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ORIGINAL RESEARCH

The Association of Systemic Immune Inflammation Index (SII) and Platelet-to-Lymphocyte Ratio (PLR) on Coagulopathy and Prognosis in Patients with Traumatic Brain Injury

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Objective: We aimed to investigate the associations between inflammatory immune indicators, specifically systemic immune inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and the coagulopathy and prognosis of traumatic brain injury (TBI) patients in ICU.

Methods: One hundred sixty-one TBI patients were grouped into four groups. The outcomes included TBI-related coagulopathy and prognosis at six months after discharge. The association between SII, PLR and coagulopathy, and prognosis in TBI patients was elucidated by applying trend analysis, sensibility analysis, spearman correlation, restricted cubic splines and so on.

Results: Sixty-four (39.75%) of 161 TBI patients were diagnosed with coagulopathy. In the unadjusted model, TBI patients in the lowest quarter of SII (≤966.60) and PLR levels (≤97.99) had a higher risk of coagulopathy than those in the highest quarter of SII (≥3096.16) [OR 0.169 (95% CI 0.052–0.547)] and PLR (≥255.39) [OR 0.098 (95% CI 0.028–0.340)]. After adjusting for covariates, the significant negative associations of results remained consistent in the sensitivity analyses. Restricted cubic splines revealed that an almost linear relationship between SII, PLR and coagulopathy risk and poor prognosis (*P* for all nonlinearities > 0.05). Finally, receiver operating characteristic (ROC) curves indicated that the SII and PLR had certain diagnostic and predictive values for TBI-related coagulopathy [$AUC_{(SII)}$ = 0.666 (95% CI 0.566–0.766), $AUC_{(PLR)}$ = 0.752 (95% CI 0.662–0.842)] and prognosis [$AUC_{(SII)}$ = 0.657 (95% CI 0.548–0.766), $AUC_{(PLR)}$ = 0.700 (95% CI 0.596–0.805)]. The stratification of isolated TBI and TBI with multi-trauma does not affect SII and PLR in predicting TBI-related coagulopathy and poor prognosis in the subgroup analysis (P > 0.05).

Conclusion: This study demonstrated that the SII and PLR had a significant correlation with coagulopathy risk and prognosis at 6 months after discharge. SII and PLR were predictive of coagulopathy and poor prognosis, specifically PLR value. It suggests that the SII and PLR might be promising biomarkers for predicting TBI-related coagulopathy and prognosis.

Trial Registration: The study was registered in the ethics committee of the Third Affiliated Hospital of Southern Medical University (2024-ER-005).

Keywords: traumatic brain injury, coagulopathy, inflammation, prognosis, SII, PLR

Introduction

Traumatic brain injury (TBI) is a common clinical emergency, with high rates of disability and mortality. The prevalence of TBI is estimated to be as high as 50 million globally, and the mortality rate of TBI patients in China is approximately

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13 cases per 100,000 people.[1] The disease progression of TBI is highly complex and heterogeneous, which has led to its treatment of TBI being a challenging clinical problem. Moreover, primary mechanical damage from TBI is difficult to avoid and intervene in. Therefore, preventing secondary injuries from causing further damage to TBI patients is currently a research priority.

Previous studies have shown that, among various secondary injuries, coagulopathy is a severe complication of TBI with a prevalence of approximately 7–63%.[2] Factors related to TBI may disrupt the balance between bleeding and thrombosis in patients,[3] leading to an impaired coagulation system and further aggravating the primary injury. Coagulopathy refers to a state of hypocoagulation prone to bleeding and a state of hypercoagulation with an increased tendency toward thrombosis. There was no standardized and definitive chronological sequence of the states after TBI.[4,5] Extensive research has elucidated various mechanisms underlying coagulation disorders after TBI.[2,6–8] However, there is still a lack of clinical indicators at admission to predict coagulation outcome in TBI patients. As the report goes, TBI-associated coagulopathy is an interdependent[9] result of the coagulation system and inflammatory response in vivo after injury. Therefore, we intend to explore some inflammatory- and immune-related indicators to predict blood coagulation function.

Over time, in addition to routine laboratory parameters, some indicators have proven their clinical utility in assessing the inflammatory response,[8] including the systemic immune inflammation index SII (platelet count × neutrophil count/ lymphocyte count) and PLR (platelet-to-lymphocyte ratio). SII and PLR were the excellent indicators that could comprehensively reflect the immune and inflammatory response, and were currently used to reflect the clinical outcome or prognosis of cancer, inflammation, cardiovascular disease[10–13] and so on, which were the highlights of recent clinical research. However, only a few studies have focused on the connection between these indicators and TBI, like constructing a predictive model of SII combined with CO_2 for prognosis in patients with TBI,[14] and PLR for inflammatory response and short-term mortality[15] in patients with moderate-to-severe TBI. To date, the focus on SII and PLR is still mainly on inflammation, with no further development or jumping out of it. Few clinical studies have explored the effects of inflammation indicators on coagulation in TBI. Meanwhile, many clinicians have limitations in the early diagnosis of coagulopathy after TBI in ICU.

Therefore, the study aimed to explore the relevance of inflammatory immune indicators SII and PLR to coagulation and prognosis in patients with TBI.

Materials and Methods

Study Design

In this retrospective cohort study, patients admitted with the first diagnosis of moderate-to-extremely severe TBI in EICU or ICU of the Third Affiliated Hospital of Southern Medical University from January 01, 2017 to November 30, 2023 were consecutively included. Data was extracted from the electronic medical records of medical institutions by professionals. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University (2024-ER-005) and was conducted in compliance with the latest version of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Study Population

All patients with TBI admitted to the ICU or EICU within the study timeframe were screened for eligibility.

Inclusion Criteria

1) Patients were diagnosed with TBI by specialized clinical practitioners; 2) Glasgow Coma Scale (GCS) score ≤ 12 on admission; 3) admission time within 24h after trauma (including 24h); and 4) primary computed tomography findings showing brain injury (epidural/inferior hematoma, subarachnoid hemorrhage, cerebral contusion, cerebral edema and so on).

Exclusion Criteria

1) Patients died within 24h (including 24h) after admission; 2) patients treated with anticoagulants or antiplatelet agents, like heparin, aspirin, rivaroxaban and warfarin before admission; 3) patients with malignant tumors, hematological

disorders, gastrointestinal tract ulcers, and other diseases with a potential bleeding risk; and 4) Patients with incomplete information.

Data Collection

Specialized investigators collected basic information, vital signs, and clinical data on admission for the included patients, including length of ICU stay and invasive mechanical ventilation, head acute injury scale (AIS) score, GCS score, platelet count, hemoglobin, lymphocyte count and coagulation function-related indicators measured firstly within 24h of admission. Glasgow Outcome Scale (GOS) scores at 6 months after discharge were measured by specialized clinicians.

EDTA-anticoagulated blood samples (2 mL) were collected for the determination of complete blood count (CBC), such as lymphocyte count and platelet count, measured by the Sysmex XN-2000 Automated Hematology Analyzer (Japan). Besides, considering the small number of missing data which is mainly the missing medical records and the follow-up prognostic outcome of 15 TBI patients at 6 months after discharge; therefore, the missing data would be deleted directly when we review the data initially, in order to avoid the error caused by the data filling-in.

Definition of Coagulopathy

Current clinical guidelines and consensus still lacked the generally acknowledged definition of TBI-associated coagulopathy. Coagulopathy was defined according to many previous conclusions and reference values proposed by laboratories in the medical facilities.[2,16]

According to the current guidelines,[17] the diagnostic criterias for coagulopathy were defined as an international normalized ratio (INR) > 1.2, activated thromboplastin time (APTT) > 35s, or platelet count < 100,000/μL, fibrinogen (FIB) < 2 g/L, or other coagulation indicators suggesting impaired coagulation function.

Outcomes

The primary outcome of the study was the association between inflammatory immune indicators SII, PLR and TBI-related coagulopathy.

The secondary outcome was the correlation between SII, PLR and the prognostic outcome at 6 months, assessed by the GOS score, after the discharge of patients.

Statistical Analysis

Continuous variables collected in this study, if normally distributed, were described as mean ± standard deviation (SD), and differences between groups were determined by Student's *t*-test; if non-normally distributed, they were described as median (interquartile range [IQR]) and used Mann–Whitney *U*-test. The remaining categorical variables were expressed as n (%), and the chi-square test or Fisher's exact test was used. In addition, Spearman correlation was performed to ascertain the association between the GOS score and SII and PLR. Using the above tests, we performed a preliminary univariate analysis of the data.

