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Trauma Early Mortality Prediction Tool (TEMPT) for assessing 28-day mortality.

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ABSTRACT
Background Prior mortality prediction models have incorporated severity of anatomic injury quantified by Abbreviated Injury Severity Score (AIS). Using a prospective cohort, a new score independent of AIS was developed using clinical and laboratory markers present on emergency department presentation to predict 28-day mortality.

Methods All patients (n=1427) enrolled in an ongoing prospective cohort study were included. Demographic, laboratory, and clinical data were recorded on admission. True random number generator technique divided the cohort into derivation (n=707) and validation groups (n=720). Using Youden indices, threshold values were selected for each potential predictor in the derivation cohort. Logistic regression was used to identify independent predictors. Significant variables were equally weighted to create a new mortality prediction score, the Trauma Early Mortality Prediction Tool (TEMPT) score. Area under the curve (AUC) was tested in the validation group. Pairwise comparison of Trauma Injury Severity Score (TRISS), Revised Trauma Score, Glasgow Coma Scale, and Injury Severity Score were tested against the TEMPT score.

Results There was no difference between baseline characteristics between derivation and validation groups. In multiple logistic regression, a model with presence of traumatic brain injury, increased age, elevated systolic blood pressure, decreased base excess, prolonged partial thromboplastin time, increased international normalized ratio (INR), and decreased temperature accurately predicted mortality at 28 days (AUC 0.93, 95% CI 0.90 to 0.96, P<0.001). In the validation cohort, this score, termed TEMPT, predicted 28-day mortality with an AUC 0.94 (95% CI 0.92 to 0.97). The TEMPT score performed similarly to the revised TRISS score for severely injured patients and was highly predictive in those having mild to moderate injury.

Discussion TEMPT is a simple AIS-independent mortality prediction tool applicable very early following injury. TEMPT provides an AIS-independent score that could be used for early identification of those at risk of doing poorly following even minor injury.

Level of evidence Level II.

INTRODUCTION
Despite advances in care, between 2000 and 2010 deaths from trauma increased by 22.8%, a number far exceeding the parallel rise in US population (9.7%) and in stark contrast to a decrease in deaths from cancer and heart disease during this same period.1 The exact cause of this increase remains unknown, but it may in part be explained by the aging baby boomer population; older age is associated with increased morbidity and mortality after trauma, and patients aged 45–64 years exhibited the greatest rise in death rates across age groups (28.5%).2 3 Implementing a precision-based approach to trauma care requires an updated system of mortality prediction that reflects the evolving trauma population and is easy to use for practical application early in care.

Predictive modeling can facilitate effective resource allocation, estimation of patient outcomes, and trauma quality assessment. Algorithms based on Abbreviated Injury Scales (AIS) such as Trauma Injury Severity Score (TRISS), Revised Trauma Score (RTS), and Injury Severity Score (ISS) are plentiful. Yet, these scoring systems primarily focus on characterizing large patient populations post hoc rather than guiding real-time clinical decision-making.3–6 In fact, the most well-established scores are nearly impossible to adopt clinically, requiring complex mathematical calculation impractical for the chaotic trauma bay as well as necessary data points unattainable during the early stages of a patient’s hospital course. Further, these scores largely predate balanced resuscitation and have been shown to demonstrate poorer prediction.7–9 Today, TRISS is the most widely used trauma mortality scoring system and is constrained by all the aforementioned limitations.

Advancing trauma outcome prediction is critical to meet the rapidly changing trauma population and resuscitation methodologies. While clinical acumen can indeed facilitate management for many trauma patients, we argue that the development of a standardised score calculable early in the care pathway could additionally serve to identify high-risk patients who might otherwise go undetected, more effectively personalise resuscitation, and focus high-value care on those who benefit the most from targeted interventions. With these principles in mind, we generated an AIS-independent prediction algorithm using simple clinical and laboratory values measured on admission and compared this to the predictive ability of historical scoring systems.

