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Original Article

Risk warning of systemic immune-inflammation index and coagulation parameters for hospital-acquired pneumonia in patients with traumatic brain injury

Chang Shu[1], Wei Meng[2], Jie Tang[1], Yi He[3]

[1]Department of Emergency Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi 214100, Jiangsu, China; [2]Department of Anesthesiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi 214100, Jiangsu, China; [3]Department of Ultrasound Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi 214100, Jiangsu, China

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Abstract: Objective: To evaluate the predictive value of a thromboinflammatory signature integrating the Systemic Immune-Inflammation Index (SII) and routine coagulation markers for Hospital-Acquired Pneumonia (HAP) in patients with Traumatic Brain Injury (TBI). Methods: This retrospective study included two cohorts of patients with imaging-confirmed TBI: a development cohort (n=204) and an external validation cohort (n=80). Candidate predictors included demographic characteristics, Glasgow Coma Scale score, mechanical ventilation (MV), SII, and all routine coagulation markers, including prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen (FIB), and thrombin time (TT). Multivariable logistic regression was used to identify factors associated with HAP. Among patients who developed HAP, ventilator-associated pneumonia (VAP) was analyzed descriptively as an exploratory subgroup only. Results: In the development cohort, 76 of 204 patients (37.3%) developed HAP. Patients with HAP exhibited significant coagulation abnormalities, including elevated FIB. Multivariable logistic regression with collinearity diagnostics (VIF analysis) identified SII, FIB, and MV as independent predictors. The combined model demonstrated good discrimination (AUC=0.824) and maintained moderate performance in the external validation cohort (AUC=0.675). Conclusions: Admission SII, FIB, and MV are independently associated with HAP in patients with TBI. A combined model based on these variables retained original discrimination and nomogram performance for HAP. VAP-related observations are presented only as exploratory subgroup findings.

Keywords: Traumatic brain injury, hospital-acquired pneumonia, systemic immune-inflammation index, coagulation function, risk warning value

Introduction

Traumatic brain injury (TBI) remains a leading cause of death and long-term disability worldwide. Improvements in intensive care and neurosurgical management have increased early survival after TBI. Nevertheless, secondary complications continue to influence clinical outcomes. Among post-TBI complications, hospital-acquired pneumonia (HAP) is common and associated with poorer prognosis [1-5]. TBI may trigger early systemic inflammatory disturbance and coagulation abnormalities. Interactions between inflammatory and coagulation responses may increase susceptibility to infection and contribute to HAP development [6-9].

The systemic immune-inflammation index (SII) integrates information related to both inflammatory activity and immune status. Recent studies have suggested that SII may have prognostic relevance in infection, pneumonia, and other critical illness settings. Newer TBI-focused prediction studies have also highlighted the importance of combining inflammatory biomarkers with bedside clinical variables rather than relying on a single index [10-14].

Coagulation abnormalities are also frequently observed after TBI [15-17]. In routine clinical practice, commonly available indices such as prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen (FIB), and thrombin

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time (TT) are used to characterize hemostatic disturbance. Recent work has further emphasized that thromboinflammation after injury is not a single-pathway process; instead, inflammatory activation and coagulation dysregulation interact dynamically and may together influence pulmonary complications after TBI [18-21].

On this basis, we conducted a retrospective cohort study to examine whether admission SII and routine coagulation markers were associated with HAP in patients with TBI. In our analysis, all routinely available coagulation markers were first considered as candidate predictors for HAP. We then used a final reduced model to preserve the originally reported receiver operating characteristic (ROC) and nomogram results. Patients who developed HAP were further compared according to subsequent VAP occurrence, but no multivariable VAP model was constructed in this manuscript.

Materials and methods

Study population

The study was designed as a retrospective cohort analysis and consisted of a development cohort together with an external validation cohort. We consecutively enrolled hospitalized patients with TBI who were treated at The Affiliated Wuxi People's Hospital of Nanjing Medical University between January 2021 and January 2023. The study focused on the clinical characteristics and risk factors of HAP in patients with TBI. Owing to the retrospective design, no study-related intervention was performed. All data were anonymized before analysis, and informed consent was waived accordingly. The study was approved by the Ethics Committee of The Affiliated Wuxi People's Hospital of Nanjing Medical University.

