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Original Article

Comparative Study between Neutrophil Gelatinase-Associated Lipocalin [NGAL] versus C - Reactive Protein for Detection of Acute Kidney Injury in Sepsis at Intensive Care Unit

Abdelrahman Gamal Mansour [1*]; Mohammed Samy[1]; Tarek Mustafa Emran[2]; AbdAlla Mohammed AbdAlla[3]

[1] Department of Anesthesiology, Intensive Care and Pain Management, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.
[2] Department of Clinical Pathology, Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt.
[3] Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

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*Corresponding author

Email: bodygamal702@gmail.com

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Abstract

Background: Neutrophil gelatinase-associated lipocalin [NGAL], a protein associated with neutrophil gelatinase, shows potential as a new biomarker that can indicate the severity and outcome of acute kidney injury [AKI]. Yet, it is uncertain whether it can be used to predict the prognosis of AKI in the early stages of sepsis in patients. This study aimed to estimate the diagnostic accuracy of plasma Neutrophil Gelatinase-Associated Lipocalin and C-reactive protein as markers in an adult general intensive care unit for early detection of acute kidney injury in sepsis

Methods: This study included 60 adult patients admitted at intensive care unit and diagnosed with sepsis. Patients were observed for 14 days for the development of AKI. CRP and NGAL were analyzed for their diagnostic accuracies.

Results: Forty-two patients [70%] developed AKI. The mean CRP level in septic patients was 258 ± 117 mg/L. The mean NGAL level in septic patients was 85.25 ± 35.94 pg/ml with a range from 20 pg/ml to 162 pg/ml. Most patients had Acute kidney injury. In univariate analysis, serum urea, creatinine, creatinine clearance, CRP and NGAL were significantly associated with AKI. Factors significant in the univariate analysis were adjusted in the multivariate model.

Conclusion: Both NGAL and CRP were considered as potential makers in predicting AKI in critically ill patients with sepsis.

Keywords: NGAL; CRP; Acute Kidney Injury, Sepsis; Intensive care.

INTRODUCTION

Sepsis is characterized as an unregulated response of the body to infection that can result in the disturbance of organ stability, failure of multiple organs, and eventually, fatalities in patients. The incidence of mortality and morbidity associated with sepsis and septic shock is significant. The in-hospital mortality rate for sepsis is around 20-30% and for septic shock, it is approximately 40-60%. Despite extensive research, the pathophysiology of sepsis is not fully comprehended. Thus, there is a lack of therapeutic options aimed at addressing the molecular cause of organ dysfunction, and the current treatment is limited to source control [such as antibiotics and drainage] and organ support [1].

As many as 60% of individuals with sepsis experience acute kidney injury [AKI], with sepsis being the primary cause of AKI in the intensive care unit [ICU]. The presence of acute kidney injury [AKI] in sepsis is connected with the dysfunction of additional organs and a rise in mortality rates [2].

Mitochondria are considered a key factor in the pathogenesis of sepsis-AKI. Maintaining healthy mitochondria is crucial for upholding renal homeostasis and is significant in providing metabolic support during sepsis [3]. During sepsis, if the mitochondria fail, it leads to depletion of ATP in the kidneys and elevated levels of reactive oxygen species [ROS], which then results in the disruption of cellular homeostasis and dysfunction of the organs [4]. Sepsis causes a decrease in ATP levels, an increase in biomarkers indicating mitochondrial dysfunction, and a reduction in antioxidant defense. These factors are linked with a lower chance of survival and contribute to a further decline in mitochondrial function, creating a vicious cycle where the production of reactive oxygen species [ROS] continues to rise [5].

Neutrophil gelatinase-associated lipocalin [NGAL] is a biomarker that belongs to the lipocalin superfamily and is produced by both neutrophils and various epithelial cells [6]**.** It is a highly researched and quickly emerging biomarker that is used to predict early signs of acute kidney injury [AKI] in various clinical settings [7].

Acute kidney injury [AKI] is characterized by both inflammatory and non-inflammatory processes, and research has shown that inflammation plays a significant role in the development and advancement of AKI. C-reactive protein [CRP], which is produced by the liver and various inflammatory cells, serves as both an inflammation biomarker and a pathogenic factor for AKI. Elevated levels of CRP are linked to poor outcomes in patients with AKI of various causes. In recent years, the role of CRP in the pathogenesis and progression of AKI has been increasingly recognized, as it contributes to local inflammation, hinders the regeneration of damaged tubular epithelial cells, and promotes fibrosis in injured renal tissue [7].

