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EFFECT OF CONTINUOUS RENAL REPLACEMENT THERAPY ON MULTI-DIMENSIONAL SERUM BIOMARKERS (IL-4, PRESEPSIN, NGAL, PD-L1, IL-10, Ang-2, sTM, HISTONES, mtDNA, ADM, AND suPAR LEVELS) AND CLINICAL SYMPTOMS IN PATIENTS WITH SEPSIS

EFEKAT KONTINUIRANE ZAMENSKE RENALNE TERAPIJE NA MULTIDIMENZIONALNE SERUMSKE BIOMARKERE (IL-4, PRESEPSIN, NGAL, PD-L1, IL-10, Ang-2, sTM, HISTONE, mtDNK, ADM I suPAR NIVOE) I KLINIČKE SIMPTOME KOD PACIJENATA SA SEPSOM

*Jun Meng[1#], Lei Kang[2#], Tao Shen[3]**

[1]Department of Emergency, Chengde Central Hospital, Chengde, 067000, China
[2]Department of ICU, Peking University Cancer Hospital (Inner Mongolia Campus)/ Affiliated Cancer Hospital of Inner Mongolia Medical University, Hohhot, 010010, China
[3]Department of Emergency Medicine, Gejiu People's Hospital, Gejiu, 661000, China

Summary

Background: To investigate the effects of continuous renal replacement therapy (CRRT) on traditional and novel multi-dimensional serum biomarkers, including inflammatory cytokines, immune regulation markers, endothelial injury markers, cellular damage indicators, and clinical symptoms in patients with sepsis.
Methods: Retrospectively, 116 sepsis patients treated with CRRT from March 2019 to June 2024 formed the observation group. Meanwhile, 219 patients receiving conventional treatment were propensity score-matched 1:1, with 116 selected as the control group. Both groups were compared post-treatment for TNF-α, IL-4, CRP, Presepsin, IL-6, NGAL, PD-L1, IL-10, mHLA-DR, Ang-2, sTM, histones, mtDNA, ADM, suPAR, and clinical indicators. Cox regression identified factors influencing 28-day survival.
Results: After treatment, the TNF-α, IL-4, CRP, Presepsin, IL-6, NGAL, PD-L1, IL-10, Ang-2, sTM, histones, mtDNA, ADM, and suPAR levels in the observation group were significantly lower than those in the control ($p<0.05$), while mHLA-DR expression was higher ($p<0.05$). The Acute Physiology and Chronic Health (APACHE II) score, Sequential Organ Failure Assessment (SOFA), body temperature, heart rate, and respiratory rate (RR) were also lower in the observation group than in the control. Still, the oxygenation index (PaO_2/FiO_2) and urine output were

Kratak sadržaj

Uvod: Cilj je bio da se ispitaju efekti kontinuirane renalne zamenske terapije (CRRT) na tradicionalne i nove multi-dimenzionalne serumske biomarkere, uključujući inflamatorne citokine, markere imunološke regulacije, markere oštećenja endotela, indikatore ćelijskog oštećenja, kao i kliničke simptome kod pacijenata sa sepsom.
Metode: Retrospektivno je analizirano 116 pacijenata sa sepsom koji su lečeni CRRT-om od marta 2019. do juna 2024. godine, koji su činili opservacionu grupu. Istovremeno, 219 pacijenata koji su primali konvencionalnu terapiju je upoređeno metodom podudaranja (propensity score matching) u odnosu 1:1, pri čemu je odabrano 116 pacijenata kao kontrolna grupa. Nakon terapije, obe grupe su upoređene u pogledu TNF-α, IL-4, CRP, presepsina, IL-6, NGAL, PD-L1, IL-10, mHLA-DR, Ang-2, sTM, histona, mtDNK, ADM i suPAR, kao i kliničkih pokazatelja. Koksova regresiona analiza identifikovala je faktore koji utiču na 28-dnevno preživljavanje.
Rezultati: Nakon terapije, nivoi TNF-α, IL-4, CRP, presepsina, IL-6, NGAL, PD-L1, IL-10, Ang-2, sTM, histona, mtDNK, ADM i suPAR bili su značajno niži u opservacionoj grupi u poređenju sa kontrolnom ($p<0,05$), dok je ekspresija mHLA-DR bila viša ($p<0,05$). APACHE II skor, SOFA skor, telesna temperatura, srčana frekvencija i

Address for correspondence:
Tao Shen
Department of Emergency Medicine, Gejiu People's Hospital, Gejiu, 661000, China
e-mail: z._z86@163.com

higher ($p<0.05$). After 28 days of treatment, the survival rates in the control and observation groups were 65.52% and 81.90%, respectively. After 28 days of treatment, survival rates were 65.52% (control) and 81.90% (observation). COX regression identified septic shock, lactate, elevated IL-4, CRP Presepsin/IL-6/PD-L1/, and Ang-2, higher APACHE II/RR, lower PaO_2/FiO_2, and lack of CRRT as factors adversely affecting 28-day survival.

Conclusion: During routine treatment of sepsis patients, CRRT can comprehensively alleviate inflammatory responses, improve immune dysfunction, reduce endothelial and cellular damage, promote the resolution of sepsis-related symptoms, and play a vital role in improving patient prognosis by modulating multiple biomarkers.

Keywords: sepsis, continuous renal replacement therapy, inflammatory cytokines, presepsin, immune checkpoint, endothelial injury, cellular damage, prognosis

respiratorna frekvencija takođe su bili niži u opservacionoj grupi, dok su indeks oksigenacije (PaO_2/FiO_2) i diureza bili viši ($p<0,05$). Nakon 28 dana lečenja, stopa preživljavanja iznosila je 65,52% u kontrolnoj grupi i 81,90% u CRRT grupi. Koksova regresija je pokazala da su septički šok, laktat, povišeni IL-4, CRP, presepsin, IL-6, PD-L1 i Ang-2, viši APACHE II i respiratorna frekvencija, niži PaO_2/FiO_2, kao i odsustvo CRRT-a faktori koji nepovoljno utiču na 28-dnevno preživljavanje.

