Original Article

Trauma severity associated with stress index in emergency settings: an observational prediction-and-validation study

Hayato Taniguchi,[1,2] Tomoki Doi,[1,2] Takeru Abe,[2] and Ichiro Takeuchi[2]

[1]*Department of Emergency and Critical Care Medicine, Yokosuka Kyousai Hospital, Yokosuka, and* [2]*Department of Emergency Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan*

Aim: Early judgments for treating severe trauma patients are essential for life-saving. Stress index (SI), obtained from a division of blood glucose level by serum potassium at arrival, might be useful for early prediction. However, the efficacy of SI was unknown. The purpose of this study was to identify and validate prediction models of severe trauma (ST) and the need for damage control operation (DCOP) and massive transfusion (MT) by using SI among trauma patients.

Methods: This study was a retrospective and prospective observational study. The prediction models were created by 1-year retrospective data of 167 trauma patients. The prediction models were validated by 6 months of prospective data of 87 trauma patients.

Results: The prediction model for ST contained respiratory rate and SI as significant factors. The prediction model for DCOP contained SI. The prediction model for MT contained systolic blood pressure and SI. The correlation of probability of MT, ST, and DCOP was $r = 0.70$ ($P < 0.001$), $r = 0.46$ ($P < 0.001$), and $r = 0.15$ ($P = 0.196$), respectively. The predicted probability of MT, ST, and DCOP showed 0.93 (95% confidence interval [CI], 0.88–0.90) and 0.80 (95% CI, 0.74–0.86), and 0.79 (95% CI, 0.70–0.88).

Conclusion: We identified and validated our prediction models for ST and the need for DCOP and MT among trauma patients using SI as a main predictor. Our models indicated that fewer variables in an early phase of the treatment process can inform clinicians regarding how severe a patient is and which intervention is needed.

Key words: Damage control operation, massive transfusion, predictor, severe trauma, stress index

INTRODUCTION

EARLY JUDGMENTS REGARDING the need for damage control operation (DCOP) and massive transfusion (MT) are essential for life-saving among severe trauma (ST) patients,[1–4] because massive hemorrhage is the most common cause of mortality in ST patients in the first hour of arrival at a trauma center.[5–7] However, timing and type of judgments depend on providers, and great variability exists even among high-volume trauma centers.[8]

With respect to an association between outcomes of ST patients and their blood tests at arrival, blood glucose level at arrival predicted ST, and the need for DCOP and MT.[9–14] Hypokalemia at arrival also predicted ST.[15,16] Stress index (SI), which was obtained by a division of blood glucose (BS) level by serum potassium (K) at arrival,[17,18] represented by the equation SI = BS/K, among patients with subarachnoid hemorrhage was associated with plasma catecholamine level.[17,19] In addition, high plasma catecholamine level was associated with ST.[20] Thus, BS and K would be important to combine as SI for evaluating ST patients.

To our knowledge, no studies have investigated SI and severity among trauma patients. Thus, the purpose of this study was to identify and validate prediction models of ST and need for DCOP and MT by using SI among trauma patients. If a prediction model on severity among trauma patients with SI was established and quick use of SI was also established in clinical settings, our findings might contribute to rapid judgements in treating patients.

METHODS

THIS STUDY WAS a single-center, retrospective and prospective observational study. Our institute, Yokosuka Kyousai Hospital (Yokosuka, Japan), treats

Corresponding: Hayato Taniguchi, MD, Department of Emergency Medicine, Yokohama City University Graduate School of Medicine, 4-57 Urafunecho, Minamiku, Yokohama, Japan. E-mail: tanipan@hotmail.co.jp.

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approximately 250 trauma patients per year and provides emergency and critical care for Yokosuka City, which has a population of 400,000 in the central part of Japan, south of the Tokyo area. The institute has 10 mixed intensive care unit beds and admits 150 patients annually to the intensive care unit. Our trauma care has been carried out with one to two emergency physicians and one to two residents dependent on patient severity. Blood transfusion can be used within 15 min on arrival, and DCOP also can be carried out within 30 min on arrival.

