Article

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Association of Peripheral Blood $CD19^+CD27^+CD24^+$ B Cells With Clinical Outcomes in Sepsis

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Background: Sepsis is characterized by a dysregulated immune response, and alterations in B-cell subsets have been increasingly recognized. However, whether $CD19^+CD27^+CD24^+$ B cells are altered in sepsis and whether they are associated with patient outcomes remain unclear. This study aimed to investigate the frequency of $CD19^+CD27^+CD24^+$ B cells in patients with sepsis and evaluate their association with disease severity and 28-day mortality.

Methods: This observational study enrolled 189 patients with sepsis and 50 non-sepsis controls. Patients were stratified into groups with normal and decreased $CD19^+CD27^+CD24^+$ B-cell proportions based on a pre-specified lower reference limit of 8.99% derived from published healthy adult data. Peripheral B-cell subsets, including $CD19^+CD27^+CD24^+$ B cells, were analyzed by flow cytometry. Differences in B-cell subsets and clinical parameters between groups, as well as correlations among variables, were analyzed.

Results: Patients with sepsis exhibited significantly reduced proportions of $CD19^+CD27^+CD24^+$ B cells ($p < 0.0001$), transitional B cells ($p < 0.0001$), and naïve B cells ($p = 0.0018$), alongside a marked expansion of plasmablasts ($p < 0.0001$), compared with non-sepsis controls. Among all subsets, $CD19^+CD27^+CD24^+$ B cells showed the strongest negative correlations with Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, and length of hospital stay (all $p < 0.0001$). In addition, patients requiring mechanical ventilation ($p = 0.0363$) or vasoactive support ($p = 0.0012$), as well as those with acute kidney injury (AKI) ($p = 0.0005$), showed significantly decreased proportions of $CD19^+CD27^+CD24^+$ B cells. Using the pre-specified 8.99% threshold, patients with decreased proportions (<8.99%, n = 129) had significantly lower 28-day survival than those with normal proportions (≥8.99%, n = 60) (log-rank $p = 0.0019$). In multivariable Cox models, decreased $CD19^+CD27^+CD24^+$ B-cell proportions were independently associated with increased 28-day mortality (hazard ratio (HR) = 2.87, 2.65, 2.50 respectively; $p = 0.007$, 0.016, 0.025 respectively). Moreover, procalcitonin (PCT) levels were significantly higher in the decreased $CD19^+CD27^+CD24^+$ B-cell group than in the normal group ($p < 0.0001$), whereas conventional inflammatory markers, such as white blood cell (WBC), neutrophil percentage, and C-reactive protein (CRP), showed no significant differences between the two groups. Patients with decreased proportions also had lower partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratios ($p < 0.0001$) and higher creatinine (Cr) ($p = 0.0219$), aspartate aminotransferase (AST) ($p = 0.0114$), and brain natriuretic peptide (BNP) ($p = 0.0404$) levels. The area under the receiver operating characteristic (ROC) curve (AUC) of $CD19^+CD27^+CD24^+$ B-cell percentage for 28-day mortality was 0.734, comparable to SOFA (0.754) and APACHE-II (0.732).

Conclusions: The proportion of $CD19^+CD27^+CD24^+$ B cells is significantly decreased in patients with sepsis, and this decrease is associated with disease severity, organ function-related laboratory abnormalities, and poor outcomes. Reflecting the breakdown of immune homeostasis, $CD19^+CD27^+CD24^+$ B-cell profiling may serve as a candidate biomarker associated with prognosis; however, external validation is required before it can be used for clinical risk stratification.

Keywords: sepsis; $CD19^+CD27^+CD24^+$ B cells; regulatory B cells; interleukin-10; acute lung injury; prognosis

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and it remains a major cause of death in intensive care units (ICUs) worldwide [1,2]. Although supportive care and antimicrobial therapy have improved, sepsis mortality remains high, largely because of its complex and dynamic pathophysiology [3]. Traditionally, sepsis has been viewed as a condition of severe immune dysregulation, in which an initial hyperinflammatory "cytokine storm" is followed by a prolonged state of immunosuppression. This sequence makes patients vulnerable to secondary nosocomial infections and progressive multiple organ dysfunction [4,5]. However, studies have shown that pro- and anti-inflammatory signaling pathways can be activated simultaneously from the earliest stages of the disease [6]. Therefore, identifying individual immune phenotypes in patients with sepsis is important for individualized, precision-oriented treatment.

The roles of neutrophils, macrophages, and T cells in sepsis have been extensively studied, whereas the contribution of B lymphocytes has long been underestimated [7,8]. B cells were traditionally regarded primarily as antibody-producing effectors in humoral immunity. However, increasing evidence shows that B lymphocytes also have antibody-independent functions, such as cytokine secretion and cellular regulation [9,10]. Importantly, B cells are a highly heterogeneous population comprising distinct phenotypic and functional subsets, ranging from classical effectors (transitional B cells, naive B cells, memory B cells, and plasmablasts) to specialized negative regulators known as regulatory B cells (Bregs) [11]. Among Bregs, $CD19^+CD27^+CD24^+$ B cells, also known as B10-like cells because of their strong capacity to produce interleukin-10 (IL-10), play an important role in maintaining immune homeostasis and limiting tissue-destructive hyperinflammation [12,13,14].

Recent clinical studies have described dynamic changes in specific B cell subsets during sepsis, including reductions in circulating B cells and decreased proportions of transitional and memory B cells [15,16,17]. However, most of these studies have examined individual subsets separately. To our knowledge, no study has systematically mapped changes across all major B-lymphocyte subsets within the same patient cohort. In addition, sepsis can rapidly lead to multi-organ failure driven by systemic infection, which is usually monitored using infection markers such as procalcitonin (PCT). Whether a decreased proportion of peripheral $CD19^+CD27^+CD24^+$ B cells is directly associated with specific infection markers and progressive multi-organ impairment remains largely unknown.

Among target organs, the lungs are especially vulnerable, and pulmonary infection is a leading cause of sepsis [18]. Sepsis-induced acute lung injury (ALI) is a major contributor to mortality and is characterized by widespread alveolar inflammation, disruption of the alveolar-capillary barrier, and respiratory dysfunction [19,20]. Findings from experimental models suggest that regulatory B cells may modulate pulmonary inflammation during acute injury, but whether $CD19^+CD27^+CD24^+$ B cells protect against sepsis-induced lung damage in humans remains unclear.

In this study, we comprehensively profiled five distinct subsets of peripheral B cells in a cohort of patients with sepsis and non-sepsis controls. We hypothesized that decreased proportions of specific regulatory B cell populations disrupt immune homeostasis, thereby exacerbating systemic inflammation and organ dysfunction. By investigating the relationships between $CD19^+CD27^+CD24^+$ B cell frequencies, clinical severity scores, infection parameters (such as PCT), and multi-organ impairment (particularly as reflected by PaO_2/FiO_2 ratios), we aimed to define the clinical implications of decreased $CD19^+CD27^+CD24^+$ B cell proportions and evaluate their potential utility as a prognostic biomarker for risk stratification in sepsis.

Methods

Participants

The current study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Shanghai General Hospital (Approval No. 2021KY037) on April 23, 2021. No intervention was administered to any patient in this study. As this study did not involve the prospective assignment of any intervention, it did not meet the ICMJE definition of a clinical trial, and clinical trial registration was therefore not applicable. A total of 189 patients with sepsis admitted to the ICU of Shanghai General Hospital between June 2021 and December 2022 were enrolled. Written informed consent was obtained from all patients or their legally authorized representatives before sample and data collection.

All patients with sepsis met the Sepsis-3 criteria, according to previous study [1]. The SOFA score assessed six organ systems: respiration (PaO_2/FiO_2), coagulation (platelets), liver (bilirubin), cardiovascular (MAP/vasopressors), central nervous system (GCS), and renal (creatinine/urine output), each scored from 0 to 4.

Patients were included if they: (1) were ≥18 years old and (2) met the Sepsis-3 criteria (with a SOFA score ≥2 points). Patients were excluded if they: (1) had malignancy; (2) had a history of organ transplantation, HIV/AIDS, or autoimmune diseases, or had received immunosuppressive therapy within the past month; (3) had chronic infectious diseases; (4) were pregnant or lactating; or (5) declined to participate or had incomplete clinical data. A control group of 50 age- and sex-matched healthy individuals was also prospectively enrolled during the same study period. To minimize selection bias, these healthy volunteers were recruited from individuals undergoing routine physical exam-

Table 1. Clinical characteristics of the study participants.

