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Original Article

Complement activation and humoral immune dysregulation drive progression of pediatric septic shock: a retrospective cohort study

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Abstract: Objective: To investigate the clinical characteristics of pediatric septic shock (SS) and analyze their correlation with immune dysregulation in affected children. Methods: A retrospective analysis was conducted on 192 pediatric sepsis patients admitted to Children's Hospital of Nanjing Medical University between January 2022 and January 2025. Among these, 54 patients who developed shock were classified into a shock group, and the remaining 138 patients were classified into non-shock group. Laboratory test results (including immune and inflammatory indices) and clinical scores (Acute Physiology and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores) were analyzed. Multivariate logistic regression was applied to verify the predictive role of immune markers for SS, and a nomogram was developed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of identified immune predictors, and their performance was compared using the Delong test. Results: The shock group showed significantly higher rates of impaired consciousness (74.07% vs 0.00%, *P*<0.001) and neurological symptoms (38.89% vs 19.57%, P=0.005), along with significantly lower immunoglobulin (Ig) G, complement component 3 (C3) and complement component 4 (C4) levels (all P<0.001) than the non-shock group. Correlation analyses revealed that APACHE II and SOFA scores were negatively associated with IgG, C3, and C4 levels (all *P*<0.05), with C3 showing additional negative correlations with white blood cell count (WBC) and procalcitonin (PCT), and C4 with PCT. Importantly, IgG, C3 and C4 were identified as independent predictors of shock risk, with C3 demonstrating the highest diagnostic performance in ROC analysis. Conclusion: Pediatric SS is characterized by complement activation (reduced C3/C4) and IgG deficiency, which strongly correlate with disease severity. C3 and IgG demonstrated high predictive accuracy for shock progression.

Keywords: Septic shock, immune-related factors, inflammatory factors, immune dysregulation, correlation

Introduction

Septic shock (SS), the clinical manifestation of sepsis and cardiovascular dysfunction, is the most severe complication of sepsis [1]. As one of the most critical clinical syndromes in pediatric intensive care units (ICU), SS continues to exhibit persistently high morbidity and mortality rates, posing a serious threat to children's health [2]. Global epidemiological data indicate that the annual incidence of SS in the pediatric population is 3-8 per 1,000, with a mortality rate as high as 20-30% [3]. These figures are even more alarming in developing countries [3]. Despite continuous advancements in treatment strategies such as fluid resuscitation, vasoactive medications, and antibiotics, the clinical prognosis of SS remains suboptimal.

The pathophysiology of sepsis involves multiorgan dysfunction caused by dysregulated immune responses to severe infection or trauma [4]. It represents not merely a systemic inflammatory response, but more importantly, a breakdown of immune regulation - progressing from hyperimmune activation to widespread immunosuppression [5]. Traditionally, SS is considered as an extreme manifestation of systemic inflammatory response syndrome induced by infection, characterized by persistent hypotension and tissue hypoperfusion [6]. However, emerging evidence increasingly dem-

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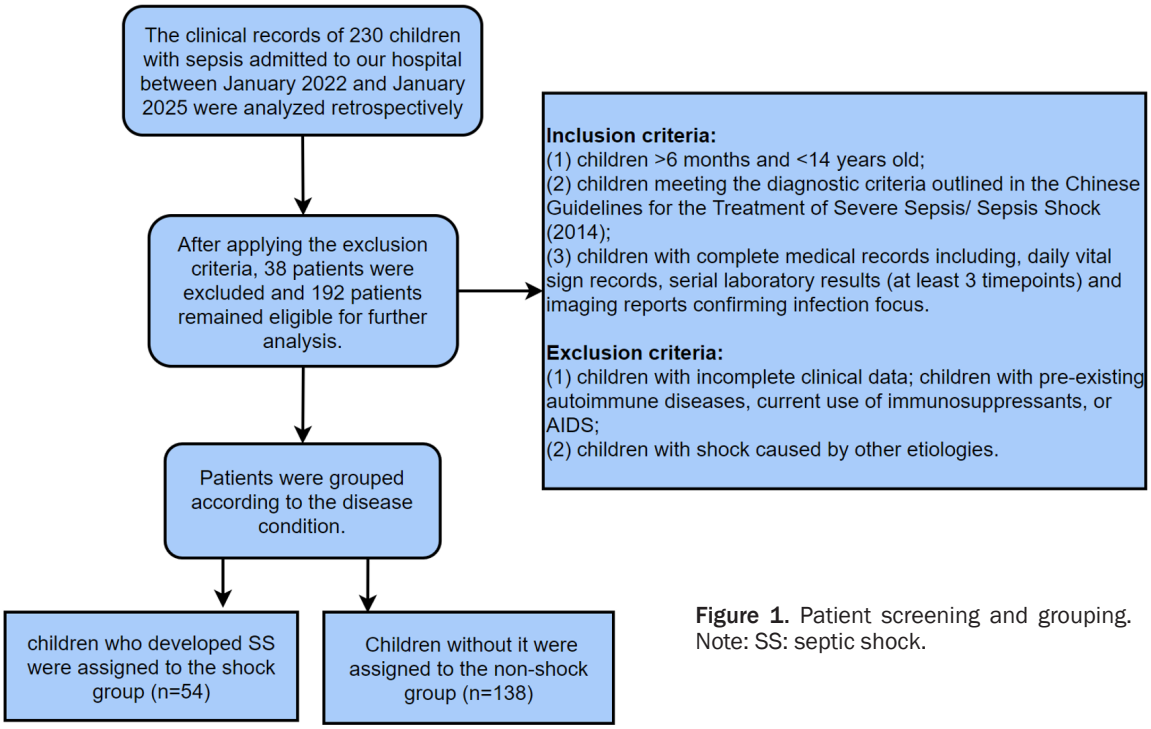

