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A Retrospective Observational Study of the Association Between Plasma Levels of Interleukin 8 in 42 Patients with Sepsis-Induced Myocardial Dysfunction at a Single Center Between 2017 and 2020

Authors' Contribution:
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Data Collection B
Statistical Analysis C
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Manuscript Preparation E
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Background: This retrospective, observational study from a single center aimed to evaluate the association between complement (C)3 and C4, lymphocytes markers CD4 and CD8, and the interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 in patients with sepsis-induced myocardial dysfunction (SIMD) and a reduced left ventricular ejection fraction (LVEF) of < 50%.

Material/Methods: Patients with sepsis from July 2017 to December 2020 were divided into a SIMD group (42 patients) and NO-SIMD group (214 patients). Diagnostic criteria of sepsis were based on SEPSIS 3.0 guidelines. SIMD was defined as LVEF <50% by echocardiography and global ejection fraction <25% by transpulmonary thermodilution during hospitalization. The lymphocyte markers and interleukins were detected by flow fluorescence immunomicrobead assay, and C3 and C4 were detected by enzyme-linked immunosorbent assay.

Results: Plasma levels of IL-8 in the SIMD group were significantly higher than those in the NO-SIMD group, 133.90 (80.20, 402.79) vs 46.35 (16.80, 125.00) pg/mL (P<0.001). Logistic regression showed that N terminal pro B type natriuretic peptide (NT-proBNP; 95%CI 1.000-1.000, P<0.001) and IL-8 (95%CI 1.000-1.002, P=0.019) were independent risk factors for SIMD. Receiver operating characteristic curve analysis showed NT-proBNP, IL-8, and cardiac troponin T (cTnT) had different predictive values for SIMD: $AUC_{NT\text{-}proBNP}$ (0.810) >$AUC_{IL\text{-}8}$ (0.748) >AUC_{cTnT} (0.710). The cut-off value of IL-8 was 67.55 pg/mL; using this cut-off value, IL-8 predicted SIMD in sepsis with a sensitivity of 83.3% and specificity of 59.3%.

Conclusions: Increased plasma levels of IL-8 were significantly associated with cardiac dysfunction in patients with SIMD.

Keywords: Interleukin-8 • Inflammatory Mediators • Sepsis • Heart Failure • Ejection Fraction

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Background

Sepsis and septic shock are medical emergencies, and SEPSIS 3.0 guidelines recommend immediate treatment and resuscitation, including initial resuscitation within the first 3 hours, norepinephrine as the first-choice vasopressor, and the use of echocardiography for further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock [1]. Sepsis-induced myocardial dysfunction (SIMD) is cardiac dysfunction caused by sepsis, which is characterized by decreased left ventricular dilation and left ventricular ejection fraction (LVEF); however, this dysfunction can resolve over 7 to 10 days after sepsis [2,3]. SIMD was first reported by Parker et al in 1984, and has a development history of nearly 40 years [4]; however, SIMD has not been totally understood. Unfortunately, 18% to 65% of incidences of myocardial dysfunction occur in patients with sepsis [5], and up to 80% occur in patients with septic shock [6]. SIMD is the main risk factor for death by sepsis, and the mortality rate can rise to 70% once it occurs [3]. Therefore, early identification of SIMD in sepsis is important; however, the obstacle is that there are no clear diagnostic criteria for SIMD at present.

The most important examination method for SIMD is echocardiography, which is widely used because it is easy to implement, noninvasive, and repeatable [7]. SIMD has been defined as an LVEF <50% and a decrease ≥10% of LVEF in patient baseline values in some studies [5,8]. However, LVEF has been increasingly regarded as an inaccurate indicator because of it is heavily dependent on cardiac preload [9-11]. Therefore, some specific serum biomarkers that provide independent relevant information for myocardial injury or cardiac function can be used as a complement to the diagnosis of SIMD [7]. Troponin T (TnT) and B type natriuretic peptide (BNP), are considered as potential indicators of myocardial dysfunction [12], and these 2 cardiac biomarkers are generally elevated in sepsis [13]. Some studies have shown that cardiac biomarkers were significantly associated with SIMD on echocardiography, such as left ventricular systolic function, diastolic dysfunction, and even atrial arrhythmia [14,15]. However, other results are inconsistent or even contrary [13,16], supporting that increased plasma BNP or TnT levels seem to reflect the severity of illness but not specifically SIMD [17,18].

