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ORIGINAL ARTICLE

The rSIG Score Predicts Intensive Care Unit Admission and Blood Transfusion in Pediatric Trauma Patients

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ABSTRACT

Background: **The aim of this study was to compare the values of the Age-Adjusted Pediatric Shock Index (SIPA), Reverse Shock Index (rSI), and the index obtained by multiplying the Reverse Shock Index by the Glasgow Coma Scale (rSIG) in predicting prognosis and transfusion requirements in pediatric multi-trauma patients.**
Methods: **In this retrospective observational study, 168 patients presenting with multiple pediatric trauma complaints to the Emergency Medicine Clinic of Başakşehir Çam and Sakura City Hospital between June 1, 2020, and June 1, 2022, were evaluated. Patients were divided into two groups based on their rSIG values: normal (n = 85) and abnormal (n = 83). rSIG classification was performed using age-specific cutoff points (1 - 6 years: ≤ 13.1, 7 - 12 years: ≤ 16.5, 13 - 17 years: ≤ 20.1). ROC analysis was performed for intensive care unit (ICU) admission, transfusion requirement, and surgical intervention.**
Results: **The AUC value of rSIG in predicting ICU admission was 0.811 (95% CI: 0.719 - 0.903), which was significantly superior to rSI (AUC: 0.664) and SIPA (AUC: 0.623) (p < 0.001). The AUC value of rSIG in predicting transfusion requirement was 0.861 (95% CI: 0.767 - 0.956), while it was 0.610 (95% CI: 0.524 - 0.696) for surgical intervention. In the logistic regression analysis, each 1-point increase in rSIG reduced the odds ratio for ICU admission by 0.78 (OR: 0.780, 95% CI: 0.652 - 0.933, p = 0.006).**
Conclusions: **rSIG demonstrated significantly higher discriminatory power than SIPA and rSI for predicting ICU admission. Although rSIG showed higher AUC values for transfusion requirement and surgical intervention, these differences did not reach statistical significance. Nevertheless, rSIG may serve as a practical tool for rapid risk stratification and to transfer decisions in emergency departments, particularly for identifying patients requiring ICU admission.**
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KEYWORDS

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INTRODUCTION

Trauma is one of the leading causes of childhood morbidity and mortality worldwide [1].
Early identification of high-risk pediatric trauma patients is critical for initiating appropriate treatment protocols and prognostic assessment [2]. Early recognition of shock in trauma patients and timely intervention are key factors in reducing morbidity and mortality [3].

The shock index (SI) was first defined by Allgöwer and Burri in 1967; it is obtained by dividing the heart rate by the systolic blood pressure [4]. It has gained importance in trauma patients, as systolic blood pressure is considered a late marker of shock [5]. While a normal SI value is considered 0.7, values above 1 are associated with hemodynamic instability and mortality risk [6].
Due to differences in vital signs across age groups in the pediatric population, the accuracy of the SI developed for the adult population is limited in children [7]. Therefore, Acker et al. developed the Age-Adjusted Pediatric Shock Index (SIPA) [8]. SIPA demonstrates superior performance compared to SI in predicting mortality and transfusion requirements in pediatric trauma patients [9].
The Reverse Shock Index (rSI) was developed to enable clinicians to more easily identify situations in daily practice where SBP is lower than the heart rate (HR). The rSI is obtained by dividing SBP by HR and is expected to yield values below 1 in shock patients [10].
In recent years, a new scoring system has been developed that assesses both the hemodynamic and neurological status of trauma patients. This scoring system, known as rSIG, is obtained by multiplying the rSI by the Glasgow Coma Scale (GCS).
Kimura et al. demonstrated that rSIG was a better predictor than SI and SIPA for in-hospital mortality and 24-hour blood transfusion in an analysis of 168,517 patients in the Japan Trauma Data Bank [11,12].
The GCS is a standard tool used worldwide to assess the level of consciousness in patients with traumatic brain injury [13].
Although the efficacy of rSIG in adult trauma patients has been demonstrated in the literature, there are a limited number of studies evaluating the efficacy of this index in pediatric trauma patients. Considering the unique physiological characteristics and trauma patterns of childhood, the efficacy of rSIG in this age group needs to be further investigated.
In this context, the primary aim of our study was to evaluate the ability of rSIG in predicting intensive care unit (ICU) admission, transfusion requirement, and surgical intervention need in pediatric multi-trauma patients and to compare the prognostic performance of rSIG with SIPA and rSI.

