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Immune and Inflammatory Predictors of Massive Transfusion and Clinical Outcomes in Patients with Severe Trauma

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ABSTRACT

Massive blood transfusion (MBT) in severe trauma represents a major emergency-care challenge associated with high mortality and poor clinical outcomes. This retrospective cohort study enrolled 186 severe trauma patients treated at Xianning Central Hospital from January 2020 to January 2024, who were stratified into massive blood transfusion (MBT, ≥10 units RBCs within 24 h, n=72) and non-MBT (n=114) groups.

The observed indicators included immune markers $CD4^+$:$CD8^+$ ratio, natural killer (NK) cells, immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM); inflammatory markers white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6); trauma severity assessment indicators Injury Severity Score (ISS) and modified Trauma Induced Coagulopathy Clinical Score (mTICCS); and clinical events including transfusion adverse events and mechanical ventilation duration. Logistic regression identified independent MBT predictors; receiver operating characteristic (ROC) curves evaluated their predictive performance.

The two groups showed comparable baseline characteristics. The MBT group presented a lower $CD4^+/CD8^+$ ratio, higher NLR, inflammatory factors, ISS and mTICCS, as well as more transfusion adverse events and longer ventilation duration. NLR≥ 9.5, $CD4^+/CD8^+$ ≤0.7, ISS≥25, and mTICCS≥12 were independent MBT predictors. ROC analysis revealed favorable predictive performance for these indicators, with the highest AUC of 0.810 for mTICCS, followed by NLR (0.806) and $CD4^+$:$CD8^+$ ratio (0.800), with no significant predictive differences among them via DeLong test.

This study demonstrates that admission immune-inflammatory status and trauma severity are reliable early biomarkers for predicting MBT in severe trauma patients.

Keywords: Immune markers; Inflammatory markers; Massive transfusion; Severe trauma

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INTRODUCTION

Trauma is a leading cause of premature mortality and morbidity in young and middle-aged populations, imposing immense socioeconomic burdens on global healthcare systems.[1,2] Severe trauma is commonly caused by high-energy injury and typically accompanied by multiple fractures, visceral rupture, and major vascular injury.[3] Massive blood transfusion (MBT) is a lifesaving intervention for severe hemorrhagic shock, which rapidly restores blood volume and oxygenation, stabilizes coagulation, and facilitates damage control resuscitation.[4] Although optimized MBT reduces early trauma mortality, transfusion-related immune suppression, uncontrolled inflammation, infection, and acute organ injury markedly impair patient prognosis.[5,6] Therefore, accurate early identification of patients requiring MBT is critical to rationalize transfusion strategies and improve clinical outcomes.

Immune and inflammatory disturbance constitutes the core pathophysiological feature of severe trauma. Traumatic ischemia-reperfusion injury and hemorrhagic shock concurrently activate innate immunity and suppress adaptive immune responses.[7,8] The excessive release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), drives systemic inflammatory response syndrome (SIRS), while decreased $CD4^+/CD8^+$ ratio, impaired natural killer (NK) cell activity, and declined immunoglobulin collectively induce persistent immunosuppression.[9] This dual pathological state exacerbates tissue damage, endothelial leakage, and coagulation dysfunction, thereby increasing hemorrhage severity and MBT dependence.

Immune-inflammatory biomarkers have been increasingly applied for trauma risk stratification.[10] Cellular immune indicators ($CD4^+/CD8^+$, NK cell activity), humoral immune indexes [immunoglobulin (Ig) G, IgA, IgM], and inflammatory markers [white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), IL-6, TNF-α] effectively reflect post-traumatic immune homeostasis and inflammatory severity.[11] Nevertheless, conventional trauma scoring systems present obvious inherent limitations: the Injury Severity Score (ISS) only evaluates anatomical damage and ignores dynamic immune-inflammatory changes; the modified Trauma Induced Coagulopathy Clinical Score (mTICCS) relies on superficial clinical signs and lacks biological evidence support.[12] Clinicians still determine MBT dependence primarily based on personal experience and real-time laboratory results, leading to delayed judgment and inconsistent transfusion decision-making.[13]

Critically, current biomarker research has prominent methodological deficiencies. Existing relevant studies predominantly focus on the prognostic value of single inflammatory or immune indicators, lacking systematic combination screening and quantitative comparison of multiple immune-inflammatory markers.[14] Few studies have clarified their predictive efficiency for MBT requirement in severe trauma populations, and whether these biomarkers outperform traditional trauma scoring systems remains poorly validated. Given the close correlation between post-traumatic immune inflammation and hemorrhage progression, we hypothesized that peripheral immune-inflammatory biomarkers can serve as independent early predictors for MBT requirement; combined biomarker models exhibit superior predictive efficacy over single indicators and conventional trauma scores.

Accordingly, this retrospective cohort study enrolled severe trauma patients to screen MBT-related immune and inflammatory biomarkers. This study aimed to explore their early predictive value for MBT demand and compare their predictive performance with ISS and mTICCS. These findings may provide objective biological evidence for early MBT risk stratification and individualized transfusion management, to reduce transfusion-related adverse events and improve the survival rate of severely injured patients.

MATERIALS AND METHODS

Study Design

This retrospective study analyzed the medical records of 190 patients with severe trauma admitted to Xianning Central Hospital (China) between January 2020 and January 2024. Four patients were excluded based on the exclusion criteria, leaving 186 patients for the study. Patients were divided into MBT group (n=72) and non-MBT group (n=114) based on the occurrence of MBT as documented in their medical records (i.e., red blood cell transfusion≥10 units of red blood cells within 24 hours).[15] It is hypothesized that abnormal immune-inflammatory biomarkers on admission and a higher ISS are independently associated with an increased risk of MBT, and can serve as early predictive indicators for MBT. The primary endpoint was the occurrence of MBT within 24 hours after admission among patients with severe trauma.