Figure 1. Patient screening and grouping. Note: SS: septic shock.

onstrates a central role of immune system dysregulation in the pathogenesis of SS. For instance, Girardis *et al.* [7] highlighted that in SS patients, the intricate interactions between the immune system, coagulation, and endothelium are crucial for modulating host responses to infection. Delano *et al.* [8] further proposed that sepsis-associated immune cell dysfunction correlates with long-term mortality. Children, as a distinct population, exhibit unique developmental characteristics in their immune systems [9]. On the one hand, innate immunity predominates, represented with active neutrophil and monocyte-macrophage systems [9]. On the other hand, the development of adaptive immune system remains incomplete, showing significant differences in T lymphocyte subsets and function compared to adults [10]. These characteristics result in distinct immunopathological mechanisms in pediatric SS. Despite these advances, pediatric-specific immune mechanisms in SS remain poorly characterized, particularly regarding complement activation patterns and immunoglobulin class-specific responses.

Although numerous studies have explored the immune mechanisms of sepsis, systematic research focusing on SS in the pediatric population remains limited. Therefore, this study was designed to systematically analyze the correlation between clinical characteristics and immune indices in children with SS, aiming to clarify the relationship between immune markers and the disease.

This study innovatively identifies three key aspects: (1) class-specific immunoglobulin depletion patterns (IgG-selective deficiency) in pediatric SS, (2) complement consumption as a severity biomarker, and (3) the dynamic interplay between complement activation and inflammatory responses. These findings may guide future immunomodulatory therapies targeting specific immune pathways in children.

Materials and methods

Study population

A retrospective analysis was conducted on the clinical data of 230 children with sepsis admitted to Children's Hospital of Nanjing Medical University between January 2022 and January 2025. According to the inclusion and exclusion criteria, 192 sepsis patients were ultimately enrolled. Among them, children who developed SS were assigned to the shock group (n=54), while those without SS were assigned to the non-shock group (n=138). The screening and grouping details are shown in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: children aged >6 months and <14 years; children meeting the diagnostic criteria outlined in the *Chinese Guidelines for the Treatment of Severe Sepsis/Sepsis Shock* (2014) [11]; children with complete medical records, including daily vital sign records, serial laboratory results (at least 3 timepoints), and imaging reports confirming an infection focus.

Exclusion criteria: children with incomplete clinical data; children with pre-existing autoimmune diseases, current use of immunosuppressants, or AIDS; and children with shock caused by other etiologies.

Ethical statements

This study was approved by the ethnical committee of Children's Hospital of Nanjing Medical University, with ethnical approval number of XXX.

Diagnostic criteria for SS [11]

The diagnostic criteria for SS include: (1) confirmed or suspected infection accompanied by fever (body temperature >38.3°C) or hypothermia (body temperature <36°C); (2) tachycardia (heart rate >90 beats/min or >2 standard deviations above age-adjusted norms); (3) concurrent clinical manifestations such as altered mental status, significant edema/positive fluid balance, or hyperglycemia; (4) laboratory abnormalities including leukocytosis (white blood cell count (WBC) >12×10^9/L), leukopenia (WBC <4×10^9/L), normal WBC with >10% immature cells, C-reactive protein >2 standard deviation above normal, or procalcitonin (PCT) >2 SD above normal; (5) concurrent cardiovascular dysfunction requiring vasoactive drugs to maintain normal blood pressure after 1-hour isotonic fluid infusion, plus ≥2 of the following: metabolic acidosis, arterial lactate >2× upper limit of normal, oliguria, capillary refill time >5 seconds, or core-to-peripheral temperature gap >3°C.

Data collection

Comprehensive clinical data were collected for all enrolled pediatric patients, including demographic characteristics (age, sex, body mass index (BMI), primary infection site, and residential area), clinical manifestations, laboratory test results (encompassing both immunological and inflammatory indices), and disease severity scores (Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores).

Outcome measures

Primary outcome measures: (1) Immunological indices (e.g., IgA, IgM, and IgG) and complement components (C3 and C4): For all enrolled children, 15 mL fasting venous blood was collected upon admission. After 30-min standing at room temperature, the samples were subjected to centrifugation (3000 rpm, 15 minutes) to separate serum, which was then aliquoted into three equal parts (5 mL each) and stored at -80°C for subsequent analysis. Immunological parameters were measured using immunoturbidimetry on the IMMAGE 800 automated specific protein analyzer (Beckman Coulter, USA), with all procedures strictly adhering to the manufacturer's standard operating protocols.

(2) Inflammatory indices (WBC and PCT): WBC was determined using the XS900i automated hematology analyzer (Sysmex), while PCT levels were quantified via dry immunofluorescence assay on the Getein1100 fluorescence immunoassay analyzer (Getein Biotech).

