B I O L I F E **R E S E A R C H   A R T I C L E**

The ratio of C-Reactive protein to Prealbumin to predict the mortality in patients with acute kidney injury

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ABSTRACT

Background: Acute kidney injury (AKI) is associated with increased mortality of in hospital patients. Serum C reactive protein (CRP) is an acute-phase protein markedly increased within hours after infection or inflammation. The relation between inflammation and nutrition is complex. The serum chemistry marker "prealbumin" is recommended to assess the nutritional status. In this study, we assessed the CRP/Prealbumin ratio as a prognostic marker in patients with AKI.
Methods: Case control study of 2 groups. Cases group was 50 adult patients with the diagnosis of AKI according to AKIN criteria of stage 3 admitted to the department of Critical Care Units. Control group was 50 healthy adult volunteers without any history of kidney disease. Both groups were subjected to measuring serum prealbumin level and C-reactive protein level at time of enrollment.
Results: The mean value of CRP/Prealbumin ratio was 12.46 in non survivors while it was 1.45 in survivors (P value= <0.001). There were no any significant differences between the 2 groups in need for MV (p= .059) and RRT (p= .816). Conclusion: Higher serum CRP/prealbumin ratio might be strongly associated with higher mortality in AKI patients.

Keywords: Critical; AKI; Prealbumin; CRP

INTRODUCTION

Acute kidney injury (AKI) is associated with increased mortality of in hospital patients. Although

great advances in the diagnosis of AKI have been made, the mortality remains high. [1-5] Among the patients with AKI, inflammation and malnutrition were common, [6,7] but there were only a few studies suggested that inflammation and malnutrition were associated with the prognosis of AKI patients. [7,8]

Serum C reactive protein (CRP) is an acute-phase protein synthesized by the liver following stimulus by various cytokines, markedly increased within hours after infection or inflammation. The relatively short half-life of approximately 19 hours makes it a useful monitor for infection and inflammatory disease. In addition, laboratory tests for CRP are easily available and less costly than cytokine tests. [9-11] Some studies suggested that increased CRP level was associated with sepsis and mortality of critical illness. [9] However, no study demonstrated that CRP as a predictor for mortality of AKI patients. [12] Malnutrition is another outstanding problem in AKI patients and has been paid attention to in recent years. [13-16]

According to the International Society of Renal Nutrition and Metabolism (ISRNM), the serum chemistry markers including albumin, prealbumin and cholesterol are recommended to assess the nutritional status. [17] Chertow et al reported that prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. [18] The study by Cano et al showed that an improvement in prealbumin during nutritional therapy

was associated with a decrease in morbidity and mortality in malnourished hemodialysis patients.[19]

Another study also reported that even though baseline serum prealbumin may not be superior to albumin in predicting mortality in maintenance hemodialysis (MHD) patients, prealbumin concentrations <20 mg/dL were associated with death risk in those patients and a fall in serum prealbumin over 6 months was independently associated with increased death risk. [20] In AKI patients, Perez-Valdivieso et al found that serum prealbumin levels <11 mg/dL were strongly associated with a higher risk of death independent of AKI severity. [21] Besides, few studies reported the predict value of prealbumin in AKI patients.

The correlation between inflammation and malnutrition was close and complex because inflammation could lead to malnutrition, as well as malnutrition was an adverse factor for the control of inflammation. [15] Pinilla et al reported that the ratio of CRP to prealbumin (CRP/prealbumin) was associated with the severity of organ dysfunction in critically ill patients. [22]

However, no study reported that the combination of the inflammatory and nutritional markers could predict the mortality of AKI patients. The aim of this study was to investigate the correlation between inflammatory marker (CRP), nutritional marker (prealbumin) and in-hospital 28 days' mortality of AKI patients. We studied the ratio of CRP/prealbumin as a tool to assess the risk of death in patients with AKI.

PATIENTS AND METHODS

After approval of the Medical Ethics Committee of Alexandria, faculty of Medicine, this study is a case control study. Cases group was 50 adult patients with the diagnosis of acute kidney injury according to AKIN criteria of stage 3 presented to Alexandria Main University Hospitals and admitted to the department of Critical Care Units. Control group was 50 healthy adult volunteers without any history of kidney disease. Informed consents from volunteers and the patient's next of kin were taken before the time of enrollment in the study.