Zaključak: U rutinskom lečenju pacijenata sa sepsom, CRRT može sveobuhvatno da smanji inflamatorni odgovor, poboljša imunološku disfunkciju, umanji oštećenje endotela i ćelija, ublaži simptome povezane sa sepsom i značajno doprinese poboljšanju prognoze modulacijom više biomarkera.

Ključne reči: sepsa, kontinuirana renalna zamenska terapija, inflamatorni citokini, presepsin, imunski kontrolni punkt, oštećenje endotela, ćelijsko oštećenje, prognoza

Introduction

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) caused by infection that disrupts host immune regulation, leading to organ dysfunction (OD) and circulatory disorders and ultimately threatening life. According to data on the global burden of disease, the standardised incidence and death rates for sepsis caused by all etiologies were 677.5 and 148.1 per 100,000, respectively. Moreover, approximately 19.7% of global deaths were due to sepsis every year (1). Despite significant progress in antibiotic treatment and organ support techniques, mortality due to sepsis remains significant, ranging from 20.6% to 50.8% (2). Moreover, the prognosis is poor in patients with organ dysfunction or shock (3). Sepsis is characterised as life-threatening organ dysfunction caused by an unregulated host response to infection (4). During the early stages of this condition, an imbalance in pro-inflammatory and anti-inflammatory responses occurs in two directions. The abnormal production of pro-inflammatory and anti-inflammatory cytokines not only increases the degree of inflammatory responses but also closely correlates with the occurrence of SS and early death (5). Although recent studies show that the biological response to sepsis is heterogeneous and that patients with sepsis follow distinct immune response trajectories (6), modulating the inflammatory response remains crucial for treating sepsis.

The existing clinical challenges have prompted medical researchers to explore more effective methods for regulating inflammation. Continuous renal replacement therapy (CRRT) has attracted significant attention due to its ability to continuously clear inflammatory mediators, maintain internal homeostasis, and improve immune function (7). Research has shown that CRRT can nonselectively clear pro-inflammatory and anti-inflammatory mediators, including tumour necrosis factor-α (TNF-α), interleukin-4 (IL-4), and interleukin-10, in patients with pancreatitis complicated by acute kidney failure via convection, adsorption, and diffusion (8).

In recent years, sepsis biomarker research has expanded beyond traditional inflammatory markers to encompass comprehensive monitoring of multiple pathophysiological processes. In addition to TNF-α, IL-4 and CRP, novel biomarkers such as Presepsin (sCD14-ST) reflecting early infection response, immune checkpoint PD-L1 and monocytic HLA-DR (mHLA-DR) indicating immunosuppressive status, endothelial injury markers Angiopoietin-2 (Ang-2) and soluble Thrombomodulin (sTM), cellular damage indicators histones and mitochondrial DNA (mtDNA), and metabolic stress markers Adrenomedullin (ADM) and soluble Urokinase Plasminogen Activator Receptor (suPAR) provide more comprehensive perspectives for assessing sepsis severity, immune status, organ damage, and treatment response. The dynamic changes in these biomarkers may more accurately reflect the impact of CRRT on the multisystem pathophysiological processes of sepsis.

This study retrospectively analyses the effects of CRRT treatment on multidimensional biomarkers, including TNF-α, IL-4, CRP, Presepsin, IL-6, NGAL, PD-L1, IL-10, mHLA-DR, Ang-2, sTM, histones, mtDNA, ADM, suPAR, and clinical symptoms in sepsis patients, and explores the influencing factors on prognosis. We hypothesised that CRRT would significantly reduce multidimensional serum biomarkers (inflammatory, immune, endothelial, and cellular damage) and improve clinical outcomes compared to conventional therapy in sepsis patients. Specific aims were: (1) compare biomarker levels pre/post-treatment between CRRT and control

groups; (2) assess clinical symptom improvements (APACHE II, SOFA, vital signs); (3) evaluate 28-day survival differences; and (4) identify prognostic factors via COX regression.

Materials and Methods

General data

PASS 15.0 was used to estimate the sample size. In the pilot experiment, the survival rate of the control group (CG, conventional treatment) patients after 28 days of treatment was P~1~=0.63, while the survival rate of the observation group (OG, CRRT treatment) patients was P~2~=0.80. Inspection level: α=0.05, Testing performance: β=0.80, Data missing rate=5%. The sample size for the CG and CRRT groups was pre-set at 1:1, and the sample size for each group was calculated to be n=116. A retrospective collection was conducted on 116 sepsis patients who received CRRT treatment in hospitals from March 2019 to June 2024, the OG, and another 219 sepsis patients who received conventional treatment as the CG. Inclusion criteria: (a) Meet the sepsis related diagnostic criteria outlined in the »NICE Guidelines: Identification, Diagnosis, and Early Management of Sepsis« (Tavaré and O'Flynn, 2017) published by the National Institute for Health and Clinical Excellence (NICE) in the United States; (b) Age ≥18 years old; (c) Complete clinical data. Exclusion criteria: (a) Accompanied by malignant tumours; (b) Accompanied by immune dysfunction; (c) Acute kidney injury caused by sepsis; (d) History of severe cardiovascular diseases such as heart failure, acute myocardial infarction, and malignant arrhythmia; (e) History of severe liver and kidney dysfunction such as acute and chronic kidney failure, liver failure, etc; (f) History of organ transplantation; (g) History of CRRT treatment; (h) Long-term use of antibiotics or corticosteroids; (i) Accompanied by active bleeding or cerebral hemorrhage. This study does not harm the rights or the physical and mental health of the subjects; therefore, an informed consent exemption has been obtained, and the study complies with the Helsinki Declaration (World Medical Association 2013). The research flowchart is detailed in *Figure 1*.