METHODS
All level I trauma patients presenting to San Francisco General Hospital between 2005 and 2015 who were simultaneously enrolled in an ongoing prospective observational cohort study entitled Activation of Coagulation and Inflammation in Trauma (ACIT) were selected for inclusion. ACIT enrolls adult patients who are highest level trauma activations in whom initial intravenous access is obtained in the emergency department (ED) for
routine clinical care. The original ACIT study aimed to elucidate mechanisms of coagulopathy and inflammation among trauma patients, and this secondary analysis examined comprehensive demographic, injury, laboratory, and in-hospital outcome data collected prospectively to 28 days. Not all patients had all laboratory samples obtained in routine clinical care and no specific laboratory tests were mandated by enrollment in the observational study. To ensure accuracy of presence of traumatic brain injury (TBI), ED notes and imaging reports for studies obtained in the ED were reviewed by physician adjudicators. Patients were classified as having TBI if they had evidence of skull fractures, epidural hematomas, subdural hematomas, subarachnoid hemorrhages, midline shifts, brain contusions, intraventricular hemorrhages, diffuse axonal injury, or intracranial hemorrhages. Exclusion criteria included those under 15 years of age, burn victims, pregnant women, and those who were incarcerated.

Following a cross-validation approach to model prediction, patients were randomised into derivation and validation cohorts to minimise overfitting. Using a true random number generator, patients were randomly assigned zeros or ones, respectively designating selection to either the derivation or validation patient group. Randomization was subsequently assessed by examining differences in baseline characteristics via Wilcoxon rank-sum and \( \chi^2 \) tests, as appropriate. In the derivation cohort, univariate analysis identified individual predictors of 28-day mortality (\( P<0.005 \)), and continuous variables were dichotomised via the Youden index.\(^{10} \) This statistical technique generates optimal threshold cut-offs by maximizing the sensitivity and specificity for each respective variable, which in practice involves finding the greatest vertical distance between the receiver operator characteristic (ROC) curve and the diagonal chance line.

Dichotomous predictors were then included in multiple logistic regression in the derivation cohort with backward variable elimination by stepwise regression (\( P\leq0.20 \) was selected to minimise residual confounding). The resulting model composed of equally weighted variables was termed Trauma Early Mortality Prediction Tool and was further assessed by multiple logistic regression in the validation cohort by ROC discrimination (area under the curve (AUC)). Missingness of data was examined using Wilcoxon rank-sum and \( \chi^2 \) tests, and calibration was evaluated by Hosmer-Lemeshow goodness of fit. Performance of TEMPT was then compared in pairwise fashion to existing historical mortality and injury scores, including TRISS, RTS, Glasgow Coma Scale (GCS), and ISS by \( \chi^2 \). Lastly, bootstrapping was employed to simulate the performance of TEMPT within a larger population. This method of repetitive random sampling with replacement (replications=1000) projects estimates for the general population.

### RESULTS

Of the 1427 total trauma patients enrolled in the ACIT study, 81% were male, 34% were Caucasian, and median age was 35 years (table 1).

Also, 56% suffered blunt injury and 36% experienced TBI. Median ISS was 14 and overall mortality was 18% (table 1). The group was randomly divided into a derivation (n=707) and a validation cohort (n=720 patients) using true random number generator technique. In order to assess bias in the creation of the two groups, the demographic and injury characteristics of the derivation and validation group were compared. There were no statistical difference in demographic or injury characteristics (table 1, \( P=\text{NS} \)).

