AFRL-RH-WP-TR-2021-0086

ADVANCED NOTIFICATION TO TRAUMA CENTER OF BLOOD PRODUCT NEEDS TO IMPROVE PATIENT OUTCOMES (ONPOINT 3)

Peter Hu
Shiming Yang

University of Maryland Baltimore

Catriona Miller
711 HPW/RHBA

AUGUST 2021
Final Report

Distribution Statement A: Approved for public release.

See additional restrictions described on inside pages

AIR FORCE RESEARCH LABORATORY
711TH HUMAN PERFORMANCE WING,
AIRMAN SYSTEMS DIRECTORATE,
WRIGHT-PATTERSON AIR FORCE BASE, OH 45433
AIR FORCE MATERIEL COMMAND
UNITED STATES AIR FORCE

NOTICE AND SIGNATURE PAGE

This report was cleared for public release by the Air Force Research Laboratory Public Affairs Office and is available to the general public, including foreign nationals. Copies may be obtained from the Defense Technical Information Center (DTIC) (http://www.dtic.mil).

AFRL-RH-WP-TR-2021-0086 HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

BURKE.ALICIA.N.1125850452
Digitally signed by BURKE.ALICIA.N.1125850452
Date: 2022.03.24 15:03:33 -04'00'

ALICIA BURKE
Program Manager
Product Development Branch
Airman Biosciences Division

BEDFORD.THERESA.A.1236006359
Digitally signed by BEDFORD.THERESA.A.1236006359
Date: 2022.03.24 15:12:41 -04'00'

THERESA A. BEDFORD, Maj, USAF, NC, FNP-BC
Nurse Scientist, En Route Care
Product Development Branch
Airman Biosciences Division

REPORT DOCUMENTATION PAGE	*Form Approved* *OMB No. 0704-0188*

1. REPORT DATE ***(DD-MM-YY)*** 08-10-21	**2. REPORT TYPE** Final	**3. DATES COVERED** ***(From - To)*** May 2017 – August 2021

4. TITLE AND SUBTITLE Advanced Notification to Trauma Center of Blood Product Needs to Improve Patient Outcomes (ONPOINT 3)	**5a. CONTRACT NUMBER** FA8650-17-2-6H09 **5b. GRANT NUMBER** **5c. PROGRAM ELEMENT NUMBER** 00000F
6. AUTHOR(S) Peter Hu, PhD, Shiming Yang, PhD, Catriona Miller, PhD	**5d. PROJECT NUMBER** 0000 **5e. TASK NUMBER** 00 **5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF MARYLAND BALTIMORE 220 ARCH ST RM 02148 BALTIMORE MD 21201-1531	**8. PERFORMING ORGANIZATION REPORT NUMBER**
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Air Force Materiel Command Air Force Research Laboratory 711th Human Performance Wing Airman Systems Directorate Airman Biosciences Division Product Development Branch Wright-Patterson AFB, OH 45433	**10. SPONSORING/MONITORING AGENCY ACRONYM(S)** 711 HPW/RHBA **11. SPONSORING/MONITORING AGENCY REPORT NUMBER(S)** AFRL-RH-WP-TR-2021-0086

12. DISTRIBUTION/AVAILABILITY STATEMENT

Distribution A. Approved for public release.

13. SUPPLEMENTARY NOTES

Report contains color. AFRL-2022-0106, cleared 14 February 2022

14. ABSTRACT

This project built predictive algorithms from pre-hospital physiological data and refined them. The algorithms have been compared with basic clinical rules, other scoring systems such as Shock Index (SI), Assessment of Blood Consumption (ABC) and Revised Trauma Score (RTS). The predictions derived from pre-hospital data are also compared with the corresponding TRU initial 15 minutes. Results show that pre-hospital data have predictive power for early decision-making support. Miniature devices for data acquisition and feature calculation have been tested and demonstrated to work.

15. SUBJECT TERMS

Pre-hospital, predictive algorithm, transfusion, helicopter

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT:**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** (Monitor)
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Alicia Burke
Unclassified	Unclassified	Unclassified	SAR	50	**19b. TELEPHONE NUMBER** *(Include Area Code)* N/A

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39-18

TABLE OF CONTENTS

LIST OF FIGURES

1.0 BACKGROUND:

1.1 Introduction

Following trauma, early recognition of hemorrhage could increase accuracy of field triage, expedite interventions to control bleeding and minimize death from exsanguination during the “golden hour” [1,2]. Even among those who reach care and survive at least 15 minutes, half are dead within 90 minutes of admission. [3] Objectives underlying the concept of the ‘golden hour of momentary pause in the act of death’ of simultaneous treatment and diagnosis, include early identification of patient triage acuity, resources needed and rapid transport to the most appropriate nearest treatment facility.

The clear association between the efficacy of early and appropriate blood product use and the efficacy of rapid, advanced-skills, emergency medical services (EMS) field evacuation has refocused research and tactical attention on these critical pre-hospital, handoff, and early trauma resuscitation unit (TRU) periods—including the possibility of carrying blood products on helicopters. [4,5] Much of the recent work of our R Adams Cowley Shock Trauma Center (STC) Shock Trauma and Anesthesiology Research (STAR) Center associated with the University of Maryland (UMD) Medical System (UMMS) and School of Medicine (UMDSOM) has centered on these issues. In particular, our work has focused on the ability of advanced computer software systems to analyze the vast amounts of continuous streams of digital vital signs (VS) data (heart rate - HR; blood pressure - BP; systolic - SBP; respiratory rate - RR; electrocardiogram - ECG; photoplethysmographic - PPG; and skin oxygenation - SpO2) collected electronically in real time from patients during TRU and intensive (ICU) care and to predict treatment outcomes. [6-10] Much of this work has used transfusion in the first hours of care as a critical outcome in itself and also as a surrogate for the need to use blood products and for high-level trauma team activation. Our direct access within a unified system to large and representative populations of trauma patients in pre-hospital and post-admission settings, and our pioneering experience in continuous patient data collection systems, again both pre- and in-hospital, positions us uniquely for this work. [11-14] We also have unique technical expertise in conception, development, testing, and general deployment of clinically relevant visual display systems now widely used at our trauma center and in active translation into deployable systems. [15] Both of these issues - epidemiologic and engineering - typically limit work in this area. [16]

Trauma transfusion is now mostly based on clinical experience, conventional VS parameters, and imperfect scoring systems, most of which require at least one in-hospital dataset and are derived from limited populations. [10] In contrast, our work has focused on signals for the need for blood support based on valid algorithms derived from the experience of large cohorts of trauma patients. We have used and/or tested commercially available software and hardware [9] and also developed prototype systems aimed toward inclusion in field-ready instrumentation. [6-8] Now, for the first time in the long association of the STC with the Maryland State Police (MSP) aeromedical evacuation system, we now have full access to the advanced continuous electronic physiologic data collection systems deployed on the MSP air-evac helicopters. Moving this analytic process and the technology development associated with it into the field via the MSP air-evac EMS is the core of the present proposal and allows us to approach two critical questions in modern trauma care: which patients are at risk of hemorrhagic death, and how early in the process of extraction, transport, handoff, and TRU care can that risk be reliably identified and appropriately addressed?

1.2 Military Relevance

Hemorrhage is the leading cause of death and most common cause of potentially preventable combat-related mortality. [11-14] Recent work has focused on moving the assessment and treatment of major bleeding as far forward as possible, [15-18] but satisfactory protocols for administering blood products in the field have lagged behind the logic and enthusiasm for carrying these products. A number of clinical scoring systems have been proposed, but none have proved optimal, mainly owing to complexity and/or the inclusion of at least one modality not available in the field.[10] Valid, robust, reliable, and easy to transport prehospital methods are urgently needed to support in-flight and early resuscitation-period clinical decision-making for these fragile and rapidly decompensating patients, including strategies for immediate intervention, triage, and mobilization of extraction, transport, and high-level care. Over a roughly two-year period 2014 – 2015, more than 20 knowledge and technical gaps in these areas were identified by USAF analysts alone. Accurate prediction of transfusion is an important outcome criterion in itself and a useful surrogate for need and for the likelihood of need for mobilization of other high-level resources. The demonstrated efficacy of rapid extraction and evacuation to high-level care and of hemostatic resuscitation once advanced care is reached suggests that focus on sophisticated physiologic data now available during aeromedical evacuation will be particularly useful in addressing many current military medical triage issues.

1.3 Previous Work

With the close collaboration and support of the USAF medical research wing, our group has established and accomplished many of the tasks of a research endeavor with the long-term goal of incorporating advanced machine-learning capabilities into robust, field-ready, portable and user-friendly instrumentation to support clinical decision-making in austere field conditions by combat medics (FA8650-11-2-6D01, FA8650-12-2-6D06, FA8650-12-2-6D08, FA8650-12-2-6D09, FA8650-13-2-6D11, and FA8650-13-2-6D15, among others.) This work has focused chiefly on analysis of the first hour of TRU care and the use of the huge streams of high-quality digital and wave-form VS data collected routinely by continuous automated electronic monitoring systems. In this work we have focused mainly on predicting patterns transfusion in these first minutes of care of the severely injured because of the importance of transfusion in modern trauma care, the quantity, accuracy, and availability of blood bank data, and what transfusion practice says about early mobilization of advanced-care resources. Our algorithms have been able to analyze in real-time any combination of continuous post-admission digital VS and PPG and/or ECG waveform data available to us to predict reliably and accurately of the need for transfusion in severely injured trauma patients. For a portion of the retrospective data that will be used in this study, we will take advantage of a study currently underway at our center with USAF funding and oversight (August 2016 – August 2017), “Validation of Automated Prediction of Blood Products, Critical Care, and Emergency Surgery Using Continuous Prehospital Non-Invasive Vital Signs (VS) Streams – ONPOINT 5” (USAF Agreement Order FA8650-16-2-6H07). ONPOINT 5 was designed to collect up to N=1000 continuous VS patient sets which are then picked up by study staff at the respective Trooper base. These data are linked with the first hour of each patient's STC-TRU, Trauma Registry, and Blood Bank data and analyzed retrospectively for transfusion prediction. In the present study, ONPOINT 3, the algorithms derived from the ONPOINT 5 data, will be refined. The novel aspect of this refinement step in the present study is its view toward the final stages of data collection and analysis, which will happen in real time.

2.0. METHODS:

2.1 Pre-hospital data collection

Helicopters have been used more and more in transporting patients from injury scenes to a trauma center. Transport by helicopter compared with ground services was associated with improved survival to hospital discharge after controlling for multiple known confounders. [19] During transportation, paramedics provide basic and necessary care for the patients and hand over the patients to the TRU / ED after arriving the hospital. The physiological data and treatment information collected in helicopters could provide early decision support.

The State of Maryland has 11 helicopters strategically placed at 7 locations. (Figure 1) They are all equipped with Propag® MD Series to collect pre-hospital VS. Continuous vital signs signals were collected at the scene and during helicopter transport of trauma patients directly to the STC. Vital signs data collected at the scene and in-flight from adult trauma patients were downloaded from patient physiological monitors (Propaq MD Series) during the period January 2016 to December 2017. Records of helicopter transportation details were obtained from the Maryland Institute for Emergency Medical Services Systems, including Emergency Medical Services dispatch time, scene helicopter arrival time, arrival (in STC) time, and unique helicopter number. The pre-hospital vital signs collected included PPG and ECG waveforms, heart rate (heart rate [HR] in beats per minute [bpm]), percutaneous oxygen saturation (SpO2 percent (%)), non-invasive cuff blood pressure (BP in millimeters of mercury [mmHg]), and respiratory rate (RR per minute).

Figure 1. Maryland State Aviation Command and locations of the helicopters

2.2 Physiological data acquisition and miniature device

To deploy predictive algorithms on board in the helicopters, it is important to get physiological data in realtime and process them in an efficient way. At the meantime, the processing unit should be compact and lightweighted, given the confined space in the helicopter. To achieve this goal, we test multiple types of devices. First, with Propaq API, we are able to get data in realtime using a mainstream desktop computer. (Figure 2) Next, we use a Raspberry Pi Model 4B to replace the desktop computer. The Raspberry Pi Model 4B has 4GM memory and quad-core CPU, which is a credit card size powerful computing unit. (Figure 3) To have better visual interaction with the users, we also test the Getac Mx50, a rugged Android tablet with 5.7” display screen. It has 4 GB memory and Intel Atom x5 processor, which are also enough to process realtime VS data. Figure 4 demonstrates a prototype design of getting VS data from Propaq and processing in a mobile device.

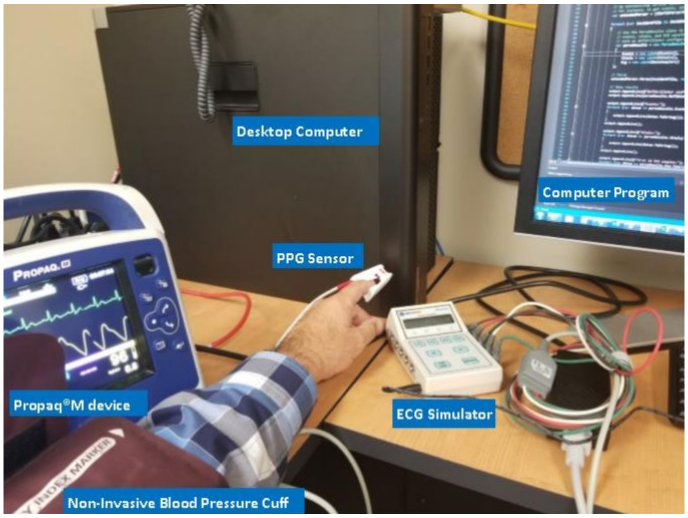


Figure 2. A demonstration of getting VS data from Propaq M device and process in a regular PC

Figure 3. A demonstration of processing VS data in a credit card size mini-computer

Figure 4. A demonstration of getting VS data from Propaq and processing in a mobile device

2.3 Data and processing methods

Patients were included if they met the following inclusion criteria: Direct trauma admission, age being greater than or equal to 18 years, and transported by Maryland State Police helicopters from the scene of injury to STC with continuous vital signs collected available for this study. Patients were excluded if they were trauma patients who died within 15 minutes of STC admission.

Demographic data, such as age, sex, mechanism and type of injury, Glasgow Coma Scale score (GCS), Injury Severity Score, and numbers of units of blood transfused hourly, were obtained from the Trauma Registry and were linked to each patient's helicopter physiologic data by matching helicopter number, arrival time at STC with Trauma Resuscitation Unit (TRU) bed reception number, vital signs data collection during on-going resuscitation and blood administration. Blood usage data included number of units of packed red blood cells (pRBCs) and time of transfusion were documented in comparison to blood bank and clinical records. We evaluated the ABC, SI and RTS scoring systems' transfusion and triage predictions compared to those of our BRI algorithm to identify trauma patients administered massive transfusion (MT), defined as ≥10 units pRBC [17] in first 24 hours and critical administration threshold (CAT), defined as ≥3 units pRBC in the first hour [20] after STC admission. The predictions for patient transfusion less than CAT and MT quantities of blood were not reported, as these were either captured within the definition of MT or were not considered life-threatening. Primary outcomes were AUROC's comparing ABC, SI, RTS and BRI for predicting CAT and MT.