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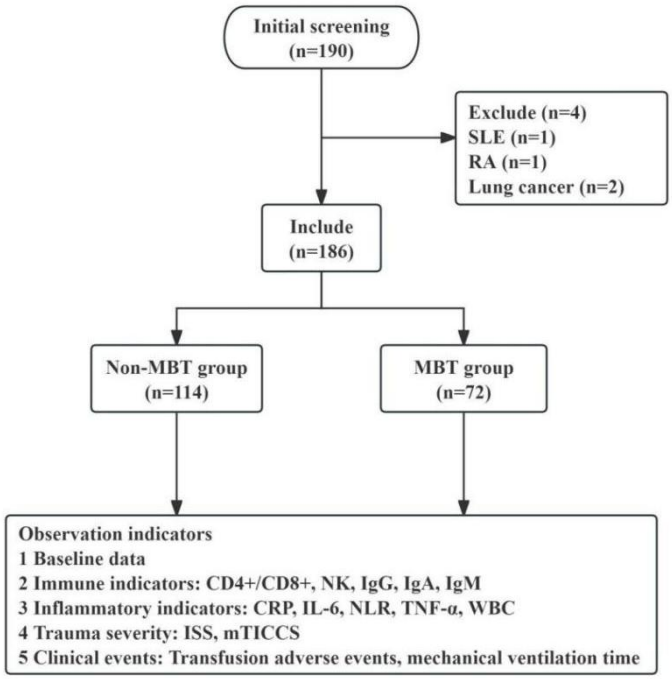

Figure 1. Research Flowchart. SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; MBT: massive blood transfusion; NK: natural killer cells; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; ISS: Injury Severity Score; mTICCS: modified Trauma Induced Coagulopathy Clinical Score; CD: cluster of differentiation.

Inclusion Criteria

(1) Patients with severe trauma with an ISS ≥ 16 at admission, in accordance with the Chinese Expert Consensus on Traumatic Hemorrhagic Shock in Emergency Medicine (2023).[15] Adopting authoritative consensus-based ISS cutoff ensures uniform definition of severe trauma and guarantees clinical homogeneity of enrolled subjects. (2) Patients with acute trauma caused by mechanical external forces, including traffic accidents, falls, crush injuries, and sharp/blunt force injuries, and with a time from injury to admission ≤ 24 hours. Restricting to mechanical acute trauma and a 24-hour admission window eliminates heterogeneity from non-mechanical causes and prolonged pre-hospital time. (3) Patients who completed relevant laboratory tests within 24 hours after admission, with test indicators including at least the immune markers of interest in this study, and with complete trauma scores (ISS score, mTICCS score), transfusion records, and clinical outcome data. This standardizes the time window for biomarker detection and ensures integrity of scoring, transfusion, and outcome data for subsequent statistical analysis. (4) Aged 18–75 years. This excludes physiological interference from minors and extremely elderly patients to reduce age-related confounding bias. (5) Patients who received standardized trauma care after admission without active abandonment of treatment or transfer to another hospital. This avoids deviations caused by inconsistent treatment strategies, abandoned therapy, and inter-hospital transfer, ensuring a consistent clinical intervention background.

Exclusion Criteria

(1) Patients with underlying immune or inflammatory diseases. This eliminates the confounding influence of pre-existing immune and inflammatory disorders on the study's immune markers. (2) Patients with severe underlying organ diseases. This avoids interference from chronic organ dysfunction on trauma progression, immune response, and clinical prognosis. (3) Patients with special injuries or conditions associated with trauma. This excludes rare or complex traumatic conditions that may cause case heterogeneity and affect result generalizability. (4) Patients with incomplete clinical data or non-standard diagnosis and treatment. This ensures data integrity and uniform diagnostic and

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therapeutic quality to guarantee the validity of statistical analysis. (5) Patients with severe infection, surgical history, or blood transfusion history within 3 months prior to admission. This rules out the residual effects of recent infection, surgery, and blood transfusion on baseline immune status. (6) Patients with severe infectious complications after trauma that occurred earlier than the decision-making time for MBT.[14] This prevents early trauma-related infection from interfering with the correlation analysis between MBT strategy and clinical outcomes.

Data Collection

This study is a retrospective cohort study. Data collection was conducted from January 2020 to January 2024. Two researchers, who had received unified training, independently completed data extraction. During the extraction process, they strictly followed a standardized data collection form. In case of data disputes, a third-party senior clinician reviewed and determined the results to ensure the accuracy and objectivity of data collection.

Observation Indicators

Baseline Data

(1) Demographic data: gender, age, weight, and past medical history; (2) Trauma-related information: cause of injury and time from injury to admission; (3) Admission vital signs: systolic blood pressure (SBP), heart rate (HR), consciousness status (Glasgow Coma Scale), and presence or absence of hemorrhagic shock. Hemorrhagic shock refers to hypovolemic shock caused by massive blood loss within a short period, leading to a sharp decrease in effective circulating blood volume, inadequate tissue perfusion, cellular hypoxia, and metabolic disorders. It is a critical clinical emergency. All baseline data were uniformly collected by trained emergency department researchers according to standardized case report forms; double data entry and cross-verification were performed to ensure the accuracy and consistency of demographic, traumatic, and vital sign information.

Immune and Inflammatory Markers

The first immune and inflammatory laboratory test results completed within 6 hours after admission were collected. All patients underwent venous blood collection,[16] of which 2 mL was injected into an anticoagulant tube for WBC, neutrophil count, lymphocyte count, T lymphocyte subsets, and NK cell detection; 5 mL was injected into a non-anticoagulant serum tube, and the serum was separated by centrifugation (3000 r/min, 10 minutes) (ST16R, Thermo Fisher Scientific, USA) for measurement of CRP, IgG, IgA, IgM, TNF-α, and IL-6.