Next, we further performed a multivariate analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) of TBI-related coagulopathy were investigated using logistic regression models, grouped by SII and PLR levels at admission (converting continuous variables into four categorical variables according to the quartile), to assess the tendency of SII, PLR, and TBI-related coagulopathy. In the trend analysis, the unadjusted group was used as the control group, and logistic regression analysis was conducted and different covariates were included to establish three models. In adjusted model 1, the adjusted covariates included age and sex. In adjusted model 2, the adjusted covariates included heart rate and GCS score on admission, and covariates in model 1. In adjusted model 3, the adjusted covariates included creatinine level, white blood cell (WBC) count, hemoglobin level, and covariates in models 1 and 2. The subsequent multivariate analysis all used the above variables, and no collinearity errors would be among the variables (Supplemental Tables 1 and 2). Sensitivity analyses using logistic regression models were performed among TBI patients taking antibiotics, anticoagulants, lower limb venous thrombosis and multi-trauma on admission.

After fitting the models with 2 to 7 knots separately, we selected the model with the smallest Akaike Information Criterion (AIC) value. The smaller the AIC value, the better the fitting effect of the model. We used this optimal model for the restricted cubic spline regression analyses adjusted for the same variables as in model 3 to account for the

relationship between the SII, PLR, as well as coagulopathy risk and prognostic outcome. Receiver operating characteristic (ROC) curves were used for diagnostic value analysis, and the area under the curve (AUC) was computed to quantify the predictive power of the SII and PLR for coagulopathy risk and prognostic outcomes. We also performed the ROC curve in isolated TBI patients and TBI patients with multi-trauma to compare the difference between them. Subgroup analyses were performed to evaluate the risk stratification values of the SII and PLR indicators for further analysis of multiple subgroups of patients with TBI.

All tests were two-way, with $P < 0.05$. Data were analyzed using R statistical software (version 4.4.1) and SPSS (version 26.0).

Results

Basic Characteristics

A total of 161 patients with TBI were enrolled in the designated hospital from January 01, 2017, to November 30, 2023. This study excluded patients with mild TBI (n = 17), admission beyond 24h after trauma (n = 17), died within 24h after admission (n = 1), and missing medical records (n = 13). Finally, 113 patients with TBI were eligible for this study (Figure 1); of these, 98 patients were successfully followed up through telephone interviews or subsequent medical records, and 15 patients failed to access.

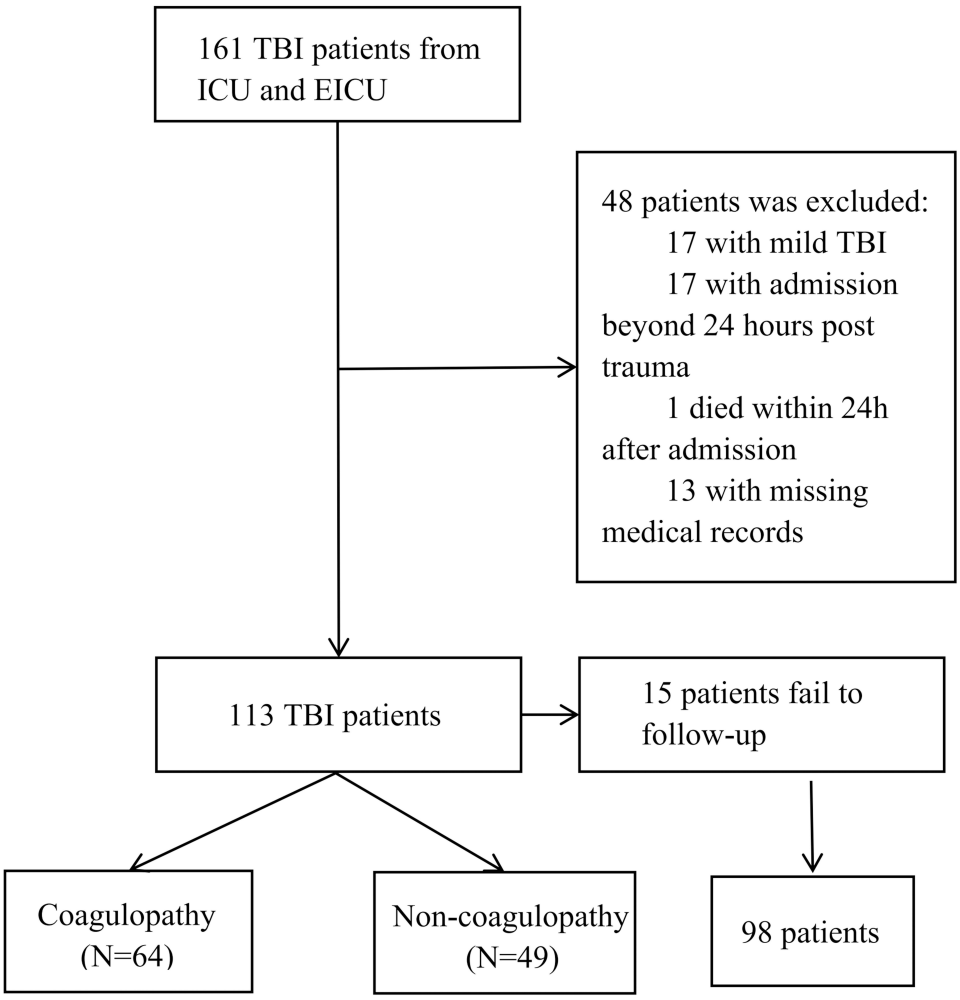

Figure 1 Flow diagram.
Abbreviation: TBI, Traumatic brain injury.

Table 1 Baseline Characteristics of 113 Patients

Variable	ALL Patients (N = 113)	Coagulopathy (N = 64)	Non-Coagulopathy (N = 49)	P-value
Age (years, mean ± SD)	48.01 ± 18.36	46.21 ± 18.06	49.65 ± 17.56	0.296
Sex (males, n, %)	89.00 (78.80%)	50.00 (78.10%)	39.00 (79.60%)	0.850
Heart rate [M(IQR)]	87.00 [76.50, 102.50]	92.00 [80.00, 108.00]	84.00 [71.75, 97.75]	0.027
Blood pressure (mmHg) [M(IQR)]				
Systolic pressure	124.00 [107.00, 137.00]	122.00 [107.50, 133.50]	124.50 [106.25, 143.25]	0.407
Diastolic pressure	75.00 [64.00, 87.00]	73.00 [60.50, 89.50]	77.00 [64.25, 82.00]	0.499
Temperature (°C) [M(IQR)]	36.80 [36.20, 37.30]	36.50 [36.15, 37.35]	36.80 [36.20, 37.30]	0.405
Time to hospital after injury (h) [M(IQR)]	5.00 [5.00, 24.00]	5.00 [2.00, 22.50]	7.00 [2.25, 24.00]	0.266
AIS score [M(IQR)]	4.00 [3.00, 5.00]	5.00 [3.00, 5.00]	3.00 [3.00, 4.00]	<0.001
GCS score [M(IQR)]	7.00 [4.00, 12.00]	6.00 [3.00, 8.00]	10.00 [7.00, 12.00]	<0.001
Abnormal Pupillary reflex (n, %)	64.00 (56.60%)	42.00 (65.70%)	22.00 (44.90%)	0.254
Blunt injury (n, %)	110.00 (97.30%)	62.00 (96.90%)	48.00 (98.00%)	0.722
Mortality in hospital (n, %)	22 (19.5%)	20 (31.3%)	2 (4.1%)	<0.001
GOS score [M(IQR)]	3.00 (1.00, 5.00)	1.00 (1.00, 4.00)	4.00 (2.00, 5.00)	0.001
ICU/EICU LOS (d) [M(IQR)]	11.00 [5.00, 21.00]	13.00 [7.25, 21.00]	9.00 [4.00, 20.00]	0.196
Respirator LOS (d) [M(IQR)]	4.00 [0.00, 11.00]	6.50 [0.00, 13.75]	1.00 [0.00, 8.00]	0.023
Total LOS (d, mean ± SD)	20.00 [12.00, 32.00]	20.00 [10.25, 30.00]	23.00 [13.00, 35.00]	0.415
Antibiotic usage (n, %)	108.00 (95.60%)	28 (43.80%)	21 (42.90%)	0.031
Anticoagulant usage (n, %)	49.00 (43.40%)	64.00 (100.00%)	44.00 (89.80%)	0.924
TBI patients with multi-trauma (n, %)	52 (46.0%)	32 (50.0%)	20 (40.8%)	0.332
Laboratory findings				
Creatinine [M(IQR)]	78.00 (61.50, 99.50)	87.00 (67.00, 116.00)	72.50 (58.50, 82.00)	0.002
Hemoglobin (mean ± SD)	105.60 ± 27.04	96.65 ± 27.82	118.67 ± 21.30	<0.001
C-reactive protein [M(IQR)]	27.39 (5.32, 86.15)	19.75 (4.32, 65.80)	36.90 (9.76, 115.00)	0.133
Neutrophile [M(IQR)]	10.66 (8.26, 16.42)	10.65 (8.66, 17.90)	10.72 (8.19, 16.06)	0.752
White blood cell [M(IQR)]	12.90 (10.02, 17.83)	13.30 (10.28, 19.70)	12.72 (9.70, 17.22)	0.576
SII [M(IQR)]	2011.89 (963.94, 3140.27)	1455.29 (627.52, 2612.37)	2322.57 (1364.92, 3982.39)	0.002
PLR [M(IQR)]	164.62 (97.65, 256.72)	118.28 (74.03, 187.83)	234.45 (159.90, 288.03)	<0.001

Note: SII = platelet count × neutrophil count / lymphocyte count.
Abbreviations: AIS score, head acute injury scale score; GCS score, Glasgow Coma Scale score; GOS score, Glasgow Outcome Scale score; IQR, interquartile range; LOS, length of stay; PLR, platelet-to-lymphocyte ratio.

