Journal of Medical and Scientific Research

JMSR
www.jmsronline.com

Kumar C et al. J Med Sci Res. 2024; 12(3):231-234
http://dx.doi.org/10.17727/JMSR.2024/12-43

ORIGINAL RESEARCH OPEN ACCESS

Correlation of C-reactive protein with clinical outcome in critically ill patients with sepsis

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Abstract

Introduction: Biomarkers like C-reactive protein (CRP) identify patients with sepsis and are helpful in predicting the severity of sepsis. The objective of the study was to correlate CRP with mortality in patients with sepsis admitted to intensive care unit.

Methods: The study was a prospective, observational study conducted in intensive care unit (ICU) of a tertiary teaching hospital over a period of two years. Critically ill patients with sepsis were included in the study. After ICU admission, patients were stabilized and samples for CRP, procalcitonin, serum lactate were analysed on the day of admission, day 2 and day 5.

Results: Out of 90 critically ill patients, 45 patients were survivors and 45 patients were non-survivors. The mean percentage drop in CRP in survivors was 14.7 % on day 2 ($p < 0.001$ on day 2) and 57.5 % on day 5 ($p < 0.001$ on day 5) and mean percentage rise in CRP in non survivors was 15.1% on day 2 ($p < 0.001$ on day 2) and 25.5% on day 5 ($p < 0.001$ on day 5). The mean percentage drop in SOFA score in survivors was 30% on day 2 ($p < 0.001$) and 74% on day 5 ($p < 0.001$).

Conclusion: Percentage change in CRP correlates with mortality, SOFA score, serum lactate values and duration of ICU stay in critically ill patients admitted with sepsis.

Keywords: C–reactive protein; ill patients; sepsis; SOFA score

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is commonly accompanied by organ dysfunction. An increase of two or more points in the Sequential Organ Failure Assessment (SOFA) score suggests development of organ dysfunction in patients with sepsis.

Technological developments in inflammatory cascade mechanisms have recently improved our understanding of sepsis. Biomarkers identify patients in sepsis and are helpful in predicting the presence and/or severity of sepsis. They are also useful in predicting mortality, especially in the initial phase of sepsis. Various biomarkers for diagnosis of sepsis are C-reactive protein (CRP), procalcitonin (PCT), D-dimer, interleukin 6 (IL-6), soluble urokinase plasminogen activator receptor (suPAR), pro-adrenomedullin, presepsin, lipopolysaccharide binding protein, soluble Triggering Receptor Expressed on Myeloid Cells (sTREM).

CRP is an acute phase reactant and is a sensitive marker synthesized in the liver in response to infection or inflammation. When there is an acute infection or inflammation, the concentration of CRP may be elevated within two hours of a triggering event. Serum CRP concentrations may rise in infections by upto 1000- fold and thus may be valuable as a biomarker of infection.

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Received 13 March 2024; *Revised* 19 April 2024; *Accepted* 26 April 2024; *Published* 17 May 2024

Citation: Kumar C, Talwar V, Kumar P, Chhabra PH. Correlation of C-reactive protein with clinical outcome in critically ill patients with sepsis. J Med Sci Res. 2024; 12(3):231-234. DOI: http://dx.doi.org/10.17727/JMSR.2024/12-43

CRP has been investigated as an attractive biomarker to diagnose sepsis because of its wide availability, good reproducibility, and low cost. A recent study showed that, if the CRP level is 0.5 times elevated from the baseline level by Day 2 (91% sensitivity, 59% specificity) prognosis is poor. Conversely, when CRP values are reduced by 0.31 or more on Day 2, when compared to the value on the previous day after starting antibiotics (Day 0), the prognosis was good (75% sensitivity, 85% specificity) [3].

The objective of the study was to correlate CRP with mortality in patients with sepsis admitted to intensive care unit and to correlate CRP with SOFA score, serum lactate and duration of ICU stay.

Methods

The study was a prospective observational study conducted in intensive care unit of Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital. Ethical approval for this study was taken from the institutional ethics committee. Critically ill patients who fulfilled the clinical criteria for diagnosis of sepsis were considered for the study. Patients with cancer / rheumatic diseases and those who died within 48 hours of admission to ICU were excluded from the study. The study was conducted between December 2020 and April 2022 and a total of 90 patients were enrolled. Informed consent was obtained from all the patients for participation in the study.

