Clinical Outcomes of Severe Sepsis and Septic Shock Patients with Left Ventricular Dysfunction Undergoing Continuous Renal Replacement Therapy: A Multicenter Retrospective Study

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Research

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Abstract

Background: Baseline left ventricular (LV) dysfunction is associated with subsequent risks of acute kidney injury (AKI) and mortality in patients with sepsis. This study investigated the therapeutic effects of continuous renal replacement therapy (CRRT) in hemodynamically unstable patients with severe sepsis and septic shock combined with LV dysfunction.

Methods: In this multicenter retrospective study, severe sepsis and septic shock patients with LV dysfunction were classified into one of two groups according to the timing of CRRT: the early group (before AKI was detected) or the control group (patients with AKI). All-cause intensive care unit (ICU) mortality and ICU stay were compared between the groups. Patients were weighted by stabilized inverse probability of treatment weights (sIPTW) to overcome differences in baseline characteristics.

Results: After sIPTW analysis, the ICU mortality was significantly lower in the early group than the control group (25.9% vs 59.0%, $p < 0.001$). Weighted multivariable analysis showed that early CRRT initiation was a protective factor for the risk of ICU mortality. Early CRRT initiation significantly improved the ICU mortality compared to the control group (OR, 0.322; 95% CI, 0.125-0.834; $p = 0.020$).

Conclusions: Early CRRT in the absence of AKI is suggested for hemodynamically unstable patients with severe sepsis and septic shock combined with LV dysfunction since it benefits survival outcomes.

Trial registration: The study was preregistered in the Chinese Clinical Trial Registry (number, ChiCTR2000033083).

Background

Sepsis is associated with life-threatening multiorgan dysfunction due to the extreme host response to infection^[1, 2]. It has become a major global health problem leading to approximately five million deaths annually^[3]. Cardiac dysfunction has been identified as a serious component of sepsis-induced organ dysfunction and is observed in 10–70% of patients^[4] with a mortality rate as high as 70%^[5]. Left ventricular (LV) dysfunction is associated with the subsequent risk of acute kidney injury (AKI) under different clinical circumstances^[6, 7]. For patients with sepsis, LV diastolic dysfunction (LVDD) and LV systolic dysfunction (LVSD) have been reported to worsen renal outcomes^[7].

Continuous renal replacement therapy (CRRT) is the predominant form of renal replacement therapy (RRT) applied in the intensive care unit (ICU) for the clearance of cytokines and endotoxins, the correction of acid-base and electrolyte disturbance, and to achieve hemodynamic stability^[1, 8]. For patients with septic shock, CRRT was suggested to facilitate management of fluid balance according to the International Guidelines for Management of Sepsis and Septic Shock: 2012/2016^[9, 10]. However, there is insufficient evidence to support the use of CRRT. In addition, although CRRT can reduce inflammatory mediators involved in sepsis, its benefits on survival have not been fully elucidated^[11]. Hence, the clinical

outcomes of CRRT in hemodynamically unstable sepsis patients combined with LV dysfunction were investigated in the current study.

Methods

Study patients and design

This multicenter retrospective study was performed using data from three ICUs located at Fujian Medical University Union Hospital and Fujian Provincial Hospital with a total of 85 beds from January 1, 2013 to December 31, 2019. All participants underwent transthoracic echocardiography within 24 hours of admission to identify the presence or absence of LV dysfunction. The exclusion criteria included: younger than 18 years of age, moderate-to-severe valvular heart disease, history of end-stage renal disease or hemodialysis, postrenal causes of renal injury, cardiopulmonary resuscitation before ICU admission, intoxication, cirrhosis, rhabdomyolysis, active malignancy, connective tissue diseases, pregnancy, expected survival less than 24 hours, normal LV function, poor echocardiographic image quality.

All patients included in this study were managed with CRRT. Some hemodynamically unstable patients receiving CRRT did not have septic AKI before CRRT. Patients were divided into one of two groups according to the baseline AKI status: the early group (no AKI) or the control group (with AKI). In the early group, early initiation of CRRT was performed in the absence of AKI, though AKI could occur thereafter. The control group received CRRT when AKI was presented. CRRT was discontinued when hemodynamics or renal function was improved. Clinical outcomes included all-cause ICU mortality and length of ICU stay.

