Trends of hemoglobin oximetry: do they help predict blood transfusion during trauma patient resuscitation?

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This report describes an observational clinical study.

This report describes cohort observational clinical study. The authors state that the report includes every item in the STROBE checklist for cohort observational clinical studies.

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Abstract:

Background: A noninvasive decision support tool for emergency transfusion would benefit triage and resuscitation. We tested whether 15 min of continuous pulse-oximetry-derived hemoglobin measurements (SpHb) predicts emergency blood transfusion better than conventional oximetry, vital signs, and invasive point-of-admission (POA) laboratory testing. We hypothesize that the trends in noninvasive SpHb features monitored for 15 min predict emergency transfusion better than pulse oximetry, shock index (SI = heart rate / systolic blood pressure) or routine POA laboratory measures.

Methods: We enrolled direct trauma patient admissions ≥18 years with pre-hospital SI≥0.62, collected vital signs (continuous SpHb and conventional pulse oximetry, heart rate, blood pressure) for 15 min after admission, and recorded transfusion [packed red blood cells (pRBCs)] within 1-3, 1-6, and 1-12 hours of admission. One blood sample was drawn during the first 15 min. The laboratory Hb was compared with its corresponding SpHb reading for numerical, clinical, and prediction difference. Ten prediction models for transfusion, including combinations of pre-hospital vital signs, SpHb, conventional oximetry, and routine POA, were selected by stepwise logistic regression. Predictions were compared via area under the receiver operating characteristic curve by De Long's method.

Results: A total of 677 trauma patients were enrolled in the study. The prediction performance of the models including POA laboratory values and SI (and the need for blood pressure) were better than those without POA values or SI. In predicting pRBC1-3hr transfusion, adding SpHb features (ROC=0.65, 95%Confidence Interval[CI]:0.53-0.77) does not improve ROC from the base model (ROC=0.64,95%CI:0.52-0.76) with p=0.48. Adding POA laboratory Hb features (ROC=0.72,95%CI:0.60-0.84) also does not improve prediction performance (p=0.18). Other

POA laboratory testing predicted emergency blood use with ROC of 0.88 (95%CI:0.81-0.96), significantly better than use of SpHb (p=0.00084), and laboratory Hb (p=0.0068).

Conclusions: SpHb added no benefit over conventional oximetry to predict urgent pRBC transfusion for trauma patients. Both models containing POA laboratory test features performed better at predicting pRBC use than pre-hospital SI, the current best noninvasive vital signs transfusion predictor.

Keywords: SpHb, decision-support, point of admission testing, transfusion prediction, noninvasive monitoring

INTRODUCTION

Hemorrhage is the most common cause of preventable death on the battlefield and in civilian trauma care.[1,2] The ability to distinguish rapidly and accurately between those patients with and those without life-threatening bleeding in the field and during point-of-admission (POA) care is a key and as yet imperfectly realized element of trauma triage, for both the initiation of primary control of bleeding and the timely provision of the appropriate range of blood products. .

Diagnosis of bleeding is difficult when the location of hemorrhage is not obvious, such as in the chest, head, or abdomen, and the extent of hemorrhage is unknown. Therefore, robust and quickly identifiable evidence would be useful to guide early imaging, hemorrhage-control, and life-saving interventions. Hemoglobin concentration is an important consideration in patient assessment during hemorrhage and trauma care, although it has limitations.[3] Invasive laboratory hemoglobin (Hb) measurement provides a single reading at the sampling time and, is subject to dilutional variation, and results take time to be processed. Pulse oximetry is an inexpensive, simple, and noninvasive technology for patient monitoring.[4,5] The Masimo Rainbow® Pulse CO-Oximetry™ (Masimo Corporation, Irvine, CA) estimates total hemoglobin concentration and is used for noninvasive continuous hemoglobin (SpHb) monitoring.[a] It therefore has potential for use in computer-aided algorithms essentially immediately, to detect changes in Hb concentration status in trauma patients and provide evidence to support clinicians' early decision-making and transfusion planning.

Our study evaluated the difference between SpHb and conventional laboratory Hb in an unstable trauma patient population during resuscitation. We also tested whether continuously measured SpHb at the point of trauma center admission can improve transfusion and mortality

[a] Masimo Corporation. Accuracy of Noninvasive and Continuous Hemoglobin Measurement by Pulse CO-Oximetry: Data Submitted by Masimo as Part of FDA 510(k) Clearance. Retrieved from www.masimo.com/pdf/whitepaper/LAB7131A.pdf on August 23, 2014.

prediction. We hypothesized that the changing trends of SpHb features predict emergency transfusion better than pre-hospital shock index [SI = heart rate (HR) / systolic blood pressure; bpm/mmHg], pulse oximetry alone or Hb alone or routine POA laboratory measures excluding Hb.

METHODS

With approval of a waiver of patient informed consent from the University of Maryland School of Medicine and United States Air Force Institutional Review Boards, adult patients (age ≥ 18 years) with abnormal pre-hospital SI (≥ 0.62) were consecutively enrolled when they were directly admitted into the Baltimore R Adams Cowley Shock Trauma Center, from Dec. 2011 to May 2013. Enrollment occurred 24 hours per day and 7 days per week when patients met entry criteria and SpHb sensors could be placed without interruption of patient care. Any patient who later developed into a SI ≥ 0.62 was not eligible for enrollment. The Shock Trauma Center is the primary adult resource center for the State of Maryland and admits more than 5,000 trauma patients per year. Continuous vital signs were collected via BedMaster (GE Marquette, Milwaukee, WI) vital signs collection system during the first hour of patient resuscitation. As the consort diagram in Figure 1 shows, 1191 patients were admitted into the trauma resuscitation unit (TRU), satisfying the age and pre-hospital SI criteria. All patients were directly transported from the scene of injury, none received blood before hospital admission. After excluding 480 eligible patients in whom the placement of an additional sensor for the purposes of continuous SpHb monitoring did not occur for logistical reasons (see study limitations), 711 patients had continuous SpHb measurement. Within this subgroup, we removed 34 patients who had incomplete laboratory POA data. For outcomes, the use of blood was documented for intervals of 3, 6, and 12 hours after admission and validated via blood bank records.

