Abstract:

Introduction: Recognizing the use of uncross-matched packed red blood cells (UnXRBC) or predicting need for massive transfusion (MT) in injured patients with hemorrhagic shock can be challenging. A validated predictive model could accelerate decision making regarding transfusion.

Methods: Three transfusion outcomes were evaluated in adult trauma patients admitted to a level one trauma center over a four-year period (2009-2012): use of UnXRBC, use of >4 units of packed red blood cells (PRBC) within 4 hours (MT1) and use of >=10 units of PRBC within 24 hours (MT2). Vital Signs (VS) features including heart rate (HR), systolic blood pressure (SBP), and shock index (SI=HR/SBP) were calculated for 5, 10 and 15 minutes after admission. Five models were then constructed. Model 1 used preadmission VS, Model 2 used admission VS, Models 3, 4 and 5 used continuous VS features after admission over 5, 10 and 15 minutes, respectively to predict use of UnXRBC, MT1 and MT2. Models were evaluated for their predictive performance via area under the receiver operating characteristic curve (AUROC), positive predictive value (PPV), and negative predictive value (NPV).

Results: Ten thousand six hundred and thirty six patients with over 5 million continuous VS data points during the first 15 minutes after admission were analyzed. Model using preadmission and admission VS had similar ability to predict UnXRBC, MT1 or MT2. Compared to these two models, predictive ability was significantly improved as duration of VS monitoring increased. Continuous VS for 5 minute had an ROC of 0.83 with confidence interval (CI) of 0.83-0.84, ROC of 0.85 (CI 0.84-0.86) and ROC of 0.86 (CI 0.85-0.88) to predict UnXRBC, MT1 and MT2, respectively. Similarly, continuous VS for 10 minutes had an ROC of 0.86 (CI 0.85-0.86),

0.87 (CI 0.86-0.88) and 0.88 (CI 0.87-0.90) to predict UnXRBC, MT1 and MT2, respectively. Continuous VS for 15 minutes achieved highest ROC of 0.87 (CI 0.87-0.88), 0.89 (CI 0.88-0.90) and 0.91 (CI 0.91-0.92) to predict UnXRBC, MT1 and MT2, respectively.

Conclusion: Models using continuous VS collected after admission improve prediction for the use of UnXRBC or MT in patients with hemorrhagic shock. Decision models derived from automated continuous VS in comparison to single prehospital and admission VS identifies the use of emergency blood use and can direct earlier blood product administration, potentially saving lives.

Level of Evidence: Level III

Study type: Retrospective study

Key Words: Massive transfusion. Transfusion prediction. Noninvasive monitoring. Vital Signs. Trauma

Introduction

Hemorrhage as a result of injury is the most common cause of preventable death in both military and civilian setting (1). Out of the patients who survive to reach advanced care, half will die in the first 2 hours after admission (2). Despite the robust advances in trauma systems, mortality remains high in patients with trauma related hemorrhage. Given the high mortality of hemorrhagic shock after trauma, real time predictors are needed to discriminate those who require lifesaving interventions (LSI) such as blood transfusion.

To optimize triage or to plan early massive transfusion (MT), simple and fast scoring systems such as the Assessment of Blood Consumption (ABC) have been developed, which can be used in field during transportation and upon admission and have demonstrated good prediction performance (3). This scoring system has great advantage for field triage with limited vital signs (VS) monitor equipment. Clinicians can quickly calculate predictive scores using paper and pen for decision making. In most modern hospitals, VS are collected as high-quality, automated and continuous electronic data streams. The high fidelity data better preserve changes and trends of physiological conditions, compared with traditional manually documented VS. However, the high quality data is often underutilized due to the lack of prediction models built and verified in a large trauma population. Extending the one-time measurement to continuous monitoring and prediction may optimize decision making. Not all bleeding trauma patients present to the hospital with classic physical findings. Even if they do, they may be missed during the potentially chaotic initial stages of trauma resuscitation. The physical findings differ in various stages of shock and are often inaccurate until patients deteriorate to a state of decompensated shock (1, 4, 5). Therefore, it is necessary to create an automated decision support prediction using the rich data sources in hospital for early prediction of MT.

Invasive monitoring and laboratory testing is time consuming and can cause delays in treatment (1). Point of care testing measurements can vary considerably between different laboratory devices in their ability to detect patients in hemorrhagic shock, and finger stick capillary blood samples are susceptible to wide differences compared to traditional laboratory measurements (1, 6). Noninvasive predictors with the ability to rapidly and reliably identify patients with life-threatening hemorrhage are highly desirable during initial presentation to a trauma center (1).

We hypothesize that continuous noninvasive VS including heart rate (HR), systolic blood pressure (SBP) and shock index (SI= HR/SBP) in the first 15 minutes of admission can better predict blood transfusion compared to single VS (preadmission and admission). The aim of this study is to compare predictions of transfusion following trauma using non-invasive VS collected before and after trauma center admission to test this hypothesis.