(3) The correlations between serum immunological parameters (IgA, IgM, IgG, C3, and C4) and inflammatory indices (WBC and PCT) as well as disease severity scores (SOFA and APACHE II scores) were also evaluated in children with SS.

Secondary outcome measures: (1) Baseline clinical characteristics were compared between the two groups, including age, sex, BMI, infection site, and place of residence.

(2) Clinical manifestations, such as impaired consciousness, respiratory symptoms, and gastrointestinal symptoms, were compared between the groups.

(3) SOFA and APACHE II scores of the children were compared. SOFA score evaluates six organ systems (respiratory, coagulation, liver, cardiovascular, neurological, and renal), with each scored 0-4 (total range: 0-24). Higher scores indicate greater disease severity [12]. APACHE II score comprises 12 physiological

Table 1. Comparison of baseline data between the two groups

	Shock group (n=54)	Non-shock group (n=138)	z/χ^2	*P*
Age (year)	2.8 (0.3, 11.4)	2.7 (0.2, 10.2)	-0.562	0.574
Sex			1.028	0.311
Male	31 (57.41)	68 (49.28)		
Female	23 (42.59)	70 (50.72)		
BMI	17.20 (15.20, 20.03)	16.90 (15.21, 18.94)	-1.767	0.077
The primary site of infection			5.143	0.273
Abdomen	12	37		
Lung	21	41		
Digestive tract	9	21		
Urinary tract	3	22		
Others	9	17		
Place of incidence			1.459	0.227
Urban areas	21	67		
Rural areas	33	71		

Note: BMI: body mass index.

variables (e.g., rectal temperature, respiratory rate, heart rate, mean arterial pressure; scored 0-60), age (0-6 points), and chronic health status (2-5 points). The total score ranges from 0 to 71, with higher scores reflecting worse prognosis and more severe illness [13].

(4) Multivariate logistic regression and receiver operating characteristic (ROC) curve analyses were performed to evaluate the predictive value of immune markers. Model discrimination was assessed using area under the curve (AUC) comparisons (Delong test), and a nomogram was developed with Bootstrap validation (1000 resamples).

Statistical analysis

Sample size was calculated using G*Power 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Germany). Based on a two-tailed independent t-test with α=0.05, power =0.95, and medium effect size (Cohen's d=0.5), the required sample size was determined to be 210. Our enrolled sample of 192 participants provided adequate power (94.3%) to detect significant differences in outcome measures. SPSS 20.0 (IBM Corp, Armonk, NY, USA) was employed for data processing, and GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) was used for graphical representations.

Counting data were presented as [n (%)], with between-group comparisons performed using chi-square tests (χ^2). The normality of measurement variables was assessed by the Kolmogorov-Smirnov test; normally distributed data were expressed as mean ± standard deviation and compared using the independent samples t-test between groups, whereas non-normally distributed data were reported as median (minimum, maximum) values and compared using Mann-Whitney U test between groups. *Pearson*'s correlation analysis was conducted to examine correlations among variables. Multivariate logistic regression was used to develop predictive models, with model performance evaluated by ROC curve analysis. Area under the curve (AUC) comparisons were performed using Delong's test. A clinical prediction nomogram was constructed and internally validated with 1000 Bootstrap resamples. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of enrolled children

Analysis of baseline characteristics revealed no significant differences in age, sex, BMI, infection sites, and place of residence between the shock and non-shock groups (all $P>0.05$; **Table 1**), indicating comparable baseline demographics between the two groups.

Clinical manifestations of enrolled children

The shock group demonstrated the following symptom profile: fever in 42 cases (77.78%), impaired consciousness in 40 cases (74.07%),

Table 2. Comparison of clinical manifestations between the two groups

	Fever	Impaired consciousness	Respiratory symptom	Gastrointestinal symptoms	Neurological symptoms	Genitourinary symptoms	Others
Shock group (n=54)	42 (77.78)	40 (74.07)	27 (50.00)	26 (48.15)	21 (38.89)	0 (0.00)	7 (12.96)
Non-shock group (n=138)	113 (81.88)	0 (0.00)	62 (44.93)	49 (35.50)	27 (19.57)	4 (2.90)	21 (15.21)
χ^2	0.421	129.110	0.402	2.605	7.729	1.599	0.158
P	0.517	<0.001	0.526	0.107	0.005	0.206	0.691

Table 3. Comparison of immunological indices between the two groups

	Shock group (n=54)	Non-shock group (n=138)	t	*P*
IgA (g/L)	0.56±0.13	0.55±0.18	0.141	0.888
IgM (g/L)	0.82±0.26	0.90±0.34	1.592	0.113
IgG (g/L)	5.32±1.03	8.16±1.94	10.230	<0.001
C4 (g/L)	0.15±0.06	0.23±0.09	6.020	<0.001
C3 (g/L)	0.70±0.24	1.42±0.39	12.670	<0.001

Notes: IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4.

