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Original Research Paper

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COMPARISON BETWEEN C-REACTIVE PROTEIN AND SERUM LACTATE IN EVALUATION OF SEPSIS INDUCED ACUTE KIDNEY INJURY AND SEPSIS WITHOUT ACUTE KIDNEY INJURY

Dr. Buchipudi Sandeep Kumar Reddy*	Post Graduate, Department of General Medicine *Corresponding Author
Dr. Mohamed Hanifah	HOD, Department of General Medicine.
Dr. Siva Sankar	Associate Professor, Department of Nephrology
Dr. S. Sumathi	HOD, Department of Biochemistry.

ABSTRACT **Background** One of the main causes of death in critically ill patients is sepsis. In Intensive care unit half of the patients develop Acute Kidney Injury, and has high mortality rates. In assessment of sepsis there are multiple markers in which C-reactive protein, serum lactate are commonly used. C-reactive protein is known biomarker of inflammation and involved in several immunological functions. **Aim** To correlate C-reactive protein and Serum lactate in evaluation of sepsis induced acute kidney injury and compare these parameters in sepsis without acute kidney injury. **Materials & Methods** This is a Cross-sectional study which will be done at Mahatma Gandhi Medical College and Research Institute, Pondicherry. This study comprises of 52 patients out of which Group 1 are 26 patients having sepsis with AKI and Group 2 are 26 patients are having sepsis without AKI. Complete case history including the socio-demographic data and other medical conditions of the patient was recorded and & the collected blood samples were recorded for CRP, Serum lactate as well as other parameters. **Results** Mean age of subjects in sepsis with AKI and sepsis without AKI are almost similar, with 55.8 % being females. 90% of sepsis with AKI group and 76% of sepsis without AKI group has CRP of >10 and 42% of sepsis with AKI group and 34% of sepsis without AKI group has Lactate of >2. **Conclusion** CRP and Serum lactate are markers of inflammation. CRP has been used to monitor the course of infection and inflammatory diseases. CRP has not only a biochemical marker of inflammation but also an active modulator of the inflammatory response.

KEYWORDS : Sepsis, Acute Kidney Injury, C-reactive Protein, Serum Lactate

INTRODUCTION :

The term "sepsis" comes from an ancient Greek word, which means "putrefaction".[1] In critically ill patients sepsis is still one of the most common causes of death.[2] It can often be challenging to tell an infection from sepsis. If the process remains localised, infection occurs without sepsis. Trauma and pancreatitis are two situations that frequently cause a sepsis-like condition without infection.[3] Sepsis symptoms like fever, leukocytosis, and tachycardia are neither sensitive nor specific indicators of infection or indicators of how effective a treatment is.[4]

According to the sepsis-3 guidelines, sepsis is the term used to describe the life threatening organ dysfunction caused by a dysregulated hosts response to infection. An increase in the SOFA score of >2 to infection indicates organ dysfunction.[5] In early course of sepsis, the most frequent type of organ dysfunction is Acute kidney injury(AKI). In Intensive care unit(ICU) nearly half of the patients develop Acute Kidney Injury, and a very high increase in mortality, upto 30-50%, is due to the presence of Acute Kidney Injury in these patients.[6]

AKI is defined as the impairment of kidney function like filtration and excretion over days to weeks which results in retention of nitrogenous and other waste products normally cleared by the kidneys. It is associated with increase in serum creatinine concentration with reduction in urine.[7]One of the most common causes of acute kidney injury is sepsis.[8] Acute kidney injury is part of multiple organ dysfunction syndrome where the in-hospital mortality is 50%.[8] In assessment of sepsis there are multiple markers in which C-reactive protein, cytokines, procalcitonin are commonly used. Under the influence of inflammatory mediators like Interleukin-6 and Interleukin-8, C-reactive protein an acute phase reactants which are anti-inflammatory and pro-inflammatory which are released from hepatic cells.[9]

C-reactive protein is known biomarker of inflammation and involved in several immunological functions. As various studies described C-reactive protein cut-off level for diagnosis of infection is 5-10 mg/dL. [10] In patients with septic shock, the level of serum lactate significantly rises. It has been shown that an useful early indicator of mortality in septic shock is serum lactate.[11] In present study, aim is to correlate C-reactive protein and Serum lactate in evaluation of sepsis with without acute kidney injury.