Table 1 described the basic characteristics, laboratory findings, and other data of TBI patients. TBI Patients with coagulopathy were mainly male (78.10%), with a mean age of 46 ± 18 years and a median time from injury to admission of 5 h. Compared with patients without coagulopathy, patients with coagulopathy showed a faster heart rate on admission (92 vs 84; $P = 0.027$) and a longer duration of invasive mechanical ventilation (6.5 vs 1.0; $P = 0.023$). Additionally, the

Table 2 Main Characteristics and Laboratory Findings of Participants According to SII Levels (n = 113)

Variable	SII level (median [range])			
	Q1 (Lowest) (545.92 [≤966.60])	Q2 (1387.21 [966.61–2011.89])	Q3 (2340.01 [2011.90–3096.15])	Q4 (Highest) (5378.72 [≥3096.16])
N	29	27	29	28
Heart rate [M(IQR)]	88.00 (78.00, 108.00)	87.50 (82.75, 101.75)	86.50 (73.50, 104.25)	84.50 (72.50, 101.75)
AIS score [M(IQR)]	4.00 (4.00, 5.00)	4.00 (3.00, 5.00)	3.50 (3.00, 4.75)	3.00 (3.00, 5.00)
GCS score [M(IQR)]	4.00 (3.00, 7.00)	8.00 (4.75, 12.00)	7.50 (5.00, 12.00)	10.00 (7.00, 12.00)
Mortality in hospital (n, %)	10 (34.5%)	4 (14.8%)	5 (17.2%)	3 (10.7%)
GOS score [M(IQR)]	1.00 (1.00, 4.00)	4.00 (1.00, 5.00)	3.00 (1.00, 4.00)	5.00 (3.00, 5.00)
Creatinine [M(IQR)]	91.00 (68.25, 119.00)	74.00 (52.00, 98.50)	69.00 (56.25, 87.75)	78.50 (64.50, 102.75)
Hemoglobin (mean ± SD)	83.55 ± 31.56	107.06 ± 21.00	118.72 ± 20.00	116.00 ± 19.78
C-reactive protein [M(IQR)]	39.86 (5.60, 78.99)	65.00 (6.97, 140.50)	21.60 (5.44, 33.63)	13.69 (3.79, 107.79)
Neutrophile [M(IQR)]	7.76 (6.19, 10.66)	10.04 (8.69, 12.37)	11.17 (8.51, 16.76)	18.21 (12.82, 19.96)
White blood cell [M(IQR)]	10.40 (7.71, 13.43)	11.97 (10.10, 14.60)	12.72 (9.70, 18.54)	19.63 (14.19, 22.37)
Coagulopathy (n, %)	23 (20.4%)	17 (15.0%)	13 (11.5%)	11 (9.7%)

coagulopathy group had higher AIS scores (5 vs 3; $P < 0.001$), lower GOS scores (1 vs 4; $P = 0.001$), and lower GCS scores (6 vs 10; $P < 0.001$) indicating that these patients had worse consciousness, more critical condition, and higher mortality rates (31.3% vs 4.1%; $P < 0.001$). According to the statistics, 46% of TBI patients with multi-trauma have no statistical difference between the groups ($P > 0.05$). The inflammatory immune indicators SII ($P = 0.002$) and PLR ($P < 0.001$) in the coagulopathy group were statistically lower than those in the non-coagulopathy group, suggesting that TBI patients with more severe inflammation were more likely to have coagulopathy.

The Association of Coagulopathy-Related Factors After TBI to SII and PLR

Next, all cases were divided into four groups, classified, respectively, by quartiles of the indicators SII and PLR (Table 2 and Table 3) (the continuous variables were converted into the categorical variables), and then the variables with

Table 3 Characteristics and Laboratory Findings of the Participants According to PLR Levels (n = 113)

Variable	PLR level (median [range])			
	Q1 (Lowest) (67.95 [≤97.99])	Q2 (131.18 [98.00–164.62])	Q3 (205.77 [164.63–255.38])	Q4 (Highest) (314.66 [≥255.39])
N	28	29	27	29
Heart rate [M(IQR)]	101.00 (85.00, 115.00)	85.00 (66.25, 99.00)	87.00 (80.00, 101.50)	82.00 (71.50, 101.00)
AIS score [M(IQR)]	4.00 (4.00, 5.00)	4.00 (3.00, 5.00)	3.00 (3.00, 5.00)	3.00 (3.00, 4.00)
GCS score [M(IQR)]	5.00 (3.00, 7.00)	7.00 (3.25, 12.00)	9.00 (5.00, 12.00)	10.00 (7.00, 12.00)
Mortality in hospital (n, %)	10 (35.7%)	7 (24.1%)	2 (7.4%)	3 (10.3%)
GOS score [M(IQR)]	1.00 (1.00, 4.00)	1.00 (1.00, 4.75)	4.00 (2.00, 5.00)	4.00 (2.25, 5.00)

(*Continued*)

Table 3 (Continued).

Variable	PLR level (median [range])			
	Q1 (Lowest) (67.95 [≤97.99])	**Q2 (131.18 [98.00–164.62])**	**Q3 (205.77 [164.63–255.38])**	**Q4 (Highest) (314.66 [≥255.39])**
Creatinine [M(IQR)]	89.00 (68.00, 118.50)	83.50 (53.00, 96.00)	71.00 (53.50, 97.00)	78.00 (63.00, 92.00)
Hemoglobin (mean ± SD)	86.76 ± 31.60	103.50 ± 23.22	117.82 ± 15.97	117.63 ± 22.71
C-reactive protein [M(IQR)]	59.00 (5.97, 111.01)	13.54 (5.16, 33.59)	31.00 (3.78, 65.91)	27.39 (8.79, 103.00)
Neutrophile [M(IQR)]	10.08 (6.49, 12.37)	10.00 (7.89, 19.09)	11.67 (9.33, 17.82)	12.74 (8.81, 18.56)
White blood cell [M(IQR)]	12.74 (8.81, 15.35)	11.90 (9.71, 21.03)	12.74 (11.06, 19.83)	13.89 (10.00, 20.03)
Coagulopathy (n, %)	23 (20.4%)	20 (17.7%)	12 (10.6%)	9 (7.9%)

Note: SII = platelet count × neutrophil count / lymphocyte count.
Abbreviations: AIS score, head acute injury scale score; GCS score, Glasgow Coma Scale score; GOS score, Glasgow Outcome Scale score; PLR, platelet-to-lymphocyte ratio.

statistical significance in the basic characteristics were again analyzed to maintain the practicability of the model. Table 2 illustrated that the fluctuations in AIS score and creatinine decreased with increasing SII level, whereas hemoglobin, GCS score, and GOS score increased with increasing SII level. Table 3 demonstrated that the PLR of TBI patients with higher heart rates (up to 110), higher AIS scores (up to 4.0), and lower GCS scores (low to 5.0) decreased accordingly. The results revealed that low SII and PLR were associated with a slightly increased risk of coagulopathy among TBI patients in univariate analysis. In addition, patients in the lowest SII and PLR groups had the highest mortality during hospitalization (34.5% and 35.7%, respectively) and the lowest post-discharge GOS scores (1.0 and 1.0, respectively), indicating that these patients tended to have worse prognostic outcomes.

