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Association Between Metabolic and Inflammatory Biomarkers and Prognosis in Traumatic Brain Injury: A Focus on Short- and Medium-Term Mortality

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Background: Traumatic brain injury (TBI) is a leading cause of disability and death worldwide, involving complex pathophysiological responses such as metabolic disturbance and systemic inflammation. This study aimed to evaluate the prognostic value of selected metabolic and inflammatory biomarkers in predicting short- and medium-term mortality in patients with moderate-to-severe TBI.

Methods: We conducted a retrospective cohort study of patients with TBI admitted between March 29, 2018, and July 31, 2023. Clinical data, including a panel of metabolic (eg, triglyceride-glucose index [TYG], APOB/A1 ratio) and inflammatory biomarkers (eg, neutrophil-to-platelet ratio [NPR]), were collected within 24 hours of admission. Mortality was assessed at 14 days, 30 days, and hospital discharge. Multivariate Cox regression models and ROC curve analysis were used to assess prognostic associations and model performance.

Results: A total of 2555 patients were enrolled, of whom 579 (22.67%) underwent surgical treatment. Multivariate Cox proportional hazards regression analysis revealed that the triglyceride-glucose index (TYG) was an independent predictor of short-term mortality in TBI patients, while the neutrophil-to-platelet ratio (NPR) and apolipoprotein B/A1 (APOB/A1) ratio were independent predictors of both short- and mid-term mortality. In addition, surgical treatment was associated with an increased risk of mid-term mortality, while tracheostomy significantly reduced mortality risk across all time points. Receiver operating characteristic (ROC) curve analysis showed that the regression model incorporating inflammatory markers had the highest areas under the curve (AUCs) of 0.904, 0.897, and 0.897, demonstrating superior performance in predicting short- and mid-term mortality. Additionally, in the subgroup analysis of non-operation patients, TYG and NPR had a more significant impact on mortality risk.

Conclusion: Metabolic and inflammatory biomarkers, including TYG, NPR, and APOB/A1 ratio, provide valuable prognostic information in patients with TBI. These markers may assist clinicians in early risk stratification and personalized treatment planning.

Keywords: traumatic brain injury, triglyceride-glucose index, neutrophil-to-platelet ratio, prognosis, cox proportional hazards model

Introduction

Traumatic Brain Injury (TBI) represents a significant global health challenge, being a leading cause of disability and mortality, with an estimated 69 million cases reported annually worldwide.[1] The complexity of TBI extends beyond the

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immediate physical trauma, encompassing a spectrum of secondary injuries, including neuroinflammation and disruption of the blood-brain barrier.[2] The inflammatory response plays a central role in the pathophysiological progression of TBI, as it activates the immune system and triggers the release of various inflammatory mediators, which may exacerbate neuronal damage and contribute to adverse outcomes.[3,4] Consequently, elucidating the relationship between metabolic and inflammatory biomarkers and mortality in TBI patients is of paramount clinical importance, as it may inform therapeutic strategies and enhance prognostic accuracy.[5]

Inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR), have emerged as valuable prognostic tools in various central nervous system disorders, including TBI.[6,7] These markers not only reflect the systemic inflammatory state of patients but also provide insights into their potential recovery trajectories. For instance, elevated NLR and MLR levels have been correlated with increased mortality and poor functional outcomes in TBI patients, thereby assisting clinicians in tailoring individualized treatment plans aimed at improving survival rates and enhancing quality of life.[8,9] The integration of these inflammatory indicators into clinical practice could facilitate more effective management of TBI, ultimately leading to better patient outcomes. Research exploring the relationship between inflammatory markers and mortality in TBI patients has gained traction in recent years. Several studies have highlighted the prognostic value of inflammatory markers such as NLR and platelet-to-lymphocyte ratio (PLR) in predicting both short-term and long-term outcomes in severe TBI cases.[10,11] For instance, a meta-analysis indicated that elevated NLR is associated with increased mortality risk in TBI patients, reinforcing the need for these markers in clinical assessments.[12] However, existing literature often focuses on isolated markers without providing a comprehensive analysis of their combined predictive capabilities. Furthermore, while some studies suggest a promising role for these inflammatory indicators in mortality prediction, the need for further validation and systematic investigation remains evident.[13,14] The complexity of TBI, coupled with the multifactorial nature of its outcomes, necessitates a more holistic approach to research that encompasses various inflammatory markers and their interactions.

In addition to inflammation, metabolic disturbances also play a crucial role in the pathophysiology and prognosis of traumatic brain injury. TBI can trigger profound alterations in glucose and lipid metabolism, including insulin resistance, hyperglycemia, dyslipidemia, and oxidative stress, which collectively contribute to secondary neuronal injury.[5,6] These metabolic changes are often associated with poor outcomes, as they may exacerbate neuroinflammation, impair cerebral perfusion, and disrupt cellular homeostasis. The triglyceride-glucose (TYG) index and lipid-related markers such as the apolipoprotein B/A1 (APOB/A1) ratio are increasingly recognized as valuable indicators of systemic metabolic stress and cardiovascular risk.[13] However, their utility in predicting outcomes after TBI remains underexplored. Incorporating metabolic biomarkers alongside inflammatory indices could provide a more comprehensive understanding of the biological mechanisms influencing mortality and recovery in TBI patients.

In the clinical management of TBI, the impact of mortality plays a crucial role in prognosis at different time points.[15,16] Short-term prognosis, typically referring to mortality within 14 days post-injury, is a key indicator for assessing the initial physiological response and the effectiveness of acute management.[15] During this phase, a patient's metabolic status, inflammatory response, and the severity of the trauma directly influence the stability of vital signs. Therefore, early risk prediction is essential for timely intervention, reducing damage, and improving survival rates. In contrast, medium- and long-term prognosis reflects the ongoing inflammatory response, neurological recovery, and the occurrence of complications, which may gradually emerge weeks or even months after the injury.[16] This study aims to explore the differences in short-term and long-term mortality risks and their underlying mechanisms, providing a multi-dimensional approach to prognosis for clinical treatment and management. This research not only helps to identify high-risk patients early but also informs later intervention strategies, ultimately improving the overall treatment outcomes and quality of life for TBI patients.

Thus, understanding the complex relationship between inflammatory responses and TBI outcomes could significantly aid in improving prognostic accuracy and optimizing therapeutic interventions for TBI patients. Therefore, this study aimed to elucidate the roles of specific inflammatory markers in TBI outcomes and their potential impact on clinical decision-making.

Methods

Ethical Consideration

The study was authorized by the Ethical Board of the Affiliated Kunshan Hospital of Jiangsu University, Suzhou, China (approval # 2022–06-025) and followed the Helsinki Declaration. To ensure an unbiased investigation, patients' identities were not revealed and a signed written consent form was acquired from all the participants.

Study Design

This retrospective cohort study was conducted in the Department of Neurosurgery at the Affiliated Kunshan Hospital of Jiangsu University, following patients from March 29, 2018, to July 31, 2023. Inclusion criteria required that patients (1) were aged 18 years or older; (2) had a confirmed diagnosis of moderate to severe TBI based on Glasgow Coma Scale (GCS) scores ≤12 upon admission;[17] and (3) had inflammatory biomarker data recorded within 24 hours post-injury.

Exclusion criteria included: (1) pregnant women; (2) patients excluded due to logistical reasons (eg, transferred to another facility shortly after admission); (3) refusal to participate; (4) non-traumatic causes of brain injury (eg, stroke, tumor); (5) cognitive impairments precluding informed consent; (6) missing essential laboratory results; and (7) follow-up period of less than one week.

In addition, while patients who received immunosuppressive or anti-inflammatory drugs prior to biomarker assessment were excluded, medications administered after blood sampling during hospitalization (such as corticosteroids, antibiotics, and analgesics) were not controlled in this retrospective analysis. However, these treatments were administered according to standardized hospital protocols and were not differentially applied between groups, thus minimizing potential confounding effects on mortality.

The surgical interventions included in this study were primarily standard neurosurgical procedures for moderate-to-severe traumatic brain injury. These consisted of decompressive craniectomy, evacuation of intracranial hematomas (epidural, subdural, or intracerebral), intracranial pressure (ICP) monitor placement, and craniotomy for fracture repair or dural repair. All procedures were performed based on the clinical indications and current guidelines for TBI management.

