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Monitoring of CRP Levels at Critically Ill Patients as a Predictor of ICU Outcome; A 2-Months Prospective Cohort Study

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Abstract

The aim of this study was to evaluate the relationship between serum C-reactive protein (CRP) levels and the mortality rate of patients who were admitted to the intensive care unit (ICU), starting from the time of discharge until two months later. In this study, 125 patients admitted to the ICU were studied. The patients' demographic data and physical examination, particularly the exact level of CRP obtained through questionnaires. All discharged patients were followed for 60 days. All data were analyzed with SPSS. The mean CRP was higher in ICU patients who died until two months after discharge ($p<0.05$). The results showed that the second CRP level was significantly higher in expired patients compared to alive subjects ($p=0.012$). The total of 25 patients and 37 patients with increasing and decreasing patterns in the three CRP measurements had a mortality rate of 56% and 29.7%, respectively. A variable pattern in the CRP levels was reported in 58 patients, 15 of whom exhibited an increasing pattern with a mortality rate of 60%., and the remaining 43 patients with a decreasing pattern showed a 51.1% increase in mortality rate. Additionally, the level of CRP and the mortality rate of patients admitted to the ICU were significantly correlated with gender ($p=0.002$). There is a direct link between mortality and serum CRP level, indicating that a higher level of CRP

is associated with an increased mortality rate. CRP level measurement could be considered an effective strategy for identifying patients with a greater risk of death.

1. Introduction

Patients with critical illness account for 10 to 25 percent of the costs associated with hospitalization in the world [1]. Roughly one-third of the mortalities reported for patients with critical illness in hospital occur after being discharged from the intensive care unit (ICU) [2]. Hence, discharging patients from the ICU or transferring patients to other wards or hospitals is a decision that cannot be taken naively [3]. However, long-term hospitalization in the ICU is not sensible due to the increasing prevalence of nosocomial infections. On the other hand, early discharge from the ICU may result in an increased predisposition to death [4]. Hence, the ability to identify patients with a poor prognosis in terms of survival could be of great help in the development of effective strategies for safer discharge of these patients [5]. Hence, adequate patient evaluation prior to discharge from the ICU is an essential step toward screening individuals at higher risk for post-discharge adverse outcomes [6-8].

Post-ICU mortalities occur primarily due to either incomplete resolution of the illness, or the development of new complications [9-11]. According to a recent hypothesis, latent inflammation and sepsis as a result of the unresolved disease may significantly contribute to the mortality rate following the seemingly successful discharge of patients from the ICU [9]. Accordingly, systemic activation of pro-inflammatory cascades appears to be an integral component of bodily response to disease or trauma [12, 13]. A number of inflammatory mediators, as potential biomarkers, are believed to play a role in the inflammatory response and organ failure. Serum levels of C-reactive protein (CRP), an acute phase reactant protein that is released from the liver a few hours after the onset of an inflammatory condition associated with the upregulation of various inflammatory cytokines [14-17], including tumor necrosis factor-alpha (TNF-α) [18], interleukin-6 (IL-6) and interleukin-1-β (IL-1β) [12]. Produced by several types of cells, these pro-inflammatory cytokines are particularly secreted by monocytes and macrophages. Accordingly, CRP is a commonly applied biomarker for monitoring immune response to ongoing inflammatory conditions [14, 19].

According to recent findings, serum CRP levels are correlated with the degree of inflammation during the early stages of the disease [20]. A number of studies have reported that CRP could be considered as a diagnostic tool for ruling out sepsis, as well as evaluating the effectiveness of treatment in ICU-admitted patients. Measurement of serum CRP levels can also be helpful in making decisions regarding the discharge of patients from the ICU [5]. Several investigations have demonstrated that CRP levels increase in patients with sepsis. However, no particular association between the level of CRP and organ dysfunction or failure has ever been reported [9, 21-25]. As for the patients residing in the ICU, persistently high levels of CRP are thought to be correlated with frequent readmission [21] and an overall poor prognosis [9, 22]. Based on the results recently reported by two investigations, subsequent hospital-associated mortality is suspected to be positively correlated with serum levels of CRP [9, 26].

