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Role of IL-18 in Comparison to Serum Creatinine in Early Detection of Sepsis Induced Acute Kidney Injury in Emergency Department in Suez Canal University Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Septic acute kidney injury is a syndrome of acute impairment of function and organ damage linked with long-term adverse outcomes depending on the extent of acute injury superimposed on underlying organ reserve. Sepsis is the most important cause of Acute Kidney Injury (AKI). Interleukin-18 (IL-18) is a pro-inflammatory cytokine expressed in the renal cortex, peritubular capillaries, and interstitium.
Aim: To assess the role of IL-18 in comparison to serum creatinine in the early detection of sepsis-induced acute kidney injury in the Emergency Department (ED) at Suez Canal University Hospital.
Subjects and Methods: A comparative cross-sectional study that included two groups of participants. Study group: patient diagnosed with sepsis-induced acute kidney injury attending to the ED at Suez Canal University Hospital. Control group: healthy individuals of the same age group. Patients were clinically assessed and managed by the ABCDE protocol. All patients were subjected to Initial assessment including History, clinical examination, and laboratory investigation, including urinary IL-8.

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Results: Cases had statistically significant higher urinary IL-18 compared to controls (121.97 ± 75.84 vs 69.07 ± 35.59) (p<0.001). IL-18, a value of 69.5 IU/L was found to be the best cut-off point for the prediction of sepsis-induced AKI among cases, with sensitivity = 6 and 5% specificity = 57.5%.
Conclusion: Urinary IL-18 can be used as an early predictor for AKI than serum creatinine in patients presenting with sepsis.

Keywords: Biomarkers; urinary; glomerulus.

ABBREVIATIONS AND ACRONYMS

AKI = *Acute Kidney Injury*
IL = *Interleukin*
ED = *Emergency Department*
LOS = *length of stay*
ICU = *intensive care unit*

1. INTRODUCTION

"Sepsis refers to the presence of a serious infection that correlates with systemic and uncontrolled immune activation. Patients die because of organ failure as the disease elicits an exacerbated and damaging immune response with approximately 250,000 cases leading to fatalities in the USA annually. As of 2009, the Centers for Disease Control and Prevention listed sepsis as the 11th leading cause of death in the United States. The treatment of sepsis is also costly. The total hospital cost for patients with severe sepsis is $24.3 billion in 2007" [1].

"Septic acute kidney injury is a syndrome of acute impairment of function and organ damage linked with long-term adverse outcomes depending on the extent of acute injury superimposed on underlying organ reserve. Implicit in this concept is that dysfunction should be reversible, and rescue is possible, but that duration of the insult and underlying renal reserve may limit restoration of renal function" [2]. "Sepsis is the most important cause of Acute Kidney Injury (AKI) , accounting for 50% or more of cases of AKI in ICU, and is associated with very high mortality" [3]. "In adults, AKI occurs in approximately 19–23% of patients with moderate/severe sepsis, and in more than 50 % of patients with septic shock" [4].

"The incidence of AKI increases with the severity of sepsis and estimates are that AKI develops within the first 24 hours in 64% of patients with severe sepsis and hypotension" [5]. "Strikingly, the mortality rate for septic patients with AKI is approximately doubled compared with sepsis alone" [6].

"Septic acute kidney injury is a clinical diagnosis based on specific, context-dependent, and imperfect definitions with azotemia and oliguria still its key diagnostic criteria. More recently the Kidney Disease Improving Global Outcomes produced a unified version of all key criteria of acute kidney injury" [2]. "Septic acute kidney injury should describe a syndrome characterized by the simultaneous presence of both sepsis and KDIGO criteria, and still, clinical judgment is required" [7]. "A more modern framework for rapid clinical diagnosis is evolving which is based on novel biomarkers of renal injury. Thus, definitions of AKI may soon include such biomarkers. The National Institutes of Health defines a biomarker as a characteristic that should objectively measure and evaluate normal biological processes or pharmacological responses to a therapeutic intervention" [8].