	Non-sepsis (n = 50)	Sepsis (n = 189)	*p*-value
Age (year), mean ± SD	66.7 ± 18.2	66.3 ± 17.9	0.7608
Male gender, n (%)	28 (56.0)	134 (70.9)	0.0605
WBC ($\times 10^9$/L), median (IQR)		8.8 (7.0–9.8)	
Neutrophils ($\times 10^9$/L), median (IQR)		8.1 (6.3–9.5)	
CRP (mg/L), median (IQR)		87.5 (45.5–173.2)	
PCT (ng/mL), median (IQR)		2.1 (0.31–22.4)	
PaO_2/FiO_2 (mmHg), median (IQR)		304.0 (163.0–524.0)	
Cr (μmol/L), median (IQR)		95.9 (68.5–169.6)	
BUN (mmol/L), median (IQR)		8.7 (6.1–13.3)	
ALT (U/L), median (IQR)		26.0 (15.7–61.0)	
AST (U/L), median (IQR)		41.0 (27.0–79.0)	
BNP (pg/mL), median (IQR)		169.8 (87.9–433.9)	
Length of hospital stay (days), median (IQR)		14.0 (8.0–20.0)	
Mechanical ventilation, n (%)		88 (46.6)	
AKI, n (%)		88 (46.6)	
CRRT, n (%)		26 (13.8)	
28-day mortality, n (%)		41 (21.7)	
Infection site, n (%)			
Lung		97 (51.3)	
Digestive tract		25 (13.2)	
Biliary tract		17 (9.0)	
Urinary tract		12 (6.3)	
Liver		7 (3.7)	
Soft tissue infections		7 (3.7)	
Central nervous system		3 (1.6)	
Peritoneal cavity		3 (1.6)	
Cardiovascular system		3 (1.6)	
Other site		15 (7.9)	

Clinical laboratory parameters were not routinely measured in the healthy control group. IQR, interquartile range; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

inations at our hospital and from the local community. Written informed consent was obtained from all non-sepsis controls before enrollment. They were strictly screened to ensure that they had no history of infection, systemic inflammation, autoimmune diseases, malignancy, or immunosuppressive therapy. The baseline characteristics of the study population are shown in Table 1.

Clinical Data Collection

Demographic and clinical characteristics, including age, sex, comorbidities, and source of infection, were recorded for each patient. Disease severity was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score [21] and the Sequential Organ Failure Assessment (SOFA) score [22]. Both scores were calculated based on the worst values recorded within the first 24 hours after ICU admission, in accordance with their original definitions. Peripheral blood samples for B cell subset analysis were collected within the same 24-hour window as the score calculations, ensuring close temporal correspondence between the immunological measurements and disease severity assessments. The SOFA and APACHE-II scores were calculated by ICU physicians as part of routine clinical care. The assessors were blinded to the patients' B cell subset results and study group assignments, and the final clinical outcomes were unknown at the time of assessment. Laboratory parameters, including white blood cell (WBC) count, neutrophil percentage, C-reactive protein (CRP), procalcitonin (PCT), serum creatinine (Cr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and brain natriuretic peptide (BNP), were measured using standard clinical laboratory methods. The oxygenation index (PaO_2/FiO_2) was calculated based on arterial blood gas analysis. Length of hospital stay and requirements for mechanical ventilation, continuous renal replacement therapy (CRRT), and vasoactive support were also recorded. Respiratory dysfunction was defined according to the Berlin definition of acute respiratory distress syndrome (ARDS) as a PaO_2/FiO_2 ratio

<300 mm Hg with PEEP or CPAP ≥5 cmH_2O [19]. AKI was defined according to the KDIGO 2012 criteria as any of the following: (1) an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; (2) an increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred within the previous 7 days; or (3) urine volume <0.5 mL/kg/h for 6 hours [23].

To evaluate the independent prognostic value of $CD19^+CD27^+CD24^+$ B cells, multivariate Cox proportional hazards regression models were constructed, adjusting for age, SOFA score, APACHE-II score, and vasoactive support.

Flow Cytometric Analysis of Peripheral B Cell Subsets

Peripheral blood (2 mL) was collected from each participant into EDTA tubes after sepsis diagnosis or at enrollment for non-sepsis controls. For surface staining, 2 mL of whole blood was transferred directly into a flow cytometry tube and incubated for 30 minutes at 4 °C in the dark with the following mouse anti-human monoclonal antibodies: FITC anti-CD45 (clone HI30, Cat. 561865), PE anti-CD24 (clone ML5, Cat. 555428), PerCP-Cy5.5 anti-CD27 (clone M-T271, Cat. 561400), PE-Cy7 anti-CD19 (clone SJ25C1, Cat. 341113), APC anti-CD56 (clone NCAM16.2, Cat. 341027), APC-Cy7 anti-CD20 (clone L27, Cat. 335829), APC anti-CD3 (clone SK7, Cat. 340440), and BV510 anti-IgD (clone IA6-2, Cat. 565243). All these antibodies were purchased from BD Biosciences (San Jose, CA, USA). Brilliant Violet 421 anti-CD38 (clone HB-7, Cat. 356625) was obtained from BioLegend (San Diego, CA, USA). All antibodies were used at dilutions ranging from 1:10 to 1:40.

Additional reagents and materials included BD FACSDiva CS&T Research Beads (Cat. 655050) and BD FACS Lysing Solution (10× concentrate, Cat. 349202) from BD Biosciences; PBS (10×, pH 7.4) from Beyotime (Shanghai, China); BD Falcon 5 mL round-bottom polystyrene tubes (Cat. 352058) from BD Biosciences; and Axygen pipette tips (10 μL, 200 μL, and 1000 μL) from Axygen (Union City, CA, USA).

B-cell subsets were analyzed using a FACS Canto II flow cytometer (v3.0, BD Biosciences, San Jose, CA, USA). Before acquisition, optical alignment was checked using BD CST beads to ensure that all optical paths were free of offset, and the Diva software fluidics startup routine was run to confirm proper system function. Fluorescence compensation was calculated automatically using BD DIVA software and single-stained compensation tubes, which also served to define positive thresholds for each channel. The compensation settings are summarized in **Supplementary Table 1**.

For gating, raw events were first displayed on an FSC-A versus SSC-A plot, and a "CELLS" gate was applied to remove debris and electronic noise while retaining intact cells. CD45-positive leukocytes were then selected from the intact cell population. Doublets and aggregates were excluded using FSC-W versus FSC-A. Events with abnormal FSC/SSC scatter patterns were excluded; no viability dye was used. Within the singlet WBC population, lymphocytes (P1) were identified based on CD45 expression and low-to-intermediate side scatter. B cells were defined as $CD19^+CD3^-CD56^-$ events within the lymphocyte gate. The $CD19^+$ B-cell population was further divided into $CD19^+CD27^+CD24^+$ B cells, naïve B cells ($CD19^+CD27^-IgD^+$), memory B cells ($CD19^+CD27^+IgD^-$), transitional B cells ($CD19^+CD24^{hi}CD38^{hi}$), and plasmablasts ($CD19^+CD38^{hi}CD20^-CD24^-$). Only gated singlet leukocytes were used for downstream subset quantification. A minimum of 5000 events within the $CD19^+$ B-cell gate were acquired per sample to ensure reliable analysis of B-cell subpopulations. The gating strategy is illustrated in **Supplementary Fig. 1**.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism (v10.6.1, GraphPad Software, Boston, MA, USA) and SPSS 20.0 (IBM, Armonk, NY, USA). As this was an observational study, no a priori sample size calculation was performed. The sample size was based on the number of eligible patients admitted to the ICU during the study period who met the inclusion criteria and had complete clinical data and available peripheral blood samples. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (SD) and were compared using Student's *t*-test (two groups) or one-way ANOVA followed by Tukey's post hoc test (multiple groups). Non-normally distributed data are presented as median (interquartile range, IQR) and were compared using the Mann-Whitney U test (two groups). Categorical variables are presented as frequencies and percentages (n, %) and were compared using the Fisher's exact test, as appropriate. Correlations between B cell subsets and clinical parameters were assessed using Spearman's rank correlation coefficient (reported as ρ). Where linear regression was additionally used to estimate the proportion of variance explained, the coefficient of determination (R^2) is reported. The linear regression is used solely to illustrate the trend of association and is not intended for predicting clinical scores. The 28-day survival rates were analyzed using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Univariate Cox regression was first performed to screen for potential prognostic factors. To evaluate the independent prognostic value of $CD19^+CD27^+CD24^+$ B cells for 28-day mortality, separate multivariable Cox proportional hazards models were constructed, each including a maximum of three covariates owing to the limited number of events. Age, SOFA score, APACHE-II score, and vasoactive support were included across these models to