Two approaches to obtaining Hb values were used. After a patient's admission to the TRU, a Masimo rainbow® Pulse CO-Oximetry™ with SpHb was applied, (in addition to a conventional pulse oximeter and vital signs sensors), to allow continuous monitoring of SpHb. Masimo Rad-87 (ver. 1405) software was used. The SpHb sensor (Rev F) was usually placed on

the finger on the opposite side to the blood pressure cuff. A black finger shield was secured over the finger sensor to prevent ambient light interference with the SpHb sensor, and the finger sensor was placed with one digit separation from the GE Marquette pulse oximeter used for patient care. If there were bilateral upper arm injuries, the sensor was applied to the left big toe.

A blood sample was drawn in tandem with intravenous access within the first 15 min after TRU admission. A co-located research assistant recorded the SpHb reading at the time of the laboratory draw. Blood samples were analyzed for Hb concentration(Sysmex® XN-2000 Automated Hematology Analyzer, Sysmex Corp., Kobe, Japan)[b], and other tests including partial thromboplastin time, international normalized ratio, fibrinogen, lactate, and glucose (Abbott Laboratories Inc., Analyzer NSN 6630015205212, Chicago, IL) within 5 to 15 min after sampling.

Statistical Analysis

Statistical analyses compared 1) absolute values of SpHb and laboratory Hb, 2) their transfusion prediction performance, and 3) the change in transfusion prediction with additional blood sample analyses. Firstly, the difference between SpHb and laboratory Hb readings was directly compared using the Bland-Altman plot.[6-8] Mean bias and 95% limits of agreement were used to quantify the difference between the two measurements.[9] Because, the Bland-Altman plot is an overall evaluation that does not distinguish subsets of different clinical meaning, a Clarke-type error grid analysis[10] was used as another way to display the difference between SpHb, as a new measuring tool, and laboratory Hb as the reference measurement and to suggest the clinical relevance of the differences.[11] Within the Clarke-type error plot, a linear regression and the

[b] XN-Series analyziers have HGB(g/dL) precision at three levels: low, normal, and high, with means 6.5, 13.49, and 17.3, and total coefficient of variation 1.08, 0.62, and 0.89. 510(k) Substantial Equivalence Determination Decision Summary, Retrieved from www.accessdata.fda.gov/cdrh_docs/reviews/K112605.pdf on May 25, 2015.

coefficient of determination (R^2) are shown to evaluate how well SpHb can be replicated by the linear model using laboratory Hb as the predictor.

Secondly, we compared the prediction performance of features derived from SpHb and laboratory Hb to show the usefulness of each measurement, even though they may be different. We asked if noninvasive continuous SpHb monitoring could be as good as, or able to improve, the prediction accuracy of invasive Hb measurement for mortality or for institution of life-saving interventions, such as blood transfusion. Thirdly, we compared the mortality prediction performance with models using laboratory tests other than Hb concentration including partial thromboplastin time, international normalized ratio, fibrinogen, lactate, and glucose, which are predictors of hemorrhage shock and mortality. Below we describe the design of predictive features and models, as well as their evaluations.

Vital Signs Features

We compared the usefulness (prediction power) of SpHb and Hb for dichotomous outcomes such as packed red blood cell (pRBC) use in the 1-3, 1-6, and 1-12 hours after admission and mortality. We included four types of features in the models and adjusted for age and sex. As SI is used as the current best predictor of transfusion[12,13] and HR is an important factor in circulatory assessment, pre-hospital HR and pre-hospital SI were included in the base models. For continuous SpHb measurements from the Masimo sensor, we used the first 15 min of data after the sensor placement, which was usually within 1-5 min of patient arrival. We designed various features to quantify the SpHb, including changing trend and "dose" below clinical thresholds, which are detailed below. Models also included other values analyzed from laboratory blood tests, obtained within the first 15 min of TRU admission that are available from three point-of-

care testing cartridges (iSTAT, Abbott Laboratories Inc., Chicago, IL) related to detection of hemorrhage and shock states. Table 1 summarizes the 10 models in terms of their variables, which can be categorized into two groups. The first five models use the pre-hospital HR, while the last five models use the pre-hospital SI. Within each group, we compare models using the addition of SpHb, Hb, other laboratory tests, and all available information.

A total of 31 features were designed for continuous SpHb analysis and used for selection in prediction models. The degree and duration of SpHb less than 10, 11, 12, 13, and 14 g/dL were calculated.[14] The first, second, and third quartiles of SpHb, as well as its interquartile range and changing trend of SpHb were assessed as features of the models.[7] To characterize the changing pattern of SpHb during the initial 15 min monitoring, SpHb values were averaged within a sequence of exclusive same size time windows, i.e., 1, 2, and 3 min (red, black, and green curves in Figure 2). The rate of change was calculated between any two averaged SpHb values in the same size window. For example, when the first 15 min of continuous SpHb measurements were averaged every minute, there were 15 data points (denoted as Ave_i, $1 \leq i \leq 15$). The slope between two distinct data points *i* and *j* was calculated as $Slope_{ij} = (Ave_j - Ave_i)/(j-i)$ with unit g/dL/min, where $1 \leq i < j \leq 15$. We then calculated the percentage occurrence of increase and decrease, the maximum increase and decrease rate, and their standard deviations (SDs).

Models

Using multivariate logistic regression models, we compared feature groups for transfusion prediction performance in terms of the area under the receiver operating characteristic curve (AUROC). To avoid over-fitting, we used stepwise feature selection to build parsimonious

models. In forward selection, features with the significance level of the Wald chi-square test ≤0.2 were included; in backward selection, features with the significance level >0.3 were removed. Furthermore, we used 10-fold cross-validation repeated 10 times with stratified sampling to examine how well-trained models could predict with previously unseen data. Because relatively few of the patients were transfused, the data were skewed, so the AUROC curve was used to evaluate the transfusion discriminant capability of each classification model,[15] and the ROCs were compared by DeLong's method, with the null hypothesis that a pair of ROCs are not significantly different.[16] A p-value less than 0.05 was considered statistically significant. The Hosmer-Lemeshow goodness of fit test was implemented for checking the model fitting.[17] All models' prediction performances are reported with their ROCs, 95% confidence interval of ROCs, sensitivity and specificity. All statistical analyses, predictive model building, 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

Table 2 summarizes the demographics of the final dataset, in comparisons to the original 1191 cases. We enrolled 677 patients (479 males) with both continuous SpHb monitoring and POA laboratory tests which included Hb.