"Biomarkers should be measured accurately and reproducibly. This is unlike medical symptoms that are restricted to indications of health or illness from the patient's perspective. Biomarkers may be used as a diagnostic tool for the identification (diagnosis) of disease or abnormal conditions, as well as for staging disease, prognosis, and response to intervention" [9].

"The definition of AKI based on S.cr has long been debated, mostly due to its shortcomings such as assay interference, dilution during fluid resuscitation, altered metabolism during critical illness, and altered clearance with drugs. Furthermore, S.cr is a late and indirect reflection of renal damage. As a result, scientists are trying to discover and develop novel biomarkers to represent kidney injury, aiming to identify the injury timely" [10].

"An ideal biomarker should be one that is able to predict AKI and its outcomes, locate the site of injury (glomerulus vs tubule), determine the type of injury, and enable the initiation of therapeutic interventions" [11]. "Several potential biomarkers have been identified and merit extensive research to establish their role in the diagnosis of

AKI. Interleukin-18 (IL-18) is a pro-inflammatory cytokine expressed in the renal cortex, peritubular capillaries, and interstitium. Urinary IL-18 is elevated within the first 6 hours after renal injury. The excretion of IL-18 is higher in sepsis-induced AKI than in non-septic AKI, IL-18 also predicted deterioration in kidney function, with increased values preceding clinically significant kidney failure by 24-48 h. Recent studies have shown that urinary IL-18 levels can be used for the early diagnosis of AKI" [12].

So, the goal of this study was to assess the role of IL-18 in comparison to serum creatinine in the early detection of acute kidney injury in the Emergency Department.

2. METERIALS AND METHODS

2.1 Study Design

A comparative cross-sectional study.

2.2 Study Setting

Suez Canal University Hospital Emergency Department (ED).

2.3 Study Population

Any patient diagnosed with sepsis attending the ED at Suez Canal University Hospital and fulfilling our inclusion criteria was included in the study.

2.3.1 Inclusion criteria

Adult (age> 18), age groups (18-45, 45-65, >65), of both sexes, and diagnosed with sepsis.

2.3.2 Exclusion criteria

Patients with pre-existing kidney disease (ESRD, CKD, Post Renal Transplant), presented to ED with sepsis and elevated serum creatinine, with any systemic illness or conditions that may elevate serum creatinine such as heart failure, or had a history of medications that elevate serum creatinine or decrease its clearance.

2.4 Sample Size

The sample size was calculated using the following formula:

$$n = 2\left[\frac{(Z_{\propto/2} + Z_{\beta}) * \sigma}{\mu_1 - \mu_2}\right]^2 \quad (13)$$

Where:

n = sample size
$Z_{\alpha/2}$ = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)
Z_{β} = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)
σ = the estimate of the standard deviation = [2]
μ_1 = mean in the study group = [2]
μ_2 = mean in the control group = [2]

So, by calculation, the sample size was equal to 40 per group, giving a total sample size of 80.

2.5 Sampling Method

The sample was collected based on Simple Random Selection, the first consecutive patients who presented with sepsis and met the criteria of inclusion were enumerated and randomly selected which patients were included in the study group. Similarly, a control group was collected in the same exact manner.

2.5.1 Methods

Data was collected in a pre-organized data sheet by the researcher from patients fulfilling inclusion and exclusion criteria. The Patient was clinically assessed and managed according to the ABCDE protocol, over an 8-month from November 2020-July 2021, we prospectively identified patients with sepsis and after stabilizing the patient, a questionnaire was filled by the researcher of the patient presented to ER by the medical team.

All sepsis patients who meet the inclusion criteria in Emergency Department were subjected to:

2.5.1.1 Full history

Full history (from the patient or relative) including 1) Patient personal data: Age, Sex, Occupation, and residence. 2) Date of admission and date of discharge to calculate the patient's length of stay (LOS) in ED. 3) Timing of presentation and timing of admission. 4) Source of sepsis. 5) Associated co-morbidity e.g., common endocrinal, cardiovascular, Drug abuse, or previous disability.