In this respect, assessment of the potential risk for developing adverse sequelae may provide a more solid ground for determining the time of discharge from the ICU or the necessity for the conduction of invasive diagnostic techniques. Hence, in the present study, we sought to evaluate the predictive value of serum CRP

regarding patient mortality the following discharge from the ICU. In this study, we explored the relationship between CRP level and mortality of ICU patients during a 60-day period, starting from the day of discharge.

2. Materials and Methods

2.1 *Study population*

This project is a kind of prospective, case-control, single-center, and observational study conducted from March 2015 to March 2016. All patients admitted for medical problems to the ICU of Ali IbneAbitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran, and discharged in living status were followed up for two months and studied in two separate groups; Group A: recovered patients, Group B: dead subjects.

2.2 *Inclusion criteria*

Our inclusion criteria for participants included; 1) discharge from the ICU in living status, 2) a minimum age of 15 years old, 3) the presence of underlying conditions resulting in admission to the ICU in the first place, 4) the ability and cooperation of the patient to be followed up for two months after being discharged from the ICU, and 5) a record of at least three CRP check-ups while residing at the ICU. Patients who did not meet any of these conditions were excluded from the study.

2.3 *Data collection*

The following data were collected: age, gender, past medical history, cause of admission to the ICU and the duration of residence, history of cardiopulmonary resuscitation (CPR), the general status of the patients within 60 days from discharge, and the serum level of electrolytes. Collected prospectively, all data were subsequently retrieved from the ICU administrative database.

2.4 *CRP analysis*

In the present study, serum CRP levels were measured via biochemical assays three times, including the first, third, and fifth days of hospitalization or during the course of admission, and the patients were followed up for two months after being discharged. Finally, the mean level of CRP and pattern of CRP change during admission were compared between the two groups.

2.5 *Statistical analysis*

Data are presented as mean±SD, unless mentioned otherwise. The normality of data distribution was evaluated with Kolmogorov-Smirnov and *Shapiro–Wilk test* tests. Differences between the mean values for each group were associated with an independent t-test. For variables without normal distribution, the Mann-Whitney *U* test was adopted. Data analysis was performed via SPSS software version 24. Pearson correlation coefficient and logistic regression were used to investigate the relationship between the mean of different levels of CRP and the condition of patients two months after discharge and between CRP level with age, sex, and underlying diseases. A p-value less than that 0.05 was considered statistically significant.

3. Results and Discussion

3.1 *Demographic properties*

Out of 125 patients, 67 (53.6%) were male, and 58 (46.4%) were female, with 112 (89.6%) and 13 (10.4%) having a positive history of hospitalization.

3.2 *CRP analysis*

3.2.1 *CRP level alterations*

Statistical analysis showed that the mean CRP was higher in ICU patients who had died until two months after discharge ($p<0.05$). According to Figure1 and Table 1, the highest average level of CRP in the group A patients (living) and group B patients (expired) were recorded in the second CRP measurement (76.78±4.28 and 88.85±4.51 respectively). The Man-Whitney test showed that the second CRP level was significantly higher in expired patients compared to alive subjects ($p=0.012$).