### Creating the TEMPT model

In univariate analysis of the derivation cohort, TBI (OR 11.52, 95% CI 7.04 to 18.83), international normalized ratio (INR) (OR 3.96, 95% CI 1.90 to 8.22), blunt injury (OR 2.46, 95% CI 1.59 to 3.80), creatinine (OR 1.75, 95% CI 1.26 to 2.43), partial thromboplastin time (PTT) (OR 1.14, 95% CI 1.90 to 8.22), age (OR 1.03, 95% CI 1.02 to 1.04), systolic blood pressure (OR 1.01, 95% CI 1.00 to 1.02), platelets (OR 0.99, 95% CI 0.99 to 1.00), base excess (OR 0.95, 95% CI 0.92 to 0.98), hemoglobin (OR 0.83, 95% CI 0.76 to 0.91), and temperature (OR 0.43, 95% CI 0.33 to 0.57) significantly predicted mortality at 28 days (\( P<0.05 \)) (table 2).

| Variable                  | All patients (n=1427) | Derivation (n=707) | Validation (n=720) |
|---------------------------|-----------------------|--------------------|--------------------|
|                           | n | Median or % | n | Median or % | n | Median or % | P value |
| **Age**                   |   |            |   |            |   |            |         |
| Male                      | 1160 | 81.2% | 569 | 80.5% | 591 | 81.9% | 0.51 |
| Female                    | 269  | 18.8%  | 138 | 19.5%  | 131 | 18.1%  |         |
| **Body mass index**       | 1083 | 26.0    | 532 | 25.8    | 561 | 26.0    | 0.59 |
| **Race**                  |   |          |   |          |   |          |         |
| Caucasian/Latino          | 783  | 54.8%   | 385 | 54.5%   | 398 | 55.1%   | 0.97 |
| Black                     | 339  | 23.7%   | 166 | 23.5%   | 173 | 24.0%   |         |
| Asian                     | 185  | 13.0%   | 95  | 13.4%   | 90  | 12.5%   |         |
| Pacific Islander          | 9    | 0.6%    | 5   | 0.7%    | 4   | 0.6%    |         |
| Native American           | 8    | 0.6%    | 4   | 0.6%    | 4   | 0.6%    |         |
| Other                     | 36   | 2.5%    | 20  | 2.8%    | 16  | 2.2%    |         |
| Unknown                   | 69   | 4.8%    | 32  | 4.5%    | 37  | 5.1%    |         |
| **Injury Severity Score** | 1389 | 14.0    | 689 | 13.0    | 700 | 14.0    | 0.24 |
| Blunt injury              | 801  | 56.3%   | 383 | 54.3%   | 418 | 58.1%   | 0.15 |
| Traumatic brain injury    | 519  | 36.4%   | 248 | 35.2%   | 271 | 37.6%   | 0.34 |
| Mortality at 28 days      | 253  | 17.7%   | 117 | 16.6%   | 136 | 18.8%   | 0.26 |
Optimal cut-offs were subsequently generated using Youden indices for all significant continuous predictors in univariate analysis (P<0.005) (table 3).

These predictors were then assessed using multiple logistic regression treating the cut-off points as categorical variables. In multiple logistic regression, the presence of TBI (OR 3.8, 95% CI 1.5 to 9.4, P=0.004), prolonged PTT (OR 4.6, 95% CI 1.7 to 12.3, P=0.003), decreased base excess (OR 9.7, 95% CI 3.6 to 26.1, P<0.001), increased age (OR 8.0, 95% CI 3.0 to 21.4, P<0.001), elevated systolic blood pressure (OR 4.6, 95% CI 1.7 to 12.3, P=0.003), decreased base excess (OR 3.8, 95% CI 1.5 to 9.4, P=0.004), prolonged PTT (OR 3.5, 95% CI 1.4 to 8.8, P=0.008), increased INR (OR 2.8, 95% CI 1.0 to 8.0, P=0.049), and decreased temperature (OR 1.9, 95% CI 0.8 to 4.6, P=0.17) accurately predicted mortality at 28 days (AUC 0.93, 95% CI 0.90 to 0.96, P<0.001) (table 4).

The variables that remained statistically significant in multiple logistic regression at the selected cut-off points compose the TEMPT score. The score includes presence of TBI, age (≥59.5 years), base excess (≥−4.35 mmol/L), PTT (≥31.45 s), INR (≥1.25), and temperature (≤36.25°C).