Data collection

Data concerning demographic and clinical information (primary diagnosis and comorbidities), physiological parameters (hemodynamic data and vasoactive medications), transthoracic echocardiographic parameters, laboratory results, and the use of invasive mechanical ventilation were extracted from electronic medical records by trained medical staff. Information of the CRRT was reviewed. The urine output (UO) and serum creatinine levels were obtained to verify the presence of AKI. The corresponding glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation^[12]. Baseline disease severity was assessed by the Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Definitions: Severe sepsis, septic shock, and septic AKI

Severe sepsis was defined as sepsis related to organ dysfunction, hypoperfusion, or hypotension^[13]. A lactate level ≥ 2.3 mmol/L (22.1 mg/dl) was considered indicative of hypoperfusion. Hypotension was defined as systolic blood pressure ≤ 90 mmHg or a decrease of 40 mmHg below baseline, organ dysfunction as SOFA score ≥ 2 ^[13]. Septic shock was defined as sepsis-induced persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg or a lactate level ≥ 2.3 mmol/L (22.1 mg/dl) after adequate fluid resuscitation^[14, 15]. Septic AKI was defined as the

simultaneous presence of sepsis criteria^[14] and the consensus criteria for AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines^[16]. The baseline creatinine value was either obtained from clinical files within seven to 365 days previous to admission or the minimum inpatient values during the first seven days of admission^[7]. AKI was defined as meeting one of the following criteria: an increase in creatinine by ≥ 0.3 mg/dl within 48 hours; an increase in creatinine to ≥ 1.5 times baseline within the previous seven days; or urine output ≤ 0.5 ml/kg/h for 6 hours.

Transthoracic echocardiographic examination

All echocardiograms were assessed by a professional cardiologist. Two-dimensional, M-mode, and Doppler data were used to obtain parameters from parasternal long- and short-axis views; apical four-chamber, two-chamber, and long-axis views; and subcostal views. Data on early diastolic velocity of mitral inflow (E), early diastolic mitral annular velocity (e'), late diastolic velocity of mitral inflow (A), E/e' ratio, and E/A ratio were collected. According to the American Society of Echocardiography 2009 guidelines^[17] and the simplified definition suggested by Lanspa *et al.*^[18], LVSD was defined as LV ejection fraction (LVEF) < 50%, and LV diastolic function was classified into four grades (normal and grades I, II, and III).

CRRT settings

CRRT was performed in either continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF) through the femoral or internal jugular veins at the discretion of attending physicians. PRISMAFLEX and AQUARIUS hemofiltration systems were used with the addition of bicarbonate or potassium if necessary. The dialysate rate, replacement fluid rate, and ultrafiltration rate were adjusted according to patients' diagnoses, hemodynamic parameters, and fluid overload. AN69 membranes or RENAFLO hemofilters were used and blood flow rates were kept between 100 and 200 mL/min during the procedure.

Statistical analyses

Continuous variables were expressed as the mean $\pm$ standard deviation for normally distributed data and differences between groups were determined using a two independent samples t-test. Data without normal distribution were expressed as the median (interquartile range, P25, and P75) and two groups were compared using the Mann-Whitney *U* test. Categorical variables were presented as counts (percentages) and compared using Pearson's chi-square test or Fisher's exact test.

Propensity score weighting (PSW) was applied to balance the baseline characteristics between groups. Firstly, the baseline characteristics were compared between the two groups. Secondly, logistic regression analysis was used to evaluate the probability of treatment with early CRRT or not. With the treatment allocation as dependent variables, and the factors with *p* values < 0.10 between the two groups at admission were taken as the candidate independent variables. The logistic regression model was constructed to calculate the individual propensity score. Thirdly, patients were weighted by the stabilized

inverse probability of treatment weighting (sIPTW) and the weighted baseline characteristics were tested again. Clinical outcomes including ICU mortality and length of ICU stay were compared between two groups by chi square analysis and an independent samples t-test before and after weighting.

The risk factors associated with ICU mortality were further analyzed, and the impact of early CRRT on mortality was evaluated. With mortality as the dependent variable, and baseline clinical characteristics at admission and at the start of CRRT as independent variables, the weighted univariate logistic regression analyses were conducted separately. According to the results of univariate regression analysis, the factors with $p < 0.05$ were selected as the candidate independent variable to construct the multivariate weighted logistic regression model. The step-by-step method was used to screen the variables. Effect size was presented as the odds ratio (OR) with the corresponding 95% confidence interval (CI). All data were analyzed using R 4.0.2 software, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics before sIPTW

A total of 1892 adult patients with severe sepsis and septic shock were initially screened and 629 patients had echocardiograms performed. Among 227 patients who met the inclusion criteria with LV dysfunction, 132 patients received CRRT. Thirty-seven, 71 and 24 patients had LVSD, LVDD, and combined LVSD and LVDD, respectively. A total of 58 patients received early initiation of CRRT due to unstable hemodynamics and 74 patients were categorized into the control group. The study flowchart was displayed in Fig. 1.

