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ORIGINAL ARTICLE

Study of Urinary Dickkopf 3 as a Novel Biomarker and Prognostic Factor for Acute Kidney Injury in Septic Cardiorenal Syndrome

Fatma M. Attia Elsayed*, Adel A.M. Ghorab, Medhat Ibrahim Mahmoud, Ahmed M Salah, Amr Labban, Mohamed Ahmed El Maghawry

¹ Internal Medicine Department, Zagazig University, faculty of medicine, Zagazig, Egypt

Corresponding Author*

Fatma M. Attia Elsayed

Email:

FMAtyaa@medicine.zu.edu.eg

Fatma.attia236@gmail.com

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ABSTRACT

Background: Cardiorenal syndrome (CRS) refers to primary dysfunction of either the heart or kidneys, which subsequently causes secondary injury to the other organ. Sepsis, redefined in 2016 as a dysregulated immune response to infection resulting in life-threatening organ damage, is one of the main triggers of CRS. This study investigated urinary Dickkopf-3 (DKK3) as a potential biomarker for CRS in septic patients. **Methods:** A prospective cohort study was conducted on 108 critically ill septic patients admitted to the Intensive Care Unit, Internal Medicine Department, Zagazig University Hospitals, between November 2022 and November 2024. All patients underwent thorough clinical assessment, echocardiography, and laboratory investigations, including CBC, renal and liver function tests, CRP, ESR, and procalcitonin. Urinary DKK3 levels were measured using enzyme-linked immunosorbent assay (ELISA). Patients were followed for ICU outcomes, including length of stay, need for mechanical ventilation, dialysis, and mortality. **Results:** Our study included 108 critically ill septic patients. A statistically significant positive correlation was observed between urinary DKK3 levels (ng/ml) and CRP, ESR, WBC count, procalcitonin, serum creatinine, urea, and duration of ICU stay. Furthermore, a significant inverse correlation was found between urinary DKK3 levels and hemoglobin, platelet count, and ejection fraction, whereas no association with age was detected. There were highly statistically significant differences between urinary DKK3 level (ng/ml) and need of ventilation, need of dialysis, and mortality. **Conclusions:** Urinary DKK3 may be a useful biomarker for early detection and a prognostic factor of acute kidney injury in septic cardiorenal syndrome. It could serve as an early indicator for adverse ICU outcomes, including the need for mechanical ventilation, hemodialysis, and increased risk of mortality in that category of patients. **Keywords:** urinary Dickkopf3; cardiorenal syndrome; sepsis; Prognostic factor; novel biomarker.

INTRODUCTION

The definition of sepsis was updated in 2016 to describe it as a life-threatening dysfunction of organs resulting from a dysregulated host response to infection. Subsequently, septic shock represents the most critical form of sepsis, marked by ongoing hypotension and raised lactate levels (>2 mmol/L) despite sufficient fluid

resuscitation, requiring vasopressor support to stabilize blood pressure. This necessitates the use of vasopressors to maintain a systolic blood pressure above 90 mm Hg [1]. Sepsis-Associated Acute Kidney Injury (SA-AKI) is a major cause of acute kidney injury (AKI) in the intensive care unit (ICU), contributing to more than half of all AKI

cases in this setting and being strongly associated with poor clinical outcomes [2]. Cardiorenal syndrome type 5 (CRS-5) refers to the concurrent dysfunction of both the heart and kidneys as a consequence of a systemic disorder affecting these organs simultaneously. Several systemic diseases are recognized as common causes of CRS-5, including sepsis, cirrhosis, systemic lupus erythematosus, sarcoidosis, systemic sclerosis, amyloidosis, and toxin exposure [3].

After sepsis begins, CRS-5 tends to evolve in stages: an initial hyperacute period (up to 72 hours), followed by an acute phase (3–7 days), then a subacute phase (1–4 weeks), and finally a chronic phase if dysfunction persists beyond a month. The diagnosis of CRS-5 is made clinically and is identified by the concurrent incidence of acute kidney and heart dysfunction and/or injury in the context of sepsis [4,5].