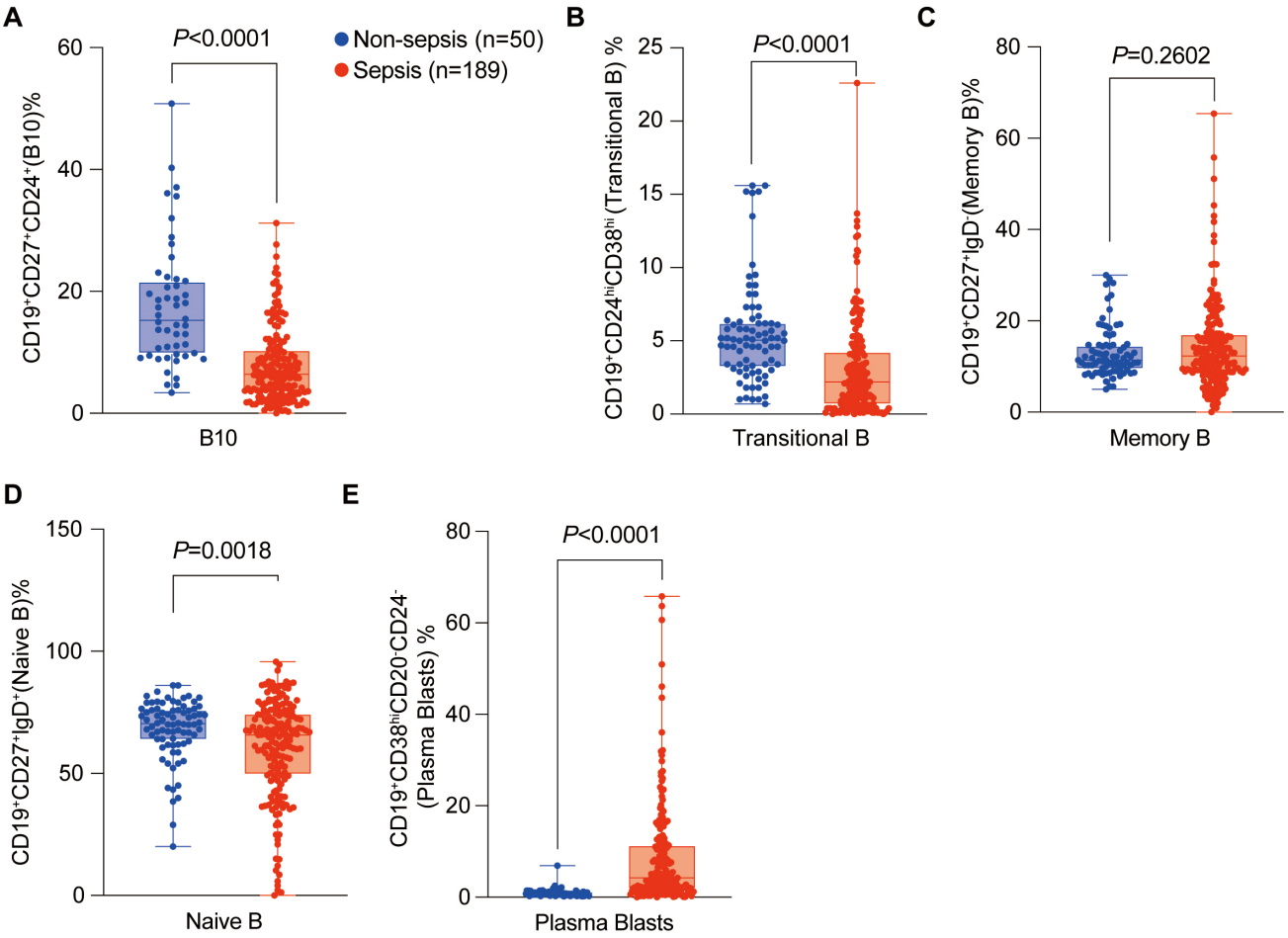


Fig. 1. Comparison of B cell subset proportions between sepsis and non-sepsis groups. Flow cytometric analysis was performed to evaluate the percentages of various B cell subsets, including (A) $CD19^+CD27^+CD24^+$ B cells, (B) transitional B cells, (C) memory B cells, (D) naïve B cells, and (E) plasmablasts. Data are presented as box plots with median, IQR, and individual data points.

adjust for potential confounders. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were calculated. Given the large number of statistical comparisons performed, correction for multiple comparisons was applied using the Benjamini-Hochberg false discovery rate (FDR) method, with adjustments performed separately for each analysis module. The FDR-adjusted q values are reported in **Supplementary Table 2**. A p value < 0.05 and an FDR-adjusted q value < 0.05 were considered statistically significant.

Results

Peripheral B-Cell Subsets Are Significantly Altered in Patients With Sepsis

Increasing evidence links B-cell dysfunction to the mechanisms of immune derangement that characterize the dysregulated host response to infection [7,15,16]. Understanding the dynamic alterations in B cell subsets is therefore critical for elucidating sepsis-induced immunosuppression and identifying potential immunotherapeutic targets. To investigate alterations in B cell immunity during sepsis, we analyzed the proportions of peripheral B cell subsets, including $CD19^+CD27^+CD24^+$ B cells, transitional B cells ($CD19^+CD24^{hi}CD38^{hi}$), memory B cells ($CD19^+CD27^+IgD^-$), naïve B cells ($CD19^+CD27^-IgD^+$), and plasmablasts ($CD19^+CD38^{hi}CD20^-CD24^-$) in patients with sepsis and non-sepsis controls. Compared with the non-sepsis control group, patients with sepsis exhibited significantly lower proportions of $CD19^+CD27^+CD24^+$ B cells ($p < 0.0001$), transitional B cells ($p < 0.0001$), and naïve B cells ($p = 0.0018$), alongside a marked increase in plasmablast frequencies ($p < 0.0001$). In contrast, the proportion of memory B cells remained comparable ($p = 0.2602$) between the two groups (Fig. 1A–E). Collectively, these findings demonstrate profound remodeling of the B cell landscape in sepsis, which may play a critical role in modulating the host immune response and ultimately affect clinical outcomes in patients with sepsis.