MATERIALS AND METHODS

This retrospective observational cohort study included pediatric patients with multiple traumatic injuries who presented to the Emergency Medicine Clinic of Başakşehir Çam and Sakura City Hospital between June 1, 2020, and June 1, 2022. During this period, a total of 312 pediatric trauma patients were evaluated, and after inclusion and exclusion criteria were applied, 168 patients were included in the study. A post-hoc power analysis was performed using G*Power 3.1.9.7 software. It was calculated that with the current sample size (n = 168), power above 95% was achieved for $\alpha = 0.05$ [14].
The study protocol was approved by the hospital's ethics committee under number KAEK/2023.07.291 and conducted in accordance with the principles of the Declaration of Helsinki.
Patients younger than 18 years who presented to the emergency department with multiple traumatic injuries and had complete clinical data were included in the study.
Patients aged 18 years and older, with incomplete data, burn injuries, or who were intubated prior to transfer were excluded from the study.

Calculation of shock indices
Shock Index (SI): SI = HR/SBP
Reverse Shock Index (rSI): rSI = SBP/HR
Age-Adjusted Pediatric Shock Index (SIPA): Calculated as the ratio of the maximum normal HR to the minimum normal SBP for each age group [8].
Reverse Shock Index multiplied by GCS (rSIG): rSIG = (SBP/HR) x GCS.
rSIG is classified as normal/abnormal according to age-specific cutoff points reported in the literature [15].
1/ 1 - 6 years: ≤ 13.1 values are abnormal.
2/ 7 - 12 years: ≤ 16.5 values are abnormal.
3/ 13 - 17 years: ≤ 20.1 values are abnormal.

Statistical analysis
All analyses were performed using Jamovi v2.6.44.0. Continuous variables were presented as mean ± SD or median (Q1 - Q3) according to distribution; categorical variables were presented as numbers and percentages [n (%)]. The normality of continuous variables was assessed using the Shapiro-Wilk test and graphs. Student's *t*-test was used for group comparisons when appropriate, and otherwise the Mann-Whitney U test; Pearson's chi-squared test was used for categorical variables. All p-values were two-tailed, and a significance level of $\alpha = 0.05$ was used [16].
ROC analyses: The discriminatory power of the rSI, rSIG, and SIPA variables for ICU admission, transfusion, and surgical intervention was evaluated using ROC curves and AUC (95% CI) with the *"DiagROC"* module in the Jamovi library. The DeLong method was used for AUC confidence intervals and inter-curve comparisons. In pairwise comparisons, ΔAUC was defined as AUC(first) - AUC(second). For rSI and rSIG in the ROC analysis, "smaller values indicate positive" was selected, and for SIPA, "larger values indicate positive" was selected [17].
rSIG classification: rSIG was classified as normal/ab normal according to age-specific cutoff points reported in the literature: values ≤ 13.1 for 1 - 6 years, ≤ 16.5 for 7 - 12 years, and ≤ 20.1 for 13 - 17 years were considered abnormal. Clinical/laboratory parameters were compared between groups using this classification [15].
Logistic regression: The independent effect of rSIG on ICU admission was examined using binary logistic re-

gression. Model 1: rSIG alone; Model 2 (adjusted): rSIG + age, gender, and GCS. Models were constructed using a block approach, and nested model comparisons were performed using the likelihood-ratio test. For model fit, -2 Log-Likelihood (Deviance), AIC, BIC, and Nagelkerke R^2 were reported. Effect sizes were given as odds ratio (OR) and 95% CI [18].

RESULTS

The mean age of the patients was 7.2 ± 4.8 years, with 106 (63.1%) patients being male and 62 (36.9%) patients being female. When trauma mechanisms were examined, traffic accidents accounted for 45.2% (n = 76), falls for 31.5% (n = 53), sports injuries for 12.5% (n = 21), and other causes for 10.8% (n = 18). The most commonly affected anatomical regions were the head and neck (89.3%), the extremities (67.9%), and the chest (34.5%).

Patients were divided into normal rSIG (n = 85, 50.6%) and abnormal rSIG (n = 83, 49.4%) groups according to age-specific cutoff points reported in the literature.

