Bio-Shock Index: Proposal and Rationale for a New Predictive Tool for In-Hospital Mortality in Patients with Traumatic Brain Injury

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■ BACKGROUND: **We proposed a novel prognostic tool for the prediction of in-hospital mortality based on a combination of hemodynamic parameters and biomarkers in patients with traumatic brain injury (TBI). We hypothesized that a combination of shock index (SI) with high sensitive troponin T (HsTnT), the Bio-Shock Index (Bio-SI), has better prognostic power than its individual components.**

■ METHODS: **A retrospective chart review was conducted (2011–2018) for patients with TBI. Patients were categorized into 2 groups (low and high Bio-SI) based on the receiver operating characteristic curve.**

■ RESULTS: **A total of 2619 patients were admitted with TBI, and 1471 fulfilled the inclusion criteria and 73% had high Bio-SI (≥10). High Bio-SI values were associated with more intraventricular hemorrhage ($P = 0.001$), brain edema ($P = 0.001$), and had lower mean arterial pressure ($P = 0.001$), admission Glasgow Coma Scale score ($P = 0.001$), and higher SI ($P = 0.001$), serum lactate ($P = 0.001$), HsTnT values ($P = 0.001$), and Rotterdam score ($P = 0.03$). Patients with high Bio-SI had a prolonged hospital ($P = 0.003$) and intensive care unit stay ($P = 0.001$); longer ventilatory days ($P = 0.001$) and had higher rates of pneumonia ($P = 0.001$), sepsis ($P = 0.001$), and in-hospital mortality ($P = 0.001$). The Bio-SI showed high sensitivity and negative predictive value (91.4% and 94.4%, respectively) as compared with elevated SI (50.2% and 87.6%, respectively) and positive troponin (79.7% and 93.7%, respectively).**

■ CONCLUSIONS: **The Bio-SI is potentially a better tool than its individual components to predict in-hospital mortality among patients with TBI; however, HsTnT alone outperforms SI. Prospective studies and multicenter trials studying troponin levels and SI in all patients with TBI with the inclusion of outcome scores will prove or disprove the predictability of the new index.**

INTRODUCTION

Early recognition of hemorrhage in patients with traumatic brain injury (TBI) might play an important role in minimizing the burden of morbidity and mortality in severely injured patients.[1] Notably, patients with TBI are at an increased risk of fatal outcome due to rapid physiologic deterioration following primary brain injury or occult hemorrhage, which often remains a clinical dilemma.[2] Therefore, early identification of reliable indicators of physiologic derangement and biomarkers of poor outcomes in patients with TBI are of great

Key words
- Bio-SI
- HsTnT
- Shock index
- Traumatic brain injury

Abbreviations and Acronyms
AIS: Abbreviated injury score
AUC: Area under the curve
Bio-SI: Bio-Shock Index
CI: Confidence intervals
ED: Emergency department
GCS: Glasgow Coma Scale
HsTnT: High sensitive troponin T
ICP: Intracranial pressure
ISS: Injury severity score
MAP: Mean arterial pressure
NPV: Negative predictive value
PP: Pulse pressure
r: Pearson correlation coefficient
ROC: Receiver operating characteristic
SBP: Systolic blood pressure
SI: Shock index
TBI: Traumatic brain injury

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Table 1. Demographics, Clinical Presentations, and Head Injury Lesions in Patients who Sustained Traumatic Brain Injury (June 2011 to June 2018)

