IJKD KIDNEY DISEASES

Evaluating Continuous Veno-venous Hemodiafiltration Treatment Effects on Biomarkers and Outcomes in Sepsis-Induced Acute Kidney Injury

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Introduction. Acute kidney injury (AKI) is commonly precipitated by sepsis. Continuous veno-venous hemofiltration (CVVHD) is a critical intervention for managing AKI, but further exploration is needed to understand its effects on novel renal injury markers and patient outcomes. The aim of this study is to evaluate the impact of CVVHD on novel renal injury markers and its prognostic significance in individuals suffering from sepsis-related AKI.
Methods. Retrospective analysis was carried out on the medical data of 84 patients with sepsis-induced AKI treated at Baoji High-Tech Hospital from February 2022 to August 2023. We assessed changes in serum biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and liver fatty acid-binding protein (L-FABP) pre- and post-CVVHDF treatment, and correlated these changes with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Cox regression was utilized to identify independent prognostic factors influencing 28-day survival, from which Kaplan-Meier curves and a prognostic nomogram were derived.
Results. A significant reduction in the serum concentrations of s-NGAL, L-FABP, and KIM-1 was observed following treatment (all $P < .001$). A positive correlation between these serum biomarkers and APACHE II scores was observed both before and after CVVHDF treatment (all $P < .001$). According to multivariate Cox regression analysis, coronary heart disease ($P = .016$), the stage of renal injury ($P = .014$), APACHE II score ($P < .001$), and s-NGAL ($P < .001$) were independent predictors of prognosis for 28-day survival.
Conclusion. CVVHD effectively decreases KIM-1, L-FABP, and NGAL levels, thereby enhancing kidney function in individuals suffering from sepsis-related AKI. Key prognostic indicators for 28-day survival include the presence of coronary artery disease, advanced kidney injury stage, APACHE II score ≥ 26, and NGAL levels ≥ 5.49.

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INTRODUCTION

Sepsis represents the most acute and critical clinical condition worldwide, with over 30 million new cases annually, resulting in more than 5 million deaths. This significant mortality rate poses a severe burden on global public health.[1,2] Acute kidney injury (AKI) is a regular outcome of sepsis, influenced by systemic diseases, nephrotoxic medication,

hypotension, and ischemia-reperfusion injury.[3] AKI which occurs in up to 50% of cases of septic patients, often leads to loss of renal function, dialysis dependence, and increased mortality.[4] Progression of sepsis typically results in multi-organ dysfunction, including pulmonary, renal, and cerebral systems dysfunction. Complications such as lactic acidosis and hypotension can escalate into septic shock, a life-threatening condition, if not promptly managed.[5]

Continuous veno-venous hemodiafiltration (CVVHD) is a pivotal treatment modality for critically ill patients, particularly in the management of severe AKI. This technique not only removes excess water and solutes but also maintains hemodynamic stability through slow, continuous ultrafiltration. Furthermore, CVVHD effectively eliminates low and medium molecular weight inflammatory cytokines and promotes immunomodulation via diffusion.[6-8] While its application is widespread, evidence from non-randomized controlled studies suggests that CVVHD can ameliorate clinical outcomes by removing inflammatory cytokines, thereby improving the health condition of patients with severe AKI.[9]

In clinical research on sepsis-induced AKI, biomarkers such as kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL) complex have shown significant potential.[10-12] The expression of these markers varies considerably across different pathological states, mirroring biological alterations in the kidneys during the disease progression. However, the dynamics of these biomarkers following therapeutic interventions such as CVVHD remain poorly understood.[13,14] The extent to which these biomarker changes during treatment and their ability to effectively forecast treatment responses and patient outcomes are still largely unexplored.

This study aims to track changes in L-FABP, NGAL and KIM-1 levels in AKI patients undergoing CVVHD treatment, exploring their potential to monitor treatment efficacy and predict patient prognosis. The findings are expected to enhance our understanding and guide the diagnosis and management of AKI more effectively.

MATERIALS AND METHODS

Clinical information and Ethical Considerations

Retrospective analysis was carried out on the medical data of 84 individuals with sepsis-induced AKI treated at Baoji High-Tech Hospital between February 2022 and August 2023.

Given its retrospective nature, the existing clinical data from patients were used.

To protect patient privacy, all data were anonymized, and the study did not involve direct patient contact. Consistent with institutional guidelines and national regulations, patient consent for the use of their anonymized medical records in research was not required. Nonetheless, all procedures adhered to ethical standards for retrospective studies, ensuring patient confidentiality and data security.

