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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2023;12(2):383-8

The effect of C-reactive protein, Procalcitonin and Neutrophil/lymphocyte ratio on mortality in patients hospitalized in the intensive care unit

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Received 13 November 2022; Accepted 13 February 2023
Available online 22.03.2023 with doi: 10.5455/medscience.2022.07.169

Abstract

Effectiveness of using inflammatory markers for prognosis assessment in the intensive care units (ICU) is still not clear. The current study aimed to examines the relationship among procalcitonin, C-reactive protein, and neutrophil/lymphocyte ratio of patients who are getting treatment in the ICU during hospitalization and mortality. The study was carried out with a total of 788 patients who were hospitalized in the ICU longer than a day. All participants were over the age of 18 years old. C-reactive protein, procalcitonin, and neutrophil/lymphocyte ratios were compared between the groups of those who died and those who were discharged from the ICU.54.6% (n= 430) of 788 patients who were admitted to the study, were male whereas45.4% (n= 358) of them were female. The median age of the study group was calculated as 79 years (IQR = 19 years) (P<0,001). The univariate Cox regression analysis performed to examine the parameters affecting mortality, the analysissuggested following P-values for the procalcitonin, C-reactive protein, and neutrophil/lymphocyte ratio; <0.001, 0.887, and 0.014 respectively. Conversely, the multivariate Cox regression analysis which is performed to examine the parameters affecting mortalityyielded following P-valuesfor the same variables respectively: 0.242, 0.116, and 0.523. Although inflammatory markers (i.e.,C-reactive protein, procalcitonin, and neutrophil/lymphocyte ratios) were high in patients who died, their relationship with mortality in the ICU could not be shown.

Keywords: SOFA score, APACHE II score, procalcitonin, neutrophil/lymphocyte ratio, intensive care unit

Introduction

Various factors such as age, underlying cause, mechanical ventilation duration, and severity of the disease may affect the mortality rate in the intensive care units (ICU). Different scoring systems are used to evaluate the severity, mortality and morbidity of the disease in ICUs [1].Two best known and the most used scoring systems among all are the the followings: The Acute Physiology and Chronic Health Assessment II (APACHE) and The Sequential Organ Failure Assessment (SOFA) [2].

C-reactive protein(CRP) and procalcitonin(PCT) are biomarkers of high specificity that are used as early markers of infection[3]. CRP is an acute phase protein produced by the liver.The plasma concentration level is found in very small amounts in the serum of healthy individuals. Increases in plasma levels occur with stimulation by interleukin 6 during trauma, tissue damage and inflammation stages [4]. CRP, which can be considered as an important indicator of the inflammation stage, interacts with the c-polysaccharide structure in the cell wall of pneumococci and causes collapse. This process activates the classical complement

CITATION
Gulsoy KY, Orhan S. The effect of C-reactive protein, Procalcitonin and Neutrophil/lymphocyte ratio on mortality in patients hospitalized in the intensive care unit. Med Science. 2023;12(2):383-8.

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DOI: 10.5455/medscience.2022.07.169

pathway and is the cause of increased phagocytosis [5]. PCT is the precursor of calcitonin produced in the parafollicular-C cells of the thyroid gland. Increased cytokine response with bacterial toxins in systemic bacterial infections stimulates PCT production from non-thyroid parenchymal tissues (kidney, liver, lung, muscle and adipose tissue), causing it to be released into the blood and detected at high levels in serum. PCT values increase to a much lesser extent in cardiogenic shock compared to the large increases seen in patients with septic shock [6]. Studies with healthy volunteers have shown that PCT stimulation is achieved by intravenous injection of a low amount of bacterial endotoxin. PCT begins to be detected in plasma approximately 2-4 hours after bacterial endotoxin injection and reaches a plateau after 6-12 hours with a rapid rise. The PCT level remains high for 24-48 hours, and after reaching its peak value, it returns to its normal level approximately two days later. PCT provides earlier and better results in determining mortality[7]. CRP, Multiple Organ Dysfunction Score (MODS),and APACHE II have been reported as independent factors in determining mortality in ICUs[8].

Neutrophils can be considered as one of the key cell types forinnate immune system since they form the very first line of cellular defense system to fight against infection. Lymphocytes are involved in adaptive immunity. The immune response to various infective conditions has different characteristics: increased neutrophil count and decreased lymphocyte count. Against persistent infections, large amounts of neutrophils which may not be apoptotic, are produced. Contrary to lymphocytes, apoptosis of neutrophils in sepsis is beneficial [9]. Lymphocytes are important for an appropriate inflammatory response. The reduction of lymphocytes as a result of apoptosis, cellular depletion, and downregulation enhances the progression of the deleterious inflammatory response [10]. The relationship between neutrophil and lymphocyte concentration was first identified by Zahorec et al.[11]. They expressed the infection as an indicator of the cellular response of the immune system.