The development and outcome of acute kidney injury [AKI] are influenced by various factors, including mitochondrial dysfunction, autophagy, the innate immune response, inflammation, and endothelial dysfunction [8], tubular injury and alteration of the microcirculation [9]. The majority of AKI cases involve an amplified inflammatory response which is a significant factor in the development and progression of the disease. Inflammation is a fundamental aspect of AKI's pathophysiology and its mitigation is essential in the treatment of AKI [10].

New findings indicate that the serum concentration of CRP is a risk factor for AKI, with higher levels being associated with an increased likelihood of developing the condition. Furthermore, there is a positive correlation between the severity of AKI and the level of CRP in the serum [11].

The objective of the research was to evaluate how accurately plasma Neutrophil Gelatinase-Associated Lipocalin and C-reactive protein could be used as indicators in a general intensive care unit for identifying acute kidney injury in septic patients at an early stage.

PATIENTS AND METHODS

This was a prospective randomized observational clinical study conducted at Al-Azhar university Hospital, New Damietta. This study was conducted on 66 adult patients of both sexes, aged from 21-70 years old admitted in ICU for management of sepsis of different cause.

After the protocol has been approved by the Local Research Committee, Studies Committee, and Research Ethics Committee of the Faculty of Medicine at Al-Azhar University, the patient or their family members will be requested to provide written consent after being informed about the study.

All patients admitted in our intensive care unit for management of sepsis of different cause with criteria of sepsis.

Sepsis is a condition that arises due to an infection-triggered systemic inflammatory response. To meet the criteria for systemic inflammatory response, two or more of the following must be present: body temperature higher than 38°C or lower than 36°C, heart rate exceeding 90 beats per minute, respiratory rate above 20 breaths per minute or PaCO2 below 32 mm Hg, and a leukocyte count above 12,000/microliter or below 4000/microliter or more than 10% immature neutrophil **[12]**.

Exclusion criteria: Grade **3** nephropathy or more for various causes, post-cardiac surgery with cardiopulmonary bypass, radiocontrast exposure and exposure to potential nephrotoxic drugs.

Method

All data collected for each patient and included: Co morbidities and admission diagnosis, clinical data as vital signs including blood pressure, pulse rate and temperature, respiratory rate, chest and cardiac examination as ECG and echo cardiography. Laboratory data such as base line level of serum creatinine, serum urea, creatinine clearance, NGAL, CRP, complete blood count and amount of urine output. Laboratory data were measured daily as part of routine patient care for up to 14 days as end point. CRP was done on fully automated chemistry analyser [Roche Cobas C311 Automated Chemistry Analyzer, Germany]. NGAL was done by ELISA technique

using kit from [Bioassay Technology laboratory] Catalog no. E1719Hu, China according to instructions of the manufacture

Acute kidney injury [AKI] is characterized by a rise in serum creatinine of 0.3 mg/dl or more by the third day of hospitalization, or a 50% or greater increase in serum creatinine from the initial level upon admission during hospital stay.

Endpoint: Up to 14 days or patient discharge from intensive care unit.

Statistical analysis: The data that was gathered was organized and subjected to statistical analysis using several software programs, including SPSS version 26.0, Microsoft Excel 2016, and MedCalC version 19.1. To describe numerical data, mean and standard deviation were used for parametric data, while median and inter-quartile range were used for non-parametric data. For categorical data, the number and percentage were used. To compare quantitative variables between two independent groups, the independent t-test was used for parametric data and the Mann Whitney U test was used for non-parametric data.

RESULTS

The present prospective randomized observational clinical study was conducted on 66 adult patients of both sexes, aged from 21-70 years old admitted in ICU for management of sepsis of different cause. There were 6 patients were excluded due to not meeting the inclusion criteria so the final study was conducted on 60 patients.

There were 60 septic patients included in our study. The age of patients ranged from 35 to 70 years with mean age [±SD] was 64 [± 10] years. the most common age group represented was age group ≥ 60 years [70%]. There were 28 males and 32 females with male to female ratio were 0.88:1. It was found that 42 [70%] of septic patients had AKI [Table 1].