Criteria for inclusion and exclusion

Criteria for participant inclusion were:

1) individuals aged 18 to 80 years, regardless of sex;
2) sepsis diagnosis following the Sepsis-3 criteria (Third International Consensus Definitions for Sepsis and Septic Shock)[15];
3) AKI diagnosis following the Renal Disease framework: Improving Global Outcomes (KDIGO) guidelines[16];
4) availability of complete clinical data for analysis, including demographics, medical history, laboratory parameters, and treatment outcomes.

Exclusion criteria

Criteria for participant exclusion were: 1) expected survival time of less than 14 days, to avoid confounding the assessment of treatment impact on renal biomarkers and survival outcomes 2) history of chronic kidney disease or pre-existing kidney dysfunction, such as glomerulonephritis or chronic kidney disease, to prevent baseline level interference of renal biomarkers. 3) use of immunosuppressive medications or presence of immunocompromised status, as these conditions could alter sepsis progression, AKI, and treatment outcomes 4) presence of malignant tumors, which could independently affect prognosis and confound the study results.

Rationale and Impact

These criteria were strategically selected to ensure a homogeneous patient cohort, enhancing the evaluation of CVVHD in treating sepsis-induced

AKI. By excluding patients with less than 14 days of expected survival, the study aimed to attribute changes in renal biomarkers and outcomes directly to the treatment rather than imminent mortality from other causes. Similarly, excluding individuals with chronic renal conditions or compromised immune systems ensures that changes in AKI markers are due to CVVHD, thus clarifying its efficacy. Although these criteria bolster the study's internal validity, they may limit its external applicability across a broader patient demographic. Future research should consider these excluded groups to assess the generalizability of findings across diverse patient subsets.

Treatment protocol

All patients underwent CVVHD and dialysis with a flow rate of 150-180 mL/min in blood, administered 12-24 hours per dose. The anticoagulation protocol included heparin-free, average heparin, and citrate in vitro, based on the patient's blood gas analysis. In the early group, continuous renal replacement therapy (CRRT) was started within 24 hours of ICU admission, while in the late group, it was started after 48 hours. Subsequent treatments for both groups were scheduled daily or every other day starting from > 72 hours after the first session. CRRT was discontinued when patients' urine output exceeded 1,000 mL over 24 hours without the aid of diuretics.

Biochemical markers

The serum levels of KIM-1 (Cat ID: ml060414), L-FABP (Cat ID: ml063226), and NGAL (Cat ID: ml064308) were measured by using ELISA kits supplied by Shanghai Enzyme-Link. The methods followed the manufacturer's guidelines.

Data recording

Patient information was obtained from digital health records, including demographics (sex, body mass index [BMI], age), clinical history (diabetes mellitus, hypertension, coronary heart disease [CHD]), kidney injury staging, and acute physiology and chronic health evaluation II (APACHE II) scores.[17] Laboratory indicators, including NGAL, KIM-1, and KIM-1 levels, were collected before treatment and 14-day post-treatment. Patient survival was monitored for 28-day post-admission (Table 1).

Table 1. Patient baseline data

Category	Value
Sex	
Male	50
Female	34
Age (years)	57.45 ± 13.96
Body mass index (kg/m^2)	24.30 ± 2.98
Hypertension history	
Yes	20
No	64
Diabetes mellitus history	
Yes	16
No	68
Coronary heart disease history	
Yes	14
No	70
Kidney injury stage	
I	15
II	20
III	49
APACHEII score	
KIM-1 before treatment (μg/L)	22.97 ± 7.95
L-FABP before treatment (μg/L)	59.24 ± 10.48
NGAL before treatment (μg/L)	5.10 ± 1.19

Note: kidney injury molecule-1 (KIM-1), Acute Physiology and Chronic Health Evaluation II (APACHE II), Liver fatty acid-binding protein (L-FABP), Neutrophil gelatinase-associated lipocalin (NGAL)

Outcome Measurement

Biomarker Assessment: Changes in KIM-1, L-FABP and NGAL levels were analyzed before and after treatment.

Correlation Analysis: The relationship between the APACHE II score and the biomarkers KIM-1 and NGAL and L-FABP was examined.

Survival Analysis: Based on their 28-day outcome, patients were assigned to either the survival or death group. Cox regression was utilized to identify independent predictors of prognosis influencing 28-day survival, and Kaplan-Meier (K-M) curves were drawn to illustrate these relationships.

Prognostic Modeling: A prognostic model was established using a nomogram based on the findings. (Refer to Figure 1 for the research flowchart).