Inclusion and exclusion criteria

Patients aged ≥18 years with imaging-confirmed TBI and a hospital stay of at least 48 hours were eligible. Patients were excluded when pulmonary infection was present before admission or when they had concomitant malignancy, hematologic disease, or autoimmune disease.

Grouping and outcome definition

Patients were assigned to the HAP or non-HAP group according to the occurrence of pneumonia during hospitalization. Based on the 2016 ATS/IDSA guidelines [22], HAP was defined as pneumonia developing ≥48 hours after admission, associated with new or progressive pulmonary infiltrates and compatible clinical manifestations. Patients with HAP were further categorized into VAP and non-VAP subgroups for exploratory descriptive comparison only.

VAP was defined as pneumonia arising ≥48 hours after endotracheal intubation and the initiation of mechanical ventilation (MV), accompanied by new or progressive pulmonary infiltrates and the clinical manifestations described above.

Data collection

Data were obtained from the electronic medical record system, including baseline characteristics and in-hospital clinical variables. Demographic factors comprised age, sex, and body mass index. Clinical variables related to injury and treatment included admission GCS score, the interval between injury and admission, neurosurgical procedures, and exposure to MV. Relevant comorbidities and lifestyle-related factors, including hypertension, diabetes, smoking history, and alcohol consumption, were also collected. Laboratory measurements from the first 24 hours after admission were reviewed for analysis. The systemic immune-inflammation index was calculated from complete blood count data using platelet count × neutrophil count/lymphocyte count. Routine coagulation parameters, including PT, APTT, INR, FIB, and TT, were collected at the same time point.

Statistical analysis

R and SPSS 26.0 were used for statistical evaluation. After normality had been checked with the Shapiro-Wilk test, continuous variables were summarized as either mean ± standard deviation or median with interquartile range, and between-group comparisons were performed with the independent-samples t test or Mann-Whitney U test as appropriate. Categorical variables were compared with the

Table 1. Baseline demographic characteristics and clinical indicators in the development and external validation cohorts

Variables	Development cohort (n=204)	Validation cohort (n=80)	$t/\chi^2/Z$	P
Demographic characteristics				
Age (years)	56.40 ± 12.50	56.90 ± 13.10	-0.290	0.772
BMI (kg/m^2)	23.70 (21.30, 25.70)	23.40 (21.50, 25.30)	-0.350	0.726
Sex			0.360	0.549
Male	118 (57.8)	43 (53.8)		
Female	76 (42.2)	37 (46.2)		
Hypertension	52 (25.5)	19 (23.8)	0.090	0.764
Diabetes mellitus	30 (14.7)	11 (13.8)	0.040	0.842
Smoking history	60 (29.4)	22 (27.5)	0.090	0.764
Alcohol consumption	42 (20.6)	19 (23.8)	0.330	0.566
History of stroke	25 (12.3)	9 (11.3)	0.050	0.823
Clinical indicators	59 (28.9)	20 (25.0)		
GCS score	10.00 (8.00, 12.00)	10.00 (8.00, 12.00)	-1.540	0.124
Time from injury to admission (h)	4.20 (2.40, 6.50)	4.30 (2.30, 6.10)	-0.140	0.889
Neurosurgical procedures	65 (31.9)	26 (32.5)	0.010	0.921
MV	75 (36.8)	32 (40.0)	0.240	0.624
SII	1420.30 (820.50, 2250.40)	1289.50 (508.90, 2416.50)	-0.680	0.497
PT (s)	14.60 (13.50, 16.40)	14.60 (13.10, 16.40)	-0.210	0.834
APTT (s)	36.60 (32.80, 40.50)	36.60 (33.60, 39.50)	-0.050	0.960
INR	1.24 (1.08, 1.40)	1.23 (1.03, 1.39)	-0.420	0.674
FIB (g/L)	3.70 (2.90, 4.60)	3.70 (2.80, 4.50)	-0.180	0.857
TT (s)	17.50 (16.20, 19.50)	17.00 (15.40, 19.00)	-1.120	0.263