Patients were resuscitated and stabilized after ICU admission and a detailed history was taken from their relatives. Diagnosis and co-morbidities were noted. On the day of admission (day 0), blood sample was taken for routine investigations (as per protocol and patient's requirements), e.g., CRP, procalcitonin, total leukocyte count, differential leukocyte count, serum lactate, serum creatinine, serum bilirubin, serum albumin. Culture was taken from trachea, blood, urine and any other relevant sites and the sample was sent for culture and sensitivity. Routine monitoring of vitals, consciousness status, Sequential Organ failure assessment (SOFA) score was done. Further monitoring of CRP levels and other clinical, biochemical and hematological parameters were done on day 2 & day 5. Duration of ICU stay, Duration of Mechanical Ventilation and outcome (transfer or mortality) were noted. Obtained values of CRP were correlated with mortality, ICU length of stay, SOFA score and serum lactate.

All the data was entered and analysed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 21.0 for windows. Quantitative variables were compared using Unpaired t-test / Mann-Whitney test (when the data sets were not normally distributed). Qualitative variables were compared using Chi-Square test/Fischer's exact test. Receiver operating characteristic curve were used to find out cut off point of CRP for predicting mortality. DeLong test were used to compare Area under the Curve (AUC) of CRP with other parameters. A p value of <0.05 were considered statistically significant.

Results

Ninety critically ill adult patients (age 18 years and above) who fulfilled the clinical criteria for diagnosis of sepsis and were admitted to the ICU are included in the study. In our study 54.4% of the patients were male and 45.6% of the patients were female. Out of 90 patients, 45 patients were shifted to the ward and 45 patients died. The mean percentage drop in CRP in survivors was 14.7 % on day 2 and 57.5 % on day 5. However, the mean percentage rise in CRP in non survivors was 151% on day 2 and 255% on day 5. The differences in the mean percentage change between survivors and non survivors groups were found to be statistically significant ($p < 0.001$ on day 2 and $p < 0.001$ on day 5) as shown in Table 1.

Table 1: Percentage change in CRP over time.

Time point comparison	*Survivors*		*Non-survivors*		*p value (Intergroup)*
	Mean (SD) of percentage change	*p value (Intragroup)*	*Mean (SD) of percentage change*	*p value (Intragroup)*	
Day 2 - Day 0	-14.7% (81.9)	0.010*	151.2% (164.4)	0.001*	<0.001*
Day 5 - Day 0	-57.5% (39.3)	<0.001*	255.6% (266.5)	<0.001*	<0.001*

Abbreviations: *: Significant.

We found that the two groups differed significantly in terms of percentage change in SOFA score on day 2 and day 5. The mean percentage drop in SOFA score in survivors was 30% on day 2 ($p < 0.001$) and 74% on day 5 ($p < 0.001$). Also, the mean percentage increase in SOFA score in non survivors was 29% on day 2 ($p < 0.004$) and 52% on day 5 ($p < 0.001$) as shown in Table 2. A strong positive correlation was observed between percentage change in CRP and SOFA score on day 2 ($p < 0.001$) and day 5 ($p < 0.001$) as shown in Table 3.

Table 2: Percentage change in SOFA score over time.

Time point comparison	*Survivors*		*Non-survivors*		*p value (Intergroup)*
	Mean (SD) of percentage change	*p value (Intragroup)*	*Mean (SD) of percentage change*	*p value (Intragroup)*	
Day 2 - Day 0	-30.1% (18.3)	<0.001*	29.3% (28.8)	0.004*	<0.001*
Day 5 - Day 0	-74.1% (24.5)	<0.001*	52.1% (49.3)	<0.001*	<0.001*

Abbreviations: *: Significant.

Table 3: Correlation between percentage change in CRP and percentage change in SOFA score.

Correlation	*Spearman correlation coefficient*	*p value*
Percentage change in CRP (mg/dL) (Day 2) vs Percentage change in serum lactate (mmol/L) (Day 2)	0.4	<0.001*
Percentage change in CRP (mg/dL) (Day 5) vs Percentage change in serum lactate (mmol/L) (Day 5)	0.5	<0.001*

The mean percentage fall in serum lactate in survivors was 20% at day 2 and 44% at day 5, but mean percentage increase in serum lactate in non survivors was 19% at day 2 and 34% at day 5. Both the changes were statistically significant as shown in Table 4. A moderate positive correlation between percentage change in CRP and serum lactate was observed at day 2 and day 5, which was statistically significant (Table 5).