Statistical processing

SPSS 26.0 was utilized to process the data, while GraphPad 9 was utilized to create the graphs. For data measurement, inter-group analysis were analyzed using t-tests for independent samples, and intra-group comparisons were assessed with paired t-tests. Pearson's test analyzed the correlations between APACHE II scores and the

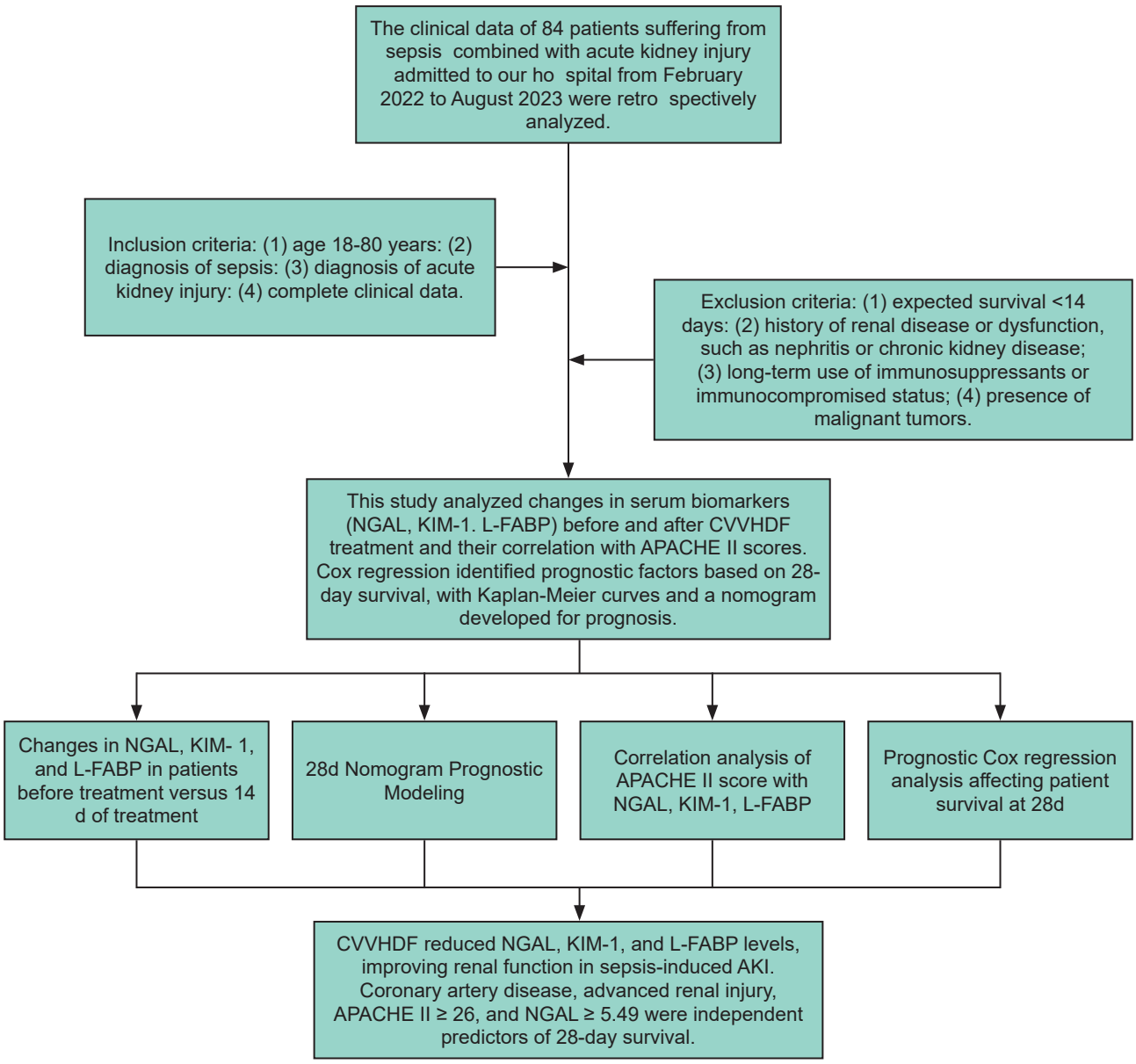

Figure 1. Research Flowchart
Kidney injury molecule-1 (KIM-1), Liver fatty acid-binding protein (L-FABP), Acute Physiology and Chronic Health Evaluation II (APACHE II), Neutrophil gelatinase-associated lipocalin (NGAL)

biomarkers KIM-1, NGAL and L-FABP. X-tile software dichotomized the values of KIM-1, s-NGAL and L-FABP for further analyses. Cox regression was utilized to determine independent factors that prognosticate 28-day patient survival. Statistical significance was set at a *P*-value of < .05.