Variable	Overall (n = 1471)	Bio-SI <10 n = 394 (26.8%)	Bio-SI ≥10 n = 1077 (73.2%)	*P* Value
Age in years, mean ± SD	33.4 ± 14.6	32.3 ± 12.6	33.8 ± 15.2	0.05
Male	1371 (93.2%)	365 (92.6%)	1006 (93.4%)	0.60
Female	100 (6.8%)	29 (7.4%)	71 (6.6%)	
Head injury lesions				
Skull fracture	945 (64.2%)	257 (65.2%)	688 (63.9%)	0.63
Brain contusion	803 (54.6%)	208 (52.8%)	595 (55.2%)	0.40
Subdural hemorrhage	449 (30.5%)	120 (30.5%)	329 (30.5%)	0.97
Epidural hemorrhage	311 (21.1%)	99 (25.1%)	212 (19.7%)	0.02
Extra-axial hemorrhage	153 (10.4%)	47 (11.9%)	106 (9.8%)	0.24
Subarachnoid hemorrhage	517 (35.1%)	130 (33.0%)	387 (35.9%)	0.29
Intraventricular hemorrhage	128 (8.7%)	17 (4.3%)	111 (10.3%)	0.001
Intracerebral hemorrhage	45 (3.1%)	11 (2.8%)	34 (3.2%)	0.71
Pneumocephalus	264 (17.9%)	76 (19.3%)	188 (17.5%)	0.41
Brain edema	344 (23.4%)	66 (16.8%)	278 (25.8%)	0.001
Diffuse axonal injury	129 (8.8%)	19 (4.8%)	110 (10.2%)	0.001
Admission Glasgow Coma Scale score	8 (3–15)	12 (3–15)	5 (3–15)	0.001
Ethanol level (n = 913)	2.2 (0–130)	2.2 (0–80)	2.2 (0–130)	0.25
Shock index (n = 1471)	0.82 ± 0.34	0.71 ± 0.18	0.87 ± 0.38	0.001
HsTnT value (n = 1471)	11.0 (0.06–5922)	5.7 (0.06–9.4)	21.7 (9–5922)	0.001
Rotterdam score (n = 653)				0.03
Score 1–3	88.2%	93.5%	87.3%	
Score 4–6	11.8%	6.5%	12.7%	

Shock index = pulse emergency department/systolic blood pressure emergency department.
Bio-SI, Bio-Shock Index; SD, standard deviation; HsTnT, high sensitive troponin T.

interest for prognostication and decision-making for goal-directed management.[3,4]

Contemporary literature suggests that assessment of the physiological characteristics in patients with TBI might help in better understanding TBI pathophysiology and would serve as prognostic indicators.[5]

Shock index (SI) derived from the ratio of pulse rate and systolic blood pressure can be used in estimating the severity of hemorrhage in trauma patients, and thus elevated SI is associated with a higher rate of mortality.[6,7] An earlier study of severely injured patients showed the frequency of concomitant TBI and hemorrhagic shock (base excess ≤ -4 and/or SI ≥ 0.9) constituted 18% and this high risk group was more likely to have severe coagulopathy prior to resuscitation and had higher than 30 days mortality than other groups.[5] Fröhlich et al.[8] advocated the use of SI to diagnose hypovolemic shock in polytrauma patients irrespective of the presence of TBI. However, an experimental study observed an altered relationship between SI and hemorrhage in postacute TBI.[1] The authors suggested that SI is markedly unreliable to assess hemorrhagic shock in moderate TBI. Despite being a good tool to predict the need for blood transfusion and worst outcome in trauma patients, there exists uncertainty regarding the applicability of SI alone in patients with TBI.

Interestingly, earlier studies have demonstrated the use of cardiac troponin as a biochemical marker of myocardial injury for prognosis after brain injuries.[9,10] However, the exact mechanism and clinical implications of elevated troponin in patients with TBI needs further exploration.[11] Considering the inherent heterogeneity and generalizability issue of multivariable prognostic systems for TBI, there is a need to develop a simple, readily available tool based on clinical parameters for early risk stratification in TBI. We hypothesize that the combination of SI with troponin into one index will have better prognostic power and outperform its individual components. Therefore, we aim to propose a new prognostic tool, the Bio-Shock Index (Bio-SI), for the prediction of in-hospital mortality based on the combination of hemodynamic parameter (i.e.,

Table 2. Comparison of Associated Injuries, Injury Severity Scores, Interventions, Complications, and Outcome