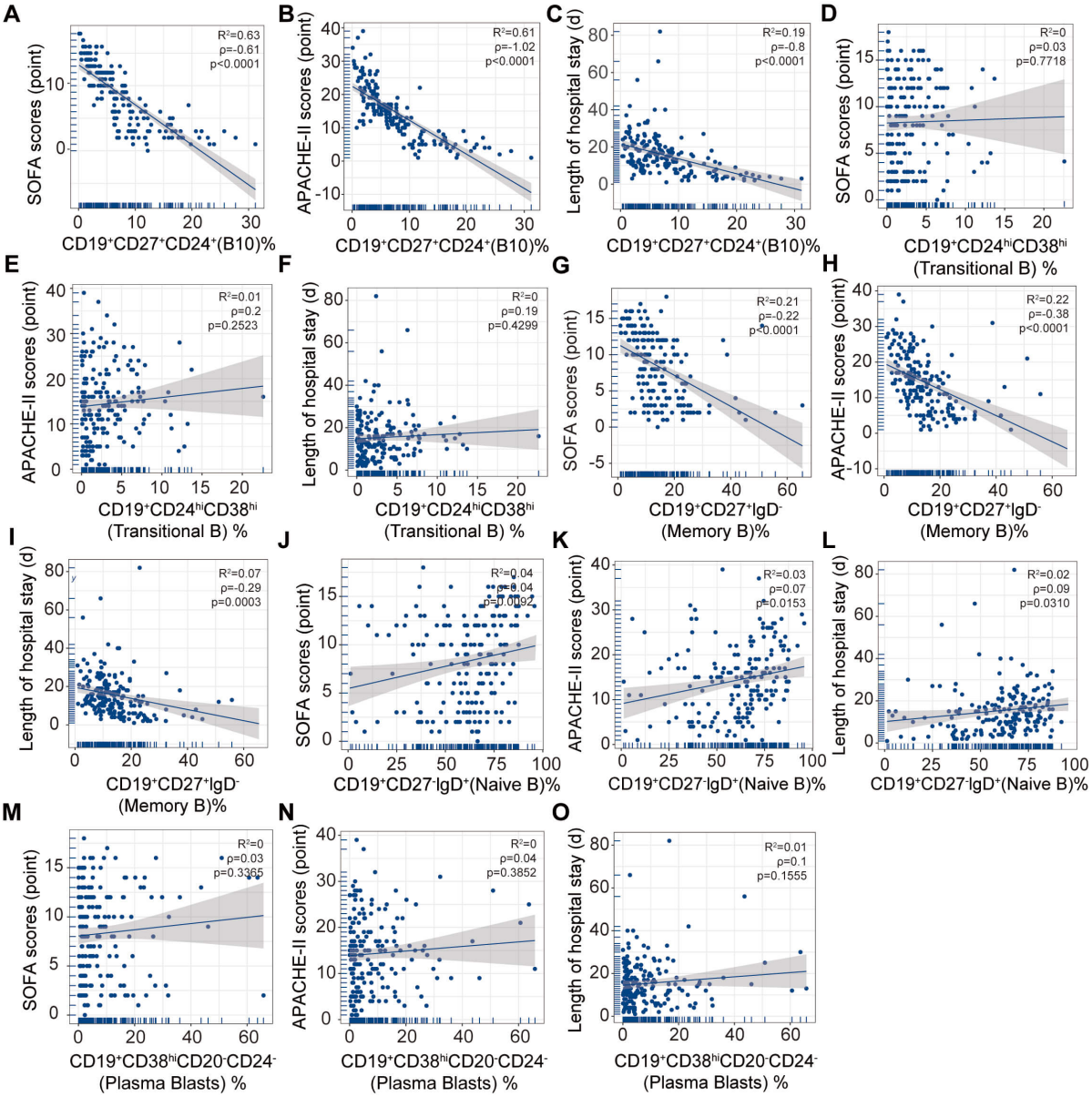


Fig. 2. Associations between peripheral B cell subsets and clinical severity indices in septic patients. Scatter plots showing the correlations of various B cell subsets with Sequential Organ Failure Assessment (SOFA) scores, Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, and length of hospital stay. (A–C) correlations of $CD19^+CD27^+CD24^+$ B cells and SOFA, APACHE-II scores and length of hospital stay. (D–F) correlations of transitional B cells and SOFA, APACHE-II scores and length of hospital stay. (G–I) correlations of memory B cells and SOFA, APACHE-II scores and length of hospital stay. (J–L) correlations of naïve B cells and SOFA, APACHE-II scores and length of hospital stay. (M–O) correlations of plasmablasts and SOFA, APACHE-II scores and length of hospital stay. Both the SOFA and APACHE-II scores were as actually recorded. Gray shaded area represents the range of uncertainty for this regression line. That is, we are 95% confident that the true population regression line falls within this gray shaded band. The fitted regression lines are presented for visualization of the observed associations only and should not be interpreted as clinically meaningful predictions outside the observed score ranges.

B-Cell Subsets Exhibit Differential Associations With Sepsis Severity

To investigate the relationship between B cell subsets and disease severity in sepsis, we analyzed the correlations between various B cell populations and clinical parameters, including SOFA scores, APACHE-II scores, and length of hospital stay (Fig. 2A–O). $CD19^+CD27^+CD24^+$ B cells showed strong and significant negative correlations with SOFA scores ($R^2 = 0.63$, $p < 0.0001$), APACHE-II scores ($R^2 = 0.61$, $p < 0.0001$), and length of hospital stay ($R^2 = 0.19$, $p < 0.0001$) (Fig. 2A–C). Memory B cells also showed significant negative correlations with SOFA scores

($p < 0.0001$), APACHE-II scores ($p < 0.0001$), and length of hospital stay ($p = 0.0003$) (Fig. 2G–I). In contrast, transitional B cells and plasmablasts exhibited no significant correlations with any of the clinical parameters (transitional B cells: SOFA $p = 0.7696$, APACHE-II $p = 0.2438$, LOS $p = 0.4299$; plasmablasts: SOFA $p = 0.2807$, APACHE-II $p = 0.3113$, LOS $p = 0.1555$; all $p > 0.05$; Fig. 2D–F,M–O). Naïve B cells showed weak positive correlations with SOFA scores ($p = 0.0015$) and length of hospital stay ($p = 0.031$), but no significant correlation with APACHE-II scores ($p = 0.053$) (Fig. 2J–L).

Collectively, these findings indicate that distinct B cell subsets exhibit differential associations with clinical outcomes in sepsis. Given that $CD19^+CD27^+CD24^+$ B cells were markedly decreased in patients with sepsis (Fig. 1A) and exhibited the strongest negative correlations with disease severity (SOFA and APACHE-II scores) and length of hospital stay among all B cell subsets examined (Fig. 2A–C), whereas none of the other four subsets exhibited both patterns, we next focused on $CD19^+CD27^+CD24^+$ B cells and analyzed their associations with clinical outcomes and organ support requirements.

Severe Clinical Phenotypes and Increased Organ Support Requirements Are Associated With Decreased Proportions of $CD19^+CD27^+CD24^+$ B Cells

We therefore compared $CD19^+CD27^+CD24^+$ B cell proportions between survivors and non-survivors (28-day mortality) and found that these proportions were significantly lower in non-survivors than in survivors ($p = 0.0001$, Fig. 3A). We next assessed whether $CD19^+CD27^+CD24^+$ B-cell proportions also differed according to organ support requirements. Patients requiring ventilatory support exhibited significantly lower proportions of $CD19^+CD27^+CD24^+$ B cells than those breathing spontaneously ($p = 0.0363$, Fig. 3B). Although $CD19^+CD27^+CD24^+$ B-cell proportions tended to be lower in patients requiring CRRT ($p = 0.0513$), the difference did not reach statistical significance (Fig. 3C). Additionally, $CD19^+CD27^+CD24^+$ B-cell proportions were significantly lower in patients with AKI ($p = 0.0005$) and those requiring vasoactive support ($p = 0.0012$) (Fig. 3D,E) than in their respective comparison groups. These results indicate that decreased proportions of $CD19^+CD27^+CD24^+$ B cells are associated with adverse clinical outcomes, including mortality, respiratory failure, acute kidney injury, and hemodynamic instability in patients with sepsis.

Decreased Baseline $CD19^+CD27^+CD24^+$ B Cell Proportion Stratifies Sepsis Severity and Is Associated With 28-Day Mortality

Given the observed association between decreased $CD19^+CD27^+CD24^+$ B-cell proportions and adverse prognosis, we further evaluated the feasibility of using $CD19^+CD27^+CD24^+$ B-cell proportions as an early prognostic indicator. Using a pre-specified lower reference limit of 8.99% derived from a published healthy adult cohort [24], we divided patients with sepsis into a normal $CD19^+CD27^+CD24^+$ B-cell group (≥8.99%, n = 60) and a decreased $CD19^+CD27^+CD24^+$ B-cell group (<8.99%, n = 129). This reference-based threshold was used for exploratory stratification and has not been independently validated as a prognostic cutoff in patients with sepsis. Patients with normal $CD19^+CD27^+CD24^+$ B-cell proportions exhibited a significantly higher 28-day survival rate than those with decreased proportions, as determined by the log-rank test ($p = 0.0019$, Fig. 4A). Furthermore, univariate (Table 2) and multivariate (Tables 3,4,5) Cox proportional hazards regression analyses were performed. In all three multivariate models, decreased $CD19^+CD27^+CD24^+$ B-cell proportions were significantly associated with an increased risk of 28-day mortality (HR 2.50–2.87, $p < 0.05$). These findings suggest that decreased $CD19^+CD27^+CD24^+$ B-cell proportions were associated with increased 28-day mortality across three models with different sets of covariates, although residual confounding cannot be excluded. The number of patients at risk at 0, 7, 14, 21, and 28 days were 60, 59, 57, 57, and 56 in the Normal group, and 129, 118, 104, 96, and 92 in the Decreased group, respectively. Patients with decreased $CD19^+CD27^+CD24^+$ B-cell proportions exhibited significantly higher APACHE-II and SOFA scores than those with normal proportions ($p < 0.0001$, Fig. 4B,C). In sepsis, peripheral blood leukocytes, neutrophils, and C-reactive protein (CRP) levels are often markedly elevated, reflecting a robust systemic inflammatory response. However, we found no significant differences in WBC counts, neutrophil percentages, or CRP levels between the two groups (all $p > 0.05$; Fig. 4D–F). In contrast, PCT levels were significantly higher in the decreased $CD19^+CD27^+CD24^+$ B-cell group than in the normal group ($p < 0.0001$, Fig. 4G), suggesting that decreased $CD19^+CD27^+CD24^+$ B-cell proportions may be more closely associated with the severity of bacterial infection than with general inflammation. These findings suggest that decreased $CD19^+CD27^+CD24^+$ B-cell proportions may serve as a potential biomarker for identifying patients with sepsis at higher risk of organ dysfunction and severe infection.