In the context of sepsis, cardiovascular dysfunction can present as circulatory failure, septic cardiomyopathy (SCM), and autonomic dysregulation. Historically, the assessment of biventricular function to identify cardiac dysfunction has been performed using hemodynamic measurements obtained from a pulmonary artery catheter [6].

Septic cardiomyopathy is typically recognized by a temporary drop in ejection fraction, enlargement of the left ventricle, and the potential for heart function to return to normal within one to two weeks [7].

Pathophysiological changes, including widespread vasodilation and the failure of multiple organs, can develop. These physiological disturbances may arise from the systemic impacts of sepsis, the interplay between cardiac and renal systems, and the influence of therapeutic interventions. (Figure 1) [8].

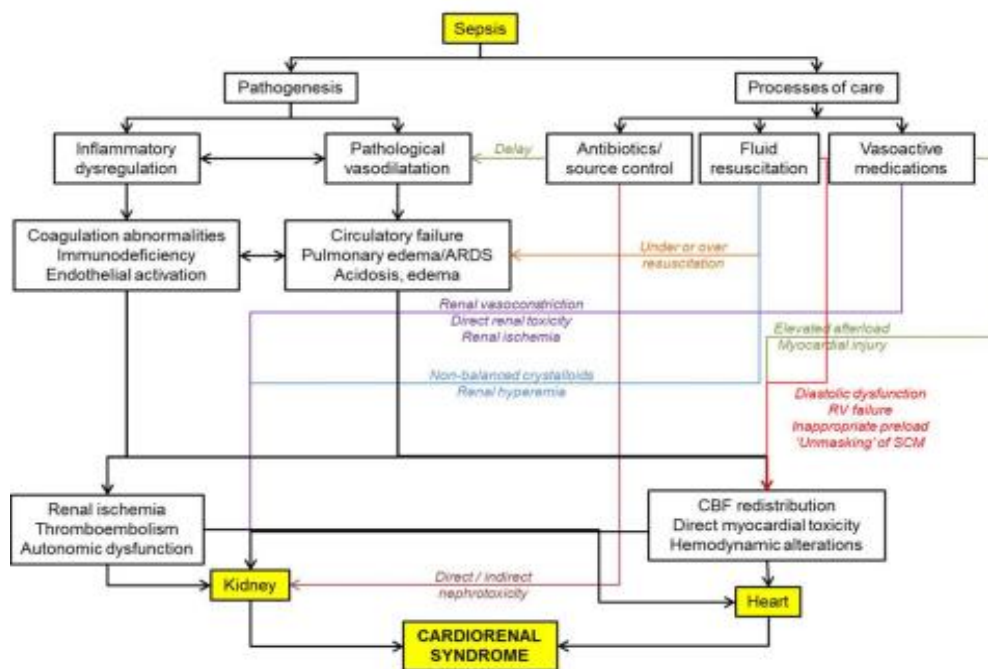


Figure (1): Pathogenesis of cardiorenal syndrome in sepsis

Septic cardiomyopathy (SCM) arises from a combination of hemodynamic instability and alterations in myocardial blood flow,

compounded by the direct cardiotoxic effects of bacterial toxins. While inadequate fluid resuscitation has been linked to the classic presentation of cold shock in sepsis, contemporary medical literature advocates

for a cautious approach to fluid administration. It has been observed that the restoration of vascular tone and sufficient fluid volume can reveal underlying left ventricular (LV) systolic dysfunction [9].

The diagnosis of SCM is supported by echocardiographic findings of new-onset systolic or diastolic dysfunction of the left or right ventricle. The definitions provided by the American Society of Echocardiography are utilized to categorize ventricular dysfunction. To define LV systolic dysfunction, various cut-off points for Left Ventricular Ejection Fraction (LVEF), ranging from 45% to 55%, have been employed in published studies [6].