RESULTS

Changes in renal biomarkers pre- and post-treatment

The concentrations of s-NGAL, KIM-1, and L-FABP were measured in patients before and 14 days after treatment. The findings indicated a notable decrease in the levels of these biomarkers post-treatment compared to pre-treatment levels, with statistically significant difference (all $P < .001$, Table 2).

Correlation analysis of APACHE II Score with renal biomarkers

This research sought to investigate the correlation of APACHE II scores with the levels

Table 2. Changes in renal biomarkers prior to and following treatment

Indicator	Before treatment	After treatment	t	*P*
KIM-1 (μg/L)	22.97 ± 7.95	13.47 ± 4.36	9.608	< .001
L-FABP (μg/L)	59.24 ± 10.48	53.56 ± 10.53	3.501	< .001
NGAL (μg/L)	5.10 ± 1.19	4.18 ± 0.98	5.476	< .001

Note: liver fatty acid-binding protein (L-FABP), Kidney injury molecule-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL)

of the emerging renal biological markers (NGAL, KIM-1, and L-FABP) before and after treatment. Our findings indicated a positive correlation of APACHE II scores with the biomarkers (KIM-1, NGAL and L-FABP) in patients at the two time points (Figure 2, all $P < .001$).

Analysis of prognostic factors affecting 28-day survival

The 28-day mortality outcome of 84 individuals were analyzed, and it was noticed that 46 (54.76%) died within this period. To identify prognostic factors influencing 28-day survival, we utilized X-tile software to establish optimal cutoff values for the APACHE II score (26), NGAL (5.49 μg/L), KIM-1 (19.83 μg/L), and L-FABP (55.55 μg/L). The data were then dichotomized based on these values. Univariate analysis via Cox regression indicated that age ($P = .001$), history of CHD ($P = .001$), kidney injury stage ($P = .017$), and pre-treatment levels of APACHE II ($P < .001$), KIM-1 ($P < .001$), NGAL ($P < .001$) and L-FABP ($P < .001$) markedly influenced patient prognosis (Table 3). Multivariate analysis via Cox regression uncovered that CHD