Note: BMI, body mass index; GCS, Glasgow Coma Scale; MV, mechanical ventilation; SII, systemic immune-inflammation index; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen; TT, thrombin time.

chi-square test or Fisher's exact test. Candidate predictors for HAP included demographic variables, Glasgow Coma Scale score, MV, SII, and all routine coagulation markers (PT, APTT, INR, FIB, and TT). Variables with potential clinical relevance and variables identified in univariable analyses were screened for multivariable logistic regression. To avoid an overparameterized final model, a reduced model was subsequently retained for presentation of the original HAP ROC and nomogram results. Model discrimination was assessed using ROC curves and area under the curve (AUC) values, with DeLong testing for pairwise comparisons where appropriate. Calibration of the HAP nomogram was evaluated with bootstrap resampling (1,000 iterations). Due to limited subgroup sample size, all VAP-related analyses among patients with HAP were descriptive and exploratory only. A two-sided $P<0.05$ was considered statistically significant.

Results

Baseline demographic and clinical characteristics

A total of 284 patients with TBI were included, with 204 patients in the development cohort and 80 patients in the external validation cohort. Baseline demographic and clinical characteristics for the two cohorts are provided in **Table 1**. Comparisons of age, sex, BMI, and the main clinical variables showed no significant differences between the cohorts (all $P> 0.05$), supporting baseline comparability.

The patient selection process is summarized in **Figure 1**. Of the 379 patients who met the eligibility criteria, 175 were excluded because of pre-existing pulmonary infection or missing ethical approval or consent-related information, leaving 204 eligible patients for analysis.

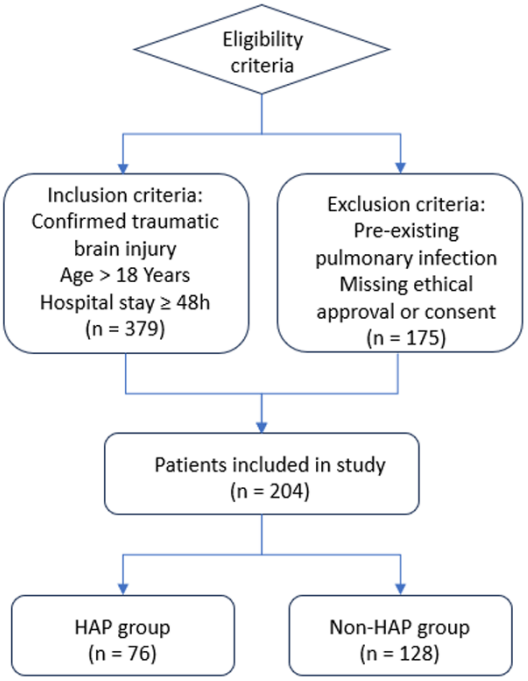

Figure 1. Flowchart of patient selection and study design. Of the 379 screened patients, 175 were excluded, leaving 204 eligible patients for analysis. Patients were stratified into the Hospital-Acquired Pneumonia group (n=76) and the Non-Hospital-Acquired Pneumonia group (n=128).

Among these, 76 patients developed HAP and 128 did not, as shown in **Figure 2**.

Incidence of HAP in patients with TBI

Among 204 patients with TBI, 76 developed HAP during hospitalization, yielding an incidence of 37.3%, indicating that HAP is a common in-hospital complication in this patient population.

Comparison of demographic and clinical characteristics between the groups

Compared with the non-HAP group, patients with HAP had significantly higher SII levels. The HAP group also showed lower GCS scores and a higher frequency of MV. Among coagulation-related indices, PT, FIB, and TT differed significantly between the groups, whereas APTT and INR did not show statistically significant differences (**Table 2**). These findings supported the subsequent inclusion of all routine coagulation markers in the overall HAP modeling strategy.