Table 4. Comparison of inflammatory indices between the two groups

	Shock group (n=54)	Non-shock group (n=138)	t	*P*
WBC ($\times 10^9$)	17.30±3.58	11.44±3.24	10.930	<0.001
PCT (ug/L)	4.28±1.32	2.72±1.06	8.518	<0.001

Notes: WBC: white blood cell count; PCT: procalcitonin.

respiratory symptoms in 27 cases (50.00%), gastrointestinal symptoms in 26 cases (48.15%), and neurological symptoms in 21 cases (38.89%); other symptoms in 7 cases (12.96%), including rash (2 cases), limb swelling/pain (1 case), abdominal mass (1 case), generalized sclerosis (1 case), skin erythema (1 case), and multi-site hemorrhage (1 case), with no genitourinary symptoms observed.

In contrast, the non-shock group exhibited the following symptom profile: fever in 113 cases (81.88%), no cases of impaired consciousness (0.00%), respiratory symptoms in 62 cases (44.93%), gastrointestinal symptoms in 49 cases (35.50%), neurological symptoms in 27 cases (19.57%), genitourinary symptoms in 4 cases (2.90%), and other symptoms in 21 cases (15.21%), including skin/soft tissue swelling/pain (13 cases), rash (2 cases), jaundice (3 cases), generalized edema (2 cases), and multi-site hemorrhage (1 case).

Statistical analysis revealed notably higher incidence of impaired consciousness (*P*<0.001) and neurological symptoms (*P*=0.005) in the shock group compared to the non-shock group, while no significant differences were observed in other clinical manifestations (all *P*>0.05, **Table 2**).

Comparative analysis of immunological indices between the two groups

Comparative analysis of immunological indices between the shock and non-shock groups revealed notably lower levels of IgG (5.32±1.03 g/L *vs.* 8.16±1.94 g/L), C3 (0.70±0.24 g/L *vs.* 1.42±0.39 g/L), and C4 (0.15±0.06 g/L *vs.* 0.23±0.09 g/L) in the shock group compared to the non-shock group (all *P*<0.001, **Table 3**). No significant differences were observed in IgA and IgM levels between the two groups (both *P*>0.05, **Table 3**).

Comparative analysis of inflammatory indices between the two groups

Evaluation of inflammatory indices revealed notably elevated WBC (17.30±3.58×10^9/L *vs.* 11.44±3.24×10^9/L) and PCT (4.28±1.32 μg/L *vs.* 2.72±1.06 μg/L) levels in the shock group compared to the non-shock group (both *P*<0.001) (**Table 4**).

Comparative analysis of disease severity scores between the two groups

Quantitative assessment of disease severity demonstrated notably higher SOFA (8.26±2.31 *vs.* 4.12±1.26) and APACHE II (34.54±7.90 *vs.* 24.06±3.23) scores in the shock group compared to the non-shock group (both *P*<0.001) (**Table 5**).

Table 5. Comparison of disease severity scores between the two groups

	Shock group (n=54)	Non-shock group (n=138)	t	*P*
SOFA	8.26±2.31	4.12±1.26	15.940	<0.001
APACHE II	34.54±7.90	24.06±3.23	13.080	<0.001

Notes: SOFA: sequential organ failure assessment; APACHE II: acute physiology and chronic health evaluation II.

Correlation analysis between immunological indices and SOFA score

Correlation analysis between immunoglobulin/complement levels and SOFA score in pediatric SS patients revealed strong negative correlations between SOFA score and IgG (r=-0.316, *P*=0.020), C4 (r=-0.320, *P*=0.019), and C3 (r=-0.351, *P*=0.009). In contrast, no strong correlations were observed between SOFA score and either IgA (r=0.114, *P*=0.413) or IgM (r=-0.069, *P*=0.621) (**Figure 2**).

Correlation analysis between immunological indices and APACHE II score

Correlation analysis between immunoglobulin/complement levels and APACHE II score in pediatric SS patients demonstrated strong negative correlations between APACHE II score and IgG (r=-0.282, *P*=0.039), C4 (r=-0.314, *P*=0.021), and C3 (r=-0.327, *P*=0.016). In contrast, neither IgA (r=0.114, *P*=0.412) nor IgM (r=-0.108, *P*=0.438) showed strong correlations with APACHE II score (**Figure 3**).

Correlation analysis between immunological indices and WBC

Correlation analysis between immunological indices and WBC in pediatric SS patients demonstrated significant positive correlation between IgA and WBC (r=0.287, *P*=0.035), and a strong negative correlation between C3 and WBC (r=-0.326, *P*=0.016). No strong correlations were observed for IgM, IgG or C4 with WBC (all *P*>0.05) (**Figure 4**).

Correlation analysis between immunological indices and PCT level

Correlation analysis of immunological indices with PCT level in pediatric SS patients revealed significant negative correlations between PCT level and IgG (r=-0.290, *P*=0.033), C4 (r=-0.278, *P*=0.042), and C3 (r=-0.300, *P*=0.027). In contrast, neither IgA nor IgM demonstrated significant associations with PCT level (both *P*>0.05) (**Figure 5**).

Multivariate logistic regression analysis of immune markers as predictors of SS

The multivariate logistic regression identified immunoglobulin and complement components as significant protective factors for SS in pediatric sepsis patients (**Table 6**). Specifically, IgG (OR=0.395, 95% CI: 0.254-0.615; P<0.001), C4 (OR=0.001, 95% CI: 0.012-0.039; P=0.007), and C3 (OR=0.003, 95% CI: 0.021-0.029; P<0.001) demonstrated significant inverse associations with SS risk, with C3 showing the strongest protective effect. Neither IgA (P=0.835) nor IgM (P=0.117) reached statistical significance in the multivariate logistic regression analysis.