In sepsis, infection results in an imbalance of the host immune response, leading to organ dysfunction and even death [1]. The pathophysiological cascade begins with the host immune system's response to invasive pathogens, then the initial immune response is activated, which promotes the release of inflammatory mediators and signaling molecules and activates positive and negative feedback in the immune system. Whether this process is beneficial or harmful has not yet been confirmed [19]. Endotoxins, cytokines, and nitric oxide (NO) have been considered the main mediators in the pathogenesis of SIMD [5,20]. An imbalance of inflammatory response is directly related to dysfunction of cardiomyocytes in SIMD. The interleukin (IL)-1β/tumor necrosis factor (TNF)-α/IL-6/P38 pathway, complement system, NO dysfunction, and PAMPs/DAMPs are considered to have important roles in the occurrence of SIMD [9,21,22]. In sepsis, the complement system is activated, leading to a cytokine storm and cardiomyopathy. In addition, the effect of complement components on intracellular calcium homeostasis is also part of the pathogenesis of SIMD [23,24]. The direct injury of inflammatory factors to myocardial cells is considered to be another mechanism of SIMD; (IL-1) can inhibit cardiac contractility by stimulating NO, and IL-6 has been shown to be involved in the pathogenesis of SIMD [25]. IL-8 may be, by its effects on neutrophils, part of an inflammatory cascade that contributes to injury of the reperfused myocardium [26]. The differences in IL-8 levels are probably more related to the acute myocardial infarction and the accompanying degree of heart failure [26]. Husebye et al suggested a possible role of IL-8 in the reperfusion-related injury and adverse left ventricular remodeling of post-ischemic myocardium [26]. However, the association between the complement, lymphocytes, and inflammatory cytokines has not been addressed in clinical trials to date.

Therefore, in this retrospective study from a single center, we aimed to evaluate the association between complement (C)3 and C4, lymphocytes markers CD4 and CD8, and the interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 in patients with SIMD with a reduced LVEF of <50%.

Material and Methods

Patients

This retrospective observational study was approved by the Medical Ethics Committee at the First Affiliated Hospital of Chongqing Medical University. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. All patients or their guardians provided written informed consent.

Definition of Sepsis and SIMD

The diagnostic criteria of sepsis were based on the following SEPSIS 3.0 guideline [1]: "Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, which can be associated with a Sepsis-related Organ Failure Assessment (SOFA) score ≥2 points consequent to the infection".

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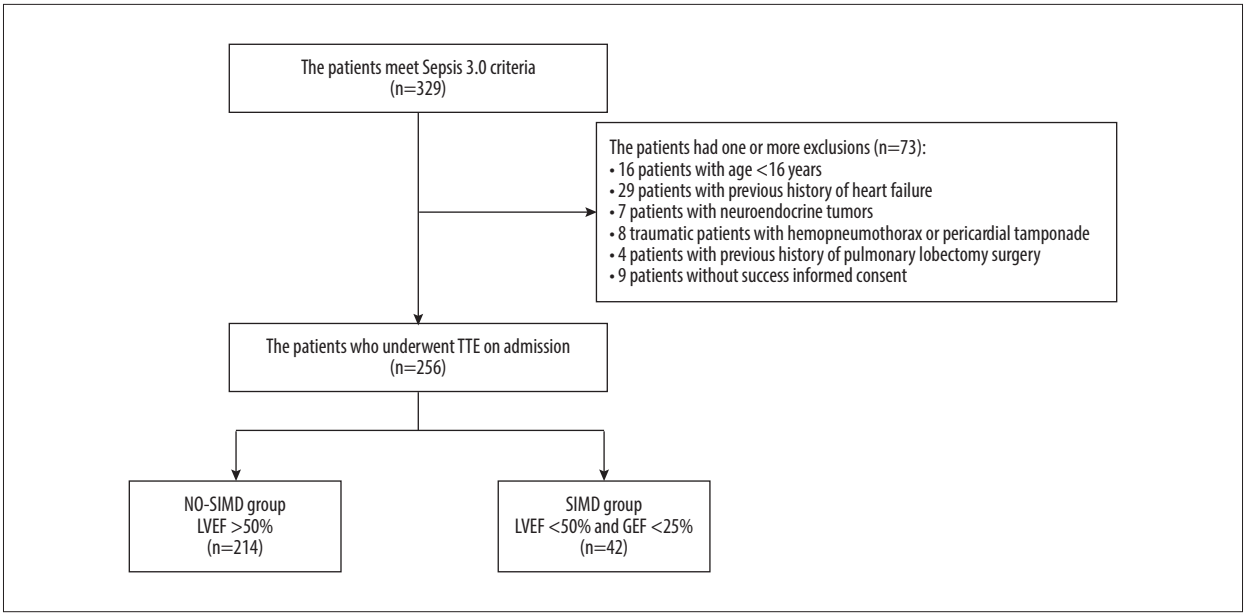

Figure 1. Study flow diagram. In total, 329 patients had sepsis or septic shock. The study included 256 patients with sepsis. Patients were divided into a sepsis-induced myocardial dysfunction group (SIMD; n=42) and a without sepsis-induced myocardial dysfunction group (NO-SIMD; n=214) by transthoracic echocardiography (TTE). LVEF – left ventricular ejection fraction; GEF – global ejection fraction.