Strict laboratory quality control was implemented: unified blood collection time, standardized specimen transportation, centrifugation, and storage procedures; all detection instruments were regularly calibrated, quality control serum was tested daily, and operation was performed by professional laboratory personnel following standard operating procedures to avoid pre-analytical and analytical errors.

(1) Immune markers: T lymphocyte subsets $CD4^+$ cell count, $CD8^+$ cell count, $CD4^+/CD8^+$ ratio, and NK cell percentage were detected using a flow cytometer (MACSQuant VYB, Miltenyi Biotec, Germany); serum concentrations of IgG, IgA, and IgM were assayed utilizing a fully automated biochemical analyzer (AU5800, Beckman Coulter, USA).

(2) Inflammatory markers: WBC, neutrophil count, and lymphocyte count were detected using a fully automated blood analyzer (XPT, Siemens Healthineers, Germany), and the NLR was calculated; serum CRP level was determined using a fully automated biochemical analyzer (AU5800, Beckman Coulter, USA); serum TNF-α and IL-6 levels were detected using an enzyme-labeling instrument (SpectraMax i3x, Molecular Devices, USA) via enzyme-linked immunosorbent assay.

Trauma Severity

Trauma severity scores were determined within 6 hours after the patient's admission.

(1) ISS: The human body is divided into 6 anatomical regions: head and neck, face, chest, abdomen/pelvis, extremities/pelvis, and body surface. First, the severity of injury in each region was assessed utilizing the Abbreviated Injury Scale (AIS) (AIS 1–6 points, corresponding to mild to severe injury, respectively). Then, the highest AIS score from the 3 most severely injured regions was squared and summed to obtain the total ISS score, with a total score range of 1–75. A score ≥ 16 indicates severe multiple traumas.[17]

(2) mTICCS: Its scoring details focus on clinically observable indicators, including rescue scene, circulatory status, and local injury. The total score is capped at 15 points. A higher score indicates a higher

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risk of post-traumatic coagulopathy and hemorrhagic shock, as well as a more urgent need for emergency transfusion and other resuscitative measures.[18]

All ISS and mTICCS scores were independently evaluated by two senior trauma physicians; any inconsistent scoring results were discussed and adjudicated by a third senior clinician to reduce subjective deviation and ensure scoring reliability.

Clinical Events

(1) Grouping criteria: Data on red blood cell transfusion volume, platelet transfusion volume, and fresh frozen plasma transfusion volume within 24 hours after admission were collected. Patients were stratified into the MBT group and the non-MBT group based on whether the 24-hour red blood cell transfusion volume was≥ 10 units.

(2) Transfusion adverse events: Transfusion adverse events were classified and judged in detail in accordance with the "Clinical Transfusion Technology Specifications", including febrile reactions, allergic reactions, hemolytic reactions, and other adverse events [transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), bacterial contamination reactions, etc].[19]

(3) Mechanical ventilation time: The total time from endotracheal intubation or tracheotomy to successful extubation was recorded.[20]

Clinical event data including transfusion volume, transfusion adverse events, and mechanical ventilation duration were retrospectively verified against electronic medical records and blood transfusion system data; unified diagnostic criteria were adopted for adverse event judgment to standardize grouping and outcome recording.

Ethical Statement

This study strictly complied with the Declaration of Helsinki[21] and has been endorsed by Xianning Central Hospital (China) Ethics Committee. In accordance with the relevant provisions of the "Measures for the Ethical Review of Life Science and Medical Research Involving Humans",[22] the application for waiving informed consent was endorsed by the Ethics Committee (Ethics Approval Number: K【2024】004).

Sample Size Calculation

Sample size estimation was performed using software (G*Power 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Germany). Based on previous study results,[23] the NLR level for transfused patients was 19.1 (12.1, 25.3), and for non-transfused patients was 13.7 (10.1, 16.8). Using the formula, Cohen's d was estimated to be 0.66. When $\alpha = 0.05$ (two-tailed) and $\beta = 0.05$, the calculation showed that one group required 51 patients and the other group required 77 patients. Considering potential data loss in retrospective studies, the MBT group consisted of 72 patients, whereas the non-MBT group comprised 114 patients, which met the sample size requirements.

Statistical Analysis

All data in this study were organized and analyzed using statistical software (SPSS 27.0.1, IBM Corp., USA). First, the normality of the measurement data was assessed using the Kolmogorov-Smirnov test, and homogeneity of variance was assessed using Levene's test. For data that were normally distributed and had homogeneous variance, the results were expressed as mean±standard deviation (SD). Independent samples t-test was used for inter-group comparison, and paired t-test was used for intra-group comparison. For measurement data failing to conform to the normal distribution, the results were expressed as median (interquartile range) [M (Q1, Q3)]. Mann-Whitney U test was used for inter-group comparison, and Wilcoxon test was used for intra-group comparison. Logistic regression analysis was used to adjust for confounding factors for each indicator. Count data were expressed as number (percentage) [n (%)], and chi-square test was used for inter-group comparison. Indicators with $p < 0.05$ in univariate analysis were included in the Logistic regression model to screen out independent risk factors for MBT. Receiver operating characteristic (ROC) curves were applied to evaluate the predictive value of the model, and the area under the curve (AUC) was calculated. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Data

Table 1 shows the baseline characteristics of 186 severe trauma patients, divided into a massive blood transfusion (MBT, n=72) and non-massive blood transfusion (non-MBT, n=114) group. No significant between-group differences were observed in age, sex, body mass index (BMI), injury-to-admission time,

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admission systolic blood pressure (SBP) on admission, heart rate (HR), injury mechanism, hypertension, diabetes, hemorrhagic shock, or Glasgow Coma Scale (GCS) score (all $p > 0.05$). Univariate analysis with odds ratios (OR) and 95% confidence intervals (95% CI) further confirmed no significant differences (all 95% CIs included 1). Baseline characteristics were well balanced, supporting valid subsequent comparative analyses.