The patient characteristics and echocardiographic parameters before sIPTW were presented in Table 1. The early group had a greater proportion of postoperative patients ($p = 0.001$). The control group had worse LV diastolic function as demonstrated by the higher E/e' ($p < 0.001$). Patients with early CRRT had a higher proportion of norepinephrine users at admission ($p = 0.033$).

Table 1
Patient characteristics before sIPTW (at baseline and at the start of CRRT)

Characteristics	Early group (n = 58)	Control group (n = 74)	<i>p</i>
Age, years	62.86 ± 10.58	62.58 ± 8.87	0.868
Male, n (%)	40 (68.97)	50 (67.57)	0.864
BMI, kg/m ²	24.34 ± 3.4	24.76 ± 3.19	0.466
MAP, mmHg	81.74 ± 5.38	83.24 ± 5.33	0.112
Laboratory tests			
Leukocyte count, ×10 ⁹ /L	14.23 ± 3.71	15.36 ± 3.37	0.070
PLT count, ×10 ⁹ /L	178.93 ± 57.44	177.72 ± 54.13	0.901
Blood pH	7.33 ± 0.06	7.34 ± 0.06	0.246
Baseline creatinine, mg/dl	0.93 ± 0.29	0.94 ± 0.3	0.842
Serum potassium, mEq/L	4.76 ± 0.66	4.84 ± 0.68	0.472
Baseline eGFR, mL/min/1.73 m ²	80.88 ± 22.81	80.05 ± 22.05	0.832
BUN, mg/dl	15.96 ± 2.88	15.91 ± 3.13	0.918
CK-MB, IU/L	27.5 ± 22.75	21.12 ± 14.81	0.067
ALT, U/L	56.24 ± 58.65	53.04 ± 51.45	0.739
Total bilirubin, mg/dl	1.3 ± 0.88	1.2 ± 0.98	0.559
Lactate, mg/dl	72.46 ± 48.73	58.7 ± 32.57	0.067
Hb, mg/dl	132.64 ± 12.05	131.19 ± 12.76	0.508
Six-hour UO at admission, ml	421.36 ± 151.25	460.50 ± 139.35	0.125
Primary diagnosis			
Pneumo-sepsis, n (%)	19 (32.76)	23 (31.08)	0.837
Urosepsis, n (%)	7 (12.07)	5 (6.76)	0.292
Abdominal sepsis, n (%)	18 (31.03)	28 (37.84)	0.416

sIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.

Characteristics	Early group (n = 58)	Control group (n = 74)	<i>p</i>
Other cause, n (%)	14 (24.14)	18 (24.32)	0.980
Postoperative, n (%)	15 (25.86)	4 (5.41)	0.001
Positive blood culture, n (%)	25 (43.1)	30 (40.54)	0.767
Invasive mechanical ventilation, n (%)	32 (55.17)	47 (63.51)	0.332
Comorbidities			
Hypertension, n (%)	14 (24.14)	19 (25.68)	0.840
Diabetes mellitus, n (%)	9 (15.52)	12 (16.22)	0.913
Coronary artery disease, n (%)	3 (5.17)	5 (6.76)	1.000
Heart failure, n (%)	7 (12.07)	9 (12.16)	0.987
Medication at admission			
Noradrenaline, n (%)	48 (82.76)	49 (66.22)	0.033
Dopamine, n (%)	17 (29.31)	12 (16.22)	0.071
Glucocorticoid, n (%)	6 (10.34)	13 (17.57)	0.241
Echocardiography			
LVEDD, mm	49.64 ± 2.67	48.67 ± 2.89	0.050
LVESD, mm	36.23 ± 3.32	35.16 ± 3.52	0.078
CO, L/min	4.02 ± 0.88	3.98 ± 0.81	0.770
LVEF, %	50.14 ± 12.37	51.47 ± 13.28	0.557
E, m/s	0.72 ± 0.23	0.81 ± 0.22	0.019
A, m/s	0.73 ± 0.17	0.8 ± 0.18	0.040
E/A	1 ± 0.29	1.05 ± 0.31	0.376
e', m/s	0.08 ± 0.02	0.07 ± 0.03	0.138
E/e'	10.16 ± 4.52	13.7 ± 6.41	< 0.001

SIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.