ROC curve analysis of immune markers for SS prediction

ROC analysis (**Figure 6** and **Table 7**) revealed that C3 provided the strongest predictive value for SS (AUC=0.926, 84.8% sensitivity, 92.6% specificity at 6.695 g/L cutoff), closely followed by IgG (AUC=0.915), while C4 showed more limited discrimination (AUC=0.744). Statistical comparisons confirmed C3's superior performance versus C4 (P<0.001), though equivalent to IgG (P=0.707) (**Table 8**). These three key markers were subsequently incorporated into a validated nomogram (Bootstrap 1000×), demonstrating excellent predictive calibration (**Figure 7**).

Discussion

SS represents the most severe stage of sepsis progression, carrying significantly higher mortality rates compared to sepsis alone [14]. Both sepsis and SS patients exhibit profound immune dysfunction, with complex pathophysiological mechanisms involving multiple immune factors in disease pathogenesis [15]. Through a comparative analysis of clinical and immunological features between children with SS and non-shock cases, this study highlighted the pivotal role of immune dysfunction in the pathogenesis of pediatric SS.

In this study, the shock group exhibited markedly higher incidences of impaired conscious-

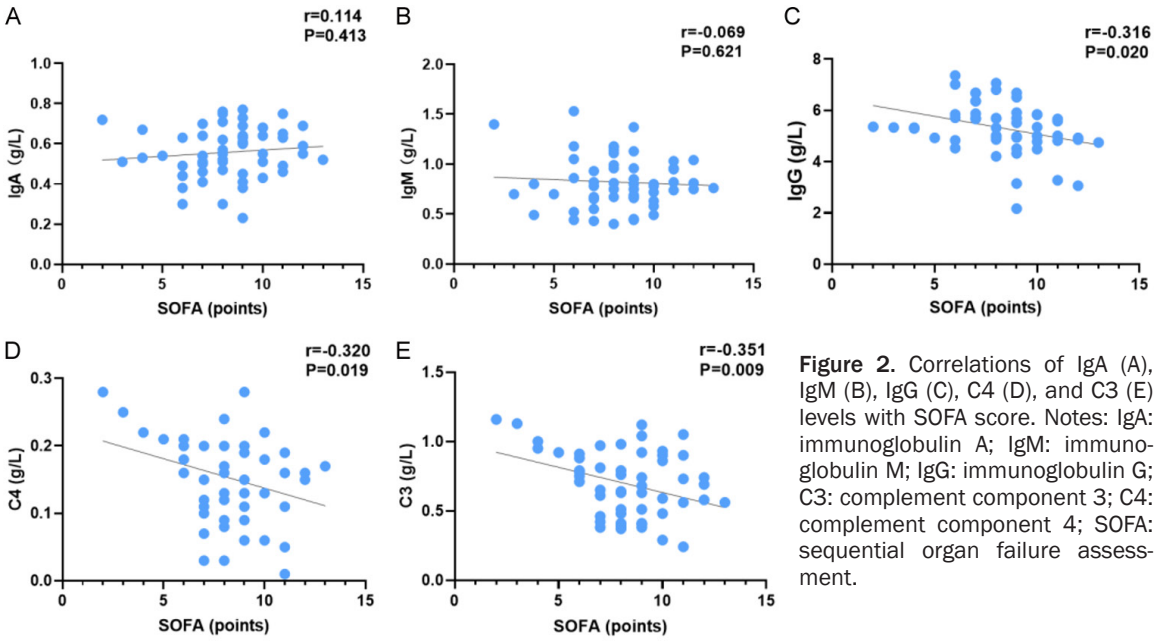

Figure 2. Correlations of IgA (A), IgM (B), IgG (C), C4 (D), and C3 (E) levels with SOFA score. Notes: IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; SOFA: sequential organ failure assessment.