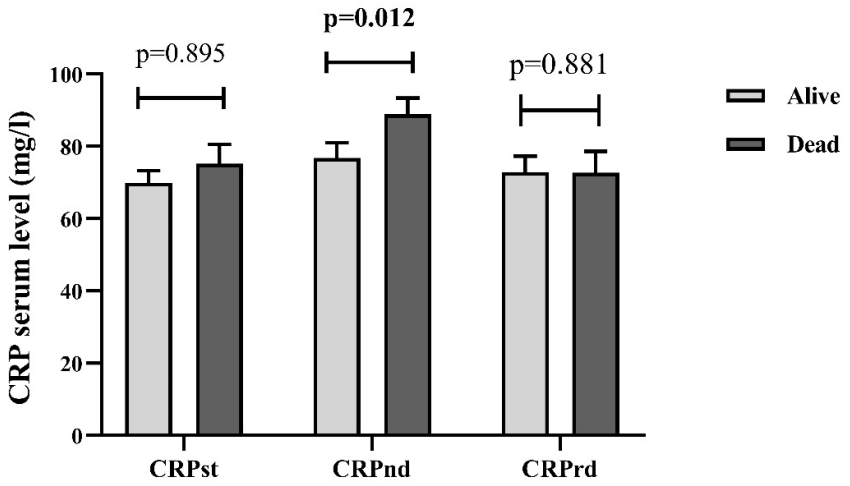

Figure 1. The average level of CRP in group A patients and group B patients. The second CRP measurement in group B was significantly higher than group A ($p<0.05$)

Table 1. CRP analysis in ICU patients who were discharged alive from the ICU and followed up to two months

Group	CRP	Number	Mean	SD
A	1st	76	69.85	3.45
	2nd	76	76.78	4.28
	3rd	76	72.88	4.42
B	1st	49	75.22	5.31
	2nd	49	88.87	4.51
	3rd	49	72.69	5.93

3.2.2 *Correlations*

Pearson correlation coefficient analysis represents the relationship between the mean of different levels of CRP and the condition of patients two months after being discharged (Table 2). The results show that there is a significant positive relationship between CRP levels and the patients' status following discharge from the ICU. In other words, a higher CRP level resulted in a higher mortality rate ($p=0.000$, $r= +0.33$), and a lower CRP indicated a higher likelihood for survival ($p=0.005$, $r= +0.43$).

Table 2. Correlation between CRP level and patient status after ICU discharge

Status	CRP						r	P-value
	1st		2nd		3rd			
	70<	70>	70<	70>	70<	70>		
Alive patients (no, percent)	25 37.31%	31 53.44%	53 67.08%	30 65.22%	21 45.77%	48 73.70%	0.43	0.005
Death subjects (no, percent)	67 62.68%	27 46.55%	26 32.91%	16 34.78%	51 54.23%	18 27.27%	0.33	0.000

Investigation on the potential correlation between CRP level with age, sex and underlying diseases revealed that, based on the 5% confidence level, the significance level of age, sex and underlying diseases was p=0.271, p=0.002 and p=0.947, respectively. Accordingly, it was concluded that the mortality rate of ICU patients during a 60-day period after being discharged from the ICU only had a significant relationship with gender (p=0.002) (Table 3).

Table 3. The correlation between CRP level with age, sex and underlying diseases

CRP level correlation two months after discharge	Number	Mean	SD	P-value
Age	125	64.73	16.08	0.271
Sex	125	1.46	0.50	0.002
Underlying diseases	125	1.88	0.32	0.947

Abbreviations; CRP: c-reactive protein, SD: standard deviation

In Table 4, all variables are reported in the logistic regression analytical model via the control of the interactions affecting them. According to the odds ratio (OR) value for the gender variable (β =1.057), the probability of mortality of women with a high CRP level was 3.48% higher than men, indicating the insignificance of these two variables, i.e., age and underlying disease, in relation with serum CRP.

Table 4. The logistic regression analytical model for the probability of mortality correlation with sex, age and underlying disease for two months after discharge

Variable	B	P-value	OR	CI (95%)	
				upper line	Lower line
Age	0.125	0.271	0.883	0.427	0.090
Sex	1.057	0.002	0.348	0.427	0.091
Underlying disease	0.191	0.947	0.826	0.183	0.052

CI: confidence interval, OR: odds ratio

3.2.3 *CRP level alterations; increasing and decreasing variables*

Figure 2 represents the CRP level alterations in group A and group B. According to results, CRP showed an increasing pattern and then decreasing pattern in each group. 2nd CRP was the higher amount in each group.