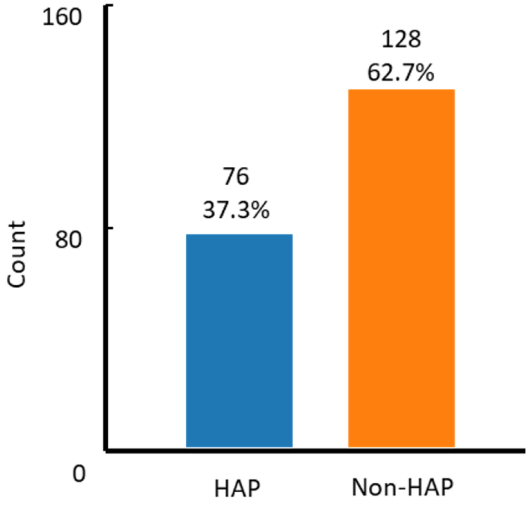

Figure 2. Distribution of patients in the Hospital-Acquired Pneumonia and Non-Hospital-Acquired Pneumonia groups. Of the 204 included patients, 76 (37.3%) developed Hospital-Acquired Pneumonia (HAP) and 128 (62.7%) did not (Non-HAP).

Among the 76 patients with HAP, 30 were subsequently diagnosed with VAP, accounting for 39.5% of the HAP subgroup. **Table 5** presents the comparison of demographic and clinical characteristics between the VAP and non-VAP groups. Compared with patients without VAP, patients in the VAP group had significantly lower GCS scores and a markedly higher frequency of MV. In addition, the VAP group showed significantly higher SII, APTT, INR, and FIB levels. PT showed a borderline difference between the two groups, whereas TT was not significantly different (**Table 5**).

Multivariable logistic regression analysis for HAP in TBI

All routine coagulation markers were initially considered in the HAP modeling strategy together with SII and clinically relevant bedside variables. Collinearity diagnostics showed VIF values of 1.262 for PT, 6.536 for APTT, 6.289 for INR, 1.097 for FIB, and 1.103 for TT (**Table 3**). Given that APTT and INR both had VIF values greater than 5, indicating relatively strong collinearity, and neither variable showed a significant between-group difference in the comparison of HAP and non-HAP patients, these two variables were excluded during model reduction. The reduced multivariable logistic regression model therefore retained SII, FIB, PT, TT, GCS score, and MV for formal estima-

Table 2. Comparison of demographic characteristics and clinical indicators between the HAP and non-HAP groups

Variables	HAP group (n=76)	Non-HAP group (n=128)	$t/\chi^2/Z$	P
Demographic characteristics				
Age (years)	58.34 ± 10.42	57.00 ± 10.62	0.877	0.382
BMI (kg/m^2)	23.70 [21.30, 25.73)	23.85 (21.58, 25.70)	-0.064	0.950
Sex				
Male	47 (61.8)	87 (68.0)	0.794	0.373
Female	29 (38.2)	41 (32.0)		
Hypertension	20 (26.3)	40 (31.2)	0.559	0.455
Diabetes mellitus	9 (11.8)	8 (6.2)	1.952	0.162
Smoking history	18 (23.7)	41 (32.0)	1.616	0.204
Alcohol consumption	19 (25.0)	38 (29.7)	0.520	0.471
History of stroke	4 (5.3)	4 (3.1)	0.579	0.447
Clinical indicators				
GCS score	9.00 (7, 11)	11 (10, 12)	-5.153	<0.001
Time from injury to admission (h)	3.65 (2.60, 4.95)	3.50 (2.30, 5.03)	-0.542	0.588
Neurosurgical procedures	25 (32.9)	34 (26.6)	0.930	0.335
MV	43 (56.6)	37 (28.9)	15.320	<0.001
SII	1907.34 (1229.19, 2519.06)	1002.15 (729.76, 1397.36)	-6.837	<0.001
PT (s)	14.64 ± 1.60	13.92 ± 1.62	-3.090	0.002
APTT (s)	36.97 ± 5.05	36.25 ± 4.14	-1.106	0.27
INR	1.22 ± 0.21	1.19 ± 0.18	-1.125	0.262
Fibrinogen (g/L)	4.16 (3.62, 4.78)	3.47 (3.05, 3.87)	-5.657	<0.001
TT (s)	18.13 (16.88, 19.48)	17.00 (16.12, 18.37)	-3.099	0.002

Note: BMI, body mass index; GCS, Glasgow Coma Scale; MV, mechanical ventilation; SII, systemic immune-inflammation index; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen; TT, thrombin time.