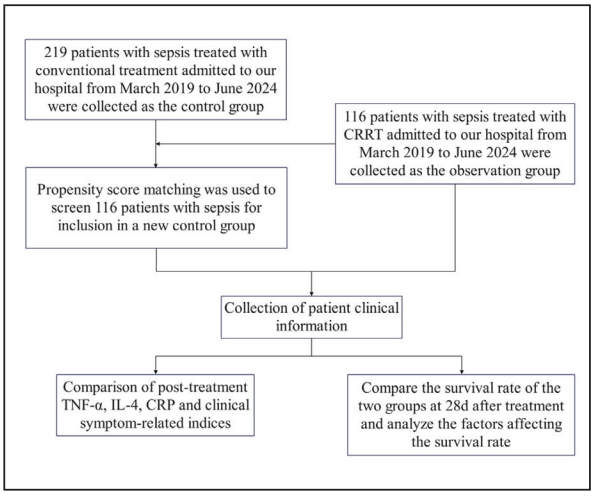

Figure 1 Research process.

Methods

Treatment method

CG adopts a conventional treatment plan: (a) Early recovery and fluid management: For patients with hypoperfusion or SS, intravenous infusion of crystalloid fluid (physiological saline or balanced salt solution) should be administered immediately upon admission. Within the first 3 h, the crystalloid infusion volume should be ≥30 mL/kg to replenish fluids quickly. Subsequently, the amount of fluid replacement should be adjusted based on indicators including Heart Rate (HR), blood pressure, urine output, central venous pressure (CVP), and mixed venous oxygen saturation until the patient's mean arterial pressure (MAP) is ≥ 65 mmHg and blood lactate levels return to the normal range. (b) Anti-infection treatment: Within 1 hour of admission, after obtaining pathogenic specimens, potent broad-spectrum antibiotics should be initiated immediately. After 48–72 hours, the antibiotic type should be adjusted based on the results of the pathogenic examination. Meanwhile, it is necessary to identify the source of infection and achieve source control within 12 hours of admission. (c) Diuretic treatment: After initial fluid resuscitation is complete and hemodynamics are stable, if there is still fluid overload (elevated extravascular lung water or CVP>12 mmHg), diuretic treatment can be initiated. Based on the patient's condition, appropriate diuretics (loop diuretics, thiazide diuretics, etc.) can be selected, and the target urine output should be maintained at ≥0.5 $mL \cdot kg^{-1} \cdot h^{-1}$. During this period, real-time monitoring of patient electrolyte and hemodynamic parameters is required. (d) Electrolyte and acid-base balance regulation: Close attention should be paid to the patient's vital signs. According to the electrolyte test results, individuals with electrolyte imbalance can supplement sodium, potassium, calcium, and chloride ions through intravenous injection or oral administration; For those with acid-base imbalance, after identifying the type of acid-base poisoning, alkaline (such as sodium bicarbonate) or acidic (such as potassium citrate granules) drugs should be selected according to the degree of acid-base imbalance to correct acid-base balance.

Based on CG, OG adopted CRRT; a double-lumen catheter (12F) was used for venous ac-

cess in the femoral vein or the right internal jugular vein. Continuous blood purification equipment (EQUAsmart 3P M03110, MEDICA S.p.A.) was employed in continuous venovenous hemodiafiltration (CVVHDF) mode using a high-flux polysulfone filter (surface area: 1.7 m^2, e.g., Equaflux 170). Initial blood flow was 100–150 mL/min, titrated to 200 mL/min, with effluent dose targeted at 25–30 mL/kg/h. Anticoagulation was heparin-free, heparin-based, or regional citrate per clinical need.

Data collection methods

Collection of clinical data of patients: gender, body mass index (BMI), age, primary infection site, sepsis grade, complications (diabetes, hypertension), white blood cell count (WBC) upon admission, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic acid (LA), activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer (D-D), serum sodium (Na^+), serum potassium (K^+). Collection of multi-dimensional biomarkers at baseline (pre-treatment) and 48–72 hours after CRRT initiation (or equivalent duration in controls): Traditional inflammatory markers: TNF-α, IL-4, CRP; Novel infection markers: Presepsin, IL-6, NGAL; Immune regulation markers: PD-L1, IL-10, mHLA-DR; Endothelial injury markers: Ang-2, sTM; Cellular damage markers: Histones (H3), mtDNA; Metabolic stress markers: ADM, suPAR. Collection of clinical scores and vital signs: APACHE II score, SOFA score, body temperature (T), HR, respiratory rate (RR), MAP, PaO_2/FiO_2, urine volume (UV), and 28-day post-treatment prognosis of patients.

Indicator detection method

5 mL of fasting elbow vein blood from the patient was collected in the morning and subjected to routine centrifugation (4 °C, 3000 rpm, 8 cm, 10 min) to obtain serum and plasma samples. The experiment used a fully automatic blood cell analyser (model: MEK-9100, Manufacturer: NIHON KOHDEN Corporation) to detect WBC and the fully automatic biochemical analyser (model: 2900, manufacturer: AWARENESS TECHNOLOGY, INC.) to detect AST, ALT, and LA. Fully automatic coagulation analyser (model: CN-6500, Manufacturer: SYSMEX Corporation) detects APTT, PT, and D-D. A fully automatic electrolyte analyser (model: EX-Z, Manufacturer: Chang Guang Co., Ltd.) detects Na^+ and K^+. An ELISA reader (model PR 4100, manufacturer BIO-RAD) detects TNF-α, IL-4, CRP, Presepsin, IL-6, NGAL, PD-L1, IL-10, Ang-2, sTM, histones, ADM, and suPAR using commercial ELISA kits according to the manufacturer's instructions. Flow cytometry (BD FACS Canto II) was used to detect mHLA-DR expression on CD14+ monocytes. Mitochondrial DNA was extracted from plasma using QIAamp DNA Blood Mini Kit (Qiagen) and quantified by real-time PCR targeting the MT-ND1 gene. The APACHE II score includes 12 physiological indicators, age, and a chronic health score, with a total score ranging from 0 to 71 points. The higher the score, the more severe the patient's condition. The SOFA score includes six parts: respiration, coagulation, liver, cardiovascular, central nervous system, and kidney, totalling 0–24 points. A higher score indicates more severe OD in the patient.