In patients with cardiorenal syndrome type 5 (CRS-5), elevated endotoxin activity has been associated with a greater degree of renal apoptosis compared to individuals with lower endotoxin levels. Furthermore, in septic patients, diminished cardiac output resulting from external compression due to abdominal compartment syndrome and/or the application of positive pressure ventilation can lead to a reduction in renal perfusion [5].

Dickkopf-3 (DKK3) belongs to the Dickkopf family of glycoproteins (DKK1–4), which act as regulators of the Wnt signaling pathway. These proteins, encoded by *DKK* genes, have a significant role in vertebrate development, where they exert localized inhibition of Wnt-mediated processes such as the formation of limbs and eyes [10].

DKK3 is thought to be part of an evolutionarily conserved gene cluster that is active during developmental stages, subsequently silenced, and then reactivated in states of disease or stress. Consequently, it is remarkable that prior in vitro investigations have indicated that DKK3 can either promote or inhibit the canonical Wnt/ β -catenin signaling pathway, contingent

on the specific tissue being examined [11,12].

The anticipated molecular weight of DKK3 is 38 kDa. However, research has indicated that DKK3 can undergo significant glycosylation, which elevates its molecular weight to a range of 60–70 kDa. This study was to measure serum and urine Dkk3 levels in patients with different 'renal status' and evaluate its role as a biomarker of renal damage. One hundred individuals, aged between 24 and 85 years (mean 53.1 ± 17.1), were enrolled in the study. confirm the potential role of Dkk3 as a biomarker of an ongoing renal injury [13].

A total of 80 patients with sepsis were included in this study, including 31 (38.75%) with SAKI, and 49 (61.25%) with sepsis but without acute kidney injury (AKI) and this study found that The increase of DKK3 is associated with the occurrence of AKI and the severity of AKI in patients with sepsis, and the combination of DKK3 and NGAL can better identify high risk groups in early stage by evaluating the occurrence of AKI and disease progression in patients with sepsis [14].

In our study, we will assess the efficacy of urinary Dickkopf 3 as a potential novel biomarker for cardiorenal syndrome in sepsis. We chose urinary DKK3 because it directly reflects renal tubular epithelial stress and injury before the onset of detectable serum changes. While anuria limits urine-based biomarkers, our study included only patients with measurable urine output to ensure reliable quantification.

METHODS

This cohort study enrolled 108 seriously ill patients with sepsis who were admitted to the Intensive Care Unit of the Internal Medicine Department at Zagazig University Hospitals. The research was conducted over a two-year period, from November 2022 to November 2024. Ethical clearance for the study was granted by the Research Ethics

Committee of the hospital and the Zagazig University Institutional Review Board (IRB-ZU # 9842). In compliance with the Declaration of Helsinki 2008, written informed consent was secured from each participant or their legal guardian prior to enrolment.

Eligibility for inclusion required patients to be between 18 and 60 years of age, presenting with cardiorenal syndrome in the context of sepsis, and having provided informed consent themselves or through their legal guardians. our study included only patients with measurable urine output to ensure reliable quantification The study population entailed of 63 males (58.3%) and 45 females (41.7%).

Individuals were excluded if they met any of the following conditions: being younger than 18 or older than 60 years of age; having a known history of cardiac disease, chronic kidney disease, or a positive swab for COVID-19 which excluded to avoid confounding effects from viral myocarditis and cytokine-mediated injury, which could alter DKK3 expression independently of bacterial sepsis.; or being pregnant or lactating. Furthermore, patients or their guardians who declined to provide informed written consent were also excluded from participation.

Upon enrolment, all participants were subjected to a series of assessments:

A) A comprehensive medical history was taken, followed by a full clinical examination.

B) Routine laboratory evaluations were performed, including liver function tests, a complete blood count, blood urea, serum creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin levels.

C) The level of urinary Dickkopf-3 was quantified using an Enzyme-linked Immunosorbent Assay (ELISA).

D) An echocardiogram was performed for all study subjects.

E) All patients were monitored throughout their ICU stay to track outcomes, including the length of hospitalization, the need for mechanical ventilation or dialysis, and overall mortality.