Methods

Study setting and population

The study was conducted at the R Adams Cowley Shock Trauma Center (STC) at the University of Maryland Medical Center. STC admits more than 5,000 trauma patients annually directly from the scene of injury. Of these patients, 5–8 % will require transfusion, and 2–3 % MT. Most transfusions occur within the first few hours of admission and often are started by administration of uncross-matched universal donor group O blood on an emergency basis (7-9). The study was approved by expedited review of Institutional Review Boards (IRB) from the University Of Maryland School of Medicine.

Inclusion/Exclusion criteria

Direct STC trauma patient admissions by helicopter or ambulance to the Trauma Resuscitation Unit (TRU) during the time period 1/2009 to 12/2012 were analyzed. Patients admitted in active cardiac arrest or dying within 15 min of trauma center arrival or those patients with missing VS (HR and SBP) or below age of 18 years were excluded from the study (Figure 1). Missing data is a frequent problem in clinical data collection, especially in retrospective studies. In urgent, chaotic field or hospital environment, recording data is often given less

priority compared to LSI. Instable device connections during transportation or during resuscitative interventions increase the chance of missing data.

Data collection

Continuous VS data were collected via Bed Master software (Excel Medical Electronics, Jupiter, FL) in the 13-bay TRU from the networked patient monitors (GE-Marquette-Solar-7000/8000, GE Healthcare, Little Chalfont, United Kingdom) using two VS data collection servers and one centralized VS data repository server. Numeric monitored trend values of HR (beats per minute) were collected every 2 seconds (0.5 Hz). If arterial blood pressure monitoring was available trend values were collected every 2 seconds, if not intermittent values of noninvasive BP (mmHg) were used as surrogate. Signal measurement of preadmission VS (Pre-HR, Pre-SBP) and admission VS (Adm-HR, Adm-SBP) were obtained from trauma registry. The source of admission VS can be either from trauma registry or from the Bed Master. Since there is published data which used admission VS from the trauma registry to predict blood transfusion (10), we compared the proposed model to an existing model.

PRBC usage was validated by cross-validation with blood bank records tracking individual PRBC product unit types and time of release from the blood bank. PRBC use was partitioned into post admission cohorts of uncrossed-matched (UnXRBC), massive transfusion category 1 (MT1) defined as more than 4 unit in 4 hours and massive transfusion category 2 (MT2) defined as more than or equal to 10 unit in 24 hours. Patient demographics (age, gender), admission status (injury type, mechanism of injury) and outcomes (in hospital mortality) were obtained from trauma registry. In the state of Maryland, blood transfusion is not permitted during transportation and hence patients only receive blood after admission. At our institution, the

decision to transfuse a patient following trauma admission is taken by board certified critical care faculty and fellows. Positive focused assessment with sonography in trauma (FAST) exam, external signs of bleeding, physical exam findings, reports of excess blood loss at scene or during transportation, positive signs and symptoms of shock, operative and radiology findings and trending physiologic and laboratory values are taken into consideration when making a decision for blood transfusion.

VS Data processing and analysis

VS were analyzed and transfusion prediction models were developed at five clinical time frames: preadmission, admission, 5, 10 and 15 minutes after admission. The last three time frames were selected based on the need for early prediction and transfusion. The 15 minute time frame model was selected as this is optimal to assess the adequacy of the ongoing resuscitation initiated during transport or within minutes of admission. Data was pre-processed to remove extreme values (HR>250 bpm and SBP>300 mmHg). The VS features extracted from HR, SBP and SI included: mean, standard deviation (SD), median, dose of VS above and below thresholds, first, second and third quartiles. The VS features were used to quantify the shape of the distribution of VS values in 5, 10, and 15 minutes of observation. To capture the episodes of abnormal VS, the dose (area above or below certain critical thresholds) of VS and percentage of dose were also calculated. The thresholds used were HR>=120 bpm, SBP<=90 mmHg, and SI>=1.0.

Two sample t-tests were used to examine the mean difference of VS at each time frame between the two groups that had or had not received UnXRBC, MT1 or MT2. The purpose of this test is two-folded. First, it could reveal some contrasting patterns between the two groups.

Second, it may provide initial evidence that the VS features can separate or predict the transfusion outcomes.

Stepwise logistic regression model was used to learn the association between the outcomes (use of blood) and VS features. To investigate the performance of VS features of various durations in predicting the use of blood products, five multivariate logistic regression models were created, composed of the following VS features: pre-hospital values, admission values, continuous observation of VS for 5, 10, and 15 minutes duration (Table 1). Patients with missing manually captured VS (HR, SBP, SI) were excluded from the study. For the post admission continuous VS, patients who lacked VS for more than two thirds of the study time duration were also excluded (Figure 1).