The mean systolic and diastolic blood pressure was 10± 17 mm/Hg and 70± 17 mm/Hg respectively. The mean heart rate was 126± 12 beats/min. while the mean respiratory rate was 26± 7 /min with ten patients was on ventilation. and the mean temperature was 37± 2ºC [Table 2].

The mean CRP level in septic patients was 258 ± 117 mg/L and ranged from 48 mg/L to 428 mg/L. The mean NGAL level in septic patients was 85.25 ± 35.94 pg/ml with a range from 20 pg/ ml to 162 pg/ml [Table 3].

In univariate analysis, serum urea, creatinine, creatinine clearance, CRP and NGAL were significantly associated with AKI. Factors significant in the univariate analysis were adjusted in the multivariate model. It was found that CRP [OR=0.697, P=0.008] and NGAL [OR = 0.590, p =0.011] can act as independent predictors for AKI [Table 4].

CRP and NGAL are good predictors for AKI in septic patients with area under the curve of 0.864 and 0.899 respectively. CRP can predict AKI with sensitivity and specificity was 100% and 63.6% respectively [p< 0.001]. NGAL can predict AKI with sensitivity and specificity was 100% and 81.8% respectively [p< 0.001] [Table 5].

Table [1]: Distribution of studied patients as per demographic characteristics

Parameters		Studied patients [n= 60]	
Sex	Male	28	46.7%
	Female	32	53.3%
Age groups	< 60 years	18	30.0%
	≥ 60 years	42	70.0%
Age [years]	Mean± SD	64± 10	
	Median	69	
	Range	35– 70	
AKI	No	18	30.0%
	Yes	42	70.0%

Table [2]: Distribution of studied patients as per vital signs

Parameters	Studied patients [n= 60]			
	Mean	**SD**	**Minimum**	**Maximum**
Systolic BP [mm/Hg]	101	17	80	160
Diastolic BP [mm/Hg]	70	17	50	90
Heart Rate [beats/min.]	126	12	100	150
Respiratory Rate / min.	26	7	15	45
Temperature [^{O}C]	37	2	35	40

Table [3]: Distribution of studied cases as per CRP and NGAL levels

		Studied patients [n= 60]
CRP [mg/L]	Mean± SD	258 ± 117
	Median	250
	Range	48- 428
NGAL [pg/ml]	Mean± SD	85 ± 36
	Median	80
	Range	20- 162

Table [4]: Regression analysis for predictors of outcomes [complications] after 6 months

Parameters	Univariate analysis				Multivariate analysis			
	Odds ratio [OR]	95%CI		P-value	Odds ratio [OR]	95%CI		P-value
		Lower limit	Lower limit			Lower limit	Upper limit	
Gender [male]	0.945	0.861	1.037	0.235				
Serum urea [mg/dl]	1054.476	140.014	7941.513	**<0.001**	1.401	0.964	2.036	0.077
Serum creatinine [mg/dl]	4123.167	490.692	34645.993	**<0.001**	1.310	0.272	6.316	0.736
Urinary output [ml/kg/h]	0.973	0.874	1.083	0.616				
Creatinine clearance [mL/min]	195.360	26.723	1428.206	**<0.001**	32.161	0.860	1202.7	0.060
CRP	0.710	0.597	0.844	**<0.001**	0.697	0.534	0.910	0.008
NGAL	0.731	0.597	0.896	**0.008**	0.743	0.590	0.935	0.011

B: Regression coefficient; S.E.: Standard error, CI: Confidence interval

Table [5]: ROC curve analysis to predict the diagnostic performance of CRP and NGAL

parameters	CRP	NGAL
Cutoff value	>346 mg/L	>97.9 pg/ml
AUC [95% CI]	0.864 [0.644 - 0.972]	0.899 [0.682 - 0.987]
Sensitivity	100%	100%
Specificity	63.6%	77.8%
PPV	73.3%	81.8%
NPV	100%	100%
P value	**<0.001**	**<0.001**

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area Under Curve

DISCUSSION

Penile anomalies are frequently observed in clinical settings. Acute kidney injury [AKI] refers to a sudden impairment in kidney function that results in the inability to maintain proper balance of fluids, acid-base levels, and electrolytes [13]. Acute kidney injury by itself is a complication experienced by between 7.2 to 20% of hospitalized patients, and between 13 to 78% of patients in the intensive care unit [ICU] [14]. Patients who are critically ill and are also suffering from acute kidney injury have a bleak prognosis and a high mortality rate. Among critically ill patients, sepsis is a frequent cause of AKI, and several observational studies have reported that sepsis accounts for 30 to 50% of all cases of AKI [15].