Study participants included all trauma patients transferred directly from the scene of trauma by an ambulance between 1 June 2016 and 31 December 2017. We defined the first 12 months, between June 2016 and May 2017, as a derivation period with a retrospective design, and the other 6 months, between June 2017 and December 2017, as a validation period with a prospective design. Exclusion criteria were under 16 years old and with cardiac arrest at arrival. Obtaining a written informed consent was waived due to the nature of the non-interventional study and use of regular medical records only. This study was approved by an institutional review board and retrospectively registered as an observational study (UMIN000034042).

We used ST, DCOP, and MT as outcomes. A patient with Injury Severity Score of 16 or greater was evaluated as being ST.[1–4] A patient who underwent damage control surgery and interventional radiology in the first 24 h after admission was evaluated as being DCOP.[1–4] A patient who received a transfusion of 10 U or more of packed red blood cells during the first 24 h after admission was evaluated as being MT.[5–7] In Japan, 1 U of packed red blood cells is approximately 120 mL.

The following parameters were evaluated: patient background (i.e., age, gender, history, type of injury [e.g., blunt, stab]); vital signs on arrival at our department (i.e., heart rate, systolic blood pressure, respiratory rate, SpO_2, body temperature, Glasgow Coma Scale score [GCS] ≤8 or >8); blood test values (i.e., blood lactate level, pH, bicarbonate, base excess, hematocrit, blood glucose level, serum potassium level); SI, which was calculated from a division of blood glucose level by serum potassium, as SI = BS/K; and location of injuries (i.e., head, face, chest, abdomen, pelvis, extremities, body surface, multiple injury with head, and multiple injury without head). A (Radiometer ABL 800 FELX®: Radiometer Medical ApS, Copenhagen, Denmark) was used for blood gas analysis in this study.

In the derivation period, we identified a prediction model of each outcome by using logistic regression analysis with a forward selection; we chose that variable selection due to avoiding the model's overfitting with a limited sample size. We set $P < 0.10$ as a criterion for variable selection. We used ST and the need for DCOP and MT as an outcome, and sex, stab injury, history of diabetes, history of psychiatric disease, heart rate, systolic blood pressure, respiratory rate, SpO_2, body temperature, GCS score ≤8, blood lactate level, pH, bicarbonate, base excess, hematocrit, and SI as independent variables. Multicollinearity was also checked with variance inflation factors (VIFs); we considered a VIF larger than 10 as an existence of multicollinearity. In the validation period, we checked the performance and evaluated validation of the prediction models by calculation, using Spearman's rank correlation coefficient between the predicted probability of each outcome and actual observed outcome. In addition, we evaluated overall performance by adding both the patient data from the derivation period and those from the validation data, applying receiver operating characteristic (ROC) curve analysis to check performances of prediction models. As a sensitivity analysis, we undertook the ROC analysis, then calculated the area under the ROC curve (AUROC) and 95% confidence interval (CI) with or without head injury.

We viewed prediction performances as high with AUROC ≥0.9, moderate when between 0.7 and <0.9, and low when <0.7.[21] To compare the patient data from the derivation period and the data from the validation period, we used the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. The level of significance in a two-tailed test was set at $P < 0.05$. All statistical analyses in this study were undertaken with JMP 13 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics for Windows, version 23.0. (IBM, Armonk, NY, USA).

RESULTS

DURING THE STUDY period, 349 trauma patients were transported to our institute by ambulance. After we excluded 39 patients based on the exclusion criteria and 66 patients due to lack of available blood gas data, we evaluated 254 patients. Among them, the derivation period contained 167 patients, and the validation period contained 87 patients (Fig. 1). Every patient received oxygen on arrival.

Table 1 shows the demographic and clinical characteristics, categorized by three outcomes, among patients from the derivation period. Stress index was a variable with significant association with all three outcomes among laboratory data ($P < 0.01$) (Table 1). Glasgow Coma Scale score ≤8 and SpO_2 were significantly associated with all outcomes (all $P < 0.05$). Table 2 shows significant variables associated with each outcome from our logistic regression models. No variable with VIF larger than 10 was considered as an existence of multicollinearity.