During transportation or resuscitation, medical sensors could capture additional noise and motion artifacts. To make VS variables more explainable and robust, we designed a collection of data pre-processing steps. First, impossible extreme values were removed from VS, such as heart rate (HR) higher than 250 bpm, or respiratory rate higher than 100 breath per minute, etc. For waveforms, values outside the sensor measurement range were flagged as ‘not available’. Second, we observed that signal segments at the initial time may be unstable with some unexpected spikes or sudden drop from unrealistic high values. We removed abruptly changed values, if they are >30% of increase or decrease from their immediate predecessors. Figure 5 shows one example for VS before and after processing. For example, in the middle, raw RR values were plotted in dark color. Smoothed (processed) RR values were plotted in bright color.

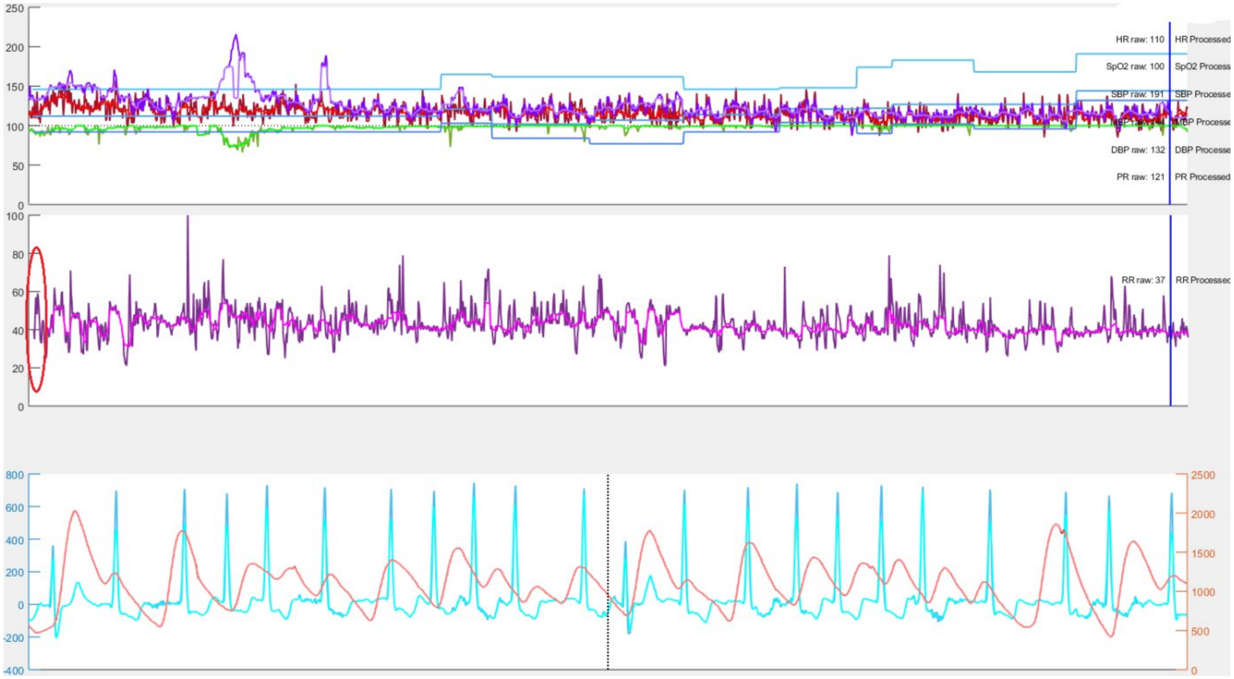


Figure 5. Example of VS signal before and after pre-processing

With pre-processed data, we not only visualized them and compared, but also checked the variables derived from them. We examined the feature variable values and see if they are correctly calculated. Figure 6 illustrates this step using the empirical distributions (blue blocks) of each variable from MBP. In addition, estimated density distributions of variables in the positive (red line) and negative (black line) outcomes are also overlayed to show if there is any difference between the two groups. This step helps us to visually examine the derived feature values, to prevent possible incorrect calculation.

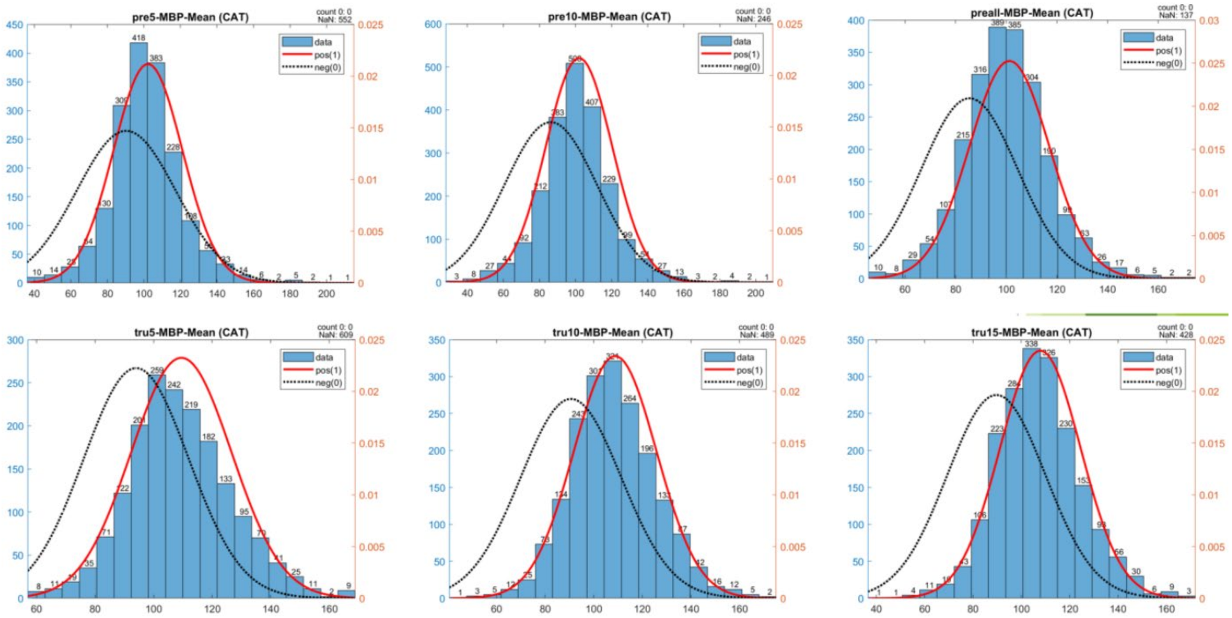


Figure 6. Examples of Mean Blood Pressure (MPB) feature value distributions (blue blocks)

Red line shows the distribution of each value in the positive outcome; black line for the negative outcome.

2.4 Model Building and evaluation

2.4.1. Feature design

We derived various feature variables from pre-hospital and TRU VS signal to represent the characteristics of patients' condition. To compare the prediction capability of VS collected at different time frames, we calculated features from initial 5, 10 minutes and the entire in-flight duration, as well as the initial 5, 10, and 15 minutes from the TRU data collection. To compare the usefulness of different sensors, we also group the feature variables by data source, such as data collected from ECG, pulse oximetry, and blood pressure cuff.

For the trend data we use statistics to summarize longitudinal data into single points. First, descriptive statistics such as mean, median, maximum, minimum, and quartiles are used to sketch the shape of VS data distributions in each observation time window. Second, we consider the episodes that VS are away from normal ranges. For example, the guidelines for field triage of injured patients recommended the use of SBP<90 mmHg or RR <10 or >29 breaths per minute as a part of the physiological criteria when considering if a patient should be transported to a facility with the highest level of care. We calculated the "pressure-times-time dose" (PTD), which is the integrated area enclosed by the VS curve and the threshold line within a given time window. [21] Moreover, we calculate the Shannon entropy of trajectories of VS in given time interval, to quantify the chaos of the physiological data. We use mutual information (MI) of two VSs, such as MI of HR and SBP, or MI of HR and SpO2, to measure the amount of information we can obtain about one VS when we observe another VS at the same time.

With waveform data, we also designed variables to extract more features to sketch patients' conditions. We mainly use ECG and PPG waveforms. Both signals are pre-processed by removing spikes and high frequency noise. Signal amplitudes that are out of sensors' measuring range are flagged as 'not available'. For ECG, the Pan-Tompkins method is used to detect QRS peaks. For PPG, the Savitzky-Golay filter is used to smooth the signa, and the peaks are found through MATLAB built-in routine 'findpeaks'. Figure 7 demonstrates a sequence of detected PQRST points in ECG and peaks/valleys in PPG.

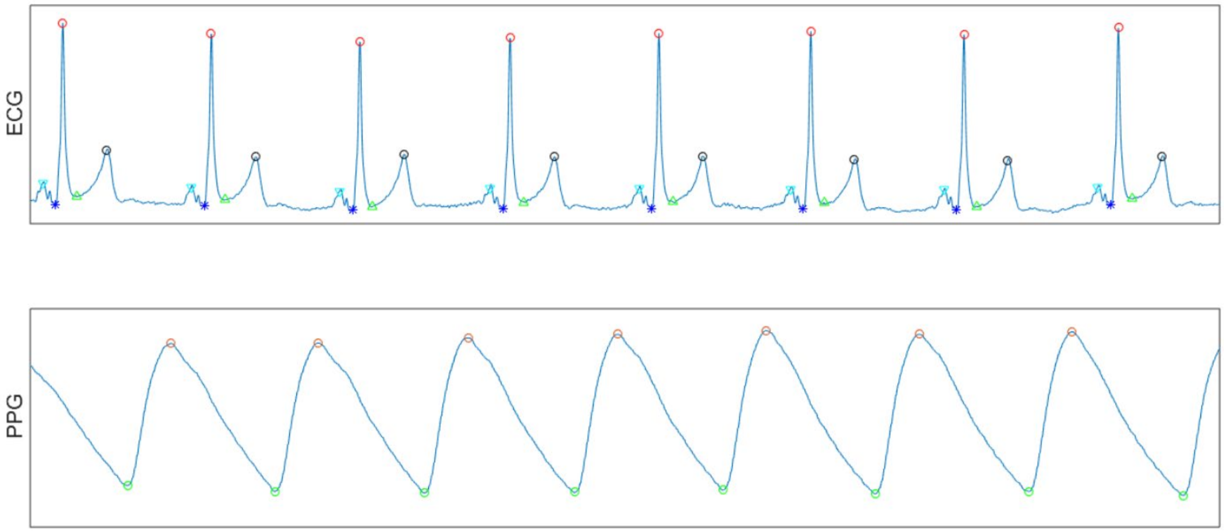


Figure 7. Illustration of detected PQRST in ECG (top), and peaks/valleys in PPG (bottom)

With detected peaks, we can calculate R to R distances. We assume that R-R distance obey some normal distribution. The R-R distance calculated from incorrectly detected R peaks should fall into tail ends of the normal distribution. We use z-test to identify such outliers. In this way, R-R distance with too small or too long gap will be removed in a statistical way. This approach reduces the amount of outliers and increases robustness of feature calculation. Using detected R peaks from ECG and PPG, heart rate variability (HRV) are calculated. Moreover, for PPG, we further calculated the systolic rising time and amplitude, as well as the diastolic falling time and amplitude. [22] For each time interval, there are 373 feature variables calculated for both trend and waveform.

In this study, the dataset contains 2364 cases, and each case has more than 300 features. In addition, some variables may be missing values, when the corresponding sensors were not used or functioning abnormally. With overall consideration, including model performance, explainability, ability to handle missing values, we use the boosting tree algorithm [23] to build prediction models. With stratified 10-fold cross-validation, we trained models and tested them in the subset of data that the trained models have not seen. We refined the hyper-parameters in the boosting tree algorithm, so that it is not eager to overfit the training set but to be generative in the testing set. Outcome probability scores (the probability of being unfavorable outcome) are compared with the ground truth (Un-Cross Matched (UnX), CAT: Critical Administration Threshold, and MT: Massive Transfusion, ≥10 units red blood cell in 24 hours).

2.4.2. Prediction scoring system comparison

To further evaluate the models' performance, we compare our models with some reported transfusion prediction scoring systems that are widely used in field triage or for trauma resuscitation. We selected three scoring systems, the revised trauma score (RTS), [24] shock index

(SI), [25-27] and Assessment of Blood Consumption (ABC) score [28]. They were compared with the bleeding risk index (BRI) for MT, CAT, mortality, and length of hospital stay≥7days (LOS≥7). RTS is often used for in-hospital survival prediction for trauma patients. Higher score is associated with higher survival chance. RTS requires collection of GCS, SBP, RR. Those variables are assigned with categorical values from 0-4 according to the pre-defined ranges. The RTS is calculated as a linear combination of those categorized values. SI (HR/SBP) is widely used for field triage due to its calculation simplicity. ABC is a scoring system for massive transfusion. It assigns score to a patient based on the following four questions: (1) is it penetrating mechanism (2) is pre-hospital systolic BP $\leq$ 90mmHg (3) is pre-hospital HR $\geq$ 120 bpm (4) is the ultrasound FAST (Focused Assessment with Sonography for Trauma) exam positive? The FAST exam is a rapid bedside ultrasound exam to screen test for blood around the heart, or abdominal organs after trauma. It looks for free fluid in the cardiac, right upper quadrant (between liver and kidney), pelvic, and left upper quadrant (spleen, diaphragm, kidney). To have FAST exam information, we reviewed a few thousand records to extract the ultrasound examination results.

2.4.3. Statistical analysis

The area under the receiver operating characteristic curve (AUROC) with 95% confidence interval (CI [29]) was calculated for predictions of CAT and MT. DeLong method was used to compare AUROCs for different scoring systems. $p<0.05$ was considered to be statistically significant. Other performance metrics based on thresholds that maximize the Youden Index [30,31] are reported, including sensitivity (true positive rate, TPR), specificity (true negative rate, TNR), positive predictive values (PPV) and negative predictive values (NPV).

3.0 RESULTS

3.1 Data

Total 2364 cases from Jan 2014 to May 2018 were identified with pre-hospital and TRU data matched. Among those patients, pre-hospital Glasgow Coma Score (GCS) median was 15 (1st and 3rd quartiles were 13 and 15). In-hospital GCS median was 15 (1st and 3rd quartiles were 14 and 15). Table 1 summarizes the demographics of the 2364 cases. Pre-hospital VS were collected by Propaq ® M series. Average collecting duration for waveforms was 28.7 minutes (SD = 9.7). In the first hour of TRU, average collecting duration for waveforms was 48.4 minutes (SD=12.7). The main reason for missing waveforms in the first hour is due to that patients were sent to CT room for initial imagery scan.