Immune Markers

See Table 2. The $CD4^+/CD8^+$ ratio was significantly lower in the MBT group (0.92±0.27) than in the non-MBT group (1.36±0.21), with $p < 0.001$ and a large effect size (Cohen's d = 1.854). In contrast, no statistically significant differences were found between the two groups in the percentage of NK cells, or the levels of IgG, IgA, and IgM ($p = 0.374$, 0.638, 0.691, and 0.667, respectively), and all of these indicators showed small effect sizes with Cohen's d values of 0.149, 0.084, 0.069, and 0.077, respectively.

Inflammatory Markers

See Table 3. The levels of NLR, CRP, TNF-α, and IL-6 were all markedly higher in the MBT group than in the non-MBT group, with all differences reaching statistical significance (all $p < 0.001$) and showing large effect sizes (Cohen's d = −1.057, −1.074, −1.201, and −1.187, respectively). By contrast, the peripheral WBC count was comparable between the two groups ($13.22±2.25×10^9$/L vs. $13.76±2.50×10^9$/L), with no significant difference ($p = 0.134$) and a small effect size (Cohen's d = −0.233).

Trauma Severity

See Table 4. Both the ISS and mTICCS were significantly higher in the MBT group than in the non-MBT group (all $p < 0.001$), with Cohen's d values of −0.534 and −0.611 respectively, indicating moderate effect sizes between the two groups.

Table 1. Baseline clinical characteristics of severe trauma patients stratified by MBT status

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	OR	95% CI for OR
Age, years	42.01±10.36	42.54±10.12	0.729	1.005	0.976–1.035
Gender, n (%)			0.728	1.121	0.589–2.133
Male	78 (68.4)	51 (70.8)			
Female	36 (31.6)	21 (29.2)			
BMI, kg/m^2	23.50 (21.00–26.00)	24.00 (21.00–26.75)	0.261	1.061	0.957–1.177
Time from injury to hospital admission, h	2.88±1.32	3.18±1.43	0.152	1.174	0.943–1.461
SBP on admission, mm Hg	88.58±9.78	86.68±9.54	0.194	0.980	0.950–1.010
HR on admission, bpm	111.00 (104.00–116.00)	113.00 (106.00–121.00)	0.109	1.024	0.995–1.053
Cause of injury, n (%)			0.732	0.947	0.693–1.294
Traffic injury	52 (45.6)	35 (48.6)			
Fall injury	33 (28.9)	20 (27.8)			
Heavy object crush injury	21 (18.4)	12 (16.7)			
Others	8 (7.0)	5 (6.9)			
Hypertension, n (%)	15 (13.2)	8 (11.1)	0.680	0.825	0.331–2.057
Diabetes, n (%)	9 (7.9)	5 (6.9)	0.811	0.871	0.280–2.710
Hemorrhagic shock, n (%)	75 (65.8)	45 (62.5)	0.648	0.867	0.469–1.602
GCS score, scores	11.00 (9.00–13.00)	10.50 (8.00–13.00)	0.216	0.933	0.835–1.042

BMI: body mass index; CI: confidence interval; GCS: Glasgow Coma Scale; HR: heart rate; MBT: massive blood transfusion; OR: odds ratio; SBP: systolic blood pressure.

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Table 2. Comparison of immune indicators between severe trauma patients with and without MBT

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	Effect size (Cohen's d)
$CD4^+/CD8^+$ ratio	1.36±0.21	0.92±0.27	<0.001	1.854
NK cells, %	13.14±2.35	12.69±3.80	0.374	0.149
IgG, g/L	9.91±1.06	9.76±2.61	0.638	0.084
IgA, g/L	1.78±0.35	1.75±0.74	0.691	0.069
IgM, g/L	1.35±0.21	1.32±0.56	0.667	0.077

IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; MBT: massive blood transfusion; NK: natural killer; CD: cluster of differentiation.

Table 3. Comparison of inflammatory indicators between severe trauma patients with and without MBT

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	Effect size (Cohen's d)
WBC count, $\times 10^9$/L	13.22±2.25	13.76±2.50	0.134	-0.233
NLR	5.66±1.07	7.18±1.88	<0.001	-1.057
CRP, mg/L	56.63±10.66	73.68±21.72	<0.001	-1.074
TNF-α, pg/mL	26.84±5.95	39.44±15.13	<0.001	-1.201
IL-6, pg/mL	216.75±51.24	325.14±132.04	<0.001	-1.187

CRP: C-reactive protein; IL-6: interleukin-6; MBT: massive blood transfusion; NLR: neutrophil-to-lymphocyte ratio; TNF-α: tumor necrosis factor-α; WBC: white blood cell.

Table 4. Comparison of trauma severity scores between severe trauma patients with and without MBT

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	Effect size (Cohen's d)
ISS score	26.84±5.95	31.01±10.08	<0.001	-0.534
mTICCS score	4.97±1.20	6.25±3.00	<0.001	-0.611

ISS: Injury Severity Score; MBT: massive blood transfusion; mTICCS: modified Trauma Induced Coagulopathy Clinical Score.

Transfusion Adverse Events

Table 5 compared transfusion adverse events between the MBT and non-MBT groups. The MBT group had a markedly higher overall adverse event rate than the non-MBT group (23.6% vs 8.8%, $p = 0.005$). Although the incidences of febrile reactions (11.1% vs 5.3%), allergic reactions (6.9% vs 2.6%), and TACO (4.2% vs 0.9%) were numerically higher in the MBT group, no statistical significance was found ($p = 0.141$, 0.158, and 0.132, respectively). Overall, patients receiving MBT had a higher rate of transfusion-related adverse events.