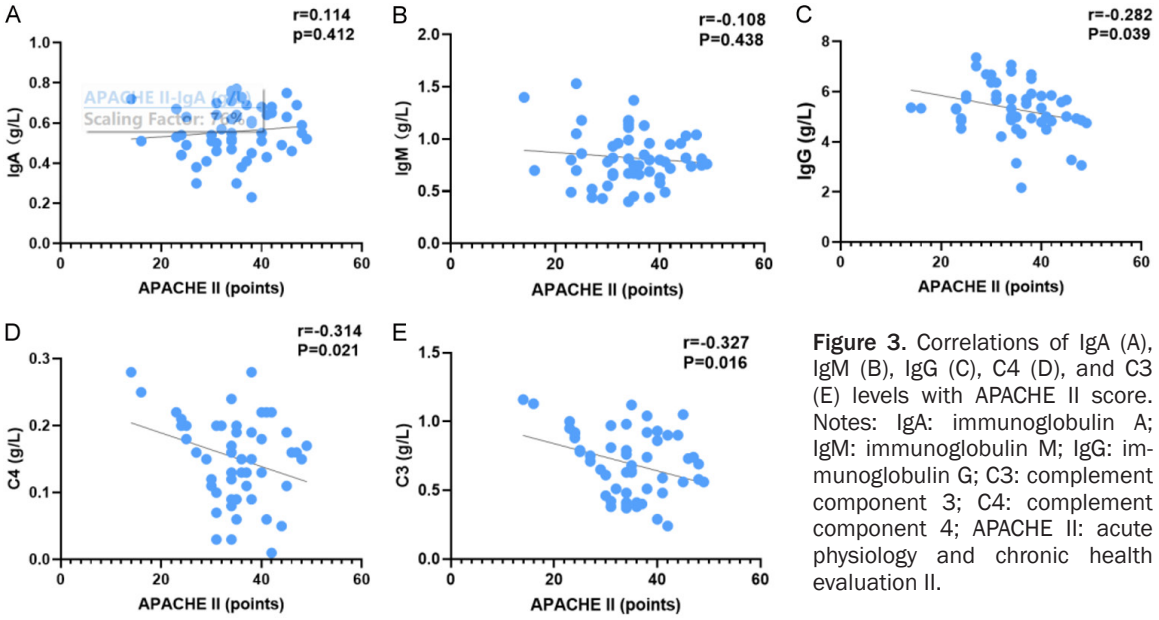

Figure 3. Correlations of IgA (A), IgM (B), IgG (C), C4 (D), and C3 (E) levels with APACHE II score. Notes: IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; APACHE II: acute physiology and chronic health evaluation II.

ness and neurological symptoms in contrast to the non-shock group, which finding aligns with the pathophysiological processes of cerebral hypoperfusion and neurological damage induced by shock [6]. Regarding humoral immune function, our results demonstrated characteristic alterations in immunoglobulins and complement components in shock patients, primarily manifested as significantly reduced levels of IgG and complement proteins C3/C4. Current research evidence suggests that these selective changes in immune components may reflect the complex immunopathological mechanisms underlying shock states [16]. As the central effector molecule of humoral immunity, decreased IgG levels consistently correlate with disease severity [4]. For instance, Shankar-Hari et al. [17] have reported that hypo-IgG represents the most prevalent immunoglobulin deficiency in adult sepsis, occurring in up to 70% of the cases. C3 and C4, pivotal elements of the complement system [18], were substan-

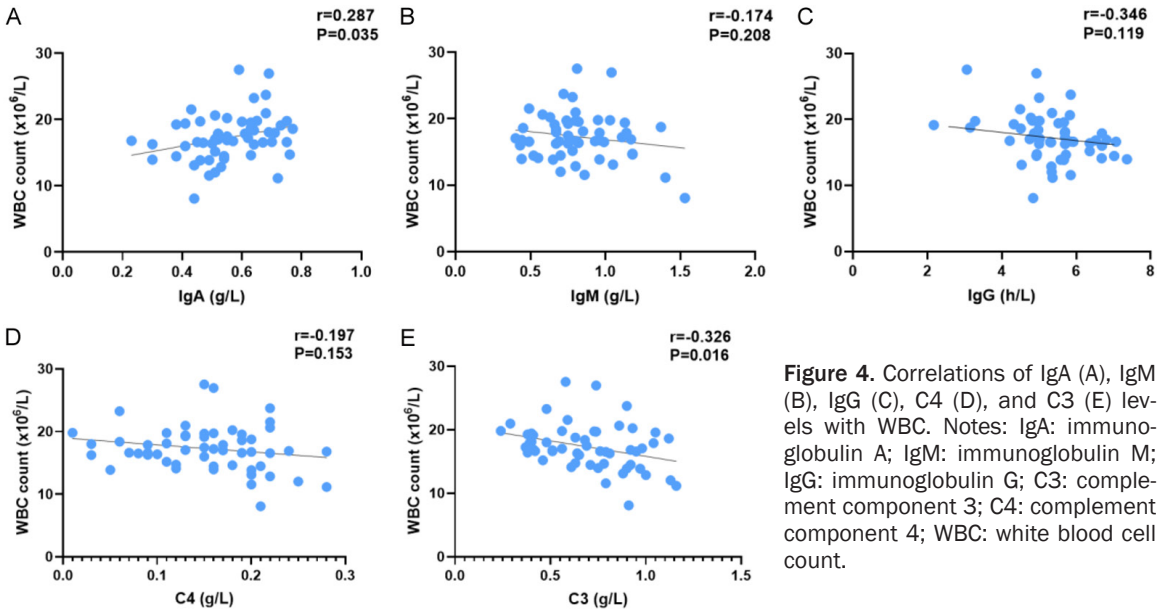

Figure 4. Correlations of IgA (A), IgM (B), IgG (C), C4 (D), and C3 (E) levels with WBC. Notes: IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; WBC: white blood cell count.