Statistical methods

SPSS 27.0 was used for data processing and analysis. The Kolmogorov-Smirnov test was used to determine whether the metric data followed a normal distribution. Normal distribution data were represented by mean ± standard deviation. An independent t-test was performed between the two groups. A one-way ANOVA was performed to compare multiple groups. The skewed distribution data are represented by the median and quartiles . The Mann-Whitney U test was used to compare two groups, and the Kruskal-Wallis test was used to compare multiple groups. The number of cases and percentage representing count data) were used, and a χ^2 test was performed. The Wilcoxon rank-sum test was performed on the grade data. COX analysis was used to verify the risk factors of sepsis patients 28 days after treatment. GraphPad Prism 9 was utilised to plot scatter plots and correlation curves. Propensity score matching (PSM) used the radius matching method. After determining the OG sample size (n=116), paired individuals were selected from CG (n=219) in a 1:1 ratio to reconstruct CG (n=116). Matching criteria: gender, age, BMI, primary infection site, sepsis type, comorbidities, patient admission indicators (WBC, AST, ALT, LA, APTT, PT, D-D), patient pre-treatment observation indicators (all biomarkers, APACHE II, SOFA, T, HR, RR, MAP, PaO_2/FiO_2, UA), clamp value=0.05. The $p<0.05$ indicates a statistically significant result.

Results

Comparison of clinical data between two groups of patients before and after PSM

Before PSM, there were statistically significant differences ($p<0.05$) in AST, PT, and PaO_2/FiO_2 in both groups (*Table I*). Using PSM and CG, 116 patients were successfully paired out of 219, and all unmatched patients in CG were excluded. After PSM, $p>0.05$ was observed for clinical data, admission indicators, and pre-treatment observation indicators across the two groups (*Tables I* and *II*).

Table I Clinical data between the first two groups of PSM patients [n (%), (), M (Q1, Q3)].

Item	CG (n=219)	OG (n=116)	c2/t/Z	p
Gender			0.120	0.729
Female	142 (64.84)	73 (62.93)		
Male	77 (35.16)	43 (37.07)		
Age	67.36±9.09	68.26±8.02	-0.895	0.371
BMI ($kg \cdot m^{-2}$)	22.46±2.62	22.24±2.34	0.763	0.446
Primary infection site			0.404	0.939
Urinary system	81 (36.99)	40 (34.48)		
Gastrointestinal system	71 (32.42)	37 (31.90)		
Respiratory system	46 (21.00)	26 (22.41)		
Others	21 (9.59)	13 (11.21)		
Sepsis classification			0.249	0.883
Sepsis	79 (36.07)	45 (38.79)		
Severe sepsis	72 (32.88)	37 (31.90)		
Septic shock	68 (31.05)	34 (29.31)		
Diabetes	20 (9.13)	10 (8.62)	0.024	0.876
Hypertension	34 (15.53)	17 (14.66)	0.044	0.833
Admission indicators				
WBC ($\times 10^9 \cdot L^{-1}$)	12.72±1.89	12.82±2.18	-0.421	0.674
AST ($U \cdot L^{-1}$)	51.60±4.24	50.33±4.18	2.626	0.009
ALT ($U \cdot L^{-1}$)	48.91±5.13	48.53±4.97	0.657	0.512
LA ($mmol \cdot L^{-1}$)	2.75±0.81	2.89±0.91	-1.423	0.156
APTT (s)	44 (40, 48)	43 (37, 46)	-1.926	0.054
PT (s)	16 (14, 18)	15 (13, 17)	-2.031	0.042
D-D ($mg \cdot L^{-1}$)	3.60±0.84	3.43±0.75	1.824	0.069
Na+ ($mmol \cdot L^{-1}$)	135.59±7.77	135.54±7.64	0.059	0.953
K+ ($mmol \cdot L^{-1}$)	4.61±0.88	4.71±0.92	-0.969	0.333
Observation indicators before treatment				
TNF-α ($pg \cdot mL^{-1}$)	2.90±0.51	2.85±0.50	0.862	0.389
IL-4 ($pg \cdot mL^{-1}$)	12.59±2.49	12.43±2.47	0.561	0.576
CRP ($mg \cdot L^{-1}$)	87.05±11.41	85.99±12.34	0.784	0.433
APACHE II score	22 (18, 25)	20 (17.5,25)	-1.435	0.151
SOFA score	11 (9, 12)	10 (9, 13)	-0.722	0.470
T (°C)	37.6 (37.3, 38.0)	37.6 (37.3, 38.0)	-0.341	0.733
HR (tpm)	102.49±17.08	105.47±17.68	-1.502	0.134
RR (tpm)	26 (24, 29)	26 (23, 29)	-0.913	0.361
MAP (mmHg)	77.15±8.60	76.28±7.55	0.914	0.361
PaO_2/FiO_2	225.93±18.72	231.59±19.91	-2.573	0.011
UV ($mL \cdot kg^{-1} \cdot h^{-1}$)	0.39±0.08	0.39±0.08	-0.226	0.821

Table II Clinical data between two groups after PSM [n (%), (), M (Q1, Q3)].