We then obtained the following prediction models (Table 2). The prediction model for ST is:

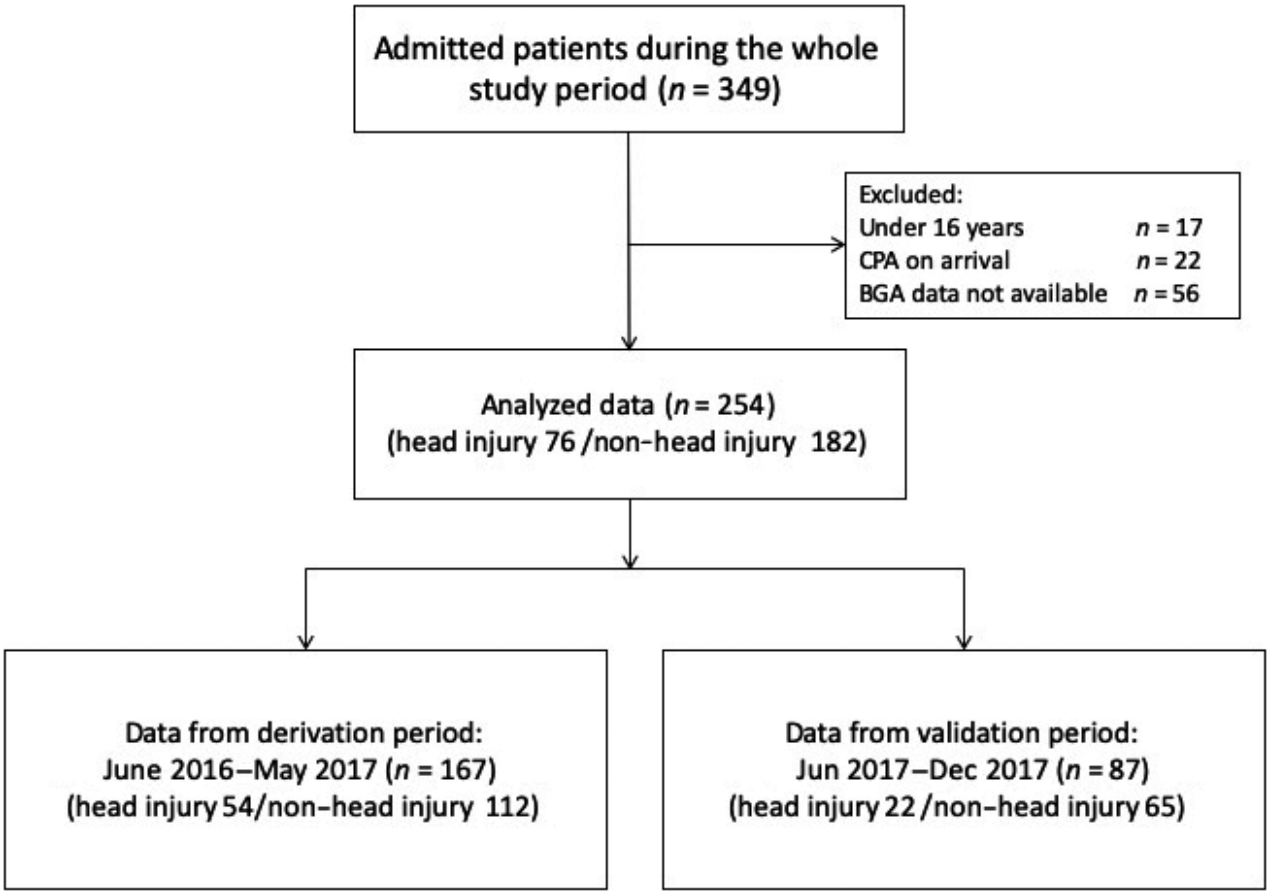

Fig. 1. Flow diagram of patient selection for this study and allocation for the derivation and validation periods. BGA, blood gas analysis; CPA, cardiopulmonary arrest.

$$p_1 = \frac{e^{y1}}{1 + e^{y1}} \quad (1)$$

where $y_1 = -4.85 + 0.04 \times \text{RR} + 0.06 \times \text{SI}$, and RR represents respiratory rate.