Regarding Patients enrolled, Inclusion criteria was adult patients diagnosed with AKI at admission or who developed AKI during their stay in ICU according to AKIN criteria. We excluded pregnant females and any patients with diseases known to affect the level of c-reactive protein and prealbumin such as patients with history of DM (diabetic nephropathy), history of heart failure or decompensated heart disease, post arrest, decompensated liver disease (child Pugh class B and C), chronic renal disease, immunocompromised (HIV and active, relapse cancer patients), polytrauma, burn and rheumatologically disease patients.

All patients included in the study were subjected to:
- Complete history taking including age, gender, past medical, surgical and drug history in addition to the symptoms of acute kidney injury e.g. oliguria and lower limb edema.

- Complete physical examination including mean arterial blood pressure, heart rate (HR), respiratory rate (RR), body temperature, urine output assessment and Lower limb edema.
- SOFA score was evaluated daily during the study to predict the mortality. APACHEII score was evaluated at enrollment to define the included patients.
- Weekly laboratory investigations in the form of complete blood picture, bleeding profile, Serum sodium (Na) mEq/l, Serum potassium (K) mEq/l, blood Urea (mg/dl), Serum Creatinine (mg/dl), Serum alanine aminotransferase(ALT) and aspartate aminotransferase (AST) IU/L, Complete urine analysis and 24h urine albumin.
- Ultrasound abdomen (US) was done to exclude chronic kidney disease in the first 24 hours of enrollment. Chest sonography, inferior vena cava (IVC) diameter and collapsibility index to exclude pulmonary congestion and for fluid assessment.

Both groups were subjected to measuring serum prealbumin level and C-reactive protein level at time of enrollment. Fasting blood samples were collected in serum-separating tubes and the serum was separated within 30 min of sample collection, and then aliquoted and stored at -80°. CRP was measured by nephelometry immunoassay; the detectable limit of CRP was 0.316 mg/dL. The levels of CRP below the detectable limit were assumed as 0.158 mg/dL. Serum prealbumin was measured using the automatic biochemistry analyzer.

During the time of study in cases only, we assessed the Development of acute renal failure, Need for renal replacement therapy (CRRT) and in-hospital 28 days' mortality as primary outcomes. The secondary outcome was the need for mechanical ventilation (MV).

RESULTS

When we compared both groups regarding demographic data as sex and age, there was no any significant between them. The median age of cases group was 41 years while it was 44 years in control group (P value = 0.585). (Table-1) Sepsis was the main cause of acute kidney injury in cases group. (Fig-1). The baseline vital signs of both groups showed statistically significant differences in mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), Temperature (T) and urine output (UOP). (Table-2).

Figure-1. Distribution of the cases group according to cause of AKI (n=50)
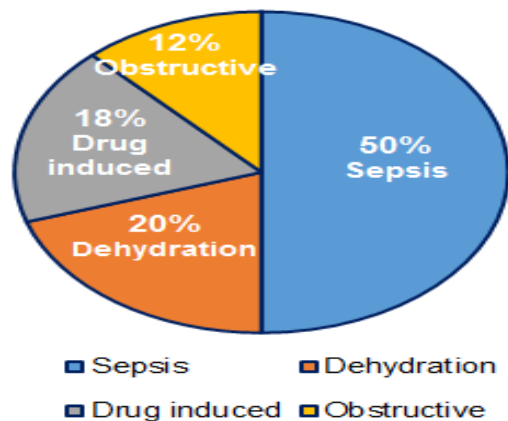
Table-1. Comparison between the two studied groups according to demographic data

	Cases (n= 50)		Control (n= 50)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	28	56.0	30	60.0	χ^2=0.164	0.685
Female	22	44.0	20	40.0		
Age (years)						
<20 – 30	7	14.0	9	18.0		
31 – 40	18	36.0	12	24.0	χ^2=2.672	0.448
41 – 50	15	30.0	21	42.0		
51 – 60	10	20.0	8	16.0		
Min. – Max.	25.0 – 59.0		18.0 – 57.0			
Mean ± SD.	42.78 ± 9.49		41.70 ± 10.2		t=0.548	0.585
Median	41.0		44.0			

χ^2, p: χ^2 and p values for Chi square test
t, p: t and p values for Student t-test

Table-2. The baseline vital signs of the two studied groups.