Table 3. Collinearity analysis of coagulation-related variables in the HAP model

Predictor	VIF	Tolerance
PT	1.262	0.792
APTT	6.536	0.153
INR	6.289	0.159
Fibrinogen (g/L)	1.097	0.911
TT (s)	1.103	0.907

Note: VIF, variance inflation factor; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time.

tion, thereby preserving the originally reported HAP discrimination and nomogram framework.

In the reduced multivariable model, SII, FIB, and MV remained independently associated with HAP during hospitalization in patients with TBI, whereas PT, TT, and GCS score did not reach statistical significance (**Table 4**).

Table 4. Multivariable logistic regression analysis of factors associated with HAP in patients with TBI

Predictor	OR	95% CI	P
Constant	5.04e-04	8.49e-06-3.00e-02	<0.001
SII	1.001	1.001-1.002	<0.001
FIB	1.961	1.212-3.173	0.006
PT	1.08	0.868-1.343	0.49
TT	1.095	0.902-1.330	0.357
GCS	0.879	0.741-1.042	0.136
MV	2.113	1.048-4.260	0.036

Note: SII, systemic immune-inflammation index; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen; TT, thrombin time.

These results indicate that inflammatory burden, coagulation-related fibrinogen response, and the need for ventilatory support contributed most strongly to the final HAP prediction model.

Table 5. Comparison of demographic characteristics and clinical indicators between the VAP and non-VAP groups

Variables	VAP group (n=30)	Non-VAP group (n=46)	$t/\chi^2/Z$	P
Demographic characteristics				
Age (years)	60.07 ± 9.78	57.22 ± 10.76	1.192	0.237
BMI (kg/m^2)	23.91 ± 2.85	23.27 ± 3.24	0.904	0.369
Sex			0.563	0.453
Male	17 (56.7)	30 (65.2)		
Female	13 (43.3)	16 (34.8)		
Hypertension	6 (20.0)	14 (30.4)	1.02	0.313
Diabetes mellitus	3 (10.0)	6 (13.0)	-	1
Smoking history	8 (26.7)	10 (21.7)	0.244	0.621
Alcohol consumption	7 (23.3)	12 (26.1)	0.073	0.786
History of stroke	1 (3.3)	3 (6.5)	-	1
Clinical indicators				
GCS score	7.87 ± 2.60	9.48 ± 2.42	-2.717	0.009
Time from injury to admission (h)	3.40 (2.23, 4.35)	3.70 (2.80, 5.10)	-1.244	0.216
Neurosurgical procedures	11 (36.7)	14 (30.4)	0.319	0.572
MV	27 (90.0)	16 (34.8)	22.535	<0.001
SII	2447.03 (2127.53, 2941.46)	1335.70 (1081.85, 1877.97)	5.6	<0.001
PT (s)	15.05 ± 1.48	14.38 ± 1.64	1.856	0.068
APTT (s)	38.59 ± 4.56	35.91 ± 5.13	2.379	0.02
INR	1.34 (1.16, 1.41)	1.18 (1.04, 1.28)	2.12	0.034
Fibrinogen (g/L)	4.58 ± 0.96	3.95 ± 0.82	2.968	0.004
TT (s)	18.21 ± 2.06	18.03 ± 1.95	0.365	0.716

Note: BMI, body mass index; GCS, Glasgow Coma Scale; MV, mechanical ventilation; SII, systemic immune-inflammation index; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen; TT, thrombin time.