The Bland-Altman analysis shows that the mean difference (bias) of the two measurements was -1.0 g/dL. The 95% limits of agreement ranged from 3.0 to -4.3 g/dL, (bias ±1.96 SD of the differences) (see Figure 3). SpHb readings were generally lower than Hb values. The histogram shows a normal distribution of differences centering near the bias; 35.2% of data points have differences within -1.0 to 1.0 g/dL, and 64.8% have differences in the range -2.0 to 2.0 g/dL.

Figure 4 shows the modified Clarke-type error grid with a fitted linear line. The scatter plot of SpHb against laboratory Hb is partitioned into three regions with clinical meaning. With the Clarke-type error grid analysis, there are 98.93% points that fall into region A. In this dataset, no data points fall into region C. Figure 5 shows the histograms of SpHb (green) and laboratory Hb (red) were mostly located above 10 g/dL. The laboratory Hb has a mean of 14.0 g/dL with an SD 1.6 g/dL (first, second, and third quartiles are 13.0, 14.1, and 15.0 g/dL, respectively). The SpHb has a mean of 12.9 g/dL with an SD of 1.7 g/dL (first, second, and third quartiles are 11.8, 13.0, and 14.0 g/dL, respectively). Moreover, using SpHb as a predictor and laboratory Hb as a response, a linear regression model was fitted with the data. The coefficient of determination, R^2 = 0.645, showed that the data fit only fairly with the linear equation, indicating SpHb and laboratory Hb in this dataset do not have a strong linear relationship.

At the level of predictive power comparison, all models had balanced training and testing performance, meaning that their AUROC differences were less than 10%. Therefore, we used the

models' training over the entire dataset for profiling their prediction performance. Moreover, the Hosmer-Lemeshow goodness of fit test shows that there was no strong evidence of poor fit for each transfusion prediction model. Tables 3a-3d summarize the performance of models in predicting pRBC use in 3, 6, 12 hours, and mortality, measured by ROC, 95% confidence interval (CI) of ROC, sensitivity, and specificity. In general, models with pre-hospital SI as a candidate feature had higher AUROCs than models with pre-hospital HR alone. In models that use either pre-hospital SI or HR, the prediction performance showed statistically significant differences among the feature groups of SpHb, laboratory Hb, and other laboratory tests. Using features from SpHb measured in the first 15 min does not significantly improve the prediction sensitivity and specificity from the base models. Although models using laboratory Hb have higher AUROC than models using SpHb (see Figures 6 and 7), they both only have fair (AUROCs<0.8) performance.

However, other laboratory test results boost the model performance, especially in predicting blood transfusion. For example, the model using pre-hospital HR and other lab tests to predict pRBC1-3hr has AUROC = 0.88 (95% CI 0.81-0.96), which is significantly higher than the model using SpHb (AUROC=0.65, 95% CI 0.53-0.77) (p=0.00084) and the model using lab Hb (AUROC=0.72, 95% CI 0.60-0.84) (p=0.00678) in predicting pRBC use in the 1-3 hours after admission. Models using pre-hospital SI further support the inference that SpHb and laboratory Hb do not contribute significantly to transfusion prediction. By adding SpHb or Hb features to the models using laboratory tests, the performance showed no statistically significant difference. Also the 95%CI of their ROCs are highly overlapped (Table 3a-3d). ROC comparison through Delong's methods show their ROCs are not significantly differenct (Table 4a-4d). Hence we conclude that SpHb and the Hb value in POA laboratory tests have no

significant contribution to transfusion prediction independent of the partial thromboplastin time, international normalized ratio, fibrinogen, lactate, and glucose. Table 4a-4d include the p-values for model AUROC comparisons.

DISCUSSION

Noninvasive continuous hemoglobin monitoring is an appealing new technique for estimation of hemoglobin concentration changes. No studies have monitored transfusion prediction performance of SpHb trends or compared these with Hb in real-time during trauma patient resuscitation. Several studies have compared SpHb with laboratory Hb with different populations monitored in stabilized conditions, most without SpHb trends. Studies compared SpHb and Hb during spine surgery,[6,8] gastrointestinal bleeding in ICU,[18] cardiac surgery,[19] general ICU patients,[20] and trauma patients in ICU.[21] Trends in differences between SpHb measurements were monitored in one paper studying ICU patients.[20] In these papers, different statistical methods were used to quantify SpHb and Hb measurement agreement. Due to the experimental and patient population differences, conclusions on SpHb accuracy also vary. In a study of 20 patients undergoing spine surgery, SpHb and laboratory Hb had a difference of <1.5 g/dL for 61% of observations and a difference of >2.0 g/dL for 22% of observations.[6] In 44 patients with repeated measures, a total of 85 pairs of SpHb and laboratory Hb analyzed by HemoCue, SpHb gave lower readings during surgery with bleeding,[22] based on linear regression and Bland-Altman analysis. Another study using 165 laboratory Hb measurements obtained from 20 subjects undergoing hemodilution demonstrated an average difference of <1.0 g/dL compared with the laboratory Hb measurements.[23] A meta-analysis of 32 studies also suggests that the wide limits of agreement between SpHb and laboratory Hb (-2.59 to 2.80 g/dL) should make clinicians cautious when using the SpHb values.[24] Even two different noninvasive SpHb sensors [the Pronto-7 monitor (Masimo, Irvine, CA) and the NBM-200MP monitor (Orsense, Nes Ziona, Israel)] were found to have limited agreement.[25]

Despite the active research in quantifying the accuracy of SpHb compared with laboratory Hb, guidance in interpreting the difference is rare. Naftalovich et al. attempted to distinguish the macro hemoglobin measured by laboratory test and the total hemoglobin estimated by SpHb using both macro and micro hemoglobin.[26] They hypothesized that more contribution from the microcirculatory hemoglobin during blood loss increases the difference. In our study, through multivariate logistic regression and ROC evaluation, we demonstrated that the changing trend of SpHb does not boost the predictive models in comparison to base models that use only age, sex, and pre-hospital vital signs. The laboratory Hb values also did not significantly improve transfusion predictions from the base models. However, other laboratory tests, such as partial thromboplastin time, international normalized ratio, lactate and glucose significantly improve the discriminant capability of the transfusion predictive models as these laboratory values are well recognized to changes with mediator release, and reperfusion injury associated with mortality and accompanying resuscitation from hemorrhagic shock.[27-29] A previous study also showed that SpHb may not improve the prediction of pRBC use, compared to the features extracted from conventional pulse oximetry. [30]

In this single-center study, the following were limitations. First, not all patients admitted during the study enrollment period were included because of logistical reasons such as multiple simultaneous admissions, concerns that adding an additional pulse oximeter and finger shield would interrupt emergency clinical care (especially in those mortally injured), emergency patient admissions occurring with insufficient notice to set up the data collection process. As a result the enrolled cohort had a greater incidence of blunt trauma, lower mortality and transfusion rate than the entire patient admission cohort, so SpHb may produce a different prediction of transfusion needs after penetrating injury, in military trauma, and among very severely injured populations.