Table 1. Demographics of 2364 cases

Demographics	
Total	2364
Male/Female/Undefined	1585/773/6 (67%/32.7%/0.3%)
Type of injury (Blunt/Penetrating/other)	1635/155/574 (69.2%/6.6%/24.2%)
Mortality	149 (6.3%)
LOS>=3 days	1094 (46.3%)
LOS>=7 days	642 (27.2%)
ICU admit	494 (20.9%)
LOS>=7 days & ICU admit	366 (15.5%)
LOS>=7 days & no ICU admit	276 (11.7%)
LOS<7 days & ICU admit	128 (5.4%)
LOS<7 days & no ICU admit	1594 (67.4%)

3.2 Clinical rules evaluation

We studied the single point vital signs (instead of continuously monitored VS) collected at the admission in pre-hospital and TRU for trauma patients. From 2016 to 2019, we have 23,557 cases from the trauma registry that are adult (age ≥ 18 years), direct admitted trauma patients. Among those cases, 3277 cases were transported by helicopters. We studied the heart rate (HR), systolic blood pressure (SBP), SI (HR/SBP) and the mechanism of injury (MOI). There are 2223 cases that have all VS and MOI available.

From clinical point of view, simple and practical rules are useful health-providers to memorize and use at bedside. In this study, four decision rules used by clinicians in the shock trauma center are evaluated. The decision rules are based on clinicians' experience and are applied to predict transfusion outcomes such as UnX, CAT, and MT.

The rules are ('P' for pre-hospital; 'T' for TRU):

- Model P1: pre-hospital SBP<=90 mmHg and HR>=120 bpm
- Model P2: pre-hospital SBP<=90 mmHg and HR>=120 bpm and MOI=penetrating
- Model P3: pre-hospital SI>=1
- Model P4: pre-hospital SI>=1 and MOI=penetrating
- Model T1: TRU initial SBP<=90 mmHg and HR>=120 bpm
- Model T2: TRU initial SBP<=90 mmHg and HR>=120 bpm and MOI=penetrating
- Model T3: TRU initial SI>=1
- Model T4: TRU initial SI>=1 and MOI=penetrating

Table 2. Summary for the 2,223 group using pre-hospital data and clinical rules P1-P4

P1	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	6	2127	30	60	0.167	0.973	0.091	0.986	0.539
CAT	8	2131	28	56	0.222	0.974	0.125	0.987	0.556
UnX	16	2052	20	135	0.444	0.938	0.106	0.990	0.548
P2	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	1	2152	5	65	0.167	0.971	0.015	0.998	0.507
CAT	1	2154	5	63	0.167	0.972	0.016	0.998	0.507
UnX	2	2068	4	149	0.333	0.933	0.013	0.998	0.506
P3	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	32	1894	263	34	0.109	0.982	0.485	0.878	0.682
CAT	31	1895	264	33	0.105	0.983	0.484	0.878	0.681
UnX	62	1839	233	89	0.210	0.954	0.411	0.888	0.649
P4	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	5	2122	35	61	0.125	0.972	0.076	0.984	0.530
CAT	5	2124	35	59	0.125	0.973	0.078	0.984	0.531
UnX	12	2044	28	139	0.300	0.936	0.080	0.987	0.533

Table 3. Summary for the 2,223 group using TRU admission data and clinical rules T1-T4

T1	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	6	2147	10	60	0.375	0.973	0.091	0.995	0.543
CAT	4	2147	12	60	0.250	0.973	0.063	0.994	0.529
UnX	7	2063	9	144	0.438	0.935	0.046	0.996	0.521
T2	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	0	2156	1	66	0.000	0.970	0.000	0.999	0.500
CAT	1	2159	0	63	1.000	0.972	0.016	1.000	0.508
UnX	1	2072	0	150	1.000	0.933	0.007	1.000	0.503
T3	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	34	2011	146	32	0.189	0.984	0.515	0.932	0.724
CAT	31	2010	149	33	0.172	0.984	0.484	0.931	0.708
UnX	64	1956	116	87	0.356	0.957	0.424	0.944	0.684
T4	**TP**	**TN**	**FP**	**FN**	**PPV**	**NPV**	**SN**	**SP**	**AUC**
MT	4	2140	17	62	0.191	0.972	0.061	0.992	0.526
CA	5	2143	16	59	0.238	0.973	0.078	0.993	0.535
Un	9	2060	12	142	0.429	0.936	0.060	0.994	0.527

The results from the pre-defined clinical decision rules show only fair performance in predicting the transfusion outcomes. It is necessary to more sophisticated models to fit the data for better predictive performance.

3.3 Models trained with pre-hospital data

From the pre-hospital data, we have three major data sources, including ECG/HR, PPG/SpO2 and blood pressure (BPs). we built a set of models to handle when only HR, or BP or SpO2 available, or any combinations of them being available. Table 4 shows possible combinations of data sources and model components. In real environment deployment, a model could be a collection of those sub-models. Given the current data availability, the internal logic can automatically switch to a sub-model that exactly use all those available data sources. In the situation that one or more data sources are offline, the model can gracefully downgrade to a sub-model that use only the remaining data sources, unless no data source available at all.

Table 4. List of sub-models and their data sources

Sub-models	Data source(s)
Model 1	ECG/HR
Model 2	PPG/SpO2
Model 3	BPs
Model 4	ECG/HR, PPG/SpO2
Model 5	ECG/HR, PPG/SpO2, BPs

We compared the models' performance in three categories, data sources (HR, SpO2, BPs, and all sources), time frames (pre-hospital 5, 10 minutes, and entire in-flight duration), and signal types (numeric value measured each 1 second, and waveform measured at 250Hz). Models based on PPG were significantly better than models of ECG in predicting CAT and MT. AUROCs for using 10 min in flight combination of PPG+ECG, PPG, ECG for predicting CAT were 0.80, 0.72, 0.64; predicting MT with AUROCs 0.81, 0.73 0.63. Using entire in-flight duration data of PPG+ECG, PPG, ECG, AUROCs for predicting CAT were 0.82, 0.75, 0.66, predicting MT with AUROCs 0.84, 0.76 0.70. (Figure 8) Predictive power (AUROC) were significantly improved with longer duration of waveform monitoring for both outcomes. Compared with ECG, PPG signal and its derived variables show to have better prediction performance in all three outcomes predictive models. From the boosting tree algorithm, we also evaluated each variable's contribution to the final model's performance, and ranked variables based on their importance. Figure 9 demonstrates a ranking in the MT prediction model, using all data sources from the entire in-flight numeric data. Low SBP variables are of the top 2 most important variables. Spread of SpO2 (SpO2 inter-quartile) ranks third.

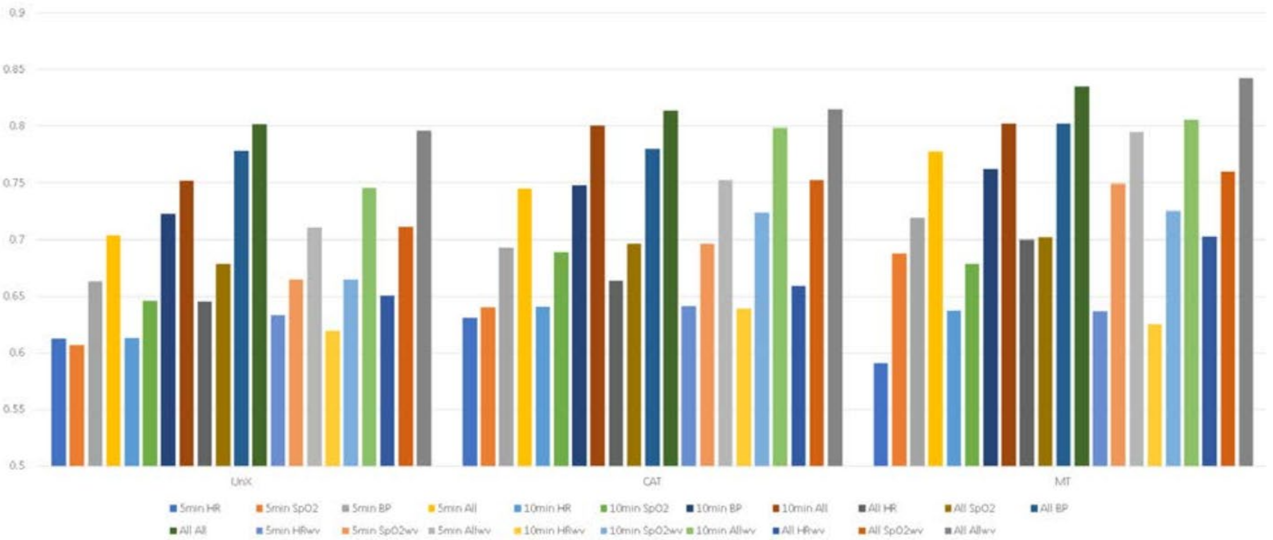


Figure 8. Predictive performance in AUROCs for models that used *pre-processed* signal in predicting UnX, CAT, MT

Bars are average AUROCs in testing sets for predicting UnX, CAT, MT, using different data sources (HR, SpO2, BPs, or all of them), using measurement from different time intervals (initial pre-hospital 5, 10 minutes or the entire in-flight duration), and using different signal types (trend data or waveform). HRwv = ECG; SpO2wv = PPG. BP = Blood pressure.

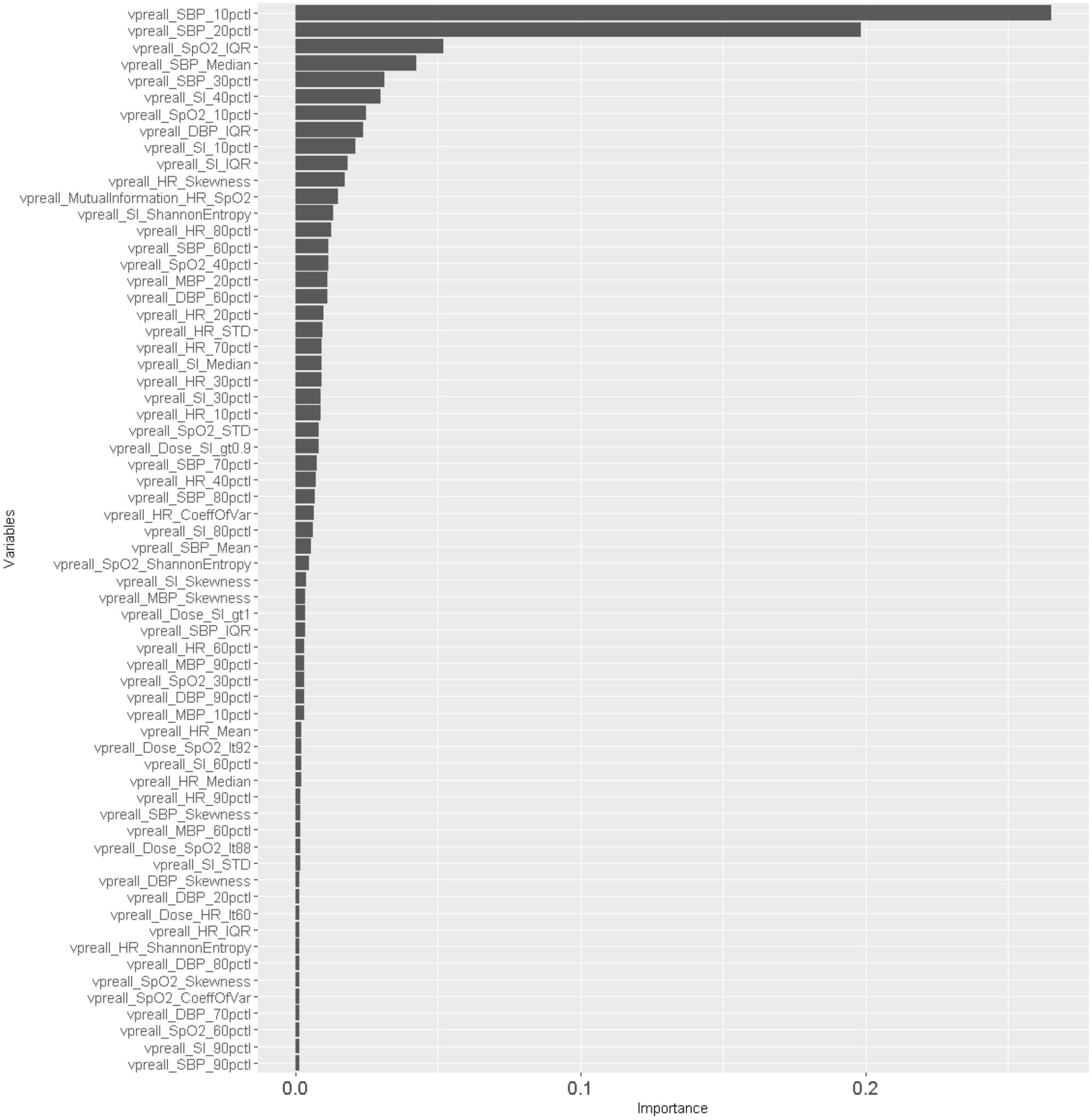


Figure 9. Ranking of variable importance in predicting MT

In above results, we included artifact removal and signal smoothing steps as pre-processing for input signals. The pre-processing was done to reduce possible negative effect from noise and motion artifacts. We hope to verify if those pre-processing steps are useful. We built another set of models that used signals without pre-processing. All features were calculated based on raw signal for the new set of models. Then we compare the models' performance and the models that used pre-processed data.

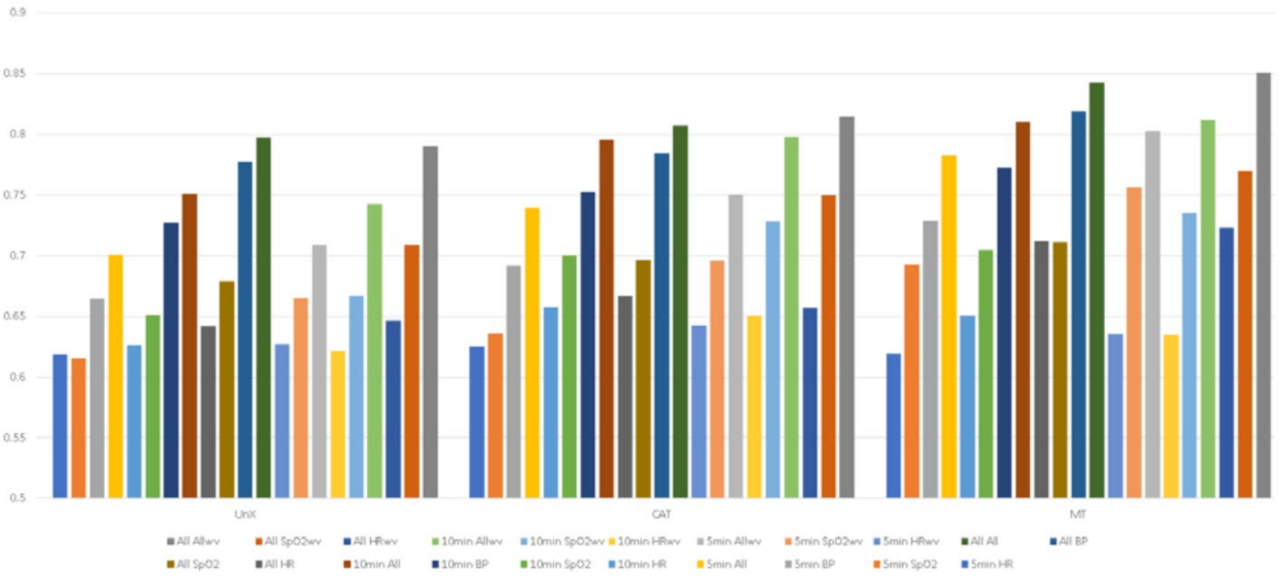


Figure 10. Predictive performance in AUROCs for models that used *raw signal* in predicting UnX, CAT, MT

The same 10-fold cross validation was done for both models sets. The averaged AUROCs in testing sets were shown in Figures 2a and 2b. By comparison, we observe that there is no significant difference between the two sets of models, in terms of AUROCs.