Variable	Overall (n = 1471)	Bio-SI <10 (26.8%)	Bio-SI ≥10 (73.2%)	*P* Value
Associated injuries				
Chest	654 (44.5%)	117 (29.7%)	537 (49.9%)	0.001
Abdomen	322 (21.9%)	40 (10.2%)	282 (26.2%)	0.001
Cardiac	15 (1.0%)	0 (0.0%)	15 (1.4%)	0.01
Head AIS	3.75 ± 1.03	3.62 ± 0.97	3.79 ± 1.04	0.004
Chest AIS	2.8 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	0.01
Abdomen AIS	2.6 ± 0.9	2.2 ± 0.5	2.6 ± 0.9	0.001
Injury severity score	24.1 ± 10.6	20.2 ± 7.9	25.5 ± 11.0	0.001
Interventions				
Intubation	1004 (68.3%)	213 (54.1%)	791 (73.4%)	0.001
Tracheostomy (n = 919)	91 (9.9%)	10 (4.3%)	81 (11.8%)	0.001
Intracranial pressure monitor	245 (16.7%)	45 (11.4%)	200 (18.6%)	0.001
Craniotomy	126 (8.6%)	46 (11.7%)	80 (7.4%)	0.01
Craniectomy	108 (7.3%)	26 (6.6%)	82 (7.6%)	0.50
External ventricular drainage	60 (4.1%)	12 (3.0%)	48 (4.5%)	0.22
Complications				
Pneumonia	288 (19.6%)	50 (12.7%)	238 (22.1%)	0.001
Acute respiratory distress syndrome	37 (2.5%)	7 (1.8%)	30 (2.8%)	0.27
Sepsis	96 (6.5%)	12 (3.0%)	84 (7.8%)	0.001
Hospital length of stay median and range	12 (1—304)	10 (1—223)	13 (1—304)	0.003
Intensive care unit length of stay	7 (1—126)	4 (1—71)	9 (1—126)	0.001
Ventilatory days	6 (1—115)	3 (1—42)	6.5 (1—115)	0.001
Mortality	257 (17.5%)	22 (5.6%)	235 (21.8%)	0.001

Bio-SI, Bio-Shock Index; AIS, abbreviated injury score.

SI) and biomarker (high sensitive troponin T [HsTnT]) in patients with TBI.

METHODS

A retrospective analysis of all patients with TBI who were admitted to a national level I trauma center between June 2011 and June 2018 was conducted. The study included all patients with TBI who required hospital admission and were subjected to screening for serum HsTnT during the initial 24 hours postinjury, and had initial vital signs taken in the emergency department (ED). Patients data were queried through a prospectively maintained trauma registry database (TraumaBase [Clinical Data Management software, USA]) and electronic medical records (Cerner Corporation [North Kansas City, Missouri, USA]).

The documentation includes detailed information on demographics, head injury lesions (skull fracture, brain contusion, subdural hemorrhage, epidural hemorrhage, extra-axial hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, intracerebral hemorrhage, pneumocephalus, brain edema, and diffuse axonal injury), initial vital signs, associated injuries, head, chest, and abdominal abbreviated injury scores (AIS), Glasgow Coma Scale (GCS) score at ED, injury severity score (ISS), SI, HsTnT values, pulse pressure (PP), mean arterial pressure (MAP), serum lactate, ethanol level, surgical interventions (craniotomy, craniectomy, external ventricular drainage), insertion of intracranial pressure (ICP) monitor, in-hospital complications (pneumonia, sepsis, acute respiratory distress syndrome), hospital length of stay, intensive care unit length of stay, ventilatory days, and mortality.

For quantitative estimation of the serum levels of HsTnT, the enzyme-linked immunosorbent assay was performed as per the manufacturer's instructions. The laboratory reference value >14 ng/L was considered for elevated HsTnT. The SI was determined by obtaining the initial ratio of heart rate to systolic blood pressure (SBP) in the ED for each patient.[12] The MAP was calculated by using the formula as MAP = [SBP + 2 diastolic blood pressure]/3. The Rotterdam score includes 4 independently scored elements: 1) degree of basal cistern compression, 2) degree of midline shift, 3) epidural hematomas, and 4) intraventricular