Mechanical Ventilation Time

See Table 6. The mechanical ventilation duration was significantly longer in the MBT group than in the non-MBT group (6.08±2.83 hours vs. 3.96±1.47 hours), with a statistically significant difference ($p < 0.001$) and a large effect size (Cohen d = −1.012).

Independent Predictors of MBT

Table 7 presents the multivariate logistic regression analysis of independent risk factors for MBT in severe trauma patients, reporting regression coefficient (β), *p* value, standard error, t value, variance inflation factor (VIF), and tolerance for CRP, IL-6, TNF-α, NLR≥9.5, $CD4^+/CD8^+$ ratio ≤0.7, ISS ≥ 25, and mTICCS≥12. NLR≥9.5 ($\beta = 1.306$, $p = 0.008$), $CD4^+/CD8^+ \leq 0.7$ ($\beta = 1.628$, $p < 0.001$), ISS≥25 ($\beta = 0.716$, $p = 0.024$), and mTICCS≥12 ($\beta = 1.490$, $p = 0.015$) were identified

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as independent risk factors for MBT. Their positive β values indicated a higher MBT risk with elevated indicator levels. By comparison, CRP, IL-6, and TNF-α were not significantly correlated with MBT ($p > 0.05$). All VIF and tolerance values suggested no obvious multicollinearity among variables, and consistent signs of β coefficients and t values validated the stability and reliability of the regression model.

Predictive Value of Immune-Inflammatory Markers

Table 8 summarizes the predictive performance (AUC, 95% CI, DeLong test, Hosmer-Lemeshow test, calibration metrics, and optimal cut-off values) of immune-inflammatory indicators and trauma severity scores for MBT. mTICCS yielded the highest AUC of 0.810 (95% CI: 0.745–0.874). NLR (AUC = 0.806, 95% CI: 0.743–0.868) and $CD4^+/CD8^+$ ratio (AUC = 0.800, 95% CI: 0.739–0.862) showed comparable predictive power to mTICCS, with no significant differences per DeLong test ($p = 0.887$ and 0.828). ISS had an AUC of 0.709 (95% CI: 0.629–0.789), which was significantly inferior to mTICCS ($p = 0.001$). All models presented good calibration and fit (all $p > 0.05$ for Hosmer-Lemeshow and calibration tests). The optimal cut-off values were ISS ≥ 25, mTICCS ≥ 12, NLR ≥ 9.5, and $CD4^+/CD8^+ \leq 0.7$. Bootstrap validation confirmed narrow 95% CIs for sensitivity, specificity, positive and negative predictive values, demonstrating stable model estimation and no obvious overfitting (Figure 2).

Table 5. Comparison of transfusion adverse events between severe trauma patients with and without MBT

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	Effect size (phi)
Febrile reaction	6 (5.3)	8 (11.1)	0.141	-0.108
Allergic reaction	3 (2.6)	5 (6.9)	0.158	-0.104
Hemolytic reaction	0 (0.0)	1 (1.4)	0.207	-0.093
TRALI	0 (0.0)	0 (0.0)	NA	NA

MBT: massive blood transfusion; TACO: transfusion-associated circulatory overload; TRALI: transfusion-related acute lung injury.

Table 6. Comparison of mechanical ventilation duration between severe trauma patients with and without MBT

Indicators	Non-MBT group (n=114)	MBT group (n=72)	*p*	Effect size (Cohen's d)
Mechanical ventilation duration, h	3.96±1.47	6.08±2.83	<0.001	-1.012

MBT: massive blood transfusion.

Table 7. Multivariate logistic regression analysis of independent risk factors for MBT in severe trauma patients

Indicators	β	*p*	SE	t	VIF	Tolerance
CRP	1.056	0.596	0.421	0.531	1.404	0.712
IL-6	0.006	0.921	0.014	0.099	1.451	0.689
TNF-α	0.935	0.159	0.336	1.410	1.361	0.735
NLR ≥ 9.5	1.306	0.008	0.218	2.652	1.302	0.768
$CD4^+/CD8^+ \leq 0.7$	1.628	<0.001	0.194	3.291	1.264	0.791
ISS ≥ 25	0.716	0.024	0.295	2.257	1.344	0.744
mTICCS ≥ 12	1.490	0.015	0.267	2.432	1.375	0.727

CRP: C-reactive protein; IL-6: interleukin-6; ISS: Injury Severity Score; mTICCS: modified Trauma Induced Coagulopathy Clinical Score; NLR: neutrophil-to-lymphocyte ratio; SE: standard error; TNF-α: tumor necrosis factor-α; VIF: variance inflation factor.

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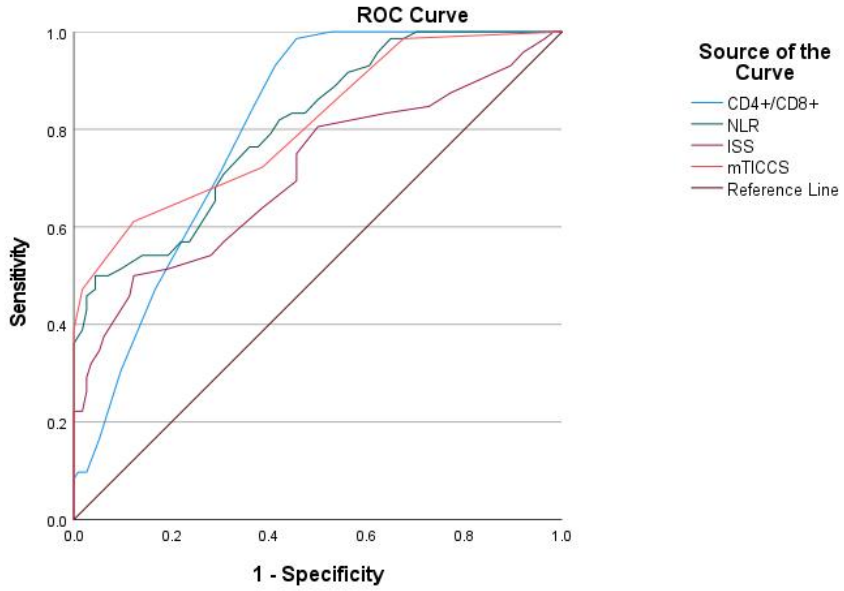