This prospective randomized observational clinical study was carried out in Al-Azhar university Hospital, New Damietta. This study was conducted on 66 adult patients of both sexes, aged from 21-70 years old admitted in ICU for management of sepsis of different cause.

The current study enrolled 60 septic patients with age range from 35 to 70 years with mean age [±SD] was 64 [± 10] years. The most common age group represented was age group ≥ 60 years [70%]. There were 28 males and 32 females with male to female ratio was 0.88:1. It was found that 42 [70%] of septic patients had AKI. In univariate analysis, we found that gender was not associated with the incidence of AKI.

Our findings align with those reported by **Dai *et al.*** [16], who found no significant correlation between age or gender and the occurrence of AKI in critically ill patients with sepsis. Their study also reported a 49% incidence rate of AKI in critically ill patients with sepsis. Similarly, **Soto *et al.*** [17] discovered that gender was not associated with the incidence of AKI in critically ill septic patients. In contrast, **Peng *et al.*** [18] revealed that age, but not gender, was significantly different between critically ill septic patients with and without AKI. Their study also reported an 83% incidence rate of AKI in critically ill septic patients.

On the other hand, **Ginting *et al.*** [19] reported that there was a statistically significant association between age [p = 0.001] and gender [p = 0.001] with the occurrence of AKI in critically ill patients with sepsis, which contrasts with our findings. The incidence of AKI in their study was 21 [52.5%] cases. However, **Khawaja *et al.*** [20] found no significant differences in terms of age between patients with and without AKI who were admitted to the intensive care unit [ICU] with suspected sepsis. Nevertheless, a significant gender difference was noted [p value<0.05]. Their study also reported a 52% incidence rate of AKI in critically ill septic patients, which is similar to our findings. The disagreement with our results could be attributed to differences in the sample size and inclusion criteria utilized.

The incidence of AKI may vary from study to another and may be attributed to the differences in severity of illness.

Regarding Vital signs among the studied group, we found that the mean systolic and diastolic blood pressure were 101± 17 mm/Hg and 70± 17 mm/Hg respectively. The mean heart rate was 126± 12 beats/min. while the mean respiratory rate was 26± 7 /min with ten patients was on ventilation. And the mean temperature was 37± 2ºC.

According to **Bagshaw *et al.*** [21], patients with septic AKI had a higher level of illness acuity [P < 0.0001], lower blood pressure [P < 0.0001], higher heart rates [P < 0.0001], and poorer pulmonary function as measured by the arterial oxygen tension/fraction of inspired oxygen ratio [P < 0.0001].

However, **Dai *et al.*** [16] revealed that Hypertension, mean arterial blood pressure and the need for mechanical ventilation were non-significantly associated with the incidence of AKI.

Regarding CBC in the studied group, we found that the mean hemoglobin was 110± 2 g/dl and the mean RDW-CV was 17± 2. The mean TLC and platelets count were 19± 8 x109/L and 206 ± 101 x109/L respectively.

Peng *et al.* [18] revealed that patients with and without AKI have comparable Hb and Platelet, but WBC was significantly higher in cases with AKI reflecting the higher inflammation among AKI cases.

In contrast, **Zhou *et al.*** [22] demonstrated that hemoglobin [Hb], platelet count, and white blood cell [WBC] count were identified as risk factors for AKI in critically ill patients with sepsis-associated acute kidney injury.

The Acute Kidney Injury Network [AKIN] criteria proposed using increased serum creatinine level and reduced urine output as indicators of AKI [23].

Regarding renal function test, the current study showed that the mean urea and creatinine were 143± 101 mg/dl and 3± 2 mg/dl respectively. The mean creatinine clearance was 34± 26 mL/min while the mean urinary output was 1286± 994 ml/kg/h. the mean serum lactate was 4± 2 mg/dl. In univariate analysis, serum urea, creatinine, creatinine clearance, but no urinary output, were significantly associated with AKI.

Yi *et al.* [24] provided support for this, as their study found that serum creatinine was identified as a risk factor for predicting AKI in high-risk patients through multivariate logistic regression analyses. Additionally, **Ralib *et al.*** [25] discovered that the baseline serum creatinine was significantly higher in patients with AKI compared to those without AKI [P < 0.01]. Similarly, **Peng *et al.*** [18] noted that patients with and without AKI had comparable levels of blood urea nitrogen, but those with AKI had significantly higher levels of serum creatinine, which reflects higher inflammation among AKI cases. **Zhou *et al.*** [22] also found that baseline serum creatinine was a risk factor for AKI in critically ill patients with sepsis-associated acute kidney injury.