Characteristics	Early group (n = 58)	Control group (n = 74)	<i>p</i>
Cardiac function			0.562
Systolic dysfunction, n (%)	19 (32.76)	18 (24.32)	
Diastolic dysfunction, n (%)	29 (50)	42 (56.76)	
Systolic and diastolic dysfunction, n (%)	10 (17.24)	14 (18.92)	
SOFA scores	12.43 ± 1.84	12.41 ± 1.95	0.939
APACHE II scores	24.76 ± 3.21	24.73 ± 3.24	0.959
At the start of CRRT			
Noradrenaline, n (%)	58 (100)	44 (59.46)	< 0.001
Noradrenaline, µg/kg/min	0.34 ± 0.20	0.22 ± 0.21	0.003
Six-hour UO before CRRT initiation, mL	391.71 ± 142.64	151.24 ± 60.72	< 0.001
Total duration CRRT, hour	84.83 ± 25.13	85.08 ± 18.79	0.949
Creatinine at the start of CRRT, mg/dl	2.21 ± 1.41	2.79 ± 1.19	0.012
MAP at the start of CRRT, mmHg	79.28 ± 5.29	89.78 ± 10.78	< 0.001
SOFA at the start of CRRT	12.74 ± 1.72	13.27 ± 1.72	0.082
APACHE II at the start of CRRT	27.62 ± 4.14	29.55 ± 4.66	0.014
sIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.			

At the beginning of CRRT, early CRRT initiated patients had lower MAP ($p < 0.001$), a higher proportion of norepinephrine users ($p < 0.001$) and were administered higher levels of noradrenaline at the start of CRRT ($p = 0.003$). Patients in the control group had worse renal function with higher creatinine ($p = 0.012$) and lower urine output ($p < 0.001$). The APACHE II scores of the control group were higher than the early group ($p = 0.014$). The mean duration of CRRT did not differ between the two groups (84.83 ± 25.13 hours vs. 85.08 ± 18.79 hours, $p = 0.949$).

Patient Characteristics After Siptw

After sIPTW, baseline characteristics of the two groups at admission were almost balanced (Table 2), but the control group had higher invasive mechanical ventilation administration ($p = 0.011$).

Table 2
Patient characteristics after sIPTW (at baseline and at the start of CRRT)

Characteristics	Early group (n = 54)	Control group (n = 78)	<i>sIPTW- adjusted</i> <i>p</i>
Age, years	63.90 ± 9.02	63.99 ± 8.75	0.954
Male, n (%)	36 (66.67)	50 (64.1)	0.761
BMI, kg/m ²	24.61 ± 3.38	24.48 ± 2.89	0.813
MAP, mmHg	81.93 ± 5.24	83.15 ± 5.55	0.206
Laboratory tests			
Leukocyte count, ×10 ⁹ /L	14.81 ± 3.54	14.19 ± 4.33	0.386
PLT count, ×10 ⁹ /L	174.56 ± 56.57	177.38 ± 51.71	0.767
Blood pH	7.33 ± 0.06	7.35 ± 0.07	0.090
Baseline Creatinine, mg/dl	0.93 ± 0.28	0.97 ± 0.29	0.431
Serum potassium, mEq/L	4.78 ± 0.60	4.96 ± 0.66	0.112
Baseline eGFR, mL/min/1.73 m ²	79.63 ± 22.26	76.31 ± 22.11	0.399
BUN, mg/dl	16.00 ± 2.67	16.34 ± 2.96	0.501
CK-MB, IU/L	23.84 ± 19.94	23.47 ± 18.07	0.912
ALT, U/L	48.30 ± 51.02	52.38 ± 55.81	0.670
Total Bilirubin, mg/dl	1.19 ± 0.76	1.17 ± 1.04	0.904
Lactate, mg/dl	64.45 ± 42.43	62.28 ± 40.96	0.769
Hb, mg/dl	133.03 ± 11.01	131.57 ± 12.28	0.485
Six-hour UO at admission, ml	440.97 ± 163.96	435.83 ± 139.25	0.847
Primary diagnosis			
Pneumo-sepsis, n (%)	15 (27.78)	21 (26.92)	0.914
Urosepsis, n (%)	6 (11.11)	5 (6.41)	0.522
Abdominal sepsis, n (%)	16 (29.63)	36 (46.15)	0.056

sIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.