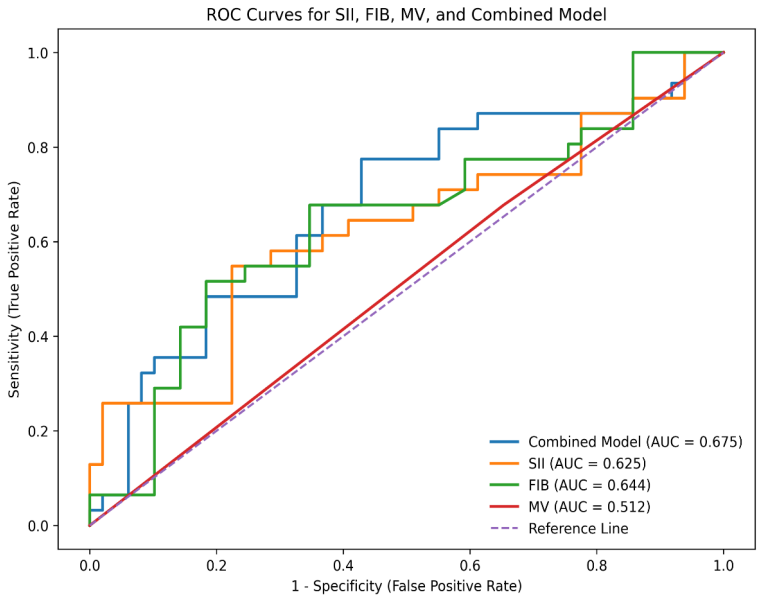

Figure 3. ROC curves of Systemic Immune-Inflammation Index, Fibrinogen, MV, and the combined predictive model for Hospital-Acquired Pneumonia (HAP) in patients with traumatic brain injury. The combined model showed superior discriminative ability compared to individual predictors, including Mechanical Ventilation (MV), Systemic Immune-Inflammation Index (SII), and Fibrinogen (FIB).

ROC curve analysis of individual indicators and the combined model

In the independent validation cohort (n=80), the combined model yielded the highest AUC value in the ROC analysis, with an AUC of 0.675. Compared with MV alone, which showed an AUC of 0.512, the combined model demonstrated better discriminative performance. The combined model also showed numerically higher discrimination than SII alone (AUC=0.625) and FIB alone (AUC=0.644), although the incremental improvement beyond these individual biomarkers should be interpreted cautiously given the relatively small validation sample (**Figure 3**).

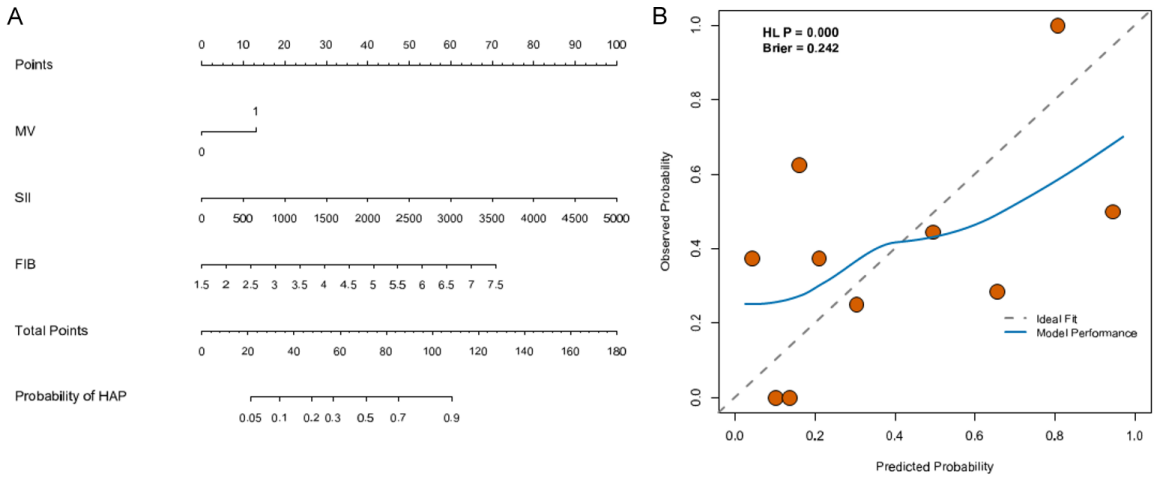

Figure 4. Nomogram for Hospital-Acquired Pneumonia risk prediction based on Systemic Immune-Inflammation Index, Fibrinogen, and Mechanical Ventilation, and model calibration. (A) Nomogram. (B) Calibration curve. (A) Nomogram for individualized prediction of Hospital-Acquired Pneumonia (HAP) risk based on Systemic Immune-Inflammation Index (SII), Fibrinogen (FIB), and Mechanical Ventilation (MV). (B) Calibration curve of the nomogram based on Systemic Immune-Inflammation Index (SII), Fibrinogen (FIB), and Mechanical Ventilation (MV).

