent expert review to determine a final classification. Two TIC experts independently reviewed the clinical, laboratory, and thromboelastometry data of each discrepant case. Disagreement was resolved by consensus with a third expert. Experts were blind to the EM algorithm result and structure of the predictive model. Inter-reviewer agreement was evaluated with the kappa-statistic and expert consistency was evaluated in a random sample of 50 patients with known coagulation status.

Clinical relevance of outcome

The clinical relevance of TIC was assessed in terms of mortality, transfusion requirements, Damage Control Surgery (DCS) requirements, and duration of ICU and hospital admission. Massive transfusion was defined as ≥ 10 units of blood transfused in 24 hours.[38] DCS was defined as immediate resuscitative surgery aimed at controlling active haemorrhage and restoring normal physiology. DCS procedures included resuscitative thoracotomy, emergency laparotomy, extra-peritoneal pelvic packing, temporary vascular shunts, and primary (life-saving) amputations; but excluded emergency craniotomy, exploratory laparotomy in patients' with normal physiology, wound debridement, and definitive fracture fixation.

Model development

The algorithm is a Bayesian Network (BN). BNs consist of two parts: a network structure that graphically describes the models' variables and their relations, and a set of parameters that captures the strength of the relationships between variables.[39] The network structure was learned from domain knowledge and the parameters were learned from ACIT data. Our method follows an iterative, step-wise, supervised machine-learning approach that has previously been described [37], and is summarised below:

Step 1) Causal structure

The BN structure was learned from domain knowledge. This enabled an evidence-based structure consistent with current understanding of the causal mechanisms of TIC to be developed. Domain knowledge informed the choice of variables, relationships between variables, and states that each variable can take. Where required, latent (unobserved) variables were introduced to model important intermediate mechanistic steps.[37] Logical and physiological constraints, defined by clinical knowledge, were applied to variables.

Step 2) Predictors

Potential predictors were identified from domain knowledge and limited to information that is available at the time the model is intended for use – during the initial patient assessment (primary survey). Continuous predictors were not catagorised and data-driven methods of selecting predictors were not used. Predictors were measured on admission by ACIT investigators prior to knowledge of the participant's outcome.

Step3) Parameter learning

In a BN, the strength of the relationship between variables is defined by a conditional probability distribution (CPD). The CPD of each of the relations determined in *Step 1* were learned from the ACIT development dataset using an Expectation-Maximisation (EM) algorithm.[40 37]

Step 4) Internal validation and model refinement

Prognostic performance was estimated by ten-fold cross validation in the development dataset.[41] Cases with inaccurate predictions were identified and underwent expert review. As the BN is compatible with domain knowledge, the reasoning mechanisms can be described, and inaccurate predictions can offer valuable lessons for model refinement. Possible causes of inaccuracies were investigated to identify 1) potential opportunities to improve the models structure, 2) data errors, and 3) limitations in the models scope. Where opportunities to improve the model were identified, the development process returned to *Step 1*, with any changes supported by evidence. Where potential data errors were identified, the original sources were examined to verify data accuracy. Limitations to the scope of the model were documented and are presented in the discussion section.

External validation and performance measures

The trained BN generates a continuous number between 0 and 1 that corresponds to the probability of developing TIC. Performance in new participants was assessed in the temporal and external validation cohorts. Predictor information, recorded by ACIT investigators during the primary survey, was entered into the model. No imputation was performed for unknown variables. Performance was assessed in terms of discrimination, calibration, and accuracy. Discrimination was measured using the

Area Under the Receiver Operating Characteristic curve (AUROC). Calibration was evaluated with the Hosmer-Lemeshow test and graphically using a calibration plot of observed against predicted values.[42] Accuracy was evaluated with the Brier Score (BS) and the Brier Skill Score (BSS). [43, 44] The BS has a value between 0 (perfect model) and 1 (worst possible model) and the BSS has a range from - ∞ to 1, where a negative value indicates a worse prediction than the average probability, and 1 indicates a perfect model.

Sensitivity analyses

We assessed the impact that each predictor variable has on the model's probability calculations using one-way sensitivity analyses. Second, we compared the model's performance to that of each individual predictor included in the model. Finally, we assessed the BN's sensitivity to missing information in the combined validation cohort (temporal and external) by comparing overall performance to performance when each predictor variable, in turn, was omitted as an input.

Statistical analysis

Statistical analyses of the results were performed using GraphPad PRISM v6 (GraphPad Software Inc., San Diego, CA, USA) and R statistical software (version 2.15.2). The BN was developed with, and is computed by, AgenaRisk software (Agena, London, UK). Numerical data are reported as median with interquartile range (IQR) and categorical data as frequency (n) and percentage (%). The Mann–Whitney U test was used to compare numerical data and Fisher's Exact test was used to compare categorical data. Outcome comparisons between groups are reported as Relative Risk (RR) with corresponding 95% Confidence Intervals (CI). Time from injury to death between groups was compared with the log-rank (Mantel-Cox) test, and results presented as Kaplan-Meier curves. AUROC was calculated and compared using the method described by Hanley and McNeil. [45] The area under correlated ROC curves was compared using a non-parametric method that accounts for the paired test design. [46] Statistical significance was set as a two tailed p-value of < 0.05.