The prediction model for the need for DCOP is:

$$p_2 = \frac{e^{y2}}{1 + e^{y2}} \quad (2)$$

where $y_2 = -4.36 + 0.05 \times \text{SI}$.

The prediction model for the need for MT is:

$$p_3 = \frac{e^{y3}}{1 + e^{y3}} \quad (3)$$

where $y_3 = -1.96 - 0.03 \times \text{SBP} + 0.08 \times \text{SI}$.

In addition, $P_{\#}$ represented the probability of falling into an outcome: RR respiratory rate, SBP systolic blood pressure, and e the base of the natural logarithm.

Table 3 shows the demographic and clinical characteristics, categorized by three outcomes, among patients from the validation period. Heart rate, pH, base excess, and lactate were significantly associated with all three outcomes (all $P < 0.01$).

Table 4 shows comparisons of variables between data from the derivation and validation periods. We found a significant difference in type of injury ($P = 0.012$), International Severity Score ($P = 0.025$), and abdominal injury ($P = 0.023$), but no other variables.

The prediction models were validated using Spearman's rank correlation coefficient between the predicted probability of each outcome and actual observed outcome. The correlation of prediction probability of the need for MT was $r = 0.70$ (95% CI, 0.46–0.86; $P < 0.001$). The correlation of prediction probability of ST was $r = 0.46$ (95% CI, 0.19–

Table 1. Demographic and clinical characteristics of trauma patients categorized by three outcomes during derivation period (n = 167)

	Severe trauma			Damage control operation			Massive transfusion		
	Yes (n = 45)	No (n = 122)	P-value	Yes (n = 19)	No (n = 148)	P-value	Yes (n = 15)	No (n = 152)	P-value
Age (years)	55.3 (24.9)	50.2 (24.2)	0.235	43.8 (24.9)	52.6 (24.6)	0.144	47.3 (26.5)	52 (24.6)	0.484
Gender (male)	33 (73.3)	84 (68.9)	0.578	14 (73.7)	103 (69.6)	0.711	14 (93.3)	103 (67.8)	0.041
Penetrating trauma	2 (4.4)	5 (4.1)	0.719	3 (15.8)	4 (2.7)	0.020	2 (13.3)	5 (3.3)	0.092
History									
Diabetes	0 (0.0)	13 (10.6)	0.021	0 (0.0)	13 (8.8)	0.366	0 (0.0)	13 (8.6)	0.238
Hypertension	9 (20.0)	22 (18.3)	0.771	5 (26.3)	26 (17.6)	0.356	3 (20.0)	28 (18.4)	0.887
Chronic kidney disease	0 (0.0)	4 (3.3)	0.219	0 (0.0)	4 (2.7)	0.468	0 (0.0)	4 (2.6)	0.524
Psychiatric illness	5 (11.1)	7 (5.7)	0.234	3 (15.8)	9 (6.1)	0.141	4 (26.7)	8 (5.3)	0.014
Vital signs on admission									
Systolic blood pressure	137.4 (40.3)	142.3 (29.4)	0.385	131.7 (46.3)	142.2 (30.5)	0.190	111.2 (38.9)	144 (30.5)	<0.001
Heart rate	92.29 (25.7)	87.13 (19.3)	0.017	97.6 (34.4)	87.3 (18.7)	0.048	104.5 (34.5)	87 (19.1)	0.003
Respiratory rate	25.55 (8.4)	20.75 (7.8)	<0.001	24.5 (8.7)	21.7 (8.2)	0.173	27 (9.3)	21.6 (8.0)	0.015
GCS score ≤ 8	15 (33.3)	8 (6.6)	<0.0001	9 (47.4)	14 (9.6)	<0.0001	5 (35.7)	18 (11.9)	0.021
Body temperature	36.11 (0.7)	36.39 (0.8)	0.089	35.9 (0.7)	36.3 (0.8)	0.086	36 (0.8)	36.3 (0.8)	0.247
SpO_2	94.7 (7.8)	98.39 (3.2)	<0.0001	93.1 (10.3)	97.9 (3.8)	<0.001	92.1 (9.5)	97.9 (4.3)	<0.0001
Laboratory data at admission									
pH	7.36 (0.0)	7.38 (0.1)	0.022	7.33 (0.1)	7.38 (0.1)	0.009	7.34 (0.1)	7.39 (0.1)	0.067
Base excess	−2.31 (3.6)	−1.2 (3.6)	0.089	−3.06 (3.8)	−1.33 (3.6)	0.066	−4.03 (4.0)	−1.25 (3.5)	0.005
Lactate	3.13 (2.7)	2.25 (1.7)	0.018	3.41 (2.9)	2.4 (1.9)	0.057	4.37 (3.3)	2.32 (1.8)	0.002
Hematocrit	37.92 (5.7)	40.45 (5.8)	0.013	37.6 (1.3)	40.1 (0.5)	0.089	36.5 (1.5)	40.1 (0.5)	0.022
Stress index	51.28 (20.1)	35.5 (11.2)	<0.0001	54.9 (16.7)	37.8 (14.6)	<0.0001	62.7 (22.4)	37.5 (13.0)	<0.0001