Item	CG (n=116)	OG (n=116)	$\chi^2/t/Z$	*p*
Gender			0.018	0.892
Female	72 (62.07)	73 (62.93)		
Male	44 (37.93)	43 (37.07)		
Age	68.51±8.61	68.26±8.02	0.229	0.819
BMI ($kg \cdot m^{-2}$)	22.10±2.68	22.24±2.34	-0.408	0.684
Primary infection site			0.032	0.998
Urinary system	41 (35.34)	40 (34.48)		
Gastrointestinal system	37 (31.90)	37 (31.90)		
Respiratory system	25 (21.55)	26 (22.41)		
Others	13 (11.21)	13 (11.21)		
Sepsis classification			0.202	0.904
Sepsis	46 (39.66)	45 (38.79)		
Severe sepsis	39 (33.62)	37 (31.90)		
Septic shock	31 (26.72)	34 (29.31)		
Diabetes	10 (8.62)	10 (8.62)	0.000	1.000
Hypertension	17 (14.66)	17 (14.66)	0.000	1.000
Admission indicators				
WBC ($\times 10^9 \cdot L^{-1}$)	12.95±1.80	12.82±2.18	0.513	0.608
AST ($U \cdot L^{-1}$)	50.41±4.08	50.33±4.18	0.153	0.878
ALT ($U \cdot L^{-1}$)	48.39±5.08	48.53±4.97	-0.210	0.834
LA ($mmol \cdot L^{-1}$)	2.92±0.85	2.89±0.91	0.263	0.792
APTT (s)	42 (38, 46)	43 (37, 46)	-0.420	0.674
PT (s)	15 (13, 16)	15 (13, 17)	-0.572	0.567
D-D ($mg \cdot L^{-1}$)	3.49±0.85	3.43±0.75	0.571	0.568
Na^+ ($mmol \cdot L^{-1}$)	135.19±7.72	135.54±7.64	-0.351	0.726
K^+ ($mmol \cdot L^{-1}$)	4.61±0.80	4.71±0.92	-0.855	0.393
Observation indicators before treatment				
TNF-α ($pg \cdot mL^{-1}$)	2.80±0.52	2.85±0.50	-0.824	0.411
IL-4 ($pg \cdot mL^{-1}$)	12.24±2.39	12.43±2.47	-0.608	0.544
CRP ($mg \cdot L^{-1}$)	86.14±11.16	85.99±12.34	0.098	0.922
APACHE II score	22 (17, 25)	20 (17.5, 25)	-0.597	0.551
SOFA score	11 (9, 12)	10 (9, 13)	-0.281	0.779
T (°C)	37.6 (37.3, 38.0)	37.6 (37.3, 38.0)	-0.018	0.986
HR (tpm)	105.18±17.68	105.47±17.68	-0.126	0.900
RR (tpm)	26 (23, 28)	26 (23, 29)	-0.169	0.866
MAP (mmHg)	76.87±9.32	79.66±18.93	0.526	0.599
PaO_2/FiO_2	229.98±20.21	231.59±19.91	-0.609	0.543
UV ($mL \cdot kg^{-1} \cdot h^{-1}$)	0.40±0.08	0.39±0.08	0.103	0.918

Table III Traditional serum inflammatory factor levels in both groups after treatment.

Serum inflammatory factors	CG (n=116)	OG (n=116)	t	p
TNF-α (pg·mL^{-1})	2.33±0.49	2.10±0.36	4.028	<0.001
IL-4 (pg·mL^{-1})	7.17±1.87	6.29±1.65	3.806	<0.001
CRP (pg·mL^{-1})	49.53±8.78	46.08±8.48	3.043	0.003

Table IV Novel multi-dimensional biomarker levels in both groups after treatment.

Biomarker Category	Specific Indicator	CG (n=116)	OG (n=116)	t/Z	p
Infection Markers	Presepsin (pg.mL)	850±210	620±180	4.56	<0.001
	IL-6 (pg.mL)	120±45	85±32	3.89	<0.001
	NGAL (ng.mL)	320±110	240±90	3.21	0.002
Immune Regulation	PD-L1 (pg.mL)	85±22	62±18	3.42	0.001
	IL-10 (pg.mL)	25±8	18±6	2.98	0.003
	mHLA-DR (%)	45±12	58±15	-3.78	<0.001
Endothelial Injury	Ang-2 (ng.mL)	5.2±1.8	3.6±1.2	4.12	<0.001
	sTM (ng.mL)	12.5±4.2	8.8±3.1	3.89	<0.001
Cellular Damage	Histones H3 (μg.mL)	3.8±1.2	2.5±0.9	3.65	<0.001
	mtDNA (copies.μL)	8500±2500	5200±1800	4.88	<0.001
Metabolic Stress	ADM (pg.mL)	45±15	32±11	3.56	<0.001
	suPAR (ng.mL)	8.5±2.8	6.2±2.1	3.21	0.002

Table V Clinical symptom-related indexes between the two groups after treatment.

Clinical Indicators	CG (n=116)	OG (n=116)	Z/t	p
APACHE II score	19 (17, 21)	16 (15, 19)	-5.442	<0.001
SOFA score	9 (7, 12)	8 (7, 10)	-2.126	0.033
T (°C)	36.9 (36.6, 37.2)	36.6 (36.4, 36.8)	-5.766	<0.001
HR (tpm)	96.80±18.68	90.21±15.56	2.921	0.004
RR (tpm)	22 (19, 25)	20 (17, 24)	-2.470	0.013
MAP (mmHg)	81.09±18.08	80.37±16.64	0.314	0.754
PaO_2/FiO_2	287.41±32.23	303.38±32.14	-3.778	<0.001
UV (mL·kg^{-1}·h^{-1})	0.45±0.08	0.48±0.09	-2.668	0.008

Comparison of traditional serum inflammatory factor levels in both groups

The post-treatment levels of TNF-α, IL-4, and CRP in OG patients were obviously lower than those in CG patients ($p<0.05$) (*Table III*).