Furthermore, we compared changes in the CRP levels in three patterns, namely, increasing, decreasing and variable (decreasing and increasing), in relation to the survival or death of patients within 60 days after being discharged from the ICU. The findings suggested that a total of 25 patients who had exhibited an increasing pattern in the three CRP measurements had a mortality rate of 56%. Thirty-seven patients with a decreasing pattern in CRP level were found to have a 70.3% survival rate. A variable pattern in the level of CRP was reported in 58 patients, 15 of whom exhibited an increasing pattern with a mortality rate of 60%. The remaining 43 patients showed a decreasing pattern, with a 51.1% increase in mortality rate (Table 5).

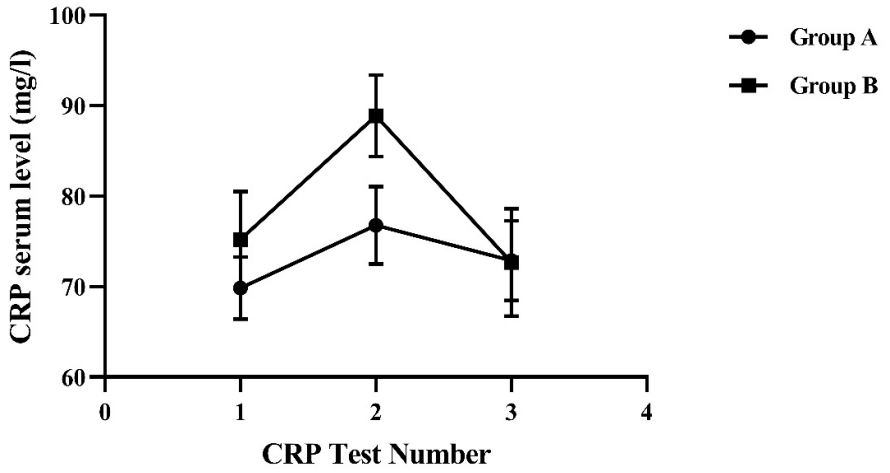

Figure 2. CRP levels according to the increasing and decreasing trends in group A and group B. CRP showed an increasing pattern and then decreasing pattern in each group. 2nd CRP was the higher amount in each group

Table 5. CRP levels according to the three trends of increasing, decreasing and variable (decreasing and increasing)

Factor/Variable	Number	Alive	Dead	CRP (mean±SD)		
		(number, percent)	(number, percent)	1st	2nd	3rd
Increasing F.	25	11	14	63.76	88.36	115.74
		44%	56%	(25.89)	(30.65)	(42.36)
Decreasing F.	37	26	11	92.32	71.02	55.24
		70.3%	29.7%	(35.21)	(28.61)	(27.45)
Increasing V.	15	6	9	72.46	45	76
		40%	60%	(29.25)	(29.67)	(34.26)
Decreasing V.	43	21	22	58.14	97.51	64.30
		48.9%	51.1%	(28.64)	(37.56)	(31.68)

Abbreviations; CRP: C-reactive protein, SD: standard deviation, F: factor, V: variable

The process of discharging patients from the ICU is a difficult task. On the one hand, staying in the ICU for a long time is associated with potential risks [6]. Nonetheless, early discharge may also be related to irreparable risks [15]. Therefore, proper evaluation of patients is required before discharge from the ICU. For this purpose, several studies have been performed to predict patient mortality and readmission in the hospital after being discharged from the ICU.

