Comparison of massive and emergency transfusion prediction scoring systems after trauma with a new Bleeding Risk Index score applied in-flight

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BACKGROUND: Assessment of blood consumption (ABC), shock index (SI), and Revised Trauma Score (RTS) are used to estimate the need for blood transfusion and triage. We compared Bleeding Risk Index (BRI) score calculated with trauma patient noninvasive vital signs and hypothesized that prehospital BRI has better performance compared with ABC, RTS, and SI for predicting the need for emergent and massive transfusion (MT).

METHODS: We analyzed 2-year in-flight data from adult trauma patients transported directly to a Level I trauma center via helicopter. The BRI scores 0 to 1 were derived from continuous features of photoplethymographic and electrocardiographic waveforms, oximetry values, blood pressure trends. The ABC, RTS, and SI were calculated using admission data. The area under the receiver operating characteristic curve (AUROC) with 95% confidence interval (CI) was calculated for predictions of critical administration threshold (CAT, ≥3 units of blood in the first hour) or MT (≥10 units of blood in the first 24 hours). DeLong's method was used to compare AUROCs for different scoring systems. $p < 0.05$ was considered statistically significant.

RESULTS: Among 1,396 patients, age was 46.5 ± 20.1 years (SD), 67.1% were male. The MT rate was 3.2% and CAT was 7.6%, most (92.8%) were blunt injury. Mortality was 6.6%. Scene arrival to hospital time was 35.3 ± (10.5) minutes. The BRI prediction of MT with AUROC 0.92 (95% CI, 0.89–0.95) was significantly better than ABC, SI, or RTS (AUROCs = 0.80, 0.83, 0.78, respectively; 95% CIs 0.73–0.87, 0.76–0.90, 0.71–0.85, respectively). The BRI prediction of CAT had an AUROC of 0.91 (95% CI, 0.86–0.94), which was significantly better than ABC (AUROC, 077; 95% CI, 0.73–0.82) or RTS (AUROC, 0.79; 95% CI, 0.74–0.83) and better than SI (AUROC, 0.85; 95% CI, 0.80–0.89). The BRI score threshold for optimal prediction of CAT was 0.25 and for MT was 0.28.

CONCLUSION: The autonomous continuous noninvasive patient vital signs–based BRI score performs better than ABC, RTS, and SI predictions of MT and CAT. Bleeding Risk Index does not require additional data entry or expert interpretation. (*J Trauma Acute Care Surg.* 2021;90: 268–273. Copyright © 2021 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Prognostic test, level III.

KEY WORDS: Autonomous prediction of transfusion; vital signs signal analysis; trauma patient triage; machine learning; in-flight prediction algorithms.

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] 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. Scoring systems, such as the Assessment of Blood Consumption (ABC),[3] Revised Trauma Score (RTS),[4] and shock index (SI = heart rate [HR]/systolic blood pressure),[5–7] have been used to estimate the need for emergency blood transfusion and triage. Our previous research efforts for early detection of hemorrhage in trauma patients focused on determining the probability of future transfusion during the first hours after trauma center admission. Real-time capture of a combination of continuous noninvasive patient vital signs, with development of real-time computer algorithms were used to predict the need for blood transfusion and other interventions after trauma center admission. Our Bleeding Risk Index (BRI) algorithms, based on the autonomous analysis of any combination of available continuous photoplethysmographic (PPG), and/or electrocardiogram (ECG) waveforms, pulse oximetry and blood pressure (BP) signals predicted blood transfusion within 6 hours

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of hospital admission with area under the receiver operating curve (AUROC) of 0.92 in severely injured trauma patients.[8–11] We hypothesized that BRI, derived from noninvasive vital signs collected in-flight, would have better performance compared with ABC, RTS, and SI in predicting emergent and massive transfusion (MT), during transport by helicopter from the scene of injury, to the University of Maryland, R Adams Cowley Shock Trauma Center (STC).