Trend Analysis

Currently, the relationship between inflammatory immune indicators and TBI-related coagulopathy was unclear. Therefore, we sequentially transformed the continuous variables (SII and PLR) into the categorical variables and then included the confounders to construct the regression models. In the unadjusted model, the association between the SII and the development of coagulopathy in TBI patients was statistically significant ($P = 0.004$; Table 4). Patients with the highest SII levels (≥3096.16) had a lower risk of coagulopathy [0.169 (95% CI 0.052–0.547); P trend = 0.004; Table 4] than those in the reference group (SII ≤ 966.60). In models 1, 2, and 3, after gradually adjusting for potential covariates (age, sex, heart rate, GCS score, WBC, creatinine, hemoglobin), the association between SII and coagulopathy remained

Table 4 Adjusted ORs and 95% CIs for SII Levels and Coagulopathy Risk (n = 113)

	SII level (median [range])				
	Q1 (Lowest) (545.92 [≤966.60])	**Q2 (1387.21 [966.61–2011.89])**	**Q3 (2340.01 [2011.90–3096.15])**	**Q4 (Highest) (5378.72 [≥3096.16])**	**P for trend**
No. of Coagulopathy (n, %)	23 (79.3%)	17 (63.0%)	13 (44.8%)	11 (39.3%)	
Unadjusted	1	0.443 (0.135, 1.459)	0.212 (0.067, 0.675)	0.169 (0.052, 0.547)	0.004
Model 1	1	0.371 (0.107, 1.287)	0.201 (0.062, 0.652)	0.153 (0.046, 0.516)	0.004
Model 2	1	0.519 (0.137, 1.965)	0.258 (0.072, 0.918)	0.250 (0.068, 0.916)	0.050
Model 3	1	0.535 (0.122, 2.342)	0.251 (0.053, 1.195)	0.093 (0.016, 0.549)	0.008

Notes: Model 1 adjusted for age and sex. Model 2 additionally adjusted for heart rate, GCS score, and covariates included in model 1. Model 3 additionally adjusted for WBC, Creatinine, Hemoglobin, and covariates included in model 1 and 2.

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Table 5 Adjusted ORs and 95% CIs for PLR Levels and Coagulopathy Risk (n = 113)

	PLR Level (median [range])				
	Q1 (Lowest) (67.95 [≤97.99])	**Q2 (131.18 [98.00–164.62])**	**Q3 (205.77 [164.63–255.38])**	**Q4 (Highest) (314.66 [≥255.39])**	**P for trend**
No. of Coagulopathy, (n, %)	23 (82.1%)	20 (69.0%)	12 (44.4%)	9 (31.0%)	
Unadjusted	1	0.483 (0.139, 1.681)	0.174 (0.051, 0.595)	0.098 (0.028, 0.340)	<0.001
Model 1	1	0.492 (0.140, 1.721)	0.170 (0.049, 0.587)	0.099 (0.028, 0.348)	<0.001
Model 2	1	0.758 (0.198, 2.904)	0.300 (0.080, 1.122)	0.181 (0.048, 0.688)	0.004
Model 3	1	0.876 (0.203, 3.786)	0.413 (0.094, 1.823)	0.203 (0.046, 0.904)	0.012

Notes: Model 1 adjusted for age and sex. Model 2 additionally adjusted for heart rate, GCS score, and covariates included in model 1. Model 3 additionally adjusted for WBC, Creatinine, Hemoglobin, and covariates included in model 1 and 2.

statistically significant, showing consistency with the former unadjusted model. Compared to the SII value of Q2 grade, the probability of developing coagulopathy decreased by 27.4% in TBI patients with Q4 grade. This finding rigorously proved that SII levels were negatively related to coagulopathy orientation after TBI.

PLR fluctuations in TBI patients with coagulopathy were approximately the same as SII value (Table 5). In the unadjusted model, a decreased risk of coagulopathy was observed in TBI patients with the highest PLR (≥255.39) compared with those with the lowest PLR (≤97.99) [0.098 (95% CI 0.028–0.340); *P* trend < 0.001; Table 5]. Patients with Q4 grade were 38.5% less likely to develop coagulopathy than patients with Q2 grade. Next, the three types of models with layer-by-layer adjustment for potential covariates were unanimous in stating that there was a statistically significant negative correlation between PLR and the incidence of TBI-related coagulopathy, which was consistent with the analysis of SII.

In all constructed regression models, the results of the trend analysis all indicated that the SII, PLR and TBI-related coagulopathy are negatively correlated, and that was possibly considered to be the trend of a linear change.

Sensitivity Analyses

To further determine whether the conclusions of our study were persuasive, the sensitivity analysis (Supplemental Tables 3–12) was performed by including TBI patients with antibiotics, anticoagulants, lower limb venous thrombosis and multi-trauma on admission. Finally, no significant interactions between these factors were observed. Consistent results were observed for all models in sensitivity analyses and trend analysis, suggesting that the analysis results were robust. At the same time, this analysis ruled out the indirect effects of antibiotics on coagulopathy by altering inflammation levels. Besides, we also divided the participants into isolated TBI patients and TBI patients with multi-trauma and separately analysed. The analysis showed that the parts of isolated TBI and TBI with multi-trauma did not affect SII and PLR in predicting TBI-related coagulopathy. It showed the same conclusion that the two parts of patients with the low values of SII and PLR generally had a higher risk of coagulopathy (Supplemental Tables 9–12).

The Association of Prognostic Outcome in TBI Patients to SII and PLR

In addition to having higher AIS and lower GCS scores, the GOS ≤ 3 group manifested lower levels of SII and PLR, which reflects more severe situations and inflammatory responses on admission compared with the GOS > 3 group (Supplemental Table 13). Furthermore, we also found that inflammatory markers commonly used clinically, such as C-reactive protein and neutrophils, had little significance in predicting the outcome of TBI patients after discharge. Thus, we concluded that SII ($P = 0.008$) and PLR ($P = 0.001$) were statistically significant for predicting prognosis of TBI patients.

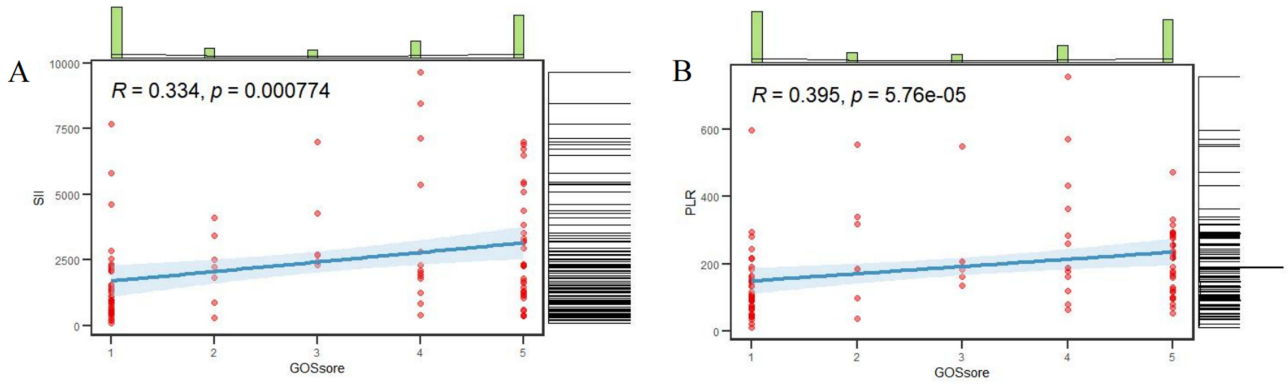

Figure 2 Correlation between GOS score and SII and PLR level. (**A**) SII, (**B**) PLR.

Later, we included sex, age, heart rate, GCS score, WBC, creatinine, and other covariates, to construct the models of trend analysis through multivariate analysis (Supplemental Tables 14 and 15). The results showed that patients with the highest values of SII and PLR owned the higher GOS scores after TBI. Through reverification, we also found a positive correlation between the GOS score at 6 months after discharge and SII (Spearman's rho = 0.334, $P < 0.001$; Figure 2A) and PLR (Spearman's rho = 0.395, $P < 0.001$; Figure 2B), implying that SII and PLR were qualified to inform clinicians about the prognosis of TBI patients ahead of time.

The Almost Linear Relationship between SII, PLR and Coagulopathy Risk, and Prognostic Outcome

Restricted cubic spline (RCS) is a specific spline function, which fits the spline function by selecting the location and number of knots. This approach can not only handle complex nonlinear relationships but also be equally applicable to describe linear regression analysis. Using RCS regression, an almost linear relationship between SII, PLR and coagulopathy risk and prognosis was found after adjustment for multiple covariates (P for all nonlinearities > 0.05) (Figure 3). The risk of TBI-associated coagulopathy increased rapidly with the decrease in SII, especially if the SII was smaller than 2000 (Figure 3A). With PLR < 165, PLR and the occurrence of TBI-associated coagulopathy were inversely proportional (Figure 3B). The RCS model was described in more detail that TBI patients were more likely to develop coagulopathy, when PLR < 165 (Figure 3B). In addition, TBI patients with the higher interval of SII and PLR values had a higher GOS score compared to those with the lower interval of SII and PLR (Figure 3C and D), which was consistent with the results of the correlation analysis. The results of the RCS models were further illustrated that an almost linear relationship existed between SII, PLR and coagulopathy risk and poor prognosis.