All patients included in this study were of Han ethnicity. All clinical and demographic data were collected systematically from electronic medical records at baseline and follow-up intervals to ensure consistency and completeness in assessing the cohort's health outcomes.

Outcome Variable

The primary outcome variable in this study was mortality status at three key time points post-injury: (1) at 14 days post-trauma, (2) at 1 month post-trauma, and (3) at discharge from the hospital. Mortality data were obtained from hospital records, and each patient's status was verified through clinical documentation and follow-up information to ensure accurate classification. These time-specific mortality outcomes allowed for an analysis of short-term and medium-term prognostic implications associated with inflammatory biomarkers in patients with traumatic brain injury.

Explanatory Variable

Demographic and clinical characteristics, such as sex, age, and surgical intervention status, were documented to assess baseline patient differences. Additionally, tracheostomy status was noted to evaluate its potential impact on patient prognosis. Biochemical markers were thoroughly assessed within 24 hours of admission. Key serum electrolyte and coagulation parameters were also recorded. The complete blood count (CBC), which included neutrophil, lymphocyte, and monocyte counts, captured variations in immune cell profiles, reflecting immune activation levels. Platelet counts were also measured to provide a broad view of the hematological response. Lipid profile parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (APO-A1) and apolipoprotein B (APO-B), were analyzed to explore the metabolic effects of TBI on lipid metabolism and inflammation. Cystatin C (CYS-C), alanine aminotransferase (ALT), aspartate

aminotransferase (AST), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), and fasting blood glucose (FBG) were measured to understand liver, kidney responses and metabolic alterations to trauma.

In addition to individual markers, a number of derived indices were calculated and analyzed. These included the systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), TYG, NLR, PLR, lymphocyte-to-monocyte ratio (LMR), and neutrophil-to-platelet ratio (NPR). These indices provided comprehensive measures of systemic inflammation and immune status.

Statistical Analysis

All statistical analyses were performed using R version 4.3.0. Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Between-group comparisons of continuous variables were conducted using the Student's *t*-test for normally distributed data. The chi-square (χ^2) test was used to compare categorical variables.

A correlation heatmap was generated to assess the relationships between different explanatory variables. Both Pearson and Spearman correlation coefficients were calculated to assess the strength of linear and nonlinear associations between variables, respectively. Kaplan-Meier (KM) survival curves were constructed to evaluate the impact of surgical intervention and tracheostomy status on mortality at 14 days and 30 days post-injury. The Log rank test was used to compare survival distributions between groups.

To identify factors associated with mortality at different time points, Cox proportional hazards models were employed. To explore the incremental predictive value of metabolic and inflammatory biomarkers, three multivariate Cox regression models were constructed in a stepwise fashion. Model 1 included basic demographic and clinical variables (age, sex, operation status, and tracheostomy). Model 2 extended Model 1 by incorporating metabolic indicators (HDL-C, LDL-C, APOB/A1 ratio, and TYG index). Model 3 included all variables in Model 2, with the addition of inflammatory indices (NPR, NLR, and PLR). These models were then used to generate ROC curves and calculate AUCs at three time points (14-day, 30-day, and discharge) to evaluate the improvement in predictive performance with additional biomarker categories. Separate models were developed for mortality at 14 days, 30 days, and at discharge. Each model was adjusted for potential confounders such as age, sex, and surgical intervention status. The predictive performance of the optimal Cox models was evaluated using Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC) was calculated to quantify the model's discriminative ability. Comparisons between models were made to determine the addition of variables that significantly improved prediction. Based on the most predictive Cox model, a nomogram was developed to provide a visual and quantitative tool for predicting individual patient mortality risk at specified time points. The nomogram incorporated the significant predictors identified in the Cox models. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Differences Between Surgical and Non-Surgical TBI Patients

During the study period, a total of 2555 TBI patients were included in this study, with 579 (22.67%) undergoing surgical intervention and 1976 (77.33%) managed non-operatively, as shown in Figure 1 and Table 1. A significant majority of the cohort was male (71.55%), with a statistically higher percentage of male patients observed in the operation group compared to the non-operation group (76.17% vs 70.19%, $p = 0.006$). In terms of injury severity, patients in the surgical group had significantly lower GCS scores upon admission compared to the non-surgical group (mean GCS: 6.29 ± 1.47 vs 8.01 ± 2.45, $p < 0.001$), indicating that those who underwent surgery presented with more severe traumatic brain injury. The average age of the patients was 50.64 years (SD = 17.85), with no significant age difference between the operation and non-operation groups ($p = 0.402$). A tracheostomy was performed more frequently in the operation group (21.24%) than in the non-operation group (2.23%), a difference that was highly significant ($p < 0.001$).

Regarding serum electrolyte levels, surgical patients had higher potassium (3.81 mmol/L vs 3.71 mmol/L, $p = 0.017$) and phosphorus levels (1.09 mmol/L vs 1.02 mmol/L, $p = 0.044$), while showing lower magnesium (0.77 mmol/L vs

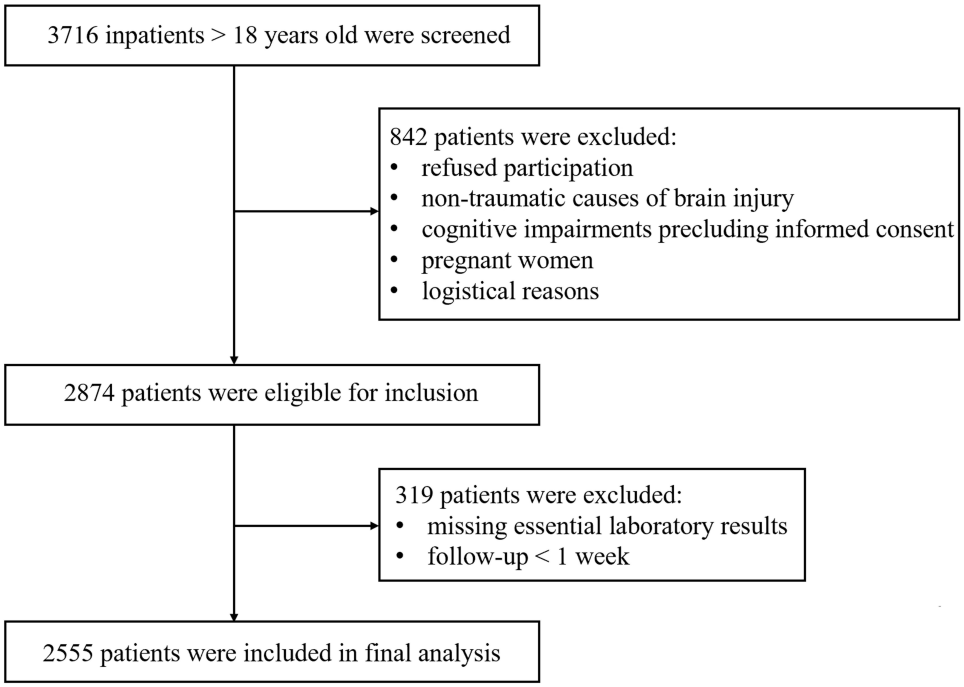

Figure 1 Flowchart of patient recruitment and study design.

0.87 mmol/L, $p < 0.001$) and sodium levels (139.05 mmol/L vs 139.57 mmol/L, $p < 0.001$) compared to non-surgical patients. Coagulation parameters differed significantly between the two groups, with higher PT, APTT, and INR observed in the surgical group ($p < 0.001$ for all). Conversely, FIB and D-Dimer levels were significantly elevated in the non-surgical group ($p < 0.001$). Inflammatory markers also varied significantly, with surgical patients exhibiting higher neutrophil counts but lower lymphocyte counts compared to non-surgical patients. Additional disparities were found in the lipid profile; total cholesterol, LDL-C, HDL-C, and APO-A1 levels were significantly lower in the surgical group, whereas triglycerides and APO-B levels were also significantly different ($p < 0.001$ for all).