All samples were collected within **24 hours of ICU admission**, prior to renal replacement therapy or diuretic administration, to capture the early sepsis phase.

Statistical Analysis

All collected data were carefully checked and validated before being processed for analysis. Statistical evaluation was performed on an IBM-compatible computer using SPSS software version 26.0 (IBM Corp., Armonk, NY), in combination with Microsoft Excel 2010 and GraphPad Prism version 6.

Descriptive statistics were applied to all study variables. Continuous data were summarized by measures such as mean, median, standard deviation (SD), minimum, maximum, and interquartile range (IQR). Categorical variables were expressed as counts and percentages.

For inferential testing, differences between two independent groups with normally distributed continuous variables were examined using the independent-samples t-test. For comparisons involving more than two normally distributed groups, one-way ANOVA was utilized. When the distribution of quantitative data deviated from normality, non-parametric methods were chosen: the Mann–Whitney U test for two-group comparisons and the Kruskal–Wallis test for three or more groups.

Statistical significance was defined using the probability (P) value, with thresholds as follows: $P > 0.05$ (not significant, NS), $P < 0.05$ (significant, S), and $P < 0.001$ (highly significant, HS).

RESULTS

Our cohort study included 108 critically ill septic patients, comprising 45 females (41.7%) and 63 males (58.3%). In terms of comorbidities, 97 patients had hypertension, 91 had diabetes mellitus, 4 had hypothyroidism, and 2 were diagnosed with breast cancer. Additionally, one patient each had chronic liver disease (CLD), prostate cancer, bladder cancer, bronchial asthma, and hepatitis C virus (HCV) infection, as shown in Table 1.

Regarding laboratory and hematological findings, CRP levels ranged from 19 to 342 mg/L, with a mean of 162.44 mg/L. The mean of ESR was 50.03 ± 25.62 mm/hr. Hemoglobin levels varied between 8.3 and 13.8 g/dL, with a mean of 10.93 g/dL. Procalcitonin levels ranged from 0.8 to 32 ng/mL, mean 7.35 ng/mL. The mean platelet count was $241.25 \pm 52.75 \times 10^9/L$. Serum creatinine levels ranged from 1.7 to 6.2 mg/dL, with a mean of 3.55 mg/dL, while urea levels ranged from 78 to 322 mg/dL, with a mean of 181.64 mg/dL. Urinary DKK3 levels varied between 22.4 and 39.4 ng/mL, with a mean of 32.22 ng/mL, as shown in Table 2.

As regards most Echo diagnosis, sepsis induced dilated cardiomyopathy found in 32 patients then Degenerative valvular changes, as shown in Table 3.

Regarding the Blood Culture, 28 patients had Staph Aureus MRSA, 23 patients had Pneumococci, 21 patients had E. COLI, 19 patients had Klebsiella, 13 patients had Pseudomonas Aeruginosa and 4 patients had Staph epidermidis as shown in figure 2.

Urinary DKK3 levels (ng/mL) demonstrated a statistically significant positive correlation with CRP, ESR, white blood cell count, procalcitonin, serum creatinine, urea, length of ICU stay, AST/ALT ratio, and bilirubin levels. Conversely, there was a significant negative correlation between urinary DKK3 and hemoglobin, platelet count, and ejection fraction. No significant association was identified between urinary DKK3 levels and patient age (Table 4).

Furthermore, urinary DKK3 levels were significantly associated with the need for mechanical ventilation, dialysis, and mortality. However, no statistically significant differences were noted in relation to sex, chronic illness, or blood culture results (Table 5).

