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Potential use of Oncostatin M in Critically ill Patients with acute Kidney Injury

Amin Soliman[1], Nora Mahmoud Ali Selim[2], Motaz Esam El-din Abdel-Motelb[1], Rasha Ahmed Darwish[1], Ahmed Soliman[1]*

[1]Department of Nephrology, School of Medicine, Cairo University, Giza, Egypt; [2]Department of Chemical Pathology, School of Medicine, Cairo University, Giza, Egypt

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***Correspondence:** Ahmed Soliman, Department of Nephrology, School of Medicine, Cairo University, Giza, Egypt. E-mail: drsolimans@yahoo.com
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Abstract

BACKGROUND: Acute kidney injury (AKI) is one of the most common complications affecting patients admitted to intensive care unit (ICU) worldwide. In response to injury, both kidneys and liver secrete acute phase reactants as a mechanism of protection. Oncostatin M (OSM) is a member of the interleukin-6 family of cytokines which was found to be elevated during renal injury as in diabetic nephropathy, glomerulonephritis, and obstructive nephropathy.

AIM: The study aimed to assess the role of OSM as an early biomarker of AKI in critically ill patients.

PATIENTS AND METHODS: We conducted a prospective case–control study that included 202 patients admitted to ICU within Kasr El-Aini University hospitals during the period between January 2022 and August 2022. Eligible patients were divided into two groups according to the occurrence of AKI, and Oncostatin was assessed in the sera of the included patients.

RESULTS: Our findings showed that the AKI group had statistically significant lower OSM levels compared to the control group, especially among those patients who had poor clinical outcomes and non-survivors. We also found that OSM is a good predictive tool for the prediction of mortality among patients admitted to ICU with sepsis complicated with AKI (Area under the curve = 0.673, 95% confidence interval: 0.532–0.814) with a sensitivity of 83.8% and specificity of 61.4%.

CONCLUSION: OSM plays an important role among critically ill patients who are admitted to the ICU with sepsis, it can significantly predict AKI development and subsequent mortality.

Introduction

Acute kidney injury (AKI) is characterized by abrupt deterioration in kidney function, manifested by an increase in serum creatinine level with or without reduced urine output. The spectrum of injury ranges from mild to advanced, sometimes requiring renal replacement therapy (RRT) [1].

Oncostatin M (OSM), a member of the interleukin-6 (IL-6) family of cytokines, has important roles in renal diseases, as IL-6 cytokine family members have been found to be elevated in the renal tissue of patients with kidney diseases, including diabetic nephropathy, glomerulonephritis and obstructive nephropathy [2].

Cells of the kidney that express and secrete IL-6 cytokine family members include podocytes, endothelial cells, mesangial cells, and tubular epithelial cells. In these cell types, IL-6 cytokine family member signaling can promote cell proliferation, impact differentiation, or increase tubulointerstitial fibrosis [3].

Several studies have shown that serum OSM was a useful early marker for inflammatory disorders [4], [5], [6], [7], but; to the best of our knowledge; there was no evidence concerning its role in diagnosis of AKI among hospitalized patients. Hence, we conducted a prospective case–control study to assess the role of OSM as an early biomarker of AKI in among critically ill patients.

Patients and Methods

We conducted a prospective case–control study that included 202 patients admitted to intensive care unit (ICUs) within Kasr El-Aini University hospitals during the period between January 2022 and August 2022, all adult patients with AKI as defined in accordance with criteria established by the AKI Network: An abrupt increase in serum creatinine ≥0.3 mg/dL within 48 h or a ≥50% increase in serum creatinine or decrease in urine output <0.5 mL/kg/h for more than 6 h were eligible for inclusion in the current study, however, patients with a previous diagnosis of chronic kidney disease, parathyroid disease, fat malabsorption or duodenal resection or under recent

therapy with elemental Vitamin D were excluded from the study.

Eligible patients were divided into two groups according to occurrence of AKI; Group 1: Patients admitted to ICU with sepsis and developed AKI and Group 2: Patients admitted to ICU without AKI.

All patients were subjected to detailed history including age, gender, weight, height, and body mass index. Full clinical examination was performed for all patients. Routine laboratories were done for all patients including complete blood count, urea, creatinine, and serum electrolytes as Na, K, Ca, and PO4.

Serum OSM was measured using ELISA-Kit; it is a sandwich-ELISA assay that measures OSM in serum samples, with a sensitivity 9.38 pg/mL and detection range 15.63–1000 pg/mL [8].