SIMD was defined as patients with sepsis with LVEF <50% by echocardiography during hospitalization (this diagnostic criterion referred to the study of Sato et al [5]), and the global ejection fraction (GEF) <25% by pulse index continuous cardiac output (PICCO). Echocardiography was performed by a cardiovascular physician or sonographer when the patient was not on cardiac stimulants on admission and was confirmed by an additional physician. PICCO involved advanced hemodynamic monitoring, integrating static and dynamic hemodynamic data by combining trans-cardiopulmonary thermodilution with pulse contour analysis, as reported by Litton [27].

Inclusion and Exclusion Criteria and Grouping

In total, 329 patients diagnosed with sepsis in the Critical Care Medicine Department of our hospital from July 2017 to December 2020 were included in this study. The following patients were excluded: those with previous history of heart failure (29 patients), neuroendocrine tumors (7 patients), trauma with hemopneumothorax or pericardial tamponade (8 patients), age younger than 16 years (16 patients), history of pulmonary lobectomy surgery (4 patients), and lack of informed consent (9 patients). The included patients were divided into the SIMD group and NO-SIMD group according to the results of LVEF by transthoracic echocardiography on admission and GEF by PICCO (**Figure 1**). The patients in the SIMD group met the definition of SIMD in this study, including LVEF <50% by echocardiography and the GEF <25% by PICCO. Patients not meeting these criteria were included in the NO-SIMD group.

Clinical Data Collection and Laboratory Examination

General clinical data including age, sex, hospitalization time, 30-day survival, vital signs at admission, and previous history were recorded. Blood routine examination, biochemical examination of liver/renal function and the cardiac biomarkers cardiac troponin T (cTnT) and N terminal pro B type natriuretic peptide (NT-proBNP) were detected in all patients within 24 h of admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and SOFA score were calculated.

The plasma concentrations of C3 and C4, lymphocytes markers CD4 and CD8, and interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 were detected by the clinical Molecular Test Center of our hospital at admission. The lymphocytes markers CD4 and CD8 were detected by flow cytometry (CD3-FITC/CD16+56-PE/CD45-PerCP-Cy5.5/CD4-PC7/CD19-APC/CD8-APC-Cy7; fluorescent monoclonal antibody kit, Beijing Tongsheng Shidai Biotech Co, Ltd; detecting instrument: BD FACSCanto II). The interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 were detected by flow fluorescence immunomicrobead assay (12 Cytokine Detection Kits, Product code R701002, Qingdao Raisecare Biotech Co, Ltd; detecting instrument: Navios Beckman Coulter). Plasma IL-8 concentration was measured in strict accordance with the kit instructions, including extraction of plasma (venous blood samples were collected with an EDTA anticoagulant tube and centrifuged at 1000 g for 30 min), preparation of matrix, calibration reagents, and flow cytometry.

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Table 1. Comparison of basic information and clinical characteristics between the 2 groups.