Liver and renal function markers, such as ALT, AST, Cr, and UA, also showed significant group differences. ALT and AST levels were elevated in surgical patients, and Cr levels were slightly higher in the surgical group (68.90 μmol/L vs

Table 1 General Characteristics of Study Population

	Total (N=2555)	Operation (N=579)	Non-operation (N=1976)	*P* value
Sex				
Male	1828(71.55%)	441(76.17%)	1387(70.19%)	0.006
Female	727(28.45%)	138(23.83%)	589(29.81%)	
Age	50.64(17.85)	51.20(15.39)	50.48(18.50)	0.402
Tracheostomy				
Yes	167(6.54%)	123(21.24%)	44(2.23%)	0.000
No	2388(93.46%)	456(78.76%)	1932(97.77%)	
GCS score	7.62(2.64)	6.29(1.47)	8.01(2.45)	0.000
Potassium	3.73(0.47)	3.81(0.65)	3.71(0.40)	0.017
Magnesium	0.85(0.11)	0.77(0.11)	0.87(0.10)	0.000
Sodium	139.45(3.27)	139.05(3.76)	139.57(3.10)	0.000
Phosphorus	1.03(0.30)	1.09(0.42)	1.02(0.26)	0.044

(*Continued*)

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Table 1 (Continued).

	Total (N=2555)	Operation (N=579)	Non-operation (N=1976)	*P* value
PT	12.11(2.09)	13.27(2.93)	11.79(1.65)	0.000
APTT	28.94(8.28)	33.39(14.34)	27.68(4.76)	0.000
INR	1.04(0.19)	1.14(0.27)	1.01(0.15)	0.000
FIB	2.45(1.04)	1.69(0.95)	2.67(0.97)	0.000
D-Dimer	14.35(22.72)	29.49(29.64)	9.95(18.04)	0.000
NT-proBNP	361.47(1246.45)	226.89(626.98)	486.59(1613.43)	0.000
Platelet	183.57(72.09)	155.93(88.23)	191.77(64.33)	0.000
HB	124.60(27.16)	110.21(33.17)	128.87(23.46)	0.000
Albumin	38.29(6.99)	32.15(9.62)	40.13(4.59)	0.000
Calcium	2.12(0.2)	1.93(0.24)	2.18(0.14)	0.000
Neutrophil	9.99(5.05)	12.99(5.4)	9.10(4.58)	0.000
Lymphocyte	1.20(0.68)	1.14(0.89)	1.21(0.60)	0.000
Monocyte	0.69(0.40)	0.80(0.59)	0.66(0.32)	0.000
TC	3.81(1.01)	3.26(1.01)	4.00(0.94)	0.000
TG	1.15(0.90)	1.06(0.87)	1.18(0.90)	0.000
HDL-C	1.26(0.33)	1.14(0.33)	1.30(0.31)	0.000
LDL-C	2.19(0.79)	1.78(0.78)	2.32(0.75)	0.000
APO-A1	1.11(0.28)	0.98(0.27)	1.16(0.27)	0.000
APO-B	0.74(0.25)	0.62(0.26)	0.78(0.24)	0.000
CYS-C	12.91(10.15)	11.81(8.98)	13.29(10.51)	0.000
ALT	30.43(41.78)	33.12(38.03)	29.63(42.81)	0.000
AST	39.91(75.87)	47.42(46.57)	37.67(82.50)	0.000
Cr	65.48(46.97)	68.90(56.87)	64.47(43.56)	0.002
BUN	5.36(2.33)	5.32(2.44)	5.37(2.30)	0.770
UA	304.25(103.10)	317.13(108.50)	300.40(101.14)	0.002
FBG	6.66(2.40)	8.09(2.98)	6.22(2.00)	0.000

64.47 μmol/L, $p = 0.002$). The FBG levels were notably higher in surgical patients (8.09 mmol/L vs 6.22 mmol/L, $p < 0.001$), indicating potential metabolic response variations to TBI between the groups.

These data indicate that surgical TBI patients display distinct biochemical profiles compared to non-surgical patients, suggesting that inflammatory and metabolic responses may differ based on intervention type. This profile may provide insight into differential inflammatory and metabolic burdens between these patient groups and their respective prognoses.

Patterns of Correlation Among Inflammatory and Metabolic Biomarkers

The Pearson correlation matrix presented in the heatmap reveals the relationships between various biochemical and hematological variables in TBI patients (Figure 2A). Each cell represents the correlation coefficient between two variables, with the color intensity reflecting the strength and direction of the correlation: dark blue indicates a strong positive correlation, while dark red indicates a strong negative correlation. Notably, coagulation parameters (PT, APTT, and INR) show strong positive correlations among themselves, which is expected, as these measurements collectively indicate the coagulation status of patients. D-Dimer and FIB also exhibit a negative relationship with themselves, likely reflecting their roles in clot formation and breakdown. Among the serum electrolytes, potassium and magnesium and sodium display a weak negative correlation. This indicates that electrolyte imbalances in TBI patients may have complex interrelationships. The lipid profile markers, including TC, HDL-C, LDL-C, and apolipoproteins (APO-A1 and APO-B), show strong positive correlations with each other, suggesting that lipid metabolism parameters are closely related. Serum albumin and HB also show a positive correlation, as both are reflective of nutritional and physiological status. In the correlation matrix, several inflammatory markers, such as neutrophils and monocytes, show positive correlations among themselves. This suggests that these markers often increase together in TBI patients, reflecting a heightened inflammatory

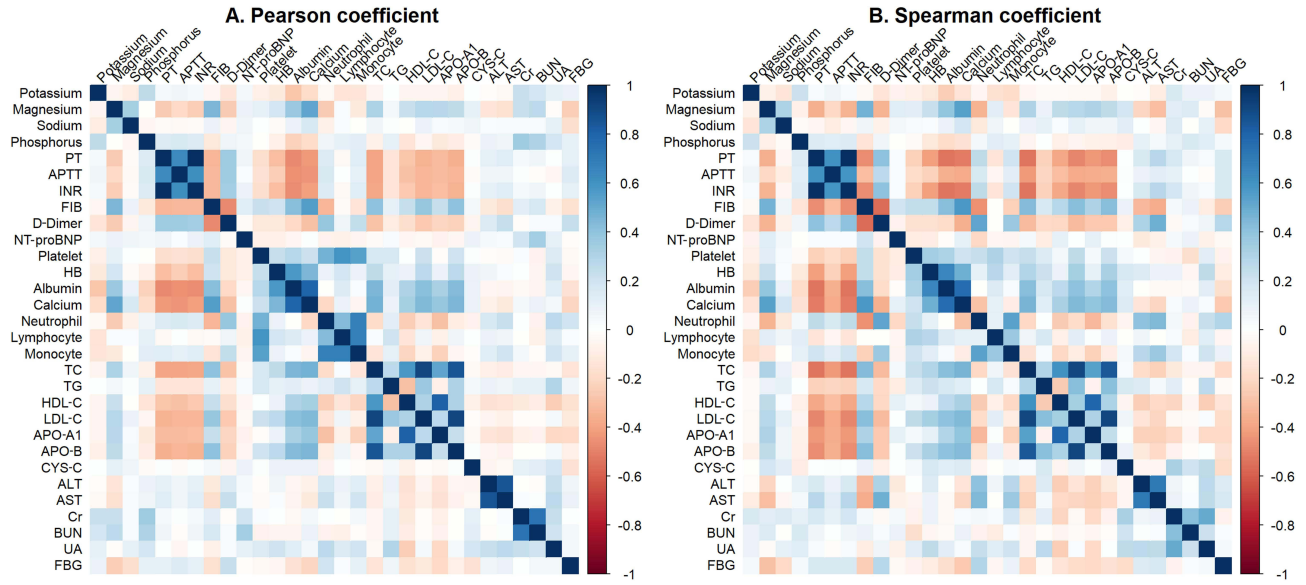

Figure 2 Correlation heatmaps of explanatory variables in TBI patients. (**A**) Pearson correlation matrix showing the linear associations among inflammatory, metabolic, and hematologic parameters. Blue and red colors indicate positive and negative correlations, respectively, with color intensity representing correlation strength. (**B**) Spearman correlation matrix illustrating nonlinear relationships between variables, with deeper red denoting stronger negative correlations. Consistency across panels suggests robust variable interactions.

response. For example, a higher neutrophil count correlates positively with monocyte levels, indicating that when the immune system is activated in response to trauma, multiple types of inflammatory cells tend to be elevated simultaneously. These correlations align with the known systemic inflammatory response in TBI, where multiple inflammatory pathways are activated concurrently, contributing to the severity and progression of secondary brain injury. This positive relationship among inflammatory markers highlights the potential utility of composite inflammatory indices, such as NLR and PLR, as they combine multiple markers to better represent the inflammatory status and its prognostic implications in TBI patients.