Table 1: Distribution of the patients studied according to demographic data and chronic illness

	N=108	Percentage
Sex		
Female	45	41.7%
Male	63	58.3%
	Mean $\pm$SD	Range
Age	41 $\pm$ 15	26-56
Chronic Illness	No.	%
HTN	97	89.8%
DM	91	84.3%
Hypothyroid	4	3.7%
Breast Cancer	2	1.9%
CLD	1	0.9%
CANCER PROSTATE	1	0.9%
Cancer Bladder	1	0.9%
Bronchial Asthma	1	0.9%
HCV	1	0.9%

HTN: Hypertension DM: Diabetes Mellitus CLD: Chronic Liver Disease HCV: Hepatitis C Virus

Table 2: Hematological distribution of the patients studied and distribution according to laboratory data and Urinary DKK3 level

	No. = 108	
	Mean $\pm$ SD	Range
CRP (mg/L)	162.44 $\pm$ 94.02	19 – 342
ESR (mm) (1st Hour)	50.03 $\pm$ 25.62	8 – 102
HB	10.93 $\pm$ 1.29	8.3 – 13.8
WBC	14.75 $\pm$ 5.37	6.4 – 30.2
PLT	241.25 $\pm$ 52.75	126 – 320
Procalcitonin	7.35 $\pm$ 7.56	0.8 – 32
Serum Creatinine (mg/dl)	3.55 $\pm$ 1.31	1.7 – 6.2
Urea (mg/dl)	181.64 $\pm$ 81.61	78 – 322
Urinary DKK3 level (ng/ml)	32.22 $\pm$ 5.49	22.4 – 39.4

CRP: C-Reactive Protein ESR: Erythrocyte Sedimentation Rate Hb: Hemoglobin WBC: White Blood Cells PLT: Platelets

Table 3: Distribution of the patients studied according to Echo Diagnosis / findings

Echo Diagnosis /findings	No.	%
Dilated cardiomyopathy	32	29.6%
Degenerative valvular changes, good LV systolic function	16	14.8%
Good systolic function and mild LV diastolic dysfunction.	12	11.1%
Mild concentric LVH with preserved systolic function and mild diastolic dysfunction	12	11.1%
Mild pericardial effusion	9	8.3%
Mild diastolic dysfunction.	6	5.6%
Pulmonary hypertension	5	4.6%
Degenerative valvular changes: mild LV diastolic dysfunction with good LV systolic function	2	1.9%
A case of severe pericardial effusion with diastolic RA	1	0.9%
A case of severe pericardial effusion with diastolic RA & RV collapse (cardiac tamponade)	1	0.9%
Aortic sclerosis	1	0.9%
Concentric LVH with good systolic function	1	0.9%
Degenerative valvular heart disease, moderate AS, moderate AR	1	0.9%
Degenerative valvular changes, severe MR	1	0.9%
Hypertensive degenerative heart disease	1	0.9%
Hypertensive heart disease and dextrocardia	1	0.9%
Mild degenerative valvular changes, dilated aortic root	1	0.9%
Mitral stenosis moderate pulmonary hypertension	1	0.9%
Mitral valve prolapse grade 2 diastolic dysfunction	1	0.9%
Moderate diastolic dysfunction	1	0.9%
Severe AR, mild AS, moderately severe MR and moderate MS.	1	0.9%
Severe tricuspid regurge and pulmonary hypertension	1	0.9%

LV: Left Ventricle LVH: Left Ventricle Hypertrophy RA : Right Atrium: RV-Right Ventricle AS : Aortic Stenosis AR : Aortic Regurge MR : Mitral Regurge MS : Mitral Stenosis