Characteristics on admission	Total (n=256)	SIMD (n=42)	NO-SIMD (n=214)	*P*
Age, years	66.00 (53.00, 74.00)	67.50 (60.00, 77.25)	66.00 (51.75, 74.00)	0.105 *U*
Male, n (%)	158 (61.72%)	21 (50.00%)	137 (64.02%)	0.087 χ^2
Need for vasoactive agents, n (%)	48 (18.75%)	17 (40.48%)	31 (14.48%)	<0.001 χ^2
Need for ventilation, n (%)	86 (33.59%)	17 (40.48%)	69 (32.24%)	0.302 χ^2
Arrhythmic complications, n (%)	107 (41.80%)	22 (52.38%)	85 (39.72%)	0.128 χ^2
Vital signs				
Temperature, °C	37.22±0.98	37.28±1.18	37.20±0.94	0.645 *t*
Pulse, beats/min	103.64±24.74	102.64±21.34	103.84±25.40	0.775 *t*
Respiratory rate, breaths/min	25.17±7.51	21.54±7.56	25.17±7.52	0.981 *t*
Mean arterial pressure, mm Hg	96.63±22.45	91.64±17.32	97.37±24.95	0.588 *t*
Glasgow Coma Scale	14 (12,15)	14 (13, 15)	14 (12, 15)	0.454 *U*
Arterial blood gas analysis				
pH	7.37±0.10	7.38±0.11	7.38±0.10	0.848 *t*
PaO_2/FiO_2, mm Hg	243.46±123.53	220.38±143.67	253.28±117.42	0.873 *t*
$PaCO_2$, mm Hg	40.00 (30.00,57.00)	36.50 (29.08, 50.43)	40.95 (30.00, 57.13)	0.577 *U*
Lactate, mmol/L	1.82 (1.10, 3.23)	2.45 (1.96, 4.78)	1.58 (1.05, 2.75)	0.001 *U*
Blood routine				
White blood cell count, $\times10^9$/L	12.55±7.79	12.28±5.98	12.60±8.10	0.807 *t*
Neutrophil, %	87.10 (82.20, 91.57)	86.00 (82.75, 91.55)	87.20 (81.80, 91.60)	0.995 *U*
Red blood cell count, $\times10^{12}$/L	3.69±1.11	3.85±1.04	3.66±1.12	0.317 *t*
Hemoglobin, g/L	107.14±32.73	109.88±27.19	106.60±33.74	0.554 *t*
Hematocrit,%	33.66±10.04	34.25±10.04	33.55±10.06	0.677 *t*
Biochemical indices				
Total bilirubin, μmol/L	23.20 (15.58, 38.20)	26.25 (15.75, 55.73)	23.20 (15.45, 35.50)	0.070 *U*
Direct bilirubin, μmol/L	12.30 (6.73, 21.43)	16.40 (7.48, 29.30)	11.95 (6.53, 18.30)	0.127 *U*
AST, U/L	44.00 (25.00, 77.75)	43.00 (28.00, 120.00)	44.00 (24.00, 76.00)	0.291 *U*
ALT, U/L	64.00 (30.00. 131.25)	65.50 (41.75, 140.25)	63.00 (27.50, 126.00)	0.300 *U*
BUN, mmol/L	9.80 (6.23, 15.30)	15.00 (11.10, 19.18)	9.20 (5.98, 14.45)	<0.001 *U*
Creatinine, μmol/L	97.00 (65.00, 151.00)	134.50 (87.50, 236.75)	91.00 (60.00, 135.00)	<0.001 *U*
Serum sodium, mmol/L	142.26±8.62	143.95±8.06	141.93±8.71	0.164 *t*
Serum potassium, mmol/L	4.2 (3.8, 4.9)	4.25 (3.875,4.925)	4.20 (3.80, 4.90)	0.354 *U*
Procalcitonin, mmol/L	1.34 (0.18, 8.71)	4.40 (2.50, 23.67)	0.84 (0.15, 5.66)	0.001 *U*

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Table 1 continued. Comparison of basic information and clinical characteristics between the 2 groups.

Characteristics on admission	Total (n=256)	SIMD (n=42)	NO-SIMD (n=214)	*P*
Cardiac biomarkers				
cTnT, ug/L	0.0420 (0.0193, 0.1040)	0.0945 (0.0405, 0.2133)	0.0360 (0.0155, 0.0795)	<0.001 *U*
NT-proBNP, ng/L	1828 (470, 5472)	7782.00 (2601.50, 28415.50)	1553.50 (422.00, 4228.00)	<0.001 *U*
APACHE II score	17.03±7.17	18.06±6.74	16.31±9.16	0.251 *t*
SOFA score	8.0 (6.0, 12.0)	8.0 (6.0, 12.0)	8.0 (7.0, 12.0)	0.647 *U*
Length of stay, days	10 (7, 22)	10 (4, 17.50)	10 (7, 22)	0.331 *U*
Mortality,%	38 (14.84%)	10 (23.81%)	28 (13.08%)	0.074 χ^2

SIMD – sepsis-induced myocardial dysfunction; NO-SIMD – without sepsis-induced myocardial dysfunction; APACHE II – Acute Physiology and Chronic Health Evaluation II; SOFA Score – Sepsis-related Organ Failure Assessment; AST – glutamic-oxaloacetic transaminase; ALT – glutamic-pyruvic transaminase; BUN – blood urea nitrogen; NT-proBNP – N terminal pro B type natriuretic peptide; cTnT – cardiac troponin T; χ^2 – chi-squared analysis was used for the comparison between SIMD and NO-SIMD groups; *t* – *t* test was used for comparison between SIMD group and NO-SIMD group; *U* – Mann-Whitney U test was used for comparison between SIMD group and NO-SIMD group.