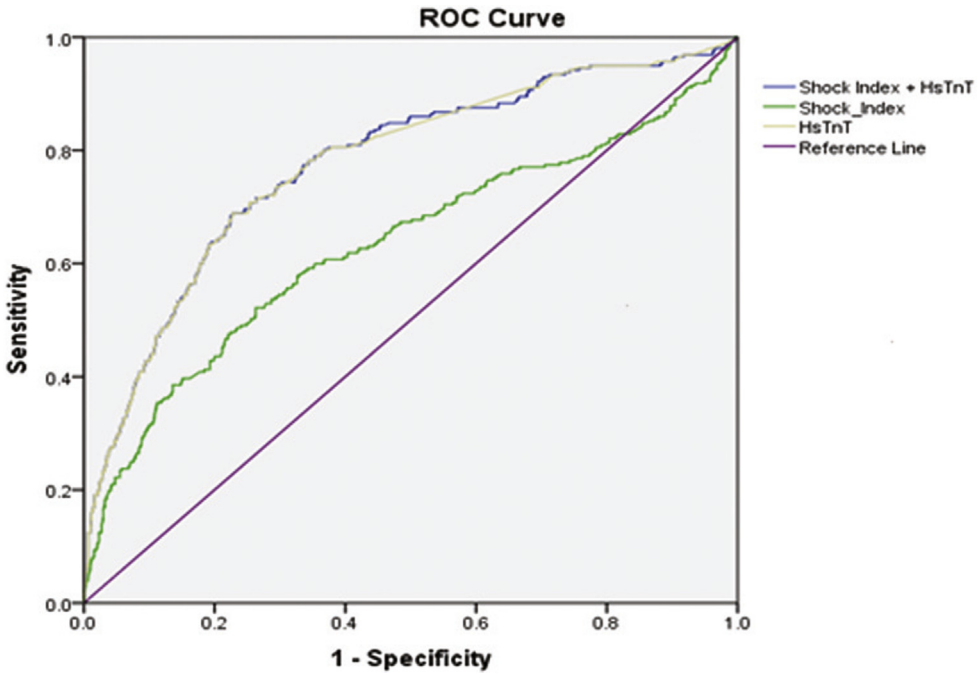

Figure 1. The receiver operating characteristic curve analysis showed area under the curve (AUC) for Bio-Shock Index (Bio-SI) (AUC, 0.775; 95% confidence interval [CI], 0.741–0.808), shock index (AUC, 0.632; 95% CI, 0.589–0.675), and high sensitive troponin T (AUC, 0.775; 95% CI, 0.741–0.808). The cutoff point of Bio-SI for predicting mortality is 10.0 (sensitivity, 91.1%; specificity, 30.6%; $P = 0.001$). HsTnT, high sensitive troponin T; ROC, receiver operating characteristic.

and/or subarachnoid blood. Each of these is given a score, and these scores are tallied with the addition of 1 to the total.[13]

The Medical Research Center (institutional review board# MRC-01-18-343) at Hamad Medical Corporation, Doha, Qatar, has approved the present study.

Statistical Analysis

Data were presented as proportions, medians, or mean ± standard deviation, as appropriate.

Bio-SI was calculated by multiplying the values of HsTnT and SI. Receiver operating characteristic (ROC) curve was plotted to determine the cutoff value of Bio-SI for predicting the in-hospital mortality. The area under the curve (AUC) was used to compare the discriminatory power of the Bio-SI, with an AUC of 1.0 considered as perfect discrimination and 0.5 considered as equal to chance. We have categorized Bio-SI into 2 groups: low Bio-SI and high Bio-SI. Differences in categorical and continuous variables were analyzed using the χ^2 test and the Student t test, as appropriate. The Yates corrected χ^2 was used for categorical variables, if the expected cell frequencies were <5. The Pearson correlation coefficient (r) was calculated to identify the linear relationship between the Bio-SI and other relevant covariates. Multivariable regression analyses were performed to determine the predictors of mortality in 2 models (model-1 used SI and HsTnT separated and model-2 used Bio-SI) after adjustment for age, sex, admission GCS score, ISS, pneumonia, SI, MAP, craniotomy, HsTnT status, ICP monitor insertion, and serum lactate. Data were expressed by the odds ratio and 95% confidence intervals (CIs). A 2-tailed P value of <0.05 was considered to be statistically significant. All data analyses were carried out using the Statistical Package for the Social Sciences, version 18 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

During the study period, there were a total of 2619 patients with TBI admitted in the hospital of which 1471 fulfilled the inclusion criteria. Based on the ROC curve, the cutoff point value of Bio-SI for predicting mortality was 10.0 (27% had low Bio-SI <10 and 73% had high Bio-SI ≥10).