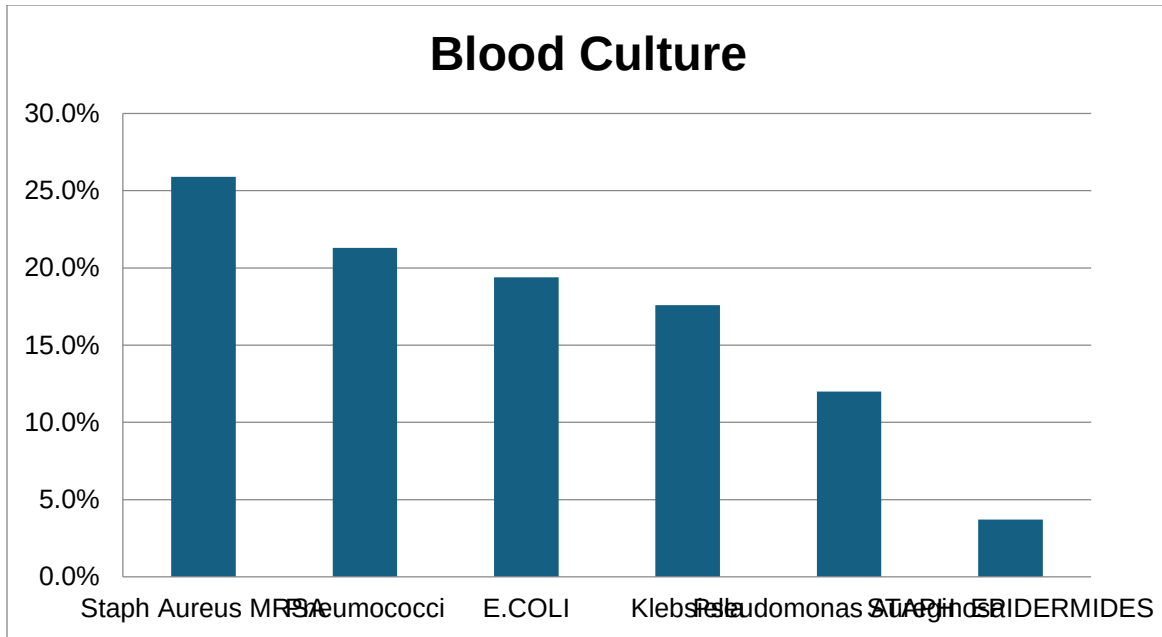


Figure 2: Distribution of the studied patients according to Blood Culture

Table 4: Correlation between Urinary DKK3 level with Age, CRP, ESR, HB, WBC, PLT, Procalcitonin, Serum Creatinine, Urea, Days of ICU Stay, AST/ALT ratio, bilirubin and EF

	Urinary DKK3 level (ng/ml)	
	r	P-value
Age (years)	0.099	0.310
CRP (mg/L)	0.806**	0.000
ESR (mm) (1st Hour)	0.682**	0.000
Hb (g/dl)	-0.233*	0.015
WBC (cells/UL)	0.738**	0.000
PLT (plt/mcL)	-0.244*	0.011
Procalcitonin (ng/mL)	0.853**	0.000
Serum Creatinine (md/dl)	0.727**	0.000
Urea (mg/dl)	0.865**	0.000
Days of ICU Stay	0.588**	0.000
AST/ALT ratio	0.813**	0.000
Bilirubin (mg/dl)	0.522**	0.000
EF (%)	-0.629**	0.000

AST: Aspartate Aminotransferase ALT : Alanine Transaminase EF : Ejection Fraction HS : Highly Significant Positive Correlation NS : Non-Significant S : Significant Negative Correlation

Table 5: Relation between Urinary DKK3 level (ng/ml) and Sex, Chronic Illness, Need of Ventilation, Need of dialysis, Mortality and Blood Culture