Decreased $CD19^+CD27^+CD24^+$ B Cell Proportion Below the Pre-specified Threshold Is Associated With More Severe Multi-Organ Impairment, Particularly Acute Respiratory Failure

Sepsis frequently leads to multiple organ dysfunction syndrome (MODS), as reflected by a decreased oxygenation index (PaO_2/FiO_2), indicating respiratory dysfunction; elevated serum creatinine (Cr) and BUN levels, indicating acute kidney injury; elevated BNP levels, indicating cardiac dysfunction; and increased AST and ALT levels, indicating

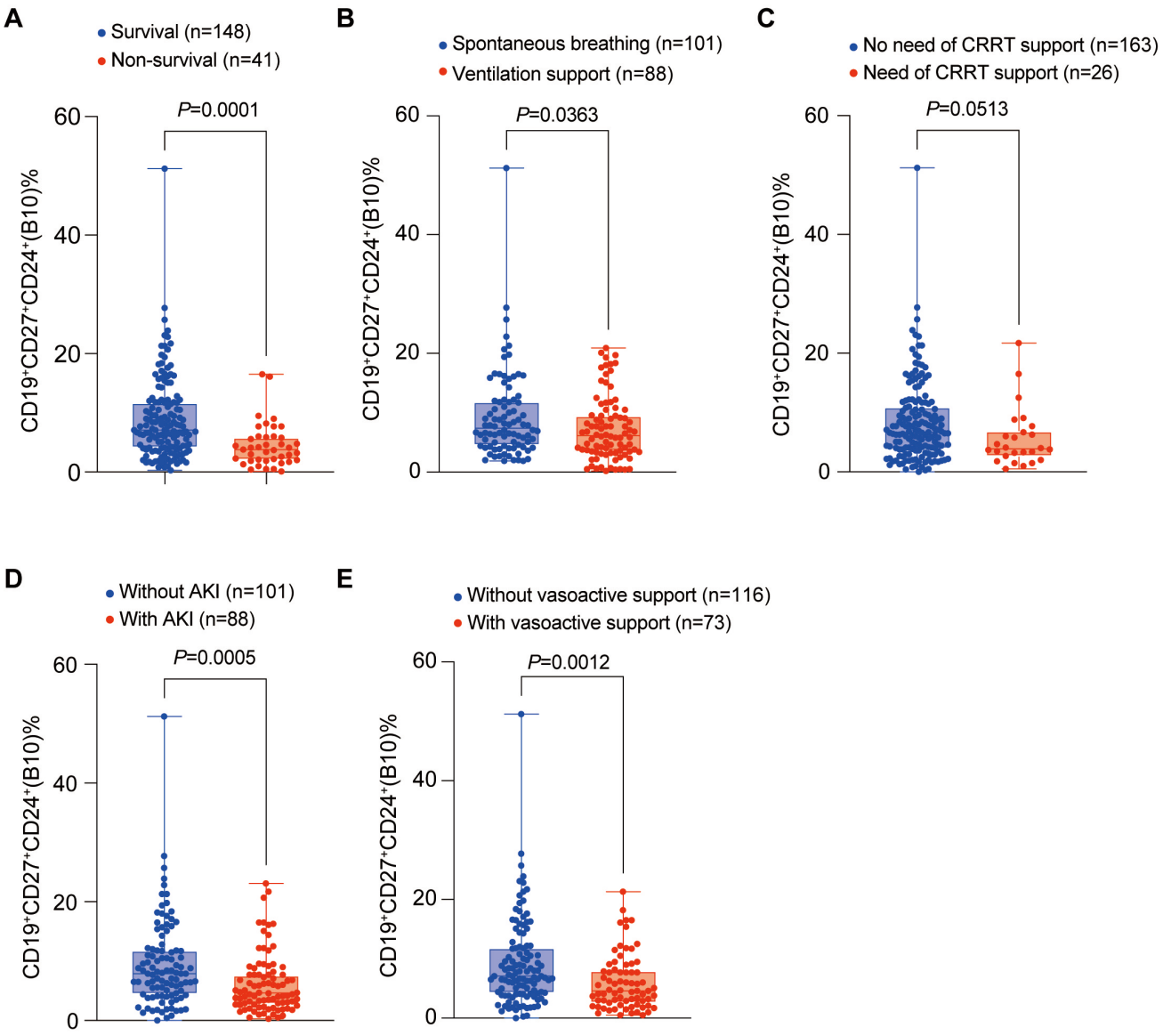


Fig. 3. Decreased proportions of $CD19^+CD27^+CD24^+$ B cells are associated with adverse clinical outcomes in patients with sepsis. Box plots with individual data points comparing $CD19^+CD27^+CD24^+$ B cell proportions between (A) survivors (n = 148) and non-survivors (n = 41), (B) patients breathing spontaneously (n = 101) and those requiring ventilatory support (n = 88), (C) patients not requiring CRRT (n = 163) and those requiring CRRT (n = 26), (D) patients without AKI (n = 101) and those with AKI (n = 88), and (E) patients not requiring vasoactive support (n = 116) and those requiring vasoactive support (n = 73).

hepatic enzyme elevation [25]. We further evaluated the association between decreased baseline $CD19^+CD27^+CD24^+$ B-cell proportions and impairment of different organ systems. We found that patients with decreased proportions of $CD19^+CD27^+CD24^+$ B cells exhibited significantly lower PaO_2/FiO_2 ratios, indicating more severe respiratory dysfunction ($p < 0.0001$, Fig. 5A), as well as higher Cr levels, suggesting impaired renal function ($p = 0.0219$, Fig. 5B). Although BUN ($p = 0.1296$, Fig. 5C) and ALT ($p = 0.2820$, Fig. 5D) levels were similar between the two groups, AST ($p = 0.0114$, Fig. 5E) and BNP ($p = 0.0404$, Fig. 5F) levels were significantly higher in the decreased $CD19^+CD27^+CD24^+$ B-cell group than in the normal group. These findings demonstrate that decreased proportions of $CD19^+CD27^+CD24^+$ B cells are associated with organ function-related laboratory abnormalities, particularly those involving the respiratory, renal, and cardiovascular systems.

$CD19^+CD27^+CD24^+$ B Cell Percentage Is Associated With 28-Day Mortality and Shows Discriminative Ability Comparable to Conventional Severity Scores

To further evaluate the discriminative ability of $CD19^+CD27^+CD24^+$ B cell percentage for predicting 28-day mortality and to compare it with established clinical