METHODOLOGY :

This is a Cross-sectional study which was done at tertiary care hospital. This study was conducted over a period of 18 months between january 2021 and June 2022.

After getting approval from Institutional Human Ethics Committee (IHEC No.MGMCRI/Res/01/2020/95/IHEC/339), informed consent was obtained from each participant.

Adult patients (≥18 years of age) with a diagnosis of sepsis at admission to medical ward and Intensive care unit(ICU) for Critical Care Management were included in the study Patients admitted with the criteria for sepsis, i.e.,

Two or more of the following conditions:

Fever(oral temperature> 38°C) or hypothermia(<36°C); Tachypnea (>24 breaths/min); Tachycardia (heart rate >90beats/min); Leukocytosis(>12,000/ L), Leucopenia (<4,000/ L) or >10% immature bands; plus proven or suspected microbial etiology.[5]

Patients with collagen vascular disease and rheumatic heart disease and Chronic kidney disease (CKD) patients were excluded from the study All the patients admitted to ICU fulfilling inclusion criteria after giving written informed consent were included in the study and examined clinically

and were evaluated with serum lactate and CRP levels in sepsis with AKI and sepsis without AKI at admission and these patients were followed up during the hospital stay.

The sample size has been calculated by a study conducted by Yin-Chou Hsu et al in 2018[12].

The total sample size calculated is 52 (Out of which Group 1 and Group 2 will consist of 26 subjects each).

All data was entered in data collection proforma sheet while maintaining privacy and confidentiality. All patients' identifiable numbers and information was stripped and replaced by anonymous number.

A detailed history, clinical examination and routine laboratory parameters were assessed as per the standard of care, then they were subjected for Serum Lactate and CRP at admission and these patients were followed up during the hospital stay for the development of AKI.

Once targeted sample size was achieved, their baseline parameters and inflammatory markers were correlated with development of AKI.

C-reactive protein in serum was measured by Immuno turbidimetry using clinical chemistry analyzers. Around 2ml of blood will be used for measuring CRP.

Lactate was measured in Arterial Blood Gas(ABG) analysis by Cartridge Based method.

RESULTS:

Age distribution **(Figure.1)***:* Age distribution in sepsis induced AKI and sepsis without AKI group. Mean age of sepsis induced AKI group was 56.88 ± 14.49 years. Majority of subjects were in group 46 to 65 years (26.92%). Mean age of sepsis without AKI group was 50.65 ± 18.80 years. Majority of subjects were in group 36 to 45 years (26.92%). P value of age is 0.187, which is not significant.

Gender distribution **(Figure.2)***:* Majority of the subjects were females (55.80%). Majority of the subjects were females (55.80%). In this study 55.8% were females and 44.2% were males. The percentage of sepsis induced AKI among female was 50.0% and among male was 50.0%. The percentage of sepsis without AKI among female was 61.5% and among male was 38.5%. There is no association of gender with sepsis induced AKI and sepsis without AKI groups(P=0.402).

Association of CRP with sepsis induced AKI and sepsis without AKI groups **(Figure.3)** *:* In this study 92.3% were having CRP of $\geq$ 10 and 7.7% were having CRP of $\leq$ 10 in sepsis induced AKI group and 76.9% were having CRP of $\geq$ 10 and 23.1% were having CRP of $\leq$ 10 in sepsis without AKI group. There is no association of CRP with sepsis induced AKI and sepsis without AKI groups(p=0.124).