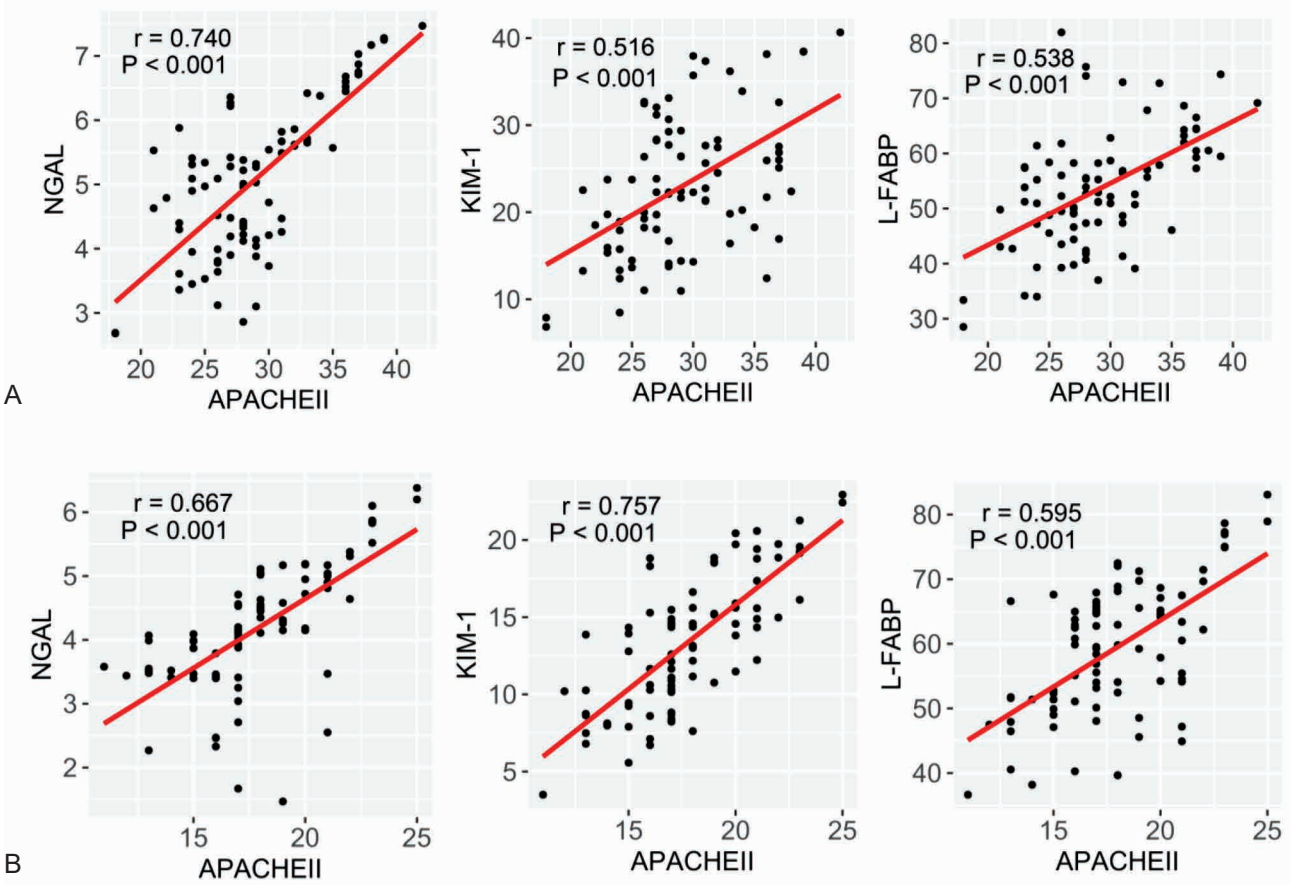

Figure 2. Correlation analysis of emerging renal biological markers (L-FABP, KIM-1, and NGAL) and APACHE II scores in patients before and after treatment. (A) Correlation analysis of emerging renal biological markers (L-FABP, KIM-1, and NGAL) and APACHE II scores in patients before treatment. (B) Correlation analysis of emerging renal biological markers (L-FABP, KIM-1, and NGAL) and APACHE II scores in patients after treatment.
Neutrophil gelatinase-associated lipocalin (NGAL), Liver fatty acid-binding protein (L-FABP), Kidney injury molecule-1 (KIM-1), Acute Physiology and Chronic Health Evaluation II (APACHE II)

Table 3. Analysis of factors affecting 28-day prognosis using univariate Cox regression

Category	Beta	Std Err	*P*	HR	Lower 95% CI	Upper 95% CI
Distinguishing between the sexes	0.133	0.302	.661	1.142	0.631	2.065
Age	0.995	0.307	.001	2.705	1.481	4.941
Body mass index	-0.030	0.310	.922	0.970	0.529	1.781
History of hypertension	-0.190	0.358	.594	0.827	0.410	1.666
History of mellitus	0.029	0.372	.938	1.030	0.497	2.135
History of Coronary heart disease	1.163	0.343	.001	3.200	1.635	6.262
Kidney injury staging	0.520	0.218	.017	1.682	1.098	2.577
APACHEII	-3.434	0.465	< .001	0.032	0.013	0.080
NGAL	-2.254	0.477	< .001	0.105	0.041	0.267
KIM-1	-1.526	0.302	< .001	0.217	0.120	0.393
L-FABP	-1.670	0.393	< .001	0.188	0.087	0.407

Note: APACHEII score, KIM-1 NGAL and L-FABP are pre-treatment data.
Neutrophil gelatinase-associated lipocalin (NGAL), Acute Physiology and Chronic Health Evaluation II (APACHE II), Kidney injury molecule-1 (KIM-1), Liver fatty acid-binding protein (L-FABP)

(P = .016), the stage of renal injury (P = .014), NGAL levels (P < .001) (P < .001), and APACHE II score were independent predictors of 28-day survival (Figure 3, Table 4).

28-day prognostic modeling using a nomogram

At the conclusion of our study, we developed a nomogram, depicted in Figure 4, which incorporates critical variables including history of CHD, stage of renal injury, APACHE II score, and NGAL levels. This model creates a scoring system that evaluates the likelihood of 28-day survival, providing a powerful tool for clinicians to evaluate patient prognosis in the intensive care setting. For validation, we applied the nomogram to a randomly selected patient with CHD, stage 2 renal injury, an APACHE II score of 26, and NGAL levels of 3.78. This patient's cumulative score was calculated as 163 (31+32+100+0), indicating a 58% probability of death within 28 days according to the nomogram.