	Cases (n = 50)	Control (n = 50)	P value
MAP			
Min. – Max.	30.0 – 75.0	65.0 – 95.0	
Mean ± SD.	57.0 ± 12.6	77.64 ± 8.01	p<0.001
HR			
Min. – Max.	77.0 – 125.0	66.0 – 100.0	
Mean ± SD.	103.14±13.85	76.66±6.99	p<0.001
RR			
Min. – Max.	18.0 – 38.0	15.0–24.0	
Mean ± SD.	25.32±4.12	17.14 ± 1.84	p<0.001
Temperature			
Min. – Max.	37.0 – 39.0	37.0 – 38.60	
Mean ± SD.	37.82 ± 0.66	37.45 ± 0.44	p<0.001
UOP			
Min. – Max.	5.0 – 25.0	50.0 – 100.0	
Mean ± SD.	19.39 ± 4.96	72.80±16.91	p<0.001

p value for **Student t-test** *: Statistically significant at p ≤ 0.05

The baseline laboratory investigation of both groups showed statistically significant differences in Hemoglobin level (Hb), Hematocrit (Hct), white blood cells (WBCs), platelets count (PLT), coagulation profile, sodium (Na) and potassium (K) level. (Table-3).

Regarding the baseline renal function of both groups, the cases groups showed statistically significant differences in all criteria of renal functions when compared with the control group. The mean blood urea nitrogen (BUN) was 91.34 in the cases group while it was 18.40 in the control group (p<0.001). The mean serum creatinine (S.cr) was 5.22 in the cases group while it was 0.83 in the control group (p<0.001) (Table-4).

Table-3. The baseline laboratory investigations of the two studied groups.

	Cases (n = 50)	Control (n = 50)	P value
Hb			
Min. – Max.	6.80 – 14.0	10.50–13.50	
Mean ± SD.	9.75 ± 1.74	11.74 ± 0.83	p<0.001
Hct%			
Min. – Max.	18.0 – 40.0	30.0 – 35.0	
Mean ± SD.	25.82 ± 4.54	33.34 ± 1.64	p<0.001
WBCs			
Min. – Max.	5.0 – 31.0	7.0 – 15.0	
Mean ± SD.	14.12 ± 6.87	8.91 ± 1.74	p<0.001
PLT			
Min. – Max.	152.0–471.0	190.0–300.0	
Mean ± SD.	234.76±59.01	220.30±29.08	p<0.001
RDW%			
Min. – Max.	10.0 – 14.0	11.0 – 12.0	
Mean ± SD.	11.77 ± 1.01	11.46 ± 0.40	p<0.001
INR			
Min. – Max.	1.0 – 3.0	1.0 – 1.40	
Mean ± SD.	1.32 ± 0.42	1.13 ± 0.13	P**=0.026
PT			
Min. – Max.	12.30 – 26.0	11.0 – 16.0	
Mean ± SD.	18.05 ± 3.78	13.94 ± 1.64	p<0.001
PTT			
Min. – Max.	21.50 – 55.0	32.0 – 36.0	
Mean ± SD.	41.47 ± 7.79	38.04 ± 6.54	p<0.001
Na+			
Min. – Max.	107.0–150.0	132.0–143.0	
Mean ± SD.	127.42±7.44	138.34±2.84	p<0.001

K+

Min. – Max.	5.0 – 6.50	3.60 – 4.30	p<0.001
Mean ± SD.	5.64 ± 0.38	3.94 ± 0.24	

p value for **Student t-test** *: Statistically significant at p ≤ 0.05

*p*** p value for **Mann Whitney test** *: Statistically significant at p ≤ 0.05

Regarding our main study marker, Cases group showed statistically significant differences in terms of CRP and prealbumin. The mean prealbumin level of cases group was 28.70 while it was 22.58 in control group (*P* value = <0.001). The mean CRP level of cases group was 95.85 while it was 9.58 in control group (*P* value=<0.001). The mean CRP/Prealbumin ratio in cases group was 3.25 but it was only 0.20 only in control group (*P* value = <0.001) (Table-5).

Table-4. The baseline renal function of the two studied groups.

	Cases (n = 50)	Control (n = 50)	*P* value
BUN			
Min. – Max.	50.0 – 212.0	12.0 – 25.0	p<0.001
Mean ± SD.	91.34± 44.31	18.40± 3.30	
S.cr			
Min. – Max.	2.60 – 10.0	0.50 – 1.0	p<0.001
Mean ± SD.	5.22 ± 2.21	0.83 ± 0.16	
BUN/ S.cr			
Min. – Max.	6.25 – 26.90	12.0 – 36.0	p<0.001
Mean ± SD.	18.35 ± 5.74	23.06± 6.21	

Table-5. Comparison between the two studied groups according to CRP/Prealbumin ratio