Second, each patient had only one blood sample in the first 15 min after TRU admission. For accurate comparison and improved transfusion prediction power, repeated samples may reduce the impact of fluid bolus given during resuscitation and identify interval changes associated with bleeding.[31] In addition, Masimo Corporation has revised the sensor used since study enrollment was completed and the new Rev K sensor may give different results. Because of proprietary issues, photoplethysmography data from Masimo pulse oximetry were not made available, so that perfusion index and pleth variability index could not be used in our prediction models. Finally, the outcomes of our dataset are imbalanced (e.g., 3.0% patients were given pRBC in the 1-3 hours after admission) and this may cause biases affecting the accuracy of models for early transfusion prediction.

CONCLUSION

Noninvasive SpHb provides continuous monitoring limits-of-agreement with laboratory Hb that are too wide for clinical use during trauma patient resuscitation. Adding SpHb trend features, such as "dose" of changes in SpHb, rate of change or identifying thresholds or changes of SpHb during the first 15 min of continuous measurement, may not improve prediction of urgent pRBC transfusion for trauma patients in comparison to use of base models including pre-hospital HR or SI alone.

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Table 1. Model Definitions for Prediction Comparison

Group	Model Name	Candidate Variables
Pre-hospital heart rate group	Base(HR)	Age, sex, pre-hospital heart rate
	+SpHb	Base(HR)+ SpHb
	+lab Hb	Base(HR) + laboratory Hb
	+other lab	Base(HR) + other laboratory tests*
	+SpHb+other lab	Base(HR) + SpHb + other laboratory tests
Pre-hospital shock index group	Base(SI)	Age, sex, pre-hospital shock index
	+SpHb	Base(SI) + SpHb
	+lab Hb	Base(SI) + laboratory Hb
	+other lab	Base(SI) + other laboratory tests
	+SpHb+other lab	Base(SI) + SpHb+ other laboratory tests

HR = heart rate, SI = shock index, Hb = hemoglobin, SpHb = noninvasive continuous hemoglobin.

*Other laboratory tests: partial thromboplastin time, international normalized ratio, fibrinogen, lactate, and glucose.

Table 2. Characteristics of Patients (N=677)

Characteristic	1191cases	677 cases
Mean age, yr (SD)	40.4 (17.7)	38.7 (16.6)
Admission Glasgow Coma Scale score	Min: 3; Max: 15	Min: 3; Max: 15
Sex, n (%)		
Male	823 (69.1)	479 (70.8)
Female	368 (30.9)	198 (29.2)
Injury type, n (%)		
Blunt	955 (80.2)	589 (87.0)
Penetrating	176 (14.8)	79 (11.7)
Other	60 (5.0)	9 (1.3)
Mechanism of injury, n (%)		
Motor vehicle associated	557 (46.8)	354 (52.3)
Falls	253 (21.2)	141 (20.8)
Interpersonal violence	230 (19.3)	132 (19.5)
Other	151 (12.7)	50 (7.4)
Outcome, n (%)		
pRBC1-3	80 (6.7)	20 (3.0)
pRBC1-6	106 (8.9)	29 (4.3)
pRBC1-12	121 (10.2)	36 (5.3)
Mortality	61 (5.1)	12 (1.8)

SD = standard deviation; pRBC = packed red blood cells.

Table 3a. ROC, 95% CI, Sensitivity, and Specificity for Models Predicting pRBC 1- to 3-Hour Use

Model	ROC	95% CI	Sensitivity	Specificity
	Pre-Hospital Heart Rate Group			
Base(HR)	0.64	0.52-0.76	0.95	0.29
+SpHb	0.65	0.53-0.77	0.40	0.86
+lab Hb	0.72	0.60-0.84	0.70	0.73
+other lab	0.88	0.81-0.96	0.85	0.84
+SpHb+other lab	0.89	0.81-0.96	0.75	0.91
	Pre-Hospital Shock Index Group			
Base(SI)	0.78	0.63-0.92	0.70	0.89
+SpHb	0.80	0.66-0.93	0.70	0.91
+lab Hb	0.78	0.65-0.92	0.75	0.85
+other lab	0.91	0.85-0.96	0.90	0.77
+SpHb+other lab	0.91	0.86-0.96	0.95	0.73

CI = confidence interval; pRBC = packed red blood cells; ROC = receiver operating characteristic curve.

Models are fully defined in Table 1.

Table 3b. ROC, 95% CI, Sensitivity, and Specificity for Models Predicting pRBC 1- to 6-Hour Use

Model	ROC	95% CI	Sensitivity	Specificity
	Pre-Hospital Heart Rate Group			
Base(HR)	0.62	0.52-0.71	0.97	0.30
+SpHb	0.66	0.56-0.77	0.41	0.87
+lab Hb	0.71	0.61-0.80	0.62	0.71
+other lab	0.85	0.77-0.92	0.76	0.84
+SpHb+other lab	0.86	0.80-0.93	0.76	0.83
	Pre-Hospital Shock Index Group			
Base(SI)	0.71	0.58-0.84	0.59	0.91
+SpHb	0.75	0.64-0.86	0.69	0.80
+lab Hb	0.74	0.63-0.85	0.62	0.85
+other lab	0.84	0.77-0.91	0.72	0.81
+SpHb+other lab	0.85	0.78-0.92	0.72	0.82

CI = confidence interval; pRBC = packed red blood cells; ROC = receiver operating characteristic curve.

Models are fully defined in Table 1.