Characteristics	Early group (n = 54)	Control group (n = 78)	<i>sIPTW- adjusted</i> <i>p</i>
Other cause, n (%)	17 (31.48)	16 (20.51)	0.152
Postoperative, n (%)	9 (16.67)	14 (17.95)	0.849
Positive blood culture, n (%)	21 (38.89)	27 (34.62)	0.616
Invasive mechanical ventilation, n (%)	24 (44.44)	52 (66.67)	0.011
Comorbidities			
Hypertension, n (%)	15 (27.78)	27 (34.62)	0.407
Diabetes mellitus, n (%)	9 (16.67)	18 (23.08)	0.369
Coronary artery disease, n (%)	3 (5.56)	5 (6.41)	1.000
Heart failure, n (%)	5 (9.26)	7 (8.97)	0.801
Medication at admission			
Noradrenaline, n (%)	44 (81.48)	60 (76.92)	0.529
Dopamine, n (%)	12 (22.22)	16 (20.51)	0.813
Glucocorticoid, n (%)	6 (11.11)	15 (19.23)	0.210
Echocardiography			
LVEDD, mm	49.04 ± 2.81	48.59 ± 3.11	0.397
LVESD, mm	35.86 ± 3.20	35.31 ± 3.56	0.365
CO, L/min	4.03 ± 0.83	3.92 ± 0.79	0.442
LVEF, %	51.24 ± 11.74	50.99 ± 13.56	0.913
E, m/s	0.75 ± 0.25	0.76 ± 0.23	0.813
A, m/s	0.78 ± 0.19	0.75 ± 0.19	0.374
E/A	0.98 ± 0.29	1.04 ± 0.31	0.264
e', m/s	0.07 ± 0.02	0.07 ± 0.03	1.000
E/e'	11.45 ± 5.31	12.13 ± 5.72	0.491

sIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.

Characteristics	Early group (n = 54)	Control group (n = 78)	<i>sIPTW- adjusted</i> <i>p</i>
Cardiac function			0.991
Systolic dysfunction, n (%)	14 (25.93)	21 (26.92)	
Diastolic dysfunction, n (%)	10 (18.52)	14 (17.95)	
Systolic and diastolic dysfunction, n (%)	30 (55.55)	43 (55.13)	
SOFA scores	12.55 ± 1.85	12.84 ± 2.07	0.410
APACHE II scores	24.51 ± 3.17	25.43 ± 3.41	0.119
At the start of CRRT			
Noradrenaline, n (%)	54 (100)	52 (66.67)	< 0.001
Noradrenaline, µg/kg/min	0.33 ± 0.19	0.20 ± 0.20	< 0.001
Six-hour UO before CRRT initiation, mL	396.66 ± 154.55	156.04 ± 55.78	< 0.001
Total duration CRRT, hour	80.14 ± 27.38	87.95 ± 18.25	0.051
Creatinine at the start of CRRT, mg/dl	2.30 ± 1.49	2.83 ± 1.11	0.021
MAP at the start of CRRT, mmHg	79.46 ± 4.98	89.56 ± 10.22	< 0.001
SOFA at the start of CRRT	12.76 ± 1.66	13.58 ± 1.77	0.008
APACHE II at the start of CRRT	27.54 ± 4.30	30.44 ± 4.71	< 0.001
sIPTW: stabilized inverse probability of treatment weights, BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output.			

Patients with early CRRT had worse hemodynamic characteristics when compared to those in the control group at the start of CRRT. Early CRRT-initiated patients had lower MAP ($p < 0.001$), higher proportion of norepinephrine users ($p < 0.001$) and were administered higher levels of noradrenaline ($p < 0.001$) at the start of CRRT. Patients in the control group had worse renal function with higher creatinine ($p = 0.021$) and lower urine output ($p < 0.001$) at the start of CRRT. The SOFA ($p = 0.008$) and APACHE II ($p < 0.001$) scores of the control group were higher than the early group.

Early Crrt Is Associated With A Reduced Icu Mortality

Before sIPTW, the length of ICU stay between the two groups were not significantly different ($p = 0.344$). The ICU mortality of patients receiving early CRRT was significantly lower than that in the control group

(32.8% VS 52.7%, $p = 0.022$). After sIPTW, the ICU duration between the two groups were comparable ($p = 0.093$). However, the ICU mortality was still significantly different in the early group versus the control group: 25.9% versus 59.0%, respectively ($p < 0.001$; Table 3).

Table 3
Clinical outcomes before and after sIPTW

Outcome	Early group	Control group	<i>p</i>
Pre-adjusted			
ICU stay, days	19.9 ± 6.55	21.12 ± 7.93	0.344
Death, n (%)	19 (32.76)	39 (52.70)	0.022
sIPTW-adjusted			
ICU stay, days	19.66 ± 6.36	21.79 ± 7.57	0.093
Death, n (%)	14 (25.93)	46 (58.97)	< 0.001
sIPTW: stabilized inverse probability of treatment weights, ICU: intensive care unit.			