Association of Serum Lactate with sepsis induced AKI and sepsis without AKI groups **(Figure.4)** : In this study 57.7% were having serum lactate of $\leq$ 2 and 42.3% were having serum lactate of $\geq$ 2 in sepsis induced AKI group and 65.4% were having serum lactate of $\leq$ 2 and 34.6% were having serum lactate of $\geq$ 2 in sepsis without AKI group. There is no association of serum lactate with sepsis induced AKI and sepsis without AKI groups(p=0.569).

Reporting Mann-Whitney U test **(Table.1)** *:* The mean value of creatinine is 3.22±1.71 in sepsis induced AKI and 0.99±0.26 in sepsis without AKI (p=0.001). The mean value of 2nd creatinine is 3.14±1.11 in sepsis induced AKI and 0.90±0.18 in sepsis without AKI (p=0.001). The mean value of urea is 104.88±62.77 in sepsis induced AKI and 29.69±14.54 in sepsis without AKI (p=0.001). The mean value of SOFA is 7.35±3.32 in sepsis induced AKI and 3.35±1.95 in sepsis without AKI (p=0.001). The mean value of CRP is 125.62±91.75 in sepsis induced AKI and 120.31±89.05 in sepsis without AKI (p=0.701). The mean value of serum lactate is 2.41±2.01 in sepsis induced AKI and 2.25±2.19 in sepsis without AKI (p=0.714).

Reporting t test ***(Table.2)****:* The mean value of sodium is 134.6±8.9 in sepsis induced AKI and 132.0±7.5 in sepsis without AKI (p=0.259). The mean value of potassium is 4.97±1.0 in sepsis induced AKI and 4.25±0.77 in sepsis without AKI (p=0.007). The mean value of chloride is 100.5±8.5 in sepsis induced AKI and 96.4±9.2 in sepsis without AKI (p=0.106).

Area Under the Curve(AUC) **(Figure.5)** *:*
The variables CRP, serum lactate, SOFA, PF ratio, platelets, urea, sodium, potassium, chloride, total counts, Hb were included in the ROC and found SOFA score, Urea and Potassium level had AUC above 50%. Hence, these three variables were included in the ROC curve and the obtained results were presented here.

Among the three variables, Urea had the highest AUC 0.93 followed by SOFA score 0.862 and potassium 0.696. All the three included in ROC were significant predictor. Hence, it may be concluded that urea level is the best predictor compared to SOFA score and potassium level.

DISCUSSION :

CRP is an inflammatory marker used to monitor inflammatory diseases and infection course. In recent years, CRP has been recognised as a active modulator of the inflammatory response and as inflammatory marker. In this study, we evaluated ***correlation of C-Reactive protein and serum lactate in evaluation of sepsis induced AKI and sepsis without AKI.*** We found that increased CRP concentrations were associated with sepsis and progression to Acute kidney injury.

AKI has a multifactorial etiology and is common in critical care environment. It must be identified early and to be treated aggressively. Aggravating factors causing AKI should be identified and modified as early as possible. Studies suggests that lighter degrees of AKI will contribute to CKD and cause significant mortality[13–15].

The incidence of AKI in ICU patients has been reported by various authors to ranging from 3% to 67%; This significant variability may be caused by differences in the definition of AKI applied, the sort of tertiary care facility that is available, and the underlying disease that causes AKI[14].

Sean M Bagshaw et al[16] in a prospective cohort study reported that when compared to non-septic AKI, septic AKI is associated with higher urine microscopy evidence of kidney injury. A urine microscopy score(UMS) of 3 predicts worsening AKI and was correlated with higher urine neutrophil gelatinase-associated lipocalin(uNGAL).

In the study higher urine microscopy was associated with sepsis induced AKI when compared to sepsis without AKI which is statistically not significant.