Table 3c. ROC, 95% CI, Sensitivity, and Specificity for Models Predicting pRBC 1- to 12-Hour Use

Model	ROC	95% CI	Sensitivity	Specificity
	Pre-Hospital Heart Rate Group			
Base(HR)	0.61	0.51-0.70	0.47	0.78
+SpHb	0.64	0.54-0.73	0.78	0.44
+lab Hb	0.69	0.60-0.78	0.47	0.86
+other lab	0.81	0.74-0.89	0.75	0.85
+SpHb+other lab	0.82	0.73-0.90	0.78	0.82
	Pre-Hospital Shock Index Group			
Base(SI)	0.69	0.58-0.81	0.50	0.92
+SpHb	0.73	0.62-0.84	0.61	0.85
+lab Hb	0.73	0.63-0.84	0.61	0.85
+other lab	0.82	0.75-0.89	0.75	0.77
+SpHb+other lab	0.83	0.75-0.91	0.72	0.83

CI = confidence interval; pRBC = packed red blood cells; ROC = receiver operating characteristic curve.

Models are fully defined in Table 1.

Table 3d. ROC, 95% CI, Sensitivity, and Specificity for Models Predicting mortality

Model	ROC	95% CI	Sensitivity	Specificity
	Pre-Hospital Heart Rate Group			
Base(HR)	0.79	0.67-0.91	0.67	0.83
+SpHb	0.85	0.74-0.96	0.83	0.74
+lab Hb	0.83	0.73-0.93	0.83	0.71
+other lab	0.86	0.76-0.96	0.83	0.75
+SpHb+other lab	0.92	0.85-0.98	1.00	0.67
	Pre-Hospital Shock Index Group			
Base(SI)	0.74	0.59-0.90	0.83	0.59
+SpHb	0.90	0.82-0.98	0.92	0.76
+lab Hb	0.78	0.63-0.93	0.75	0.78
+other lab	0.81	0.66-0.96	0.75	0.82
+SpHb+other lab	0.91	0.84-0.98	0.92	0.79

CI = confidence interval; pRBC = packed red blood cells; ROC = receiver operating characteristic curve.

Models are fully defined in Table 1.

Table 4a. ROC comparisons for model predicting pRBC1-3hr

Pre-Hospital Heart Rate Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(HR)	0.47683	0.17767	0.00033	0.00033
+SpHb		0.24740	0.00084	0.00060
+lab Hb			0.00678	0.00642
+other lab				0.68570
Pre-Hospital Shock Index Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(SI)	0.31849	0.67330	0.04610	0.05093
+SpHb		0.59831	0.06837	0.06639
+lab Hb			0.05008	0.05245
+other lab				0.41333

Table 4b. ROC comparisons for model predicting pRBC1-6hr

Pre-Hospital Heart Rate Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(HR)	0.21356	0.13101	0.00046	0.00016
+SpHb		0.48355	0.00809	0.00181
+lab Hb			0.00239	0.00127
+other lab				0.22711
Pre-Hospital Shock Index Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(SI)	0.08486	0.22488	0.00779	0.00478
+SpHb		0.74888	0.02692	0.01278
+lab Hb			0.02972	0.02117
+other lab				0.44628

Table 4c. ROC comparisons for model predicting pRBC1-12hr

Pre-Hospital Heart Rate Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(HR)	0.49690	0.16335	0.00116	0.00102
+SpHb		0.33927	0.00349	0.00145
+lab Hb			0.00206	0.00255
+other lab				0.76447
Pre-Hospital Shock Index Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(SI)	0.09813	0.12228	0.00470	0.00582
+SpHb		0.95343	0.01410	0.00850

+lab Hb			0.02402	0.02565
+other lab				0.29616

Table 4d. ROC comparisons for model predciting mortality

Pre-Hospital Heart Rate Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(HR)	0.13832	0.38688	0.09659	0.00258
+SpHb		0.67459	0.79909	0.10765
+lab Hb			0.03617	0.00064
+other lab				0.02646
Pre-Hospital Shock Index Group				
	+SpHb	+lab Hb	+other lab	+SpHb +other lab
Base(SI)	0.00342	0.18648	0.06054	0.00122
+SpHb		0.01384	0.07995	0.04533
+lab Hb			0.01979	0.00552
+other lab				0.03535

Models are fully defined in Table 1.

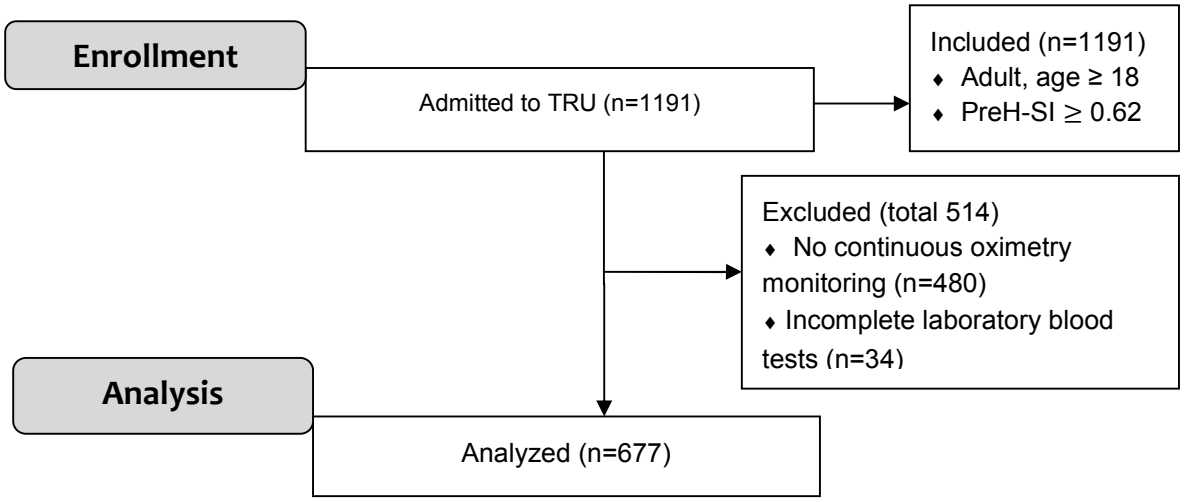


Figure 1. Diagram of case enrollment. TRU = trauma resuscitation unit; PreH-SI = pre-hospital shock index.