To avoid over-fitting, stepwise feature selection was used to build parsimonious models. The Wald Chi-square test was used to determine whether a variable should be included (forward step; p-value<0.05) or excluded (backward step; p-value>0.01). In the models that use prehospital or admission VS, the features were the actual measurement. In the models that use continuous VS, the raw measurements were transformed into single values via the summary statistics to simplify the models (Table 1). Furthermore, 10-fold cross-validation repeated 10 times with stratified sampling was used to verify the trained models' prediction performance on new data (11). Area under the receiver operating characteristic curve (AUROC) was used as a performance metric. Sensitivity and specificity were calculated from the optimal threshold determined by the Youden index. Delong's method was used to evaluate and compare the AUROC results for the five models with $p<0.05$ considered to be statistically significant (25).

AUROCs and their confidence intervals (CI) are reported for the testing sets which are a more accurate reflection of new patient performance than those of the training data sets.

All statistical analysis, predictive model learning, and evaluation were implemented with R software version 3.1.1 (R Development Core Team, Vienna, Austria). Stepwise logistic regression used SAS 9.3 PROC LOGISTIC (SAS Institute Inc., Cary, NC).

Results

Of the 18,285 trauma patients admitted in 4 years, 10,636 patients met inclusion criteria (Figure 1). Patients were predominantly male (68%) with mean age of 42.9 ±19 years. 23% had Injury Severity Score (ISS) >=15. Among all patients 7.6 % received blood transfusion out of which 4.1%, 2.2% and 1.3% received UnXRBC, MT1 and MT2 respectively. While the mortality for the cohort is 2.4%, the mortality in UnXRBC/MT1/MT2/any transfusion groups is 23.6%, 33.9%, 40.9%, 29.59% respectively (Table 2). The injury-to-admission time was an average of 1 hour. Table 2 summarizes the characteristics of the analyzed patients.

Patient demographics in groups who did or did not receive blood transfusion exhibit different patterns. The 1st, 2nd, and 3rd quartiles of ISS score, incidence of penetrating injury type and incidence of motor vehicle associated injury were higher in patients who received UnXRBC, MT1 and MT2 compared to patients who were not transfused, $p < 0.0001$ (Table 3).

The difference in SBP (mmHg), HR (beats per minute) and SI across the five time frames (preadmission, admission, 5, 10, 15 minutes continuous VS) were compared between the three transfusion groups. To better characterize those patients who received blood transfusions and those who did not, patients who received UnXRBC, MT1 and MT2 had higher HR, lower SBP,

and higher SI compared to patients who were not transfused as depicted in Figure 2. The difference in the mean VS between patients who received blood transfusion (UnXRBC, MT1 and MT2) and those who did not was calculated at each time frame using two-sample t-tests. All pairs were found to be statistically significant (p-values < 0.0001) with assumption of different variance between groups.

For all five models built on VS features measured at each time frame, the AUROC in prediction of blood transfusion improves for the three outcome measures of interest; UnXRBC, MT1 and MT2, respectively. The model that uses single point measurement of admission VS did not significantly improve in comparison to the model using preadmission VS for predicting UnXRBC (ROC 0.80, CI 0.79-0.80 vs ROC 0.77, CI 0.76-0.78), MT1 (ROC 0.82, CI 0.81-0.83 vs ROC 0.81, CI 0.80-0.81) or MT2 (ROC 0.85, CI 0.83-0.86 vs ROC 0.82, CI 0.81-0.84). For predicting UnXRBC transfusion, continuous VS for 5 minutes model has better predictive value (ROC=0.83, CI 0.83-0.84) than preadmission VS and admission VS (ROC 0.76 and 0.78). Continuous VS for 10 minutes model has significantly improved predictive value (ROC of 0.85, CI 0.85-0.86) over preadmission, admission and continuous VS for 5 minutes models. Continuous VS for 15 minutes model has the best predictive value, compared to the rest of the models with ROC of 0.87 (CI 0.87-0.88). Similar pattern is appreciated for predicting MT1 by continuous VS for 15 minutes model which achieves ROC of 0.89 (CI 0.88-0.90). For predicting MT2 the ROC for continuous VS for 15 minutes model is 0.91(CI 0.91-0.92) and continuous VS for 10 minutes model is 0.88 (CI 0.87-0.90) which are statistically significantly better when compared to models using preadmission, admission and continuous VS for 5 minutes. Continuous VS for 15 minutes model has the greatest predictive value for all transfusion groups, with ROC of 0.87, 0.89 and 0.91 for the UnxRBC, MT1 and MT2 respectively (Table 4).