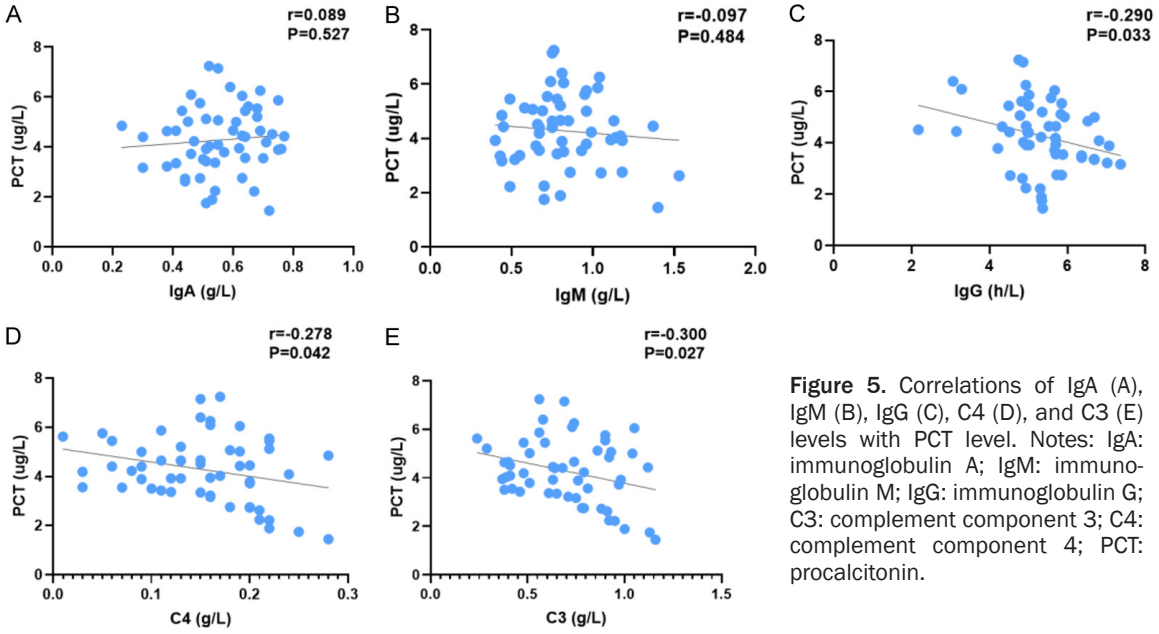

Figure 5. Correlations of IgA (A), IgM (B), IgG (C), C4 (D), and C3 (E) levels with PCT level. Notes: IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; PCT: procalcitonin.

Table 6. Multivariate logistic regression analysis of risk factors for SS

Factors	B	S.E.	Wals	df	Sig.	Exp (B)	95% C.I. For EXP (B)	
							Lower limit	Upper limit
IgA	-0.402	1.933	0.043	1	0.835	0.669	0.015	29.604
IgM	-1.852	1.180	2.464	1	0.117	0.157	0.016	1.585
IgG	-0.928	0.225	16.968	1	<0.001	0.395	0.254	0.615
C4	-11.651	4.286	7.391	1	0.007	0.001	0.012	0.039
C3	-5.692	1.104	26.559	1	<0.001	0.003	0.021	0.029

Notes: SS: septic shock; IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4.

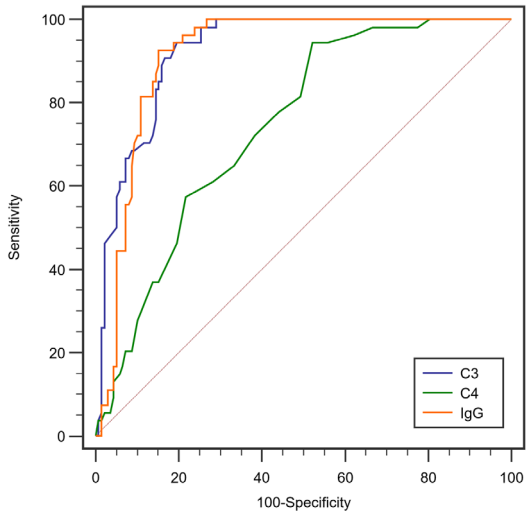

Figure 6. ROC curves for immune markers in predicting SS in pediatric sepsis patients. Notes: IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; SS: septic shock.

tially reduced in shock patients, reflecting more profound immune dysregulation in pediatric SS. These observations suggest that complement concentrations may serve as biomarkers for sepsis severity [19], potentially due to complement hyperactivation-induced consumption coupled with suppressed synthesis capacity from innate immune inhibition and impaired macrophage function [20]. Notably, the stable IgA and IgM levels across both groups indicate a distinct, class-specific immunoglobulin regulation pattern during shock progression.

The progression from sepsis to SS fundamentally represents a dynamic pathophysiological process in which infection triggers systemic inflammation that progressively worsens [21]. Substantial evidence demonstrates that abnormal elevation of inflammatory indices strongly correlates with poor outcomes. For instance, Rimmer et al. [22] demonstrated in their study of 917 SS patients that elevated WBC served as an independent risk factor for increased mortality (*HR*=3.41, 95% CI: 1.86-6.26, *P*< 0.001). Similarly, Liu *et al.* [23] identified PCT as an independent risk factor for SS. Our study corroborates these findings, showing characteristic elevations in both WBC and PCT levels in shock patients, thereby reinforcing the central role of excessive inflammatory response in shock pathogenesis. Our correlation analysis of immunological indices and inflammatory indices in pediatric SS patients revealed two key findings: (1) a significant positive correlation between IgA and WBC, potentially reflecting compensatory activation of the mucosal immune system; and (2) significant negative correlations between C3 and both WBC/PCT, suggesting complement system overconsumption. These results substantiate the "inflammatory-immunological imbalance" theoretical framework [24], wherein early-stage hyperinflammation triggers complement depletion through excessive activation, while persistent inflammation subsequently induces acquired immunosuppression, manifested by reduced IgG levels [25]. This dynamic immunopathological evolution provides a mechanistic explanation for the characteristic clinical paradox observed in shock patients: the simultaneous presentation of hyperinflammation and increased susceptibility to secondary infections. Our in-depth analysis revealed significant negative correlations between IgG, C3, and C4 levels with both SOFA and APACHE II scores in pediatric SS patients. As internationally recognized critical illness assessment tools [26], SOFA and APACHE II scores provide crucial clinical value in quantifying organ dysfunction and disease severity. The observed inverse relationships - where higher scores (indicating worse condition) corresponded with lower IgG, C3, and C4 concentrations - further substantiate the close association between these immune parameters and disease progression in SS. These findings suggest that dynamic monitoring of immunological markers could enhance clinical assessment, and modulation of the complement system may represent a potential therapeutic target for outcome improvement.