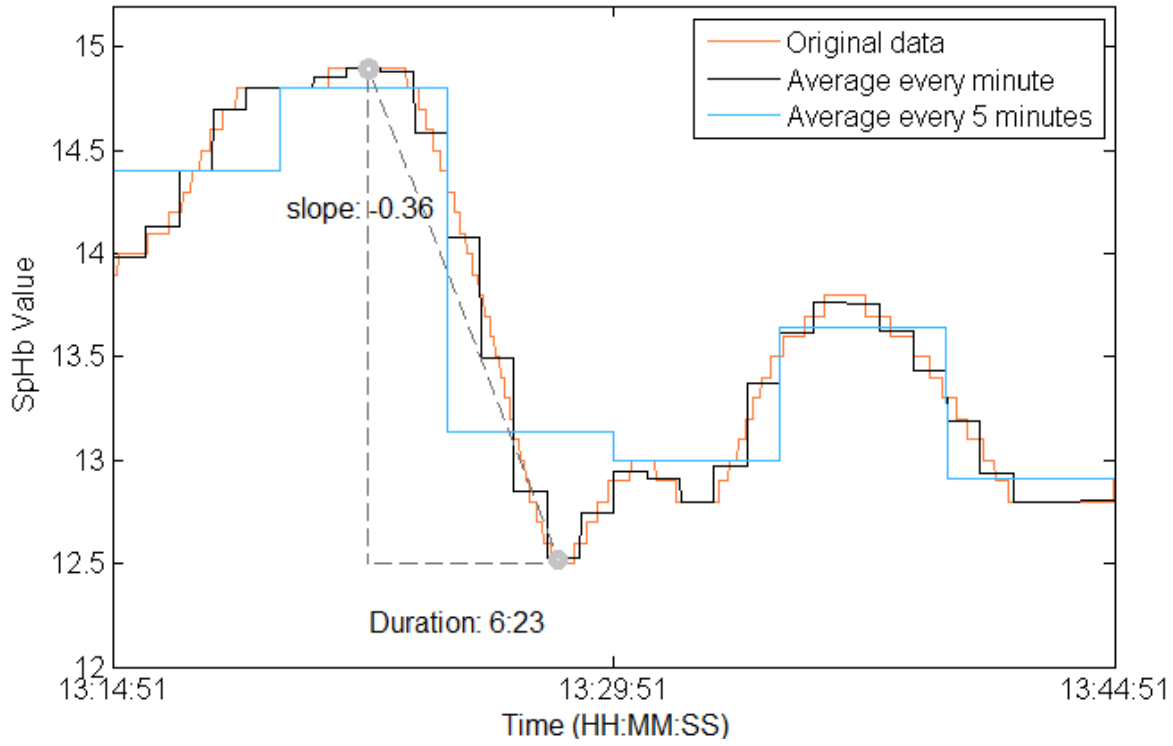


Figure 2. An example of calculation of changing rate of continuously monitored SpHb. Orange, black, and blue curves show 1, 2, and 3 min averaging of the original SpHb measurement provided by Masimo. Two gray dots are the start and end points of a time window for calculating the slope between the two SpHb readings. The slope between the two points was calculated as -0.36. SpHb = noninvasive continuous hemoglobin.

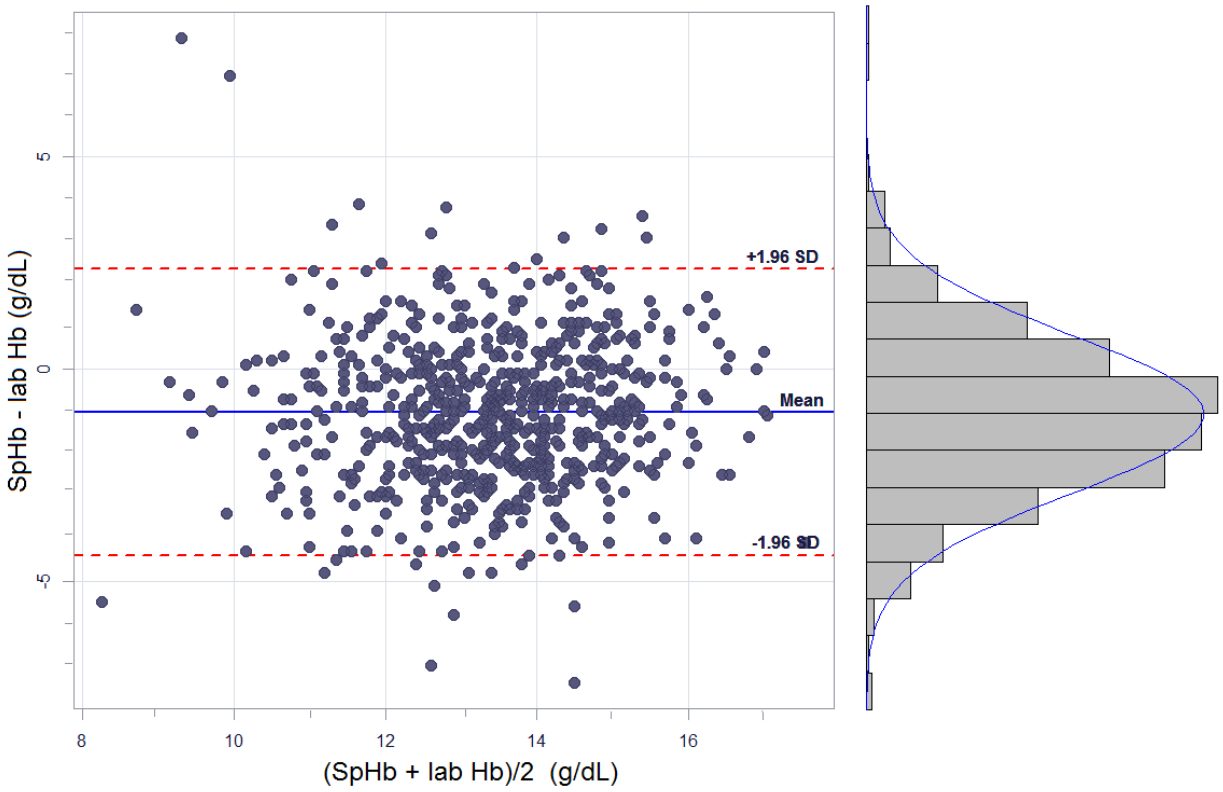


Figure 3. Left panel shows the Bland-Altman plot for the agreement of hemoglobin measured by the Masimo Pulse CO-Oximetry™ with SpHb (SpHB) and the laboratory Hb. The horizontal red dashed lines are the limits of agreement. The horizontal blue dashed line represents the bias. Right panel shows the histogram of points falling into each bin with size of 1 g/dL in the vertical axis. Hb = hemoglobin; SpHb = noninvasive continuous hemoglobin.