Table 1 compares the Bio-SI status with respect to the demographics, clinical presentations, and head injury lesions in patients who sustained TBI. The mean age of the patient was 33.4 ± 14.6 years, and the majority (93.2%) were men. The 2 groups were comparable for age, sex, frequency of skull fracture, brain contusion, and subdural, extra-axial, subarachnoid, and intracerebral hemorrhage. Patients with elevated Bio-SI were more likely to have intraventricular hemorrhage (10.3% vs. 4.3%; P = 0.001), brain edema (25.8% vs. 16.8%; P = 0.001), and diffuse axonal injury (10.2% vs. 4.8%; P = 0.001). However, patients with lower Bio-SI had a significantly higher frequency of epidural hemorrhage (25.1% vs. 19.7%; P = 0.02). In comparison

Table 3. Clinical Presentation, Management, and Complications by Outcome

Variable	Survivors (n = 1214)	Nonsurvivors (n = 257)	*P* Value
Age in years, mean ± SD	32.8 ± 14.2	36.3 ± 15.8	0.001
Males	1129 (93.0%)	242 (94.2%)	0.50
Head injury lesions			
Skull fracture	760 (62.6%)	185 (72.0%)	0.004
Brain contusion	666 (54.9%)	137 (53.3%)	0.65
Subdural hemorrhage	329 (27.1%)	120 (46.7%)	0.001
Epidural hemorrhage	281 (23.1%)	30 (11.7%)	0.001
Extra-axial hemorrhage	126 (10.4%)	27 (10.5%)	0.95
Subarachnoid hemorrhage	369 (30.4%)	148 (57.6%)	0.001
Intraventricular hemorrhage	84 (6.9%)	44 (17.1%)	0.001
Intracerebral hemorrhage	39 (3.2%)	6 (2.3%)	0.45
Pneumocephalus	213 (17.5%)	51 (19.8%)	0.38
Brain edema	202 (16.6%)	142 (55.3%)	0.001
Diffuse axonal injury	102 (8.4%)	27 (10.5%)	0.27
Shock index	0.78 ± 0.29	1.01 ± 0.49	0.001
Bio-Shock Index	10.8 (0.9–3026)	73.3 (1.6–5922)	0.001
Pulse pressure	49.8 ± 16.3	46.2 ± 20.1	0.007
Mean arterial pressure	95.1 ± 16.7	87.6 ± 26.4	0.001
Serum lactate	2.7 (0.5–70.6)	3.9 (0.1–20.1)	0.001
Cardiac injury	11 (0.9%)	4 (1.6%)	0.34
Head AIS	3.6 ± 0.9	4.6 ± 0.8	0.001
Injury severity score	22.1 ± 9.7	33.2 ± 9.6	0.001
Admission Glasgow Coma Scale score	10 (3–15)	3 (3–15)	0.001
HsTnT positive	442 (36.4%)	205 (79.8%)	0.001
Interventions			
Intubation	749 (61.7%)	255 (99.2%)	0.001
Intracranial pressure monitor	211 (17.4%)	34 (13.2%)	0.10
Craniotomy	117 (9.6%)	9 (3.5%)	0.001
Craniectomy	84 (6.9%)	24 (9.3%)	0.17
Complications			
Pneumonia	255 (21.0%)	33 (12.8%)	0.003
Acute respiratory distress syndrome	20 (1.6%)	17 (6.6%)	0.001
Sepsis	84 (6.9%)	12 (4.7%)	0.18

SD, standard deviation; AIS, abbreviated injury score; HsTnT, high sensitive troponin T.

to lower Bio-SI, patients with elevated Bio-SI had significantly lower PP (48.6 ± 17.8 vs. 50.8 ± 14.9; P = 0.01), MAP (92.8 ± 20.3 vs. 96.4 ± 14.1; P = 0.001), and admission GCS score (5 [3–15] vs. 12 [3–15]; P = 0.001). The mean SI (P = 0.001) and median serum lactate (2.9 [0.1–50.0] vs. 2.5 [0.6–70.6]; P = 0.001), and HsTnT values (P = 0.001) were significantly higher in the Bio-SI ≥10 group.