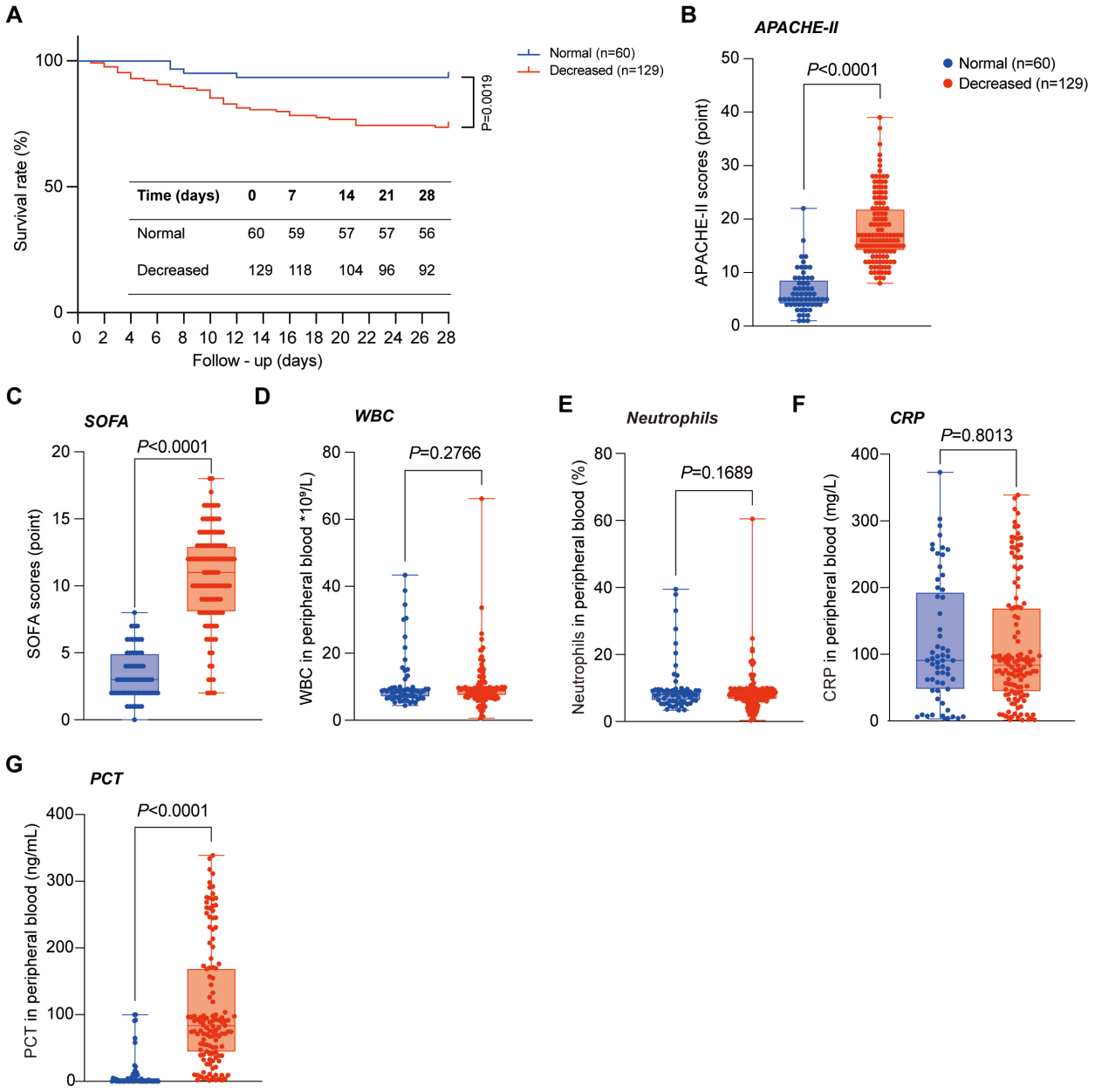


Fig. 4. Decreased baseline proportions of CD19$^+$CD27$^+$CD24$^+$ B cells (<8.99%) are associated with higher 28-day mortality and greater disease severity. (A) Comparison of 28-day survival rates between the normal CD19$^+$CD27$^+$CD24$^+$ B-cell group (n = 60) and the decreased CD19$^+$CD27$^+$CD24$^+$ B-cell group (n = 129), with "a number at risk" table below the Kaplan-Meier curves. Box plots with individual data points comparing (B) APACHE-II scores, (C) SOFA scores, (D) white blood cell (WBC) counts, (E) neutrophil percentages, (F) C-reactive protein (CRP) levels, and (G) procalcitonin (PCT) levels between the two groups.

severity scores, ROC curve analysis was performed for CD19$^+$CD27$^+$CD24$^+$ B cell, SOFA score, and APACHE-II score (Fig. 6A). The AUC was 0.734 (95% CI: 0.652–0.812) for CD19$^+$CD27$^+$CD24$^+$ B-cell percentage, 0.754 for SOFA, and 0.732 for APACHE-II. The optimal cut-off value was 6.00% for CD19$^+$CD27$^+$CD24$^+$ B cell percentage (sensitivity 80.5%, specificity 62.8%, Youden index 0.433), 9.00 for SOFA (sensitivity 87.8%, specificity 59.5%, Youden index 0.473), and 16.00 for APACHE-II (sensitivity 70.7%, specificity 66.9%, Youden index 0.376) (Fig. 6B). The 8.99% threshold was pre-specified from the healthy adult reference range and was used for group stratification [24]; it was not derived from the current sepsis cohort. The ROC-derived 6.00% cutoff was exploratory and was not used to define the primary groups. The proximity of these two values is hypothesis-generating, but the 6.00% cutoff requires external validation. These results indicate that the discriminative ability of CD19$^+$CD27$^+$CD24$^+$ B cell percentage was comparable to that of SOFA and APACHE-II.