Table 1. Baseline characteristics of the studied groups

Variables	Groups		P-value
	Study group (n= 40)	Control (n= 40)	
Age (years), mean ± SD	59.78 ± 17.36	51.30 ± 20.81	0.052[a]
Sex, n (%)			
Male	19 (47.5)	22 (55)	0.50[2b]
Female	21 (52.5)	18 (45)	

[a] *p-values are based on an independent-t test. Statistical significance at P < 0.05*
[b] *p-values are based Chi-square tests. Statistical significance at P < 0.05*

Table 2. Clinical characteristics of the studied groups

Variables	Groups		P-value
	Study group (n= 40)	Control (n= 40)	
Clinical parameters			
Systolic blood pressure (mmHg)	93.0± 8.124	109.20± 10.82	**<0.001*** [a]
Diastolic blood pressure (mmHg)	66.75± 9.164	75.90± 8.476	**<0.001*** [a]
Pulse (beat/min.)	84.33± 10.141	76.13± 12.740	**0.002*** [a]
Respiratory rate (cycle/min.)	17.38± 1.690	15.28± 1.840	**<0.001*** [a]
GCS			
13	8 (20)	0 (0)	**<0.001*** [b]
14	13 (32.5)	0 (0)	
15	19 (47.5)	40 (100)	

[a] *p-values are based on an independent t-test. Statistical significance at P < 0.05*
[b] *p-values are based on the Chi-square test. Statistical significance at P < 0.05*

2.5.1.2 Clinical evaluation

Clinical evaluation of the patients was carried out on arrival to ED regarding Initial assessment of ABCDE (airway and cervical spine control, breathing, circulation, dysfunction of the central nervous system, GCS, and exposure) and O_2 saturation. Then careful examination was done to identify the source of infection. Assess the condition of the patients either stable or unstable which determined the needed investigations and plane of management.

2.5.1.3 Investigations

Investigations include: 1) Routine laboratory investigations, such as complete blood count, blood typing and cross match and coagulation profile, serum creatinine, serum electrolytes, and arterial blood gases. 2) Urinary IL-18: commercially available kit (Duoset ELISA kits from R&D systems). Urine was collected using a metabolic cage. particulates were removed by centrifugation for 15 minutes at 1000 x g, 2-8°C, and stored immediately at -20°C. Centrifuged again before assaying to remove any additional precipitates that may appear after storage. Samples were transferred to a private lab for assay.

2.5.1.4 Treatment

It was concerned with surviving sepsis campaign guidelines in managing patients with sepsis.

2.5.1.5 Fate at emergency department

The fate of the patient was recorded whether 1) Admitted to the intensive care unit (ICU). 2) Remain under observation in the emergency room. 3) Admitted to inpatient under observation.

3. RESULTS

3.1 Baseline Characteristics of the Studied Groups

Table 1 summarizes the baseline characteristics of the studied groups. The study group was found to have higher age than the controls (p=0.052). Meanwhile, the sex distribution was comparable in both groups (p=0.502).

3.2 Clinical Characteristics

Table 2 summarizes the clinical characteristics of the studied groups. It was found that patients with sepsis had significantly lower mean systolic and diastolic blood pressure compared to controls (p<0.001). Moreover, patients with sepsis had significantly higher RR and heart rate compared to controls (p<0.001). The study group with GCS 13/ 15 formed 20% of the cases while GCS 15/ 15 formed 20% of the controls.

3.3 Laboratory Measures

Table 3 shows that the study group had statistically significantly lower pH, PO_2 and HCO_3 compared to controls. Meanwhile, the study group had statistically significantly higher TLC compared to controls (31.07 ± 9.75 vs 8.15 ± 2.68) (p<0.001).