		Urinary DKK3 level (ng/ml)		Test value	P-value
		Mean $\pm$ SD	Range		
Sex	Female	31.96 $\pm$ 5.36	22.40 – 39.40	0.177*	0.675
	Male	32.41 $\pm$ 5.61	22.40 – 39.40		
HTN		32.14 $\pm$ 5.47	22.40 – 39.40	0.177*	0.675
DM		32.90 $\pm$ 5.37	22.40 – 39.40	9.648*	0.062
Hypothyroid		31.10 $\pm$ 3.56	25.90 – 33.40	0.172*	0.679
Breast Cancer		34.75 $\pm$ 6.15	30.40 – 39.10	0.431*	0.513
CLD		24.90 $\pm$ 0.00	24.90 – 24.90	1.811*	0.181
CANCER PROSTATE		38.20 $\pm$ 0.00	38.20 – 38.20	1.202*	0.275
Cancer Bladder		39.40 $\pm$ 0.00	39.40 – 39.40	1.741*	0.190
Bronchial Asthma		32.80 $\pm$ 0.00	32.80 – 32.80	0.011*	0.916
HCV		36.20 $\pm$ 0.00	36.20 – 36.20	0.529*	0.469
Need of Ventilation	No	27.40 $\pm$ 3.02	22.40 – 33.40	373.760*	0.000
	Yes	37.04 $\pm$ 2.07	31.70 – 39.40		
Need of dialysis	No	26.45 $\pm$ 2.27	22.40 – 31.70	415.011*	0.000
	Yes	36.34 $\pm$ 2.63	30.40 – 39.40		
Mortality	No	28.55 $\pm$ 3.72	22.40 – 35.60	259.130*	0.000
	Yes	37.99 $\pm$ 0.90	36.20 – 39.40		
Blood Culture	E. COLI	31.58 $\pm$ 4.80	24.90 – 39.10	0.660•	0.654
	Klebsiella	32.35 $\pm$ 5.87	23.80 – 39.40		
	Pneumococci	33.03 $\pm$ 5.06	23.80 – 38.70		
	Pseudomonas aeruginosa	30.76 $\pm$ 6.15	22.40 – 38.80		
	Staph epidermides	35.73 $\pm$ 5.02	28.30 – 39.40		
	Staph aureus MRSA	32.13 $\pm$ 5.91	22.40 – 39.10		

P-value >0.05: Non-significant (NS); P-value <0.05: Significant(S); P-value< 0.01: highly significant (HS) *: Independent t-test, •: One Way ANOVA Test

DISCUSSION

Cardiorenal syndrome (CRS) represents a clinical condition that arises from complex, bidirectional pathological interactions between the heart and kidneys. In recent years, significant research has focused on identifying biomarkers in cardiovascular disease patients to enhance renal function assessment and identify individuals at risk for acute or chronic kidney decline. [15]

Sepsis is recognized as a major etiological factor in cardiorenal syndrome type 5 (CRS-5), which is characterized by the simultaneous occurrence of acute kidney and cardiac dysfunction in the setting of sepsis [16]

This study included 108 patients with CRS in sepsis admitted to the ICU at Zagazig University Hospitals. The gender distribution observed in our cohort was consistent with findings by Schröder J et al. (1998), who reported that among septic patients, 36% were women and 64% were men [17]. Similarly, Sakr Y (2013) noted that severe sepsis was less common among females compared to males [18].

The prevalence of hypertension (89.8%) and diabetes mellitus (84.3%) in our study was markedly higher than that reported by Kang C et al. (2024), where hypertension and diabetes were present in 46.7% and 23.6% of septic patients, respectively [19].

Likewise, Jiang L et al. (2022) found diabetes mellitus in only 20% of septic cases [20].

Our findings showed no significant correlation between Dickkopf 3 (DKK3) levels and chronic illnesses, in contrast to Schäfer C et al., who demonstrated that patients with resistant hypertension are at increased risk of CKD progression, with urinary DKK3 (uDKK3) proposed as a marker of ongoing renal damage and eGFR decline [21]. The discrepancy may be attributable to the limited sample size in our study.

Conversely, several statistically significant positive correlations were identified between urinary DKK3 levels and CRP, ESR, WBC, procalcitonin, serum creatinine, urea, ICU stay duration, AST/ALT ratio, and bilirubin. These results align with Hu et al. (2023), who also observed positive associations of DKK3 with procalcitonin, WBC, and serum creatinine [22].

Echocardiographic assessment revealed Sepsis induced dilated cardiomyopathy in approximately 30% of patients, which is comparable to the findings of L'Heureux M et al. (2020), who reported sepsis-induced cardiomyopathy rates between 10–70%, depending on diagnostic variability and under-recognition [7].