Data are shown as frequency (%) or mean (standard deviation).
GCS, Glasgow Coma Scale.

Table 2. Significant factors among trauma patients, based on three multivariate logistic regression models with a forward selection

Outcomes	Significant factors	Beta	Odds ratio	95% CI	*P*-value
Severe trauma	Stress index	0.06	1.06	1.04–1.11	<0.001
	Respiratory rate	0.04	1.04	1.00–1.10	0.045
Massive transfusion	Stress index	0.08	1.08	1.04–1.13	<0.001
	Systolic blood pressure	−0.03	0.97	0.95–0.99	0.001
Damage control operation	Stress index	0.05	1.05	1.03–1.08	<0.001

CI, confidence interval.

Table 3. Demographic and clinical characteristics of trauma patients, categorized by three outcomes during the validation period (n = 87)

	Severe trauma			Damage control operation			Massive transfusion		
	Yes (n = 18)	No (n = 69)	*P*-value	Yes (n = 9)	No (n = 78)	*P*-value	Yes (n = 8)	No (n = 67)	*P*-value
Age (years)	42 (17.0)	55 (22.4)	0.0210	46 (17.4)	53 (22.4)	0.3230	39 (17.2)	54 (22.0)	0.070
Gender (male)	15 (83.3)	45 (65.2)	0.1650	9 (100.0)	51 (65.4)	0.0520	14 (93.3)	103 (67.8)	0.050
Penetrating trauma	0 (0.0)	10 (14.5)	0.1130	1 (11.1)	9 (11.5)	0.9700	1 (12.5)	9 (11.4)	0.970
History									
Diabetes	4 (22.2)	12 (17.4)	0.7340	0 (0.0)	16 (20.5)	0.2010	0 (0.0)	16 (18.4)	0.340
Hypertension	0 (0.0)	13 (18.8)	0.0620	0 (0.0)	13 (16.7)	0.3440	0 (0.0)	13 (14.9)	0.600
Chronic kidney disease	0 (0.0)	2 (2.9)	0.4650	0 (0.0)	2 (2.6)	0.6270	0 (0.0)	2 (2.5)	0.530
Psychiatric illness	3 (16.7)	7 (10.1)	0.4250	2 (22.2)	8 (10.3)	0.2750	1 (12.5)	10 (11.4)	0.930
Vital signs on admission									
Systolic blood pressure	126 (50.9)	141 (36.7)	0.1580	102 (12.8)	142 (4.4)	0.0040	84 (32.8)	143 (36.3)	<0.001
Heart rate	102 (25.4)	86 (17.7)	0.0020	115 (6.2)	86 (2.1)	<0.0010	124 (6.2)	86 (2.0)	<0.001
Respiratory rate	26 (14.8)	29 (23.1)	0.5570	37 (22.9)	27 (21.4)	0.1760	33 (7.7)	28 (2.5)	0.520
GCS ≤ 8	2 (11.1)	2 (2.9)	0.1880	1 (11.1)	3 (3.9)	0.3590	2 (25.0)	2 (2.5)	0.040
Body temperature	36.1 (0.8)	36.4 (1.0)	0.1830	35.6 (0.8)	36.4 (1.0)	0.0430	35.7 (0.8)	36.4 (1.0)	0.090
SpO_2	97 (4.2)	98 (5.2)	0.5850	96 (4.9)	98 (5.0)	0.2750	91 (9.1)	98 (4.1)	<0.001
Laboratory data on admission									
pH	7.32 (0.2)	7.42 (0.1)	<0.0100	7.277 (0.1)	7.41 (0.8)	<0.0001	7.22 (0.1)	7.41 (0.1)	<0.001
Base excess	−5.5 (6.3)	−1.0 (2.8)	<0.0001	−7.5 (5.3)	−1.3 (3.5)	<0.0001	−10.4 (5.1)	−1.1 (3.0)	<0.001
Lactate	5.0 (4.0)	2.1 (1.6)	<0.0001	5.4 (3.6)	2.4 (2.3)	0.0010	7.1 (3.2)	2.3 (2.1)	<0.001
Hematocrit	41.8 (6.1)	39.6 (5.8)	0.1500	38.9 (4.1)	40.2 (6.0)	0.5280	38.5 (4.3)	40.2 (6.0)	0.420
Stress index	55.1 (21.8)	37.7 (13.2)	<0.0001	51.6 (14.2)	40.1 (16.8)	0.0510	66.1 (24.3)	38.8 (13.8)	<0.001