3.4 Urinary IL-18 between Cases and Control

Table 4 shows that the study group had statistically significantly higher Urinary IL-18 compared to controls (121.97 ± 75.84 vs 69.07 ± 35.59) (p<0.001).

3.5 Urinary IL-18 at Presentation for Prediction of Sepsis-induced AKI

Table 5 shows that for Urinary IL-18, a value of 69.5 pg/ml was found to be the best cut-off point for prediction of sepsis-induced AKI among cases, with sensitivity = 65%, specificity = 57.5%, PPV= 60.5%, NPV= 62.2% and accuracy= 61.25%.

3.6 Serum Creatinine at Presentation for Prediction of Sepsis-induced AKI

Table 6 shows that for serum creatinine, a value of 0.65 mg/ dl or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 50%, specificity = 55%, PPV= 52.6%, NPV= 52.4% and accuracy= 52.5%.

3.7 Urinary IL-18 at 24 hours for Prediction of Sepsis-induced AKI

Table 7 shows that for Urinary IL-18 at 24 hours, a value of 116.01 pg/ml or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 68.3%, specificity = 70%, PPV= 82.4 %, NPV= 51.9% and accuracy= 68.8%.

Table 3. Comparison of laboratory measures between study group and control

Variables	Groups		p-value
	Study group (n= 40)	Control (n= 40)	
Arterial blood gas			
pH	7.32 ± 0.029	7.39 ± 0.32	**<0.001***
PO_2	72.80± 8.59	94.72± 3.28	**<0.001***
PCO_2	31.07± 3.22	29.80± 2.90	0.067
HCO_3	18.37± 1.59	22.82± 1.44	**<0.001***
Laboratory measures			
Hemoglobin (g/ dl)	12.935 ±1.625	12.57 ±1.37	0.512
TLC	31.07 ± 9.75	8.15 ± 2.68	**<0.001***
PLT count	312.88 ± 82.67	320.13 ± 89.93	0.708
INR	1.12 ± 0.15	1.12 ± 0.15	1.000
Creatinine (mg/ dl)	0.54 ± 0.27	0.547 ± 0.279	1.000
Bilirubin (IU/L)	0.31 ± 0.12	0.317 ± 0.127	1.000

[a] *p-values are based on an independent t-test. Statistical significance at P < 0.05*

Table 4. Comparison of Urinary IL-18 between cases and control

Variables	Groups		p-value
	Study group (n= 40)	Control (n= 40)	
Urinary IL-18			
mean ± SD	121.97 ± 75.84	69.07 ± 35.59	**<0.001*[a]**
median (range)	116.50 (25 - 294)	65 (14 - 125)	

[a] *p-values are based on an independent t-test. Statistical significance at P < 0.05*

Table 5. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the best cut of point of Urinary IL-18 at presentation for prediction of sepsis-induced AKI

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	Accuracy
Urinary IL-18 69.50	65%	57.5%	60.5%	62.2%	61.25%

Table 6. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy at different cut-off levels of serum creatinine at presentation for prediction of sepsis-induced AKI

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	Accuracy
Serum creatinine 0.65 mg/dl	50%	55%	52.6%	52.4%	52.5%

Table 7. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the best cut of point of Urinary IL-18 at 24 hours for prediction of sepsis-induced AKI

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	Accuracy
116.01 pg/ml	68.3%	70%	82.4%	51.9%	68.8%

3.8 Creatinine and IL-8 at Presentation

Table 8 shows that there was no statistically significant correlation between serum creatinine and urinary IL-18 at presentation.

Table 8. Correlation between creatinine and another laboratory marker at presentation

Variables	Creatinine	
	r	p-value
Urinary IL-18	-0.100	0.376

3.9 Creatinine and Another Laboratory Marker after 24 hours

Table 9 shows that there is a negative significant correlation between serum creatinine and urine output at 24 hours (r= -0.759) (p<0.001).