Sample size calculation

After reviewing the literature, we used G power 3.0.01 for calculating the sample size representative of the population. We found that with a power of 80%, α error of 5%, and effect size of 0.219, the sample size will be 202 patients. With an allocation ratio of 1:1, 101 patients admitted to ICU with AKI along with 101 control patients were the minimal required sample to detect such effect size.

Statistical analysis

We used Statistical Package for the Social Sciences version 24 for windows for analyzing the data. Qualitative data will be expressed in terms of frequencies and percentages. Quantitative data will be expressed in terms of means and standard deviations if normally distributed and median and interquartile ranges if not normally distributed. The Chi-square test will be used to test the association between categorical variables. Fissure exact test will be used to test the violation of assumptions. Student's t-test will be used to test the difference of numerical variables between the two study groups. In the case of non-parametric data, Mann–Whitney test will be used. $p < 0.05$ will be considered statistically significant.

Results

We enrolled 202 patients who were admitted to the ICU, and 101 patients developed AKI, comparison of demographics characteristics showed that AKI group was significantly older that controls with $p < 0.001$, males showed significantly higher predominance in the AKI group $p < 0.001$. As well, hypertension and pneumonia were exclusively present among cases ($p < 0.001$, $p = 0.003$).

Table 1: The difference between both AKI and control groups concerning Sociodemographic characteristics and associated comorbidities

Variable	Case group (n = 101) (%)	Control group (n = 101) (%)	p-value
Age	48.6 ± 15.7	31.02 ± 12.8	<0.001[t]
Gender			
Male	74 (73.3)	50 (49.5)	0.001[c]
Female	27 (26.7)	51 (50.5)	
DM	55 (54.7)	74 (73.3)	0.008[c]
HTN	42 (41.6)	0	<0.001[c]
SLE	6 (5.9)	11 (10.9)	0.311[c]
Pneumonia	9 (8.9)	0	0.003[f]
Mortality	44 (43.6)	5 (5)	<0.001[c]

t; Independent sample T-test, c; Chi-square test, f; Fissure exact test, AKI: Acute kidney injury.

On the other hand, AKI group showed significantly lower prevalence of diabetes (54.7% vs. 73.3%) compared to controls with $p = 0.008$. Mortality rate was significantly higher among patients who developed AKI when compared to others. (43.6% of the case group vs. 5% of the control group, $p < 0.001$) as shown in Table 1 and Figure 1.

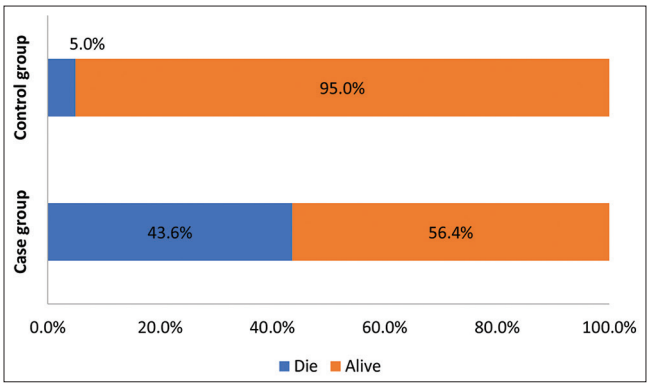

Figure 1: The difference between both groups concerning mortality rate

Comparison of laboratory findings showed that blood urea, serum creatinine, potassium, sodium, and phosphorus were significantly higher among the AKI group with $p < 0.05$ than the control group, while OSM and calcium levels were significantly lower among AKI group with $p < 0.001$ and <0.001, respectively, than the control group (Table 2 and Figure 2).

Table 2: The difference between both groups concerning laboratory findings

Variable	Case group (n = 101)	Control group (n = 101)	p-value
Urea	180 (100–202)	33 (28–40)	<0.001[m]
Creatinine	3.73 ± 1.67	1.16 ± 0.67	<0.001[t]
Na	138.36 ± 5.91	136.5 ± 5.58	0.024[t]
K	5.2 ± 0.76	4.65 ± 0.93	<0.001[t]
Ca	8.15 ± 0.84	8.96 ± 0.59	<0.001[t]
PO4	3.75 ± 1.31	3.43 ± 0.95	0.044[t]
Oncostatin m	2 (2–38)	37 (30–46)	<0.001[m]

m; Mann–Whitney U test. t; Independent sample T test.

We found that OSM is a good predictive tool for the prediction of mortality among patients admitted to ICU with sepsis and developed AKI (Area under the curve [AUC] = 0.673, 95% confidence interval: 0.532–0.814) with a sensitivity of 83.8% and specificity of 61.4% as shown in Table 3 and Figure 3.