The mean (SD) duration of ICU stay in the survivors group was 9.82 (3.40) days and non survivors group was 6.91 (4.73) days. There was a significant difference between the 2 groups ($p < 0.001$). We did not find a statistically significant correlation between percentage change in CRP and duration of ICU stay at day 2, but at day 5 there was a moderate positive correlation between the two variables which was statistically significant as shown in Table 6.

Table 4: Percentage change in serum lactate over time.

Time point comparison	*Survivors*		*Non-survivors*		*p value (Intergroup)*
	Mean (SD) of percentage change	*p value (Intragroup)*	*Mean (SD) of percentage change*	*p value (Intragroup)*	
Day 2 - Day 0	-20.1% (63.7)	<0.001*	19.6% (45.5)	0.125	<0.001*
Day 5 - Day 0	-44.7% (39.1)	<0.001*	34.0% (46.6)	<0.001*	<0.001*

Abbreviations: *: Significant.

Table 5: Correlation between percentage change in CRP and percentage change in serum lactate.

Correlation	*Spearman correlation coefficient*	*p value*
Percentage change in CRP (mg/dL) (Day 2) Vs Percentage change in serum lactate (mmol/L) (Day 2)	0.4	<0.001*
Percentage change in CRP (mg/dL) (Day 5) Vs Percentage change in serum lactate (mmol/L) (Day 5)	0.5	<0.001*

Table 6: Correlation between percentage change in CRP and duration of ICU stay.

Correlation	*Spearman correlation coefficient*	*p value*
Percentage change in CRP (mg/dL) (Day 2) Vs Duration of ICU stay (Days)	-0.4	0.096
Percentage change in CRP (mg/dL) (Day 5) Vs Duration of ICU stay (Days)	0.3	0.017*

Discussion

We performed this study to evaluate the role of CRP in determining the clinical outcome in patients who fulfilled the clinical criteria for diagnosis of sepsis i.e., defined as a proven or suspected infection and an increase of 2 points or more in the SOFA score and were admitted to ICU.

Serum CRP levels significantly correlate with mortality in critically ill patients admitted to the ICU with sepsis. The percentage change in values is more important than absolute values. The differences in the mean percentage change in CRP between survivors and non survivors groups were found to be statistically significant. Similar results were obtained in studies conducted by Meeval

M et al. [4] who found that the percentage drop of the mean CRP from day 0 to day 2 was 23.33% in the living group, and there was an increase of 4.73 % in the expired group. Lobo Francisco R.M et al. [5] conducted a prospective cohort study in critically ill patients. They found that CRP concentrations correlated with mortality and with the presence and number of organ failures. Serum CRP levels of more than 10 mg/dl on ICU admission were associated with significantly higher mortality and increased incidence of respiratory, renal and coagulation failure than CRP level less than 1 mg/dl. In patients with CRP concentration more than 10 mg/dl on ICU admission, a decrease in CRP level after 48 hours was associated with a mortality rate of 15.4% while an increased CRP level was associated with a mortality rate of 60.9% ($p < 0.05$).

There was also a significant correlation of CRP with SOFA score and serum lactate on both day 2 and day 5. Results similar to our study were obtained in the study conducted by Özkan Devran et al. [6] in a 20-bed respiratory ICU in a chest disease center. The area under the curve (AUC) for CRP values and SOFA scores on admission and on the 3rd day in ICU were calculated as 0.57; 0.72; 0.72 and 0.76 respectively. CRP value > 100 mg/L, higher SOFA scores on 3 rd day and sepsis due to nosocomial infection were found to be risk factors for mortality. $p < 0.013$, and $p < 0.0001$, respectively. Imran Siddiqui et al. [7] found that non survivors had a significantly higher lactic acid (4.7 mmol/L [2.07–7.6]; $P < 0.05$) than survivors (2 mmol/L [1.3–3]; $p < 0.05$) and they concluded that in comparison to procalcitonin (PCT) and CRP, high plasma lactic acid levels are associated with the development of all-cause multiple organ dysfunction syndromes (MODS) and worse outcome in critically ill children admitted in pediatric intensive care unit (PICU).

Conclusion

CRP can be an important tool in determining the clinical outcome in critically ill patients. Percentage change in CRP significantly correlates with mortality in critically ill patients admitted with sepsis. Moreover, it significantly correlates with SOFA score and serum lactate values. A significant moderate positive correlation was also found between percentage change in CRP and duration of ICU stay.

Conflicts of interest

Authors declare no conflicts of interest.

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