### Model validation

The TEMPT score model was then tested in the validation cohort, and it performed similarly with an AUC 0.89 (95% CI 0.83 to 0.94, P=0.15), 2009 updated TRISS (AUC 0.83, 95% CI 0.75 to 0.90, P=0.75), RTS (AUC 0.80, 95% CI 0.77 to 0.89, P=0.38), and GCS (AUC 0.83, 95% CI 0.78-0.89, P=0.52), and significantly outperformed ISS (AUC 0.68, 95% CI 0.78 to 0.80, P=0.03) (table 6). Bootstrapping projected similar 95% CIs for all patient groups (table 6).

### DISCUSSION

In 1983, the advent of TRISS provided a common mechanism for capturing trauma mortality. TRISS included both anatomic and physiological data as a comprehensive approach to injury evaluation. For decades, TRISS was widely accepted as the standard method for mortality prediction. However, Rogers et al recently found that TRISS significantly overestimates trauma mortality and does so by an increasing margin annually. This likely reflects advances in trauma and critical care as well as changing population demographics that have affected outcomes.

Between 2002 and 2010, Sise et al identified a substantial increase in mortality due to falls (46%) and decrease due to motor vehicle traffic (27%). In addition, McGwin et al, Gunst et al, and Evans et al noted a shift away from the classic trimodal distribution of immediate (<1 hour after injury), early (several hours after injury), and late (days to weeks after injury) deaths and toward a bimodal profile with fewer deaths beyond 1 week. These shifts have occurred simultaneously with advances in resuscitation. Historically, crystalloid was the initial fluid replacement strategy for hemorrhaging patients and often patients would have exposure to large volumes. In the past decade, there has been a diffusion of the adoption of balanced resuscitation with physiological ratios of packed red blood cells (PRBCs), platelets, and plasma while limiting crystalloid. The net result has been an increase in mortality due to falls (46%) and decrease due to motor vehicle traffic (27%).

With advances in critical care and trauma resuscitation, it is likely that the TRISS score has demonstrated poorer performance compared to more recent models.
recently because a proportion of patients have been converted from those with a high probability of death due to complications of hemorrhage to a lower risk group. Although TRISS has undergone several iterations in the form of coefficient revisions since its first inception, its real-time clinical utility remains limited by the need to have fully defined anatomic injury for calculation. This has restricted the use of TRISS to essentially a retrospective tool designed to benchmark performance after all care is complete. Generating a novel mortality prediction score in real time that could augment early clinical management to mitigate poor outcome is the next step toward achieving precision health solutions for trauma care. To achieve this, an AIS-independent prediction tool would be required.

In this study, we generated a novel AIS-independent trauma mortality prediction score (TEMP) that accurately assesses survival after injury and can be practically adopted in an acute setting. All predictor variables selected for TEMP are often available on ED admission and are similarly well documented in trauma and critical care literature to be important for trauma mortality.2 19–26 Further, despite its AIS independence, the tool has equivalent performance to the most recent revision of TRISS for all patients and exceeds its performance in the minor injured population. One of the most important advantages of TEMP compared with TRISS is that TRISS cannot be calculated until the AIS scores are known for individual patients. In most trauma centers, these values are obtained after the patient care episode has been concluded and all the injuries are known. The purpose of the TEMP score is that it can be used early in care prospectively before the full spectrum of injuries are known.

This is an important distinction. Prediction tools calculated at the end of care are useful for benchmarking and research purposes; however, they provide little prospective benefit at the point of care for the bedside practitioner considering treatment options. As we move toward the goal of precision medicine in trauma care, we will require the ability to discern those more likely to do poorly earlier in care. Earlier identification of these patients creates opportunity to apply precision medicine techniques in an effort to personalise care pathways to mitigate poor outcome. Although most practitioners recognise obviously ill or not ill persons, the value in these types of prediction rules is the ability to discern between the large group in the middle. The TEMP score performs particularly well in this patient group. Considering the present push toward precision medicine, we believe the accuracy and practical simplicity of TEMP as an AIS-independent prediction algorithm offers considerable advantages toward directing personalised care in an acute setting.