Supplemental Digital Content (SDC) 1-3 outlines the ROC comparison of all the models and their p values in predicting each transfusion outcome. The sensitivity, specificity, CI, positive predictive value (PPV) and negative predictive value (NPV) of the prediction models is depicted in Table 4. The NPV of all the five models (preadmission, admission, 5 minutes, 10 minutes, and 15 minutes continuous VS) is between 0.98-0.99 for the three transfusion outcomes (UnXRBC, MT1 and MT2). Continuous VS for 15 minutes model has the greatest PPV for all transfusion groups, with PPV of 0.21, 0.15 and 0.11 for the UnxRBC, MT1 and MT2 respectively (Table 4).

Discussion

Model as rapid and noninvasive predictor of blood transfusion

Automated continuous analysis of VS features collected for 15 minutes after hospital admission without additional user input can predict the use of UnXRBC and the use of MT early during resuscitation better than the current best predictors that use preadmission single point SI or HR alone (12). At present, SI is often used as baseline VS in emergency transfusion decision making (12-15). SI based on field VS has been shown to be correlated with transfusion, where SI of 0.9 to1.1 had a 1.5-fold increased risk (RR, 1.61; 95% CI, 1.13–2.31) for transfusion of greater than 10 U of red blood cells in 24 hours, the traditional definition of MT (16).

Predicting the need for massive transfusion in trauma patients is not a novel concept. The strengths and limitations of the multiple MT scoring systems have recently been reviewed by Shackelford et al (2). Beekley et al used tissue oxygen saturation (StO2), international normalized ratio (INR) and Hemoglobin (Hg) to predict MT with AUROC of 0.91 (27).

Vandromme et al in 2010 studied the comparison between blood lactate levels obtained in the ED upon admission versus preadmission and admission SBP in predicting six or more units of PRBC within 24 hours of injury and demonstrated that serum lactate level was a better predictor of transfusion, as defined above, than VS (AUROC value 0.74 vs 0.6) (2). The Trauma-Associated Severe Hemorrhage (TASH) scoring system utilizes base excess (BE) and FAST exam in addition to other variables and the Traumatic Bleeding Severity Score (TBBS), by using ultrasound, pelvic radiograph and lactate level, can predict ongoing hemorrhage and transfusion after severe trauma with AROC of 0.91 and 0.98 respectively (1, 17, 18). These scoring systems require radiologic tools such as plain radiographs and computed tomography (CT) scan, and laboratory analyses such as hemoglobin, base excess, INR, and lactate, or non-standard monitors such as StO2 to make these predictions regarding hemorrhage and need for blood transfusion (12). These variables require some amount of time and resources to obtain making them unavailable in the immediate period after admission. Additionally, they may not be available in most prehospital care or austere military environments. Our prediction model using 15-minute continuous VS data, which had an AUROC of 0.87 (CI 0.87-0.88) and PPV of 0.21 for prediction of uncrossed-matched transfusion and AUROC of 0.91 (CI 0.91-0.92) and PPV of 0.11 for MT uses automatically-collected and processed HR, SBP and SI derived from conventional VS monitors without any user input, laboratory testing or imaging. In addition, it has the advantage of rapid prediction within 5- 15 minutes of admission.

Nunez et al. and Cotton et al. developed the ABC score to predict MT. It involves four simple yes/no assessments available upon trauma center admission: penetrating mechanism of injury, SBP of 90 mm Hg or less, HR of 120 beats per minute or greater, and positive FAST findings. The predictive ability of this simple score has an AUROC between 0.83 and 0.90 (18)

and a PPV of 0.55 (3, 19, 20). In the case of an equivocal FAST exam, inexperienced user or inter personnel variability objective VS trends can assist in decision making. In tertiary care trauma hospital, the proposed model can supplement other predictors and in regions with limited resources the model can replace other predictors.

Significance of continuous automated monitoring, big data approach

The resuscitation period is a notoriously difficult one to make assessments of clinical performance because the need for emergency treatment clearly takes priority over the requirement for documentation (21). In a study of 177 patients by Hu et al significant differences were observed between the highest and lowest HR, SBP, and pulse oximeter from the vital signs data recorder (VSDR) and the manually recorded trauma registry data ($p< 0.001$). If applied to the pre-hospital environment, real-time continuous VS monitoring and data acquisition can identify dynamic prehospital changes, which may be missed compared with VS recorded manually (22).

The traditional scoring systems for prediction of blood transfusion use limited vital sign features and have an advantage of easy calculation. With the prolific advances in medical sensor technology, the volume of real time physiological patient data has exponentially increased. However, it is a challenge to collect and interpret data from multiple sources and formats. Using small sized noninvasive data sensors and reliable collection techniques, fractional information from heterogeneous data sources can be assembled in a real time fashion and applied for clinical care (23). The proposed blood transfusion prediction model which used about 5 million VS data points, promotes the idea of automated monitoring and automated prediction, as part of future autonomous resuscitation.