METHODS

After Institutional Review Board approval of a waiver of informed consent, 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 prehospital vital signs collected included PPG and ECG waveforms, HR (bpm), percutaneous oxygen saturation (SpO_2%), noninvasive cuff BP (in mm Hg), and respiratory rate (RR per minute).

Outcomes

Demographic data, such as age, sex, mechanism and type of injury, Glasgow Coma Scale (GCS) score, 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 with those of our BRI algorithm to identify trauma patients administered MT, defined as 10 units or greater pRBC[12] in first 24 hours and critical administration threshold (CAT), defined as 3 units or greater pRBC in the first hour[13] 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 AUROCs comparing ABC, SI, RTS, and BRI for predicting CAT and MT.

The BRI Score

The BRI score is derived from an algorithm developed as a result of previously reported studies in which the algorithm was independently trained and tested[8,11] using pre-2016 patient data obtained from the first 15 minutes of trauma admission continuous vital signs. The BRI score is continuous ranging from 0 to 1, with higher score corresponding to higher probability of receiving CAT or MT. The BRI scores were calculated based on features derived from PPG and ECG waveforms[11] (both captured at 250 Hz) continuously collected at the scene and during prehospital helicopter transport, including oximetry SpO_2 numeric values and systolic BP trends (captured at 1 Hz). For the high-fidelity PPG and ECG waveforms, data were preprocessed by removal of signal artifacts before extraction of features used in the transfusion prediction models as previously reported.[8–11] In this study, we applied the BRI model to prehospital data, and evaluated its prediction performance for in-hospital CAT and MT outcomes. The initial 5 minutes, 10 minutes, and entire prehospital data were used as input to calculate BRI score.

Other Predictions of Triage and Transfusion

We compared existing scoring systems for early identification of uncontrolled hemorrhage and triage and found ABC, SI, and RTS had the best combination of prediction and utility.[12] The ABC score[3] is a scoring system for MT, which assigns a score from 0 to 4 based on the following questions: (a) Is it the mechanism of injury penetrating? (b) Is the prehospital systolic BP 90 mm Hg or less? (c) Is the prehospital HR 120 bpm or greater? (d) Is the ultrasound Focused Assessment with Sonography for Trauma (FAST) examination positive? The RTS[4] is used for field triage and in-hospital survival prediction for trauma patients. A higher RTS is associated with increased survival. It is also used as a prediction tool for massisve transfusion.[14] Revised Trauma Score requires collection of GCS score,[15] SBP, and RR. Categorical values from 0 to 4 are assigned according to predefined ranges. The RTS is calculated as a linear combination of those categorized values. The SI (SI = HR / SBP) is widely used for prediction of transfusion and field triage in trauma patients because of the simplicity of calculation. In this study, ABC, SI, and RTS were calculated using STC admission data.

Inclusion and Exclusion Criteria

Patients were included if they met the following inclusion criteria: Direct trauma admission, 18 years or older, 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.

Statistical Analysis

The AUROC with 95% confidence interval (CI)[16] was calculated for predictions of CAT and MT. DeLong method was used to compare AUROCs for different scoring systems. A p value less than 0.05 was considered to be statistically significant. Other performance metrics based on thresholds that maximize the Youden Index[17,18] are reported, including sensitivity (true positive rate [TPR]), specificity (true negative rate [TNR]), positive predictive values (PPVs), and negative predictive values (NPVs).