We also investigated the model components. Figures 11a-c display the rank of variable importance for predicting MT, CAT and UnX. For variables that are important in the models from raw data, they are generally important in the models from pre-processed data. For example, in predicting MT, low SBP (e.g. 20 percentile SBP, or 10 percentile SBP) are ranked top two in the model that used raw data features. They are also ranked on the top list in the model that used pre- processed data features. Some variables, such as shock index (SI) median was top 6 important in the model that used raw data features. It slides to top 22 important in the model that used pre-processed data features.

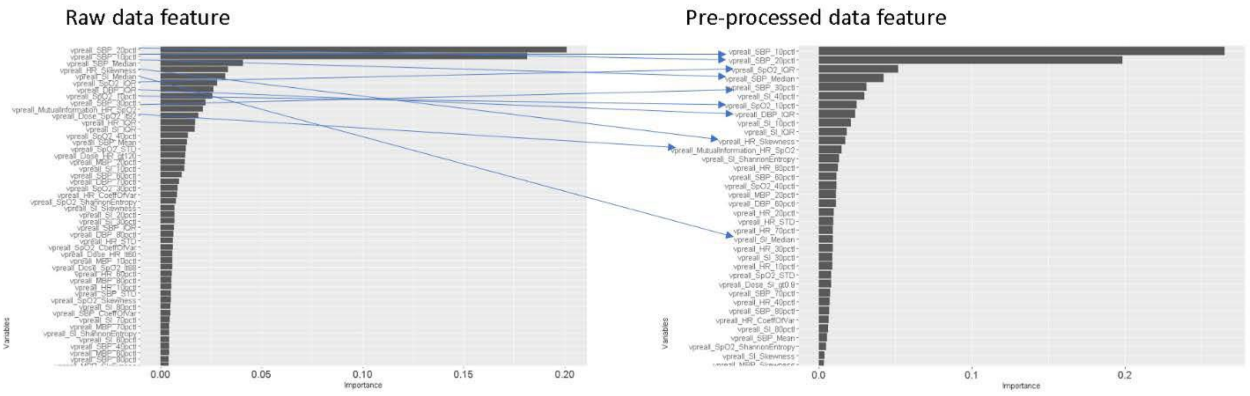


Figure 11a. Comparison of variable importance ranking for models that used raw data and models that used pre-processed data in predicting MT

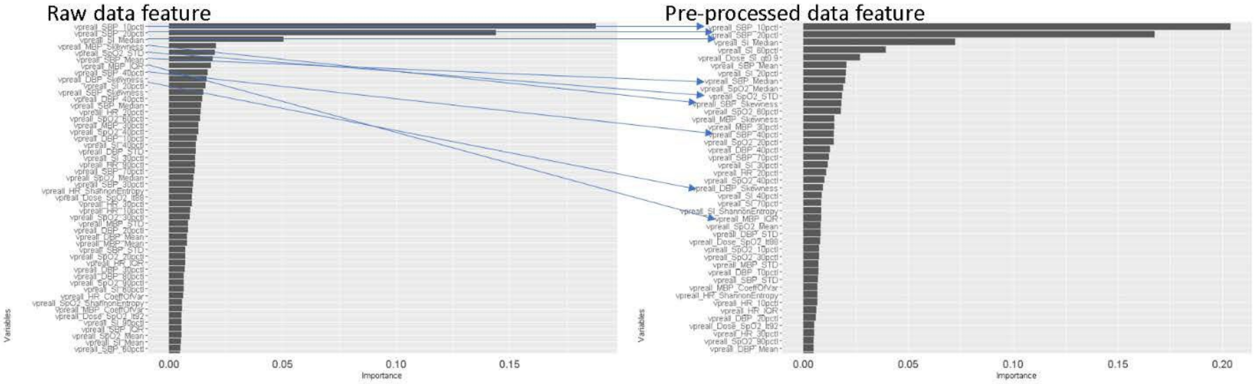


Figure 11b. Comparison of variable importance ranking for models that used raw data and models that used pre-processed data in predicting CAT

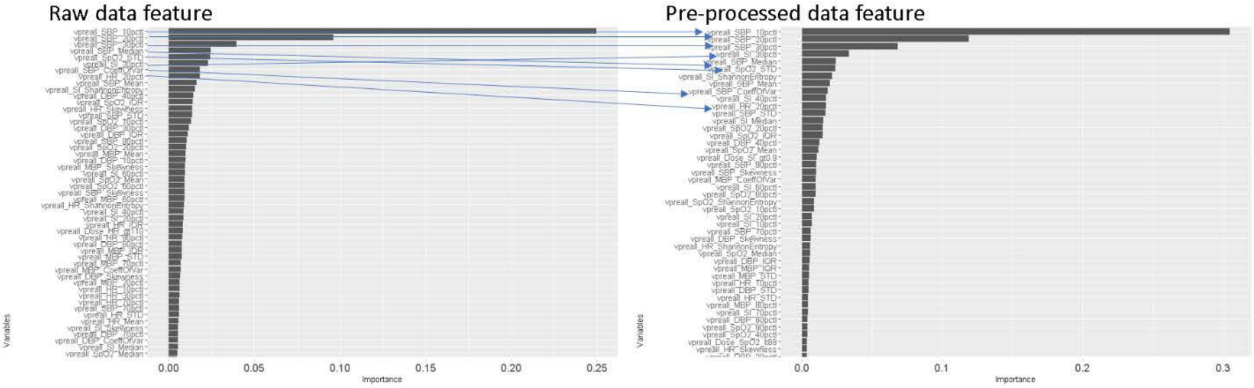


Figure 11c. Comparison of variable importance ranking for models that used raw data and models that used pre-processed data in predicting UnX

3.4 Predictive scoring systems comparison

To further test our algorithm's (BRI: bleeding risk index) performance, we compared the BRI with other scoring systems that are used for estimating the need of emergence blood transfusion and triage. In this experiment, we used a subset of the group that had pre-hospital data while was not use in the predictive model training step. This is to prevent over-optimistic estimation of the results. Total 1396 cases satisfy this criterion. Mean age is 46.5 years old (SD ±20.1) and 67.1% were male. Table 5 summarizes the patient demographics and prevalence of positive outcomes. MT rate was 3.2% and CAT 7.6%. Overall mortality rate was 6.6%. Among all patients 92.8% sustained blunt trauma, 5.0% penetrating trauma, and 1.4% were other injury types. ISS had 1st 2nd and 3rd quartiles of 5, 10, and 17 respectively. Average pre-hospital time (scene arrival to hospital) was 35.3±10.5 minutes with a mode of 29.4 minutes (Figure 12). In this subset, 6.3% were FAST exam positive. For the FAST exam positive group, mortality rate was 12.3%, while the FAST exam negative group had mortality rate 6.2% (p=0.02). For transfusion rate, the FAST positive group had Uncross matched blood use (UnX) 49.4%, critical administration threshold (CAT) 45.8%, and massive transfusion (MT) 26.5%. While the negative group had UnX 9.5%, CAT 5.2% and MT

1.8% ($p<0.0001$). This shows that the group with a positive FAST exam were more severely injured patients and had overall worse outcomes.

Table 5. Patient demographics. Adm = Admission, CAT= Critical Administration Threshold, MT = Massive Transfusion, GCS = Glasgow Coma Scale, SD = standard deviation

N	1396
Age (1st, 2nd, 3rd quartile)	28.8, 45, 60 years
Sex	Male 67.1%, Female 32.9%
Adm GCS (1st, 2nd, 3rd quartile)	14,15,15
Injury Severity Score (1st, 2nd, 3rd quartile)	5, 10, 17
PreHospital time (at the scene to hospital arrival)	Mode:29.4 minutes. Mean(SD): 35.3±10.5 minutes
Mechanism of Injury	
Blunt	1295 (92.8%)
Penetrating	70 (5.0%)
Blunt & Penetrating	12 (0.8%)
Other	19 (1.4%)
Transfusion and Mortality Outcomes	
CAT	106 (7.6%)
MT	45 (3.2%)
Mortality	92 (6.6%)

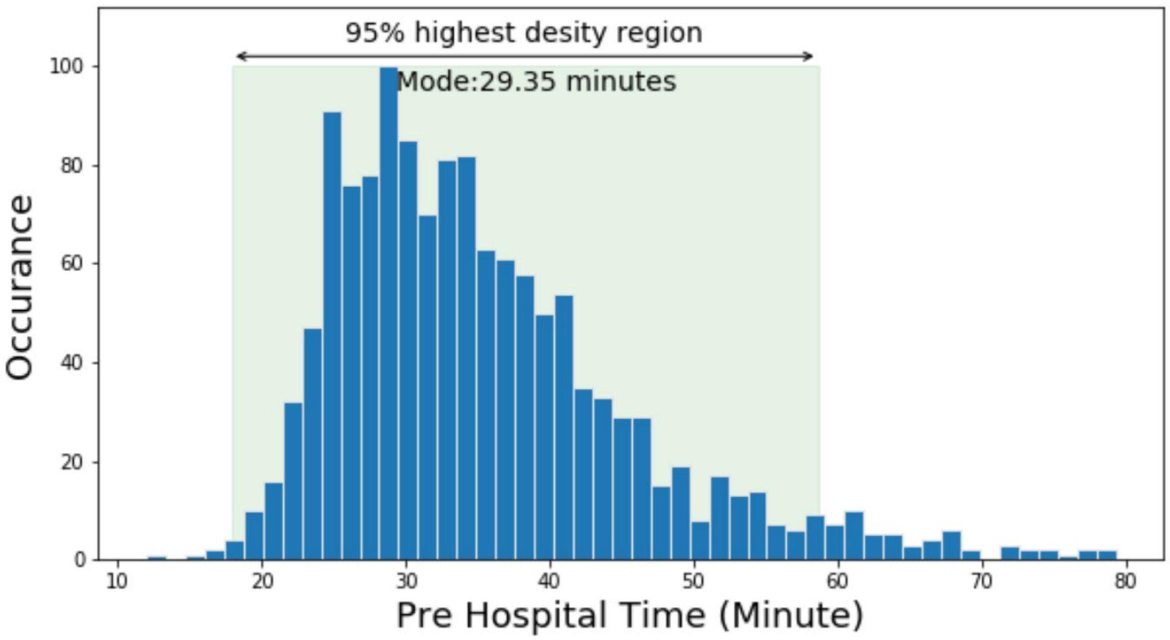


Figure 12. Distribution of at the scene to hospital arrival time

Patients who potentially may need MT could die within 24 hours before the transfusion volume reaches the outcome definition. The CAT transfusion definition has less such survival bias [32]. Total of 92 patients died after 15 minutes in TRU. A Kaplan Meier survival curve for 24-hour mortality shows the numbers of patients within the CAT (1 hour) and MT (24 hours) definition time range. (Figure 13). Six of the 92 deaths occurred within 1 hour (3 CAT positive and 3 CAT negative). 86 deaths occurred after 1 hour (29 CAT positive and 57 CAT negative). 41 died within 24 hours after trauma admission (9 MT positive and 32 MT negative). 51 died after 24 hours (6 MT positive and 45 MT negative). For those cases that died before the outcome definition time range, clinical judgement of their poor prognosis is usually indicative.

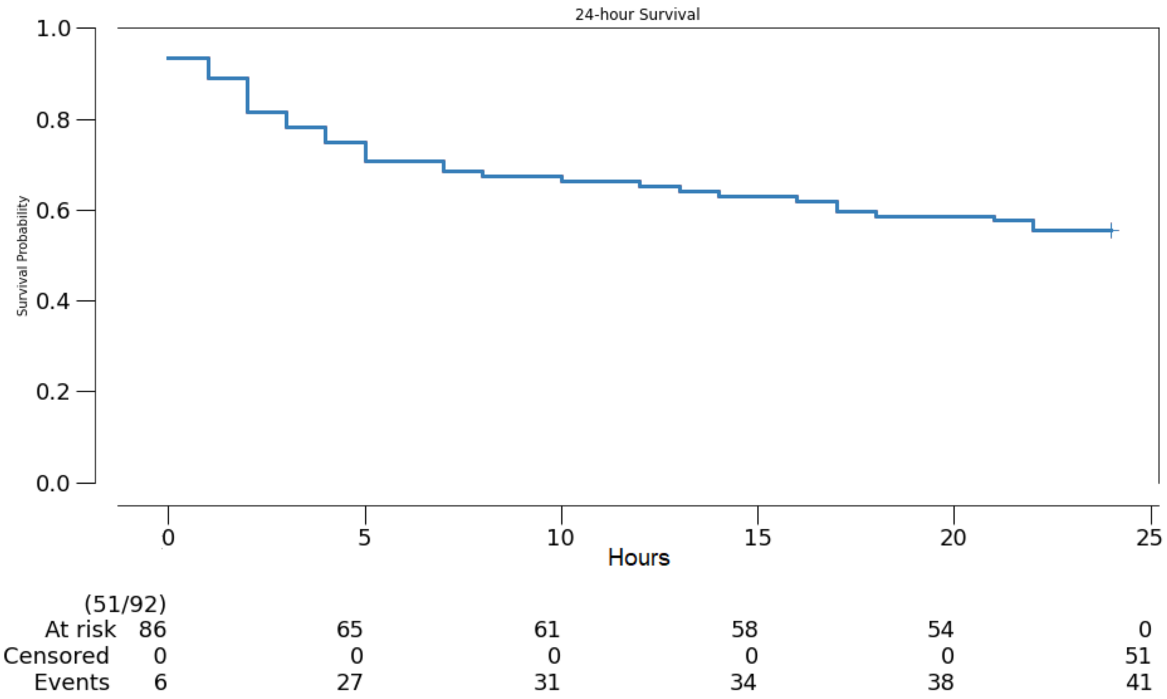


Figure 13. Kaplan-Meier curve of 24-hour survival for 92 patients who died in hospital. 6 patients died between 15 minutes and 1 hour after admission. 41 patients died within 24 hours after admission

We calculated the SI, RTS, ABC and BRI scores. In addition, we also calculated a score for mortality prediction based on our models (a.k.a. MRI, mortality risk index) and for length of stay (> 3 days and >7 days). Tables 6-11 summarize the performance metrics. BRI shows to outperform other scoring systems in predicting transfusion related outcomes. RTS is excellent in predicting mortality. None of the models are good in predicting length of stay in hospital. The first 5 minutes, 10 minutes, and All prehospital bar graphs with confidence intervals (CI) of AUROC for BRI show progressively more robust and better predictions of CAT and MT as over time more vital signs data accumulate. BRI prediction for MT, using entire pre-hospital data, performs significantly better than ABC, SI and RTS. For prediction of MT, AUC for BRI was 0.92 (CI: 0.89-0.95), which was significantly better than the ABC (AUROC=0.80, CI: 0.73- 0.87), SI (AUROC=0.83, CI: 0.76-0.90) and the RTS (AUROC=0.78, CI: 0.71-0.85). For predicting CAT, BRI (AUROC=0.91, CI: 0.86-0.94) was significantly better than ABC (AUC=0.77, CI: 0.73-0.82) and RTS (AUROC=0.79, CI: 0.74-0.83). The ROC curves in Figure 14 show that the BRI performs better than other scoring systems, since its ROC curve dominates the others. Figure 15 shows the sensitivity (blue) and specificity (orange) CAT and MT given any BRI score threshold. With the threshold cutoff BRI = 0.25 that maximizes the Youden Index for CAT, the sensitivity was 0.83 and specificity 0.85. For MT, at cutoff of BRI = 0.28, the sensitivity was 0.85 and specificity 0.82. Different thresholds could be used for BRI, if alternative sensitivity or specificity was needed. Figure 16 illustrates the comparisons of precision and recall curves (PRCs) for CAT and MT. The BRI model is still better than other scoring systems since its PRC curve dominates others'.