Results

The study population comprised 1091 injured patients, with 600 patients in the development cohort and 491 patients in the validation cohorts. Their median age was 37 (range: 15 - 95) years, 873 (80.0%) were male, and 890 (81.6%) suffered a blunt mechanism of injury. The median time from injury to hospital admission was 76 (58 – 95) minutes. Baseline characteristics of the development and validation cohorts are presented in Table 1. Overall, 124 (11.4%) patients developed TIC. Characteristics of patients who developed TIC were significantly different to those with normal coagulation (SDC Table 1). With the exception of admission body temperature, missing data for clinical variables was minimal (Table 1).

Outcome classification

TIC classification was achieved by agreement between laboratory and EM methods in 978 (89.6%) patients and by expert review in the remaining 113 (10.4%) patients. The reasons for expert review were 1) no available PTr result due to haemolysis of the blood sample (66 cases, 6.1%) and 2) a discrepancy between the laboratory and EM classification (47 cases, 4.3%). Inter-reviewer agreement was excellent ($\kappa = 0.94$ [95% CI: 0.88 – 1.0]) and expert consistency was perfect.

Clinical relevance of TIC

Patients that developed TIC had substantially worse outcomes than those with normal coagulation (Table 2). Overall, patients that developed TIC were ten times more likely to die than those with normal coagulation, and the majority of deaths in coagulopathic patients occurred soon after injury (SDC Figure 1). Blood transfusion requirements, DCS requirements, ICU and hospital length of stay were all significantly greater in patients that developed TIC, compared to those with normal coagulation (Table 2).

Model development

Domain knowledge describes five potential causes of TIC: tissue hypoperfusion, tissue injury, acidaemia, hypothermia, and haemodilution. These causal factors, and the relationships between them, formed the core structure of the prognostic model (Figure 1). Domain knowledge also describes several potential predictors for these causal mechanisms, which would be available during a standard primary survey. Fourteen predictor variables were incorporated in the final model and are defined in Table 3. The relationships between predictor variables, causal variables, and TIC are represented by the structure of the BN (Figure 2). Full details of the evidence supporting the BN's structure are presented in the supplemental information (SDC Table 2A to E) and a web-based evidence browser (www.traumamodels.com). [33]

Internal validation

The BN had excellent predictive performance in the development cohort (AUROC 0.93 (95% CI: 0.90 to 0.95)). The predicted risk of TIC calibrated well with observed outcomes (Figure 2A) and the Hosmer-Lemeshow goodness-of-fit test result was non-significant (P = 0.32). The BN's predictions were accurate, with a Brier Score of 0.06 (95% CI: 0.05 – 0.08) and a Brier Skill Score of 0.40 (95% CI: 0.30 – 0.51). All predictor variables contributed to the BN's performance (SDC Figure 2). Continuous variables related to hypoperfusion – specifically blood gas variables (Base Deficit, Lactate, pH), systolic blood pressure and heart rate – had the greatest impact on the model's result.

External Validation

The BN's performance in new populations matched the performance in the development cohort (Figure 2 and Table 4). AUROC was 0.96 (95% CI: 0.94 – 0.99) in the temporal validation cohort, and 0.93 (95% CI: 0.85 – 1.0) in the external validation cohort (Figure 2C). The model remained accurate and well calibrated in both validation cohorts (Figure 2 and Table 4).

Sensitivity analyses

The BN was a better predictor of TIC than any individual variable in the model (SDC Figure 3 and 4). Omission of each predictor in turn from the models inputs did not have any significant effect on overall prognostic performance (Figure 2D). Indeed, the omission of all blood gas variable inputs, the three strongest individual predictors, had minimal effect on the BN's performance (overall performance: AUROC 0.95 (0.93 - 0.98) versus performance without blood gas information: AUROC 0.94 (0.91 – 0.98); P = 0.286).

Model presentation

The BN is available at http://www.traumamodels.com. Entering predictor variable values allows the calculation of an individual patients risk of TIC.

Discussion

Injured patients that present to hospital with trauma-induced coagulopathy (TIC) can be difficult to identify, but are responsible for almost all early trauma deaths, and require immediate, resource intense, resuscitative interventions. This study validates the clinical relevance of TIC, and describes the development and validation of a predictive model that enables early and accurate estimation of the risk of TIC in an injured patient.