When the predicted outcome was TBI-related coagulopathy, the AUC values of the SII and PLR were 0.666 (95% CI 0.566–0.766) and 0.752 (95% CI 0.662–0.842) by ROC curve (Figure 4A and B). The AUC values of the SII and PLR were 0.657 (95% CI 0.548–0.766) and 0.700 (95% CI 0.596–0.805) in predicting prognosis at 6 months after discharge (Figure 4C and D). It is suggested that SII and PLR have some predictive effect on coagulopathy and prognosis in TBI patients. PLR has a more superior prediction capability than SII, judging from the AUC value of the models. These results were consistent with our conclusions and had been validated a priori. Subsequently, we compared the predictive value of SII and PLR in isolated TBI patients and TBI patients with multi-trauma. It suggested that the predictive value of SII and PLR in TBI patients with multi-trauma was greater than isolated TBI patients [($AUC_{(PLR\text{-}coagulopathy)}$: 0.750 vs 0.730), ($AUC_{(PLR\text{-}prognosis)}$: 0.744 vs 0.663), ($AUC_{(SII\text{-}coagulopathy)}$: 0.706 vs 0.657), and ($AUC_{(SII\text{-}prognosis)}$ 0.721 vs 0.611)] (Supplemental Figures 1 and 2).

Subgroup Analysis

The risk stratification value of the SII and PLR for TBI-related coagulopathy and prognosis was further analyzed in multiple subgroups of the enrolled patients through stratified logistic regression analysis and interactive effect analysis,

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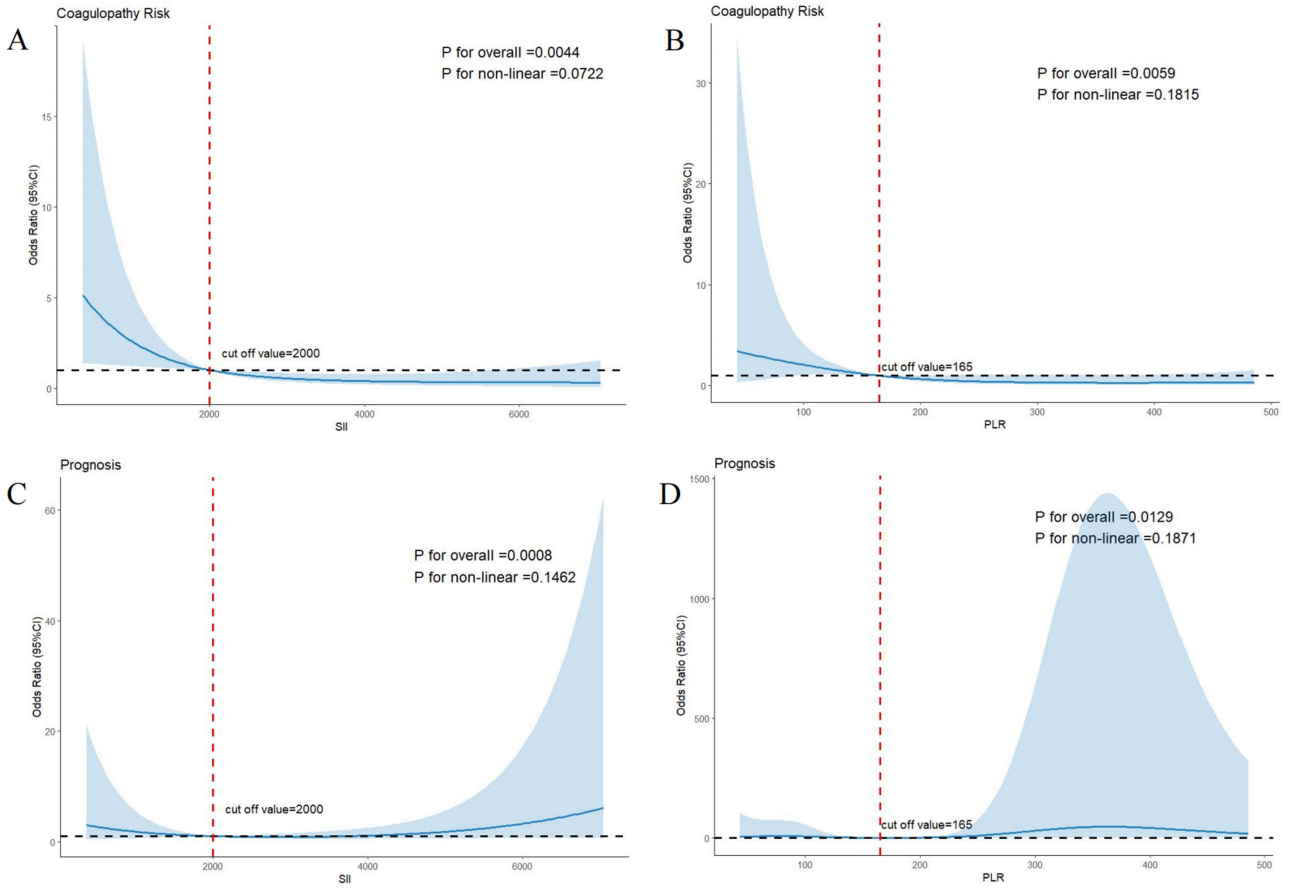

Figure 3 RCS analysis on the association between the SII and TBI-associated coagulopathy (**A**). RCS analysis on the association between the PLR and TBI-associated coagulopathy (**B**). RCS analysis on the association between the SII and poor prognosis (**C**). RCS analysis on the association between the PLR and poor prognosis (**D**).

including sex, age, anticoagulant use, blood products, traumatic wet lung disease and multi-trauma (Figure 5A–D). Only patients who used blood products may have influenced the association between the SII and secondary coagulopathy among all TBI patients (P = 0.003; P for interaction = 0.047) (Figure 5A). Elderly patients (>65Y) with anticoagulant use might show a more pronounced risk of worse prognosis than other patients.

In addition, no significant interactions ($P > 0.05$ for interaction tests; Figure 5B–D) were observed for coagulopathy risk and poor prognosis in the remaining subgroups. In particular, the group of patients who combined with multi-trauma similarly did not show a statistically significant effect on SII and PLR in predicting TBI-associated coagulopathy and poor prognosis (all $P > 0.05$ for interaction in multi-trauma subgroup). The statistical differences between individual subgroups were not significant, further demonstrating the reliability of our conclusions. The SII and PLR can be used to predict secondary coagulopathy and prognosis in TBI patients and were nearly unaffected by the above risk stratification factors, with more convenience and flexibility to operate in clinical practice.

Discussion

In this study, we investigated the relationship between inflammatory immune indicators SII, PLR and secondary coagulopathy and poor prognosis at 6 months after discharge by using routinely available clinical data and statistical methods to further identify high-risk TBI patients admitted to the ICU and implement corresponding clinical preventive measures as soon as possible.

Firstly, we conducted an initial screening using univariate analysis, and investigated the effects of SII and PLR separately on coagulopathy after TBI and selected significant variables. Then, we converted the continuous variables (SII and PLR) into categorical variables by interquartile range. Trend analysis was used to initially explore whether there was

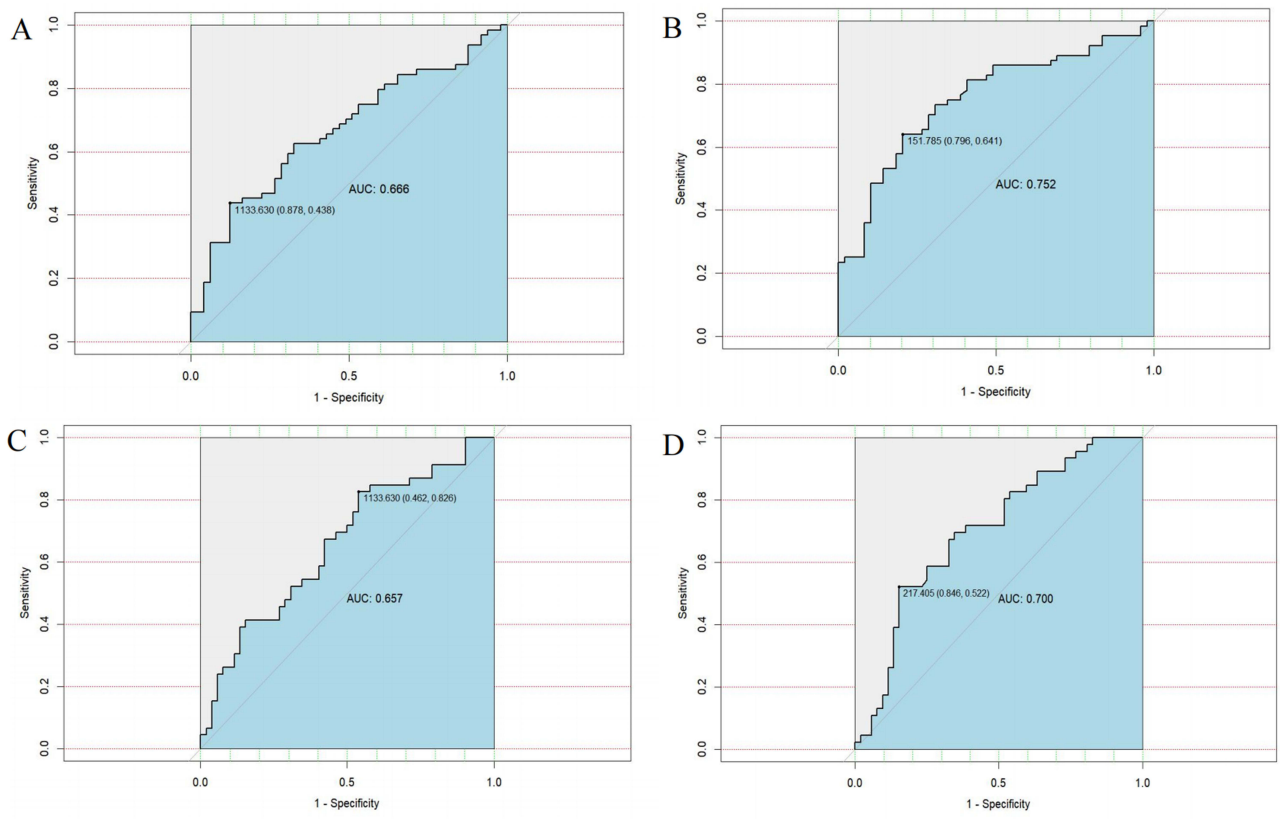

Figure 4 ROC curves of SII and PLR for predicting coagulopathy risk (**A** and **B**) and prognosis at 6 months after discharge (**C** and **D**).