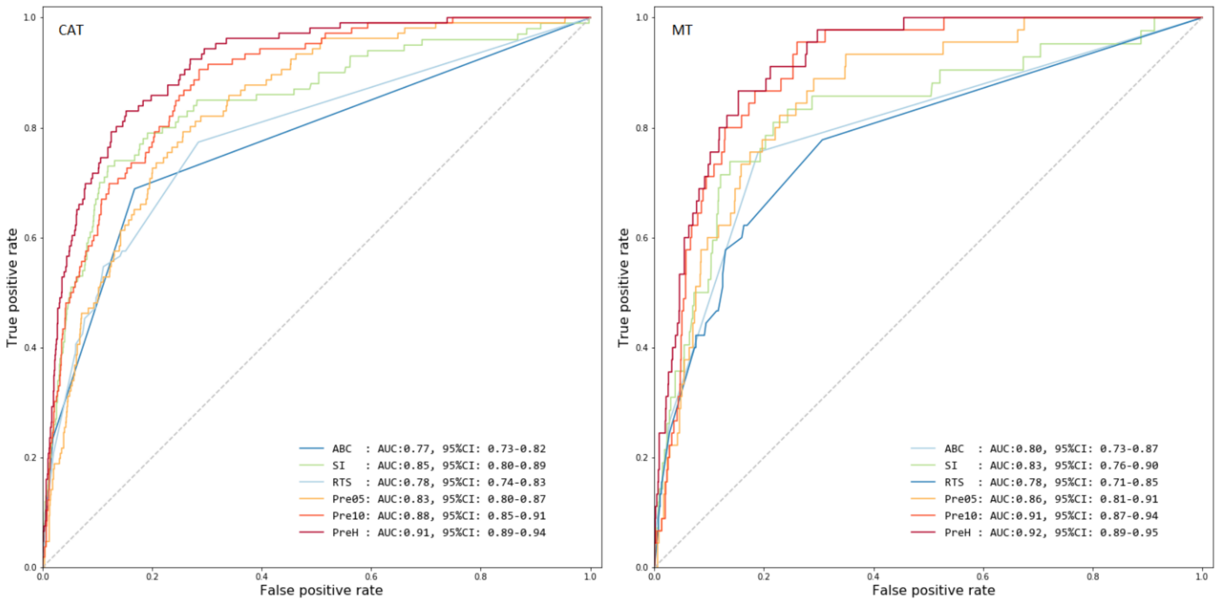


Figure 14. Receiver Operating Curves (ROC) curves (left: Critical Administration Threshold (CAT)

Right: Massive Transfusion (MT) for the ABC (blue), SI (light green), RTS (light blue), BRI (light orange for using data from pre-hospital first 5 minutes, orange for using data from pre-hospital first 10 minutes, red for using data from entire pre-hospital).

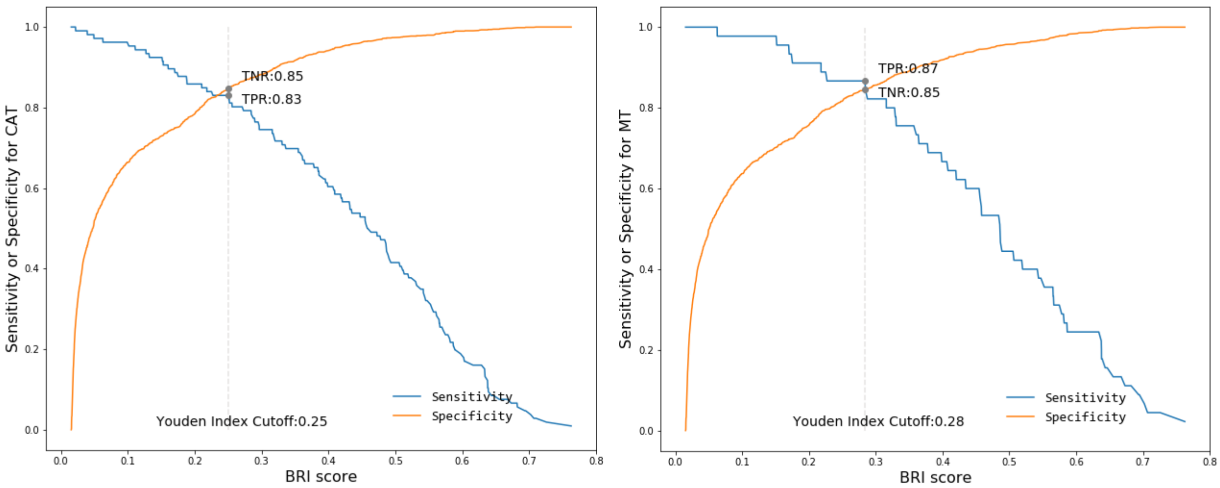


Figure 15. BRI score cutoffs and their corresponding sensitivity (blue) and specificity (orange). Left: for Critical Administration Threshold (CAT), using BRI = 0.25 as cutoff, the sensitivity (TPR) is 0.83, and the specificity (TNR) is 0.85. Right: for Massive Transfusion (MT), using BRI = 0.28 as cutoff, the sensitivity (TPR) is 0.87, and the specificity (TNR) is 0.85.

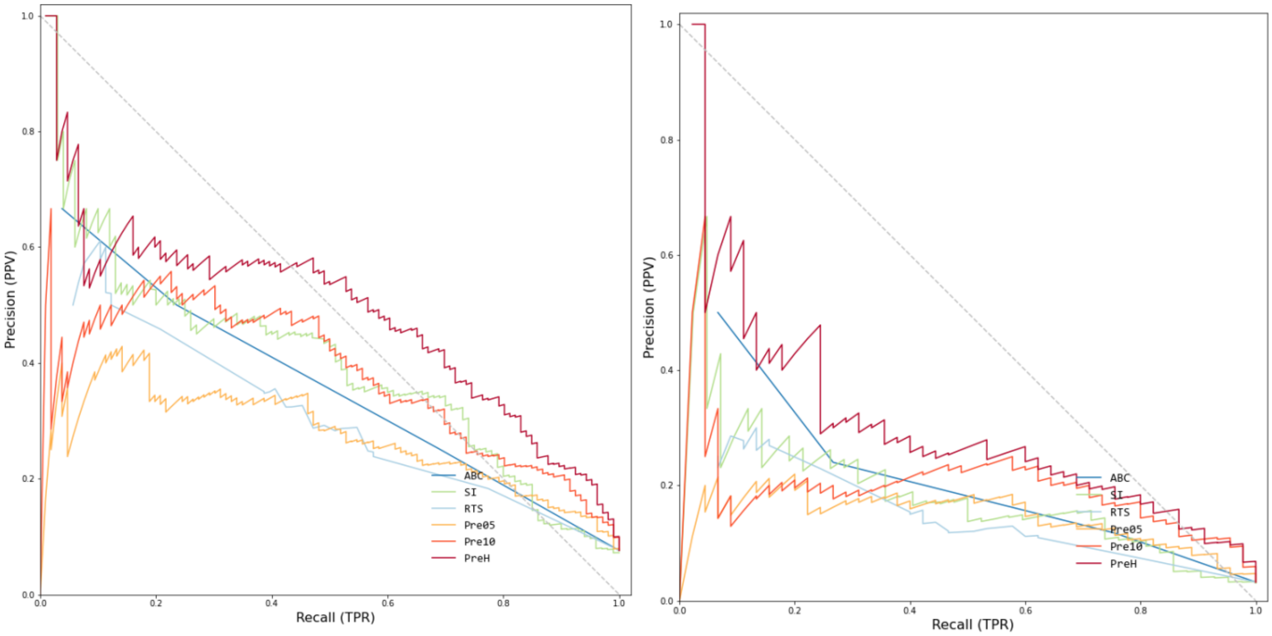


Figure 16. Precision and Recall Curves (PRC) curves (left: Critical Administration Threshold (CAT)

Right: Massive Transfusion (MT) for the ABC (blue), SI (light green), RTS (light blue), BRI (light orange for using data from pre-hospital first 5 minutes, orange for using data from pre-hospital first 10 minutes, red for using data from entire pre-hospital).

Table 6. Performance metrics for predicting UnX

UnX	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.928	0.90-0.95	0.13	0.88	0.12	0.87	0.48	0.98
SI	0.825	0.78-0.87	0.08	0.65	0.35	0.92	0.49	0.95
ABC	0.737	0.70-0.78	0.15	0.60	0.40	0.85	0.35	0.94
RTS	0.758	0.72-0.80	0.27	0.70	0.30	0.73	0.26	0.95

Table 7. Performance metrics for predicting CAT

CAT	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.91	0.86-0.94	0.15	0.83	0.17	0.85	0.31	0.98
SI	0.85	0.80-0.89	0.12	0.73	0.27	0.88	0.32	0.98
ABC	0.77*	0.73-0.82	0.17	0.69	0.31	0.83	0.25	0.97
RTS	0.78*	0.74-0.83	0.28	0.77	0.23	0.72	0.18	0.97

Table 8. Performance metrics for predicting MT

MT	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.92	0.89-0.95	0.15	0.87	0.13	0.85	0.16	0.99
SI	0.83*	0.76-0.90	0.14	0.74	0.26	0.86	0.14	0.99
ABC	0.8*	0.73-0.87	0.19	0.76	0.24	0.81	0.12	0.99
RTS	0.78*	0.71-0.85	0.31	0.78	0.22	0.69	0.08	0.99

Table 9. Performance metrics for predicting mortality

Mortality	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.783	0.73-0.83	0.17	0.65	0.35	0.83	0.21	0.97
SI	0.558	0.48-0.64	0.15	0.41	0.59	0.85	0.14	0.96
ABC	0.661	0.61-0.71	0.18	0.5	0.5	0.82	0.16	0.96
RTS	0.889	0.85-0.93	0.10	0.79	0.21	0.90	0.36	0.98

Table 10. Performance metrics for predicting LOS>3 days

LOS>3 days	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.643	0.61-0.67	0.23	0.46	0.54	0.77	0.65	0.61
SI	0.591	0.56-0.62	0.16	0.32	0.68	0.84	0.65	0.57
ABC	0.564	0.54-0.58	0.14	0.27	0.73	0.86	0.63	0.56
RTS	0.603	0.58-0.63	0.23	0.42	0.58	0.77	0.63	0.59

Table 11. Performance metrics for predicting LOS>7 days

LOS>7 days	AUROC	95% CI	FPR	TPR	FNR	TNR	PPV	NPV
BRI PreHAll	0.699	0.67-0.73	0.27	0.58	0.42	0.73	0.47	0.82
SI	0.612	0.58-0.65	0.24	0.44	0.56	0.76	0.43	0.77
ABC	0.565	0.54-0.78	0.17	0.29	0.71	0.83	0.41	0.75
RTS	0.644	0.62-0.67	0.25	0.51	0.49	0.75	0.45	0.79

3.5 Evaluation with TEG

In another evaluation of our predictive algorithms, we compared the BRI score to Thromboelastography (TEG). TEG is a method of testing the efficiency of blood coagulation. It assesses coagulation factor function, platelet function, clot strength, and fibrinolysis. The TEG result is used as part of transfusion decision. From the 1396 cases we used in the previous study periods, we reviewed and identified 378 cases with TEG. Table 12 summaries the demographics of this subset data. We were interested in two problems. First, could the algorithm scores could predict the TEG outcomes. Second, how well are the TEG values associated with the transfusion outcomes. In this study, the TEG outcomes are INR (international normalized ratio)>1.2, INR>1.5, TEG coagulopathy, TEG thrombocytopenia, TEG hypofibrinogen, TEG fibrinolysis and the combination of all TEG criteria. The algorithm scores were calculated using the first 5, 10 minutes, entire pre-hospital data, and the first 5, 10, 15 minutes in-hospital data.

Table 12. Demographics of a subset of 378 cases with TEG values

N = 378 (yr 2016-2017)	
Age	1st, 2nd, 3rd quartiles 29, 44, 60; mean(SD): 46 ±19.3
Sex	Male 300 (79.4%) Female 78 (20.6%)
MOI	
Blunt	327 (86.5%)
Penetrating	51 (13.5%)
Adm GCS	1st, 2nd, 3rd quartiles 8, 14, 15
ISS	1st, 2nd, 3rd quartiles 9, 16, 26
Mortality	55 (14.6%)
UnX, CAT, MT	83 (22%), 49(13%), 22(5.8%)
INR>1.2, INR>1.5	69, 52
TEG coagulopathy	181
TEG thrombocytopenia	58
TEG hypofibrinogen	50
TEG fibrinolysis	124
Coagulopathy Any TEG Criteria	233

Figures 17 and 18 show the receiving operating curves (ROCs) and their AUCs for the INR>1.2 and INR>1.5. For easy comparison, Table 13 summaries the ROCs, and TPR, TFR, PPV and NPV for all seven TEG outcomes. We could observe from Table 13 that the BRI scores are not very well associated with the TEG outcomes.