The findings of this study have some important implications for trauma care. The model's outputs could be used to guide and support rational decisions on the effective activation and implementation of damage control resuscitation and surgery. Early identification of high-risk patients, potentially prior to hospital arrival, could be used to objectively activate in-hospital pathways and protocols, thereby minimising logistic delays in the provision of critical interventions such as blood component transfusions, emergency surgery, and interventional radiology. On a wider scale the model has the potential to underpin quality assurance within trauma systems e.g. audit of major haemorrhage protocol activations and damage control decisions, in addition to patient stratification in clinical trials to select at risk populations most likely to benefit from novel therapies for TIC.

Three models have previously been developed to identify patients with TIC.[47-49] Cosgriff and colleagues derived a simple score using four binary predictors (systolic blood pressure < 70mmHg, temperature < 34 °C, pH <7.1, and ISS > 25), and suggest that their score may assist damage control surgery decision-making. [47] A critical limitation of this score is that one of the variables, ISS, is unknown when the score is intended for use. More recently, two scores have been developed to predict TIC using prehospital information.[48, 49] Mitra and colleagues score uses five predictors that are all available during the early phase of care (entrapment; systolic blood pressure < 100mmHg; temperature < 35 °C; suspected abdominal or pelvic injury; and chest decompression), while Peltan and colleagues score uses six predictors (age, injury mechanism, prehospital shock index ≥1, Glasgow Coma Score, and need for prehospital tracheal intubation and/or CPR. [48, 49] Both scores achieved only moderate performance in new patients, with sensitivity less than 30% when operated at the

recommended thresholds.[49] Although these scores demonstrate that TIC is predictable from clinical information, none are accurate enough to reliably support clinical decision-making.[26] The moderate performance may be the result of a number of methodological limitations (Table 5). First, simple scores may not be sufficiently powerful to accurately predict complex pathophysiological processes. Second, by limiting the number of predictors and dichotomising continuous variables, much of the prognostic potential of available information is lost.[50, 51] Finally, although developed to predict patients with TIC, these scores actually predict a laboratory test result, and using an imperfect surrogate outcome may limit the clinical relevance of the score. [52]

The findings of this study have implications for methodology used to develop prognostic models for use in other emergency settings. Our results support the use of domain knowledge to reduce over-fitting and develop evidence-based models with better generalisability. An advantage of Bayesian networks is that they provide a platform that facilitates the incorporation of a broad range of evidence, not just data, in model development. [37, 39] Furthermore, we have shown that Bayesian networks can produce robust models that are able to use a variable selection of predictor information, and capable of handling missing or uncertain information. This is likely to be a meaningful advantage in emergency settings, and overcomes a major limitation of traditional prognostic models, which require accurate and complete predictor information to function. [39]

The scope of our model may be limited in certain circumstances. First, although the models structure was learned from knowledge, the parameters were learned from data. The ACIT study provides an optimal source of data for developing a TIC prediction model. However, certain study exclusions applied, and the model may not be accurate in these populations. Patients on anticoagulation medication or with significant liver disease were excluded, and the model is not designed to predict coagulation abnormalities resulting from these causes. Patients who could not be recruited within two hours of injury were also excluded. Although the model includes predictors for all known causes of TIC, accuracy may be affected following prolonged periods of resuscitation. Haemodilution is an important iatrogenic cause of TIC but patients administered more than two litres of prehospital fluid

were excluded from ACIT. Published evidence was used to learn the relationship for higher volumes[8], however, accuracy in these circumstances has not been validated.

Second, during development, subgroups of injured patients in which the model performed less well were identified. Although the model accurately predicts coagulopathy in the majority of patients with a head injury, it underestimates the degree of coagulopathy in patients with catastrophic head injuries (Head AIS≥5, extensive intracranial bleed, brain herniation). Indeed, patients with catastrophic head injuries, and no evidence of major extracranial injury, account for over 80% of false negative predictions. The mechanisms of coagulopathy following traumatic brain injury are uncertain.[53] As the model is derived from existing knowledge, the incomplete understanding of the causes of coagulopathy in patients with isolated severe brain injuries is reflected in the model's performance in this subgroup of injured patients. Finally, patients who suffered an assault, with a relatively minor injury, but presented with a marked metabolic acidosis following extreme physical exertion, also resulted in some inaccurate predictions (false positive). In these patients the model was unable to accurately differentiate the acute physiological changes resulting from decreased oxygen delivery in compensated haemorrhagic shock from those caused by increased oxygen requirements following extreme physical exertion.

This study has some limitations. First, a BN's predictive performance depends on how accurately its structure and parameters approximate reality. Our BN's structure was informed by existing knowledge. However, our current understanding of the causes and mechanisms of traumatic coagulopathy is not complete. This may explain the model's underperformance in certain subgroups, such as patients with catastrophic head injuries, where knowledge of the mechanism of coagulopathy is weak. The excellent performance in the majority of injured patients, however, provides evidence that existing knowledge of the key causes of TIC is reliable. Network parameters were learned from data, which was collected in a standardised way as part of a prospective observational study investigating TIC. This represents the optimal source of data for developing a prognostic model, as it limits missing data and information bias. However, one variable (temperature) had a large amount of missing data, which may introduce bias to its parameter estimate.