a strong correlation between inflammatory immune markers and coagulopathy and prognostic outcome. After that, it illustrated that TBI patients with the highest SII (≥3096.16) and PLR (≥255.39) had the lowest hazard of secondary coagulopathy. Different covariates (TBI patients with antibiotics, anticoagulants, lower limb venous thrombosis and multi-trauma on admission) were progressively included in the models of the sensitivity analysis to further validate the results of trend analysis, and finally the conclusions drawn were consistent with those repeatedly validated. Patients with low SII and PLR had stronger inflammatory responses and were more likely to develop coagulopathy. We used restricted cubic spline regression to again identify a linear relationship between the SII, PLR and coagulopathy risk and prognosis. ROC curves were used to quantify the predictive power of SII and PLR. In our study, a strong correlation between SII, PLR and coagulopathy risk and prognostic outcome was confirmed with multiple dimensions and depth gradation. The final subgroup analysis indicated that the SII and PLR can be widely used and flexible in clinical practice, without excessive consideration of the influence of age and sex, anticoagulant use, and other factors.

Previous studies had been elucidated that SII and PLR were mainly used to predict the clinical outcome or prognosis of cancer, inflammation, cardiovascular disease[10–13] and other respects. Piotr Defort and his teammates demonstrated that SII and PLR had predictive value for GCS score and prognosis in patients with traumatic cerebral haemorrhage, with the predictive value of SII being slightly better than PLR ($AUC_{(SII)}$= 0.816; $AUC_{(PLR)}$= 0.570).[18] Another studies showed by univariate analysis that TBI patients in the coagulopathy group had lower PLR values ($P < 0.001$).[17] However, until now current studies did not deeply explore the association between inflammatory indicators and coagulopathy. Considering that a vital knowledge gap exists in understanding the interactions between inflammatory indicators and TBI-related coagulopathy, we conducted the study by multiple validation and found that SII and PLR have predictive value for TBI-related coagulopathy and poor prognosis based on previous results and references. In conclusion, SII and PLR were strongly associated with the incidence of

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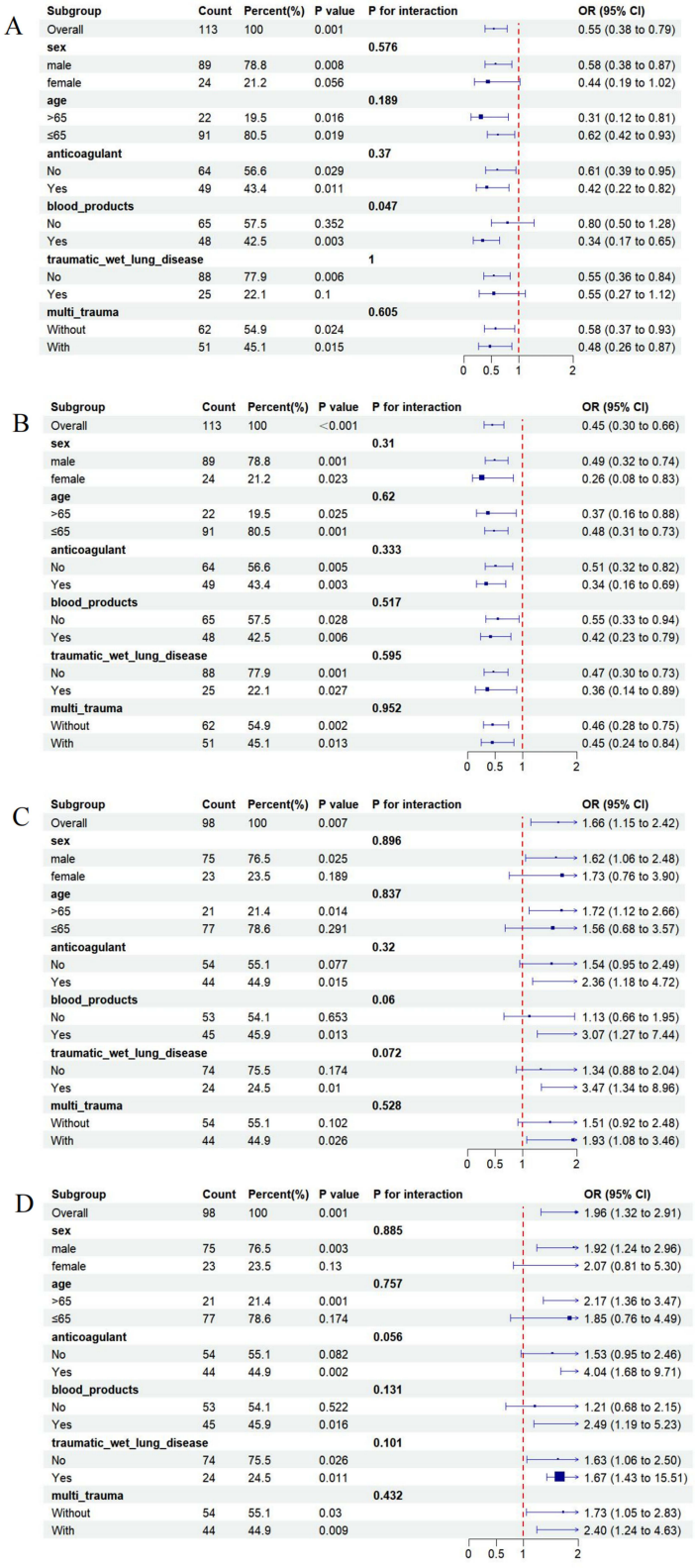

Figure 5 Subgroup analysis of the effect of SII on TBI-associated coagulopathy (**A**). Subgroup analysis of the effect of PLR on TBI-associated coagulopathy (**B**). Subgroup analysis of the effect of SII on poor prognosis at 6 months after TBI patients discharge (**C**). Subgroup analysis of the effect of PLR on poor prognosis at 6 months after TBI patients discharge (**D**).

Abbreviations: OR, odds ratio; CI, confidence interval.

TBI-related coagulopathy and poor prognosis at 6 months after discharge. In particular, the PLR compared to SII has an excellent predictive value for the outcome of coagulopathy and poor prognosis.

The pathophysiology of TBI involves a complex series of biochemical reactions, mainly including primary and secondary injuries. Among them, secondary injury involves the neuroinflammatory response in TBI patients. Inflammatory response is a common pathophysiological response after TBI, including the release of several cytokines and chemokines. Previous basic experiments showed that inflammatory factors (eg TNF-α, IL-1β) can activate exogenous coagulation pathway by upregulating tissue factor (TF).[2,19–21] There is also another article suggesting that inflammation and coagulation systems are interactive.[22] The pathophysiology of TBI-related coagulopathy was similar to the results observed in the study. Moreover, we have demonstrated that inflammatory immune indicators had a strong correlation with TBI-related coagulopathy in this study, which can be used to predict coagulopathy and poor prognosis of TBI patients. It followed that, in addition to the molecular level of the basic experiments, the inflammatory immune response occurring after TBI is closely associated with coagulopathy from the perspective of clinical research. Based on the above conclusions, we can have a more profound understanding of the pathophysiological process of TBI, especially in inflammation and coagulation.