Table 2 compares the associated injuries, ISS, interventions, complications, and outcome according to Bio-SI. Patients who had an elevated Bio-SI were more likely to have associated chest (P = 0.001), abdomen (P = 0.001), and cardiac (P = 0.01) injuries, and had higher mean ISS (P = 0.001), greater head AIS (P = 0.004), chest AIS (P = 0.01), and abdomen AIS (P = 0.001) scores than those with lower Bio-SI. Also, the need for

Table 4. Predictive Value of Different Scores and Biomarker for Outcome

Scores	Mortality
Shock index (≥0.9)	
Sensitivity	50.2%
Specificity	74.1%
Positive predictive value	29.1%
Negative predictive value	87.6%
Positive likelihood ratio	1.94
Negative likelihood ratio	0.67
AUC (95% CI)	0.632 (0.589–0.675)
Bio-Shock Index (≥10)	
Sensitivity	91.4%
Specificity	30.6%
Positive predictive value	21.8%
Negative predictive value	94.4%
Positive likelihood ratio	1.32
Negative likelihood ratio	0.28
AUC (95% CI)	0.775 (0.741–0.808)
HsTnT (>14)	
Sensitivity	79.7%
Specificity	63.6%
Positive predictive value	31.7%
Negative predictive value	93.7%
Positive likelihood ratio	2.19
Negative likelihood ratio	0.32
AUC (95% CI)	0.775 (0.741–0.808)

AUC, area under the curve; CI, confidence interval; HsTnT, high sensitive troponin T.

intubation (P = 0.001), tracheostomy (P = 0.001), and ICP monitor insertion (P = 0.001) was associated with higher Bio-SI values, whereas the rate of craniotomy was significantly higher in patients with lower Bio-SI values. The rate of craniectomy and external ventricular drainage was comparable between the 2 groups. Also, patients with elevated Bio-SI had a prolonged hospital (P = 0.003) and intensive care unit stay (P = 0.001), remained mechanically ventilated for a longer duration (P = 0.001), and had higher rates of in-hospital complications such as pneumonia (P = 0.001) and sepsis (P = 0.001). Around one fifth (17.5%) of the cases died in the hospital; the in-hospital mortality rate was 4 times higher in patients with elevated Bio-SI than those who had lower Bio-SI (21.8% vs. 5.6%; P = 0.001).

Figure 1 shows the ROC analysis with an AUC for Bio-SI (AUC, 0.775; 95% CI, 0.741–0.808), SI (AUC, 0.632; 95% CI, 0.589–0.675), and HsTnT (AUC, 0.775; 95% CI, 0.741–0.808).

Table 3 demonstrates the clinical presentation, management, and complications by outcome. Patients with TBI who died were 3 years older (P = 0.001), and had significantly higher mean SI (P = 0.001), median Bio-SI (P = 0.001), and serum lactate (P = 0.001) and had lower PP (P = 0.007), and MAP (P = 0.001), and as compared with survivors. Also, the presence of skull fracture (P = 0.004), subdural hematoma (P = 0.001), subarachnoid hemorrhage (P = 0.001), interventricular hemorrhage (P = 0.001), and brain edema (P = 0.001) were significantly associated with mortality. Although survivors were more likely to have epidural hematoma (P = 0.001), they frequently underwent craniotomy (P = 0.001) and developed pneumonia (P = 0.003) during the hospital course in comparison to nonsurvivors. Moreover, those who died had significantly higher mean ISS (P = 0.001), head AIS (P = 0.001), lower median admission GCS score (P = 0.001), and were more likely to have positive HsTnT results (P = 0.001) and developed acute respiratory distress syndrome (P = 0.001).

The Rotterdam computed tomography score was available for 653 patients and was significantly higher in patients with high Bio-SI in comparison with patients with low Bio-SI.

The univariate correlation (Pearson correlation coefficient [r]) between Bio-SI and other relevant covariates showed a positive correlation between Bio-SI and Rotterdam score (r = 0.170; P = 0.001), head AIS (r = 0.147; P = 0.001), serum lactate (r = 0.154; P = 0.001), and a negative correlation with GCS score (r = −0.182; P = 0.001) and MAP (r = −0.189; P = 0.001).