In contrast to the Pearson analysis, the Spearman correlation matrix revealed more pronounced negative associations. In Figure 2B, the results of a correlation analysis using the Spearman correlation coefficient are presented. Overall, both figures demonstrate consistency in the correlations among multiple indicators. For instance, there remains a significant positive correlation among inflammatory markers, especially between the counts of neutrophils and monocytes, which are related to inflammation. However, some negative correlations between variables are more pronounced, particularly in the deeper red areas (Figure 2B). For example, the negative correlation between albumin and inflammatory markers is stronger, which may reflect the clinical trend that as inflammatory responses intensify, albumin levels tend to decrease. Furthermore, negative correlations between lipid variables and coagulation indicators are also more evident, suggesting that as lipid levels fluctuate, there may be an associated impact on coagulation profiles.

Survival Outcomes Stratified by Operation and Tracheostomy Status

In Figure 3A, the Kaplan–Meier (KM) curve of 14-day mortality by operation status shows a marked difference between the non-operation group (blue line) and the operation group (red line), with higher survival probability observed in the non-operation group ($p < 0.0001$). In contrast, Figure 3B presents the KM curve of 14-day mortality by tracheostomy status, which shows no significant difference between the non-tracheostomy and tracheostomy groups, with similar survival probabilities ($p = 0.3$).

When examining the 30-day mortality, the KM curve by operation status continues to show a significant difference ($p < 0.0001$). The survival probability of the non-operation group is higher than that of the operation group, indicating a statistically significant difference (Figure 3C). Conversely, the KM curve for 30-day mortality by tracheostomy status

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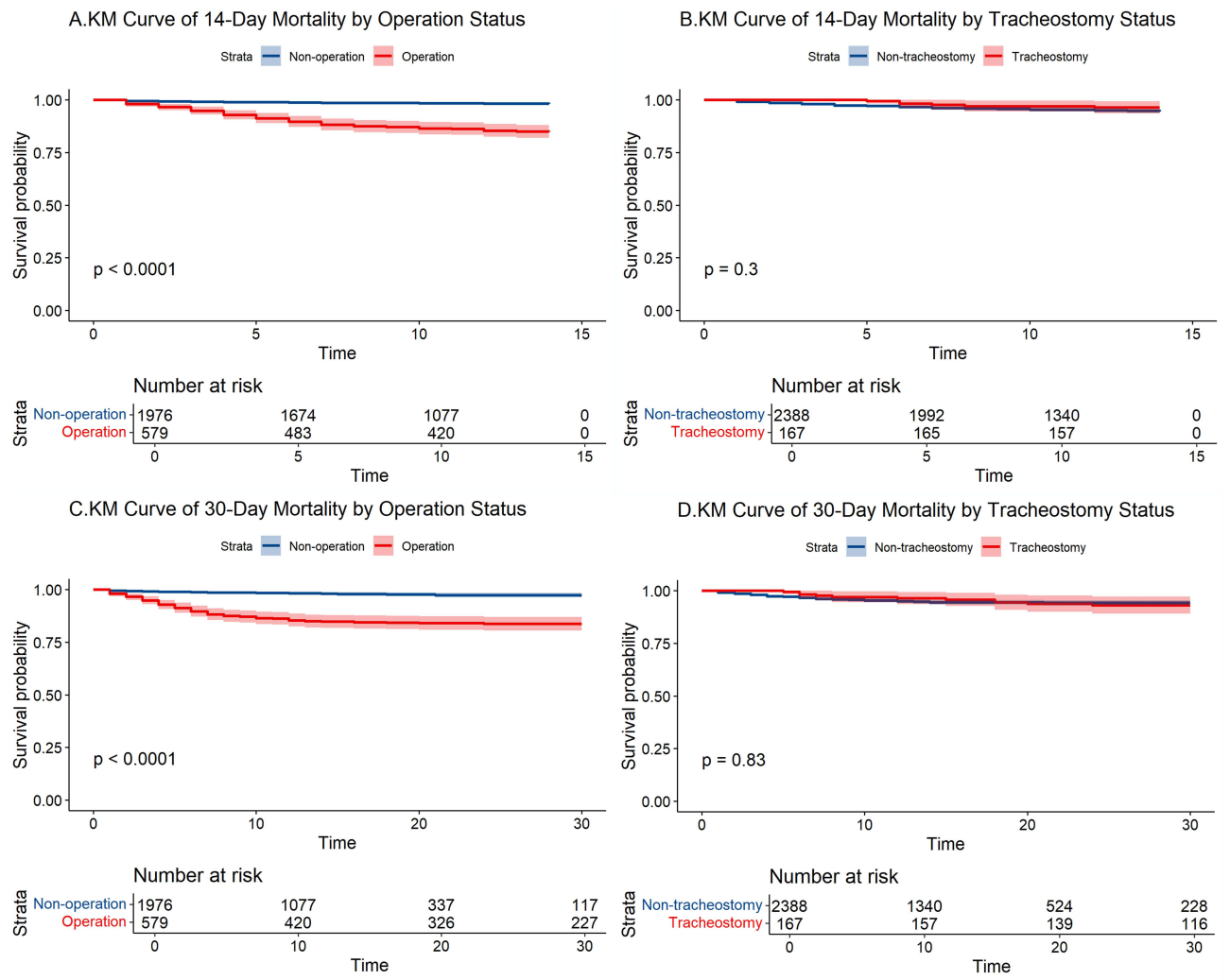

Figure 3 Kaplan-Meier survival curves for mortality outcomes stratified by intervention type. (**A**) 14-day mortality by operation status, showing significantly lower survival in the operation group (red) than in the non-operation group (blue). (**B**) 14-day mortality by tracheostomy status, showing no significant difference in survival. (**C**) 30-day mortality by operation status, again indicating higher mortality in the operation group. (**D**) 30-day mortality by tracheostomy status, with no statistically significant survival difference.

reveals a non-significant difference ($p = 0.83$), which is consistent with the 14-day analysis, suggesting that tracheostomy status does not significantly influence 30-day mortality rates (Figure 3D).

Key Predictors of Short- and Mid-Term Mortality

The results of the Cox proportional hazards regression analysis are presented in Table 2, Supplementary Tables 1 and 2. The hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values for inflammatory factors at 14 days, 30 days, and at discharge are shown. The impact of surgical intervention is particularly noteworthy, with operation status demonstrating a substantial increase in the risk of mortality, reaching statistical significance at 30 days (HR = 2.72, 95% CI: 1.04, 7.14, $p = 0.042$) and at discharge (HR = 3.10, 95% CI: 1.24, 7.79, $p = 0.016$). However, the operation status was not significant at 14 days when adjusting for other variables, compared to the KM curve analysis in Figure 3. This suggests that patients undergoing surgery may face a higher likelihood of mortality when considering midterm-term prognosis, which is an important consideration in clinical decision-making.