Second, the model's performance was validated in a civilian trauma population, where all patients were treated in well-resourced specialist trauma centres and therefore its performance in military casualties or less well-resourced settings is not known. Third, the model is designed to enable early identification of coagulopathy risk to support rapid activation of targeted haemostatic interventions. The model was not designed to measure the response of the coagulation system to these interventions, and has not been validated for this purpose. Near-patient tests, such as thromboelastography, are able to describe specific coagulation function defects, and may be better suited to assess the response to therapy and tailor damage control interventions accordingly. [54] Last, although the Bayesian network provides fundamental information to support rational damage control decisions, the impact of this information on decision-making, and ultimately patient outcomes, has not been assessed. Further research is warranted to examine the impact of using the model on clinical decisions, patient outcome, and cost-effectiveness of care, compared to standard trauma care.

In conclusion, this study demonstrates that an individual patients risk of TIC can be reliably predicted from available clinical information using a Bayesian Network. This information may be used to support early and rational decisions on the use of damage control interventions and guide rapid and efficient activation of damage control resuscitation protocols, which in turn, may prevent an established coagulopathy and lead to improved outcomes.

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The authors state that they have no conflict of interest.

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Figure legends

Figure 1: Structure of the Bayesian Network predictive model. Black variable represents the predicted outcome. Grey (latent) variables represent the five identified causal factors, and white variables represent predictors associated with the causal factors. HR, Heart Rate; SBP, Systolic Blood Pressure; BD, Base Deficit; °C, measured temperature in degrees Celsius; Fluid, volume of prehospital resuscitation fluid administered; GCS, Glasgow Coma Scale; MOI, Mechanism Of Injury; Temp, Temperature.

Figure 2: Discrimination and calibration of the trauma-induced coagulopathy (TIC) predictive model. The calibration plot shows the relationship between ideal (dashed line) and observed (solid line) predicted values in the development cohort (**A**) and the combined (temporal and external) validation cohort (**B**). The rug plot along the bottom demonstrates the distribution of predicted probabilities. The circles with 95% confidence intervals indicate observed frequencies by decile of predicted probability. The Receiver-Operating-Characteristic (ROC) Curves show the relationships between true positive and false positive TIC predictions in the development, temporal, and external validation cohorts (**C**). The forest plot compares the performance of the model at predicting TIC in the combined (temporal and external) validation cohort when each of the models predictors in turn was omitted as inputs (**D**). Performance was measured by calculating the Area Under the ROC curve with 95% Confidence Intervals.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplementary Digital Content 1: Table comparing baseline characteristics of 1091 injured patients according to their coagulation function.

Supplementary Digital Content 2: Figure illustrating Kaplan-Meier estimates of the probability of survival for 1091 injured patients with either normal coagulation or trauma-induced coagulopathy. The p-value was calculated using the log-rank (Mantel-Cox) test.

Supplementary Digital Content 3: Tables (2A-E) presenting the evidence supporting the causal structure of the trauma-induced coagulopathy prediction model.

Supplementary Digital Content 4: Figure illustrating one-way sensitivity analyses of the impact individual predictor variables have on the models result. Analyses were performed using data from the development cohort. The dotted line represents the prior probability of trauma-induced coagulopathy in the development population.

Supplementary Digital Content 5: Figure illustrating the Area under the Receiver Operating Characteristic (ROC) curve with 95% Confidence Intervals for trauma-induced coagulopathy predictions in 491 injured patients (combined validation cohort) using individual predictors and the full predictive model. The area under the ROC curve was calculated for each continuous and ordinal predictor in the model.

Supplementary Digital Content 6: Figure illustrating the Odds Ratios with 95% Confidence Intervals (CI) for trauma-induced coagulopathy in 491 injured patients (combined validation cohort), according to individual predictors and the full predictive model. An Odds Ratio was calculated for each binary predictor in the model. The full model was operated at the threshold that achieved 90

percent sensitivity for trauma-induced coagulopathy in the development cohort. FAST, Focused Assessment with Sonography for Trauma; MOI, Mechanism Of Injury.

Table 1: Baseline characteristics of the study populations.