RESULTS

Among 1,396 trauma patient data collected during transportation by the Maryland State Police helicopters, median patient age was 45 years (first and third quartiles of 28.8 and 60 years). There were 67.1% male patients. Table 1 summarizes the patient demographics and prevalence of positive outcomes. The MT rate was 3.2%, and the CAT was 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. Injury Severity Score had first, second, and third quartiles

TABLE 1. Patient Demographics

N	1,396
Age (1st, 2nd, 3rd quartiles)	28.8, 45, 60 y
Sex	Male, 67.1%; Female, 32.9%
Adm GCS (1st, 2nd, 3rd quartiles)	14, 15, 15
Injury Severity Score (1st, 2nd, 3rd quartiles)	5, 10, 17
PreHospital time (at the scene to hospital arrival)	Mode: 29.4 min. Mean (SD): 35.3 ± 10.5 min
Mechanism of injury	
Blunt	1,295 (92.8%)
Penetrating	70 (5.0%)
Blunt and penetrating	12 (0.8%)
Other	19 (1.4%)
Transfusion and mortality outcomes	
CAT	106 (7.6%)
MT	45 (3.2%)
Mortality	92 (6.6%)

Adm, admission; SD, standard deviation.

of 5, 10, and 17, respectively. Average prehospital time (scene arrival to hospital) was 35.3 ± 10.5 minutes with a mode of 29.4 minutes (Fig. S1, http://links.lww.com/TA/B857).

Bleeding Risk Index and other three score's prediction, including AUROCs, 95% CI ranges, and AUROC comparison *p* values for CAT and MT, are shown in Tables 2 and 3, respectively. The first 5 minutes, 10 minutes, and all prehospital bar graphs with CIs of AUROC for BRI show progressively more robust and better predictions of CAT (Fig. S2, http://links.lww.com/TA/B857) and MT (Fig. S3, http://links.lww.com/TA/B857) as over time more vital signs data accumulate. The BRI prediction for MT, using entire prehospital data, performs significantly better than ABC, SI, and RTS. For prediction of MT, AUC for BRI was 0.92 (95% CI, 0.89–0.95), which was significantly better than the ABC (AUROC, 0.80; 95% CI, 0.73–0.87), the SI (AUROC, 0.83; 95% CI, 0.76–0.90), and the RTS (AUROC, 0.78; 95% CI, 0.71–0.85). For predicting CAT, BRI (AUROC, 0.91; 95% CI, 0.86–0.94) was significantly better than ABC (AUROC, 0.77; 95% CI, 0.73–0.82) or RTS (AUROC, 0.79; 95% CI, 0.74–0.83) and better than SI (AUROC, 0.85; 95% CI, 0.80–0.89). The receiver operating curves (ROCs) in Figure 1 show that the BRI performs better than other scoring systems, since its ROC dominates the others. Figure 2 shows the sensitivity (blue) and specificity (orange) for CAT and MT given any BRI score threshold. With the threshold cutoff BRI of 0.25 that maximizes the Youden Index for CAT, the sensitivity was 0.83 and specificity was 0.85. For MT, at a cutoff of BRI of 0.28, the sensitivity was 0.85 and specificity was 0.82. The FPR, TPR, FNR, TNR, PPV, NPV are reported in Tables 2 and 3. Different thresholds could be used for BRI, if alternative sensitivity or specificity was needed. Figure 2 illustrates the change of sensitivity and specificity for different BRI thresholds.

TABLE 2. Performance Metrics for Predicting 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
ABC	0.77*	0.73–0.82	0.17	0.69	0.31	0.83	0.25	0.97
SI	0.85	0.80–0.89	0.12	0.73	0.27	0.88	0.32	0.98
RTS	0.78*	0.74–0.83	0.28	0.77	0.23	0.72	0.18	0.97

*Mean AUROC is significantly different from BRI's.
BRI algorithm uses data from the entire prehospital transportation.
preHAll, entire prehospital data.