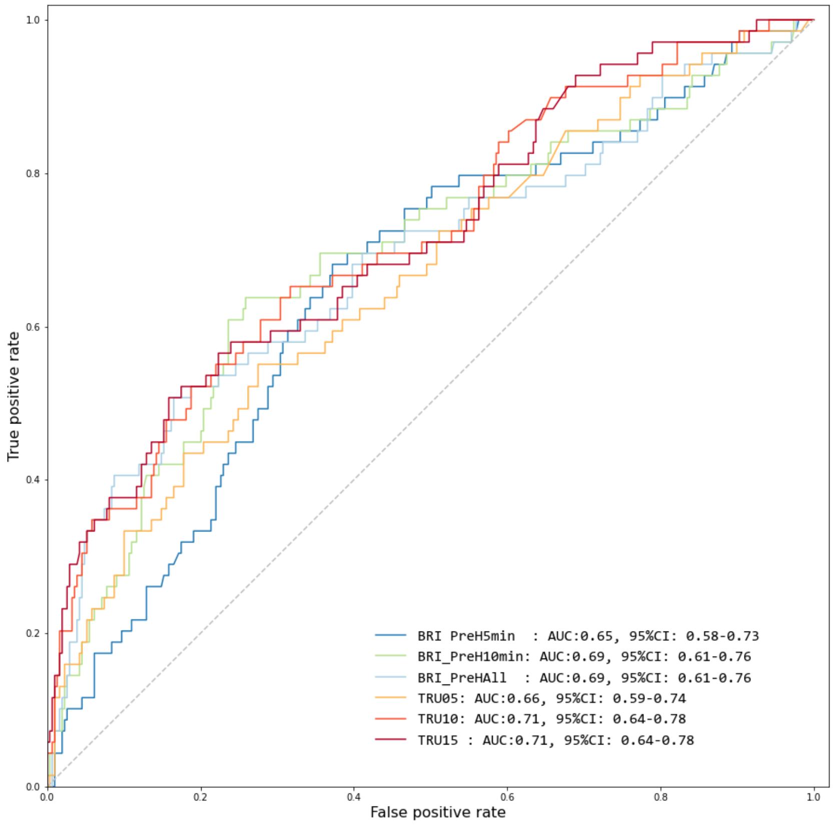


Figure 17. ROC curves and AUCs using all scores to predict INR>1.2

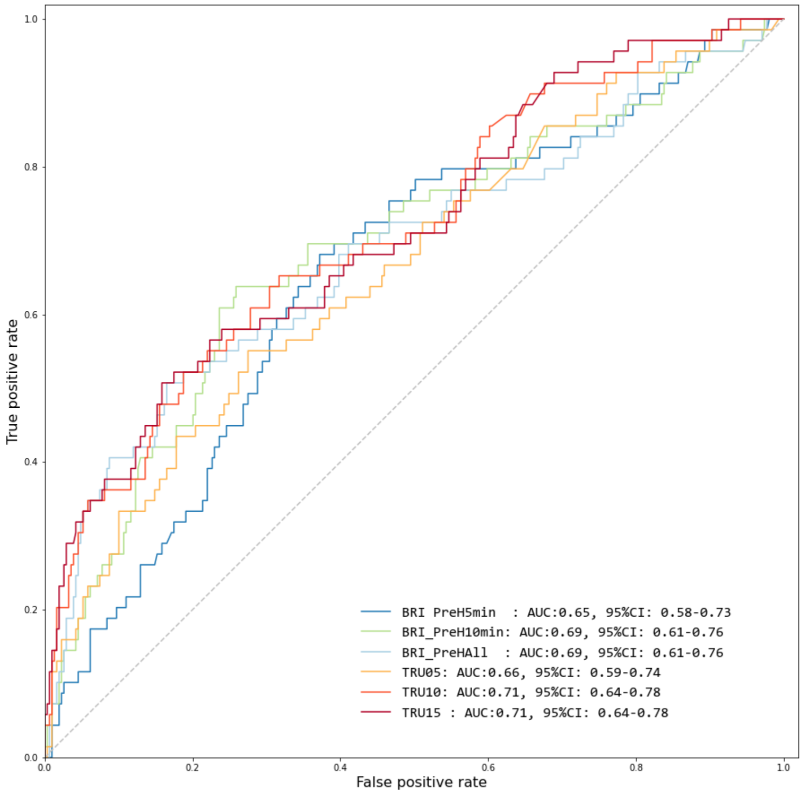


Figure 18. ROC and AUCs using all scores to predict INR>1.5

Table 13. Summary of prediction metrics for all seven TEG outcomes

Outcome	Variable	**auc**	**auc_CI low**	**auc_CI high**	**tpr**	**tnr**	**ppv**	**npv**
INR>1.2	**PreH5min**	0.655	0.583	0.726	0.681	0.628	0.290	0.898
	PreH10min	0.689	0.614	0.763	0.638	0.741	0.355	0.902
	PreHAll	0.685	0.608	0.762	0.507	0.835	0.407	0.884
	TRU5min	0.664	0.591	0.737	0.551	0.725	0.309	0.878
	TRU10min	0.713	0.643	0.784	0.652	0.683	0.315	0.898

	TRU15min	0.713	0.643	0.784	0.507	0.841	0.417	0.884
INR>1.5	**PreH5min**	0.680	0.591	0.768	0.690	0.640	0.193	0.943
	PreH10min	0.693	0.599	0.788	0.667	0.720	0.230	0.945
	PreHAll	0.714	0.617	0.811	0.524	0.902	0.400	0.938
	TRU5min	0.650	0.552	0.747	0.429	0.842	0.254	0.922
	TRU10min	0.694	0.600	0.788	0.405	0.935	0.436	0.926
	TRU15min	0.710	0.617	0.804	0.548	0.830	0.288	0.936
TEG coagulopathy	**PreH5min**	0.564	0.506	0.621	0.779	0.365	0.530	0.643
	PreH10min	0.546	0.488	0.604	0.790	0.315	0.514	0.620
	PreHAll	0.515	0.456	0.573	0.133	0.939	0.667	0.541
	TRU5min	0.559	0.501	0.618	0.597	0.528	0.537	0.588
	TRU10min	0.537	0.479	0.596	0.160	0.939	0.707	0.549
	TRU15min	0.542	0.483	0.600	0.182	0.904	0.635	0.546
TEG thrombocytopenia	**PreH5min**	0.659	0.581	0.738	0.517	0.772	0.291	0.898
	PreH10min	0.639	0.555	0.722	0.569	0.703	0.258	0.900
	PreHAll	0.651	0.564	0.738	0.483	0.819	0.326	0.897
	TRU5min	0.663	0.582	0.744	0.500	0.784	0.296	0.896
	TRU10min	0.670	0.590	0.751	0.345	0.934	0.488	0.887
	TRU15min	0.668	0.587	0.748	0.379	0.909	0.431	0.890
TEG hypofibrinogen	**PreH5min**	0.602	0.515	0.690	0.440	0.753	0.214	0.898
	PreH10min	0.626	0.536	0.716	0.540	0.710	0.221	0.910
	PreHAll	0.663	0.569	0.756	0.420	0.896	0.382	0.910
	TRU5min	0.560	0.467	0.653	0.420	0.738	0.196	0.893
	TRU10min	0.602	0.509	0.695	0.320	0.896	0.320	0.896

	TRU15min	0.615	0.521	0.709	0.340	0.896	0.333	0.899
TEG fibrinolysis	**PreH5min**	0.640	0.581	0.700	0.581	0.677	0.468	0.768
	PreH10min	0.612	0.552	0.672	0.935	0.236	0.374	0.882
	PreHAll	0.599	0.537	0.660	0.435	0.720	0.432	0.723
	TRU5min	0.619	0.557	0.682	0.411	0.815	0.520	0.739
	TRU10min	0.617	0.553	0.680	0.516	0.689	0.448	0.745
	TRU15min	0.620	0.557	0.684	0.516	0.705	0.460	0.749
Coagulopathy Any TEG Criteria	**PreH5min**	0.569	0.508	0.629	0.811	0.352	0.668	0.537
	PreH10min	0.557	0.497	0.618	0.893	0.255	0.658	0.597
	PreHAll	0.545	0.486	0.605	0.768	0.324	0.646	0.465
	TRU5min	0.549	0.490	0.609	0.648	0.448	0.654	0.442
	TRU10min	0.542	0.483	0.602	0.197	0.897	0.754	0.410
	TRU15min	0.552	0.493	0.611	0.631	0.483	0.662	0.449

We also tested the BRI scores and the TEG outcomes association with the transfusion outcomes, such as the UnX, CAT and MT. Figures 18-20 show the ROCs of BRI scores and TEG values in predicting the transfusion outcomes. Table 14 summaries the performance metrics of each score. In this subset, the BRI scores still perform well in predicting the transfusion outcomes. While the TEG values are not very well associated with the transfusion outcomes. One possible reason is that the TEG values are one of many factors to be considered in transfusion decision.