Characteristic	Missing Data (%)	Development cohort (N=600)	Validation cohort	
			Temporal (N=373)	External (N = 118)
Age – years (range)	<1	35 (16 – 95)	38 (16 – 93)	45 (16 – 92)§
Gender - male	0	486 (81.0)	309 (82.8)	78 (66.1)§
Mechanism of Injury - Blunt	0	475 (79.2)	299 (80.2)	116 (98.3)§
Pre-Hospital fluid (ml)	<1	0 (0 – 500)	0 (0 – 100)	100 (0 – 350)
Primary Survey:				
Respiratory Rate (bpm)*	1.3	20 (16 – 24)	18 (15 – 20)§	17 (14 – 22)
Heat Rate (bpm)	<1	95 (76 – 118)	87 (75 – 104)§	84 (74 – 108)§
Systolic Blood Pressure (mmHg)	1.9	130 (107 – 148)	134 (116 – 149)	136 (114 – 150)
Body Temperature (°C)	39.8	35.8 (35.1 – 36.5)	36.1 (35.7 – 36.7)§	36.0 (35.3 – 36.6)
Glasgow Coma Scale*	<1	15 (11 – 15)	15 (13 – 15)§	15 (10 – 15)
Suspected Haemothorax	<1	89 (14.9)	49 (13.2)	13 (11.1)
Suspected unstable pelvic fracture	<1	58 (9.7)	31 (8.3)	23 (20)§
Suspected long bone fracture	<1	132 (22.2)	89 (23.9)	28 (24.4)
FAST - Positive	<1	49 (8.2)	26 (7.0)	15 (12.7)
Baseline Blood Gas Analysis:				
pH	5.2	7.35 (7.30 – 7.40)	7.36 (7.31 – 7.39)	7.34 (7.25 – 7.39)
Lactate	6.2	2.1 (1.3 – 3.6)	2.3 (1.4 – 3.5)	2.6 (1.6 – 3.5)
Base Deficit	5.6	1.8 (-0.2 – 4.4)	0.6 (-1.5 – 3.3)§	1.6 (-0.7 – 5.1)
Baseline Thromboelastography:				
EXTEM CA5 (mm)	7.6	44 (38 – 49)	44 (39 – 50)	46 (42 – 52)§
EXTEM MCF (mm)	7.6	61 (56 – 65)	63 (59 – 68)§	63 (57 – 68)§
FIBTEM MCF (mm)	7.6	14 (10 – 17)	15 (11 – 20)§	16 (11 – 20)§
Baseline laboratory values:				
PTr	6.1	1.1 (1.0 – 1.1)	1.1 (1.0 – 1.1)§	1.0 (1.0 – 1.1)§
APTT (seconds)	7.2	23 (22 – 26)	23 (22 – 26)	27 (25 – 30)§
Haemoglobin (g/dL)	4.4	13.9 (12.4 – 14.9)	14.1 (12.9 – 15.0)§	13.7 (12.2 – 14.8)
Platelet count ($x10^9$ /L)	5.0	231 (193 – 272)	219 (182 – 264)§	245 (209 – 288)§
Injury severity:				
Injury Severity Score	2.4	16 (9 – 29)	13 (5 – 25)§	17 (9 – 29)
Head AIS ≥ 3	2.8	173 (28.8)	89 (25.9)	33 (28.0)
Chest AIS ≥ 3	2.8	257 (42.8)	106 (30.8)§	50 (42.4)
Abdomen AIS ≥ 3	3.4	62 (10.3)	44 (12.8)	15 (12.7)
Extremity AIS ≥ 3	2.7	198 (33.0)	100 (29.1)	52 (44.1)§

Outcomes:				
Trauma-Induced Coagulopathy	0	71 (11.8)	39 (10.5)	15 (12.7)
Mortality	0	71 (11.8)	28 (7.5) [§]	21 (17.8)

Data presented as number (%) or median (IQR) unless otherwise stated.

* Admission measurement or, if patient arrived intubated, pre-hospital measurement prior to sedation and intubation.

§ The characteristic differs significantly ($p < 0.05$) compared with the development cohort.

FAST, Focused Assessment with Sonography for Trauma; CA5, Clot Amplitude at 5 minutes; MCF, Maximum Clot Firmness; PTr, Prothrombin Time ratio; APTT, Activated Partial Thromboplastin Time; AIS, Abbreviated Injury Score.

Table 2: Comparison of outcomes and resuscitation resource requirements in 1091 injured patients stratified by coagulation status.

Outcome	Missing Data (%)	Trauma-Induced Coagulopathy (N=124)	Normal Coagulation (N=967)	Relative Risk (95% CI)	P-Value
In-hospital mortality:					
< 24-hour	0	41 (33.1)	9 (0.9)	35.5 (17.7 – 71.3)	< 0.0001
Overall	0	67 (54.0)	53 (5.5)	9.9 (7.2 – 13.4)	< 0.0001
Emergency intervention in first 24 hours:					
Transfusion	<1	114 (91.9)	193 (20.0)	4.6 (4.0 – 5.3)	< 0.0001
Massive transfusion	<1	54 (43.5)	11 (1.1)	38.3 (20.6 – 71.2)	< 0.0001
DCS	4.8	67 (55.8)	31 (3.4)	16.6 (11.3 – 24.2)	< 0.0001
*Length of stay (days)**					
Critical Care	0	13 (3 – 21)	0 (0 – 2)	-	< 0.0001
Hospital	0	32 (19 – 50)	8 (2 – 20)	-	< 0.0001

Data presented as number (%) or median (IQR). Risk Ratios are for the coagulopathic group, as compared with the normal coagulation group. * Median length of stay of survivors. DCS, Damage Control Surgery

Table 3: Definitions of predictor variables in the trauma-induced coagulopathy model.