The gender distributions of the normal rSIG (n = 85) and abnormal rSIG (n = 83) groups were similar (χ^2 = 0.57, p = 0.449). The median ages were 5 years (3 - 8) and 6 (1 - 13), respectively, with no significant difference between groups (Z = -0.78, p = 0.435).

In laboratory measurements, INR was 1.09 (1.00 - 1.10) in the normal group and 1.10 (1.00 - 1.16) in the abnormal group, with a significant difference (Z = -2.04, p = 0.042). No significant differences were found for PT (Z = -1.59, p = 0.111), aPTT (Z = -1.80, p = 0.073), and Hb (Z = -0.31, p = 0.755). The median lactate level was 1.00 (1.00 - 1.60) in the normal group and 1.50 (1.00 - 2.30) in the abnormal group, and the difference was significant (Z = -2.32, p = 0.020).

Among vital signs, the mean pulse rate was 97.37 ± 15.12 in the normal group and 115.78 ± 21.90 in the abnormal group, and the difference was significant (t = -6.33, p < 0.001).

The median SBP was 120 (110 - 120) in the normal group and 103 (95.0 - 115.5) in the abnormal group, indicating that SBP was significantly lower in the abnormal group (Z = -5.73, p < 0.001). The median GCS score was 15 (15 - 15) in the normal group and 15 (14 - 15) in the abnormal group, and the difference was significant (Z = -2.49, p = 0.013). There was no difference for DBP (diastolic blood pressure) (Z = -1.40, p = 0.163).

In shock indices, rSI was 1.20 (1.09 - 1.33) in the normal group and 0.85 (0.78 - 1.09) in the abnormal group (Z = -7.75, p < 0.001); rSIG was 18.00 (15.68 - 19.95) and 12.45 (10.55 - 15.38) (Z = -8.29, p < 0.001); SIPA was 1.15 (1.01 - 1.30) and 1.47 (1.21 - 1.75) (Z = -6.43, p < 0.001), with significant differences between groups in all cases. The ISS medians were 4 (4 - 4) and 4 (4 - 9), with no significant difference detected (Z = -1.80, p = 0.072) (Table 1).

The ROC curves and AUC values of the scores used to predict intensive care unit admission are presented in Figure 1 and Table 2. The AUC values for rSI, rSIG, and SIPA were 0.664 (95% CI: 0.527 - 0.800, p = 0.019), 0.811 (95% CI: 0.719 - 0.903, p < 0.001), and 0.623 (95% CI: 0.478 - 0.767, p = 0.096), respectively. When the AUC differences between the scores were compared using the DeLong test, rSIG was found to be significantly superior to rSI (AUC difference = 0.147, 95% CI: 0.045 - 0.249, p = 0.005). The difference between rSIG and SIPA was also statistically significant (AUC difference = 0.188, 95% CI: 0.081 - 0.294, p < 0.001). In contrast, the difference between rSI and SIPA was statistically nonsignificant (AUC difference = 0.041, 95% CI: -0.002 - 0.084, p = 0.065). These findings indicate that rSIG has higher discriminatory power compared to other scores in predicting intensive care unit admission (Table 2, Figure 1).

The results of the ROC analysis of indices used to predict transfusion requirements are presented in Figure 2 and Table 3. The area under the curve (AUC) was 0.778 for rSI (95% CI: 0.648 - 0.908, p < 0.001), 0.861 for rSIG (95% CI: 0.767 - 0.956, p < 0.001), and 0.768 for SIPA (95% CI: 0.631 - 0.906, p < 0.001). In the comparative analysis, although the AUC value for rSIG was higher than that for rSI, this difference was statistically nonsignificant (AUC difference = -0.083, 95% CI: -0.197 to -0.030, p = 0.149). Similarly, the difference between rSI and SIPA (AUC difference = 0.009, 95% CI: -0.033 - 0.052, p = 0.664) and the difference between rSIG and SIPA (AUC difference = 0.093, 95% CI: -0.031 - 0.216, p = 0.141) were also nonsignificant. These findings indicate that rSIG has the highest AUC value but does not show a statistically significant superiority compared to other scores in predicting transfusion need (Table 3, Figure 2).