Statistical Analysis

SPSS version 17.0 was used for statistical analysis and PASS was used for power analysis. Continuous variables were expressed as mean±standard deviation or median (quartile) depending on whether the data conformed to a normal distribution or not. Groups were compared using the *t* test or Mann-Whitney U test for continuous variables and chi-squared test for categorical data. The logistic regression model was used to analyze risk factors. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive ability of SIMD. A value of $P<0.05$ represented statistical significance.

Results

Comparison of Clinical Data and Laboratory Examinations Between SIMD and NO-SIMD Groups

A total of 256 patients with sepsis were included in this study. The average age of the patients was 66 years (53-74 years), and 61.72% were men. A total of 48 patients required vasoactive agents to maintain blood pressure, 86 patients underwent mechanical ventilation, 107 patients developed a new arrhythmia, mainly atrial arrhythmia. According to the results of transthoracic echocardiography and PICCO, patients were divided into either the SIMD group (42 patients) or NO-SIMD group (214 patients). More patients in the SIMD group than in the NO-SIMD group needed vasoactive drugs ($P<0.001$). The plasma concentrations in the SIMD and NO-SIMD groups were cTnT 0.0945 (0.0405, 0.2133) vs 0.0360 (0.0155, 0.0795) ug/L; NT-proBNP 7782.00 (2601.50, 28415.50) vs 1553.50 (422.00, 4228.00) ng/L; lactate 2.45 (1.96, 4.78) vs 1.58 (1.05, 2.75) mmol/L; blood urea nitrogen (BUN) 15.00 (11.10, 19.18) vs 9.20 (5.98, 14.45) mmol/L; creatinine 134.50 (87.50, 236.75) vs 91.00 (60.00, 135.00) μmol/L; and procalcitonin 4.40 (2.50, 23.67) vs 0.84 (0.15, 5.66) mmol/L, respectively. The differences between groups were statistically significant ($P<0.05$). No significant differences were found in general clinical data, mortality, blood gas analysis, and routine blood and other laboratory examinations (**Table 1**).

We compared the differences of C3 and C4, lymphocytes markers CD4 and CD8, and interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 between the SIMD and NO-SIMD groups in this study (**Table 2**). The results showed that the concentration of plasma C4 in the SIMD group (0.18±0.04 g/L) was significantly lower than that in the NO-SIMD group (0.21±0.07 g/L), $P=0.028$. The concentrations of plasma IL-1β, IL-2R, IL-10, and IL-8 in the SIMD group were significantly higher than those in the NO-SIMD group: IL-1β 5.00 (5.00, 5.86) vs 4.90 (4.90, 5.00) pg/mL, $P<0.001$; IL-2R 1673.00 (1027.00, 4024.25) vs 1136.50 (584.00, 2744.00) IU/mL, $P=0.015$; IL-10 19.40 (8.78, 55.86) vs 7.10 (4.90, 26.05) pg/mL, P=0.002; and IL-8 133.90 (80.20, 402.79) vs 46.35 (16.80, 125.00) pg/mL, $P<0.001$, respectively. There were no differences in other immune parameters (C3, CD4, CD8) and IL-6 between the SIMD and NO-SIMD groups.

Risk Factors of SIMD in Sepsis

Binary logistic regression was used to analyze the independent risk factors of SIMD. The results showed that only NT-proBNP

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Table 2. Comparison of immune parameters and inflammatory mediators between the 2 groups.

Variables	Total (n=256)	SIMD (n=42)	NO-SIMD (n=214)	*P*
C3, g/L	0.65 (0.54, 0.85)	0.63 (0.54, 0.70)	0.65 (0.54, 0.86)	0.148 *U*
C4, g/L	0.20±0.62	0.18±0.04	0.21±0.07	0.028 *t*
CD4, /ul	216.00 (134.00, 344.00)	175.50 (84.50, 259.75)	239.00 (137.00, 366.00)	0.055 *U*
CD8, /ul	162.00 (103.00, 365.00)	148.00 (85.25, 250.50)	173.00 (112.25, 377.00)	0.064 *U*
CD4/8	1.34 (0.72, 1.97)	1.29 (0.59, 2.01)	1.36 (0.73, 1.91)	0.795 *U*
IL-1β, pg/mL	5.00 (4.90, 5.0)	5.00 (5.00, 5.86)	4.90 (4.90, 5.00)	<0.001 *U*
IL-2R, IU/mL	1231.00 (591.25, 2760.00)	1673.00 (1027.00, 4024.25)	1136.50 (584.00, 2744.00)	0.015 *U*
IL-6, pg/mL	61.15 (27.00, 335.00)	107.50 (34.10, 394.43)	57.20 (26.88, 334.00)	0.123 *U*
IL-8, pg/mL	64.45 (17.60, 162.22)	133.90 (80.20, 402.79)	46.35 (16.80, 125.00)	<0.001 *U*
IL-10, pg/mL	8.575 (4.90, 29.03)	19.40 (8.78, 55.86)	7.10 (4.90, 26.05)	0.002 *U*

SIMD – sepsis-induced myocardial dysfunction; C – complement; CD – cluster of differentiation; IL – interleukin; *t* – *t* test was used for comparison between SIMD group and NO-SIMD group; *U* – Mann-Whitney U test was used for comparison between SIMD group and NO-SIMD group.