Table 4 shows the predictive value of SI (≥0.9), HsTnT (≥14), and Bio-SI (≥10) with respect to mortality in patients with TBI. The Bio-SI showed higher sensitivity and negative predictive value (NPV) (91.4% and 94.4%, respectively) as compared with elevated SI (50.2% and 87.6%, respectively) and positive troponin (79.7% and 93.7%, respectively).

Multivariate Logistic Regression Analysis

On multivariate analysis (Table 5), model-1 showed that HsTnT was an independent predictor of mortality after adjusting for the relevant covariates (adjusted odds ratio, 3.086; 95% CI, 1.841–5.174; P = 0.001), whereas SI was not a predictor of mortality. In model-2, the Bio-SI was an independent predictor of mortality (adjusted odds ratio, 3.28; 95% CI, 1.410–7.630; P = 0.001).

DISCUSSION

To date, various scoring systems have been proposed using anatomic and physiological parameters to predict the outcomes of trauma patients.[14-16] There are few reports to investigate the clinical relevance of SI[8,17-19] or cardiac troponin[9-11,20] in patients with TBI. Prior data showed that the post-TBI release of cardiac troponin was mainly related to stress-induced sympathetic surge, even in the absence of direct cardiac trauma.[9,20,21]

The present study attempted to propose a novel prognostic score: Bio-SI that is a combination of SI and troponin for TBI. In our series, almost three quarters of patients with TBI had high Bio-SI (≥10). Notably, patients with elevated Bio-SI were more likely to be sicker with lower PP, MAP, and admission GCS scores, and having higher serum lactate, and greater Rotterdam scoring. Also, we highlighted a significant positive correlation between Bio-SI and ISS, head AIS, and serum lactate, however, it was not a perfect correlation. Approximately one fifth of TBI cases died in

Table 5. Multivariate Regression Analysis for the Independent Predictors for Mortality

Variables	*P* Value	Odds Ratio	95% CI	
Model 1 using SI and HsTnT separated				
Age	0.001	1.032	1.016	1.049
Sex	0.566	1.351	0.484	3.770
Admission GCS score	0.001	0.802	0.756	0.852
Injury severity score	0.001	1.085	1.058	1.113
Pneumonia	0.001	0.244	0.115	0.514
Shock index	0.778	1.144	0.449	2.916
Mean arterial pressure	0.626	1.004	0.988	1.020
Craniotomy	0.225	0.499	0.162	1.533
HsTnT status	0.001	3.086	1.841	5.174
Intracranial pressure monitor	0.001	0.292	0.151	0.562
Serum lactate	0.018	1.056	1.009	1.104
Model 2 using the Bio-SI				
Age	0.001	1.032	1.016	1.049
Sex	0.460	1.490	0.520	4.240
Admission GCS score	0.001	0.790	0.750	0.840
Injury severity score	0.001	1.090	1.060	1.112
Pneumonia	0.001	0.280	0.130	0.570
Mean arterial pressure	0.831	0.990	0.980	1.010
Craniotomy	0.110	0.410	0.140	1.230
Intracranial pressure monitor	0.001	0.284	0.148	0.545
Serum lactate	0.004	1.070	1.020	1.120
Bio-SI	0.001	3.280	1.410	7.630

CI, confidence interval; SI, shock index; HsTnT, high sensitive troponin T; GCS, Glasgow Coma Scale; Bio-SI, Bio-Shock Index.