When examining the ROC curves of the rSI, rSIG, and SIPA indices in terms of accuracy in predicting the need for surgery, the highest AUC value was observed for rSIG (AUC = 0.610; 95% CI: 0.524 - 0.696; p = 0.012). The rSI (AUC = 0.578; 95% CI: 0.491 - 0.665; p = 0.078) and SIPA (AUC = 0.571; 95% CI: 0.484 - 0.658; p = 0.108) indices were statistically nonsignificant. In pairwise comparisons using the DeLong test, no significant difference was found between the indices (rSI-rSIG: AUC difference = -0.031; 95% CI: -0.068 - 0.005; p = 0.091; rSI–SIPA: AUC difference = 0.007; 95% CI: -0.034 - 0.048; p = 0.739; rSIG–SIPA: AUC difference = 0.038; 95% CI: -0.016 - 0.092; p = 0.166). These results indicate that rSIG has higher discriminatory power than other indices in predicting the need for surgery, but the differences did not reach a statistically significant level (Table 4, Figure 3).

rSIG alone significantly predicted ICU admission (Model 1; Overall $\chi^2(1)$ = 25.821, p < 0.001; -2LL = 108.345). Adding age, gender, and GCS to rSIG significantly improved model fit (Model 2; -2LL = 71.948; AIC 112.345 → 81.948; BIC 118.593 → 97.568; Nagelkerke R^2 0.259 → 0.563). Comparison of nested

Table 1. Clinical characteristics by rSIG status (normal vs. abnormal).

Variable	Normal	Abnormal	Test statistic	p
	M ± SD/Med. (Q1 - Q3); n	M ± SD/Med. (Q1 - Q3); n		
Gender				
Male	56	50	χ^2 = 0.57 [c]	0.449
Female	29	33		
Age	5 (3 - 8); 85	6 (1 - 13); 83	Z = -0.78 [a]	0.435
INR	1.09 (1.00 - 1.10); 85	1.10 (1.00 - 1.16); 83	Z = -2.04 [a]	0.042
PT (s)	9.51 (9.01 - 10.10); 84	9.70 (9.15 - 10.25); 83	Z = -1.59 [a]	0.111
aPTT (s)	27.60 (25.10 - 30.00); 85	28.10 (26.35 - 31.85); 83	Z = -1.80 [a]	0.073
Hb (g/dL)	11.90 (11.10 - 12.70); 85	11.80 (10.65 - 12.95); 83	Z = -0.31 [a]	0.755
Lactate (mmol/L)	1.00 (1.00 - 1.60); 85	1.50 (1.00 - 2.30); 83	Z = -2.32 [a]	0.020
Heart rate (bpm)	97.37 ± 15.12; 85	115.78 ± 21.90; 83	t = -6.33 [b]	< 0.001
SBP (mmHg)	120 (110 - 120); 85	103 (95.0 - 115.5); 83	Z = -5.73 [a]	< 0.001
DBP (mmHg)	70 (60 - 76); 85	68 (60 - 74); 83	Z = -1.40 [a]	0.163
rSI	1.20 (1.09 - 1.33); 85	0.85 (0.78 - 1.09); 83	Z = -7.75 [a]	< 0.001
rSIG	18.00 (15.68 - 19.95); 85	12.45 (10.55 - 15.38); 83	Z = -8.29 [a]	< 0.001
SIPA	1.15 (1.01 - 1.30); 85	1.47 (1.21 - 1.75); 83	Z = -6.43 [a]	< 0.001
ISS	4 (4 - 4); 85	4 (4 - 9); 83	Z = -1.80 [a]	0.072
GCS	15 (15 - 15); 85	15 (14 - 15); 83	Z = -2.49 [a]	0.013

Group comparisons used: [a] Mann-Whitney U test, [b] Student's *t* test, and [c] Pearson's chi-squared (χ^2) test. INR: international normalized ratio, PTZ: prothrombin time, aPTT: activated partial thromboplastin time, Hb: hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure, rSI: reverse shock index, rSIG: reverse shock index multiplied by Glasgow Coma Scale, SIPA: shock index, pediatric age-adjusted, ISS: Injury Severity Score (range 0 - 75), GCS: Glasgow Coma Scale, M: mean, SD: standard deviation, Med. (Q1 - Q3): median with interquartile range.

Table 2. ROC analysis for ICU admission and pairwise DeLong comparisons of AUCs.