Tracheostomy, on the other hand, is associated with a significantly reduced risk of mortality across all time points, with the most pronounced effect observed at discharge (HR = 0.32, 95% CI: 0.12, 0.87, $p = 0.026$). This indicates that tracheostomy may be a beneficial procedure in reducing mortality risk in this patient population. Hemoglobin levels also

Table 2 Cox Proportional Hazards Regression Analysis of Inflammatory Factors at 14 days, 30 days, and at Discharge, Under Model 3

	14-Day			30-Day			At Discharge		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Sex	2.25	(0.87, 5.83)	0.096	2.03	(0.81, 5.14)	0.133	1.99	(0.86, 4.63)	0.109
Age	1.02	(0.99, 1.05)	0.130	1.02	(1.00, 1.05)	0.075	1.02	(1.00, 1.05)	0.094
Operation	2.53	(0.94, 6.83)	0.067	2.72	(1.04, 7.14)	0.042	3.10	(1.24, 7.79)	0.016
Tracheostomy	0.25	(0.07, 0.88)	0.030	0.34	(0.11, 1.03)	0.057	0.32	(0.12, 0.87)	0.026
Potassium	1.51	(0.74, 3.08)	0.257	1.42	(0.72, 2.83)	0.315	1.24	(0.65, 2.35)	0.511
Magnesium	34.81	(0.37, 3314.20)	0.127	12.47	(0.14, 1072.80)	0.267	2.98	(0.05, 180.33)	0.602
Sodium	1.07	(0.94, 1.21)	0.315	1.06	(0.94, 1.19)	0.366	1.07	(0.96, 1.20)	0.218
Phosphorus	0.84	(0.24, 2.93)	0.779	0.74	(0.22, 2.56)	0.637	0.72	(0.23, 2.28)	0.578
PT	4.69	(0.43, 51.58)	0.206	4.73	(0.41, 54.37)	0.212	4.89	(0.57, 42.27)	0.149
APTT	1.03	(0.99, 1.07)	0.112	1.03	(0.99, 1.07)	0.092	1.03	(0.99, 1.07)	0.095
INR	0.00	(0.00, 27768.28)	0.231	0.00	(0.00, 41819.05)	0.236	0.00	(0.00, 1294.32)	0.171
FIB	0.99	(0.59, 1.67)	0.969	1.07	(0.67, 1.72)	0.775	0.96	(0.58, 1.61)	0.890
D-Dimer	1.01	(0.99, 1.02)	0.223	1.01	(1.00, 1.03)	0.185	1.01	(0.99, 1.02)	0.302
HB	1.03	(1.01, 1.05)	0.013	1.02	(1.00, 1.04)	0.062	1.01	(1.00, 1.03)	0.088
Calcium	0.07	(0.00, 1.22)	0.068	0.15	(0.01, 2.40)	0.180	0.22	(0.02, 2.84)	0.246
TG	0.89	(0.33, 2.42)	0.826	1.16	(0.52, 2.56)	0.722	1.13	(0.51, 2.49)	0.764
HDL-C	3.52	(1.01, 12.30)	0.049	3.70	(1.09, 12.62)	0.036	3.45	(1.06, 11.28)	0.040
LDL-C	0.16	(0.06, 0.43)	0.000	0.16	(0.06, 0.41)	0.000	0.25	(0.11, 0.59)	0.001
APOB/A1	12.68	(2.28, 70.55)	0.004	12.28	(2.46, 61.34)	0.002	8.62	(1.90, 39.08)	0.005
CYS-C	0.99	(0.95, 1.04)	0.806	1.00	(0.96, 1.04)	0.883	1.00	(0.96, 1.04)	0.914
ALT	0.99	(0.96, 1.01)	0.333	0.99	(0.96, 1.01)	0.354	0.99	(0.97, 1.01)	0.374
AST	1.01	(0.99, 1.02)	0.259	1.01	(0.99, 1.02)	0.322	1.00	(0.99, 1.02)	0.456
Cr	1.00	(0.99, 1.01)	0.881	1.00	(0.99, 1.01)	0.624	1.00	(0.99, 1.01)	0.626
BUN	0.94	(0.74, 1.19)	0.626	0.94	(0.75, 1.17)	0.575	0.98	(0.80, 1.20)	0.852
UA	1.00	(1.00, 1.01)	0.141	1.00	(1.00, 1.01)	0.211	1.00	(1.00, 1.01)	0.199
SIRI	0.99	(0.93, 1.06)	0.795	1.01	(0.95, 1.07)	0.845	1.00	(0.95, 1.05)	0.993
TYG	2.67	(1.03, 6.95)	0.044	2.09	(0.88, 5.00)	0.096	1.99	(0.86, 4.61)	0.109
SII	1.00	(1.00, 1.00)	0.503	1.00	(1.00, 1.00)	0.910	1.00	(1.00, 1.00)	0.623
NLR	0.97	(0.91, 1.04)	0.455	0.95	(0.89, 1.02)	0.174	0.95	(0.89, 1.01)	0.112
PLR	1.01	(1.00, 1.01)	0.118	1.00	(1.00, 1.01)	0.338	1.00	(1.00, 1.01)	0.244
LMR	0.74	(0.40, 1.38)	0.345	0.80	(0.45, 1.41)	0.436	0.74	(0.43, 1.27)	0.273
NPR	1.12	(1.05, 1.21)	0.001	1.12	(1.04, 1.20)	0.002	1.13	(1.05, 1.20)	0.000

show a significant relationship with mortality, with higher levels correlating with increased risk at 14 days (HR = 1.03, 95% CI: 1.01, 1.05, $p = 0.013$). Lipid profiles, specifically HDL-C and LDL-C, exhibit significant associations with mortality rates. Higher HDL-C levels are linked to increased mortality risk at 14 days (HR = 3.52, 95% CI: 1.01, 12.30, $p = 0.049$) and 30 days (HR = 3.70, 95% CI: 1.09, 12.62, $p = 0.036$), while lower LDL-C levels are associated with reduced mortality risk at all time points, with the most significant reduction observed at 14 days (HR = 0.16, $p < 0.0001$) and 30 days (HR = 0.16, $p < 0.0001$).

APOB/A1 ratio levels are significantly associated with higher mortality risk, with the strongest effect at 14 days (HR = 12.68, 95% CI: 2.28, 70.55, $p = 0.004$). This suggests that APOB/A1 ratio may be a valuable biomarker for predicting mortality risk. TYG indicates a significant association with mortality within the short term of 14 days, where a higher TYG index is linked to an increased risk of mortality, with an HR of 2.67 (95% CI: 1.03, 6.95, $p = 0.044$). This suggests that the TYG index could serve as a valuable early predictor of mortality risk in the acute phase post-admission. However, this association does not persist in the mid-term, as evidenced by the non-significant HRs at 30 days (HR = 2.09, 95% CI: 0.88, 5.00, $p = 0.096$) and at discharge (HR = 1.99, 95% CI: 0.86, 4.61, $p = 0.109$). The NPR also shows a significant association with increased mortality risk across all time points, with the highest HR observed at discharge (HR = 1.13, 95% CI: 1.05, 1.20, $p < 0.0001$). This indicates that NPR could be a useful prognostic indicator in clinical practice.

To evaluate the predictive power of different biomarker categories, we constructed three separate multivariate Cox regression models. Model 1 included demographic and clinical variables (age, sex, operation status, and tracheostomy); Model 2 added metabolic indicators (eg, HDL-C, LDL-C, APOB/A1 ratio, and TYG index); and Model 3 further incorporated inflammatory markers (eg, NPR, NLR, and PLR). This stepwise approach allowed us to assess the incremental value of metabolic and inflammatory biomarkers in predicting mortality risk at different time points. The ROC curves presented in Figure 4 provide a comprehensive assessment of the predictive accuracy of three distinct models for 14-day, 30-day, and discharge mortality outcomes. For the 14-day mortality prediction (Figure 4A), Model 3 demonstrates the highest AUC of 0.904, indicating superior discriminative power compared to Model 1 (AUC = 0.796) and Model 2 (AUC = 0.876). This suggests that Model 3 has a better ability to distinguish between patients who will and will not experience mortality within 14 days. At the 30-day mark (Figure 4B), Model 3 shows the most promise with an AUC of 0.897, closely followed by Model 2 (AUC = 0.875), and then Model 1 (AUC = 0.770). The higher AUC values for Models 3 and 2 indicate that these models are more effective in predicting 30-day mortality, which is crucial for medium-term patient risk assessment.

Upon discharge, Model 3 again outperforms the others with an AUC of 0.897, while Model 2 has an AUC of 0.857, and Model 1 has the lowest AUC of 0.774 (Figure 4C). The consistently high AUC for Model 3 across all time points suggests that it incorporates variables that are particularly informative for predicting patient survival. Overall, the ROC analysis indicates that Model 3 incorporating metabolic and inflammatory markers has the most robust predictive performance for mortality outcomes at 14 days, 30 days, and at discharge.