Table 9. Correlation between creatinine and another laboratory marker after 24 hours

Variables	Creatinine	
	R	p-value
Urinary IL-18	-0.026	0.821
Urine output	-0.759	**<0.001***

4. DISCUSSION

"Sepsis remains a serious problem in critically ill patients, and the mortality rate in patients with sepsis is increased dramatically when complicated by AKI. Therefore, accurate evaluation of AKI is essential in patients with sepsis. In clinical practice, AKI is typically diagnosed by measuring the urine output and serum creatinine level; however, creatinine has been shown to be a relatively late indicator of AKI" [14].

"IL-18 has the ability to induce the production of IFN-γ in the presence of IL-12 and also to induce chemokines attracting monocytes and macrophages to the sites of infection, thereby initiating the inflammatory process linked to the development of sepsis" [15]. "Specific blockade of IL-18 can alleviate the effects of sepsis on organ damage or improve host survival, and their concentrations fall abruptly with a specific treatment, thus supporting the idea that Urinary IL-18 levels participate in the pathologic processes of sepsis and that both may be helpful for the early diagnosis of sepsis" [16].

So, this study aimed to improve the outcome of patients with sepsis by assessing of role IL-18 in comparison to serum creatinine in the early detection of acute kidney injury in ED in Suez Canal University Hospitals.

This comparative cross-sectional study included two groups, the study group included 40 patients diagnosed with sepsis attending the ED at Suez Canal University Hospital and fulfilling our inclusion criteria, and the control group included 40 healthy individuals of the same age group, not complaining of either of any chronic illness or acute illness.

The present study showed the baseline characteristics of the studied patients, as the mean age was 59.78 ± 17.36 and 51.30 ± 20.81

in the case group and the control respectively. No statistical significance between the case group and the control group was observed in relation to gender, and age. These results were similar to the results by Feng et al. [17] in which the mean age of the sepsis group was 51.18 ± 16.17 while in the control group was 47.57 ± 11.81 with no statistical significance between the control group and the sepsis group.

Regarding the source of infection in patients with sepsis, this study showed that the most frequent source of infections was GIT (27.5%), respiratory tract infection (22.5%), and UTI (20%) [18]. Liu et al. [19] in a systematic review and meta-analysis, found that there were 20 factors statistically significant that predispose to sepsis-associated AKI, one of them included infections and their prevalence was respiratory infections in 41.22% while abdominal infection in 32.12% and UTI in 12.01%. The difference in both results was due to the large sample size and different population in a meta-analysis done by Liu et al. [19] and that our sample population was collected during the COVID era and COVID respiratory infection was not included in our study.

The current study showed that the most frequent of chronic illnesses among patients with sepsis as 55% had diabetes and 50% HTN. In a study by Leem et al. [20] it was found that HTN and Diabetes were the most common chronic illnesses in the studied patients with AKI (47.8% and 35.4% respectively).

In the present study, it was found that patients with sepsis had significantly lower mean systolic and diastolic blood pressure compared to controls (p<0.001). Moreover, patients with sepsis had significantly higher RR and heart rate compared to controls (p<0.001). In Al-Amodi et al. [21] it was found that the median systolic and diastolic blood pressure was lower in septic shock patients compared to controls. Whereas the heart rate and respiratory rate in the sepsis group were significantly higher than those in the control group (all p < 0.05) in Feng et al. [18].

Our study showed that cases had statistically significant lower pH and HCO3 compared to controls. Meanwhile, cases had statistically significantly higher TLC compared to controls (31.07 ± 9.75 vs. 8.15 ± 2.68) (p<0.001). In Feng et al. [22] the WBC count in the sepsis group was significantly higher than those in the control group (all p < 0.05). Similar to our study results Samanta S, et al. [23] in a study from India reported metabolic acidosis to be associated with mortality and target organ dysfunction as AKI in the ICU.