DISCUSSION

Sepsis is a prevalent condition within the ICU, not solely triggered by bacteria or toxins but predominantly resulting from immune system dysfunction caused by activation of inflammatory mediators.[18] This condition progressively impairs organ function and circulation, leading to high mortality and complicating clinical management. AKI is particularly critical, characterized by high morbidity rates. Patients with AKI, typically exhibit symptoms such as electrolyte disturbances, and uremia.[19] The extended duration of treatment, slow recovery of renal function, and potential for irreversible renal damage underscore the necessity of monitoring renal function indices in AKI management.[20]

In this study, we noticed significant reductions in s-NGAL, KIM-1, and L-FABP levels post-treatment, indicating the effectiveness of CVVHD in removing excess water and metabolic waste through continuous blood purification. CVVHD also facilitates the removal of inflammatory mediators, including cytokines, which are essential for mitigating the systemic inflammatory response and subsequent renal damage.[21] This process not only alleviates the strain on the kidneys but also enhances hemodynamic stability, promoting renal function recovery. A notable decline in s-NGAL levels suggest the control over AKI and possibly initiates renal regeneration and repair processes.[22]

The decrease in serum KIM-1 suggests significant mitigation of damage to renal tubular cells, potentially indicating a restoration of kidney structure and function.[23] Similarly, a reduction in serum L-FABP, a sensitive marker of tubular hypoxia, implies improved renal ischemic conditions and enhanced tissue oxygenation.[24]

Petrova *et al.* reported that while s-NGAL levels showed significant fluctuations in patients with kidney injury post-coronary angiography, serum creatinine levels remained largely unchanged, highlighting the sensitivity of s-NGAL compared to traditional markers.[25] Furthermore, Musiał *et al.* observed elevated serum KIM-1 and NGAL in children with kidney injury undergoing hematopoietic stem cell transplantation, suggesting their utility as early indicators of kidney dysfunction.[26] Additionally, Tang *et al.* reported