the hospital, and the mortality rate was 4-fold higher in the elevated Bio-SI group. In addition, Bio-SI outperforms its individual components to predict worse outcomes; however, HsTnT alone could relatively act in a similar way. A high admission Bio-SI or its individual components could be used as a red-flag for the attending physicians and nurses in the ED and triage area for better risk-stratification. We performed sensitivity analyses in predicting mortality for Bio-SI, SI, and HsTnT. The discriminatory power to predict in-hospital mortality as demonstrated by the AUC curves for Bio-SI was comparable to HsTnT (AUC 0.77). The findings of the previous study confirms the earlier described observations in patients with TBI that showed a relatively similar AUC (0.75) for HsTnT to predict all-cause mortality.[9] However, on considering the sensitivity and NPV for mortality to indicate the best model, the Bio-SI showed a better sensitivity and NPV in comparison to HsTnT or SI alone. Both HsTnT and Bio-SI showed a significant correlation with Rotterdam score ($r = 0.17$; $P = 0.001$), whereas SI showed very weak correlation ($r = 0.09$; $P = 0.01$). A prior study[22] showed that in adult patients with mild-to-severe TBI, more deaths occurred among patients with higher Marshall and Rotterdam scores. The AUCs indicated that both scoring systems had similarly good discriminative power in predicting early death (AUC = 0.85),[22] however, both need exhaustive radiologic evaluation and calculation.

Our study demonstrated that positive troponin was independently associated with a 3-fold increased risk of mortality. Moreover, SI alone was not an independent predictor of mortality in our study cohort.

Previous studies have reported the use of SI for stratification of overall trauma patients at a high risk of early mortality.[12,23] Particularly, an earlier study of patients with TBI categorized admission SI into 4 classes and observed that the groups with highest SI were associated with higher injury severity and in-hospital mortality.[8] However, McMahon et al.[1] observed no linear relationship between SI and progressive hemorrhage among nonsurvivors of a moderate severity group. This suggests that SI is unreliable to assess progressive hemorrhage in acute TBI and should be considered carefully. Therefore, it is important to consider other factors that might influence the pathophysiology of patients with TBI.

Crewdson et al.[14] demonstrated the use of admission cardiac troponin T as a potential marker of worse outcome in polytrauma patients. More precisely, the predictive value of cardiac troponin for the prognosis of patients with brain injury has been highlighted by a recent study from our center.[9] However, the current evidence for the association and clinical relevance of elevated cardiac troponin in TBI is not fully described and needs further exploration to be considered as a prognostic marker in TBI.[9-11] Still, there is a compelling need to develop an inexpensive clinical tool based on hemodynamic parameters and/or routine biomarkers that can be readily available for early prognostication in TBI with superior predictive values.

Multivariate analysis showed that the Bio-SI was an independent predictor of mortality. In another model, HsTnT was also a predictor of mortality.

In our study, the risk of mortality was 3-fold in the presence of positive HsTnT. In-line with our findings, Salim et al.[10] showed that elevated cardiac troponin I was independently associated with mortality, even after adjustment for severity of injury.

There are certain limitations of the current study. First, this was a retrospective analysis from a single center with the possibility of missed information that may limit the generalizability. Second, the primary outcome was confined to in-hospital mortality, and we did not assess the long-term outcome on follow-up. Third, we lack information on the administration of medications (beta blockers, vasopressors, or sedations) at the ED that could affect the components of the Bio-SI. Finally, we cannot comment on the exact timing and frequency of measurements of vital signs and HsTnT values postinjury in the trauma room. As we believe that the trauma-induced sympathetic surge causes cardiac troponin release, increases heart rate and SBP, and eventually leads to higher Bio-SI, we still need further explanation as to why Bio-SI significantly increases with certain brain lesions (i.e., intraventricular hemorrhage, brain edema, and diffuse axonal injury) and does not in other lesions. This could be explained in part by the anatomic specifications and severity of lesion, and other associated body injuries. Furthermore, as we do not have postmortem findings, we cannot assume the cause of death associated with high Bio-SI.

CONCLUSIONS

Recognition of prognostic factors early after TBI is important to improve outcome. Thus the Bio-SI has emerged as a potentially better predictive tool for in-hospital mortality among patients with TBI as compared with elevated SI or positive HsTnT, however, HsTnT alone could relatively act in a similar way. Therefore, we are confident that the Bio-SI-based stratification is reliable and can be considered as a potential marker for predicting in-hospital mortality in TBI. Moreover, Bio-SI also correlates well with severity of injury, and other physiological and laboratory parameters. Thus prospective studies and multicenter trials studying troponin levels and SI in all patients with TBI with the inclusion of outcome scores will prove or disprove the predictability of the new index.

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