Table 3. Risk factors of sepsis-induced myocardial dysfunction using a binary logistic regression model.

Factors	Exp(B)	95% CI	B	*P*
cTnT	3.924	0.837-18.38	1.367	0.083
NT-proBNP	1.000	1.000-1.000	0.000	0.000
BUN	1.062	1.007-1.121	0.060	0.072
Creatinine	0.995	0.989-1.001	-0.005	0.077
Procalcitonin	0.989	0.975-1.004	-0.011	0.154
Lactate	1.066	0.919-1.236	0.064	0.399
C4	0.012	0.000-7.585	-4.404	0.179
IL-1β	1.038	0.984-1.094	-0.037	0.174
IL-2R	1.000	1.000-1.000	0.000	0.890
IL-8	1.001	1.000-1.002	0.001	0.019
IL-10	0.999	0.996-1.002	0.000	0.485

cTnT – cardiac troponin T; NT-proBNP – N terminal pro B type natriuretic peptide; BUN – blood urea nitrogen; C – complement; IL – interleukin.

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Table 4. Pearson correlation between interleukin 8 and other variables.

Pearson correlation	cTnT	NT-proBNP	Creatinine	BUN	IL-2R	IL-10
r	0.490	0.328	0.458	0.285	0.160	0.184
P	<0.001	<0.001	<0.001	<0.001	0.010	0.003

NT-proBNP – N terminal pro B type natriuretic peptide; cTnT – cardiac troponin T; BUN – blood urea nitrogen; IL – interleukin.

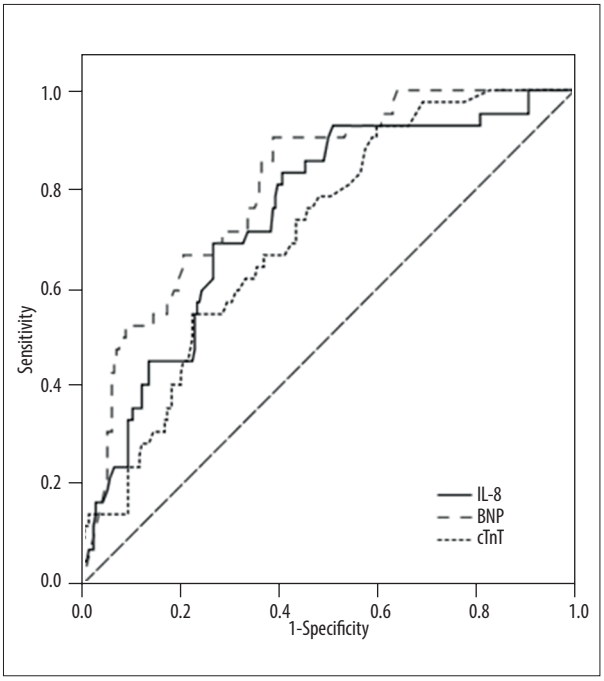

Figure 2. Receiver operating characteristic curve of cardiac troponin T (cTnT), N terminal pro B type natriuretic peptide (NT-proBNP), and interleukin (IL)-8 to predict sepsis-induced myocardial dysfunction (SIMD) in sepsis.

(*P*<0.001) and IL-8 (*P*=0.019) were independent risk factors for SIMD in this study (**Table 3**). The logistic regression model also revealed that cTnT (*P*=0.083), BUN (*P*=0.072), creatinine (*P*=0.077), procalcitonin (*P*=0.154), lactate (*P*=0.399), C4 (*P*=0.179), IL-1β (*P*=0.174), IL-2R (*P*=0.890), and IL-10 (*P*=0.485) were not associated with SIMD in our study.

Analysis of Correlation Between IL-8 and Other Variables in Sepsis

Pearson correlation analysis showed that plasma IL-8 concentration levels were significantly correlated with the concentration of cTnT (r=0.490, *P*<0.001), NT-proBNP (r=0.328, *P*<0.001), creatinine (r=0.458, *P*<0.001), BUN (r=0.285, *P*<0.001), IL-2R (r=0.160, *P*=0.010), and IL-10 (r=0.184, *P*=0.003) in patients with sepsis (**Table 4**).