Our study showed that cases had statistically significant higher urine IL-18 compared to controls at presentation and 24 hours (121.97 ± 75.84 vs 69.07 ± 35.59) (p<0.001). In a study by Feng et al. [18] it was found that Urinary IL-18 levels in the sepsis group were significantly higher than those in the control group at presentation and 24 hours interval (119.30 ± 29.33 vs 32.51±16.21) with a p-value <0.05. Also, it was found that urine IL-18 was higher in the AKI group compared to the non-AKI group in a study by Nejat et al. [24] (22 vs 1.6 ng/mmol) with a p-value <0.001.

Our study showed that for Urinary IL-18, a value of 69.5 IU/L was found to be the best cut-off point for prediction of sepsis-induced AKI among cases, with a sensitivity of 65%, specificity of 57.5%, PPV of 60.5%, NPV of 62.2%, the accuracy of 61.25% and AUC was 0.710. In a study by Endre et al. [25] urinary IL-18 showed an AUC of 0.62, and cut off point was 36 (pg/ml) with a sensitivity of 34%, specificity of 78%, PPV of 37%, and NPV of 75% in the detection of AKI in patients on admission to the ICU. In contrast to our results, Feng et al. [18] found that the sensitivity and the specificity of IL-18 were 77.8% and 83.3%, respectively, and the corresponding optimal cut-off point of IL-18 that achieved the highest values of sensitivity and specificity was 116.01 pg/ml. This may contribute to the different cut-off points that had been chosen in our study.

For serum creatinine, in our study a value of 0.65 mg/ dl or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 50%, specificity = 55%, PPV= 52.6%, NPV= 52.4% and accuracy= 52.5% and AUC was 0.544. Unlike our results, Azzam et al. [26] found that serum creatinine had a sensitivity of 80.00%, specificity of 100.00 %, PPV of 100.0 0%, NPV of 17.85 %, and accuracy of 23.30%, this may be explained by that the studied population in their study were acute critically ill conditions, poly-trauma, and post-operative critically ill patients who admitted in the ICU.

Regarding IL-18 at 24 hours, a value of 116.01 pg/ ml or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with a sensitivity of 68.3%, specificity of 70%, and accuracy= 68.8% with AUC of 0.755. In a study by Siew et al. [27] in which they evaluated the

capacity of uIL-18 measured within 24 hours of ICU admission to predict AKI, they found that the median IL-18 levels of the patients who developed AKI within 24 hours were 412 pg/mg The AUC for the utility of IL-18 for prediction of AKI within 24 hours were 0.62 with the highest median IL-18 levels were observed in patients with sepsis with a cut-off value of 508 pg/mg. These results were not like ours due to the different cut-off values and the enrolled patients in their study were admitted to one of four ICUs (Medical, Cardiac, Surgical, Trauma) not only including sepsis-induced AKI.

In our study, there was no statistically significant correlation between serum creatinine with urinary IL-18 at presentation.

Our study has some limitations. First, this cross-sectional study design was a single-center study with relatively small sample size. However, serial follow-up for biomarkers for kidney injury was carried out to potentially compensate for this weakness. Second, other new biomarkers, such as neutrophil gelatinase-associated lipocalin, were not analyzed. Third, although serum IL-18 level is less influenced by age, sex, and muscle mass, compared with serum creatinine level, it may still be affected by other unmeasured variables, such as levels of glucocorticoids, thyroid hormones, and insulin.

5. CONCLUSION

Urinary IL-18 can be used as an early predictor for AKI than serum creatinine in patients presenting with sepsis.

CONSENT

1. Written informed consent was obtained from all participants after regaining consciousness with a full explanation of the hazards and benefits of the procedure.
2. Standardized protocols were used for the diagnosis and management of these patients.
3. Patients were informed about any abnormal results of procedures and tests performed and were instructed and treated accordingly.
4. The patient had the right to refuse participation without affecting the medical care expected to be offered to her.
5. Confidentiality of all data and test results of all the study population was preserved.
6. All samples were discarded after doing an investigation and were used in this research only.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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