Early Crrt Initiation Reduces The Risk Of Icu Death

The weighted univariate logistic regression analysis showed that early CRRT initiation was a protective factor and significantly reduced the risk of ICU mortality compared with the control group (OR, 0.251; 95% CI, 0.118–0.536; $p < 0.001$; Table 4). By weighted multivariable analysis (Table 5), early CRRT initiation was a protective factor for the risk of ICU mortality when the variables were screened using a step-by-step method, and early CRRT could significantly reduce the ICU mortality compared with the control group (OR, 0.322; 95% CI, 0.125–0.834; $p = 0.020$).

Table 4
Weighted univariate logistic regression analysis

Characteristic	OR	95% CI	P
Age, years	0.969	0.931, 1.009	0.130
Gender (Female vs Male)	0.912	0.444, 1.873	0.802
BMI, kg/m ²	0.965	0.862, 1.080	0.533
MAP, mmHg	1.029	0.965, 1.097	0.385
Laboratory tests			
Leukocyte count, ×10 ⁹ /L	0.881	0.803, 0.967	0.007
PLT count, ×10 ⁹ /L	0.994	0.987, 1.000	0.068
Blood pH, per 0.1	1.377	0.791, 2.399	0.258
Baseline Creatinine, mg/dl	1.669	0.501, 5.557	0.404
Serum potassium, mEq/L	1.853	1.043, 3.293	0.036
Baseline eGFR, mL/min/1.73 m ²	0.997	0.982, 1.013	0.701
BUN, mg/dl	1.063	0.940, 1.203	0.328
CK-MB, IU/L	1.004	0.985, 1.022	0.702
ALT, U/L	1.004	0.997, 1.011	0.244
Total Bilirubin, mg/dl	1.061	0.734, 1.534	0.752
Lactate, mg/dl	1.004	0.996, 1.013	0.355
Hb, mg/dl	0.985	0.956, 1.014	0.312
Six-hour UO at admission, mL	0.998	0.996, 1.001	0.127
Primary diagnosis			
Pneumo-sepsis	0.752	0.346, 1.634	0.471
Urosepsis	0.656	0.178, 2.414	0.526
Abdominal sepsis	2.753	1.339, 5.657	0.006
Other cause	0.423	0.181, 0.988	0.047
BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output, OR: odds ratio, CI: confidence interval.			

Characteristic	OR	95% CI	P
Postoperative	1.922	0.768, 4.809	0.162
Positive blood culture	1.645	0.805, 3.363	0.172
Invasive mechanical ventilation	20.257	7.586, 54.089	< 0.001
Comorbidities			
Hypertension	1.908	0.906, 4.019	0.089
Diabetes mellitus	2.808	1.159, 6.799	0.022
Coronary artery disease	5.788	0.912, 36.721	0.063
Heart failure	1.568	0.485, 5.070	0.453
Admission			
Noradrenaline	1.189	0.508, 2.783	0.690
Dopamine	1.783	0.767, 4.146	0.179
Glucocorticoid	1.180	0.458, 3.038	0.732
Echocardiography			
LVEDD, mm	1.014	0.903, 1.138	0.813
LVESD, mm	1.013	0.916, 1.121	0.803
CO, L/min	0.955	0.623, 1.465	0.833
LVEF, %	0.993	0.967, 1.020	0.622
E, m/s	0.275	0.061, 1.241	0.093
A, m/s	0.048	0.007, 0.344	0.003
E/A	2.337	0.718, 7.607	0.159
e', per 0.1 m/s	0.958	0.238, 3.854	0.952
E/e'	0.962	0.903, 1.026	0.242
Cardiac function			
Systolic dysfunction	Ref		

BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output, OR: odds ratio, CI: confidence interval.