Predictive Value of IL-8, cTnT and NT-proBNP for SIMD in Sepsis

ROC curve analysis was used to evaluate the predictive value of IL-8, cTnT, and NT-proBNP for SIMD in sepsis. The results showed that NT-proBNP, IL-8, and cTnT had different predictive values for SIMD (**Figure 2**), with an area under the ROC curve (AUC) of $AUC_{NT\text{-}proBNP}$ (0.810) >$AUC_{IL\text{-}8}$ (0.748) >AUC_{cTnT} (0.710) (**Figure 2, Table 5**). The cut-off value of IL-8 was 67.55 pg/mL, and with this cut-off value IL-8 could predict SIMD in sepsis with a sensitivity of 83.3% and specificity of 59.3%.

Power Analysis

Using the cut-off value of IL-8 to define exposed patients, the exposure percentage was P1=35/42=83% in the SIMD group and P2=87/214=41% in the NO-SIMD group. The odds ratio (OR) between the SIMD group and the NO-SIMD group=[P1/(1-P1)]/[P2/(1-P2)]=7.3. Power analysis was based on the comparison of 2 independent sample rates. The null hypothesis was H0: OR=1, alternative hypothesis was H1: OR≠1, and the overall class I error level was α=0.05. PASS software was used to calculate the power=100% under the current sample size.

Table 5. Receiver operating characteristic curve analysis of cardiac troponin T, N terminal pro B type natriuretic peptide, interleukin 8 in predicting sepsis-induced myocardial dysfunction.

	AUC	95% CI	Cut-off	P
NT-proBNP	0.810	0.745-0.874	2033.5	<0.001
IL-8	0.748	0.671-0.826	67.55	<0.001
cTnT	0.710	0.634-0.786	0.0275	<0.001

AUC – area under the receiver operating characteristic curve; CI – confidence interval; NT-proBNP – N terminal pro B type natriuretic peptide; cTnT – cardiac troponin T; IL – interleukin.

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Discussion

We performed a retrospective study to evaluate the association between C3 and C4, lymphocyte markers CD4 and CD8, and interleukins IL-1β, IL-2R, IL-6, IL-10, and IL-8 in patients with SIMD and found that increased plasma levels of IL-8, NT-proBNP, and cTnT were significantly associated with cardiac dysfunction in patients with SIMD. Plasma IL-8 concentration was a potential biomarker for predicting SIMD in sepsis, with the predictive value of IL-8 having been even better than that of cTnT but inferior to that of NT-proBNP. The diagnostic criteria of SIMD are controversial, and more biomarkers are urgently needed as diagnostic evidence [9]. Chen et al found the value of using multi-biomarker strategy for prediction of myocardial dysfunction and mortality in sepsis [28], and the goal of our study was to explore more potential biomarkers for predicting SIMD in patients with sepsis.

SIMD is a reversible cardiac dysfunction caused by sepsis [3], and the SEPSIS 3.0 guidelines recommend further assessment of hemodynamics and cardiac function [1]. Because circulatory dysfunction plays a central role in multiple organ dysfunction syndrome, it is essential to understand the pathological mechanism of SIMD [3]. SIMD can be manifested in a variety of forms, including systolic or diastolic dysfunction of left and/or right ventricles, insufficient cardiac output and oxygen supply, and primary myocardial cell damage [9]. The development of echocardiography makes it possible to visualize the hemodynamics in SIMD [7]. It was found that the main manifestations of SIMD were left ventricular dilatation and LVEF reduction, and these dysfunctions can be restored within 7 to 10 days [5]. The molecular mechanisms of SIMD have been researched in recent years but still has not been fully elucidated. Some researchers have proposed that they may be related to endotoxin, inflammatory cytokines, and NO [5,29]. These factors include myocardial ischemia caused by decreased coronary flow, physiological disorders of cardiomyocytes, and the influences of inflammatory mediators, all of which can caused endothelial cell hyperpermeability, oxidative stress, and mitochondrial dysfunction [30]. Clinical indicators related to SIMD diagnosis include TTE, cTnT, and BNP, but there was no single indicator identified that could independently diagnose SIMD. Therefore, specific indicators for combined diagnosis have received particular attention in recent discoveries. The study by Chen et al evaluated the diagnostic value of heart-type fatty acid-binding protein, myeloperoxidase, and pregnancy-associated plasma protein-A [28]. However, sepsis is a clinical syndrome of imbalance between inflammation and immune function; therefore, the predictive value of some immune and inflammatory markers of SIMD should be further investigated.