	Cases (n=50)	Control (n=50)	MW	p
Pre albumin				
Min. – Max.	10.0 – 35.0	18.0 – 35.0	690.0	<0.001*
Mean ± SD.	22.58 ± 7.70	28.70± 5.44		
Median	23.50	29.50		
CRP				
Min. – Max.	5.0 – 280.0	4.0 – 60.0	381.50*	<0.001*
Mean ± SD.	95.85 ± 89.88	9.58 ± 10.05		
Median	75.0	7.0		
CRP/Pre albumin				
Min. – Max.	0.10 – 25.0	0.10 – 3.0	379.0*	<0.001*
Mean ± SD.	6.0 ± 7.14	0.33 ± 0.53		
Median	3.25	0.20		

U, p: U and p values for **Mann Whitney test** for comparing between the two groups
   *: Statistically significant at p ≤ 0.05

Regarding the main outcome of the study in the cases group. The relation between 28 days in-hospital mortality and the CRP/Prealbumin ratio showed that the mean value of CRP/Prealbumin ratio was 12.46 in non survivors while it was 1.45 in survivors (*P* value= <0.001) (Fig-2). There were no any significant differences between the 2 groups in need for mechanical ventilation during the study period (*p*= .059) (Fig-3). There were no any significant differences between the 2 groups in need for Renal replacement therapy during the study period (*p*= .816) (Fig-4).

Figure-2. The CRP/Prealbumin ratio in survivors and non-survivors of the cases group
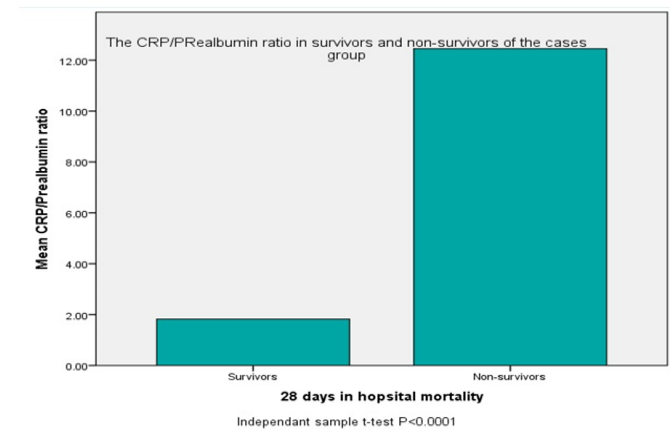
Figure-3. The relation between CRP/Prealbumin ratio and need for mechanical ventilation in the cases group.
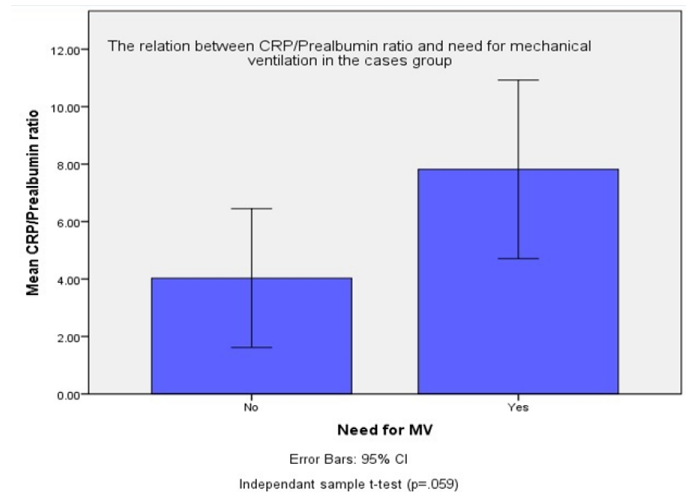
Figure-4. The relation between CRP/Prealbumin ratio and need for renal replacement therapy in the cases group.

The relation between CRP/Prealbumin ratio and need for RRT in the cases group

Error Bars: 95% CI

Independant sample t-test (p=0.816)
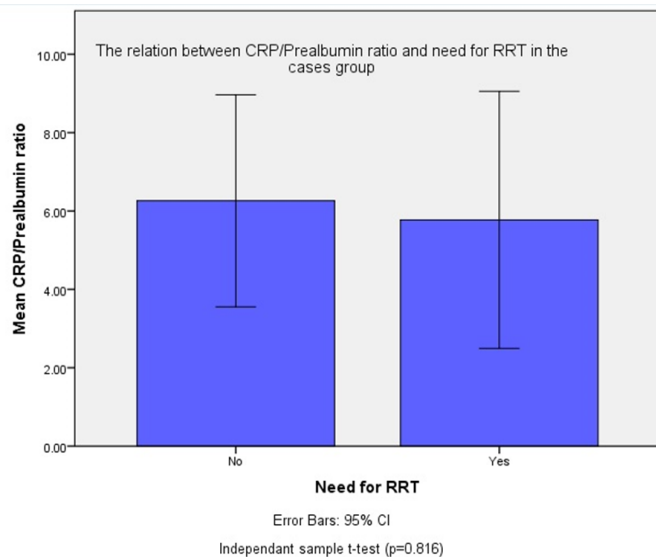
DISCUSSION