Comparison of novel multi-dimensional biomarker levels in both groups

The post-treatment levels of Presepsin, IL-6, NGAL, PD-L1, IL-10, Ang-2, sTM, histones, mtDNA, ADM, and suPAR in OG patients were significantly lower than those in CG ($p<0.05$), while mHLA-DR expression was significantly higher in OG ($p<0.05$) (*Table IV*).

Comparison of clinical symptom-related indicators between the two groups

The post-treatment APACHE II score, SOFA score, T, HR, and RR levels of OG patients were significantly lower than those of CG, while PaO_2/FiO_2 and UV were significantly higher than those of CG ($p<0.05$) (*Table V*).

Table VI All multivariable COX analyses of 28-d survival of sepsis patients after treatment.

Item	B	SE	wald χ^2	p	HR (95%CI)
Gender					
Female	1				
Male	-0.238	0.314	0.577	0.448	0.788 (0.426~1.457)
Age	-0.021	0.018	1.337	0.248	0.979 (0.944~1.015)
BMI ($kg \cdot m^{-2}$)	0.005	0.061	0.007	0.933	1.005 (0.892~1.133)
Primary infection site					
Urinary system	1				
Gastrointestinal system	0.039	0.353	0.012	0.911	1.040 (0.521~2.076)
Respiratory system	-0.383	0.429	0.798	0.372	0.682 (0.294~1.581)
Others	0.441	0.437	1.022	0.312	1.555 (0.661~3.659)
Sepsis classification					
Sepsis	1				
Severe sepsis	0.516	0.381	1.840	0.175	1.676 (0.795~3.532)
Septic shock	0.822	0.363	5.117	0.024	2.275 (1.116~4.639)
Diabetes	0.717	0.460	2.428	0.119	2.049 (0.831~5.049)
Hypertension	-0.077	0.404	0.037	0.848	0.926 (0.420~2.042)
Admission indicators					
WBC ($\times 10^9 \cdot L^{-1}$)	-0.031	0.078	0.157	0.692	0.970 (0.832~1.130)
AST ($U \cdot L^{-1}$)	0.009	0.036	0.060	0.807	1.009 (0.940~1.083)
ALT ($U \cdot L^{-1}$)	0.020	0.027	0.540	0.463	1.020 (0.967~1.077)
LA ($mmol \cdot L^{-1}$)	0.394	0.179	4.840	0.028	1.483 (1.044~2.108)
APTT (s)	-0.011	0.027	0.152	0.696	0.989 (0.938~1.044)
PT (s)	-0.045	0.065	0.481	0.488	0.956 (0.841~1.086)
D-D ($mg \cdot L^{-1}$)	-0.312	0.183	2.913	0.088	0.732 (0.511~1.047)
Na^+ ($mmol \cdot L^{-1}$)	0.012	0.021	0.319	0.572	1.012 (0.972~1.054)
K^+ ($mmol \cdot L^{-1}$)	-0.303	0.175	2.974	0.085	0.739 (0.524~1.042)
Observation indicators before treatment					
TNF-α ($g \cdot L^{-1}$)	0.119	0.281	0.180	0.672	1.126 (0.650~1.952)
IL-4 ($pg \cdot mL^{-1}$)	0.123	0.061	4.009	0.045	1.131 (1.003~1.276)
CRP ($mg \cdot L^{-1}$)	0.039	0.014	7.499	0.006	1.040 (1.011~1.069)
APACHE II score	0.108	0.027	16.035	<0.001	1.114 (1.057~1.175)
SOFA score	-0.012	0.052	0.052	0.819	0.988 (0.893~1.093)
T (°C)	-0.323	0.284	1.296	0.255	0.724 (0.415~1.263)
HR (tpm)	0.002	0.009	0.058	0.809	1.002 (0.985~1.020)
RR (tpm)	0.077	0.038	4.205	0.040	1.080 (1.003~1.163)
MAP (mmHg)	0.005	0.010	0.241	0.623	1.005 (0.985~1.026)
PaO_2/FiO_2	-0.029	0.008	12.357	<0.001	0.971 (0.955~0.987)
UV ($mL \cdot kg^{-1} \cdot h^{-1}$)	1.422	2.049	0.482	0.488	4.144 (0.075~229.690)
Treatment Plan					
Conventional therapy	1				
CRRT	-0.904	0.301	9.042	0.003	0.405 (0.225~0.730)