Predictor Variable	**Type of Node**	**Definition**
Heart rate	Continuous	Heart rate in beats per minute
Systolic blood pressure	Continuous	Systolic Blood Pressure in mmHg
Temperature	Continuous	Body temperature in °C
Haemothorax	Boolean	*Present*: Clinically suspected, based on examination or CXR findings. *Absent*: Not suspected
FAST result	Boolean	*Positive*: Free peritoneal fluid identified. *Negative*: No free peritoneal fluid or investigation not clinically indicated.
Unstable pelvic fracture	Boolean	*Present*: Clinically suspected, based on examination or PXR findings. *Absent*: Not suspected
Long bone fracture	Boolean	*Present*: Clinically suspected fracture of femur, tibia or humerus. Traumatic amputation proximal to ankle or elbow. *Absent*: Not suspected
GCS	Ranked	Glasgow Coma Score on admission or prior to intubation
Lactate	Continuous	Admission Arterial or Venous Blood Gas Analysis
Base Deficit	Continuous	Admission Arterial or Venous Blood Gas Analysis
pH	Continuous	Admission Arterial or Venous Blood Gas Analysis
Mechanism of Injury	Boolean	*Blunt / Penetrating*
Energy	Boolean	*High-Energy*: High-velocity GSW; fall > 20 feet (6 meters); Pedestrian or cyclist versus vehicle > 20mph; Road Traffic Collision with mechanical entrapment, ejection from vehicle or death in same passenger compartment; Entrapment under a train or vehicle; Crush injury; Blast injury. *Low-Energy*: Stab; low-velocity GSW; and blunt injury excluding injuries above.
Volume of fluid administered	Continuous	Volume of crystalloid or colloid fluid administered in ml.

CXR, Chest X-Ray; PXR, Pelvic X-Ray; GSW, Gun Shot Wound

Table 4: Predictive performance measures for the trauma-induced coagulopathy model in the development, temporal validation, and external validation cohorts.

Performance Measure	Development Cohort	Validation Cohort	
		Temporal	External
AUROC	0.93 (0.90 - 0.95)	0.96 (0.94 - 0.99) [§]	0.93 (0.85 - 1.0)
Calibration slope	0.96 (0.77 - 1.15)	1.30 (0.95 - 1.65)	1.15 (0.62 - 1.68)
Calibration intercept	0.18 (-0.15 - 0.51)	0.62 (0.18 - 1.06)	0.42 (-0.29 - 1.12)
Hosmer-Lemeshow Statistic	9.3 (P = 0.32)	11.0 (P = 0.20)	8.7 (P = 0.37)
Brier Score	0.06 (0.05 – 0.08)	0.05 (0.03 – 0.07)	0.06 (0.03 – 0.09)
Brier Skill Score	0.40 (0.30 – 0.51)	0.48 (0.37 – 0.59)	0.45 (0.26 – 0.64)

[§] Performance differs significantly ($p < 0.05$) compared with the development cohort.

AUROC, Area Under the Receiver Operating Characteristic Curve.

Table 5: Comparison of key steps in model development and validation, and associated Risk of Bias (ROB), for existing Trauma Induced Coagulopathy (TIC) prediction models and the TIC Bayesian network.

	Cosgriff [47]	**COAST** [48]	**PACT** [49]	**TIC-BN**	**Risk o step**
Model development					
Outcome					
Definition	PT > 2x normal and PTT > 2x normal	INR > 1.5 or aPTT > 60 sec	INR > 1.5	INR > 1.2 and E-M clustering [b] Expert consensus [c]	Conv have may outcc
Clinical relevance	Not assessed	Assessed	Assessed	Assessed	No m little patie
Participants					
Data source	Transfusion registry (SC)	Trauma registry (SC)	Trauma registry (MC)	Prospective cohort study (MC)	High retros collec
Sample size (n)	58	1680	1963	600	High
Study population	Severely injured adults requiring massive blood transfusion	Adult major trauma patients (ISS>15/surgery/ITU)	Severely injured adults (died/ surgery/ ITU)	Adult trauma patients who meet local criteria for trauma team activation	High targe
Predictors					
Predictor selection	Data-driven (Univariable then Multivariable analyses)	Data-driven (Univariable then Multivariable analyses)	Data-driven (Univariable then Multivariable analyses)	Knowledge-driven (Domain knowledge)	High univa ROB estab
Number of predictors	4	5	6	14	
Handling of continuous predictors	Dichotomized	Categorized	Dichotomized	No conversion	High categ
Available at time model intended for use?	No	Yes	Yes	Yes	High time
Prediction model					
Model/Algorithm type	Logistic regression	Simple score	Weighted score	Bayesian Network	Simpl powe proce
Handling of missing data during parameter learning	Unclear	Exclusion of cases with missing data	Multiple imputation	No exclusions	High analy
Ability of model to handle missing predictor information?	No	No	No	Yes	Missi cases perfo
Validation of Predictive Performance					
Discrimination	Not assessed	AUROC (I,T,E)	AUROC (I,E)	AUROC (I,T,E) Brier Score[d] (I,T,E) Brier Skill Score[d] (I,T,E)	High evalu
Calibration	Not assessed	Hosmer-Lemeshow test (T,E)	Calibration plot (E) Hosmer-Lemeshow test (I,E)	Calibration plot (I,T,E) Calibration slope (I,T,E) Calibration intercept (I,T,E)	High evalu Hosm calibr calibr