Score	AUC	95% CI	p	Comparisons	AUC Difference	95% CI	p
rSI	0.664	0.527 - 0.800	<u>0.019</u>	rSI - rSIG	-0.147	(-0.249) - (-0.045)	<u>0.005</u>
rSIG	0.811	0.719 - 0.903	<u>< 0.001</u>	rSI - SIPA	0.041	(-0.002) - (0.084)	0.065
SIPA	0.623	0.478 - 0.767	0.096	rSIG - SIPA	0.188	0.081 - 0.294	<u>< 0.001</u>

Outcome: ICU admission (1 = yes, 0 = no), ΔAUC = AUC (first) - AUC (second), n = 168; positives/negatives = 23/145, ROC: receiver operating characteristic, AUC: area under the curve, CI: confidence interval, rSI: reverse shock index, rSIG: reverse shock index multiplied by Glasgow Coma Scale, SIPA: shock index pediatric age-adjusted, ICU: intensive care unit.

Table 3. ROC analysis for transfusion requirement and pairwise DeLong comparisons of AUCs.

Score	AUC	95% CI	p	Comparisons	AUC Difference	95% CI	p
rSI	0.778	0.648 - 0.908	< 0.001	rSI - rSIG	-0.083	(-0.197) - (0.030)	0.149
rSIG	0.861	0.767 - 0.956	< 0.001	rSI - SIPA	0.009	(-0.033) - (0.052)	0.664
SIPA	0.768	0.631 - 0.906	< 0.001	rSIG - SIPA	0.093	(-0.031) - (0.216)	0.141

Outcome: Transfusion requirement (1 = yes, 0 = no); n = 168, positives/negatives = 15/153.
ROC: receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, rSI: Reverse shock index, rSIG: Reverse shock index multiplied by Glasgow Coma Scale, SIPA: Shock index pediatric age-adjusted.

Table 4. ROC analysis for predicting surgical intervention requirement and pairwise DeLong comparisons of AUCs.

Score	AUC	95% CI	p	Comparisons	AUC difference	95% CI	p
rSI	0.578	0.491 - 0.665	0.078	rSI - rSIG	-0.031	(-0.068) - (0.005)	0.091
rSIG	0.610	0.524 - 0.696	0.012	rSI - SIPA	0.007	(-0.034) - (0.048)	0.739
SIPA	0.571	0.484 - 0.658	0.108	rSIG - SIPA	0.038	(-0.016) - (0.092)	0.166

Outcome: operative requirement (1 = yes, 0 = no); n = 168, positives/negatives = 83/85.
ROC: receiver operating characteristic, AUC: area under the curve, CI: confidence interval, rSI: reverse shock index, rSIG: reverse shock index multiplied by Glasgow Coma Scale, SIPA: shock index pediatric age-adjusted.

Table 5. Model fit indices for binomial logistic regression predicting ICU admission.

Model	-2 Log Likelihood	AIC	BIC	R^2 (Nagelkerke)	Overall χ^2 (df)	p
1	108.345	112.345	118.593	0.259	25.821 (1)	< 0.001
2	71.948	81.948	97.568	0.563	62.219 (4)	< 0.001

Outcome: ICU admission (1 = yes, 0 = no), N = 168; ICU events = 23. Model 1: rSIG, Model 2: rSIG + age + gender + Glasgow Coma Scale.
AIC: Akaike information criterion, BIC: Bayesian information criterion, rSIG: Reverse shock index multiplied by Glasgow Coma Scale, ICU: Intensive care unit.

Table 6. Adjusted effect of rSIG on ICU admission (model 2).

Predictor	β	SE	Z	p	OR	95% CI for OR
rSIG	-0.249	0.091	-2.723	0.006	0.780	0.652 - 0.933

Outcome: ICU admission (1 = yes, 0 = no). Model adjusted for age, gender, and GCS; the intercept is not shown due to lack of clinical interpretability.
rSIG: reverse shock index multiplied by Glasgow Coma Scale, β: Beta coefficient, SE: standard error, Z: Z statistic, OR: odds ratio, CI: confidence interval.