In this prospective observational study conducted on 125 patients discharged from the ICU in living status, we evaluated the potential correlation between serum levels of CRP upon being discharged from ICU, and post-ICU mortality within the next two months. The mean CRP was higher in ICU patients who had died until two months after discharge. The second CRP level was significantly higher in expired patients in comparison with alive subjects. In addition, a significantly positive relationship was observed between CRP levels and death within two months after being discharged. Following discharge from the ICU, a significant positive relationship was observed between CRP levels and the patients' status. In other words, a higher CRP level resulted in a higher mortality rate, and a lower CRP indicated a higher likelihood of survival.

Our results were consistent with the findings of previous studies. In 2003, Lobo et al. followed up 313 patients admitted to the ICU patients during a 4-month period. They noted that patients with higher CRP levels at the time of admission more frequently and severely experienced organ dysfunction, and showed a higher mortality rate than those patients with normal serum levels of CRP upon admission to the ICU ($p<0.05$). A decrease in the CRP level of patients with an initial concentration >10 mg/dL, within 48 hours after being admitted was correlated with a mortality rate of 15.4 percent. On the contrary, elevated serum CRP was shown to be associated with an overwhelming mortality rate of 60.9% ($p<0.05$) [22]. Three years later, a prospective observational 14 months long cohort study, led by Povoa, on 181 patients suspected to have ICU-acquired infections indicated that CRP time course was positively associated with a significant increase in the likelihood of being infected ($p<0.001$), with an area under the curve (AUC) of 0.86. With a sensitivity and specificity of 92.1 and 71.4 percent, respectively, a maximal daily increase >4.1 mg/dl in the level of the CRP was deemed to have a significant predictive value for infection. An elevation >8.7 mg/dl was indicated to improve the specificity of the CRP test up to 82.1 percent [27]. A prospective cohort investigation in 2008 reported 26 cases of in-hospital mortality (4.3%) in a population of 603 patients consecutively discharged from the ICU (CRP of non-survivors = 174 vs. survivors=85.6mg/l, $p=0.001$). With an AUC of 0.85, CRP levels were significantly correlated with post-ICU-discharge mortality (10-mg/l) [9]. Three years later, in 2011, a study on 891 patients by Póvoa et al. [28] failed to identify any meaningful differences between the CRP level of survivors and non-survivors until the second day of antibiotic therapy. During the next three days, however, the CRP levels of survivors were measured to be significantly lower ($p<0.001$), suggesting a potential correlation with mortality ($p<0.001$). In the same year, Wang et al. [29] explored 576 patients, who had not been selected based on specific criteria, and reported that CRP might predict ICU-associated mortality ($p<0.01$). Later that year, Genderen et al. [12] followed up with 63 patients who had undergone elective esophagectomy followed by admission to the ICU. Their findings indicated that CRP levels at T24 and T48 were remarkably higher in the patients who had developed postoperative complications, implying a negative association with a 1-year survival rate. In 2012, Ranzani et al. [30] investigated the CRP ratio level in 409 patients 24 hours before they were discharged from the ICU. Subjects with a less than 25% decrease in the level of CRP 24 hours prior to being discharged, as compared with the level of CRP 48 hours before discharge from the ICU had a worse prognosis, greater mortality ($p=0.002$), and post-ICU length of stay ($p=0.036$). The same year, Devran et al. [31] evaluated 314 ICU patients with severe sepsis in an observational cohort study. The AUC for the CRP level on the day of admission to the ICU, and on the third day, following admission, was measured to be 0.57 and 0.72, respectively. A CRP level>100 mg/L, along with a higher SOFA score on the third day, were recognized as risk factors for increased mortality. Hatami and Javad Mousavi [32] in 2015 investigated the correlation between the serum levels of CRP with mortality rates of 150 patients admitted to the ICU, through a retrospective study. They found that CRP level significantly correlated directly with patients' mortality rate ($p<0.001$). In 2016, Gülcher et al. reported that the post-ICU mortality rate in 998 patients, who had been classified into high CRP (≥75 mg/L) and low CRP (<75 mg/L) groups was 6.9 % and 4.7 %, respectively ($p=0.127$). The high CRP group also exhibited higher combined readmission and mortality rates compared to the low CRP group ($p=0.001$) [24]. In 2017, Li et al. [33] prospectively compared the hospital mortality and the total length of stay in hospital (TLSH) in patients with a CRP-to-prealbumin (CRP/PAB) ratio ≤0.24, only to find that these values were significantly increased in patients with CRP/PAB>0.24 ($p<0.05$). Cui et al. [34], in 2019, investigated 59 patients with sepsis/septic shock (divided into survivor and non-survivor groups) to determine the prognostic value of serum CRP. The CRP level