Hosmer-Lemeshow test (I,T,E)

[a] Risk of bias occurs when shortcomings in study design, conduct, or analysis could lead to systematically distorted estimates of a model'
clustering using individual clinical, laboratory and thromboelastometry information. [c] Expert consensus of outcome classification in case
methods. [d] Brier Score and Brier Skill Score are measures of overall predictive performance that combine features of discrimination and c
predicted outcomes are to actual outcomes. (SC), Single Centre; (MC), Multicentre; PT, Prothrombin Time; PTT, Partial Thromboplastin T
International Normalised Ratio; E-M, Expectation-Maximization; ISS, Injury Severity Score; ITU, Intensive Treatment Unit; AUROC, Area U
Internal validation; (T), Temporal validation; (E), External validation

Figure 1

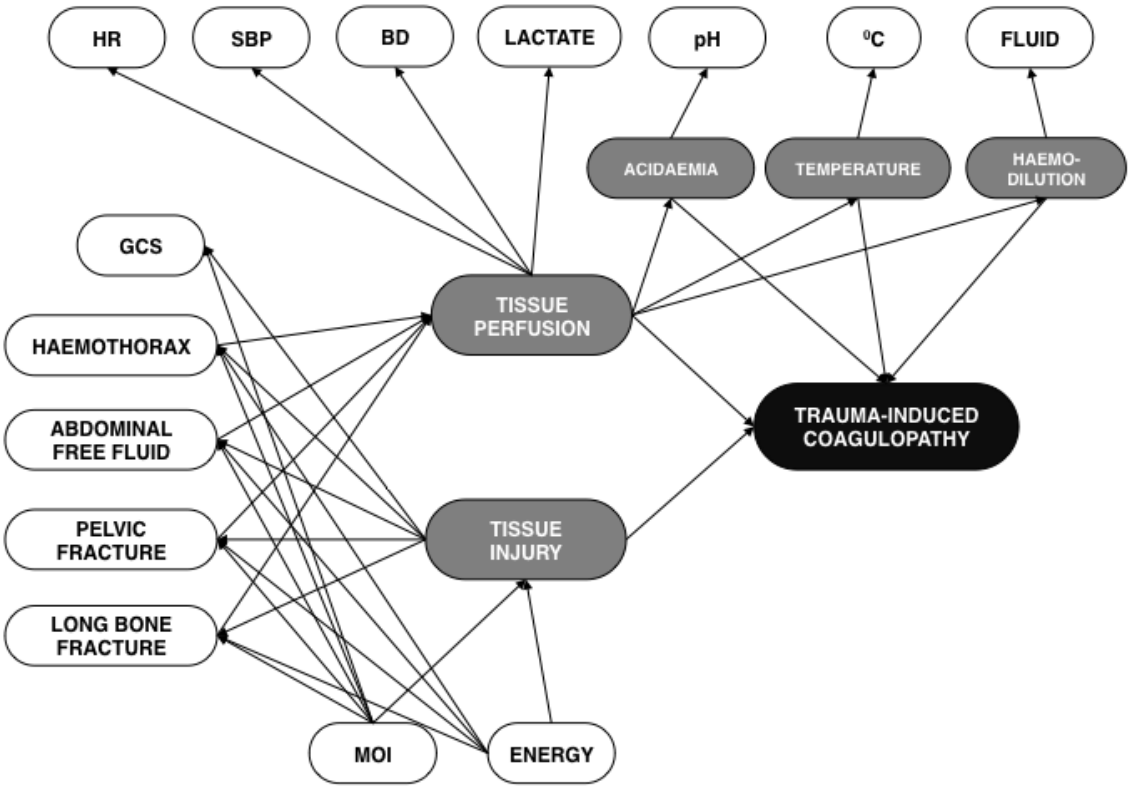
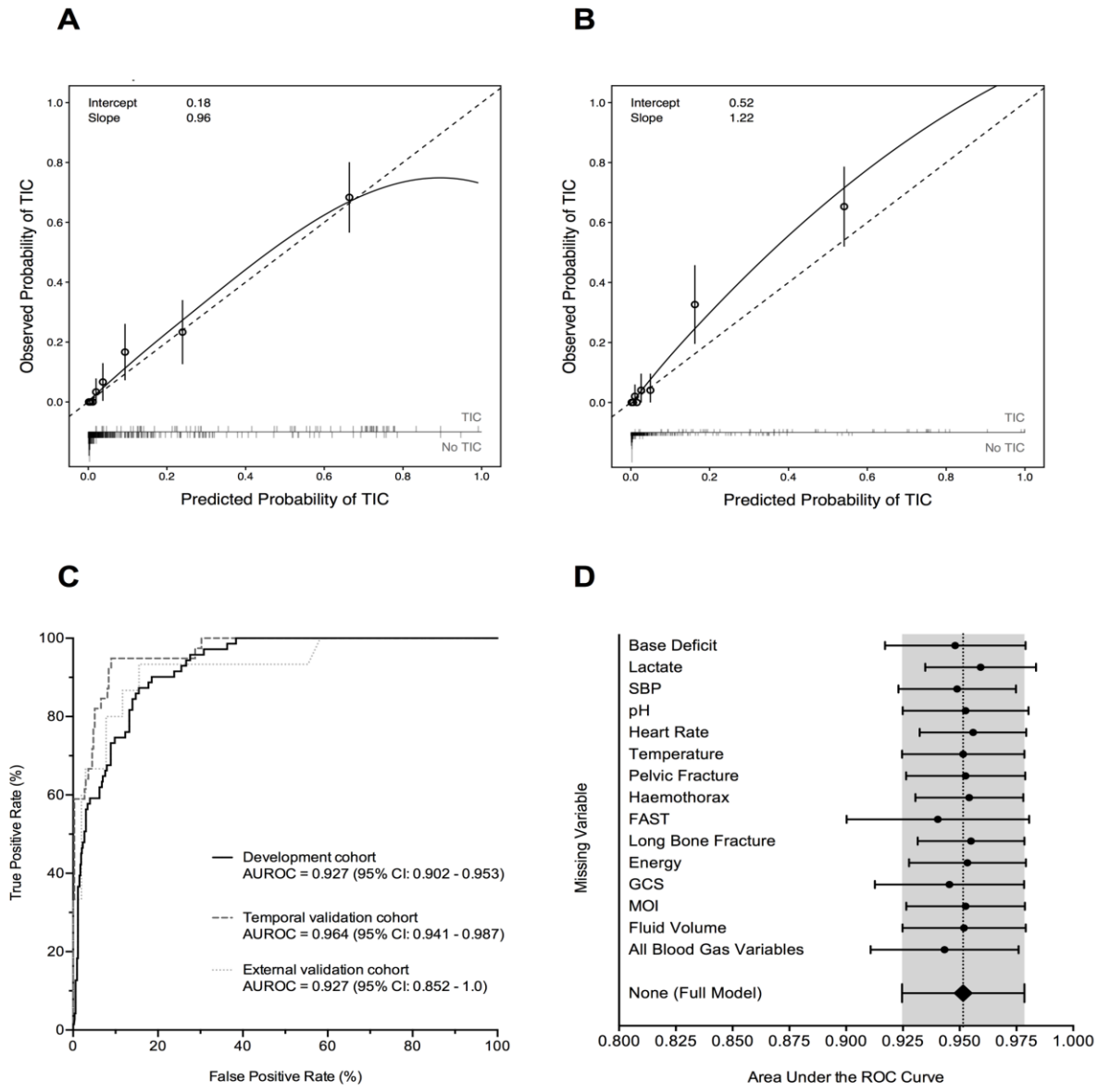