TABLE 3. Performance Metrics for Predicting 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
ABC	0.8*	0.73–0.87	0.19	0.76	0.24	0.81	0.12	0.99
SI	0.83*	0.76–0.90	0.14	0.74	0.26	0.86	0.14	0.99
RTS	0.78*	0.71–0.85	0.31	0.78	0.22	0.69	0.08	0.99

DISCUSSION

The BRI, using continuously recorded noninvasive vital signs in trauma patients, is an algorithm for predicting the probability of transfusion in both prehospital and early in-hospital use.[8–11] The current study shows that the same BRI algorithm performs well (AUROC, 0.91–0.92) using prehospital data to predict emergency and MT as it did when used on a different data set for in-hospital prediction of transfusion (AUROC, 0.92).[9] 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.[9] Bleeding Risk Index requires no user input from a busy prehospital 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 prehospital triage decision making, and can also assist with prehospital, trauma center and blood-bank planning. Bleeding Risk Index might be especially useful in remote field or natural disaster scenes, and BRI could be used when availability of medical expertise is limited. Bleeding Risk Index 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 examination 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 requires additional expertise to carry out a FAST examination (for calculation of ABC[3]) and to collect and enter a GCS (for calculation of RTS[4]). Bleeding Risk Index and SI do not require manual evaluation and are suitable

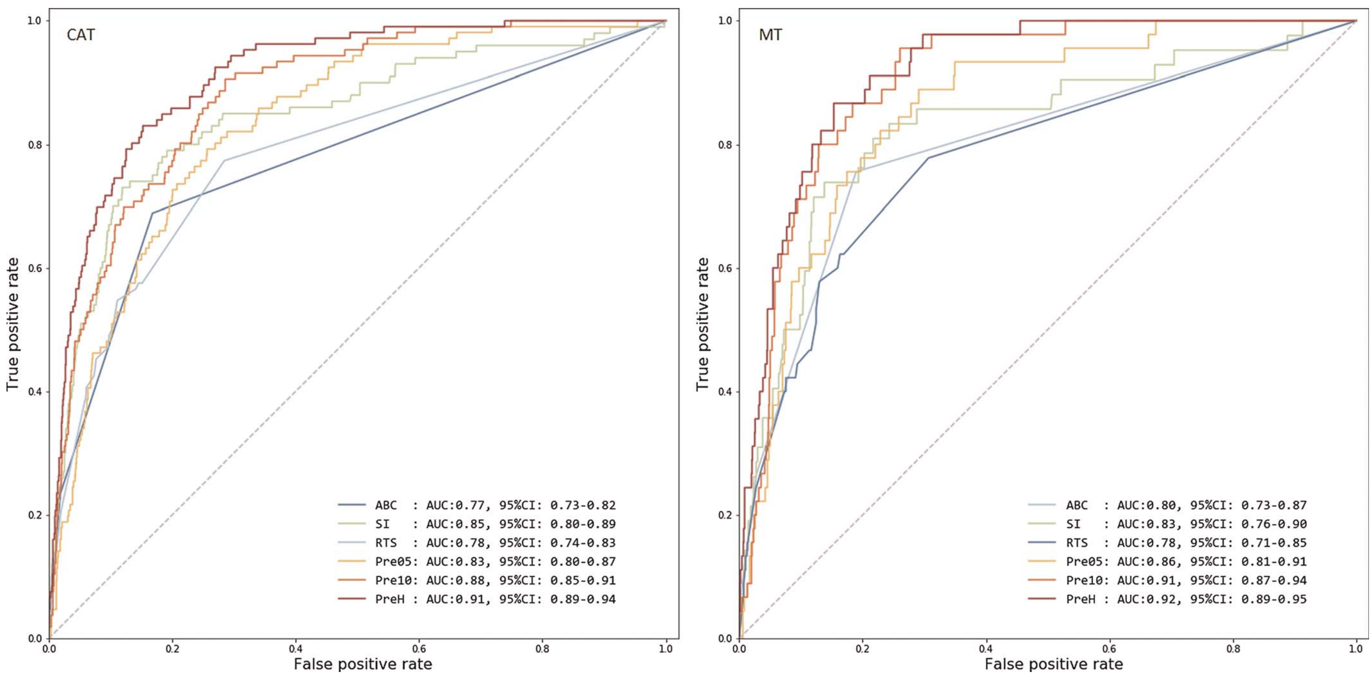

Figure 1. ROCs (left: CAT. Right: MT for the ABC (blue), SI (light green), RTS (light blue), BRI (light orange for using data from prehospital first 5 minutes, orange for using data from prehospital first 10 minutes, red for using data from entire prehospital).