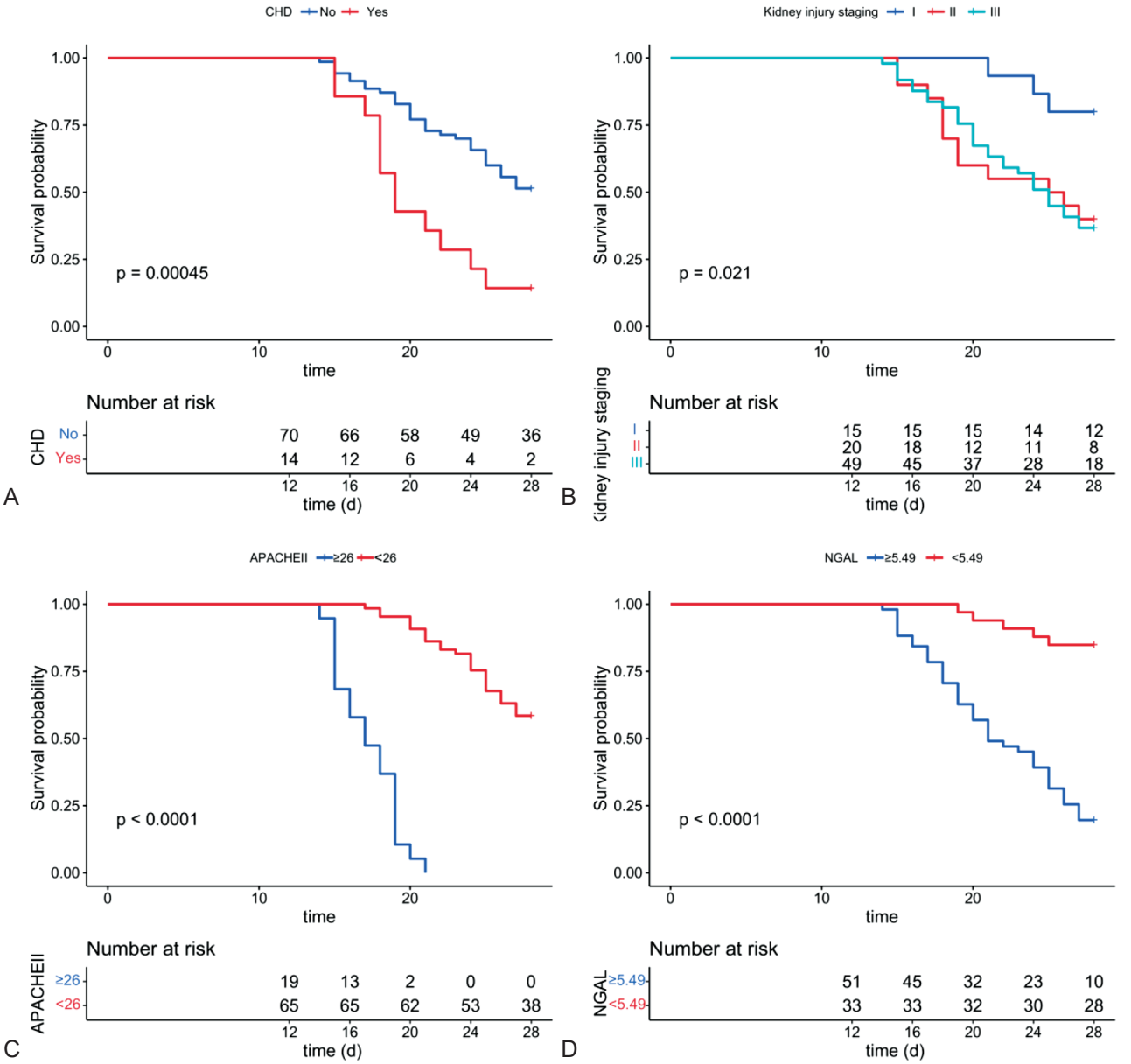

Figure 3. Survival curves using K-M analysis for independent prognostic factor. (A) 28-day survival curves using K-M analysis for patients with coronary heart disease. (B) 28-day survival curves using K-M analysis for patients by renal injury staging. (C) 28-day survival curves using K-M analysis for patients by APACHEII scores. (D) 28-day survival curves using K-M analysis for patients by NGAL levels.
Note: Neutrophil gelatinase-associated lipocalin (NGAL), Kaplan-Meier (K-M), Acute Physiology and Chronic Health Evaluation II (APACHE II)

Table 4. Analysis of independent factors affecting 28-day prognosis using multifactorial Cox regression

Category	Beta	Std Err	*P*	HR	Lower 95% CI	Upper 95% CI
Age	0.639	0.326	.050	1.894	1.001	3.586
Coronary heart disease	0.967	0.402	.016	2.631	1.196	5.786
Kidney injury staging	0.658	0.267	.014	1.931	1.144	3.259
APACHEII	-3.215	0.624	< .001	0.040	0.012	0.136
NGAL	-1.909	0.502	< .001	0.148	0.055	0.396
KIM-1	-0.699	0.380	.066	0.497	0.236	1.048
L-FABP	-0.753	0.421	.074	0.471	0.206	1.075

Note: Neutrophil gelatinase-associated lipocalin (NGAL), Liver fatty acid-binding protein (L-FABP), Kidney injury molecule-1 (KIM-1), Acute Physiology and Chronic Health Evaluation II (APACHE II)

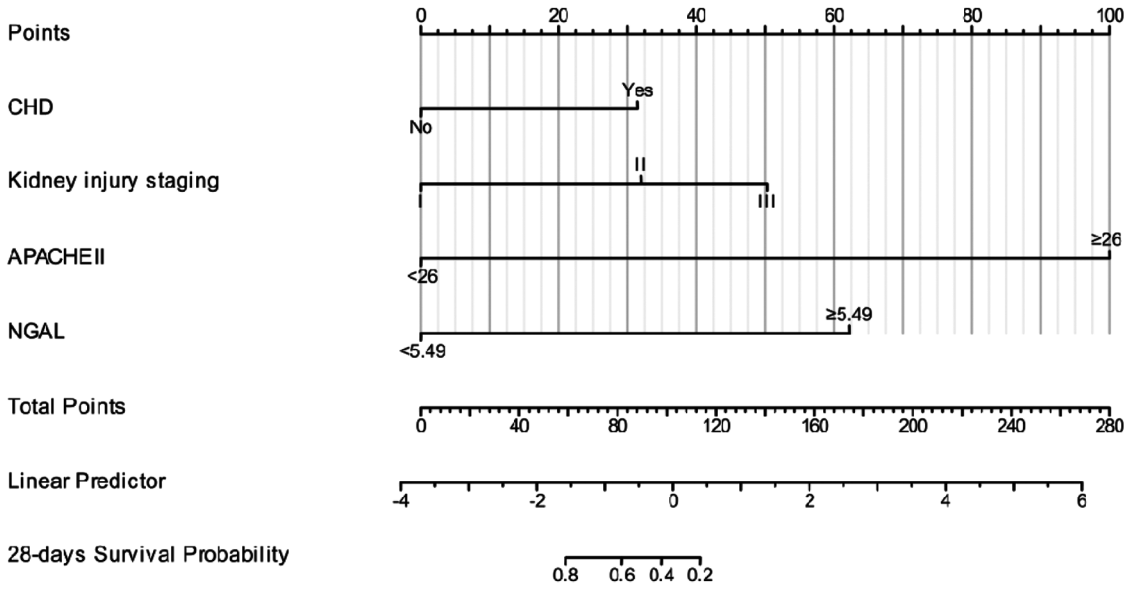

Figure 4. Nomogram Model
Note: Neutrophil gelatinase-associated lipocalin (NGAL), coronary artery disease (CHD), Acute Physiology and Chronic Health Evaluation II (APACHE II)