Bonig et al[17] reported that after transplantation of hematopoietic stem cells in children, CRP levels > 10 mg/dL were indicative of poor outcomes. In cardiovascular diseases, chronic inflammation plays important role and raised serum CRP levels even healthy individuals are involved with risk of increasing myocardial infarction and cardiac arrest Elevated

C-reactive protein values in patients who underwent hemodialysis were associated with atherogenic risks and cardiac deaths. In the pre-dialytic phase of renal failure, it has been reported that renal function and serum levels of C-reactive protein and interleukin 6 are directly correlated as reported by ***Zimmermann et al***[18]

In current study elevated C-reactive protein levels were associated with AKI at admission and had a prolonged hospital stay

Basu G et al[19], ***Cruz DN et al***[20], ***Bhadade R et al***[21] reported that patients with AKI were found to be older and male when compared to all ICU admissions.

In the study number of AKI cases were observed equally in both male(50%) and female(50%) patients.

Patients with sepsis had significantly higher CRP levels. The CRP levels in non-infected patients was lower than in infected patients in a study conducted by ***P. Póvoa et al***[10] between CRP and body temperature.

In another study conducted by ***pedro Póvoa et al***[1], retrospective comparisons were made between the routinely measured CRP with a preceding similar-length period involving 187 and 144 patients. Though it is not statistically significant, the regular measurement of CRP was associated with a trend of lower rates of morbidity and mortality.

In another study done by ***pedro Póvoa et al***[22], CRP concentrations were significantly lower in Negative and Uncertain groups than in the Certain and Definite ones. More than 50 mg/l of plasma CRP was highly indicative of sepsis and concluded that comparative to currently used markers like BT and WBC, daily CRP measurement is useful in the diagnosis of sepsis.

In the study also patients with sepsis had significantly higher CRP values. Regular CRP measurement could not be done due to financial constraints.

Positive culture and elevated CRP levels were shown to be associated in a more statistically significant than PCT levels as per study done by ***Mina Hur et al***[23]

In the study negative cultures in both the sepsis groups showed significant elevation in crp values which is statistically not significant When compared to the SOFA score, CRP can be a more useful tool for predicting recovery and outcome in sepsis patients as per an prospective observational study done by ***Meeval m Anush et al***[24]

In the study SOFA score had an association with sepsis induced AKI and sepsis without AKI which is statistically significant

In the study urea, creatinine and potassium had association with sepsis induced AKI and sepsis without AKI which is statistically significant.

CONCLUSION

CRP and Serum lactate are markers of inflammation. CRP has been used to monitor the course of infection and inflammatory diseases. CRP has not only a biochemical marker of inflammation but also an active modulator of the inflammatory response.

Table 2 : Reporting t-test

	Group	N	Mean±SD	t	df	P
Sodium	Sepsis induced AKI	26	134.6±8.9	1.141	50	0.259
	Sepsis without AKI	26	132.0±7.5			
Potassium	Sepsis induced AKI	26	4.97±1.0	2.795	50	0.007
	Sepsis without AKI	26	4.25±0.77			
Chloride	Sepsis induced AKI	26	100.5±8.5	1.646	50	0.106
	Sepsis without AKI	26	96.4±9.2			

Table 1 : Reporting Mann-Whitney U test

Variable	Group	N	Mean ±SD	Median	Mean rank	Sum of the ranks	Mann Whitney U	Z Value	P-value
Creatinine	Sepsis induced AKI	26	3.22±1.71	2.74	39.50	1027.00	0.00	-6.18	0.001
	Sepsis without AKI	26	0.99±0.26	0.93	13.50	351.00			
2nd Creatinine	Sepsis induced AKI	26	3.14±1.11	3.12	39.50	1027.00	0.00	-6.18	0.001
	Sepsis without AKI	26	0.90±0.18	0.89	13.50	351.00			
Urea	Sepsis induced AKI	26	104.88±62.77	82.50	37.69	980.00	47.00	-5.32	0.001
	Sepsis without AKI	26	29.69±14.54	25.50	15.31	398.00			
SOFA	Sepsis induced AKI	26	7.35±3.32	7.00	35.90	933.50	93.50	-4.50	0.001
	Sepsis without AKI	26	3.35±1.95	3.00	17.10	444.50			
CRP	Sepsis induced AKI	26	125.62±91.75	84.66	27.31	710.00	317.00	-0.38	0.701
	Sepsis without AKI	26	120.31±89.05	119.62	25.69	668.00			
Serum lactate	Sepsis induced AKI	26	2.41±2.01	1.60	27.27	709.00	318.00	-0.36	0.714
	Sepsis without AKI	26	2.25±2.19	1.30	25.73	669.00			