The nomograms presented in Figures 5–7 provide a systematic approach to predicting mortality risks at 14-day (Figure 5), 30-day (Figure 6), and discharge (Figure 7) time points using optimal models established in Figure 4. Each nomogram incorporates a range of clinical variables, allowing for a personalized assessment of patient risk. The variables included are tracheostomy, operation status, HB levels, HDL-C, LDL-C, APOB/A1 ratio, TYG index, and NPR.

The 14-day nomogram (Figure 5) serves as a critical tool for early risk stratification, emphasizing factors like tracheostomy and hemoglobin levels, which are particularly impactful in the immediate post-acute phase. The points allocated for these variables are indicative of their influence on short-term outcomes, with tracheostomy showing a significant impact on reducing the risk of early mortality. In contrast, the 30-day (Figure 6) and discharge (Figure 7) nomograms incorporate operation status, reflecting the midterm-term implications of surgical interventions on patient survival. These models demonstrate a shift in emphasis toward factors that have a sustained influence on patient outcomes over time. The operation status variable, in particular, underscores the importance of surgical decisions in the trajectory of patient recovery and survival.

The consistent inclusion of HDL-C, LDL-C, APOB/A1 ratio, and NPR across all nomograms underscores their enduring relevance in predicting mortality risks. However, the points assigned to these variables vary, reflecting the changing significance of these factors over time. For instance, HDL-C and LDL-C maintain their importance, but the

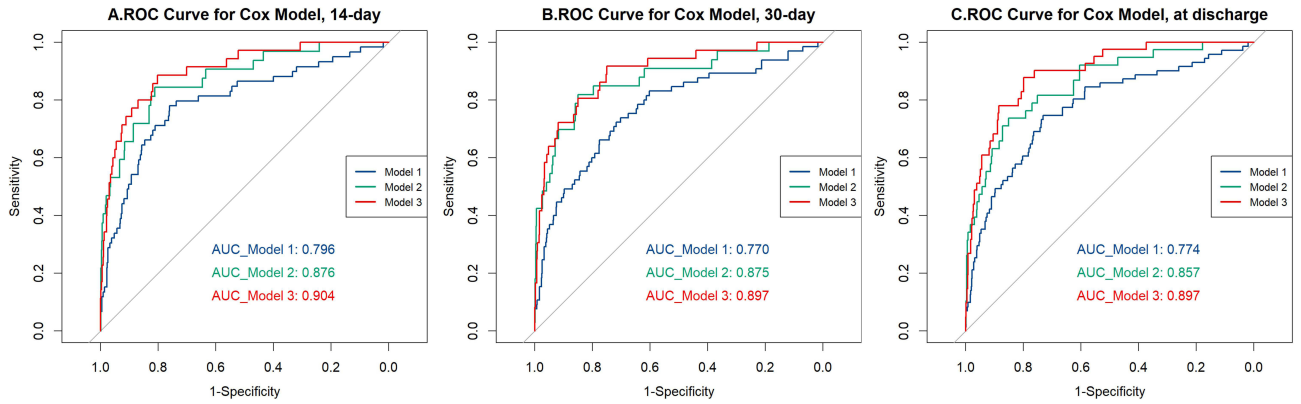

Figure 4 Comparison of ROC curves for three Cox models predicting mortality. (**A**) ROC curves for 14-day mortality prediction. Model 3 outperforms Model 1 and Model 2 with the highest AUC. (**B**) ROC curves for 30-day mortality, again showing Model 3 with superior discriminative performance. (**C**) ROC curves for mortality at discharge, where Model 3 continues to show the highest AUC.

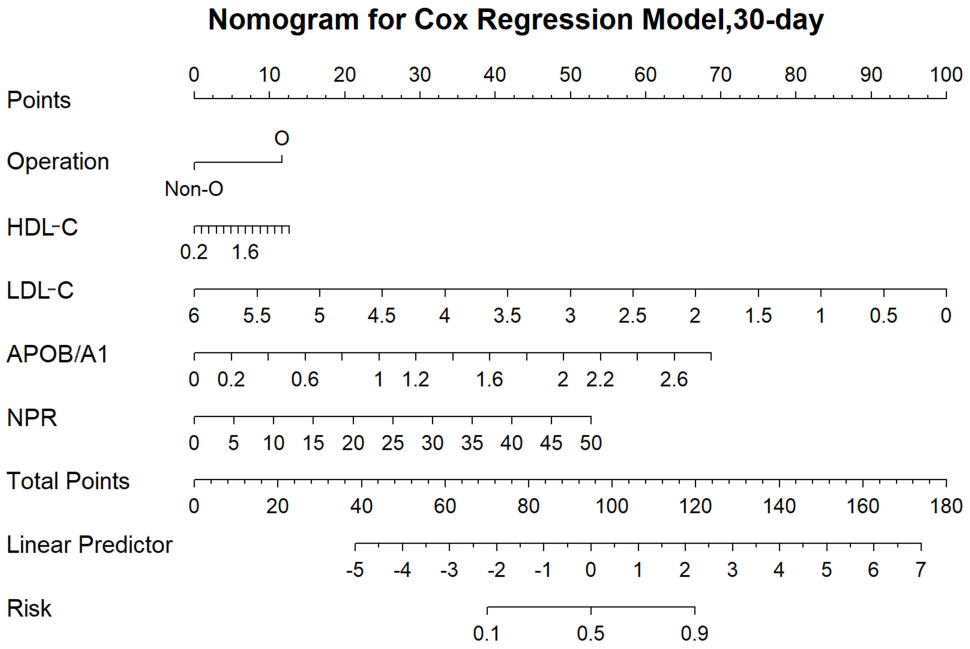

Figure 5 Nomogram for predicting 14-day mortality in TBI patients.

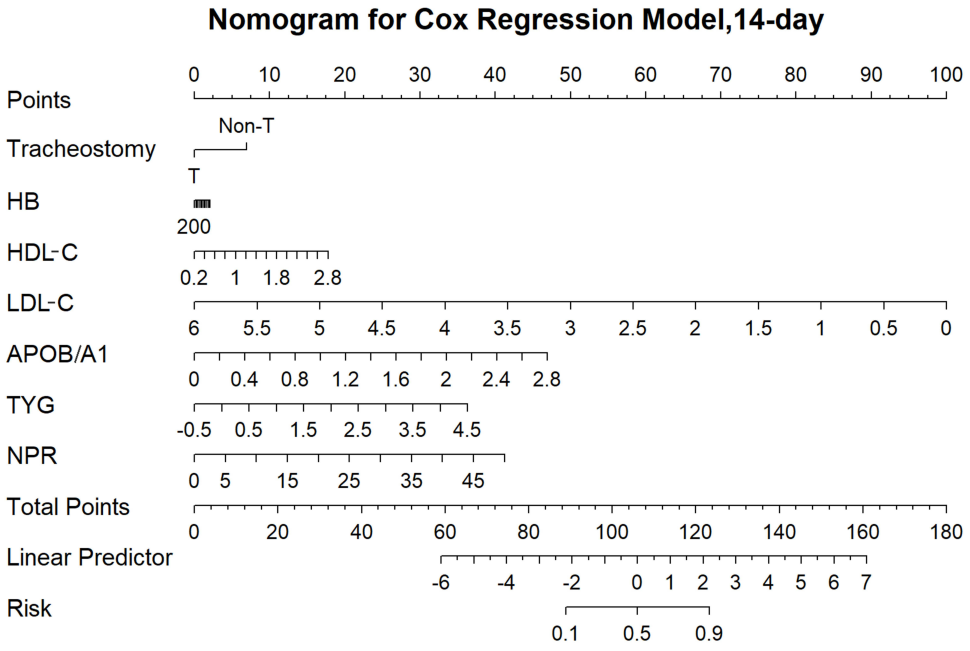

Figure 6 Nomogram for predicting 30-day mortality in TBI patients.

points allocated suggest a nuanced influence that is context-dependent on the time frame considered. This distinction is vital for clinical decision-making, as it allows healthcare providers to focus on the most relevant factors at each stage of patient care.