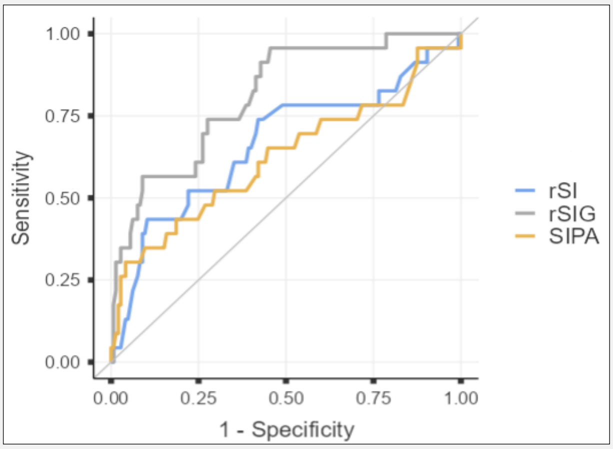

Figure 1. Receiver operating characteristic (ROC) curves for predicting intensive care unit admission.

ROC: receiver operating characteristic, rSI: Reverse Shock Index, rSIG: Reverse Shock Index multiplied by Glasgow Coma Scale, SIPA: Shock index Pediatric Age-Adjusted, ICU: intensive care unit.

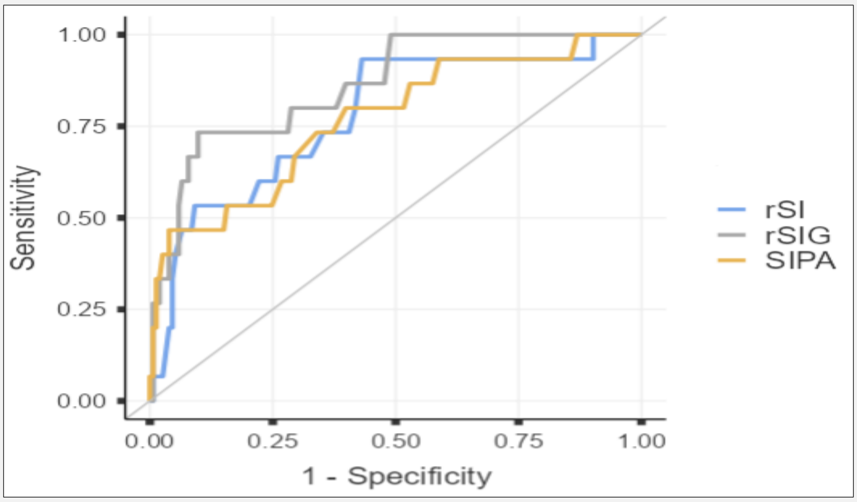

Figure 2. Receiver operating characteristic (ROC) curves for predicting transfusion requirement.

ROC: receiver operating characteristic, rSI: Reverse Shock Index, rSIG: Reverse Shock Index multiplied by Glasgow Coma Scale, SIPA: Shock Index Pediatric Age-Adjusted.

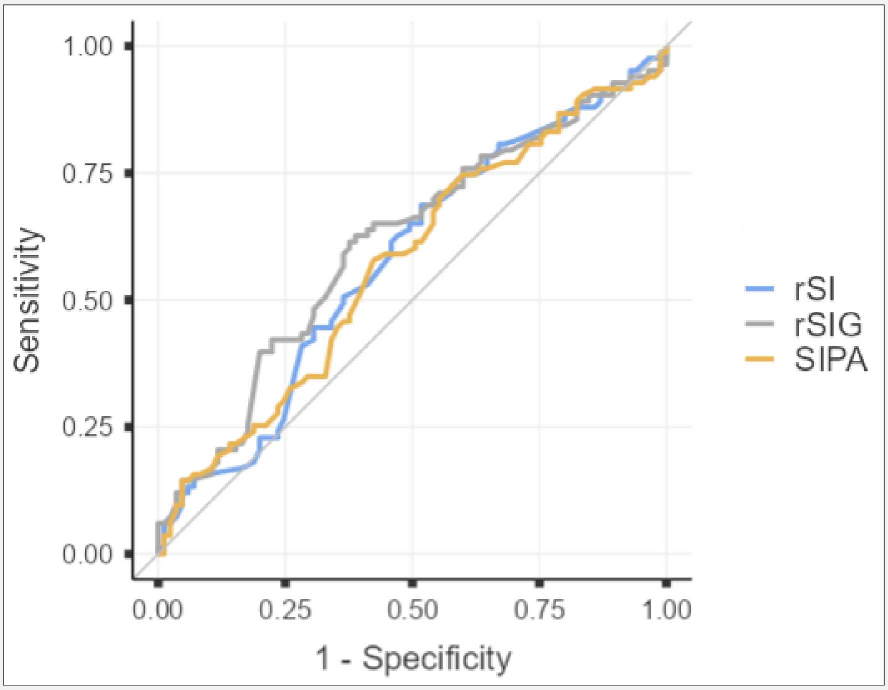

Figure 3. Receiver operating characteristic (ROC) curves for predicting surgical intervention.