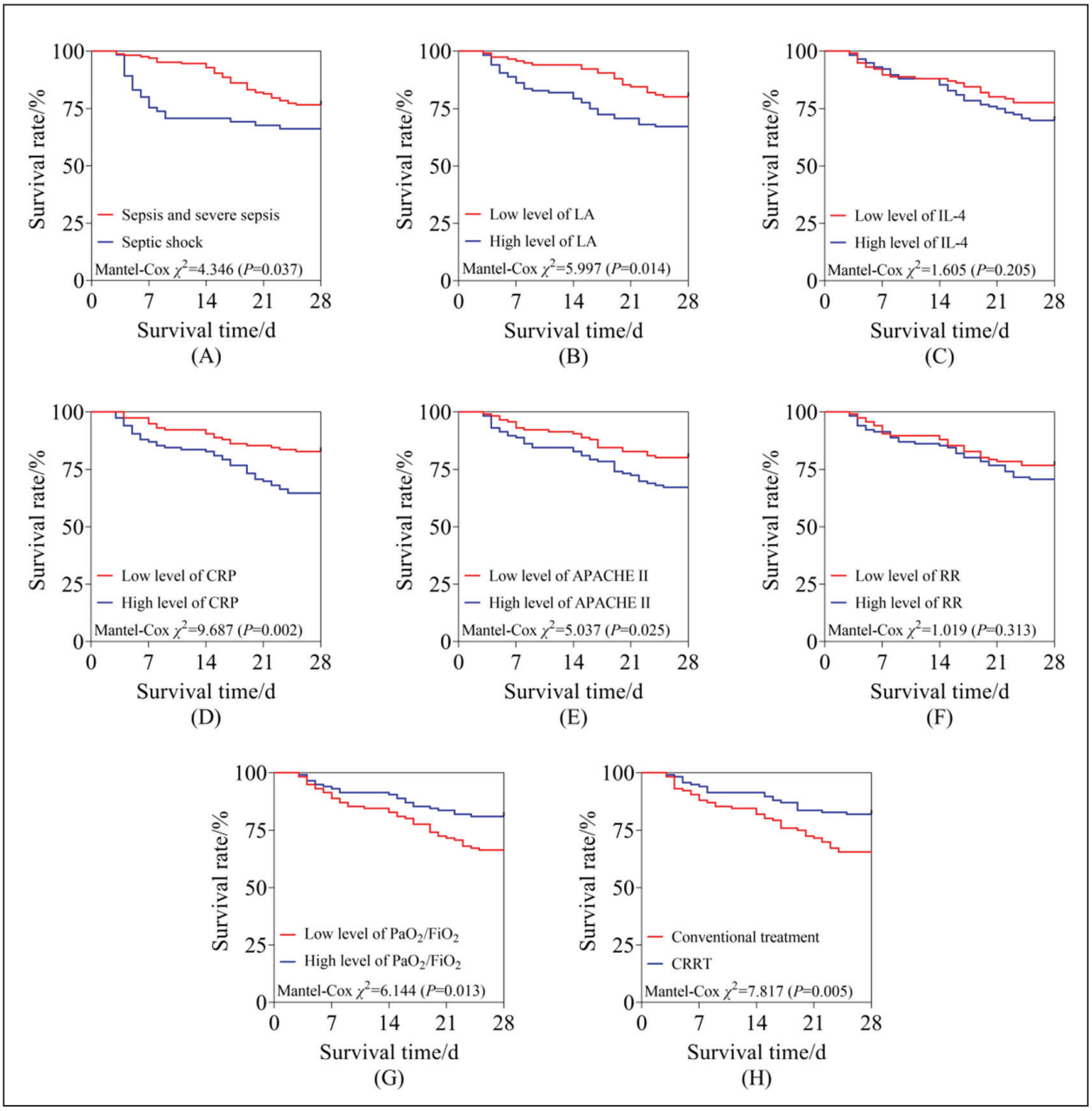

Figure 2 Kaplan-Meier 28-day survival curves by clinical characteristics. Panels: (A) Sepsis classification; (B) Lactate; (C) IL-4; (D) CRP; (E) APACHE II; (F) RR; (G) PaO_2/FiO_2; (H) Treatment (CRRT vs conventional; red=conventional, blue=CRRT). Log-rank Mantel-Cox p<0.05 for all. Legends: Solid red=high-risk/conventional; solid blue=low-risk/CRRT.

28-day survival rate and related risk factors of the two groups after treatment

After 28 days of treatment, 76 cases of CG survived, with a survival rate of 65.52% and a survival time of 3–28 days, with an average survival time (AST) of (22.84 ± 8.29) days; 95 cases of OG survived, with a survival rate of 81.90% and a survival time of 3–28 d, with a AST of (25.18±6.66) days. The difference in AST in both groups was significant (t=-2.365, p=0.019). The 28-day survival status of sepsis patients after treatment were utilised as the dependent variable (0=survival, 1=death); The gender, age BMI, primary infection site, sepsis type, comorbidities, patient admission indicators (WBC, AST, ALT, LA, APTT, PT, D-D), pre-treatment observation indicators (all biomarkers, APACHE II, SOFA, T, HR, RR, MAP, PaO_2/FiO_2, UA) were used as independent variables. Multiple factor COX analysis was conducted. SS, LA, IL-4, CRP, Presepsin, IL-6, PD-L1, Ang-2, APACHE II score, RR, PaO_2/FiO_2, and CRRT were identified as influencing fac-

tors for 28-day survival in sepsis patients after treatment (*Table VI*). The Mantel-Cox test was conducted based on the above influencing factors. The survival rates with SS, high levels of LA, CRP, Presepsin, IL-6, PD-L1, Ang-2, high APACHE II score, PaO_2/FiO_2 levels, and conventional treatment were significantly lower ($p<0.05$).

Discussion

Sepsis has a poor prognosis and a high mortality rate. This study included 232 patients, of whom 61 died within 28 days after treatment, with a mortality rate of 26.29% (61/232). This is similar to the 28.94% reported by Ren et al. (3), but is significantly lower than the sepsis mortality rate of 58.33% reported by Gai et al. (4). The lower mortality rate in this study (26.29%) compared to Gai et al. (4), (58.33%) may primarily result from our stringent exclusion of acute kidney injury (AKI) patients (see Methods 1.1), alongside younger age and fewer severe comorbidities, thereby enriching for less critically ill sepsis cases.

TNF-α was the core mediator of pro-inflammatory response. The excessive release of TNF-α in early sepsis was closely related to SIRS and OD. Reports were suggesting that TNF-α may be an important serum biomarker for predicting secondary sepsis in patients with closed abdominal injury accompanied by severe multiple injuries (9). Some studies downregulated TNF-α using a macrophage-targeted RNAi system to treat acute inflammatory sepsis (10). In addition, a meta-analysis showed that TNF-α levels in surviving sepsis patients were lower after treatment than in non-surviving sepsis patients (11). Multiple studies have shown that TNF-α is closely correlated to the occurrence, development, and prognosis of sepsis. IL-4 was a Th2 anti-inflammatory factor that reflected the immunosuppressive state in the late stage of sepsis (12), and immunosuppression might raise the risk of secondary infection and death.