Coagulation dysfunction after TBI is mainly due to the imbalance[3] between bleeding and coagulation. And, after experiencing brain damage, whether the body is in a hypercoagulable or hypocoagulable state is still[4,5] uncertain. This uncertainty made it difficult for clinicians to quickly capture the changes in coagulation status after TBI and make response plans. In addition, especially for patients with moderate and severe TBI admitted to ICU, the collapse of the coagulation system was often instantaneous and then broke out a sudden disseminated intravascular coagulation (DIC).[23,24] In the current clinical practice, we had plenty of diagnostic methods[25] for coagulation disorders after TBI, but no effective predictors on admission. The purpose of this article was to identify the patients who were more likely to develop coagulopathy at the earliest stage of brain injury. Although the predictive value of SII was not so perfect after quantified by ROC curves, clinicians can still mainly use PLR to predict TBI-related coagulopathy and prognosis, supplemented by the judgment of SII as a reference.

In this case, clinicians can make a preliminary judgment of patients with moderate-to-severe TBI based on inflammatory immune indicators, and found the trend of changes in the coagulation system and poor prognosis in advance, which made them more cautious in the use of anticoagulants or blood products. It will be beneficial to reduce the occurrence of the breakdown of coagulation system and subsequent DIC. In the future, we still need to expand the sample size, or build the validation model with the help of the database, to deeply consider the relationship between the inflammatory immune indicators SII and PLR on TBI-related coagulopathy and prognosis and verify their quantified predictive value. Or, the PLR or SII can combine with multiple indicators to construct models, which not only improve the accuracy of prediction but also optimize the choice of threshold, providing important reference and guidance for the diagnosis and treatment of TBI-related coagulopathy.

In the subgroup analysis, we found that only the patients who used blood products would affect the relationship between SII and TBI-related coagulopathy ($P = 0.003$; P for interaction = 0.047). No such interaction effect was seen in the remaining subgroups. Besides, the results of analysis also mentioned that patients using blood products may also affect the accuracy of PLR in predicting TBI-related coagulopathy ($P = 0.006$; P for interaction = 0.517). As illustrated in the previous literature, infusion of blood products can cause hemodilution and prolonged surgical times,[26] which might eventually worsen the clinical outcome. These results could explain the conclusions we reached in the subgroup analysis that the use of blood products might affect the predictive accuracy of SII and PLR for TBI-associated coagulopathy. Moreover, the infusion of different blood components or different proportions would have different influences on TBI patients. The PROMMTT[27] study showed that patients with a higher survival rate after 6 hours may receive higher ratios of plasma to RBC or platelets to RBC. However, the PROPPR[28] study evaluating 1:1:1 (plasma: platelets: RBC) vs 1:1:2 transfusion strategies revealed a statistically insignificant reduction in 30-day mortality in 680 severely injured patients. Thus, there had still been a great debate on the use of blood transfusion strategy in coagulopathy therapy. And there was also no clear conclusion in the latest guidelines.[29] In our study, we only roughly classified TBI patients who had received any blood component into the "blood products" group, but did not divide patients with different blood components or

different proportions in more detail, to discuss the influence of this baseline on SII and PLR in predicting TBI-related coagulopathy. It will require a deeper exploration in the future studies.

The mechanism of TBI-related coagulopathy is mainly related to the destruction of blood–brain barrier and cerebrovascular endothelial cells and other factors caused by trauma,[4,7] which finally destroys the balance of coagulation system. While the mechanism of traumatic coagulopathy is not limited to craniocerebral injury, it also includes other forms of severe trauma. It also mainly involves inflammatory response, shock, acidosis and other systemic factors.[5,30] Some scholars had even suggested that, traumatic coagulopathy can be understood as a global inflammatory state.[31] SII and PLR happen to be inflammatory immune indicators, which may have a more obvious correlation and predictive effect on traumatic coagulopathy. This result was consistent with the conclusion that we got from the ROC curve. It suggested that the predictive value of SII and PLR in TBI patients with multi-trauma was greater than isolated TBI patients. However, isolated TBI patients and TBI patients with multi-trauma had no statistical differences between the coagulopathy and non-coagulopathy groups in the sensitivity analysis and subgroup analysis. The stratification of isolated TBI and TBI with multi-trauma did not affect SII and PLR in predicting TBI-related coagulopathy and poor prognosis. Therefore, SII and PLR still have the strong correlation with TBI-related coagulopathy and poor prognosis, and had predictive values. Subsequent prospective studies with large samples were still needed to prove the conclusion.

According to previous studies, age and sex may influence normal coagulation function. In clinical tests, coagulation parameters were mainly age-dependent,[32] whether in adults[33] or children.[34] When talking about sex, it is mainly manifested as that sex hormones were associated with[35] partial thromboplastin time,[36] antithrombin and other factors. In addition, based on our statistical analysis, the heart rate ($P = 0.027$) and GCS score ($P < 0.001$) of the coagulopathy group were significantly different from those of the other group, proving that these factors influenced the development of coagulopathy. Identically, this was also in line with the previous study that the development of coagulopathy after TBI was related to the severity of trauma.[2,16] Moreover, clinical test indicators such as white blood cells, hemoglobin, and creatinine[37–39] were also considered risk factors for coagulopathy after TBI. Studies had shown that[37] creatinine, combined with other factors, was helpful in predicting the prognosis of patients with TBI in an established clinical model. Patients with low hemoglobin levels were found to have a slightly hypercoagulable state[38] on ROTEM, and other studies had indicated that some components of hemoglobin[39] may be related to the hyperfibrinolytic state. Therefore, we performed the sensitivity analysis. After adjusting for covariates such as age, sex, heart rate, GCS score, and laboratory indicators (WBC, creatinine, and hemoglobin), we found that the main result, namely, a statistically significant difference between SII and PLR and coagulopathy occurring after TBI, remained consistent, indicating that the negative association was independent of these adjusted covariates.

One of the tangible strengths of this study was that, based on basic experiments and physiopathological characteristics, it explored the relationship between clinical inflammatory immune indicators and TBI-related coagulopathy and prognosis, the association of which had not been widely discussed. In the analysis, we selected uncomplicated and easily obtained inflammatory indicators, and gained the approximately predicted ranges for SII and PLR. Therefore, the clinician can make a preliminary judgment of coagulation function based on the SII and PLR values on admission and prevent its deterioration. The study provided new insights into the identification of a simplified assessment of coagulopathy and potential future therapeutic interventions. Furthermore, we considered comprehensive potential covariates, including age, sex, GCS score, laboratory indicators and different subgroups, and made multiple adjustments to draw highly credible conclusions.

Inevitably, this study had some limitations. First, because of its retrospective design, it was difficult to longitudinally analyze the causal relationship between inflammatory indicators and TBI-related coagulopathy by only analyzing the lateral correlation. Second, this was a single-center study with a small number of patients. Third, the study only analyzed the coagulation parameters of TBI patients on admission but did not gain insight into the timing and process of normal coagulation recovery. Cases still need to be included prospectively for further large-scale cohort studies to clarify the specific values of the SII and PLR. Researchers can use public database to establish a validation cohort or combine with other indicators to construct a composite prediction model in order to validate the findings. Fourth, in addition to the relevant confounders adjusted for in this study, the occurrence of coagulopathy after TBI may also be related to the patient's BMI[40,41] and hemorrhage volume[42] and other factors after injury.

In conclusion, we found that inflammatory immune indicators, both SII and PLR, can reflect TBI-related coagulopathy and show a negative correlation. The SII and PLR also had a slightly strong correlation with the GOS score at six months after discharge. The predictive value of SII and PLR in TBI patients with multi-trauma was greater than isolated TBI patients, however the two subgroups did not influence the prediction of the indicators. It suggests that SII and PLR may be the promising biological indicators with clinical utility for predicting the development of coagulopathy and prognostic outcomes after TBI. However, more in-depth research is required to explore relevant mechanisms and causality.

Conclusion

Our study demonstrated a negative association between inflammatory immune indicators SII and PLR on admission and the risk of TBI-related coagulopathy (all $P < 0.05$). In addition, the SII and PLR are strongly correlated, to some extent, with poor prognosis of TBI patients (Spearman's rho = 0.334, and 0.395, $P < 0.001$). And PLR had a better predictive value for TBI-related coagulopathy and poor prognosis. From another perspective, it also suggests that SII and PLR may be the promising biomarkers for predicting coagulopathy and prognosis after TBI, providing a more scientific basis. While these indicators have potential utility, further validation by expanded sample size and a prospective study are required.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This article is a study of medical records and biological specimens obtained from previous clinical treatment and meets all the following conditions: 1) the study risk to the subjects is not greater than the minimum risk, 2) the exemption of informed consent will not adversely affect the rights and health of the subjects, 3) subjects' privacy and personally identifiable information were protected. Therefore, we applied for exemption from informed consent. Then, the Clinical Trial Ethics Committee of the Third Affiliated Hospital of Southern Medical University approved our application for exemption from informed consent.