Figure 2. Prediction of Immune Inflammatory Indicators and Trauma Severity Score. ROC: receiver operating characteristic; ISS: Injury Severity Score; mTICCS: modified Trauma Induced Coagulopathy Clinical Score; NLR: neutrophil-to-lymphocyte ratio.

Table 8. AUC and predictive performance of immune-inflammatory indicators and trauma severity scores for MBT

Indicators	AUC	95% CI for AUC	*p* (DeLong test)	Hosmer-Lemeshow (*p*)	Calibration χ^2	Calibration *p*	Cut-off value	Sensitivity, % (95% CI for bootstrap)	Specificity, % (95% CI for bootstrap)	PPV, % (95% CI for bootstrap)	NPV, % (95% CI for bootstrap)
ISS	0.709	0.629–0.789	0.001	0.255	8.214	0.412	≥25	68.35 (58.33–79.17)	71.42 (63.16–78.97)	69.00 (62.35–75.20)	72.00 (65.05–78.50)
mTICCS	0.810	0.745–0.874	NA	0.412	6.773	0.562	≥12	79.18 (69.44–88.89)	76.53 (69.30–84.21)	77.00 (70.97–82.80)	78.00 (72.03–83.30)
NLR	0.806	0.743–0.868	0.887	0.182	9.342	0.314	≥9.5	77.94 (68.06–86.11)	75.86 (66.67–83.33)	76.00 (69.89–82.20)	77.00 (70.97–82.80)
$CD4^+/CD8^+$	0.800	0.739–0.862	0.828	0.121	10.125	0.256	≤0.7	76.41 (66.67–86.11)	74.29 (66.67–82.46)	75.00 (69.35–81.10)	76.00 (69.35–81.70)

AUC: area under the curve; ISS: Injury Severity Score; mTICCS: modified Trauma Induced Coagulopathy Clinical Score; NLR: neutrophil-to-lymphocyte ratio; NPV: negative predictive value; PPV: positive predictive value.

DISCUSSION

Severe trauma represents a leading cause of mortality and morbidity from accidental injuries worldwide. MBT constitutes a core component of resuscitation strategies for patients with severe trauma.[24] Currently, clinical decisions regarding the need for MBT in these patients are predominantly based on empirical judgment, with a paucity of precise early predictive markers. Therefore, exploring immunological and inflammatory predictive markers associated with MBT in patients with severe trauma and clarifying their

predictive value have emerged as key research priorities in the field of trauma care.[25] This study was specifically designed to address this critical clinical need, aiming to provide evidence-based insights for early prediction and precision management of MBT in severe trauma patients.

A retrospective comparative analysis was conducted on the clinical data of 186 patients with severe trauma. The results showed that a significantly lower $CD4^+/CD8^+$ ratio at admission was observed in the MBT group compared with the non-MBT group, while the levels of inflammatory markers including NLR, CRP, TNF-α, and IL-6 were significantly higher in the MBT group. Additionally, significantly higher ISS, mTICCS, as well as higher incidence of transfusion adverse events and longer mechanical ventilation duration were observed in the MBT group relative to the non-MBT group. Logistic regression analysis revealed that $CD4^+/CD8^+$ ratio ≤ 0.7, NLR ≥ 9.5, ISS ≥ 25, and mTICCS ≥ 12 at admission were independently correlated with the occurrence of MBT in patients with severe trauma. ROC curve analysis indicated that the discriminative ability of NLR and $CD4^+/CD8^+$ ratio was comparable to that of the mTICCS score.

The association between the $CD4^+/CD8^+$ ratio, an immunological marker, and MBT is characterized as follows. $CD4^+$ T cells primarily function in helper immune regulation, participating in antigen recognition, and the initiation of immune responses.[26] In contrast, $CD8^+$ T cells are predominantly cytotoxic, responsible for clearing damaged cells and pathogens.[27] Under normal physiological conditions, the $CD4^+/CD8^+$ ratio is maintained within a balanced range of 1.2–2.0. A reduction in this ratio is observed in states of suppressed immune function. During severe trauma, the body sustains significant mechanical injury, accompanied by a stress response and immune activation. The release of a large number of inflammatory mediators is associated with impaired function of immune cells.[27] In patients with MBT, trauma severity is typically greater, involving a broader tissue injury scope, and is accompanied by a more intense stress response. This coincides with massive apoptosis or functional exhaustion of $CD4^+$ T cells, while the activity of $CD8^+$ T cells is relatively enhanced, ultimately reflecting a significant decrease in the $CD4^+/CD8^+$ ratio. Concurrently, MBT itself is associated with immune disorders. The infused allogeneic blood components may be linked to immune rejection reactions or immune tolerance, which are associated with suppressed cell-mediated immune function.[28] A low $CD4^+/CD8^+$ ratio upon admission is observed concurrently with severe impairment of immune function and an intense trauma stress response, and is associated with a higher likelihood of severe blood loss and the need for MBT support.