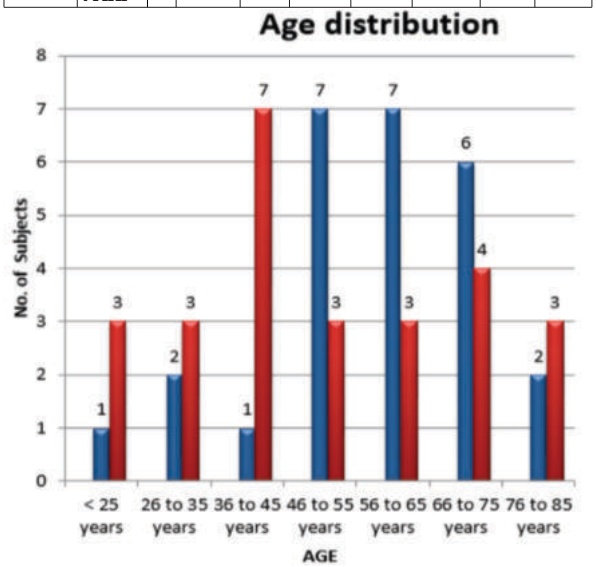

Figure 1: Column diagram showing Age distribution in sepsis induced AKI and sepsis without AKI groups

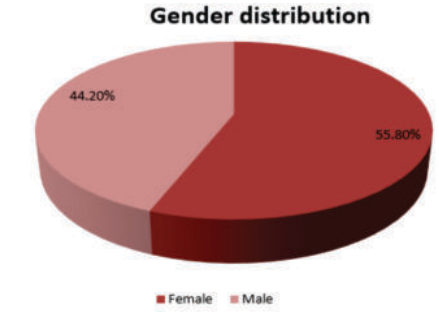

Figure 2: Pie diagram showing Gender distribution

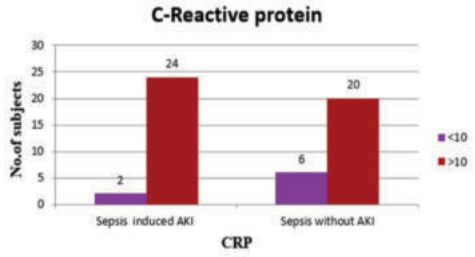

Figure 3 : Column diagram showing CRP in sepsis induced AKI and sepsis without AKI groups

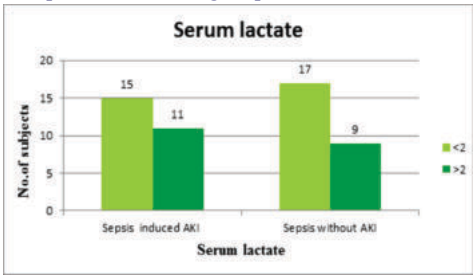

Figure 4 : Column diagram showing Serum lactate in sepsis induced AKI and sepsis without AKI groups

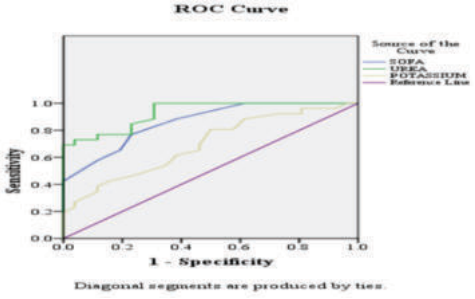

Figure 5 : Area under ROC curve

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