This study identified IgG, C3, and C4 as significant protective factors against SS in sepsis patients, with C3 showing the strongest predictive value, followed by IgG, while C4 exhibited more modest performance. C3's superior predictive performance may stem from its dual role in both innate immunity (as opsonin via C3b fragments) and adaptive immunity (through complement receptor signaling), as evidenced by a study by Cheng *et al.* [27], supporting that circulating C3-α chain levels independently predict survival in SS (AUC=0.65, P<0.001). These findings highlight the critical roles of humoral immunity and complement activation in mitigating SS progression, suggesting that monitor-

Table 7. Predictive performance of immune markers for SS analyzed using ROC curve analysis

	Cutoff	Sensitivity	Specificity	Accuracy	AUC	Confidence interval
C3	6.695	84.78%	92.59%	86.98%	0.926	0.879 to 0.958
C4	0.225	47.83%	94.44%	60.94%	0.744	0.676 to 0.804
IgG	1.055	80.44%	94.44%	84.38%	0.915	0.867 to 0.951

Notes: IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4; ROC: receiver operating characteristic; AUC: area under the curve.

Table 8. Pairwise comparison of immune markers' predictive performance

	Area Difference	Standard Error[a]	95% Confidence Interval	z	P
C3-C4	0.182	0.041	0.102 to 0.261	4.455	P<0.001
C3-IgG	0.0101	0.0268	-0.0424 to 0.0626	0.376	0.7072
C4-IgG	0.171	0.0411	0.0910 to 0.252	4.175	P<0.001

Notes: [a]DeLong et al., 1988; IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4.

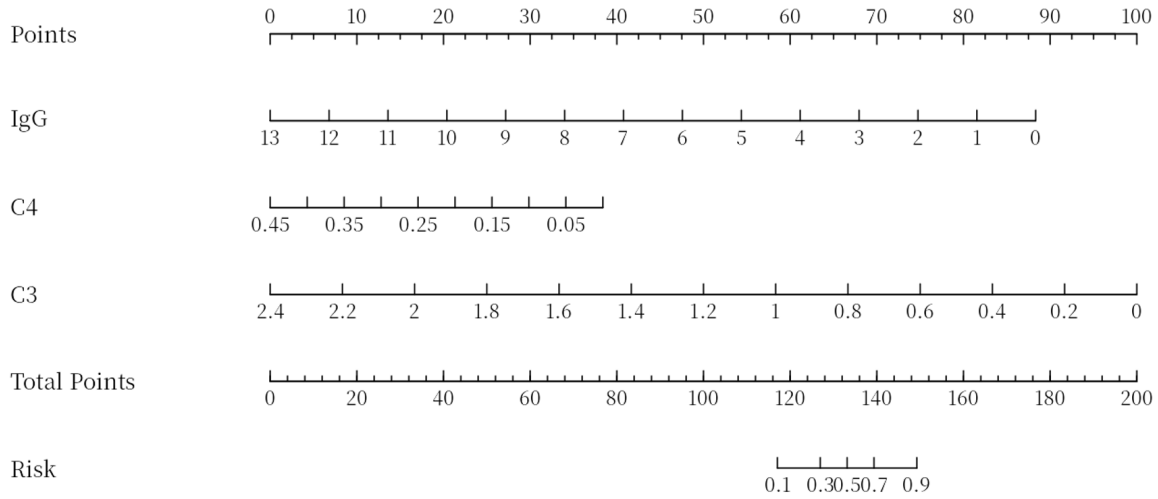

Figure 7. Nomogram for predicting the risk of septic shock in pediatric sepsis patients. Notes: IgG: immunoglobulin G; C3: complement component 3; C4: complement component 4.

ing these markers could enhance early risk stratification and guide targeted interventions, such as immunoglobulin supplementation or complement modulation, to improve outcomes in sepsis patients. Further validation in larger cohorts and mechanistic studies are warranted to refine their clinical utility.

While the findings of the current are promising, the study's single-center, retrospective design limits generalizability. Prospective multicenter studies are needed to validate the nomogram's performance. Additionally, mechanistic studies should explore whether C3 or IgG supplementation could improve outcomes in pediatric SS. Moreover, this study is limited by its single-timepoint measurement of immunological markers, which precludes analysis of their dynamic changes during disease progression.

In summary, low IgG, C3, and C4 levels are strongly associated with SS in pediatric sepsis and correlate with disease severity. C3, in particular, emerges as a highly sensitive and specific predictor of shock risk.

Disclosure of conflict of interest

None.

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