Table 3: The diagnostic accuracy of Oncostatin M in the prediction of mortality among patients with sepsis and AKI (n = 101)

AUC	p-value	95% (95% CI)	Sensitivity	Specificity
0.673	0.019	0.532–0.814	83.8%	61.4%

AUC: Area under the curve, AKI: Acute kidney injury, CI: Confidence interval.

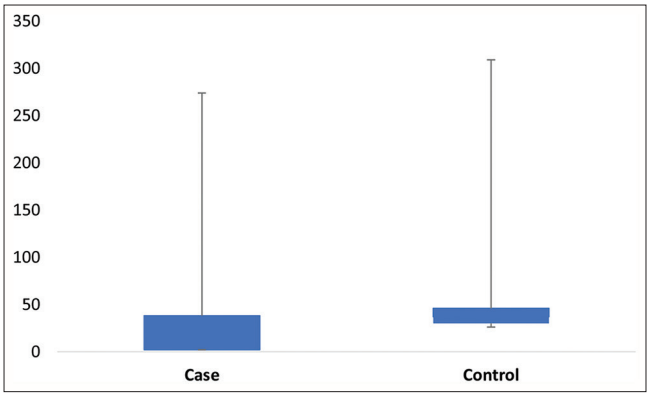

Figure 2: The difference between both groups concerning Oncostatin m serum levels

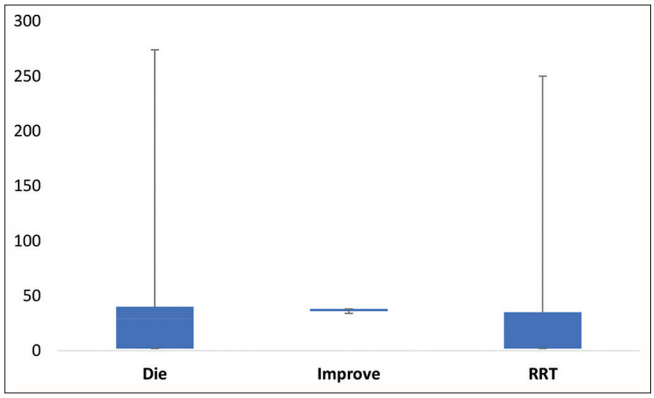

Figure 4: The association between Oncostatin m and outcome among cases group

We found that median serum OSM serum levels were significantly higher among those who improved clinically when compared to those with poor outcome (death, RRT); p = 0.048 as shown in Table 4 and Figure 4.

Table 4: The association between Oncostatin M serum levels and outcome among cases group (n = 101)

Outcome	Oncostatin m	p-value
Die (n = 44)	29 (2–40)	0.048
Improve (n = 2)	38 (36–38)	
RRT (n = 55)	2 (2–35)	

Kruskal–Wallis test. RRT: Renal replacement therapy.

Discussion

AKI is one of the most common complications affecting patients admitted to ICU worldwide (Cruz and Ronco, 2007). In 2018, Hoste *et al*. reviewed the literature in a trial for the estimation of the global prevalence of AKI. They found that AKI incidence was varying between 3% and 18.3% in high-income countries and reached 21% in low- and middle-income countries, with one to two-thirds of patients admitted to ICU experience AKI and nearly 10–15% of those patients require RRT in the form of either hemodialysis or renal transplantation [9].

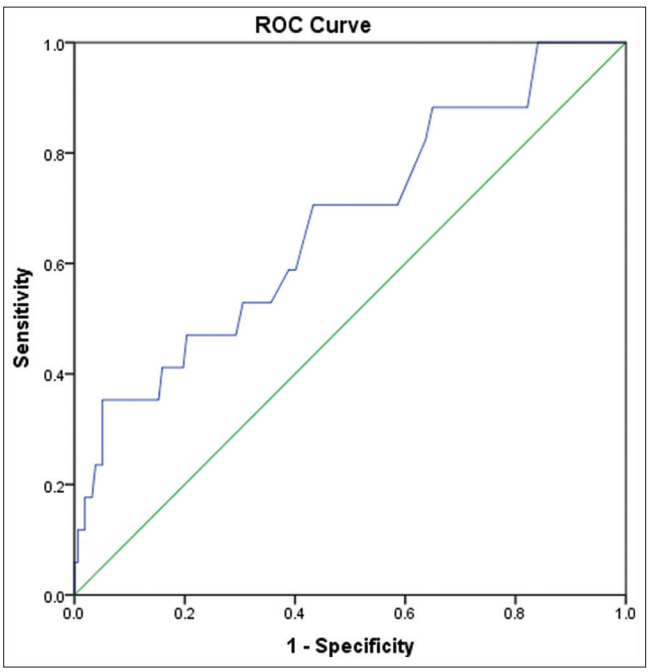

Figure 3: Receiver operating characteristic curve for prediction of mortality among intensive care unit patients with sepsis and acute kidney injury