Additionally, IL-4 might exacerbate sepsis-induced immune paralysis (13) and increase the risk of poor prognosis due to its synergistic effect with other anti-inflammatory factors. A rapid rise of CRP within 4–6 hours of infection was observed. It did not have high specificity in diagnosing sepsis (14), but its dynamic changes could still be used to assess disease progression (15). In this study, TNF-α, IL-4, and CRP levels in OG patients were significantly lower than in CG ($p<0.05$), indicating that CRRT is more effective at inhibiting the inflammatory response in sepsis patients. The CRRT treatment mode was CVVHDF, which was a combination of Continuous Venovenous Hemofiltration (CVVH) and Continuous Venovenous Hemodialysis (CVVHD). CVVHDF combined the dual effects of convection and dispersion, effectively removing small-molecule toxins, such as urea and creatinine, from the blood, as well as large-molecule substances, such as TNF-α, IL-4, and CRP. Therefore, while compensating for CVVH's poor clearance of small molecules via simple convection, it could further enhance the clearance of large molecules, such as inflammatory factors. Domestic reports have shown that CVVHDF treatment was performed on patients with SS and acute kidney injury. The post-treatment levels of inflammatory indices in patients were significantly lower than pre-treatment levels (16), consistent with the results.

Among novel biomarkers, presepsin (sCD14-ST), a soluble CD14 subtype, serves as a highly specific early marker of bacterial infection and sepsis severity (17). Programmed death-ligand 1 (PD-L1) reflects T-cell exhaustion and immunosuppression, correlating with poor outcomes. Angiopoietin-2 (Ang-2) indicates endothelial dysfunction and vascular leak, predicting organ failure, while soluble thrombomodulin (sTM) signifies coagulopathy and endothelial injury. Cellular damage markers, such as histone H3 and mtDNA signals, indicate NETosis and mitochondrial injury, and adrenomedullin (ADM)/suPAR denote metabolic stress and persistent inflammation. CRRT significantly reduced these ($p<0.01$), suggesting broad immunomodulation beyond traditional cytokines (18, 19).

The severity of the patient's condition was assessed using the APACHE II score, and the OD using the SOFA score. Both scores were closely related to patient prognosis (20, 21). Some patients with sepsis may also suffer from respiratory disorders or acute lung injury, while others have fever, palpitations, and shortness of breath. Additionally, UV reflected the success of diuretic treatment for SS. In this study, the APACHE II score, SOFA score, T, HR, RR, PaO_2/FiO_2, and UV were used as clinical indicators for post-treatment evaluation. A significant decrease in APACHE II and SOFA scores, T, HR, and RR levels in OG patients after treatment was observed, along with a significant increase in PaO_2/FiO_2 and UV levels, indicating that CRRT treatment can be effective in reducing sepsis-related symptoms. Based on an analysis of the reasons, CRRT reduced organ damage caused by excessive pro-inflammatory reactions by clearing inflammatory factors from the body. Aside from reducing oxidative stress and microcirculatory disorders, inhibiting the inflammatory response could also improve tissue oxygen supply and reduce vascular endothelial damage. In patients with sepsis, CRRT corrected metabolic disorders and fluid balance, and provided good conditions for recovery of cardiovascular and pulmonary function.

In terms of survival rate and survival time, OG patients after 28 days of treatment had significantly better outcomes than CG patients, indicating that CRRT can help lower the risk of death in sepsis patients. This study found through COX analysis that the mortality risk of patients treated with CRRT was 0.405 times higher than that of patients treated with conventional therapy (95%CI=0.225–0.730). In addition, SS, LA, IL-4, CRP, APACHE II score, RR, and PaO_2/FiO_2 were all factors affecting the 28-day survival of sepsis patients after treatment. According to survival analysis, high LA and CRP levels, a high APACHE II score, and low PaO_2/FiO_2 could all significantly reduce the survival rate of sepsis patients. Therefore, when sepsis patients are admitted, the severity of their condition should be actively evaluated, and indicators such as LA, IL-4, and CRP should be monitored in real time. Based on this, the treatment plan should be adjusted in real time to improve the patient's prognosis as much as possible. However, this study still had certain limitations. Although potential confounding factors were excluded as much as possible through PSM, some were not included in the study due to missing data. The inclusion of a single sample source in this study may lead to biased results and reduced reliability of the conclusions.

However, this study still had certain limitations. Limitations include the retrospective, single-centre design, which limits causal inference; potential residual confounding despite PSM; and the lack of serial biomarker measurements beyond 48–72h. Future multicenter RCTs are warranted to validate CRRT's multi-dimensional effects. The inclusion of a single sample source in this study may lead to biased results and reduced reliability of the conclusions. Future multicenter prospective studies are needed to validate these findings.

Conclusion

This study used a retrospective approach to confirm that CRRT treatment can comprehensively improve multiple pathophysiological processes in sepsis patients by reducing traditional inflammatory factors and novel multi-dimensional biomarkers, including Presepsin, PD-L1, Ang-2, histones, ADM, etc. These improvements collectively alleviate sepsis-related clinical symptoms and significantly improve patient survival rates. The identification of multiple novel biomarkers as prognostic factors provides new targets for sepsis monitoring and treatment. In clinical practice, it is recommended to strengthen monitoring of these multidimensional biomarkers and to adjust treatment plans in real time based on these results to improve treatment efficiency further. Future research should further explore the dynamic changes of these biomarkers and their specific mechanisms in CRRT treatment.

Authors' contribution

Jun Meng and Lei Kang contributed equally to this work and share co-first authorship.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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