The main aim of this study was to assess whether serum inflammatory and nutritional markers expressed as CRP/Prealbumin ratio can predict mortality in a case control of patients with AKI. Our results suggested that when AKI was diagnosed, higher levels of CRP/prealbumin in patients with AKI indicated, at least partly, a poorer prognosis and more aggressive diagnostic and therapeutic interventions were needed to avoid complications.

Consistent with previous studies, malnutrition and inflammation was common in patients with AKI [7, 23]. In Fiaccadori's study in 1999, severe malnutrition, defined by Subjective Global Assessment (SGA) class C, was documented in about 40% of patients [7]. According to the International Society of Renal Nutrition and Metabolism (ISRNM), the serum albumin <3.8 g/dl was recommended as a main diagnostic indicator of malnutrition [17]. Not surprisingly, approximate 80% patients in this cohort presented with serum albumin values <3.8 g/dl. Prealbumin is a nutritional marker used to evaluate recent nutritional status with a short half-life and a rapid synthesis rate [24,25], and it is also a negative acute-phase protein and inverse associated with inflammation. According to the Nutritional Care Consensus Group, serum prealbumin >15 mg/dl indicates that patients are not at risk for malnutrition [25]. The mean of serum prealbumin value of our cases group was 22.58 with SD= 7.70 which reflects that 50% of patients might have serum prealbumin <15 mg/dl.

CRP is one of the wildly used biomarkers for monitoring the course of infection and inflammation [9,11]. Compared with healthy control, MHD and PD patients, CRP in these patients with AKI were significantly higher. Previous studies suggested that malnutrition and inflammation had a negative impact on the prognosis of AKI patients. The meta-analysis by Wiedermann et al. provided evidence that hypoalbuminemia is a significant

independent predictor of death following AKI development [13].

There are only a few studies examined the association between CRP or prealbumin and mortality of these subjects [8, 12, 21]. The PICARD study showed that there were no significant differences in CRP levels between acute renal failure (ARF) patients who died during hospitalization and survivals [8]. According to Valdivieso et al., serum prealbumin levels <11 mg/dl were strongly associated with a higher risk of death, independent of AKI severity, comorbidities and serum CRP [21].

Pinilla et al demonstrated a strong correlation between the ratio of CRP to prealbumin and the severity of organ dysfunction in critically ill patients [26]. However, the association of CRP/prealbumin and prognosis of AKI patients hasn't been reported. Our study suggested that CRP/prealbumin when AKI was diagnosed was independently associated with mortality of these patients after adjustment for the severity of illness. CRP/prealbumin levels >3 having a particularly higher mortality suggested that inflammation activity and malnutrition indicated a poor prognosis. These data provide evidence supporting the measurement of serum CRP/prealbumin levels may be an inexpensive and useful tool in the evaluation of the risk profiles of AKI patients.

In addition, 50% of the AKI patients suffered from sepsis in our study. However, septic AKI obviously did not play a role in AKI prognosis. This is different from many previous studies. The PICARD study showed that sepsis in AKI patients portended a poor prognosis, with higher mortality rates and relatively longer length of stay [27]. Different study population may contribute to the discrepancy that our patients were not confined to the ICU or critical ill patients. There were some limitations in this study. Firstly, this was an observational, single-center and relatively small size study, and our results only described the association between inflammatory or nutritional markers and 28 days' mortality. Secondly, the studied population was composed by heterogeneous AKI patients in a tertiary comprehensive hospital. Selection bias may have influence the result.

CONCLUSION

In conclusion, the present study firstly assesses the correlation between CRP/prealbumin levels and mortality in AKI patients. Higher serum CRP/prealbumin levels were strongly associated with higher mortality after adjusting for the severity of illness (SOFA). So it was a good marker of mortality in these patients. In addition, the measurement of CRP and prealbumin may be a valuable addition to SOFA scores to predict the risk of death in AKI patients.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

Trial Registration

IRB No: 00007555 FWA No: 00015712 The Ethics Committee of the faculty of medicine Alexandria University.

Ethics

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria University and the department of critical care, Informed consents for participating and publishing were taken from patients or the next of kin after approval by critical care department committee.

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