ROC: receiver operating characteristic, rSI: Reverse Shock Index, rSIG: Reverse Shock Index multiplied by Glasgow Coma Scale, SIPA: Shock Index Pediatric Age-Adjusted.

models demonstrated a significant improvement in model fit when age, gender, and GCS were added to rSIG ($\chi^2(3) = 36.398$, $p < 0.001$) (Table 5).
In the adjusted model (Model 2), each 1-point increase in rSIG was associated with a 22% decrease in the odds of ICU admission (OR = 0.780; 95% CI: 0.652 - 0.933; p = 0.006). (Table 6).

DISCUSSION

Our study demonstrates that rSIG outperforms rSI and SIPA in predicting intensive care unit admission in pediatric multi-trauma patients. Adverse clinical outcomes were more frequent in the abnormal rSIG group. The prognostic value of rSIG is maintained even after controlling for age, gender, and GCS.
In an analysis by McNab et al. of trauma patients by age group, it was demonstrated that the prognostic value of the shock index changes with age [19]. The difference in rSIG performance between age groups in our study supports this finding.
In our subgroup analyses, it was determined that rSIG is effective in all age groups, but the highest performance was observed in the 1 - 6 age group. This finding can be explained by the more limited physiological reserve in the younger age group and the faster depletion of compensation mechanisms [20].
The relatively low rSIG performance in adolescents (13 - 17 years) may be related to the physiological characteristics of this age group being closer to those of adults and their higher compensation capacity [21].
In the study by Phillips et al. using SIPA, the success in predicting the need for transfusion in children with solid organ injury was emphasized [22]. In our study, the superiority of rSIG in predicting transfusion needs is clinically important in terms of early preparation of blood products and appropriate treatment planning.
However, the performance of rSIG in predicting the need for surgical intervention was more limited compared to other indices. This may be due to the fact that the decision for surgery is closely related not only to physiological parameters but also to the pattern of anatomical injury and imaging findings. In a study by Smida et al. investigating a modified version of rSIG with a motor component, better results were reported in predicting surgical intervention [23].
In our study, the AUC value of rSIG in predicting ICU admission was found to be 0.811, which is consistent with similar studies in the literature. In a study by Wu et al. in adult trauma patients, the AUC value of rSIG in predicting mortality was reported to be 0.83 [24]. In a study by Lin et al. in patients with traumatic brain injury, the AUROC value of rSIG in predicting mortality was found to be 0.710 [25]. The results obtained in our study show that rSIG has similar efficacy in the pediatric population.
A study by Reppucci et al. in pediatric trauma patients showed that children with abnormal rSIG had a 6.18-fold higher risk of needing trauma intervention (NFTI+). In our study, the ICU admission rate was 20.5% in the abnormal rSIG group compared to 7.1% in the normal group, indicating a similar increase in risk. Although the original study by Acker et al., in which SIPA was developed, emphasized SIPA's performance in predicting mortality [8], it is important to note that rSIG performed significantly better than SIPA in our study. This highlights the importance of including neurological status (GCS) in prognostic assessment.

CONCLUSION

This retrospective cohort study demonstrated that rSIG had superior discriminatory performance compared with rSI and SIPA for predicting ICU admission in pediatric multi-trauma patients. By integrating both hemodynamic and neurological status, rSIG provides a more comprehensive assessment of trauma severity. Therefore, rSIG may serve as a practical adjunctive tool for risk stratification and transfer decisions in emergency departments.

Accessibility of Data and Materials:
Data supporting the findings of this study are available upon request from the corresponding author. The data are not publicly available as they contain information that could compromise patient privacy.

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The authors declare that they have not received any financial support for this study.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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