Data are shown as frequency (%) or mean (standard deviation).
GCS, Glasgow Coma Scale.

Table 4. Demographic data of trauma patients between derivation and validation periods

	Derivation period n = 167	Validation period n = 87	P-value
Age (years)	51.6 (24.7)	52.6 (21.9)	0.766
Gender (male)	117 (70.1)	60 (68.9)	0.857
Penetrating trauma (yes)	6 (3.6)	10 (11.5)	0.027
History of diabetes (yes)	13 (7.8)	11 (12.6)	0.112
Systolic blood pressure	141.1 (32.6)	138.0 (40.2)	0.516
Stress index	39.8 (15.8)	41.3 (16.8)	0.477
Severe trauma (yes)	45 (26.9)	18 (20.7)	0.273
Damage control operation (yes)	19 (11.4)	9 (10.3)	0.803
Massive transfusion (yes)	15 (9.0)	8 (9.2)	0.952
Injury Severity Score	13.2 (0.9)	9.85 (1.2)	0.025
Length of stay on ICU (days)	1.95 (2.4)	1.85 (2.1)	0.728
Length of use of ventilator (days)	1.51 (4.2)	0.84 (1.9)	0.155
Mortality	4 (2.4)	3 (3.5)	0.694
Location of injury			
Head and neck	38 (23.6)	14 (16.9)	0.166
Face	9 (5.4)	1 (1.2)	0.171
Thorax	18 (10.8)	16 (18.3)	0.119
Abdomen	14 (8.4)	1 (1.2)	0.023
Pelvis and extremities	19 (11.4)	17 (19.5)	0.089
External	32 (19.6)	19 (21.8)	0.613
Multiple with head	16 (9.6)	8 (9.2)	0.921
Multiple without head	20 (12.0)	11 (12.6)	0.874

Data are shown as frequency (%) or mean (standard deviation). ICU, intensive care unit.

0.64; $P < 0.001$). The correlation of prediction probability of the need for DCOP was $r = 0.15$ (95% CI, −0.02 to 0.39; $P = 0.196$).

As a result of sensitivity analysis using patient data from the whole periods, the predicted probability for the need of MT showed high accuracy, with 0.93 (95% CI, 0.88–0.90) of AUROC. The predicted probability of ST and the need for DCOP showed moderate accuracy, with 0.80 (95% CI, 0.74–0.86) and 0.79 (95% CI, 0.70–0.88), respectively. In addition, without head injury, the predicted probability for the need for MT showed high accuracy, with 0.94 (95% CI, 0.90–0.98) of AUROC. The predicted probability of ST and the need for DCOP showed moderate accuracy, with 0.79 (95% CI, 0.70–0.88) and 0.76 (95% CI, 0.64–0.88), respectively.