$CD4^+/CD8^+ \leq 0.7$ is observed concurrently with an increased risk of hemorrhage through multiple pathways. Hypofunction of $CD4^+$ T cells is associated with reduced inhibitory regulation on monocytes, coinciding with overexpression of tissue factor and activation of the extrinsic coagulation pathway. Meanwhile, T-helper (Th)1/Th2 imbalance is observed concurrently with impaired platelet aggregation and altered fibrinolytic system activity. An NLR ≥ 9.5 reflects increased formation of neutrophil extracellular traps (NETs). NETs are observed concurrently with accelerated thrombin generation and increased plasma extravasation, which is associated with degradation of the vascular basement membrane via elastase. Reduction of $CD4^+$ T cells is linked to diminished negative regulation of NETs by regulatory T cells, coinciding with a self-sustaining immune-coagulation pattern. In addition, massive transfusion itself is associated with a second-hit phenomenon: free hemoglobin and microparticles released by stored red blood cells are linked to neutrophil activation through the toll-like receptor 4 (TLR4)/nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) pathway, while iron overload-induced oxidative stress is associated with lymphocyte apoptosis, coinciding with a bidirectional relationship between immune dysregulation and transfusion demand. The post-traumatic decline in the $CD4^+/CD8^+$ ratio is associated with selective alterations in T-cell dynamics. Within 0–6 hours after injury, catecholamines are linked to $CD4^+$ T cell redistribution in secondary lymphoid organs via β_2-adrenergic receptors, whereas $CD8^+$ T cell migration toward inflamed sites is associated with C-X3-C motif chemokine receptor 1 (CX3CR1) expression, coinciding with an altered peripheral blood ratio. Subsequent activation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with elevated glucocorticoid levels; $CD4^+$ T cells, which highly express glucocorticoid receptors, are linked to Bax/Fas-mediated apoptosis, while $CD8^+$ T cells are associated with partial resistance through 11-beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This stress-induced

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lymphopenia is observed concurrently with altered tissue repair capacity — impaired Th2 responses are associated with sustained M1 macrophage predominance and prolonged wound bleeding — altered endothelial barrier integrity (reduced Ang-1 secretion is linked to capillary leakage), and weakened intestinal immune barrier (T-cell apoptosis in gut-associated lymphoid tissue [GALT] is associated with endotoxin translocation). Ultimately, these pathological changes are associated with massive transfusion demand via coagulation dysfunction and insufficient effective circulating blood volume.

NLR, CRP, TNF-α, and IL-6 are all core indicators associated with the degree of the body's inflammatory response. Following severe trauma, tissue injury is associated with neutrophil activation, coinciding with their massive release and recruitment to the injury site, while lymphocyte proliferation and activity are observed to be relatively suppressed, coinciding with an elevation in NLR. As an acute-phase reactant protein, the level of CRP is associated with the severity of trauma and the intensity of the inflammatory response.[29] TNF-α and IL-6 are key cytokines in the early inflammatory response; they are rapidly secreted by macrophages, neutrophils, and other cells after trauma, coinciding with a cascading inflammatory response and an amplified inflammatory effect.[30,31] In this study, the levels of the aforementioned inflammatory indicators in the MBT group were significantly higher. This finding is associated with more severe trauma in these patients, with more profound tissue damage, ischemia, and hypoxia, coinciding with a more intense inflammatory response. Vascular rupture and tissue necrosis associated with severe trauma are linked to the release of a large number of damage-associated molecular patterns, which are associated with activation of the innate immune pathway and coinciding with massive activation of inflammatory cells and the release of inflammatory mediators, reflecting a sharp increase in the levels of inflammatory indicators.[32] Moreover, excessive activation of the inflammatory response is observed concurrently with increased vascular permeability, increased blood loss, and tissue edema, and an enhanced demand for blood transfusion. The elevation of inflammatory indicator levels is associated with an increased likelihood of requiring MBT.

In this study, both the ISS and mTICCS in the MBT group were significantly higher than those in the non-MBT group, and both showed independent correlations with MBT, which is consistent with clinical observation. Increased trauma severity is observed concurrently with a higher risk of vascular injury and organ rupture, as well as increased blood loss rate and volume, coinciding with a greater likelihood of requiring MBT for resuscitation.[33] Notably, the predictive efficacy of mTICCS was superior to that of ISS. This finding is associated with the fact that mTICCS not only considers the degree of injury but also incorporates additional clinical information, which aligns with the risk assessment logic in clinical practice and is associated with more accurate evaluation of the patient's blood loss risk and transfusion demand.[18]

The incidence of transfusion adverse events was higher in the MBT group, which was associated with two factors. Firstly, MBT involves the transfusion of multiple blood components, and the probability of reactions between antigenic substances in allogenic blood and antibodies in the patient's body is increased, coinciding with a higher frequency of allergic reactions, hemolytic reactions, and other adverse events. Secondly, MBT is associated with coagulation disorders, electrolyte imbalances, and other clinical complications, which are linked to an increased risk of adverse events. The prolonged duration of mechanical ventilation is associated with higher trauma severity and more significant immune-inflammatory disorders in patients.[34] Severe trauma and excessive inflammatory responses are observed concurrently with complications, coinciding with affected respiratory function and a need for long-term mechanical ventilation support. Meanwhile, immune function suppression is associated with reduced anti-infective capacity in patients, coinciding with prolonged courses of complications such as pulmonary infections and an increased duration of mechanical ventilation.[20]

In a study exploring the predictive value of four traumatic hemorrhage scores for early massive transfusion in prehospital trauma patients,[35] the AUC of mTICCS was 0.795, which is relatively close to the results of this study. A 4-year retrospective analysis of 1199 patients with abdominal trauma showed that the AUC of NLR for predicting massive transfusion was 0.55 (95% CI: 0.510–0.598),[23] showing low predictive efficacy, which is inconsistent with the conclusion of this investigation that NLR is an independent predictive factor for MBT (AUC = 0.806). The study also pointed out that the platelet-to-lymphocyte ratio (PLR) had an AUC of 0.69 for predicting massive transfusion and was