for autonomous continuous monitoring. However, BRI and SI do not use information from medical experts when FAST examination 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 prehospital 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,[19–22] and lower 30-day mortality rate.[23,24] 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. The 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

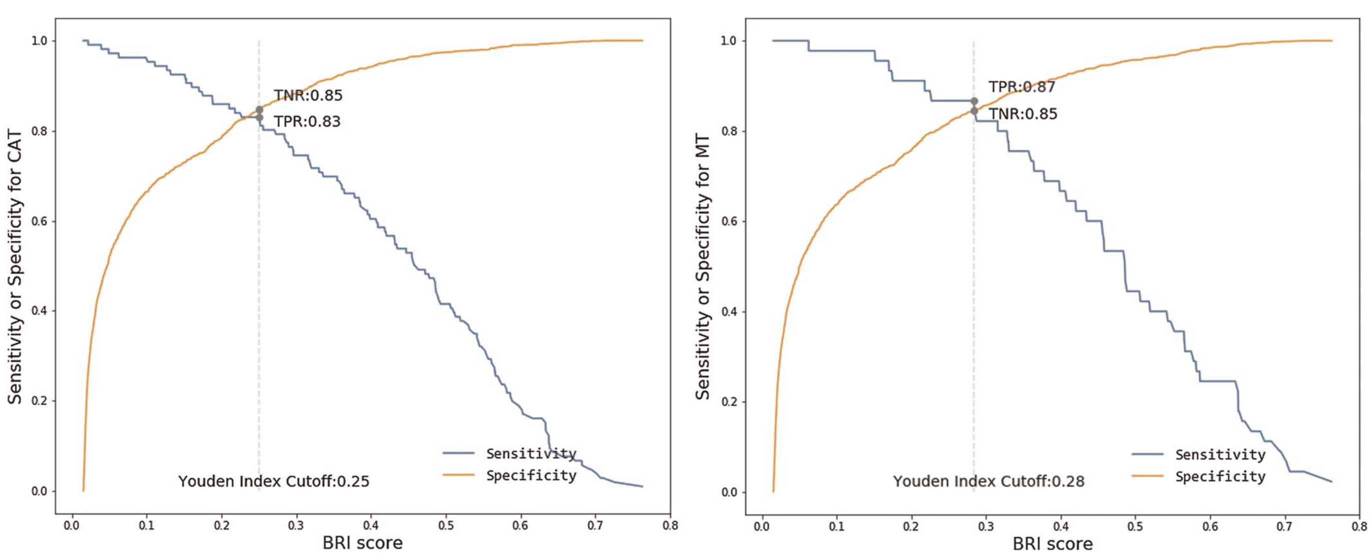

Figure 2. BRI score cutoffs and their corresponding sensitivity (blue) and specificity (orange). Left: for CAT, using BRI = 0.25 as cutoff, the sensitivity (TPR) is 0.83, and the specificity (TNR) is 0.85. Right: for MT, using BRI = 0.28 as cutoff, the sensitivity (TPR) is 0.87, and the specificity (TNR) is 0.85.

the average 35 minutes prehospital 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 six units of pRBC, six units thawed ABO plasma, and one 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 noncompressible "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.[19–21]

Limitations of this study include vital signs data in trauma patients that 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. 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.[25] Total of 92 patients died after 15 minutes in trauma resuscitation unit. 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 (Fig. S4, http://links.lww.com/TA/B857). Six of the 92 deaths occurred within 1 hour (3 CAT CAT-positive and 3 CAT CAT-negative). Eighty-six deaths occurred after 1 hour (29 CAT-positive and 57 CAT-negative). Forty-one 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 judgment of their poor prognosis is usually indictive.