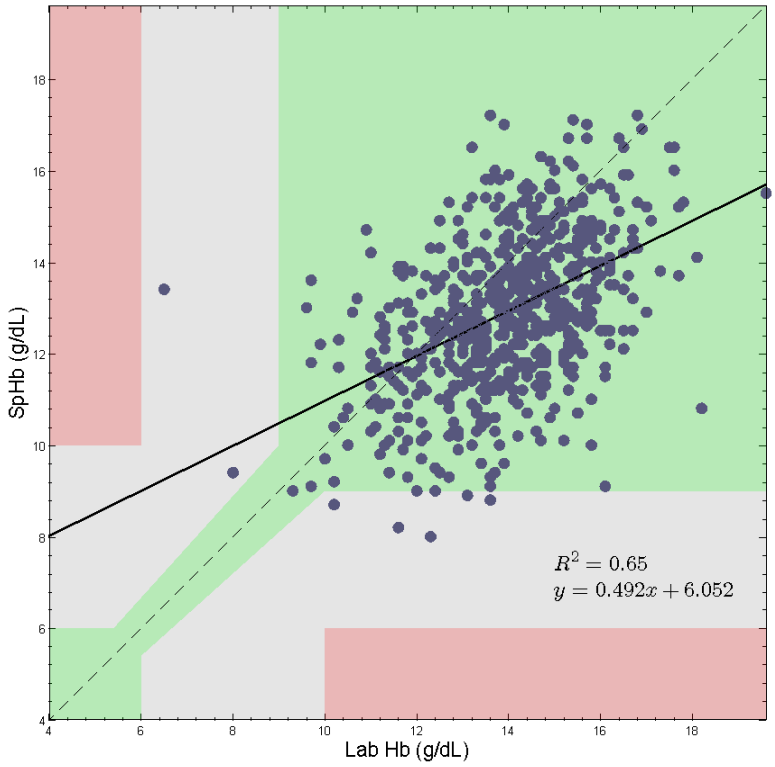


Figure 4. Clarke-type error grid analysis of SpHb versus laboratory Hb. In region A the values indicate the difference between SpHb and laboratory Hb is clinically acceptable. Region B contains data points with significant errors when Hb and SpHb are compared . Region C contains data points that may result in major therapeutic errors due to their large differences. Hb = hemoglobin; R^2 = coefficient of determination; SpHb = noninvasive continuous hemoglobin.