The retrospective study was approved by the Clinical Trial Ethics Committee of the Third Affiliated Hospital of Southern Medical University (2024-ER-005).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Jiang JY, Gao GY, Feng JF, et al. Traumatic brain injury in China. *Lancet Neurol*. 2019;18(3):286–295. doi:10.1016/S1474-4422(18)30469-1
2. Maegele M, Schochl H, Menovsky T, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol*. 2017;16(8):630–647. doi:10.1016/S1474-4422(17)30197-7
3. Laroche M, Kutcher ME, Huang MC, et al. Coagulopathy after traumatic brain injury. *Neurosurgery*. 2012;70(6):1334–1345. doi:10.1227/NEU.0b013e31824d179b
4. Zhang J, Zhang F, Dong JF. Coagulopathy induced by traumatic brain injury: systemic manifestation of a localized injury. *Blood*. 2018;131(18):2001–2006. doi:10.1182/blood-2017-11-784108
5. Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. *Nat Rev Dis Primers*. 2021;7(1):30. doi:10.1038/s41572-021-00264-3
6. McCully SP, Schreiber MA. Traumatic brain injury and its effect on coagulopathy. *Semin Thromb Hemost*. 2013;39(8):896–901. doi:10.1055/s-0033-1357484
7. Maegele M, Aversa J, Marsee MK, et al. Changes in coagulation following brain injury. *Semin Thromb Hemost*. 2020;46(2):155–166. doi:10.1055/s-0040-1702178
8. Wang RH, Wen WX, Jiang ZP, et al. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. *Front Immunol*. 2023;14:1115031. doi:10.3389/fimmu.2023.1115031
9. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood*. 2019;133(9):906–918. doi:10.1182/blood-2018-11-882993
10. Lin KB, Fan FH, Cai MQ, et al. Systemic immune inflammation index and system inflammation response index are potential biomarkers of atrial fibrillation among the patients presenting with ischemic stroke. *Eur J Med Res*. 2022;27(1):106. doi:10.1186/s40001-022-00733-9
11. Chen T, Yang M. Platelet-to-lymphocyte ratio is associated with cardiovascular disease in continuous ambulatory peritoneal dialysis patients. *Int Immunopharmacol*. 2020;78:106063. doi:10.1016/j.intimp.2019.106063
12. Liu J, Li S, Zhang S, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. *J Clin Lab Anal*. 2019;33(8):e22964. doi:10.1002/jcla.22964
13. Nost TH, Alcala K, Urbarova I, et al. Systemic inflammation markers and cancer incidence in the UK Biobank. *Eur J Epidemiol*. 2021;36(8):841–848. doi:10.1007/s10654-021-00752-6
14. Chen L, Xia S, Zuo Y, et al. Systemic immune inflammation index and peripheral blood carbon dioxide concentration at admission predict poor prognosis in patients with severe traumatic brain injury. *Front Immunol*. 2022;13:1034916. doi:10.3389/fimmu.2022.1034916
15. Li W, Deng W. Platelet-to-lymphocyte ratio predicts short-term mortality in patients with moderate to severe traumatic brain injury. *Sci Rep*. 2022;12(1):13976. doi:10.1038/s41598-022-18242-4
16. Harhangi BS, Kompanje EJ, Leebeek FW, et al. Coagulation disorders after traumatic brain injury. *Acta Neurochir*. 2008;150(2):165–175. doi:10.1007/s00701-007-1475-8
17. Chen Y, Tian J, Chi B, et al. Factors associated with the development of coagulopathy after open traumatic brain injury. *J Clin Med*. 2021;11(1). doi:10.3390/jcm11010185
18. Defort P, Retkowska-Tomaszewska N, Kot M, et al. Inflammatory predictors of prognosis in patients with traumatic cerebral haemorrhage: retrospective study. *J Clin Med*. 2022;11(3):705. doi:10.3390/jcm11030705
19. Demetz G, Ott I. The Interface between inflammation and coagulation in cardiovascular disease. *Int J Inflam*. 2012;2012:860301. doi:10.1155/2012/860301
20. Witkowski M, Landmesser U, Rauch U. Tissue factor as a link between inflammation and coagulation. *Trends Cardiovasc Med*. 2016;26(4):297–303. doi:10.1016/j.tcm.2015.12.001
21. Shi J, Tang Y, Liang F, et al. NLRP3 inflammasome contributes to endotoxin-induced coagulation. *Thromb Res*. 2022;214:8–15. doi:10.1016/j.thromres.2022.04.001
22. Levi M, van der Poll T. Inflammation and coagulation. *Crit Care Med*. 2010;38(2 Suppl):S26–S34. doi:10.1097/CCM.0b013e3181c98d21
23. Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. *Nat Rev Dis Primers*. 2016;2:16037. doi:10.1038/nrdp.2016.37
24. Gando S, Saitoh D, Ishikura H, et al. A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. *Crit Care*. 2013;17(6):R297. doi:10.1186/cc13163
25. Da LL, Nascimento B, Shankarakutty AK, et al. Effect of thromboelastography (TEG(R)) and rotational thromboelastometry (ROTEM(R)) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. *Crit Care*. 2014;18(5):518. doi:10.1186/s13054-014-0518-9
26. Yanagida Y, Gando S, Sawamura A, et al. Normal prothrombinase activity, increased systemic thrombin activity, and lower antithrombin levels in patients with disseminated intravascular coagulation at an early phase of trauma: comparison with acute coagulopathy of trauma-shock. *Surgery*. 2013;154(1):48–57. doi:10.1016/j.surg.2013.02.004
27. Poole D. Coagulopathy and transfusion strategies in trauma. Overwhelmed by literature, supported by weak evidence. *Blood Transfus*. 2016;14(1):3–7. doi:10.2450/2015.0244-15
28. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377(9771):1096–1101.
29. Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. *Crit Care*. 2023;27(1):80. doi:10.1186/s13054-023-04327-7
30. Maegele M. Coagulopathy and progression of intracranial hemorrhage in traumatic brain injury: mechanisms, impact, and therapeutic considerations. *Neurosurgery*. 2021;89(6):954–966. doi:10.1093/neuros/nyab358
31. Buzzard L, Schreiber M. Trauma-induced coagulopathy: what you need to know. *J Trauma Acute Care Surg*. 2024;96(2):179–185. doi:10.1097/TA.0000000000004170
32. Nakae R, Fujiki Y, Takayama Y, et al. Age-related differences in the time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury. *Int J mol Sci*. 2020;21(16):5613. doi:10.3390/ijms21165613

33. Curry NS, Davenport R, Wong H, et al. Traumatic coagulopathy in the older patient: analysis of coagulation profiles from the Activation of Coagulation and Inflammation in Trauma-2 (ACIT-2) observational, multicenter study. *J Thromb Haemost*. 2023;21(2):215–226. doi:10.1016/j.jtha.2022.11.005
34. Toulon P, Berruyer M, Brionne-Francois M, et al. Age dependency for coagulation parameters in paediatric populations. Results of a multicentre study aimed at defining the age-specific reference ranges. *Thromb Haemost*. 2016;116(1):9–16. doi:10.1160/TH15-12-0964
35. Gee AC, Sawai RS, Differding J, et al. The influence of sex hormones on coagulation and inflammation in the trauma patient. *Shock*. 2008;29(3):334–341. doi:10.1097/SHK.0b013e3181506ee5
36. Ohkura N, Oishi K, Atsumi G. Blood coagulation and metabolic profiles in middle-aged male and female ob/ob mice. *Blood Coagul Fibrinolysis*. 2015;26(5):522–526. doi:10.1097/MBC.0000000000000267
37. Zheng B, Fan J, He R, et al. Antioxidant status of uric acid, bilirubin, albumin and creatinine during the acute phase after traumatic brain injury: sex-specific features. *Int J Neurosci*. 2021;131(9):833–842. doi:10.1080/00207454.2020.1758697
38. Roh DJ, Chang TR, Kumar A, et al. Hemoglobin concentration impacts viscoelastic hemostatic assays in ICU admitted patients. *Crit Care Med*. 2023;51(2):267–278. doi:10.1097/CCM.0000000000005700
39. Morton AP, Hadley JB, Ghasabyan A, et al. The alpha-globin chain of hemoglobin potentiates tissue plasminogen activator induced hyperfibrinolysis in vitro. *J Trauma Acute Care Surg*. 2022;92(1):159–166. doi:10.1097/TA.0000000000003410
40. Thangaraju K, Katneni U, Akpan IJ, et al. The impact of age and BMI on the VWF/ADAMTS13 axis and simultaneous thrombin and plasmin generation in hospitalized COVID-19 patients. *Front Med*. 2021;8:817305. doi:10.3389/fmed.2021.817305
41. Foldesi M, Merkei Z, Ferenci T, et al. Fibrinogen level at hospital admission after multiple injury correlates with BMI and is negatively associated with the need for transfusion and early multiple organ failure. *Injury*. 2021;52(Suppl 1):S15–S20. doi:10.1016/j.injury.2020.12.002
42. Kinnunen J, Satopaa J, Niemela M, et al. Coagulopathy and its effect on treatment and mortality in patients with traumatic intracranial hemorrhage. *Acta Neurochir*. 2021;163(5):1391–1401. doi:10.1007/s00701-021-04808-0