Model as triage and decision assist predictor of blood transfusion

In a recent meta-analysis of US trauma centers, average time from injury to presentation in the hospital were in excess of 30 minutes for road ambulances and over 60 minutes for helicopter transports (24). This time encompasses the "golden hour" of trauma resuscitation during which standard physical examination, expert opinion and point of care testing may not be available (13, 22). In the state of Maryland the emergency medical services (EMS) protocol allows the use of only crystalloids as bolus or maintenance therapy for resuscitation during transport. Whole blood or blood products are not carried on the helicopters or ground EMS (17) and FAST is not performed. Although the current study was focused on VS obtained immediately upon admission, this methodology can be easily applied to the prehospital environment. VS prediction models can help first responders to triage injured patients, initiate appropriate resuscitation to maintain physiologic stability until arrival at definitive care, alert the receiving trauma center regarding the critical nature of the patient and thereby help allocate resources, including blood products (12). New studies are in effect at University of Maryland to validate the model in the prehospital setting.

Recent studies recommended that quality improvement measures and computer modelling-based decision-support could reduce errors of LSI commission and omission found during resuscitation at major trauma centers and enhance decision-making in austere trauma settings by less well-trained providers (26). Equipping the prehospital personnel with an objective assessment tool will empower decisions to identify and start resuscitative measures to manage hemorrhagic shock in the critical first minutes to hours after injury.

Given the high negative predictive value, proposed blood transfusion prediction models may help identify low risk populations in the prehospital setting and avoid over triage. This could reduce the burden of admissions to level 1 trauma centers, the implications of which will be significant in times of military conflicts, mass casualties, or in other settings of limited resources.

Medical errors, especially during the initial minutes of patient reception and resuscitation occur because of time pressure, varying levels of experience, reliance on memory, multitasking, and failures in trauma team coordination (21). Human variables that confound a standardized environment and lead to avoidable errors have been addressed by industries using immediate feedback by computer prompts. Implementation of such support is deficient in medical practice. A randomized, controlled interventional study that evaluated the effect of real-time, computer-prompted, evidence-based decision and action algorithms on error occurrence during initial resuscitation showed that a critical decision was required every 72 seconds, and error-free resuscitations increased from 16.0% to 21.8% ($p = 0.049$) during the first 30 minutes of resuscitation. Morbidity from shock management ($p = 0.03$), blood use $p < 0.001$), and aspiration pneumonia ($p = 0.046$) were also decreased with the use of computer-prompted evidence-based decision and action algorithms (21). The advocated study models using continuous automated VS can easily be incorporated into computer modelling-based decision-support tools to decrease the number of avoidable blood transfusion and medical errors.

Early versus accurate prediction

Patients with overt signs of bleeding and those in cardiac arrest after injury will be emergently transfused based on clinical judgement alone. In such scenarios clinical judgement

surpasses all predictors. Patients who present in compensated shock, with masked internal bleeding, atypical physical exam and polytrauma patients are in the grey zone and could benefit from transfusion predictors. Although trained trauma surgeons can trigger lifesaving interventions within 5 minutes, not all physicians who intermittently care for a trauma patient in rural or community hospitals have the exposure and training to do so. Fifteen minutes timeframe is a fine balance between early prediction and time to assess ongoing resuscitation. Taking into consideration adverse effects of unnecessary blood transfusion, a model that can rapidly yet accurately predict transfusion is preferred. Although early prediction within 5 minutes with the least amount of data would be ideal, the study results support 15 minutes time frame as it has better predictive power. The 15 minutes VS data predicted UnXRBC and PRBC use in 4 hours and 24 hours post admission. Compared to this long prediction horizon, 15-minute is a relatively short time period and can still be useful. Even during the 15-minute measurement, all necessary interventions can continue. Also, prediction based on continuous monitoring can quickly discover a developing situation and may facilitate change of clinical decisions. Therefore, it is necessary to build models that use continuous measured data for automated decision support.

Limitations

This study is limited by a number of factors. First, this is a single institution study therefore the patient demographics, injury pattern, and transfusion practices may not be entirely generalizable to other populations. Additionally, only 23% of the patient population had injury severity score >= 15 leading to very low PPV. Non-invasive blood pressure (NIBP) which is typically utilized in the field and first minutes of resuscitation is intermittent and prone to great variability due to the size of the cuff, device employed, and frequency of cycling. Because the

study is retrospective, each model did not predict the need for blood transfusion but instead predict use of transfusion following trauma. Also, all or any of the resuscitative efforts can affect the VS trends leading to competing risk and intervention bias. In addition, due to the limitation of regression model, significant quantities of missing values render the current models inaccurate or unreliable. During rapid resuscitative period or during travel of the patient without monitoring to the operating room or imaging suites, stable and high quality VS recording still remains a challenge. Therefore, future models should consider other algorithms that are more tolerant to missing values, such as decision trees, or Bayesian models. In addition, this study has all the limitations of a retrospective observational study in which interventions were already performed without any reflection on the reasoning leading to the intervention. Since the decision to transfuse was made by trained trauma surgeons at our institution we have not challenged the use of the blood products. Models and the feature selection were calibrated for specific blood transfusion outcome. Blood products are not administered during transportation in state of Maryland and hence patient receives blood only after admission. Since blood bank data are reliable the study was focused on transfusion outcome. Models to predict other intervention like intravenous fluid (IVF) usage were not examined. The timing and amount of IVF resuscitation en route is not well documented in the trauma registry making a retrospective analysis difficult.