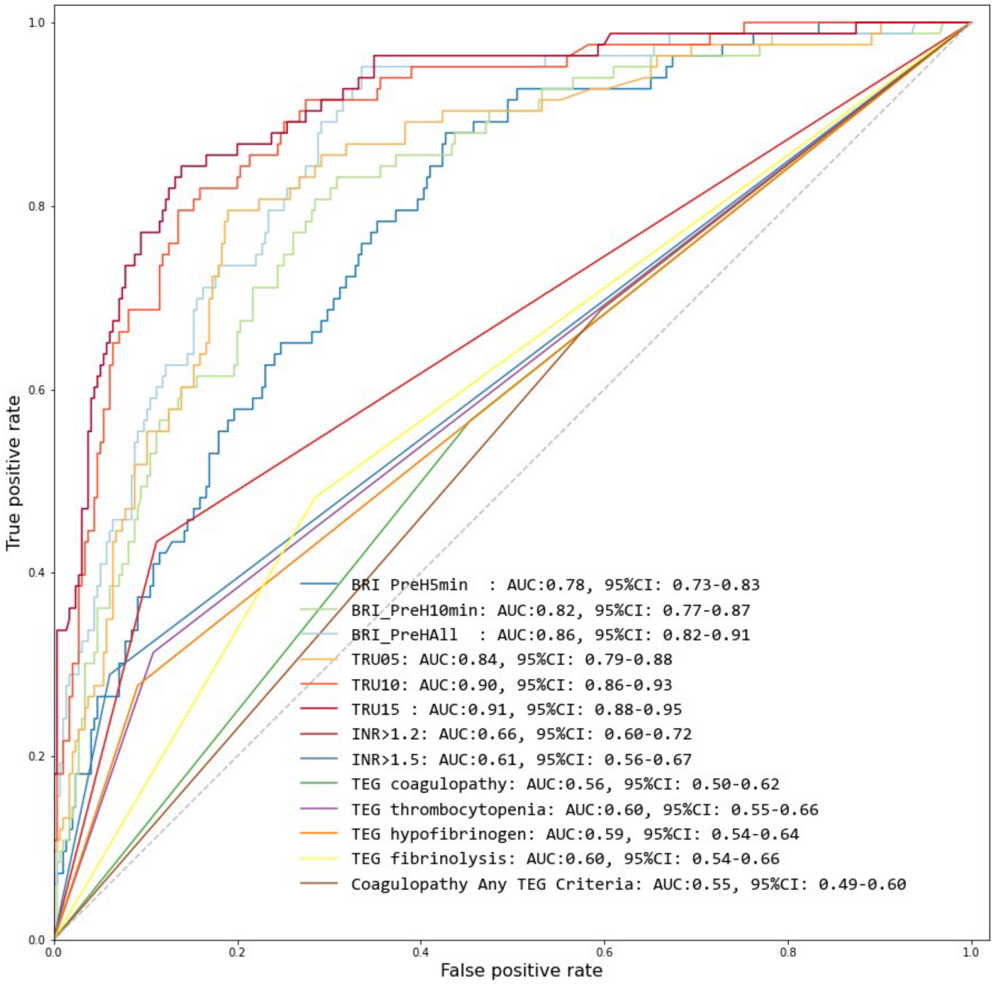


Figure 19. ROCs and AUCs of BRI scores and TEG values in predicting UnX

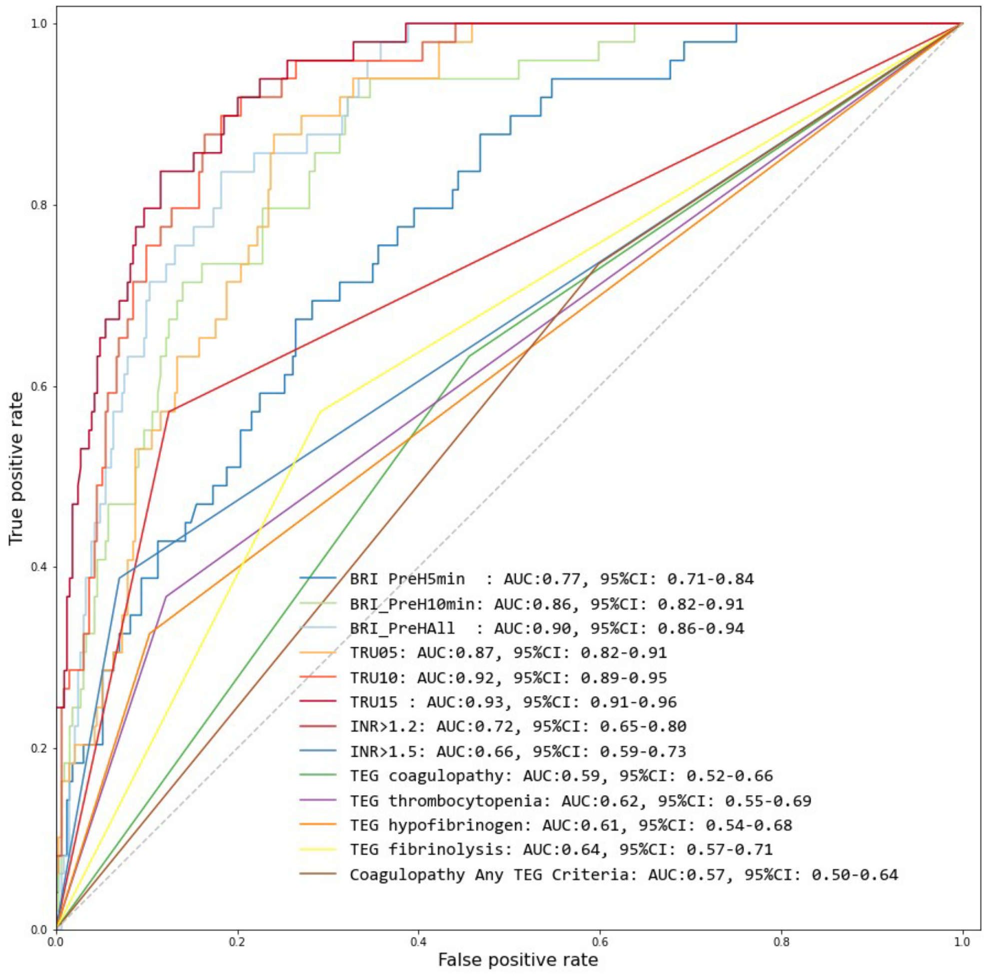


Figure 20. ROCs and AUCs of BRI scores and TEG values in predicting CAT

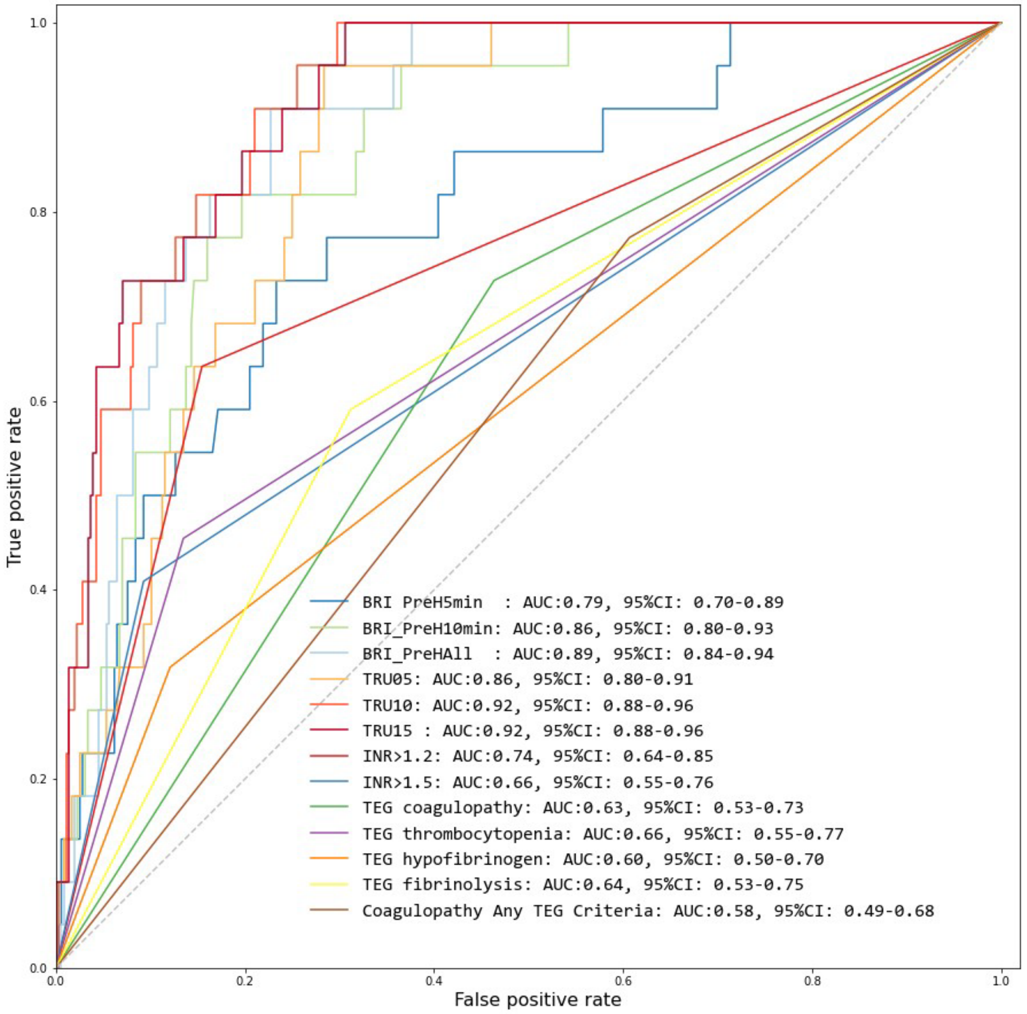


Figure 21. ROCs and AUCs of BRI scores and TEG values in predicting MT

Table 14. Summary of prediction metrics for BRI scores and seven TEG values in predicting UnX, CAT and MT

Outcome	Variable	**auc**	**Auc cilow**	**Auc cihigh**	**tpr**	**tnr**	**ppv**	**npv**
UnX	**INR>1.2**	0.661	0.604	0.718	0.434	0.888	0.522	0.848
	INR>1.5	0.614	0.563	0.665	0.289	0.939	0.571	0.824

	TEG coagulopathy	0.556	0.495	0.617	0.566	0.546	0.260	0.817
	TEG thrombocytopenia	0.602	0.549	0.656	0.313	0.892	0.448	0.822
	TEG hypofibrinogen	0.593	0.542	0.644	0.277	0.908	0.460	0.817
	TEG fibrinolysis	0.599	0.539	0.659	0.482	0.715	0.323	0.831
	Coagulopathy Any TEG Criteria	0.545	0.488	0.603	0.687	0.403	0.245	0.821
CAT	**INR>1.2**	0.723	0.651	0.796	0.571	0.875	0.406	0.932
	INR>1.5	0.659	0.589	0.729	0.388	0.930	0.452	0.911
	TEG coagulopathy	0.588	0.515	0.662	0.633	0.544	0.171	0.909
	TEG thrombocytopenia	0.623	0.552	0.693	0.367	0.878	0.310	0.903
	TEG hypofibrinogen	0.612	0.543	0.680	0.327	0.897	0.320	0.899
	TEG fibrinolysis	0.640	0.566	0.714	0.571	0.708	0.226	0.917
	Coagulopathy Any TEG Criteria	0.568	0.500	0.636	0.735	0.401	0.155	0.910
	INR>1.2	0.741	0.636	0.846	0.636	0.846	0.203	0.974
	INR>1.5	0.658	0.552	0.764	0.409	0.907	0.214	0.961
	TEG coagulopathy	0.632	0.533	0.731	0.727	0.537	0.088	0.970

MT	**TEG thrombocytopenia**	0.660	0.552	0.768	0.455	0.865	0.172	0.963
	TEG hypofibrinogen	0.599	0.498	0.700	0.318	0.879	0.140	0.954
	TEG fibrinolysis	0.640	0.532	0.747	0.591	0.688	0.105	0.965
	Coagulopathy Any TEG Criteria	0.583	0.490	0.676	0.773	0.393	0.073	0.966

3.5 Miniature device test

We implemented a mobile device application for data acquisition and feature extraction. Based on the communication library developed by the Starix company (which we reported the reliability and efficiency of their library in a previous quarter), we did secondary development. Figure 22 shows the communication architecture. In this setting, wireless communication is used. Both Propaq and the mobile device are connected to a wifi router so that they can communicate with each other under the same network domain. The mobile device sends data requests to Propaq and receives responds from it. Figure 23 shows the basic interface of connecting and displaying. To establish a connection, the IP address of Propaq in the network and username with password are required.

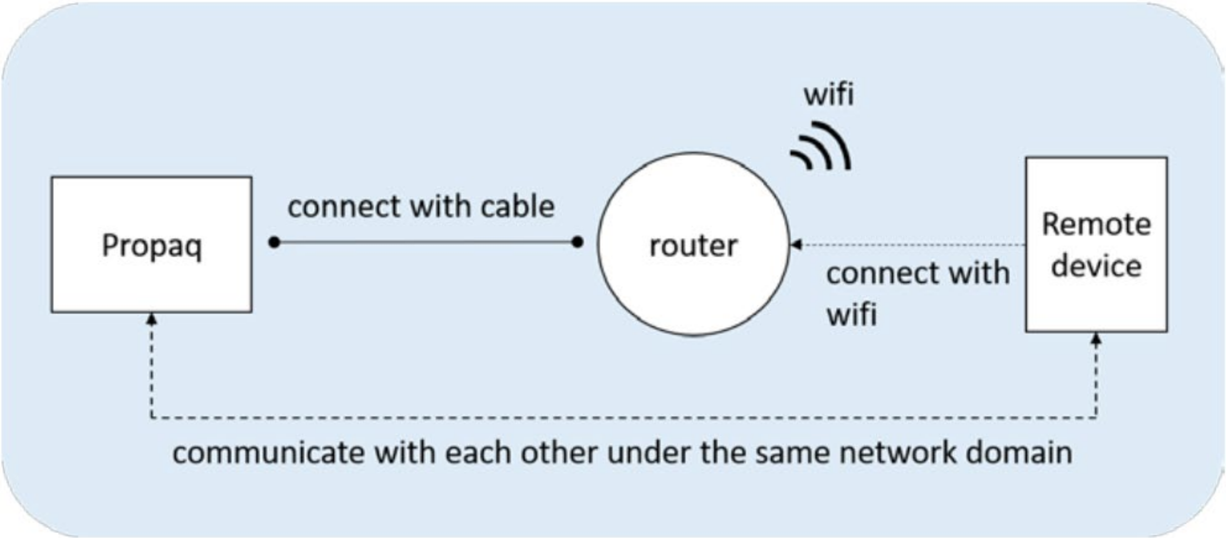
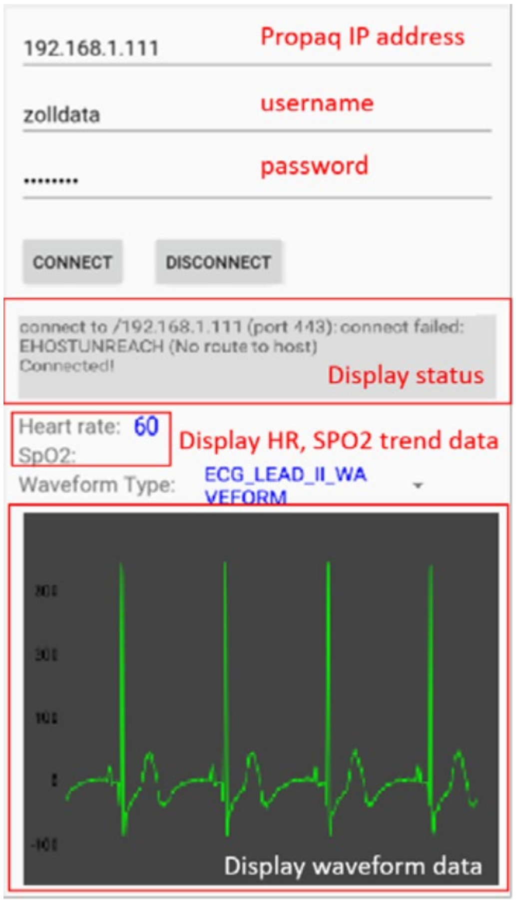


Figure 22. Communication architecture



192.168.1.111 Propaq IP address

zolldata username

•••••••• password

connect to /192.168.1.111 (port 443): connect failed: EHOSTUNREACH (No route to host)
Connected!

Display status

Heart rate: 60
SpO2:

Display HR, SPO2 trend data

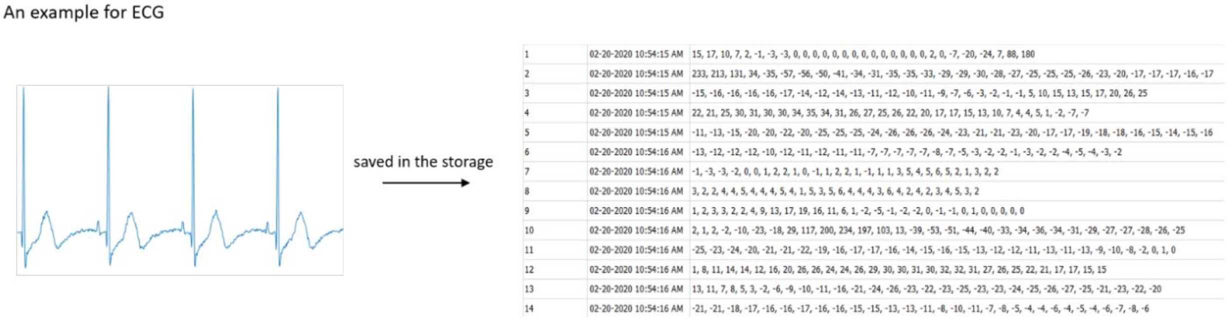
Waveform Type: ECG_LEAD_II_WAVEFORM

Display waveform data

Figure 23. Mobile application interface

Figure 24. Rugged Android device that used for running the data acquisition software

We tested the code on two android devices, one is a Samsung galaxy S5 and another one is a ruggeddevice (Figure 24). The later one could be used in adverse environment, such as helicopter during flight. To verify the data integrity received from Propaq, we collected 15 minutes ECG waveform data generated by an ECG simulator. The initial heart rate (HR) was set as 60 beats per minute (bpm). After 5 minutes, HR was set as 120 bpm. It was increased to 160 bpm since the 11th minute. Waveform data were saved to both Propaq and the mobile device. We verified the changing points at every 5 minutes, by checking if the recorded HR was changed to the set values. We also compared the Propaq saved values with the mobile device saved values. The two sets of waveform data were shown to be identical through point-by-point comparison. Figure 25 illustrates the ECG waveform and its numeric values.



1	02-20-2020 10:54:15 AM	15, 17, 10, 7, 2, -1, -3, -3, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 2, 0, -7, -20, -24, 7, 88, 180
2	02-20-2020 10:54:15 AM	233, 213, 131, 34, -35, -57, -56, -50, -41, -34, -31, -35, -35, -33, -29, -29, -30, -28, -27, -25, -25, -25, -26, -23, -20, -17, -17, -17, -16, -17
3	02-20-2020 10:54:15 AM	-15, -16, -16, -16, -16, -17, -14, -12, -14, -13, -11, -12, -10, -11, -9, -7, -6, -3, -2, -1, -1, 5, 10, 15, 13, 15, 17, 20, 26, 25
4	02-20-2020 10:54:15 AM	22, 21, 25, 30, 31, 30, 30, 34, 35, 34, 31, 26, 27, 25, 26, 22, 20, 17, 17, 15, 13, 10, 7, 4, 4, 5, 1, -2, -7, -7
5	02-20-2020 10:54:15 AM	-11, -13, -15, -20, -20, -22, -20, -25, -25, -25, -24, -26, -26, -26, -24, -23, -21, -21, -23, -20, -17, -17, -19, -18, -18, -16, -15, -14, -15, -16
6	02-20-2020 10:54:16 AM	-13, -12, -12, -12, -10, -12, -11, -12, -11, -11, -7, -7, -7, -7, -7, -8, -7, -5, -3, -2, -2, -1, -3, -2, -2, -4, -5, -4, -3, -2
7	02-20-2020 10:54:16 AM	-1, -3, -3, -2, 0, 0, 1, 2, 2, 1, 0, -1, 1, 2, 2, 1, -1, 1, 1, 3, 5, 4, 5, 6, 5, 2, 1, 3, 2, 2
8	02-20-2020 10:54:16 AM	3, 2, 2, 4, 4, 5, 4, 4, 4, 5, 4, 1, 5, 3, 5, 6, 4, 4, 4, 3, 6, 4, 2, 4, 2, 3, 4, 5, 3, 2
9	02-20-2020 10:54:16 AM	1, 2, 3, 3, 2, 2, 4, 9, 13, 17, 19, 16, 11, 6, 1, -2, -5, -1, -2, -2, 0, -1, -1, 0, 1, 0, 0, 0, 0, 0
10	02-20-2020 10:54:16 AM	2, 1, 2, -2, -10, -23, -18, 29, 117, 200, 234, 197, 103, 13, -39, -53, -51, -44, -40, -33, -34, -36, -34, -31, -29, -27, -27, -28, -26, -25
11	02-20-2020 10:54:16 AM	-25, -23, -24, -20, -21, -21, -22, -19, -16, -17, -17, -16, -14, -15, -16, -15, -13, -12, -12, -11, -13, -11, -13, -9, -10, -8, -2, 0, 1, 0
12	02-20-2020 10:54:16 AM	1, 8, 11, 14, 14, 12, 16, 20, 26, 26, 24, 24, 26, 29, 30, 30, 31, 30, 32, 32, 31, 27, 26, 25, 22, 21, 17, 17, 15, 15
13	02-20-2020 10:54:16 AM	13, 11, 7, 8, 5, 3, -2, -6, -9, -10, -11, -16, -21, -24, -26, -23, -22, -23, -25, -23, -23, -24, -25, -26, -27, -25, -21, -23, -22, -20
14	02-20-2020 10:54:16 AM	-21, -21, -18, -17, -16, -16, -17, -16, -16, -15, -15, -13, -13, -11, -8, -10, -11, -7, -8, -5, -4, -4, -6, -4, -5, -4, -6, -7, -8, -6

Figure 25. ECG waveform and its corresponding numeric data and timestamps

In addition to data acquisition, we also implement the feature extraction functions for trend data on the mobile device. With Java code, variables that sketch vital signs characteristics, such as their mean, standard deviation, percentiles, etc. could be calculated from the data received.