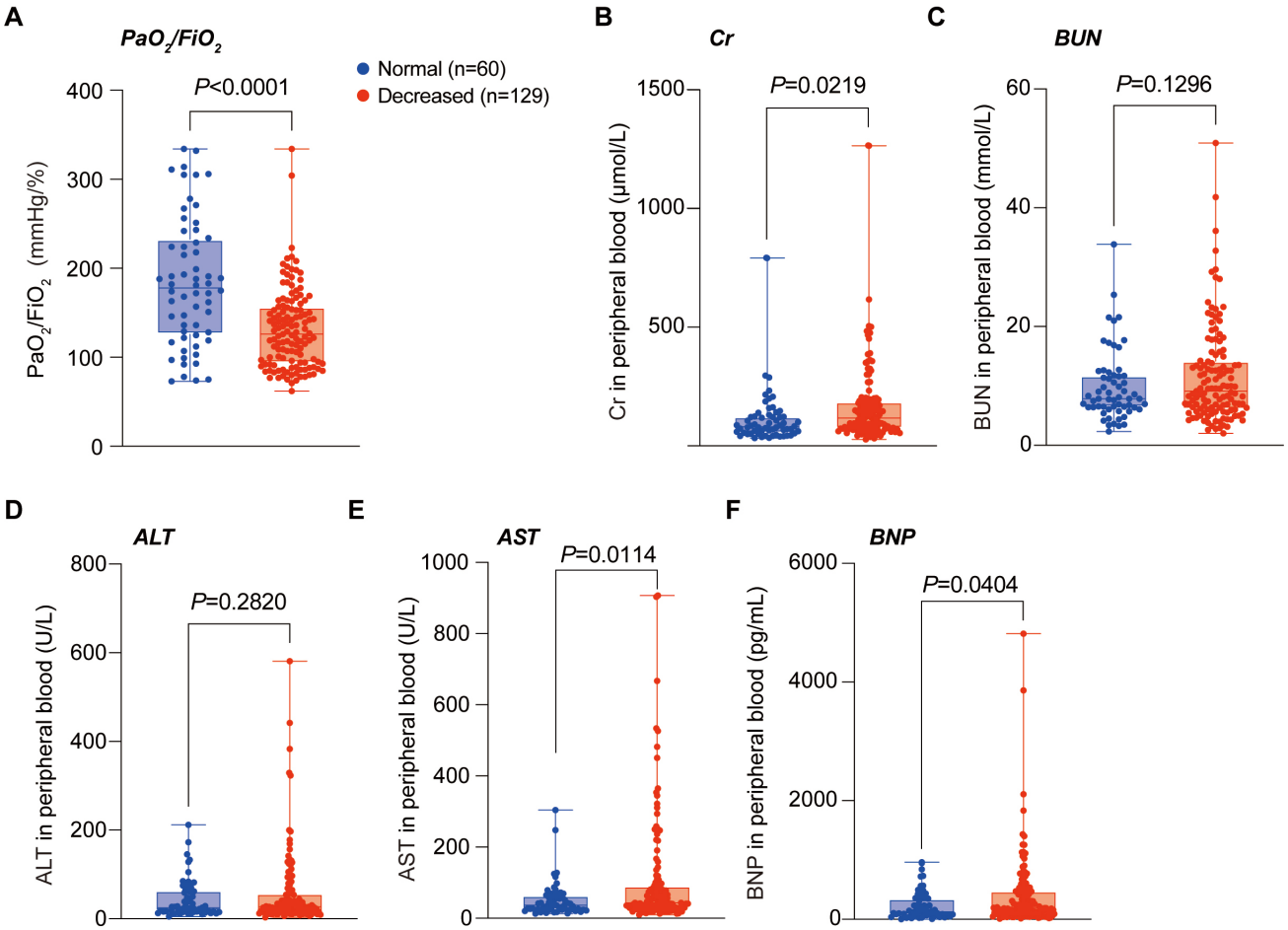


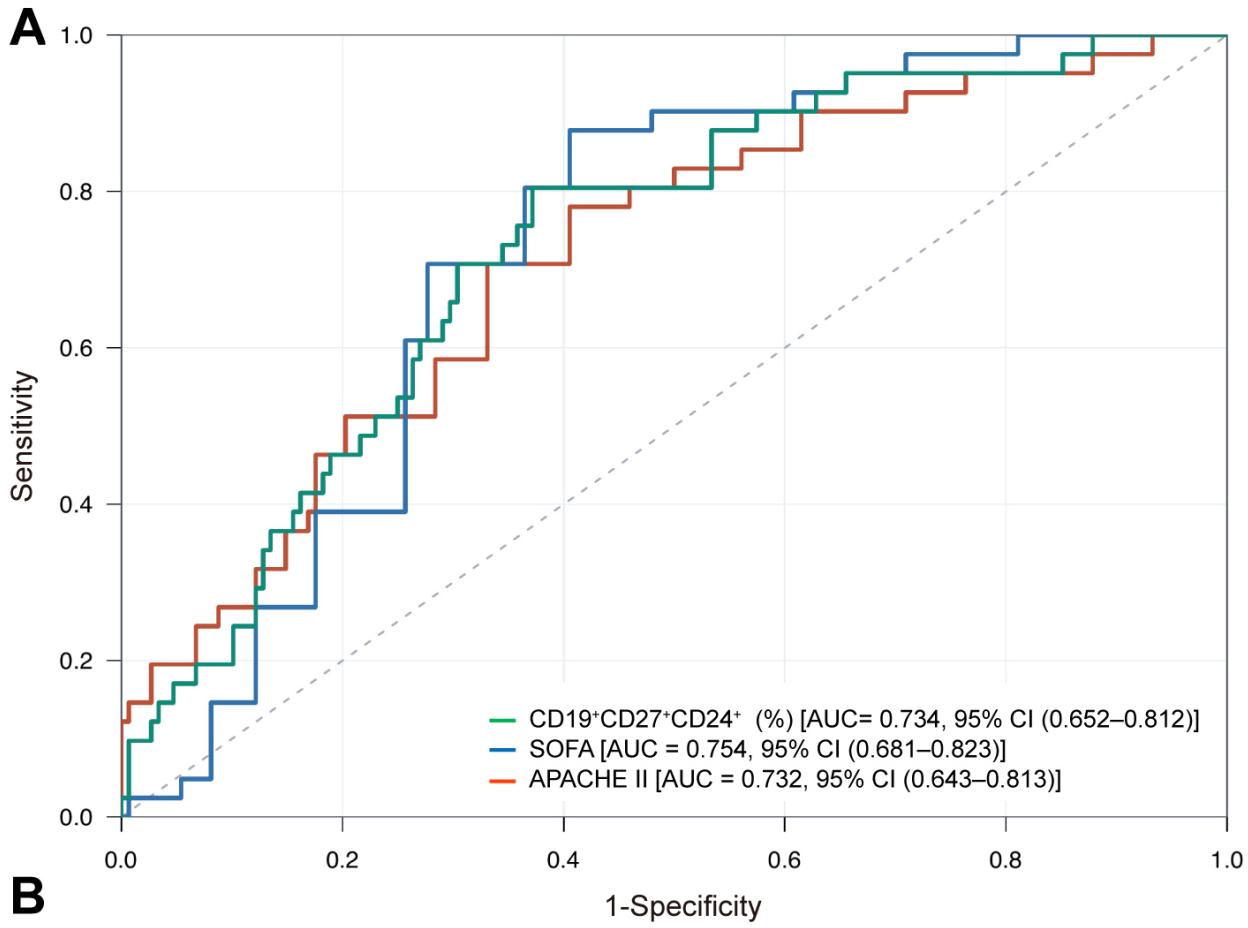
Fig. 5. Decreased CD19$^+$CD27$^+$CD24$^+$ B cell proportions are associated with worse organ function-related laboratory parameters. Box plots with individual data points comparing (A) the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen (PaO_2/FiO_2), (B) creatinine (Cr) levels, (C) blood urea nitrogen (BUN) levels, (D) alanine aminotransferase (ALT) levels, (E) aspartate aminotransferase (AST) levels, and (F) brain natriuretic peptide (BNP) levels between the normal CD19$^+$CD27$^+$CD24$^+$ B-cell group (n = 60) and the decreased CD19$^+$CD27$^+$CD24$^+$ B-cell group (n = 129).

Discussion

In this study, we characterized the peripheral B cell subset landscape in 189 patients with sepsis. We found substantial remodeling of the B cell compartment, with decreased proportions of CD19$^+$CD27$^+$CD24$^+$ B cells, transitional B cells, and naive B cells, alongside a marked expansion of plasmablasts. Among all subsets examined, CD19$^+$CD27$^+$CD24$^+$ B cells showed the strongest negative correlations with disease severity and poor prognosis. Decreased CD19$^+$CD27$^+$CD24$^+$ B-cell proportions were significantly associated with higher 28-day mortality and organ function-related laboratory abnormalities involving the respiratory, renal, and cardiovascular systems. Together, these findings suggest that decreased CD19$^+$CD27$^+$CD24$^+$ B-cell proportions may serve as a useful biomarker for early risk stratification in sepsis.

Sepsis remains a leading cause of death in intensive care units worldwide, and its pathophysiology involves systemic hyperinflammation, immune dysfunction, and multiorgan failure [3,4]. Although dysregulation of innate immunity and T lymphocytes has been extensively studied, B lymphocytes have traditionally been regarded mainly as antibody-producing effectors, and the roles of their functional subsets in sepsis have received less attention. By mapping these B cell subpopulations, our study provides a more detailed clinical view of sepsis-induced humoral immune remodeling.

One interesting finding of our study is what we refer to as the “plasmablast paradox”, which suggests that immune homeostasis may be more important than the magnitude of the effector response. Patients with sepsis showed a marked expansion of circulating plasmablasts, reflecting active adaptive immune activation, but this expansion was not correlated with disease severity scores (SOFA and APACHE-II) or length of hospital stay. This dissociation suggests that a strong humoral effector response alone does not necessarily provide a direct clinical benefit or accelerate



Variables	Optimal cutoff value	AUC	95% CI	Sensitivity	Specificity	Youden index
$CD19^+CD27^+CD24^+$ B cell percentage	6.00%	0.734	0.652-0.812	80.5%	62.8%	0.433
SOFA scores	9.00	0.754	0.681-0.823	87.8%	59.5%	0.473
APACHE-II scores	16.00	0.732	0.643-0.813	70.7%	66.9%	0.376

Fig. 6. ROC curves of $CD19^+CD27^+CD24^+$ B-cell percentage, SOFA score, and APACHE-II score for 28-day mortality in patients with sepsis. (A) The AUC was 0.734 (95% CI: 0.652–0.812) for $CD19^+CD27^+CD24^+$ B-cell percentage, 0.754 for SOFA, and 0.732 for APACHE-II. (B) The optimal cutoff value was 6.00% for $CD19^+CD27^+CD24^+$ B cell percentage (sensitivity 80.5%, specificity 62.8%, Youden index 0.433), 9.00 for SOFA (sensitivity 87.8%, specificity 59.5%, Youden index 0.473), and 16.00 for APACHE-II (sensitivity 70.7%, specificity 66.9%, Youden index 0.376).

recovery. In sepsis, mortality and poor outcomes are rarely caused by an absolute deficiency in antibody production; instead, they are more often associated with the host's inability to control tissue-destructive inflammatory cascades [4]. Thus, plasmablasts may serve as an internal biological control: their expansion indicates active immune engagement, while the lack of correlation with clinical outcomes suggests that immune activation without regulatory balance may not be sufficient to ensure a favorable prognosis.

In contrast, $CD19^+CD27^+CD24^+$ B cells were markedly reduced in patients with sepsis, showing the strongest and most consistent negative correlations with disease severity and length of hospital stay among all evaluated subsets. Functionally, the regulatory capacity of $CD19^+CD27^+CD24^+$ B cells provides a critical negative feedback loop that constrains excessive immune activation [12,13,26,27]. Conventional intuition might suggest that a reduction in these regulatory cells would alleviate immune suppression and enhance antimicrobial defense. However,

Table 2. Univariate Cox regression analysis of 28-day mortality.

Variables	HR	95% CI	*p* value
$CD19^+CD27^+CD24^+$ B cells group (Decreased vs Normal)	3.68	1.73–7.84	<0.001
$CD19^+CD27^+CD24^+$ B cells proportion (%)	0.86	0.80–0.93	<0.001
Age (years)	1.01	0.99–1.04	0.29
Sex (Male vs. Female)	1.12	0.53–2.37	0.77
APACHE-II scores (points)	1.13	1.08–1.19	<0.001
SOFA Scores (points)	1.22	1.14–1.31	<0.001
Vasoactive support	4.26	1.94–9.36	<0.001
Mechanical ventilation	2.51	1.23–5.12	0.011
AKI	3.12	1.51–6.45	0.002
PCT (ng/mL)	1.08	0.94–1.25	0.28

Abbreviations: HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; APACHE-II, Acute Physiology and Chronic Health Evaluation II; AKI, acute kidney injury; PCT, procalcitonin.

Table 3. Multivariate Cox regression analysis of 28-day mortality (adjusted for age and SOFA score).

Variables	HR	95% CI	*p* value
$CD19^+CD27^+CD24^+$ B cells group (Decreased or Normal)	2.87	1.33–6.19	0.007
Age (years)	1.00	0.97–1.03	0.930
SOFA Scores (points)	1.20	1.11–1.30	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

Table 4. Multivariate Cox regression analysis of 28-day mortality (adjusted for age and APACHE-II score).

Variables	HR	95% CI	*p* value
$CD19^+CD27^+CD24^+$ B cells group (Decreased or Normal)	2.65	1.20–5.85	0.016
Age (years)	1.00	0.97–1.03	0.960
APACHE-II Scores (points)	1.11	1.06–1.17	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; APACHE-II, Acute Physiology and Chronic Health Evaluation II.

Table 5. Multivariate Cox regression analysis of 28-day mortality (adjusted for SOFA scores and vasoactive support).