significant increases in urinary L-FABP and NGAL during the initial phase of postoperative cardiac AKI in children, preceding changes in blood creatinine and facilitating early AKI prediction.[27] These findings reinforce the roles of s-KIM-1, s-NGAL and s-L-FABP as key biological markers for early diagnosis and monitoring of AKI. They offer a more sensitive and earlier response to renal injury compared to traditional indicators like serum creatinine. Moreover, our study demonstrated that the levels of these biomarkers were positively associated with APACHE II scores, both prior to and following treatment. This correlation further suggests that KIM-1, s-NGAL and L-FABP are not only indicative of kidney injury but also reflect the overall severity of the patient's health status and the systemic inflammatory response, given that the APACHE II score is widely utilized to evaluate the severity and clinical outcomes of critically ill patients.[28]

A 28-day mortality rate of 36.67% among Sepsis-associated AKI patients was reported in a comprehensive review and meta-analysis, underscoring the severity of the condition.[28] Similarly, Kim *et al.*[29] observed a 28-day death rate of 48.84% in individuals suffering from sepsis-related AKI. In this study, the 28-day death rate was 54.76% among 84 patients. Independent prognostic factors that identified through Cox regression analysis included the presence of CHD, high-stage kidney injury, an APACHE II score of ≥ 26, and NGAL levels of ≥ 5.49 (μg/L), each contributing to the 28-day survival outlook: (1) Patients with CHD often have compromised cardiovascular health, which reduces cardiac resilience and stability during septic states, thereby increasing mortality risks. The need for high cardiac output to maintain systemic tissue oxygenation during sepsis is hindered by existing CHD, limiting the heart adaptive response. (2) The outcome of AKI is strongly tied to the severity of renal injury. Higher stages indicate severe kidney damage, with diminished capacity to maintain fluid and electrolyte balance and clear metabolic waste. This impairment can exacerbate metabolic disturbances and precipitate further deterioration in other organ functions. (3) The APACHE II scoring system is utilized to assess the severity and clinical outcomes of critically ill patients. A score of ≥ 26 indicates a highly severe condition with abnormal physiological parameters, correlating with a heightened risk of mortality. It reflects the extent of multiorgan dysfunction and inversely correlates with patient survival. (4) As a rapidly responsive biomarker of kidney injury, elevated s-NGAL levels signify the presence and intensity of renal damage, providing early indications of AKI severity.[10]

These findings emphasize the importance of monitoring and managing the aforementioned

factors to improve survival outcomes in individuals suffering from sepsis-related AKI. In individuals suffering from sepsis-related AKI, four key factors—CHD history, higher stage of kidney injury, an APACHE II score of 26 or greater, and an s-NGAL level above 5.49 (μg/L), emerge as independent prognostic indicators of 28-day survival. These factors collectively reflect the seriousness of the patient's medical condition and the extent of multiorgan dysfunction. Early initiation of CVVHD can help prevent further renal damage and improve patient outcomes. Monitoring these biomarkers allows clinicians to customize CVVHD therapy, potentially improving both short-term and long-term survival rates.

Study Limitations

Despite these insights, there are several limitations to this research: the Small study population, retrospective data review, absence of a randomized control group, single-center focus, and the lack of a long-term follow-up. Moreover, potential confounders such as comorbid conditions and concurrent treatments may skew the biomarker levels such as KIM-1, s-NGAL and L-FABP, complicating result interpretation. It is recommended that future studies with larger cohort size and randomized controlled prospective study, which include multicenter involvement, and extended duration of follow-up be performed. Additionally, further research is warranted to explore new biomarkers, refine prognostic models, and elucidate the mechanistic pathways of CVVHD in sepsis-induced AKI.

CONCLUSION

CVVHD effectively reduces levels of KIM-1, s-NGAL and L-FABP, thereby improving kidney function in individuals suffering from sepsis-related AKI. Our findings underscore the necessity for early intervention and continuous monitoring of renal biomarkers. Addressing the current study limitations and investigating the long-term effects of CVVHD are imperative for advancing treatment strategies and patient care in this domain.

ETHICAL CODE REQUIRED

The study's protocol was authorized by the Medical Ethics Committee of Baoji High-Tech Hospital.

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