was measured to be higher on the second, third, and fifth days in the non-survivor group, compared with that of the survivor group. Furthermore, a higher serum CRP level was recorded in patients with septic shock in relation to the subjects who had only sepsis. However, there were some controversial reports. Following a 14 months long investigation on 156 patients discharged alive from the ICU, Silvestre et al. [5], in 2010, found that there were no significant differences in the levels of CRP between the survivor and non-survivor groups at the time of being discharged from the ICU. Their results indicated an AUC of 0.64, implying that CRP level at the time of discharge from the ICU might not be a valuable marker for determining post-ICU prognosis.

In our study, there was a significant gender-exclusive relationship between CRP level and mortality of patients admitted to the ICU from the time of discharge until two months later ($p=0.002$). According to the OR value, for the gender variable ($\beta=1.057$), the probability of mortality of women with high CRP levels was 3.48% higher than that of men, and the results were not significant for the two variables of age and underlying disease. Our results were partially consistent with the previous studies. Gülcher et al [24] demonstrated through multivariate logistic regression analysis that age (0.018) and female sex (0.035) were significantly associated with adverse outcomes. Park et al. performed multivariate analyses to predict 28-day mortality after ICU admission, and reported underlying diseases like cancer as significant risk factors ($p=0.012$, $p=0.071$). Ho et al., Povoa et al., Ranzani et al., and Wang et al. reported significant correlation between age and mortality rate ($p=0.001$, $p<0.001$, $p<0.001$ and $p=0.001$, respectively) [9, 28]. Devran et al., Hatami et al., Povoa et al., Li et al., and Silvestre et al. did not find any significant correlation between age and sex with mortality rate [5, 27, 31-33]. In 2020, Yoldas H et al. reported both the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), as well as CRP, could be applied to predict mortality in critically ill patients [35]. In 2021, Lavillegrand JR et al. [36], in SARS-CoV-2+ patients admitted to ICU, reported a considerable positive correlation between systemic pro-inflammatory signature with clinical worsening and 60-day mortality.

4. Conclusion

The results of this study show that the mean CRP was higher in patients who had died until two months after discharge from ICU. In other words, group B patients had a higher second CRP level compared to alive subjects. In terms of the correlation between CRP levels and patient mortality, there is a direct relationship indicating that with a decreasing CRP level, the probability of patient death is lower, and vice versa, with an increasing CRP level, the probability of patient death will also increase. The lower the CRP, the more likely they are to be transferred to the ward. The present study was restricted by a number of limitations. Firstly, this was a single-center analysis, implying that the findings of these investigations may not be extrapolated to other ICUs. Secondly, a cause-and-effect relationship between adverse outcomes and pro-inflammatory cytokines cannot be established due to the design of the present study. In this regard, one might speculate that the routine measurements of CRP level at our ICU could have somehow influenced our decision-making regarding the time of discharge from the ICU. Nonetheless, as noted by our study, the presence of a multitude of risk factors can be of great value in raising the awareness of clinicians toward post-ICU morbidity and mortality. However, the potential beneficial effects of certain interventions, e.g., postponement of ICU discharge or additional diagnostic tests and therapeutic procedures on the final outcome, remain to be elucidated in future investigations.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Ethics

This study was approved by Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran. All subjects had signed informed consent (Ethic code: IR.ZAUMS.REC.1396.101).

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