Variables	HR	95% CI	*p* value
$CD19^+CD27^+CD24^+$ B cells group (Decreased or Normal)	2.50	1.12–5.57	0.025
SOFA Scores (points)	1.14	1.04–1.25	0.005
Vasoactive support	2.20	0.95–5.10	0.067

Abbreviations: HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

our clinical data suggest the opposite. Higher baseline $CD19^+CD27^+CD24^+$ B cells were consistently associated with a more favorable clinical status. When considered alongside the plasmablast paradox, this pattern is particularly revealing. Unchecked immune hyperactivation does not necessarily clear infection more effectively; rather, it can drive uncontrolled inflammation and collateral tissue damage [14]. Conversely, the improved prognosis associated with higher proportions of immunosuppressive $CD19^+CD27^+CD24^+$ B cells suggests that this subset was associated with a more favorable clinical status; whether this reflects a protective effect requires functional and causal studies. This contrast further reinforces the importance of maintaining immune homeostasis, rather than merely mounting an aggressive effector response, for recovery from sepsis.

The clinical translational value of $CD19^+CD27^+CD24^+$ B cell profiling is further highlighted by our two-tiered analytical approach. First, by stratifying patients according to clinical trajectories, we established that a marked decrease in $CD19^+CD27^+CD24^+$ B-cell proportions is associated with severe physiological decompensation. Non-survivors and patients requiring mechanical ventilation or vasoactive support exhibited significantly lower proportions of $CD19^+CD27^+CD24^+$ B cells than their respective hemodynamically stable comparison groups. These patterns indicate that decreased proportions of $CD19^+CD27^+CD24^+$ B cells are closely associated with critical physiological dysfunction, particularly acute respiratory failure and circulatory shock. Although $CD19^+CD27^+CD24^+$ B-cell proportions also tended to be lower in patients requiring continuous renal replacement therapy, this difference did not reach statistical significance, possibly because of the limited size of this subgroup.

However, associations based on clinical outcomes alone are insufficient for proactive clinical decision-making. Therefore, to assess the utility of $CD19^+CD27^+CD24^+$ B cells as an early prognostic biomarker, we stratified the cohort into 'normal' and 'decreased' groups based on a predefined physiological baseline threshold (8.99%). In the present study, the ROC-derived optimal cutoff for predicting 28-day mortality was 6.00%. Interestingly, this value is quite close to the 8.99% cutoff reported in previous literature, which was used for patient stratification in our cohort [24]. This consistency across different studies suggests that the $CD19^+CD27^+CD24^+$ B cell percentage may be used for identifying high-risk patients, although slight variations may exist due to differences in cohort characteristics and statistical methods. However, this requires further experimental validation. This forward-looking analysis yielded our most compelling clinical evidence: patients in the decreased $CD19^+CD27^+CD24^+$ B-cell group experienced a significantly worse clinical course, characterized not only by elevated disease severity scores (APACHE-II and SOFA) but, most importantly, by a markedly reduced

28-day survival rate. Furthermore, multivariate Cox regression confirmed that decreased $CD19^+CD27^+CD24^+$ B-cell proportions were independently associated with increased 28-day mortality, and ROC analysis showed discriminative ability comparable to that of SOFA and APACHE-II scores (AUC 0.734 vs. 0.754 and 0.732, respectively). The systemic biomarker profile of this high-risk group with decreased $CD19^+CD27^+CD24^+$ B-cell proportions revealed a striking divergence. Although these patients exhibited markedly elevated PCT levels, a robust indicator of bacterial infection and the associated endotoxin-driven host responses, they showed no significant differences in conventional acute-phase markers such as WBC counts, neutrophil percentages, or CRP levels. This distinction suggests that decreased $CD19^+CD27^+CD24^+$ B-cell proportions may be more closely associated with the severity of the host–pathogen immunodynamic state than with general, non-specific inflammation.

Unchecked inflammatory activation ultimately compromises multi-organ function [28,29,30]. In our cohort, patients with decreased proportions of $CD19^+CD27^+CD24^+$ B cells (<8.99%) exhibited more severe systemic organ impairment, marked by reduced PaO_2/FiO_2 ratios, elevated serum creatinine, increased AST, and elevated BNP levels. In particular, the significantly lower PaO_2/FiO_2 ratios in patients with decreased proportions of $CD19^+CD27^+CD24^+$ B cells provide indirect clinical evidence linking the reduction in these cells to more severe respiratory dysfunction in sepsis. The concomitant changes in renal, hepatic, and cardiac markers further support a vital role for $CD19^+CD27^+CD24^+$ B cells in maintaining systemic organ homeostasis during severe infection. These findings may help identify high-risk patients in a research setting; however, the current single-center evidence is not sufficient to support clinical risk stratification or decision-making. Multicenter, large-sample studies with external validation are required.

Several limitations of this study should be noted. First, this was a single-center observational study with a limited sample size and no external validation; the findings require validation in larger, multicenter cohorts with diverse sepsis etiologies before clinical use. Additionally, owing to the limited number of mortality events, the multivariable Cox models included only a restricted number of covariates, and residual confounding from unmeasured factors, such as comorbidities and infection characteristics, cannot be excluded. Second, IL-10 expression or intracellular cytokine assay was not performed; therefore, the reduction in this phenotype cannot be equated with functional B10-cell deficiency. Longitudinal sampling paired with functional assays would provide deeper mechanistic insight into the dynamics of decreased $CD19^+CD27^+CD24^+$ B-cell proportions during the ICU stay. Third, due to the observational design, a direct causal relationship between decreased proportions of $CD19^+CD27^+CD24^+$ B cells and organ dysfunction cannot be definitively established. Fourth, the previously used 8.99% threshold was derived from the reference range of healthy adults rather than from a prognostic model based on this cohort, and its validity as a prognostic threshold for sepsis has not been established. Fifth, all B-cell subsets were analyzed as proportions rather than absolute counts. Sepsis may cause global lymphopenia, and a decreased proportion may not fully reflect absolute cell numbers. Future studies should validate these findings using absolute counts and longitudinal sampling. We also performed ROC curve analysis to determine the optimal cutoff value of the $CD19^+CD27^+CD24^+$ B-cell percentage for predicting 28-day mortality. A total of 189 patients were included, of whom 41 died (Outcome = 1) and 148 survived (Outcome = 0). The AUC was 0.734 (95% CI: 0.652–0.812), indicating that the $CD19^+CD27^+CD24^+$ B-cell percentage has moderate predictive value for 28-day mortality. The optimal cutoff value was 6.00%, with a sensitivity of 80.5% and a specificity of 62.8% (Youden index = 0.433). When patients were stratified by this cutoff, those with a $CD19^+CD27^+CD24^+$ B-cell percentage below 6.00% had a significantly increased risk of death. Notably, the discriminative ability of the $CD19^+CD27^+CD24^+$ B-cell percentage for 28-day mortality (AUC = 0.734) was comparable to that of SOFA (AUC = 0.754) and APACHE-II (AUC = 0.732). As a single immunological parameter, the $CD19^+CD27^+CD24^+$ B-cell percentage showed predictive value similar to that of conventional clinical severity scores (Fig. 6). These findings indicate that lower $CD19^+CD27^+CD24^+$ B-cell percentages are associated with a higher mortality risk, suggesting that higher proportions of this subset may be associated with a more favorable clinical status in sepsis. Future studies utilizing *in vivo* animal models, particularly focusing on sepsis-induced respiratory dysfunction, are essential to mechanistically elucidate the protective role of $CD19^+CD27^+CD24^+$ B cells and validate their potential as a therapeutic target.

Conclusions

In conclusion, our study demonstrates that peripheral $CD19^+CD27^+CD24^+$ B cells are significantly reduced in septic patients and that this reduction is closely associated with disease severity, increasing organ support requirements, organ function-related laboratory abnormalities, and mortality. By contrasting the prognostic value of $CD19^+CD27^+CD24^+$ B cells with the non-prognostic expansion of effector plasmablasts, our findings highlight that the loss of immune homeostasis-rather than a failure of immune activation-is a central driver of adverse outcomes in sepsis. $CD19^+CD27^+CD24^+$ B-cell profiling may represent a candidate approach for prognostic research, providing a rationale for future multicenter validation and precision immunomonitoring studies.

Abbreviations

IL-10, interleukin-10; ICU, intensive care unit; APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; Cr, creatinine; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; ALI, acute lung injury; MODS, multiple organ dysfunction syndrome.

Availability of Data and Materials

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

Author Contributions

QS and RLW designed the study; QS, XXM, YZ, YX, QT, JFW, LiuW, and HX performed the research; QS, LuW, DNC, and QT collected and analyzed the data. QS drafted the manuscript. RLW, XXM, YZ, YX, QT, LiuW, DNC, JFW, LuW, and HX revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Shanghai General Hospital (Approval No. 2021KY037) on April 23, 2021, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all septic patients or their legal representatives, and from all non-sepsis controls prior to enrollment.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this manuscript, the authors used DeepSeek-V3 solely for language polishing and grammar correction. The authors confirm that no AI tools were used for data analysis, data interpretation, or generation of scientific content. After using this tool, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy, originality, and scientific integrity. The authors take full responsibility for the final version of the manuscript.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638214.284.

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