Conclusion

Despite the limitations, the study has high statistical power, narrow confidence intervals and significance in predicting transfusion based on noninvasive continuous VS monitoring. In the cohort studied, continuous vital signs collected at 2 second intervals for 15 minutes by noninvasive vital sign devices can rapidly and accurately predict the use of blood transfusion in

trauma patients without user input. The performance of the model could support triage and resuscitation decisions by prehospital providers and the trauma team as well as blood bank preparations upon arrival to the hospital.

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Author Contribution:

N. P., C.F.M., P.F.H and S.Y. performed the data analysis, data interpretation and literature search. P.F.H., C.F.M, D.M.S. and S.Y were involved in study design and critical revision of the manuscript. S.Y. performed the statistical analysis. N.P. wrote the manuscript. S.T.B, T.M.S. and D.M.S. supervised the project and provided invaluable clinical support.

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Figure 1. Flow diagram for patient enrollment and analysis. (* Models require atleast one third of vital signs observation)

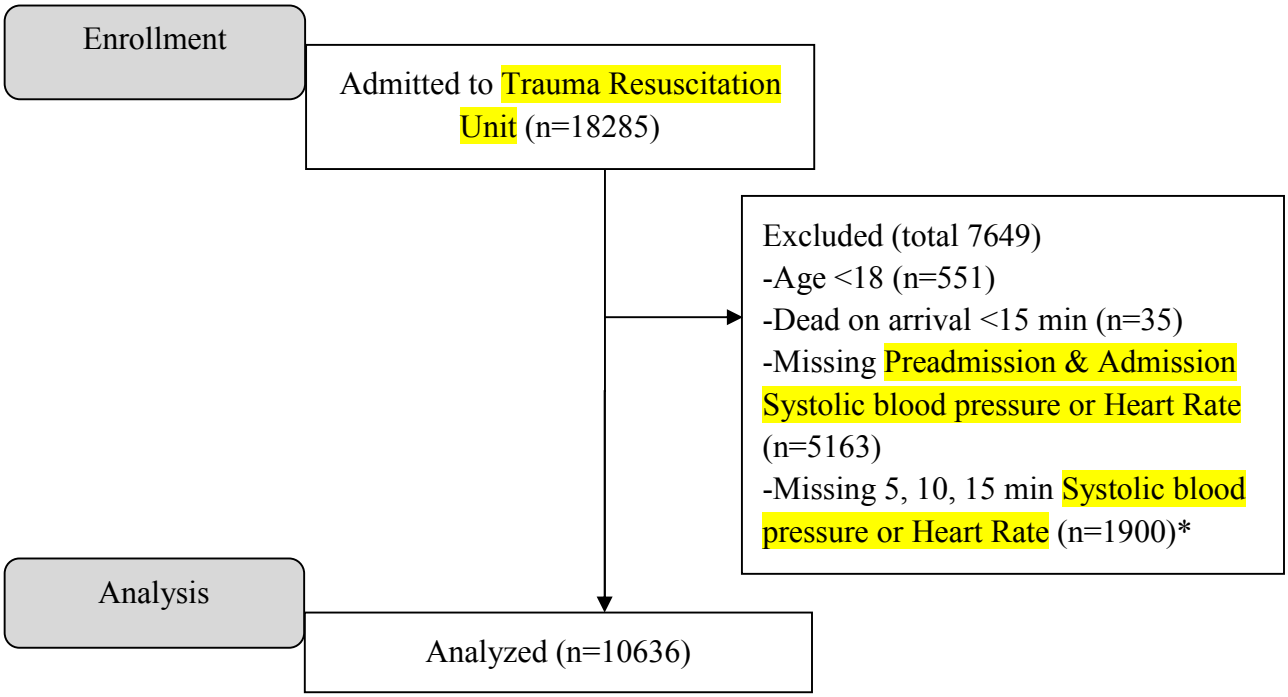

Figure 2. Line graph illustration of mean and standard deviation of heart rate (beats per minute), systolic blood pressure (mmHg), and shock index differences between negative (blue) and positive (red) groups for uncross-matched packed red blood cells (UnXRBC) , massive transfusion (MT) category 1 and 2 at time frames of preadmission, admission, 5, 10, and 15 minutes. Differences in the mean VS between positive and negative groups for UnXRBC, MT1 and MT2 are statistically significant (p-values < 0.0001)