DISCUSSION

IN THE PRESENT study, we first identified and validated our prediction models for ST and the need for DCOP and MT among trauma patients. We found that combining SI and respiratory rate or SI and systolic blood pressure at arrival could significantly predict ST and MT, respectively, whereas SI could predict DCOP with moderate to high accuracy. Thus, our models indicated that a small number of variables in the early phase of treatment can inform clinicians about various aspects of patients in emergency settings, such as how severe a patient is and which intervention they would need. If clinicians know those aspects of patients in the early phase of treatment, they would be able to prepare blood transfusion and operation sooner, which could contribute to improving patients' outcomes.

Regarding the model validation, the high correlation in MT between the derivation and validation groups warranted an adequacy of the prediction in both groups ($r = 0.70$). However, the moderate to weak correlation in ST and DCOP might suggest that there would be a possibility of existing variances among the two groups ($r = 0.46$ and 0.15, respectively).

An association of severity with plasma catecholamine level[20] and of SI with plasma catecholamine level[17] might indirectly explain the significant associations between SI and severity of trauma patients. Increased plasma catecholamine level leads to increased blood glucose level and decreased serum potassium level.[19] Increased plasma catecholamine level was also observed in ST.[20] Thus, an indirect association between ST and SI might support the moderate accuracy of our prediction models (AUROC 0.80; 95% CI, 0.74–0.86).

In previous studies among severe trauma patients with massive bleeding, it was reported that increased plasma catecholamine levels contract capillary vessels to maintain tissue perfusion.[22] In addition, blood glucose level is significantly related to MT.[9–14] Thus, these results might support a strong association between SI and MT in our prediction models.

The relationship between head injury and hyperglycemia and hypokalemia has also been reported.[16,23,24] For that reason, the prediction formula using SI could be affected by head injury. However, in our sensitivity analysis, we found the model would be stable because of the AUROCs for MT, ST, and DCOP (AUROC for MT, ST, and DCOP with head injuries or not: 0.93 versus 0.94, 0.80 versus 0.79, and 0.79

versus 0.76, respectively). Thus, the prediction formulas have proven useful with or without head injury.

In this study, the prediction formula using SI has proven useful for predicting ST and the need for DCOP and MT at arrival in trauma patients. The prediction formulas consist of simple, quickly available parameters, with no need of X-ray or ultrasound. Therefore, the prediction formulas are more likely to be independent of provider setting or equipment. Because the advantage could be useful in prehospital settings, we plan to evaluate SI as a prehospital triage tool in the future.

The present study has limitations. First, this study was a single-center, observational study, with limited generalizability of study findings with other institutions and/or in other countries. As pointed out in previous studies, choice and timing of MT and DCOP could depend on institutional policy or professional experience. The present study showed a stability of findings using two different recruiting periods. However, the limitation in generalizability requires that our findings be interpreted carefully. Second, distributions of variables of the validation period differed from those of the derivation period. The sample size for the derivation period might be relatively small, so that our prediction models could be unstable for other settings. Third, knowledge of the prediction from the derivation period might somewhat influence staff during the validation period. A future blinded study might be needed to overcome this limitation. Fourth, we did not measure other confounding factors, such as plasma catecholamine level or PaO_2 in this study. A measurement of factors should be considered in the future study. Fifth, there were significant differences in some variables between the derivation and validation periods, which would indicate background differences due to sampling limitation at a single center. Selection bias might limit internal validity of our study findings. Although we obtained validity on our prediction models with statistical tests, caution should be drawn to whom the predictions apply. Finally, a unit of packed red blood cells might be different between Japan and other countries. In the case of Japan, 1 U packed red blood cells is approximately 120 mL. Thus, our study findings should be cautiously applied to other countries' practices. Future international studies might solve this limitation.

CONCLUSIONS

IN THE PRESENT study, we identified and validated our prediction models for ST and the need for DCOP and MT among trauma patients using SI as a main predictor. Our models indicated that fewer variables in the early phase of treatment can inform clinicians regarding how severe a patient is and which intervention is needed when treating a trauma patient in an emergency setting. We need to undertake an international, multicenter study to verify our study findings.

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DISCLOSURE

Approval of the research protocol: The protocol was approved by the Ethics Committee of Yokosuka Kyousai Hospital as the corresponding institution.
Informed consent: The requirement for informed consent of patients was waived.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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