4.0 DISCUSSION:

The BRI, using continuously recorded non-invasive vital signs in trauma patients, is an algorithm for predicting the probability of transfusion in both pre-hospital and early in-hospital use [6,7,10,22]. The current study shows that the same BRI algorithm performs well (AUROC 0.91-0.92) using pre-hospital data to predict emergency and massive transfusion as it did when used on a different data set for in-hospital prediction of transfusion (AUROC 0.92) [7]. In a previously reported study, BRI used after trauma center arrival, performed as well or better than STC trauma attending faculty, senior nurses and helicopter paramedics at predicting future blood transfusion [7]. BRI requires no user input from a busy pre-hospital provider who may be involved with multiple interventions (airway management, intravascular catheter insertion, monitoring vital signs etc.), history taking and documentation. Use of BRI does not require additional equipment, data entry or expert interpretation. Data collection is automated by interfacing with the vital signs data and the hemodynamic monitoring system and shows the probability of future transfusion. Automated transfusion prediction with machine learning and artificial intelligence using BRI may assist pre-hospital triage decision-making, and can also assist with pre-hospital, trauma center and blood-bank planning. BRI might be especially useful in remote field or natural disaster scenes and BRI could be used when availability of medical expertise is limited. BRI also has applicability as a monitor of the probability of future transfusion because BRI score can be continuously updated in real-time. Together with history, physical exam and Emergency Medical Services protocols, BRI can add to the accuracy of decision making and assist with patient triage. In pragmatic decision-making, the threshold could be fine-tuned for the preference of higher sensitivity or specificity as needed by other longer term priorities, such as delayed transportation.

The transfusion prediction scoring systems compared in this study are all feasible to be used in the field, as all measurement and calculation devices could be mobile and small. A portable ultrasound device would allow use of ABC in the field. Derivation of ABC and RTS require additional expertise to carry out a FAST exam (for calculation of ABC) and to collect and enter a GCS (for calculation of RTS). BRI and SI do not require manual evaluation and are suitable for autonomous continuous monitoring. However, BRI and SI do not use information from medical experts, when FAST exam results or GCS are available. Therefore, the quest for a more accurate and easy-to-use transfusion predictor should continue.

Blood and/or plasma is not routinely administered in the Maryland State Police helicopters, though BRI would be a useful tool for selecting trauma patients who could potentially benefit from early pre-hospital transfusion intervention. In both military and civilian trauma patients, after early ‘en route’ transfusion of plasma and pRBC administration, patient outcomes and survival have been shown to benefit with less overall use of pRBC, platelets and fresh frozen plasma [33-36], and lower 30-day mortality rate [37,38]. The ability to automatically process early evidence of trauma patient instability with routinely collected vital signs, can assist clinicians in the rapid diagnosis of bleeding, triage and bleeding control intervention following injury. BRI score calculation may be helpful in austere environments, prolonged field care with limited resources and where medical expertise may not be immediately available, or where there are limited evacuation transport resources. Given the average 35 minutes pre-hospital time for our patients, vital signs data collection could be processed in real-time to automatically trigger a warning to the trauma receiving team and the blood bank of the impending need to initiate protocols for MT and CAT, including availability of blood products and operating room standby, until trauma center assessment. At STC, uncrossmatched blood and plasma are available in the trauma bays. These blood products are checked regularly by the blood bank and replenished as needed. The STC adult MT protocol is 6 units of pRBC, 6 units thawed ABO plasma and 1 unit apheresis platelets. These products are used for a 1:1:1 hemostatic resuscitation. In austere environments during prolonged field care, when resources are limited and evacuation may not be available for days, rapid and early diagnosis of bleeding following injury is needed to preserve available blood and other resources. This is especially important for non-compressible "hidden" compartments of the thorax, abdomen, hard-to-detect pelvic bleeding, and for exsanguinating hemorrhage, where there is only a brief window of opportunity for therapeutic intervention, to detect and control acute blood loss [33-35].

Limitations of this study include: vital signs data in trauma patients were collected from a single trauma center, which may not be applicable to other centers, areas and circumstances because of different geographic and patient characteristics. Validation of the BRI by testing using additional new data from other hospitals and regions is needed. With a short duration of in-hospital observation, BRI prediction performance could be improved for short-term outcomes of other interventions besides blood transfusion.

Another limitation is the potential survival bias from the definition of outcomes. As we mentioned above, patients who potentially may need MT could die within 24 hours before the transfusion volume reaches the outcome definition. The CAT transfusion definition has less such survival bias [32]. In this study, we only removed cases that died on arrival (within 15 minutes after TRU admission). For those cases that died before the outcome definition time range, clinical judgement of their poor prognosis is usually indictive.

BRI could have important potential as a platform for field-ready algorithms to be integrated into patient monitoring systems with no added size or weight. The validated algorithms also could support the efforts of trauma care and emergency medical services to forward-deploy instrumentation capable of automated collection of continuous, high-quality vital signs data for future generations of clinical decision-support instrumentation. If point-of-care testing and other devices are added [37,39], potentially simple software upgrades to existing pre-hospital monitors could "call" ahead to warn the blood bank, advise the trauma team and operating team to start preparations for these interventions, activate blood product processing to reduce the coagulopathy of trauma, and coordinate other logistics for trauma patient reception and resuscitation. The same BRI algorithm has been shown to be a good predictor of un-crossmatched and emergency blood transfusion during trauma center reception and resuscitation, and of other life-saving interventions. BRI score collected in-flight, performs better than ABC, SI and RTS predictions of MT and CAT. BRI does not increase patient evaluation burden, require additional data entry or expert interpretation.

5.0 CONCLUSION:

Our transfusion predictive algorithms have been tested with pre-hospital data, and compared with clinical rules, other scoring systems (ABC, SI, RTS) and TEG values. This study showed that continuously physiological data collected from pre-hospital helicopter transportation could predict short-term transfusion outcomes. Using those predictive algorithms could push the decision-making time earlier, possibly to TRU admission time or even during the transportation. Since the algorithms only use data automatically collected from a device, they do not require additional data entry or expert interpretation. They are suitable for use in environments that lack medical experts, such as remote areas or natural disaster scenes.

6.0 REFERNECES:

1. R A Cowley. A Total Emergency Medical System for the State of Maryland. Md State Med J. 1975; 24:37-45.
2. Roger FB, Rittenhouse KJ, Gross, BW: The golden hour in trauma: Dogma or medical folklore. (Editorial) Injury. 2015; 46:525-527
3. Dutton RP, et al. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008.J Trauma. 2010; 69:620-626
4. Powell-Dunford N, et al. Army Air Ambulance Blood Product Program in the Combat Zone and Challenges to Best Practices. Aerosp Med Hum Perform. 2016; 87:728-34.
5. Hervig T, et al. Prehospital use of plasma: the blood bankers' perspective. Shock. 2014; 41 Suppl 1:39-43
6. Mackenzie C, et al. Automated Prediction of Early Blood Transfusion in Trauma Patients, J Trauma Acute Care Surgery, 2014;76:1379-85
7. Mackenzie CF, et al. Comparison of Decision-Assist and Clinical Judgment of Experts for Prediction of Lifesaving Interventions. Shock. 2015; 43:238-43.
8. Dezman ZD, et al. Computer Modelling Using Prehospital Vitals Predicts Transfusion and Mortality. Prehosp Emerg Care. 2016; 20:609-14.
9. Yang S, et al. Trends of Hemoglobin Oximetry: Do They Help Predict Blood Transfusion During Trauma Patient Resuscitation? Anesth Analg. 2016; 122:115-25.
10. Parimi N, et al. Automated continuous vital signs predict use of uncrossed matched blood and massive transfusion following trauma. J Trauma Acute Care Surg. 2016;80:897-906
11. Hu PF, et al. Reliable Collection of Real-Time Patient Physiologic Data from less Reliable Networks: a "Monitor of Monitors" System (MoMs). J Med Syst. 2017; 41:3.
12. Hu PF, et al. Statewide real-time in-flight trauma patient vital signs collection system. AMIA Annu Symp Proc. 2008 Nov 6:980.
13. Hu PF, et al. Advanced visualization platform for surgical operating room coordination: distributed video board system. Surg Innov. 2006; 13:129-35.
14. Mackenzie CF, Hu PF, Horst RL. An audio-video system for automated data acquisition in the clinical environment. LOTAS Group. J Clin Monit. 1995; 11:335-41.
15. Kahraman S, et al. Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a brain trauma index that predicts outcome in patients with
severe traumatic brain injury. J Trauma. 2011; 70:547-53.
16. Liu J, et al. Automated analysis of vital signs to identify patients with substantial bleeding before hospital arrival: a feasibility study. Shock. 2015; 43:429-36
17. Shackelford SA, et al. Early identification of uncontrolled hemorrhage after trauma: current status and future direction. J Trauma Acute Care Surg. 2014; 77(3supl2):S222-S227.
18. Bellamy RF. The causes of death in conventional land warfare. Mil Med. 1984;149:55–62
19. Galvagno, S.M., Haut, E.R., Zafar, S.N., Millin, M.G., Efron, D.T., Koenig, G.J., Baker, S.P., Bowman, S.M., Pronovost, P.J. and Haider, A.H., 2012. Association

between helicopter vs ground emergency medical services and survival for adults with major trauma. Jama, 307(15), pp.1602-1610.

20. Meyer DE, Cotton BA, Fox EE, Stein D, Holcomb JB, Cohen M, Inaba K, Rahbar E. A comparison of resuscitation intensity and critical administration threshold in predicting early mortality among bleeding patients: A multicenter validation in 680 major transfusion patients. J Trauma Acute Care Surg. 2018; 85:691.
21. Kahraman S, Dutton RP, Hu P, Xiao Y, Aarabi B, Stein DM, Scalea TM. Automated measurement of "pressure times time dose" of intracranial hypertension best predicts outcome after severe traumatic brain injury. Journal of Trauma and Acute Care Surgery. 2010 Jul 1;69(1):110-8.
22. Yang S., Hu, P. Mackenzie, C. F. "Chapter 24: Trauma Outcome Prediction in the Era of Big Data: From Data Collection to Analytics", Signal Processing and Machine Learning for Biomedical Big Data, Eds. E. Sejdic, T.H. Falk, CRC Press, Boca Raton, FL, (p477-492), 2018.
23. Chen, T. and Guestrin, C., 2016, August. Xgboost: A scalable tree boosting system. In Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining (pp. 785-794).
24. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME. A revision of the Trauma Score. J Trauma. 1989; 29:623-9.
25. Zarzaur BL, Croce MA, Fischer PE, Magnotti LJ, Fabian TC. New vitals after injury: shock index for the young and age× shock index for the old. J Surgl Res. 2008; 147:229-36.
26. Olaussen A, Peterson EL, Mitra B, O'Reilly G, Jennings PA, Fitzgerald M. Massive transfusion prediction with inclusion of the pre-hospital Shock Index. Injury. 2015; 46:822-826
27. Schroll R, Swift D, Tatum D, Couch S, Heaney JB, Llado-Farrulla M, Zucker S, Gill F, Brown G, Buffin N, et al.. Accuracy of shock index versus ABC score to predict need for massive transfusion in trauma patients. Injury. 2018, 49:15-19.
28. Cotton BA, Dossett LA, Haut ER, Shafi S, Nunez TC, Au BK, Zaydfudim V, Johnston M, Arbogast P, Young PP. Multicenter validation of a simplified score to predict massive transfusion in trauma. J Trauma Acute Care Surg. 2010 Jul 1;69(1):S33-9.
29. Cumming G, Finch S. Inference by eye: Confidence intervals, and how to read pictures of data. Am Psychol. 2005 Feb-Mar;60(2):170–8
30. Youden, W.J. (1950). "Index for rating diagnostic tests". Cancer. 3: 32–35.
31. Schisterman, E.F.; Perkins, N.J.; Liu, A.; Bondell, H. (2005). "Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples". Epidemiology. 16 (1): 73–81.
32. Sim ES, Guyette FX, Brown JB, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Neal MD, Forsythe R, et al.. Massive transfusion and the response to prehospital plasma: It is all in how you define it. J Trauma Acute Care Surg. 2020 Jul 1;89(1):43-50.
33. Rehn M, Weaver A E, Eshelby S Røislien J, Lockey D J. Pre-hospital Transfusion of Red Blood Cells in Civilian Trauma Patients. Transfus Med .2018 :277-283.

34. Henriksen HH, Rahbar E, Baer LA, Holcomb JB, Cotton BA, Steinmetz J, Ostrowski SR, Stensballe J, Johansson PI, Wade CE. Pre-hospital transfusion of plasma in hemorrhaging trauma patients independently improves hemostatic competence and acidosis. Scand J Trauma, Resus Emerg Med. 2016; 24: 145
35. Holcomb JB, Donathan DP, Cotton BA, Del Junco DJ, Brown G, von Wenckstern T, Podbielski JM, Camp EA, Hobbs R, Bai Y, et al. Prehospital transfusion of plasma and red cells in trauma patients. Prehosp Emerg Care. 2015; 19: 1-9.
36. Pusateri AE, Moore Ernest A, Moore HB, Le TD, Guyette FX, Chapman MP, Sauaia A, Ghasabyan A, ChandlerJ, McVaney K, et al. Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes. JAMA Surg. 2020;155(2)
37. Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, Gurney J, Butler FK, Gross K, Stockinger ZT. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. JAMA. 2017 Oct 24;318(16):1581-91.
38. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, Adams PW, Daley BJ, Miller RS, Harbrecht BG, et al.. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018 Jul 26;379(4):315-26.
39. Galvagno SM, Sikorski SA, Floccare DJ, Rock P, Mazzeffi MA, Dubose JJ, Scalea TM, Miller C, Richards JE, O'Connor JV, et al. Prehospital point of care testing for the early detection of shock and prediction of lifesaving interventions. Shock. In Press 2020

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ABC	Assessment of Blood Consumption
AUROC	Area under the receiver operating characteristic
BP	Blood Pressure
Bpm	beats per minute
BRI	Bleeding Risk Index
CAT	critical administration threshold
CI	Confidence Interval
ECG	Electrocardiogram
ED	Emergency Department
EMS	Emergency medical services
FAST	Focused Assessment with Sonography for Trauma
GCS	Glasgow Coma Scale
HR	Heart Rate
HRV	Heart Rate Variability
ICU	Intensive Care Unit
INR	international normalized ratio
MI	mutual information
mmHg	millimeters of mercury
MOI	mechanism of injury
MSP	Maryland State Police
MT	Massive Transfusion
NPV	Negative predicted value
PPG	Photoplethysmographic
PPV	Positive predicted value
pRBC	packed red blood cells
PTD	pressure times time dose
RST	Revised Trauma Score
RR	Respiratory Rate
SBP	Systolic Blood Pressure
SD	Standard deviation
SI	Shock Index
SpO2	Oxygenation
STAR	Shock Trauma and Anesthesiology Research
STC	Shock Trauma Center
SpO2	skin oxygenation
TEG	Thromboelastography
TNR	True negative rate
TPR	True positive rate
TRU	trauma resuscitation unit
UMD	University of Maryland
UMMS	University of Maryland Medical System
UMSOM	University of Maryland School of Medicine
UnX	Un-cross matched
USAF	United States AirForce
VS	Vital Signs