In response to injury, both kidneys and liver secrete acute phase reactants as a mechanism of protection. These proteins serve as protein molecules interacting through interleukin cytokines [4].

Experimental studies have shown that OSM is an important mediator of sepsis-related inflammation and tissue injury, and it may be a potential target for the treatment of sepsis [5]. OSM expression had shown to be upregulated among patients with various inflammatory diseases resembling inflammatory bowel disorders [6], allergic asthma [7], chronic rhinosinusitis [10], or hepatocellular carcinoma [11].

AKI is associated with poor outcomes; increased rates of morbidity and mortality worldwide; thus, we conducted a case–control study to assess the role of oncostatin in the prediction of AKI among critically ill patients in a tertiary care hospital.

Our findings showed that the AKI group showed statistically significant lower OSM levels compared to the control group, OSM serum levels were significantly lower among those who had poor clinical outcomes and non-survivors. We also found that OSM is a good predictive tool for prediction of mortality among patients admitted to ICU with sepsis and developed AKI (AUC = 0.673, 95% CI: 0.532–0.814) with a sensitivity of 83.8% and specificity of 61.4%.

To the best of our knowledge, this is the first study to assess the role of OSM in the prediction of AKI development, need for RRT, and mortality. The previous studies have investigated the role of OSM in the prediction of outcomes among ICU-admitted patients with severe sepsis; however, their findings were contradicting with the present study.

Gong *et al*. compared OSM levels among ICU-admitted patients with severe sepsis versus ICU

patient controls, and healthy volunteers and they found that OSM is significantly higher among the septic group compared to control patients and healthy group with $p < 0.05$. They also reported that higher levels of OSM were associated with a higher risk of mortality on the 28th admission day; they also added that OSM levels were significantly higher in non-survivors with sepsis than survivors with sepsis on the day of ICU admission [5].

Same study reported that 36.8 pg/mL cutoff point level can predict mortality on 28th day of admission with sensitivity and specificity of 82.9% and 69.7%, respectively, and the logistic regression model showed that the OSM level on the day of ICU admission is an independent predictor for 28-day mortality in the patients with sepsis [5].

The acute phase response is traditionally characterized by the hepatic synthesis of proteins as an inflammatory response to injury, with IL-6 being the key mediator. In contrast, microarray studies in human renal transplant implantation biopsies indicate a strong acute phase response in the deceased donor kidney, associated with a significant upregulation of OSM receptor β (OSMR). The kidney can generate a strong acute phase response, mediated by the OSM/OSMR gateway [3].

This acute phase response generated by the kidney during sepsis with upregulation of OSMR might consume serum OSM resulting in lower levels in septic cases with AKI. The lower level of serum OSM in our study might be due to the upregulation of kidney OSMR as an acute phase reaction with a worse outcome and increased mortality [3].

On the other hand, certain hemodialysis procedures eliminate inflammatory mediators, such as interleukins [12], other hemodialysis filters may adsorb cytokines [13]. This mechanism can explain the lower levels of OSM among AKI patients who underwent RRT.

Few limitations were faced in the current study including the evaluation a small number of patients with sepsis in a single-center observational study; therefore, current results must be verified in larger, multicenter studies. We did not investigate factors affecting OSM secretion and the variables that regulate its release in sepsis.

Conclusion

OSM plays an important role among critically ill patients who are admitted to ICU with sepsis, it can significantly predict AKI development and subsequent mortality. Further studies are needed to assess factor affecting OSM secretion and its association with other comorbidities among critically ill in the ICU admitted population.

Ethical Consideration

All study procedures followed the ICH-CGP guidelines, and declaration of Helsinki, Ethical approval was obtained on the study protocol from the Local Ethical Committee of Cairo University. All patients were consented orally prior blood sample withdrawal.

Data Security

All collected data were only reviewed by the data collector; all patients were deidentified and were given unique ID. Data were kept secure in closed cabinet and encrypted on a computer until processed by the study statistician after completion of all data required from study participants.

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