Bleeding Risk Index 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,[23,26] potentially simple software upgrades to existing prehospital 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 uncrossmatched and emergency blood transfusion during trauma center reception and resuscitation, and of other lifesaving interventions.[9–11] The BRI score collected in-flight performs better than ABC, SI, and RTS predictions of MT and CAT. Bleeding Risk Index does not increase patient evaluation burden, require additional data entry or expert interpretation.

AUTHORSHIP

S.Y., P.H. were involved in designing the study, data analysis and writing the article. C.L., F.S., C.W. were involved in the data acquisition and analysis. C.F.M. was involved in designing the study and writing the article. P.R., D.F., T.S., S.G., C.M., D.S. were involved in designing the study and contributing critical revisions to the article.

DISCLOSURE

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The other authors declare no conflicts of interest.

REFERENCES

1. Cowley RA. 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. 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;69(1):S33–S39.
4. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME. A revision of the trauma score. *J Trauma*. 1989;29:623–629.
5. 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 Surg Res*. 2008;147:229–236.
6. 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.
7. Schroll R, Swift D, Tatum D, et al. Accuracy of shock index versus ABC score to predict need for massive transfusion in trauma patients. *Injury.* 2018;49:15–19.
8. Mackenzie CF, Wang Y, Hu PF, Chen SY, Chen HH, Hagegeorge G, Stansbury LG, Shackelford S, ONPOINT Study Group. Automated prediction of early blood transfusion and mortality in trauma patients. *J Trauma Acute Care Surg*. 2014;76:1379–1385.
9. Mackenzie CF, Gao C, Hu PF, et al. Comparison of decision-assist and clinical judgment of experts for prediction of lifesaving interventions. *Shock*. 2015;43:238–243.
10. Parimi N, Hu PF, Mackenzie CF, Yang S, Bartlett ST, Scalea TM, Stein DM. 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. Yang S, Hu P, Mackenzie CF. Chapter 24: Trauma Outcome Prediction in the Era of Big Data: From Data Collection to Analytics. In: Sejdic E, Falk TH, eds. *Signal Processing and Machine Learning for Biomedical Big Data*. Boca Raton, FL: CRC Press; 2018:477–492.
12. Shackelford SA, Colton K, Stansbury LG, Galvagno SMJr., Anazodo AN, DuBose JJ, Hess JR, Mackenzie CF. Early identification of uncontrolled hemorrhage after trauma: Current status and future direction. *J Trauma Acute Care Surg*. 2014;77(Suppl 2):S222–S227.
13. 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;85:691–696.

14. Cancio LC, Wade CE, West SA, Holcomb JB. Prediction of mortality and of the need for massive transfusion in casualties arriving at combat support hospitals in Iraq. *J Trauma*. 2008;64:S51–S55.
15. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;7872:81–84.
16. Cumming G, Finch S. Inference by eye: confidence intervals, and how to read pictures of data. *Am Psychol*. 2005;60(2):170–178.
17. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32–35.
18. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. *Epidemiology*. 2005;16(1):73–81.
19. Rehn M, Weaver AE, Eshelby S, Røislien J, Lockey DJ. Pre-hospital Transfusion of Red Blood Cells in Civilian Trauma Patients. *Transfus Med*. 2018; 28:277–283.
20. 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.
21. Holcomb JB, Donathan DP, Cotton BA, et al. Prehospital transfusion of plasma and red cells in trauma patients. *Prehosp Emerg Care*. 2015;19:1–9.
22. Pusateri AE, Moore Ernest A, Moore HB, 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):e195085.
23. 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;318(16):1581–1591.
24. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med*. 2018;379(4):315–326.
25. Sim ES, Guyette FX, Brown JB, et al. Massive transfusion and the response to prehospital plasma: it is all in how you define it. *J Trauma Acute Care Surg*. 2020;89(1):43–50.
26. Galvagno SM, Sikorski SA, Floccare DJ, et al. Prehospital point of care testing for the early detection of shock and prediction of lifesaving interventions. *Shock*. In Press 2020.