HR
SBP
BD
LACTATE
pH
⁰C
FLUID
ACIDAEMIA
TEMPERATURE
HAEMO-
DILUTION
GCS
HAEMOTHORAX
ABDOMINAL
FREE FLUID
PELVIC
FRACTURE
LONG BONE
FRACTURE
TISSUE
PERFUSION
TISSUE
INJURY
TRAUMA-INDUCED
COAGULOPATHY
MOI
ENERGY

Figure 2


A
Intercept 0.18
Slope 0.96
Observed Probability of TIC
Predicted Probability of TIC
TIC
No TIC
B
Intercept 0.52
Slope 1.22
Observed Probability of TIC
Predicted Probability of TIC
TIC
No TIC
C
True Positive Rate (%)
False Positive Rate (%)
Development cohort
AUROC = 0.927 (95% CI: 0.902 - 0.953)
Temporal validation cohort
AUROC = 0.964 (95% CI: 0.941 - 0.987)
External validation cohort
AUROC = 0.927 (95% CI: 0.852 - 1.0)
D
Missing Variable
Base Deficit
Lactate
SBP
pH
Heart Rate
Temperature
Pelvic Fracture
Haemothorax
FAST
Long Bone Fracture
Energy
GCS
MOI
Fluid Volume
All Blood Gas Variables
None (Full Model)
Area Under the ROC Curve