Blood culture analysis showed infections with *Staphylococcus aureus* (MRSA) in 28 patients, *Pneumococcus* in 23, *E. coli* in 21, *Klebsiella* in 19, *Pseudomonas aeruginosa* in 13, and *Staphylococcus epidermidis* in 4 patients. These findings are consistent with Timsit JF et al. (2020), who reported that *E. coli*, *S. aureus*, *K. pneumoniae*, and *S. pneumoniae* account for more than 70% of community-acquired bloodstream infections [23]. However, Nejtek T et al. (2023) emphasized that pathogen prevalence may vary by geography, hospital setting, and patient population [24].

Furthermore, a significant inverse correlation was found between urinary DKK3 levels and hemoglobin, platelet count, and ejection fraction, whereas no association with age was detected. These findings agree with Allam et al. (2023), who reported an inverse association between DKK3 and hemoglobin, alongside a direct correlation with eGFR in CKD patients [25]. Importantly, our study confirmed a strong positive correlation between urinary DKK3 and serum creatinine, suggesting its potential role as a biomarker for acute kidney injury (AKI). This corroborates Schunk et al. (2021), who demonstrated that elevated preoperative DKK3 levels predicted AKI and persistent renal dysfunction in critically ill patients. In their research, urine specimens were gathered within the initial 24 hours following ICU admission, irrespective of whether the diagnostic criteria for AKI had been fulfilled. They concluded that an elevated urinary DKK3 level was associated with a greater risk of both AKI and severe AKI [26].

Additional studies support the prognostic significance of DKK3 across inflammatory and autoimmune conditions. Sciascia S et al. (2022) linked elevated DKK3 with renal inflammation, lupus nephritis, and interstitial fibrosis in SLE patients [27]. Their findings indicated a positive and significant correlation between Dickkopf 3, serum creatinine, and ESR.

Similarly, Schäfer C et al. (2023) demonstrated a positive correlation between uDKK3, serum creatinine, and blood pressure in resistant hypertension [21].

Our investigation identified a significant positive correlation between Dickkopf 3 and serum creatinine, as well as a significant negative correlation with left ventricular ejection fraction.

This aligns with Roscigno G et al. (2021), who studied Dickkopf 3 in the context of

contrast-associated acute kidney injury. They also found a positive association with serum creatinine, although they did not observe a relationship with left ventricular ejection fraction. Nevertheless, they proposed that DKK3 could be a dependable marker for enhancing the identification of CKD patients undergoing invasive procedures who are at risk for AKI and persistent kidney dysfunction [28].

Further supporting this, a 2023 study by Arzne S et al. showed that uDKK3 has a significant positive correlation with serum creatinine in the context of adult polycystic kidney disease (ADPKD) [29].

In agreement with Schunk et al. 2019, a positive association with serum creatinine was noted in the absence of a correlation with left ventricular ejection fraction, suggesting DKK3 is a promising marker for identifying CKD patients undergoing invasive coronary and peripheral procedures who are at risk for AKI and persistent kidney dysfunction [30].

A highly significant statistical difference was observed between the urinary DKK3 level (ng/ml) and the clinical outcomes of ventilation requirement, need for dialysis, and mortality. In contrast, there was no statistically significant association found between the urinary DKK3 level and patient characteristics such as sex, presence of chronic illness, or blood culture results. This aligns with the findings of Pickkers P, et al. (2021), who highlighted that acute kidney injury (AKI), often signaled by elevated urinary DKK3 levels, affects 30–60% of critically ill patients and is associated with prolonged mechanical ventilation and higher mortality rates [31].

Conversely, Zewinger S, et al. (2018) did not find any significant associations between the urinary DKK3-to-creatinine ratio and factors like age, sex, estimated glomerular filtration rate (eGFR), presence of diabetes,

hypertension, or albuminuria within the general population [32].

CONCLUSIONS

Urinary DKK3 may be a useful biomarker for early detection of acute kidney injury in septic cardiorenal syndrome. It could serve as an early indicator for adverse ICU outcomes, including the need for mechanical ventilation, hemodialysis, and increased risk of mortality in those categories of patients.

Conflict of interest There are no relevant conflicts of interest declared by the author of this work.

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Ethical approval Institutional review boards' approval was obtained.

Informed consent All patients signed a written informed consent form.

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