Impact of Biomarkers in Surgical vs Non-Surgical Subgroups

In the subgroup analysis detailed in Table 3, we delved into the modifying effects of specific variables on mortality within distinct subgroups of patients stratified by operational intervention. We observed subgroup differences in the

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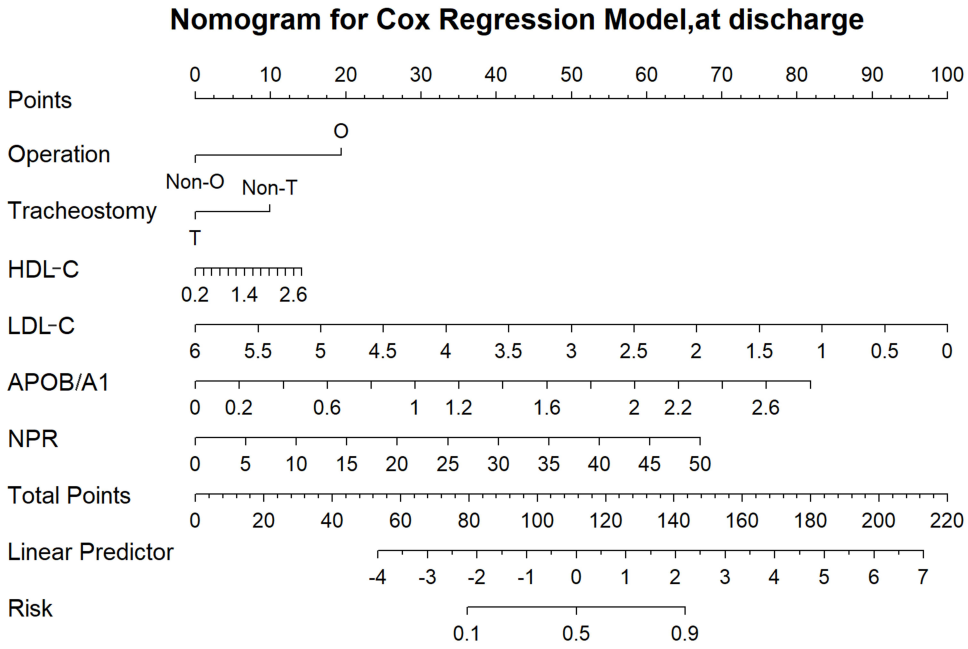

Figure 7 Nomogram for predicting in-hospital mortality at discharge.

impact of various factors on mortality at 14 days, 30 days, and discharge. In the non-operation group, TYG was significantly associated with mortality risk, consistent with the findings in the overall population in Table 2 where TYG was a risk factor (14-day HR = 2.71, 95% CI: 1.21 to 6.06; $p = 0.015$; 30-day HR = 2.43, 95% CI: 1.11 to 5.30; $p = 0.026$; discharge HR = 2.41, 95% CI: 1.10 to 5.28; $p = 0.028$), which may reflect the adverse impact of metabolic disturbances on prognosis in the non-operation group. However, this association was not significant in the operation group. In both subgroups, TYG showed a trend of gradually diminishing effects on prognosis with increasing hospital stay, which verified that TYG is more suitable as a short-term predictor.

Additionally, NPR was significantly associated with mortality risk in the non-operation group (14-day HR = 2.22, 95% CI: 1.42 to 3.48; $p < 0.001$; 30-day HR = 2.12, 95% CI: 1.39 to 3.24; $p = 0.000$; discharge HR = 2.15, 95% CI: 1.41

Table 3 Subgroup Analysis of Significant Factors Under Different Operational States Identified in Cox Regression at 14 days, 30 days, and at Discharge

		14-Day			30-Day			At Discharge		
		HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Operation	Tracheostomy	0.13	(0.04, 0.43)	0.001	0.27	(0.11, 0.66)	0.004	0.30	(0.14, 0.65)	0.002
	HB	1.06	(0.78, 1.45)	0.712	1.03	(0.77, 1.36)	0.857	1.04	(0.80, 1.35)	0.768
	HDL-C	1.23	(0.85, 1.78)	0.283	1.22	(0.85, 1.76)	0.272	1.23	(0.87, 1.72)	0.243
	LDL-C	0.48	(0.27, 0.87)	0.015	0.51	(0.30, 0.90)	0.019	0.62	(0.37, 1.03)	0.065
	APOB/A1	1.08	(0.83, 1.41)	0.565	1.06	(0.82, 1.38)	0.630	1.08	(0.84, 1.39)	0.553
	TYG	1.12	(0.69, 1.81)	0.651	1.03	(0.68, 1.57)	0.888	1.01	(0.67, 1.50)	0.970
	NPR	0.97	(0.78, 1.20)	0.771	1.00	(0.81, 1.24)	0.967	1.02	(0.84, 1.23)	0.876
Non-operation	Tracheostomy	1.74	(0.44, 6.84)	0.428	2.10	(0.64, 6.83)	0.219	2.16	(0.66, 7.03)	0.201
	HB	1.08	(0.68, 1.71)	0.747	0.95	(0.65, 1.39)	0.795	0.95	(0.65, 1.40)	0.808
	HDL-C	1.05	(0.58, 1.92)	0.867	1.03	(0.56, 1.90)	0.916	1.04	(0.57, 1.91)	0.892
	LDL-C	1.07	(0.49, 2.33)	0.857	1.09	(0.49, 2.38)	0.838	1.07	(0.49, 2.35)	0.863
	APOB/A1	1.13	(0.66, 1.93)	0.664	1.10	(0.65, 1.87)	0.717	1.11	(0.66, 1.88)	0.689
	TYG	2.71	(1.21, 6.06)	0.015	2.43	(1.11, 5.30)	0.026	2.41	(1.10, 5.28)	0.028
	NPR	2.22	(1.42, 3.48)	0.000	2.12	(1.39, 3.24)	0.000	2.15	(1.41, 3.28)	0.000

to 3.28; $p = 0.000$), whereas this association was not significant in the operation group. Moreover, the HR for NPR in the non-operation group was higher than that in the overall population. This suggests that NPR may be a stable, mid-term predictor of mortality risk in non-operation TBI patients. In the surgical group, patients who underwent tracheostomy had a lower mortality risk, with HRs of 0.13 (95% CI: 0.04 to 0.43; $p = 0.001$), 0.27 (95% CI: 0.11 to 0.66; $p = 0.004$), and 0.30 (95% CI: 0.14 to 0.65; $p = 0.002$) at 14 days, 30 days, and discharge, respectively. This indicates that tracheostomy may be an effective intervention to reduce short-term and mid-term mortality risk in operational TBI patients.

Discussion

This retrospective cohort study investigated the prognostic value of inflammatory biomarkers in predicting mortality among patients with TBI. Our results demonstrate that surgical TBI patients exhibit distinct biochemical patterns, including elevated neutrophil counts, altered coagulation parameters, and significant variations in lipid metabolism compared to non-surgical patients. The Results of the multivariate Cox regression models indicate that inflammatory markers such as the TYG and NPR show strong associations with both short- and mid-term mortality. The predictive model that incorporates these inflammatory markers shows a higher AUC, highlighting their potential role as predictive biomarkers. The integration of these markers into clinical practice could facilitate more effective risk stratification and tailored therapeutic approaches, improving patient outcomes in the management of TBI.