Some results directly parallel findings in the literature. Similar to our own age cut-off of ≥59.5 years, Campbell-Furtick et al recommended age 60 to be considered the new ‘elderly’ in the setting of trauma as it marked the start of the most accelerated rise in mortality rate in relation to advancing age.27 A base excess threshold of ≤−4.35 mmol/L aligns with classifications for class II mild shock (<2 to −6 mmol/L), and in an analysis of >16 000 patients of the TraumaRegister DGU database, this cohort exhibited an average aPTT of 32.1 s, thus, mirroring our own PTT cut-off of ≥31.4 s.28 Mutschler and colleagues found individuals presenting in class II shock or greater (base excess ≤−2 mmol/L) displayed a mortality rate more than twice that of non-shock patients (19% vs 7.4%).28 Neville et al identified that among elderly trauma patients this rate becomes even more pronounced as those with an initial base excess of ≤−4.35 mmol/L were more than five times more likely to die than patients with a base excess of >−4 mmol/L.29 Lastly, systolic blood pressure as a predominant upper limit cut-off (≥163.5 mm Hg) likely represents the Cushing’s reflex in the setting of severe brain injury, thus signifying the overwhelming detriment of central nervous system injury. TBI is the leading cause of death immediately after trauma and is also associated with a threefold increased odds of mortality.30

In contrast, other variable cut-offs that we have identified on first pass would not raise concern in most providers; however, we found them to be predictive of poor outcome. This underscores the utility of analytic solutions and precision approaches that have potential to enhance clinician diagnostic abilities especially in patients that initially appear stable. A trauma patient presenting with a hemoglobin of 12.75 g/dL or temperature of 36.25°C does not raise red flags, but these results suggest perhaps they should. It may be time to revise the classic paradigm ‘sick or not sick’ as seemingly innocuous thresholds may now be required for sufficient sensitivity to identify those at risk of higher mortality. The findings suggest that there is inherit value in seemingly benign cut-offs to detect individuals at risk of poor outcome despite initially appearing to be less injured patient. Detecting these patients early may allow for more rigorous care or stratification along a different care pathway that may serve to alter outcomes in a more favorable direction.

Table 4 Multiple logistic regression of the derivation and validation cohorts

| Variables                      | Derivation (n=334) | Validation (n=327) |
|-------------------------------|-------------------|-------------------|
|                               | OR    | 95% CI | P value | OR    | 95% CI | P value |
| Traumatic brain injury        | 9.7   | 3.6 to 26.1 | <0.001 | 10.6  | 3.7 to 30.9 | <0.001 |
| Age (years)                   | 8.0   | 3.0 to 21.4 | <0.001 | 9.6   | 3.6 to 25.4 | <0.001 |
| Systolic blood pressure (mm Hg) | 4.6   | 1.7 to 12.3 | 0.003  | 5.3   | 1.9 to 14.6 | 0.001  |
| Base excess (mmol/L)          | 3.8   | 1.5 to 9.4 | 0.004  | 3.0   | 0.8 to 4.8 | 0.16   |
| PTT (s)                       | 3.5   | 1.4 to 8.8 | 0.008  | 5.8   | 2.1 to 15.7 | 0.001  |
| INR                           | 2.8   | 1.0 to 8.0 | 0.049  | 2.2   | 1.1 to 8.5 | 0.04   |
| Temperature (°C)              | 1.9   | 0.8 to 4.6 | 0.17   | 1.9   | 0.9 to 4.8 | 0.09   |

Table 5 Calibration of models

| Model                        | n     | P value |
|------------------------------|-------|---------|
| Trauma Early Mortality Prediction Tool | 305   | 0.45    |
| Trauma Injury Severity Score (2009) | 305   | 0.11    |
| Trauma Injury Severity Score (1995) | 305   | 0.18    |
| Revised Trauma Score         | 305   | 0.04    |
| Glasgow Coma Scale           | 305   | 0.045   |
| Injury Severity Score        | 305   | 0.26    |

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Nearly 30 years have passed since the original development of TRISS (1983), RTS (1989), GCS (1974), and ISS (1974), and these findings insinuate their limitations may lie in the assessment of mild to moderately injured patients. In cases of severe injury, irreparable damage often dictates outcomes; within this subset, these scores still perform accurately as even the most aggressive care is minimally beneficial for the patient with an anatomically non-survivable injury. In contrast, the historic prediction algorithms are not as effective at discerning outcome in those less severely injured and the TEMPT score appears to offer an advantage in this patient group.