The diagnostic criteria of SIMD are controversial, and the existing diagnostic methods have different limitations. In the past decade, the use of bedside echocardiography has resulted in detailed and rapid assessment of the causes of the cardiac hemodynamic abnormalities in sepsis [1]. The LVEF is one of the earliest indicators used to represent systolic dysfunction and diagnose SIMD [7]. In the present study, we used LVEF <50% by echocardiography [5] and GEF <25% by PICCO as the diagnostic criteria of SIMD. This diagnostic criterion could be combined with invasive and noninvasive hemodynamic monitoring to more accurately determine which patients had cardiac dysfunction and avoid the inaccuracy of echocardiography alone. However, LVEF has been increasingly regarded as an inaccurate indicator of cardiac function [10,31]. A meta-analysis of 1247 patients showed there was no association between LVEF and septic shock mortality [32]. The left ventricular pressure-volume conductivity catheter provides another method to measure real-time cardiac function, making the quantitative measurement of systolic and diastolic function correspond more to the criterion standard; however, the significance of this method to SIMD needs further verification [33]. Serum cardiac biomarkers could provide independent information related to cardiac function. The serum concentrations of cTnT and BNP increase with the severity of the disease [34,35]. Røsjø et al showed that the level of cTnT reflected cardiomyocyte damage in a clinical study of patients with sepsis [36]. The increase of serum cTnT level may be due to the leakage of cTnT caused by the destruction of myocardial cell membrane integrity [37]. Similar results were obtained in the present study, in which serum levels of cTnT and NT-proBNP in the SIMD group were significantly higher than in the NO-SIMD group. Also, we found that NT-proBNP was an independent risk factor for SIMD and had predictive value for diagnosis of SIMD. However, the results of other studies suggest that although serum levels of cTnT and NT-proBNP can reflect the severity of sepsis, neither have specific predictive value for SIMD [17,18].

Sepsis is a systemic inflammatory response syndrome caused by infection, with varying degrees of activation of inflammatory factors and an imbalance of immune response [1]. Inhibitory effects of cytokines to cardiac myocytes have been studied in SIMD. In SIMD animal models, histological examination showed that myocardial cells were infiltrated with inflammation and resulted in the destruction of contractile function, and IL-1β/TNF-α/IL-6 and the complement system all played a role in this pathological process [38,39]. In a sepsis mice model, it was found that the activation of C5 led to cytokine storm, lymphocyte apoptosis, immune deficiency of polymorphonuclear leukocytes, release of proinflammatory cytokines (IL-1β, IL-6, TNF-α), inhibition of myocardial cell function, and SIMD finally occurred [23,40]. In the present study, we investigated the predictive value of common immune parameters (C3, C4, CD4, and CD8) and inflammatory mediators (IL-1β, IL-2R, IL-6, IL-10, and IL-8) for SIMD. The results showed that plasma IL-8-concentration was a potential biomarker for predicting SIMD.

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In addition, the predictive value of IL-8 was better than that of cTnT but inferior to that of NT-proBNP.

In this study, we found that LVEF decreased and IL-8 concentration increased when SIMD occurred. IL-8 is mainly produced by monocytes and macrophages, and its main biological activity is the ability to attract and activate neutrophils [26]. Previous studies have reported that IL-8 is associated with myocardial cell injury. Shetelig et al found that serum IL-8 levels are positively correlated with infarct size and left ventricular function recovery in patients with STEMI and demonstrated that IL-8 plays a key role in post-myocardial infarction inflammation [41]. This may be because the overexpression of IL-8 in endothelial cells could reduce cardiac remodeling and dysfunction following myocardial infarction and increase neovascularization around infarcted tissue [42]. The correlation between IL-8 and SIMD has not been reported, and we need more data to confirm our results. The results of this study can alert clinicians to the early detection of cardiac dysfunction in patients with sepsis with high IL-8 levels.

Limitations

There were some limitations in our study. First, it was a single-center retrospective study with a small sample size, in which we attempted to explore the correlation between some cytokines and SIMD but not the specific mechanism of IL-8 in SIMD. The small cohort population and unblinded design are major confounders for this study. Second, sepsis is an acute syndrome caused by infection, and the inclusion of patients was heterogeneous owing to differences in primary disease. Third, this study did not completely exclude patients with pre-existing cardiovascular disease.

Conclusions

In this study, increased plasma levels of IL-8 were most significantly associated with cardiac dysfunction in patients with SIMD. Plasma IL-8-concentration was a potential biomarker for predicting SIMD in sepsis.

Informed consent

This study was approved by the hospital ethics committees, and written informed consent was provided by the patients or their family members.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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