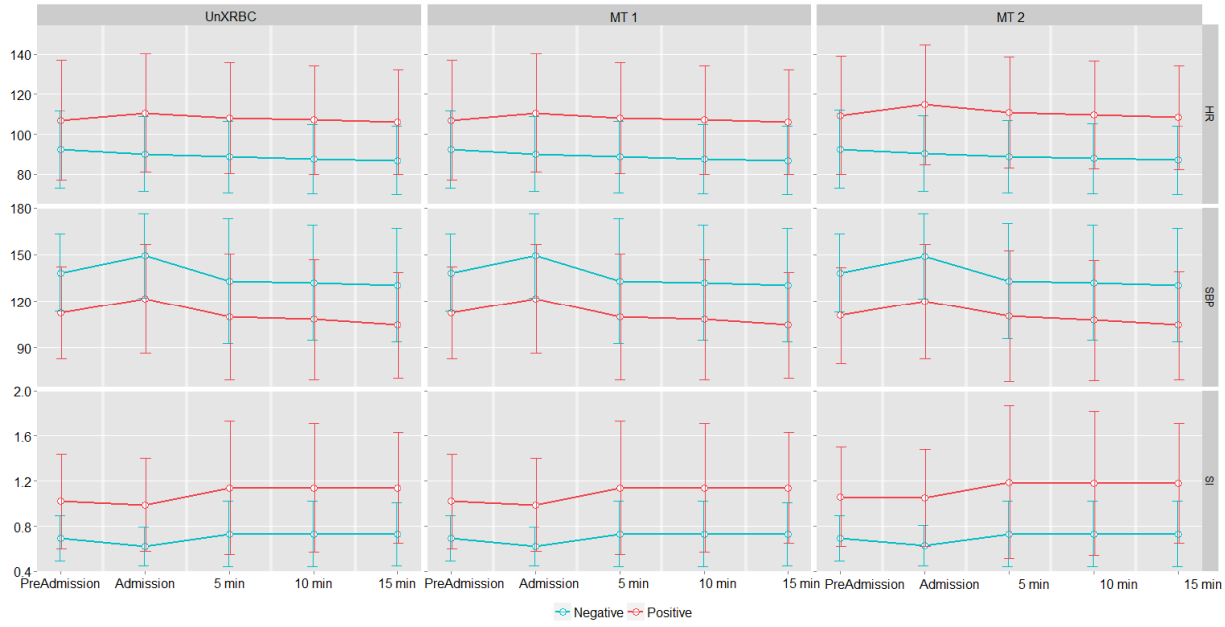

Table 1: Model definition and vital signs data requirement

Model	Name	Features
Model 1	Preadmission	Prehospital Heart rate (HR), Systolic blood pressure (SBP) and Shock index (SI)
Model 2	Admission	Admission Heart rate, Systolic blood pressure and Shock index
Model 3	5-min	Continuous VS (Heart rate, Systolic blood pressure and Shock index) for 5 minutes. Features include mean, SD, quartiles, dose, % dose, for HR>=120, SBP <=90, SI >=1
Model 4	10-min	Continuous VS (Heart rate, Systolic blood pressure and Shock index) for 10 minutes. Features include mean, SD, quartiles, dose, % dose, for HR>=120, SBP <=90, SI >=1
Model 5	15-min	Continuous VS (Heart rate, Systolic blood pressure and Shock index) for 15 minutes. Features include mean, SD, quartiles, dose, % dose, for HR>=120, SBP <=90, SI >=1

Table 2. Characteristics of analyzed patients and mortality rates in the Uncross-matched packed red blood cells (UnXRBC), Massive transfusion (MT) 1 and MT 2 groups.

Characteristic	Analyzed
Total cases	10636
Mean age, yr (SD)	42.9 (19.3)
ISS Score, n (%)	
ISS >=15	2447 (23.0)
ISS <15	7836 (73.7)
ISS not available	353 (3.3)
Sex, n (%)	
Male	7254 (68.2)
Female	3382 (31.8)
Injury type, n (%)	
Blunt	9352 (87.9)
Penetrating	1062 (10.0)
Other	222 (2.1)
Mechanism of injury, n (%)	
Motor vehicle associated	5307 (49.9)
Falls	2770 (26.0)
Interpersonal violence	1158 (10.9)
Other	1397 (13.1)
Undocumented	4 (0.04)
Outcome, n (%)	
UnXRBC	433 (4.1)
MT1	236 (2.2)
MT2	142 (1.3)
Mortality, n (%)	259 (2.4)
Mortality in transfused group	
UnXRBC	103 (23.6)
MT1	79 (33.9)
MT2	59 (40.9)
Any transfusion	114 (29.59)

Table 3. Demographic comparison of groups by Uncross-matched packed red blood cells (UnXRBC), Massive transfusion (MT) category 1 and 2.