Characteristic	OR	95% CI	<i>P</i>
Diastolic dysfunction	1.019	0.451, 2.307	0.963
Combined systolic and diastolic dysfunction	1.044	0.365, 2.985	0.935
SOFA scores	1.220	1.017, 1.464	0.032
APACHE II scores	1.107	0.995, 1.232	0.061
At the start of CRRT			
Noradrenaline	1.302	0.539, 3.141	0.557
Noradrenaline, per 0.1 µg/kg/min	0.980	0.815, 1.180	0.834
Six-hour UO before CRRT initiation, mL	0.996	0.994, 0.999	0.007
Total duration CRRT, hour	1.007	0.991, 1.022	0.395
Creatinine at the start of CRRT, mg/dl	1.147	0.879, 1.497	0.312
MAP at the start of CRRT, mmHg	0.995	0.960, 1.030	0.762
SOFA at the start of CRRT	1.373	1.108, 1.702	0.004
APACHE II at the start of CRRT	1.089	1.010, 1.175	0.027
Early CRRT (vs Control)	0.251	0.118, 0.536	< 0.001
BMI: body mass index, MAP: mean arterial pressure, PLT: platelet, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, CK-MB: Creatine kinase-MB, ALT: alanine aminotransferase, LV: left ventricle, LVEDD: LV end diastolic dimension, LVESD: LV end systolic dimension, CO: cardiac output, LVEF: LV ejection fraction, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II, CRRT: continuous renal replacement therapy, UO: urine output, OR: odds ratio, CI: confidence interval.			

Table 5
Weighted multivariable logistic regression analysis

Characteristic	OR	95% CI	<i>p</i>
Early CRRT (vs Control)	0.322	0.125, 0.834	0.020
Abdominal sepsis	4.110	1.454, 11.613	0.008
Invasive mechanical ventilation	25.531	8.320, 78.346	< 0.001
CRRT: continuous renal replacement therapy, OR: odds ratio, CI: confidence interval.			

In addition, the risk factors associated with ICU mortality included abdominal sepsis (OR, 4.110; 95% CI, 1.454–11.613; $p = 0.008$), and invasive mechanical ventilation (OR, 25.531; 95% CI, 8.320–78.346; $p < 0.001$).

Discussion

Currently, there is no consensus regarding early vs. late CRRT initiation in patients with septic cardiorenal syndrome (CRS). However, increasing evidence has been favoring an earlier start^[19, 20]. The current study, to the best of our knowledge, was the first study validating that an early CRRT improved the ICU mortality for severe sepsis and septic shock patients with LV dysfunction even before the onset of AKI.

The all-cause mortality of severe sepsis and septic shock patients with LV dysfunction and initiated CRRT enrolled in our study was 43.9%, which was similar to the 28-day all-cause mortality (43.1%) of LV systolic asynchrony in patients with septic shock^[21]. However, the mortality of all patients receiving early CRRT was 32.8%, which was lower significantly and also appeared better than the recently reported data on septic patients with AKI treated with CRRT (62.0%)^[22]. It is noteworthy that those treated with early CRRT had worse hemodynamics than those receiving delayed CRRT, as reflected by a higher proportion of norepinephrine users, higher noradrenaline levels, and lower MAP at the initiation of treatment.

Sepsis-related LV dysfunction, known as septic cardiomyopathy, was observed in nearly 48% of the severe sepsis and septic shock patients^[13]. In the present study, the number of patients with sepsis-related LV dysfunction was 116 (87.9%), and only 16 (12.1%) patients had pre-existing heart failure (HF). Regarding the treatment of septic cardiomyopathy, there have been no specific therapeutics so far. The current guidelines for the management of septic shock, for example infection control with adequate antibiotics and hemodynamic stabilization with inotropic and vasopressor agents and fluids, represent the cornerstone of septic cardiomyopathy therapy. Innovative therapeutic management strategies of septic cardiomyopathy are therefore urgently needed^[5, 23].

The pathophysiological interplay between the heart and kidney was defined as CRS, which has been associated with all-cause mortality in patients with sepsis^[6, 7, 24–27]. In the current study, type 5 and type 1 CRS were witnessed. Systemic diseases, especially sepsis, are the most common causes of type 5 CRS^[28], which was detected in 67–76% of the septic population and was an independent predictor of in-hospital mortality^[29]. Cardiovascular dysfunction in septic CRS-5 can manifest as septic cardiomyopathy, circulatory failure, and autonomic dysregulation^[28]. Septic cardiomyopathy is a fundamental feature of sepsis-associated cardiac dysfunction^[5] that includes LVSD and LVDD, contributing to renal hypoperfusion^[30, 31]. Type 1 CRS in sepsis patients was represented by decreased LVEF and cardiac output. Elevated central venous pressure increases “kidney afterload” and leads to renal dysfunction, which plays a major role in the pathophysiology of CRS in acute cardiac dysfunction^[27]. Other contributing factors are the activation of neurohormonal pathways and proinflammatory responses^[32].