The TYG index emerged as a significant predictor of short-term mortality.[18] In this study, we found that elevated TYG values were strongly associated with an increased risk of death within the first 14 days following injury. The TYG index, calculated from fasting triglyceride and glucose levels, serves as a surrogate marker of insulin resistance and metabolic stress.[18] Insulin resistance, commonly triggered by acute trauma, promotes a pro-inflammatory state by impairing glucose uptake, enhancing lipolysis, and increasing free fatty acid levels.[19] These metabolic disruptions lead to oxidative stress, mitochondrial dysfunction, and systemic inflammation—all of which are known to exacerbate secondary brain injury. Moreover, hyperglycemia and elevated triglycerides themselves are independently associated with endothelial dysfunction and immune dysregulation, both of which can worsen outcomes after TBI.[20] Inflammatory cytokines, such as IL-6 and TNF-α, are often elevated in patients with high TYG values, reinforcing the mechanistic link between TYG, systemic inflammation, and mortality risk.[18,20] Therefore, the TYG index may not only reflect metabolic burden but also serve as an early indicator of heightened inflammatory response, which contributes to poor prognosis in TBI patients. Our observation is consistent with previous reports linking the TYG index to adverse outcomes across a range of health conditions, supporting its potential role as a reliable indicator of systemic health and metabolic status in critically ill patients.[19] Inflammatory responses following TBI can lead to a cascade of events that exacerbate brain injury, making the identification of reliable biomarkers essential for early intervention and management. Given its simplicity, cost-effectiveness, and predictive value, the TYG index could serve as a practical tool for early risk stratification and guiding acute clinical interventions in TBI patients. For instance, patients with elevated TYG indices could be prioritized for interventions aimed at mitigating inflammation and improving metabolic control, potentially leading to better outcomes.[21]

The NPR has been identified as a consistent predictor of mortality across various time points in patients with TBI, highlighting its significance as both a short- and medium-term prognostic marker.[22] The NPR integrates two critical components of the body's response to TBI: neutrophils, which are key mediators of inflammation, and platelets, which play a vital role in clot formation and maintaining vascular integrity.[23] Elevated NPR values indicate heightened systemic inflammation and increased disruption of the blood-brain barrier, both of which are associated with secondary brain injury and poor clinical outcomes.[24] High NPR values reflect an exacerbated inflammatory response, which can lead to further complications following the initial injury. The inflammatory cascade initiated by TBI can result in the release of pro-inflammatory cytokines and chemokines, contributing to neuronal damage and impairing recovery.[25] Studies showed that an NPR greater than 7.44 has been identified as an independent risk factor for mortality in intensive care unit (ICU) settings, underscoring the importance of monitoring this biomarker in critically ill TBI patients.[26,27] Although neutrophils do not typically cross the intact blood-brain barrier (BBB), TBI leads to its disruption, permitting the infiltration of peripheral immune cells—including neutrophils—into the brain parenchyma.[28] This process plays a pivotal role in the propagation of neuroinflammation. Once inside the CNS, neutrophils release reactive oxygen species, proteolytic

enzymes, and pro-inflammatory cytokines that exacerbate neuronal injury and contribute to secondary damage.[28] Additionally, neutrophils can interact with resident microglia and endothelial cells, amplifying the inflammatory cascade.[28] The NPR, as a circulating biomarker, reflects this peripheral immune activation and the imbalance between pro-inflammatory neutrophils and platelets, the latter of which are also involved in BBB integrity and cerebral microcirculation.[29] Therefore, a high NPR may indirectly indicate the extent of BBB breakdown and neuroinflammatory burden after TBI.

The differential predictive capabilities of the TYG and the NPR in TBI patients are of particular interest, with TYG acting as a short-term predictor and NPR as a mid-term predictor. The TYG index is a marker of metabolic stress and insulin resistance, which are often exacerbated in the acute phase of critical illness, including TBI.[20,30] The TYG index reflects the acute phase response to trauma, where inflammation and metabolic dysregulation are most pronounced.[30] As such, it serves as a reliable short-term predictor, identifying patients who are at immediate risk of worsening outcomes within the first few days to weeks following injury. Once the acute metabolic derangements are addressed, and inflammation is controlled, the predictive power of TYG diminishes. In contrast, NPR is more reflective of chronic or ongoing inflammatory and immune responses.[24] Elevated NPR values suggest persistent systemic inflammation and endothelial dysfunction, which can contribute to secondary brain injury and impair recovery over an extended period.[23,24] Ongoing inflammation can result in neuroinflammation, neuronal damage, and delayed recovery.[24] As a result, NPR acts as a more stable mid-term prognostic marker, reflecting the prolonged inflammatory burden and its impact on recovery. Additionally, NPR's association with vascular integrity and the blood-brain barrier makes it relevant for predicting long-term outcomes, as chronic inflammation can lead to persistent neurovascular disruption, impairing brain function and recovery in the months after the injury.[25]

TYG and NPR were identified as markers of inflammation and immune response, showing an association with mortality in the overall population.[18,30] However, in subgroup analysis, their relationship with mortality differed between the operation and non-operation subgroups. In the non-operation group, the TYG index likely reflects the severity of metabolic stress and inflammatory response induced by trauma. Elevated TYG values may be associated with insulin resistance, hyperglycemia, and hypertriglyceridemia, all of which are markers of inflammation and poor prognosis.[18,19] Operation intervention may reduce the association between TYG and mortality by mitigating metabolic stress through control of direct injury, reduction in intracranial pressure, and improvement in local cerebral blood flow.[18] Furthermore, operational patients may benefit from more aggressive inflammation control and metabolic regulation, including the use of antibiotics, analgesics, and nutritional support, which could attenuate the adverse effects of elevated TYG.[21]

For NPR, in the non-operation group, the ratio likely reflects the activation of systemic inflammation and coagulation pathways due to TBI. Elevated NPR values may indicate the activation of inflammatory cells and vascular endothelial damage, which could be more pronounced in the absence of operational intervention.[24] Surgery offers an opportunity to directly control inflammation and coagulation processes through debridement of damaged tissue, reduction of inflammatory mediators, and improvement in local blood flow. These mechanisms may explain why TYG and NPR remain significant risk factors for mortality in the non-operation subgroup, but not in the operation subgroup.

This study highlights the APOB/A1 ratio as a novel prognostic marker for mortality, particularly within the first 14 days following the injury. A higher APOB/A1 ratio indicates an imbalance in lipid metabolism, which is associated with a pro-inflammatory and pro-thrombotic environment.[31] This finding is significant because it suggests that lipid-related processes may play a critical role in the pathophysiology of TBI, particularly in relation to neuroinflammation and endothelial dysfunction.[31,32]

The APOB/A ratio has been previously established as a predictive marker in cardiovascular diseases, where it reflects the balance between atherogenic (LDL-C and APO-B) and athero-protective (HDL-C and APO-A1) lipoproteins.[33,34] In the context of TBI, the relevance of this ratio underscores the broader implications of lipid metabolism in the inflammatory response following brain injury. Elevated levels of APO-B and a corresponding decrease in APO-A1 can lead to increased vascular permeability and inflammation, which may exacerbate neuronal damage and hinder recovery.[35,36] Future research should focus on validating this ratio in larger cohorts and exploring its potential as a therapeutic target in the management of TBI.[37,38]

Our study, while yielding significant findings, acknowledges its inherent limitations. The retrospective design limits our ability to establish causality. Future studies should focus on validating these factors in larger, prospective cohorts, with an emphasis on long-term follow-up, such as survival rates at 1-year and 3-year intervals. This would provide a more comprehensive understanding of the sustained prognostic value of these markers. Besides, the treatments and interventions that patients receive in both the non-surgical and surgical subgroups may differ, which could influence the relationship between TYG, NPR, and patient outcomes. Furthermore, the pathophysiology of TBI is highly complex, involving a range of cellular and molecular pathways. Our study may not have fully captured the intricate interactions, particularly in terms of inflammation and immune response. Future research could explore more advanced techniques, such as network analysis, to better understand these complex relationships and their effects on outcomes.

Conclusion

This study underscores the prognostic significance of metabolic and inflammatory biomarkers in TBI, with the TYG, NPR index, and APOB/A1 ratio emerging as promising tools for mortality risk stratification. These findings provide a foundation for further research into the underlying mechanisms and clinical validation in prospective studies. Ultimately, incorporating these biomarkers into clinical practice could enhance the early identification of high-risk patients and inform targeted therapeutic strategies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Ethics Approval and Consent to Participate

The study was authorized by the Ethical Board of the Affiliated Kunshan Hospital of Jiangsu University, Suzhou, China (approval # 2022-06-025) and followed the Helsinki Declaration. To ensure an unbiased investigation, patients' identities were not revealed and a signed written consent form was acquired from all the participants.

Consent for Publication

The patient provided written informed consent for publication.

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 report no conflicts of interest in this work.

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