Characteristic	UnXRBC		MT1		MT2	
	No	Yes	No	Yes	No	Yes
N (%)	10193(95.9)	433 (4.1)	10400(97.8)	236 (2.2)	10494(98.7)	142 (1.3)
Injury severity score (1^{st},2^{nd},3^{rd} quartile)	4, 5, 14	17, 29, 41	4, 5, 14	25, 34, 45	4, 5, 14	26, 35, 49
Injury type, n (%)						
Blunt	9042 (88.6)	310 (71.6)	9183 (88.3)	169 (71.6)	9247 (88.1)	105 (73.9)
Penetrating	947 (9.3)	115 (26.6)	1000 (9.6)	62 (26.3)	1028 (9.8)	34 (23.9)
Other	214 (2.1)	8 (1.9)	217 (2.1)	5 (2.1)	219 (2.1)	3 (2.1)
Mechanism of injury, n (%)						
Motor vehicle	5053 (49.5)	254 (58.7)	5160 (49.6)	147 (62.3)	5210 (49.7)	97 (68.3)
Falls	2730 (26.8)	40 (9.2)	2757 (26.5)	13 (5.5)	2767 (26.4)	3 (2.1)
Interpersonal violence	1059 (10.4)	99 (22.9)	1107 (10.6)	51 (21.6)	1128 (10.8)	30 (21.1)
Other	1357 (13.3)	40 (9.2)	1372 (13.2)	25 (10.6)	1385 (13.2)	12 (8.5)
Undocumented	4 (0.04)	0 (0.0)	4 (0.04)	0 (0.0)	4 (0.04)	0 (0.0)

Table 4. Receiver operating characteristic curve (ROC), 95% CI, Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) for Models 1-5 ; preadmission vital signs (VS), admission VS, 5 min , 10 min, 15 min continuous VS respectively .

Outcomes	Model	ROC	95% CI	Sensitivity	Specificity	PPV	NPV
Uncross-matched packed red blood cells (UnXRBC)	Preadmission VS	0.77	0.76-0.78	0.68	0.82	0.14	0.98
	Admission VS	0.80	0.79-0.80	0.67	0.86	0.19	0.98
	5-min VS	0.83	0.83-0.84	0.73	0.85	0.18	0.99
	10-min VS	0.86	0.85-0.86	0.76	0.86	0.21	0.99
	15-min VS	0.87	0.87-0.88	0.79	0.85	0.21	0.99
Massive transfusion1	Preadmission VS	0.81	0.80-0.81	0.72	0.84	0.10	0.99
	Admission VS	0.82	0.81-0.83	0.71	0.87	0.13	0.99
	5-min VS	0.85	0.84-0.86	0.78	0.85	0.12	0.99
	10-min VS	0.87	0.86-0.88	0.80	0.87	0.14	0.99
	15-min VS	0.89	0.88-0.90	0.82	0.87	0.15	0.99
Massive transfusion2	Preadmission VS	0.82	0.81-0.84	0.77	0.83	0.07	0.99
	Admission VS	0.85	0.83-0.86	0.77	0.87	0.10	0.99
	5-min VS	0.86	0.85-0.88	0.83	0.85	0.08	0.99
	10 min VS	0.88	0.87-0.90	0.83	0.88	0.10	0.99
	15-min VS	0.91	0.91-0.92	0.87	0.89	0.11	0.99

CI = confidence interval; ROC = receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value.

SCD 1. p values for ROC comparison of models 1-5 in predicting uncross-matched packed red blood cells

	Admission VS	5-min VS	10-min VS	15-min VS
Preadmission VS	0.0900	1.69E-05	4.49E-10	1.35E-14
Admission VS		1.18E-07	1.75E-12	6.12E-15
5-min VS			6.12E-05	9.30E-08
10-min VS				0.0005

VS, vital signs

SDC 2. p values for receiver operating characteristic curve (ROC) comparison of models 1-5 in predicting massive transfusion 1

	Admission VS	5-min VS	10-min VS	15-min VS
Preadmission VS	0.3743	0.0108	6.86E-05	5.82E-07
Admission VS		0.0004	5.42E-08	1.87E-09
5-min VS			0.0023	0.0001
10-min VS				0.0224

VS, vital signs

SDC 3. p values for receiver operating characteristic curve (ROC) comparison of models 1-5 in predicting massive transfusion 2

	Admission VS	5-min VS	10-min VS	15-min VS
Preadmission VS	0.3567	0.0540	0.0017	3.35E-06
Admission VS		0.0224	2.45E-05	2.74E-06
5-min VS			0.0052	5.68E-05
10-min VS				0.0042

VS, vital signs