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an independent predictor of patient death. However, PLR was not included in this study, which may also lead to differences in research conclusions. The core reasons for the inconsistent results between the aforementioned study and this study are as follows: Firstly, the study population focused on a single site of abdominal trauma, while this study involved multiple-site severe trauma. The activation pathways of inflammatory responses induced by trauma at different sites may differ; abdominal trauma may be more likely to affect platelet function, thereby making the predictive value of PLR more prominent and weakening the predictive efficacy of NLR. Secondly, a statistically meaningful discrepancy in sample size was observed between the two study groups. The aforementioned study included 1199 patients with a single trauma site, and its indicator thresholds and predictive efficacy may be more suitable for the local trauma population, while this study was a small sample (186 cases) of multiple-site trauma with differences in indicator distribution characteristics. Thirdly, this study used a transfusion volume of red blood cells ≥10 units within 24 hours as the standard for MBT, while the aforementioned study used massive transfusion activation as the criterion. Different definitions of MBT may also lead to differences in the predictive value of indicators. In addition, differences in treatment timing and resuscitation protocols among patients in different studies exist; early precise resuscitation can effectively control blood loss and inflammatory responses, which may reduce the correlation between inflammatory indicators and transfusion demand, and this is also an important reason for the differences in study results.

The innovation of this study lies in combining immunological indicators with inflammatory indicators, while incorporating two classic trauma severity scores (ISS and mTICCS) to comprehensively explore the combined predictive value of immune-inflammatory status and trauma severity for MBT demand. The present study addresses a limitation of prior research that mostly focused on a single type of parameter, rather than exploring multiple factors simultaneously.

LIMITATIONS OF THE STUDY

This study used a retrospective design, which inevitably has inherent selection bias. The study samples were derived from a single center, and the trauma types and treatment protocols of the included patients had certain homogeneity, which may limit the generalizability of our results, and there is a potential risk of overfitting. This study only focused on the indicator levels at admission and did not dynamically monitor changes in the indicators throughout the treatment process, so it was unable to clarify the correlation between the dynamic evolution of inflammatory and immune markers, MBT demand, and long-term clinical prognosis. In addition, the impact of patients' underlying chronic diseases on baseline immunological and inflammatory indicators was not fully adjusted, which may interfere with the validity and accuracy of the study results.

Notably, although this study controlled major clinical confounding variables through statistical adjustment, unmeasured residual confounding factors still existed and could not be completely eliminated. Differences in pre-hospital rescue time, emergency intervention timing, emergency operation priority, individual differences in stress response, and inconsistent nutritional status among patients may independently affect the expression levels of inflammatory factors and immune indexes, and indirectly alter the matching relationship between predictive markers and MBT demand. These invisible residual confounders may weaken the stability of independent predictive factors and deviate the true association strength between indicators and adverse outcomes, thus affecting the clinical popularization and external validity of the prediction model. Meanwhile, limited by retrospective clinical data, detailed information such as perioperative medication, stress hormone secretion, and complication progression was incomplete, which further aggravated the interference of residual confounding effects on study conclusions.

In the future, multi-center, prospective cohort studies can be carried out to expand the sample size, include patients with diverse trauma types from different geographical regions, and verify the effectiveness and universal applicability of the predictive indicators screened in this study. Standardized unified treatment specifications should be formulated to minimize systematic deviation caused by heterogeneous clinical interventions, and strict stratification analysis should be performed to reduce the interference of residual confounding on statistical results. Dynamic continuous indicator monitoring studies can be conducted to analyze the temporal changing rules of immunological-inflammatory indicators and trauma severity scores during treatment, and explore the early warning predictive

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value of dynamic indicator trends for MBT demand and patient short-term and long-term prognosis. Future studies should further incorporate indicators such as procalcitonin (PCT), interleukin-10 (IL-10), and refined lymphocyte subsets to further explore the critical time points of immune-inflammatory phenotype transformation and their close dynamic association with MBT requirements. Clinical confounding factors including patients' underlying diseases, age stratification, trauma severity, and genetic polymorphisms can be comprehensively incorporated to construct a multi-dimensional integrated nomogram prediction model, to further optimize model discrimination and improve the accuracy of individualized MBT demand prediction. Based on the optimized screening predictive indicators, targeted clinical interventional studies can be carried out to explore the effects of early precise hemostatic resuscitation, immune homeostasis regulation, and hierarchical intervention measures for high-risk groups on improving survival and clinical outcomes, and provide more systematic and comprehensive diagnosis and treatment strategies for severe trauma patients. Subsequent multicenter large-sample prospective studies will supplement calibration curves, decision curve analysis, and clinical impact curves to further optimize model calibration performance, clinical applicability evaluation, and external validation, and reduce bias caused by residual confounding and single-center sampling.

The results of the present study suggest that immunological and inflammatory indicators in patients with severe trauma may be associated with their requirement for MBT. In clinical practice, in addition to focusing on blood loss, monitoring and modulation of the immune-inflammatory status should also be considered. Early intervention aimed at attenuating excessive inflammatory responses and improving immune function may potentially reduce the need for MBT and improve clinical outcomes in this population. Further multicenter and prospective studies are warranted to validate the predictive value of these indicators, establish more comprehensive predictive models and intervention strategies, and thereby contribute to the optimization of management for patients with severe trauma.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Xianning Central Hospital, The First Affiliated Hospital of Hubei University of Science and Technology (Ethics Approval Number: K【2024】004). This study strictly complied with the Declaration of Helsinki, and the application for waiving informed consent was endorsed by the Ethics Committee in accordance with the relevant provisions of the “Measures for the Ethical Review of Life Science and Medical Research Involving Humans”.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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None.

DATA AVAILABILITY

The data supporting the findings of this study can be obtained from the corresponding author, upon request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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