TEMPT statistically outperformed 1995 updated TRISS, RTS, and GCS in the less severely injured patient group. While differences in performance with the most recent version of TRISS did not achieve statistical significance, TRISS had a low AUC and wide CI raising concern about precision, accuracy, and overfitting. Simulation in a larger population through the use of bootstrapping further supports these conclusions and suggests the score would be beneficial within a larger generalised trauma population. Although bootstrapping enhances confidence in the results, it is important to acknowledge that the derivation and validation groups were derived from a population from a single center. The trauma population this sample was drawn from is similar to those previously studied in multicenter studies with our cohort having similar ages, percentage of males, race and blunt mechanism prevalence. The patients in the current study are slightly less injured compared with these studies, which reflect a selection bias in the comparison studies as these amendments do indeed detract from TEMPT’s predictive ability, we argue the added simplicity provides a considerable advantage for adoption within the hospital. Further, we surmise these statistically derived cut-offs themselves pose exciting implications for the current state of injury assessment.

In conclusion, this study provides a novel, prospectively derived, AIS-independent trauma mortality prediction score that can be used on ED presentation and improves detection of poor outcome in mildly injured patients. Further validation is needed in a larger patient cohort, but TEMPT may provide an alternate assessment tool that is more reflective of current resuscitation practices and better aligns with precision medicine goals.

**Table 6 Performance of the Trauma Early Mortality Prediction Tool compared with previously published scores**

| Model                                             | Mild to moderately injured (n=157) | Severe injured (n=148) |
|---------------------------------------------------|-----------------------------------|------------------------|
|                                                   | Area under the curve | 95% CI | 95% CI* | P value | Area under the curve | 95% CI | 95% CI* | P value |
| Trauma Early Mortality Prediction Tool            | 1.00                 | 0.99 to 1.00 | 0.99 to 1.00 | 0.84 | 0.82 to 0.93 | 0.76 to 0.90 |
| Trauma Injury Severity Score (2009)              | 0.69                 | 0.22 to 1.00 | 0.38 to 0.95 | 0.20 | 0.83 | 0.75 to 0.90 |
| Trauma Injury Severity Score (1995)              | 0.78                 | 0.59 to 0.97 | 0.63 to 0.90 | 0.02 | 0.89 | 0.83 to 0.94 |
| Revised Trauma Score                             | 0.71                 | 0.77 to 0.89 | 0.62 to 0.78 | <0.001 | 0.80 | 0.77 to 0.89 |
| Glasgow Coma Scale                                | 0.72                 | 0.78 to 0.89 | 0.63 to 0.79 | <0.001 | 0.83 | 0.78 to 0.89 |
| Injury Severity Score                             | 0.69                 | 0.79 to 0.90 | 0.51 to 0.87 | 0.03 | 0.68 | 0.79 to 0.90 |

*Bootstrap result.

**CONCLUSION**

In conclusion, this study provides a novel, prospectively derived, AIS-independent trauma mortality prediction score that can be used on ED presentation and improves detection of poor outcome in mildly injured patients. Further validation is needed in a larger patient cohort, but TEMPT may provide an alternate assessment tool that is more reflective of current resuscitation practices and better aligns with precision medicine goals.

**Contributors**  
Literature search, data analysis and writing: RCK and RAC. Study design: RCK, MIC and RAC. Data collection and data interpretation: Lzk, MIC, RCK and RAC. Critical revision: Lzk, MIC and RAC.

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