CRRT is a predominant form of RRT applied in the ICU^[33]. Septic cardiomyopathy is primarily caused by the release of inflammatory cytokines, including interleukin-1 beta (IL-1 β), IL-6, and tumor necrosis factor-alpha (TNF- α), in addition to tissue hypoxia and mitochondrial dysfunction that leads to cardiac myocyte injury^[13, 34–37]. Administration of endotoxin in healthy volunteers results in an increase in LV end diastolic

volume and a reduction in LVEF^[37]. The improvement of myocardial suppression by CRRT accelerates the recovery of cardiac function and improves hemodynamics. However, standard CRRT was performed in the current study and we did not investigate whether high cut-off membrane therapy or the use of the CytoSorb filter could increase the clearance of cytokines, such as TNF- α and IL-10.

The physiological benefits of ultrafiltration include the removal of inflammatory mediators and precise targeting of fluid removal^[27]. The pre-existing LV dysfunction may abruptly worsen, resulting in renal hypoperfusion through a reduction in blood flow or an increase in central venous pressure, eventually leading to type 1 CRS^[6]. Ultrafiltration had beneficial effects on hemodynamic changes, which might improve kidney function by reducing renal venous pressure and optimizing renal perfusion^[27, 38]. In HF patients, CRRT had positive effects on hemodynamics by improving myocardial performance, measured by increased stroke volume, cardiac output and cardiac cycle efficiency^[11, 38]. Therefore, the accurate volume control and achievement of hemodynamic stability is extremely important and should be carried out as early as possible after detection of a myocardial dysfunction in a patient with sepsis.

We found that early CRRT reduced the risk of ICU death even after weighted multivariable analysis. In addition, abdominal sepsis and invasive mechanical ventilation were risk factors associated with ICU mortality. We suggest that hemodynamically unstable patients with severe sepsis and septic shock complicated with LV dysfunction should be treated with CRRT before the onset of AKI, since hemodynamic stability and clearance of endotoxin is likely to improve cardiac function and survival rates.

This study has several limitations. Due to the retrospective nature of the study, it is impossible to carry out continuous monitoring and follow-up of LV function in patients with persistent cardiac dysfunction, which may influence the primary outcome. Meanwhile, we did not investigate the effect of different CRRT patterns on clinical outcomes. Furthermore, other mechanisms of action including mitochondrial dysfunction, nitric oxide and danger-associated molecular patterns (DAMPs) are closely linked to sepsis-induced myocardial dysfunction and prognosis^[5]. Whether CRRT is effective for the treatment of all these pathological reactions remains unknown. Hence, animal experiments and prospective randomized multicenter trials are necessary to determine the effect of a CRRT strategy for septic cardiac dysfunction, especially on persistent dysfunction in severe sepsis and septic shock.

Conclusions

For hemodynamically unstable patients with severe sepsis and septic shock combined with LV dysfunction, an early CRRT performed before the presence of AKI may decrease ICU all-cause mortality.

Abbreviations

LV: left ventricular; AKI: acute kidney injury; LVDD: left ventricular diastolic dysfunction; LVSD: left ventricular systolic dysfunction; CRRT: continuous renal replacement treatment; RRT: renal replacement

treatment; ICU: intensive care unit; UO: urine output; eGFR: estimated glomerular filtration rate; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; MAP: mean arterial pressure; KDIGO: Kidney Disease: Improving Global Outcomes; BMI: body mass index; PLT: platelet; BUN: blood urea nitrogen; ALT: alanine aminotransferase; CK-MB: creatine kinase-MB; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; CO: cardiac output; E: early diastolic velocity of mitral inflow; A: late diastolic velocity of mitral inflow; e': early diastolic mitral annular velocity; CVVH: continuous veno-venous hemofiltration; CVVHDF: continuous veno-venous hemodiafiltration; PSW: propensity score weighting; sIPTW: stabilized inverse probability of treatment weighting; CRS: cardiorenal syndrome; HF: heart failure; IL: interleukin; TNF: tumor necrosis factor.

Declarations

Authors' contributions

GWY, FHL, KC, ZHZ and WWW conceived and designed the study. GWY and KC performed statistical analyses. GWY, WWW, FHL, XHL, KC, and QL collected and interpreted data. GWY drafted the manuscript. WWW and XHL critically revised the manuscript. GWY[†] and KC[†] contributed equally to this work. All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Availability of data and materials

The dataset used and analyzed in this study is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the research ethics committee of Fujian Medical University Union Hospital (Ethics Code: 2019KJCX006) and Fujian Provincial Hospital (Ethics Code: K2020-05-014). Informed consent was waived because of the retrospective and observational nature of the study.

Consent for publication

Not applicable.

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Figures

Figure 1

Patient and analysis flowchart.

Figure 1

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