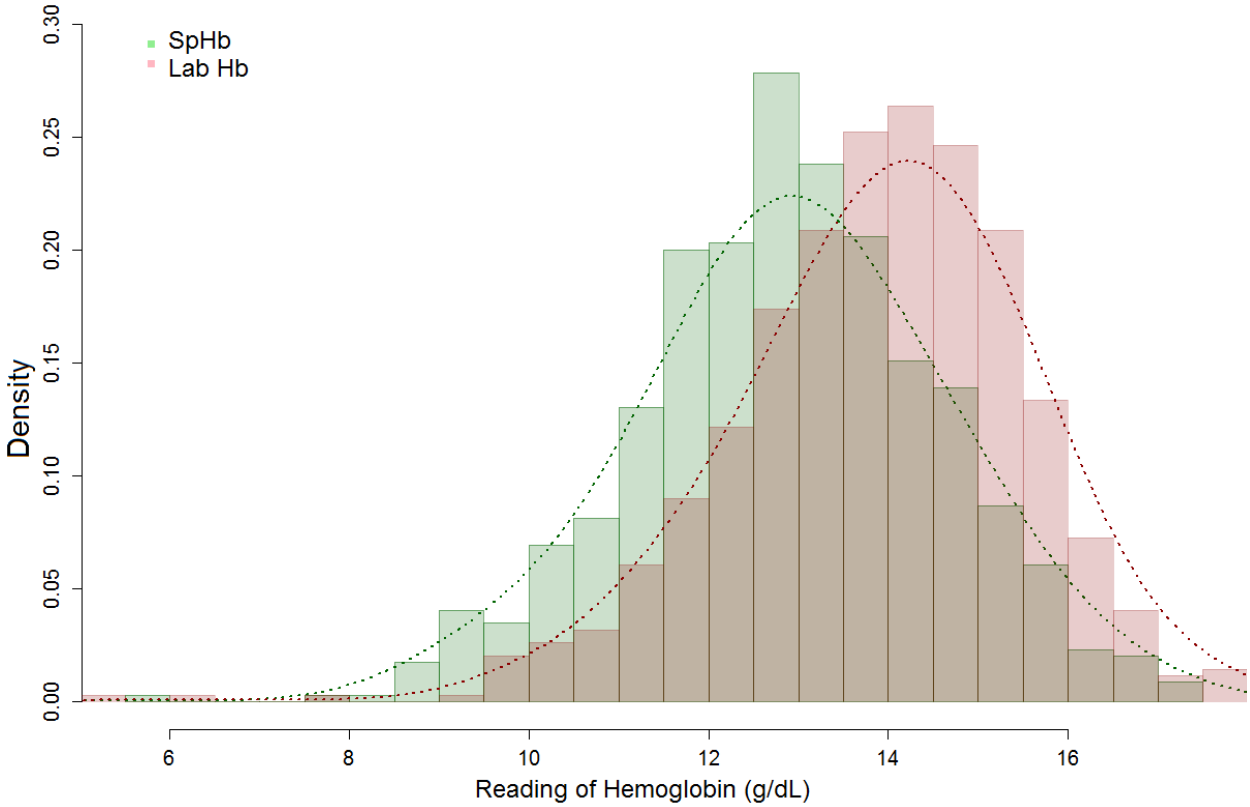
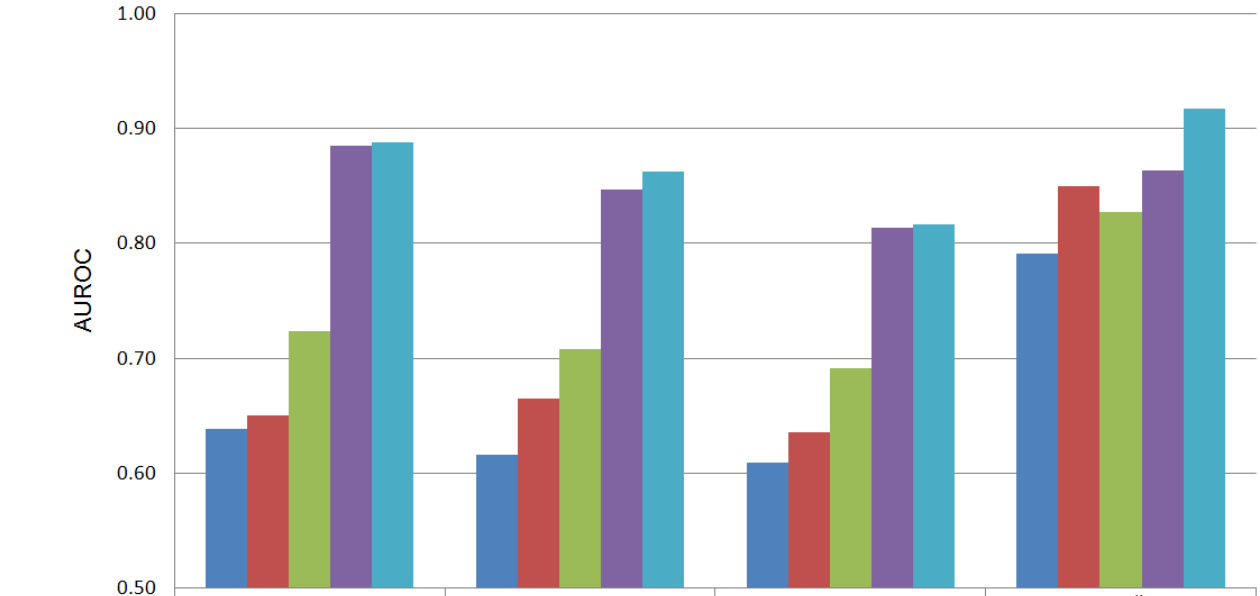
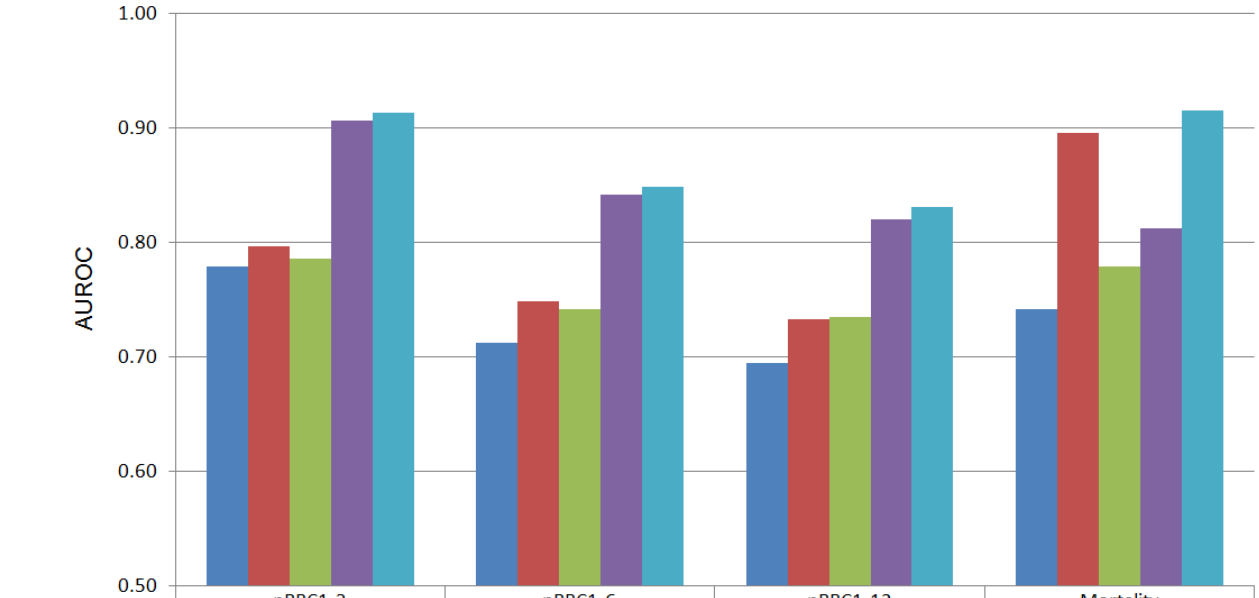


Figure 5. Histogram with probability density curves for SpHb and laboratory Hb readings. SpHb has a mean of 12.9 g/dL. Laboratory Hb has a mean of 14.0 g/dL. Hb = hemoglobin; SpHb = noninvasive continuous hemoglobin.



	pRBC1-3	pRBC1-6	pRBC1-12	Mortality
Base(HR)	0.64	0.62	0.61	0.79
+SpHb	0.65	0.66	0.64	0.85
+lab Hb	0.72	0.71	0.69	0.83
+other lab	0.88	0.85	0.81	0.86
+SpHb+other lab	0.89	0.86	0.82	0.92

Figure 6. Comparisons of AUROCs for models using pre-hospital HR. AUROC = area under the receiver operating characteristic curve; HR = heart rate; pRBC = packed red blood cells. Models using other laboratory tests have higher AUROCs, while adding SpHb features does not significantly improve model performance.



	pRBC1-3	pRBC1-6	pRBC1-12	Mortality
Base(SI)	0.78	0.71	0.69	0.74
+SpHb	0.80	0.75	0.73	0.90
+lab Hb	0.79	0.74	0.73	0.78
+other lab	0.91	0.84	0.82	0.81
+SpHb+other lab	0.91	0.85	0.83	0.91

Figure 7. Comparisons of AUROCs for models using pre-hospital SI. AUROC = area under the receiver operating characteristic curve; pRBC = packed red blood cells; SI = shock index. Models using other laboratory tests have higher AUROCs, while adding SpHb features does not significantly improve model performance.