In the present study, US was performed to our studied patients and the results showed that 30% cases had grade I nephropathy, 15% of them had grade II nephropathy and 5% cases had severe pyelonephritis. Regarding Echocardiography, 23.3% reported degenerative heart disease.

The study by **Liu *et al.*** [26] revealed that the US features can be used to understand the underlying pathophysiology of SA-AKI.

Regarding the CRP level among the studied cohort, the present study showed that the mean CRP level in septic patients was 258 ± 117 mg/L and ranged from 48 mg/L to 428 mg/L. In univariate analysis, CRP was significantly associated with AKI. And in the multivariate model, we found that CRP [OR=0.697, P=0.008] can act as independent predictors for AKI.

In agreement with our results **Zhou *et al.*** [22] also showed that high CRP level was identified as a risk-factor for AKI in sepsis associated-acute kidney injury in critically ill patients. Also, **Katayama *et al.*** [27] revealed that higher CRP was significantly associated with AKI in patients with sepsis.

However, **Dai *et al.*** [16] revealed that higher CRP and WBC were non-significantly associated with the incidence of AKI. The disagreement may be due to the difference in sample size and inclusion criteria.

Regarding the NGAL level among the studied cohort, we found that the mean NGAL level in septic patients was 85.25 ± 35.94 pg/ml with a range from 20 pg/ml to 162 pg/ml. In univariate analysis, NGAL was significantly associated with AKI. And in the multivariate model, we found that NGAL [OR = 0.590, p =0.011] can act as independent predictors for AKI.

To assess the diagnostic ability of CRP and NGAL, we utilized ROC curve analysis and discovered that both CRP and NGAL were effective predictors for AKI in septic patients, with an area under the curve of 0.864 and 0.899, respectively. CRP exhibited a sensitivity and specificity of 100% and 63.6%, respectively [p<0.001], while NGAL had a sensitivity and specificity of 100% and 81.8%, respectively [p<0.001].

The present study indicated that NGAL superior than CRP in the prediction of AKI in patients with Sepsis at Intensive Care Unit.

Our findings are consistent with those of **Ginting *et al.*** [20], who reported that NGAL had a sensitivity, specificity, and accuracy of 66%, 89%, and 78%, respectively, for early prediction of AKI occurrence in critically ill patients. Additionally, **Yi *et al.*** [24] found that the area under the receiver operating characteristic curve [AuROC] of plasma NGAL for predicting AKI was larger than that of urine NGAL [0.79 vs. 0.66, P=0.010], while in the CKD group [N=16], the opposite was true [0.94 vs. 0.76, P=0.049]. Furthermore, **Soto *et al.*** [17] demonstrated that plasma neutrophil gelatinase-associated Lipocalin was an accurate biomarker for predicting AKI in patients admitted from the emergency department.

The findings of our study were reinforced by the systematic review and meta-analysis conducted by **Zhang *et al.*** [28], which analyzed 15 studies involving a total of 1,478 patients. The meta-analysis revealed that for plasma NGAL, the combined sensitivity and specificity with corresponding 95% confidence intervals [CI] were 0.83 [95% CI: 0.77-0.88] and 0.57 [95% CI: 0.54-0.61], respectively.

To our knowledge, no published studies have conducted a direct comparison of the diagnostic effectiveness of NGAL and CRP in adult patients. However, **Rabeea *et al.*** [29] evaluated the diagnostic value of Neutrophil Gelatinase-associated Lipocalin and highly sensitive C-reactive protein as markers for early detection of AKI in neonatal sepsis. Their findings suggested that both biomarkers were useful in the early detection of AKI in septic neonates, with NGAL exhibiting superior diagnostic performance. This supports the results of our study.

Conclusion*:* NGAL and CRP were considered as possible indicators for predicting acute kidney injury [AKI] in critically ill patients suffering from sepsis. The study found that NGAL and CRP may help identify AKI in these patients. However, more research is needed with larger groups of participants and longer study time periods. Bigger studies are needed to confirm the results and identify factors that increase the risk of bad outcomes.

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