Construction of the nomogram and individualized risk assessment

A nomogram incorporating MV, SII, and FIB was developed for individualized estimation of HAP risk in patients with TBI. The calibration curve showed visible deviation between predicted and observed probabilities, with a Hosmer-Lemeshow test *P* value of 0.000 and a Brier score of 0.242 (**Figure 4**). These findings suggest that although the model had acceptable discriminatory value, its calibration was imperfect and may require further recalibration or validation in larger independent cohorts.

Discussion

In this single-center retrospective cohort of 204 patients with imaging-confirmed TBI, 37.3% developed HAP during hospitalization. This finding indicates that nosocomial pulmonary infection is a common complication in this population. After revision of the statistical strategy, all routine coagulation markers were first screened as candidate variables. The reduced HAP model retained SII, FIB, and MV as the most informative factors. The combined model maintained good discrimination in the development cohort and moderate discrimination in the external validation cohort.

Through neuro-immune interactions, TBI may trigger a dysregulated state. In this state, systemic inflammation coexists with secondary immunosuppression, thereby increasing susceptibility to infection [23-25]. At the molecular level, the inflammatory response following TBI is tightly regulated by post-translational modifications, particularly ubiquitination. The activation of key pro-inflammatory transcription factors, such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), is dependent on ubiquitin signaling cascades [26]. Dysregulation of these pathways may contribute to the exaggerated and protracted systemic inflammation observed after TBI, thereby increasing susceptibility to hospital-acquired pneumonia. SII captures this imbalance by integrating neutrophil, lymphocyte, and platelet signals into a single index. In the present study, SII remained associated with HAP after model reduction. This finding supports the view that inflammatory burden contributes materially to pulmonary infection risk after TBI. This interpretation is consistent with recent literature showing that inflammatory indices may improve pneumonia risk stratification when combined with bedside clinical information [27, 28].

The variables included in the final HAP model were all obtained from routine clinical assessment and commonly performed laboratory testing, which may facilitate their use in clinical practice. Notably, FIB emerged as a pivotal predictor and remained independently associated

with HAP. In contrast, conventional coagulation markers such as PT, TT, APTT, and INR did not provide the same degree of retained predictive contribution after screening and model reduction [29-31]. This finding highlights the central role of coagulation status, specifically FIB, in the risk stratification of post-TBI infections. The predictive superiority of fibrinogen is biologically plausible, as it is not only a coagulation factor but also an acute-phase reactant that reflects thromboinflammatory activation after injury [32, 33]. Recent methodological guidance has also emphasized that parsimonious prediction models are generally preferable when they preserve discrimination and calibration while avoiding unnecessary complexity [34, 35].

Among patients with HAP, 39.5% subsequently developed VAP, indicating that ventilator-associated infection remained a clinically relevant complication after hospital-acquired pneumonia had occurred. However, because the VAP subgroup was limited in size and the original multivariable analysis showed unstable estimates, we removed the VAP multivariable model and retained only descriptive subgroup comparisons. Accordingly, the VAP-related findings should be interpreted as hypothesis-generating rather than as definitive evidence of independent predictors.

This study has several limitations. First, due to the retrospective design, selection bias could not be completely excluded. Second, although an independent external validation cohort was included, the validation sample remained modest in size. Third, only baseline admission indicators were evaluated, and dynamic changes over time were not assessed. Fourth, because the number of VAP events was limited, reliable multivariable modeling for this subgroup was not pursued. Additional prospective studies with larger samples are needed to confirm and refine these findings.

Conclusion

In patients with TBI, admission SII, FIB, and MV were independently associated with HAP. The combined model showed good discrimination in the development cohort and moderate performance in the external validation cohort, where it remained better than MV alone. Overall, the model may be useful for early risk stratification in this population, especially when a single clinical indicator provides limited predictive information.

Disclosure of conflict of interest

None.

Address correspondence to: Yi He, Department of Ultrasound Medicine, The Affiliated Wuxi People's Hospital of Nanjing Medical University, No. 299, Qingyang Road, Liangxi District, Wuxi 214100, Jiangsu, China. Tel: +86-0510-85350315; E-mail: heyisci@126.com

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