Effectiveness of using inflammatory markers for prognosis assessment in the ICU is still not clear yet. Through the current study, we aimed to investigate the relationship between PCT, CRP, and NLR of patients who are getting treatment in the ICU during hospitalization and mortality.

Material and Methods

We pursued this retrospectively planned study in Burdur public hospital ICU. The study took place between the fallowing dates: 01.01.2020 and 01.04.2022.Ethical committee approval, which was obtained in 2022 from the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University Faculty of Medicine (decision no: 256, dated: 2022), enabled us to conduct the study. All patients participated in the study were over the age of 18. They all were hospitalized and stayed in the ICU longer than 24 hours. Demographic characteristics, laboratory findings, prognosis and mortality data of the patients hospitalized in the ICU were evaluated. Data was obtained through the patient file information stored in the hospital automation system. The patients were grouped in two: First group included the patients who died in the ICU whereas the second group contained the patients who were discharged. The mean scores of APACHE II, SOFA, CRP, PCT and NLR, obtained during the ICU admission, of two groups (i.e., patients who died, and patients who were discharged) were compared.

Statistical Analysis

Categorical variables obtained from the patients were presented as percentages and frequencies. The Shapiro Wilk test of normality took place to check determine whether the continuous variables deviate from normal distribution. Normally distributed continuous variables were presented in terms of mean (SD), whereascontinuous variables do not follow normal distribution were presented in terms of median and interquartile range (IQR). To compare the categorical variables of those who died in the ICU and those who were discharged we conducted the chi-square test. Additionally, we used Fisher's exact test when it was necessary. We used the independent samples t-test for comparing continuous variables between the groups (i.e.,patients who died, and patients who were discharged) where the data in each group is normal distributed. In cases where the data does not meet the normal distribution criteria, we applied the Mann-Whitney U tests. Univariate and multivariate Cox regression analyzes were used to determine the parameters that increase the risk of mortality. The parameters to be included in the univariate and multivariate analysis were determined. The predictive value of CRP, PCT, NLR, APACHE II and SOFA scores were examined through Receiver Operating Characteristic (ROC), in short ROC, analysis. Optimal cutoff values were determined by the Youden Index.

Results

Of the 788 patients in the study, 430 (54.6 percent of total participant) were male whereas 358 (45.4%) were female. The median of the study group age was calculated as 79 years (IQR=19 years). During the course of the study, 408 (51.8% percent of total participant) patients in ICU's became exitus, while 380 (48.2 percent of total participant) patients were discharged. Of the patients, 96,8% (n=762) had at least one comorbidity,the most common being chronic heart failure (26,7%, n=211), hypertension (26%, n=205), chronic obstructive pulmonary disease(COPD) (20%, n=162), chronic kidney disease(CKD) (16,4%, n=130)diabetes mellitus (15,8%, n=125), sequelae of cerebrovascular disease (CVD) (15,3%, n=121) (Table 1).

The most common reasons for ICU admission were pneumonia (24.3%, n=192), sepsis (20,4%, n=161), decompensated heart failure (14.7% n=116), acute cerebrovascular disease (%11.9, n=94), acute kidney injury (9,9%, n=78), malnutrition (6.8%, n=54), postopretaive complication (6,6%, n=52), and trauma (5.2%, n=41) (Table 1).

While PCT was 0.32 (0.09-1.19) ng/mL in patients who were discharged, it was 1.24(0.42-5.45) ng/mL in those who

DOI: 10.5455/medscience.2022.07.169

died (P<0.001). CRP (mg/L) was found to be 106.11(52.07-181.55) in patients who died and 55.52(9.77-126) in those who were discharged (P<0.001). While NLR was 11.95 (7.30-20.37) in patients who died, it was 8.81(5.22-14) in those who were discharged (P<0.001). The comparison of the groups (i.e.,deceased patients vs discharged patients) in terms of characteristics is presented in Table 2.

Table 1. Reasons for ICU admission and comorbidity

	Non-survival (n= 408)	Survival(n= 380)	p
Principal diagnosis leading to ICU admission			
Malnutrition	24(%44.4)	30(%55.6)	0.164**
Pneumonia	114 (%59.4)	78 (%40.6)	0.001**
Sepsis	103 (%64)	58 (%36)	0.001**
AKI	27 (%34.6)	51 (%65.4)	0.001**
Trauma	7 (%17.1)	34 (%82.9)	<0.001**
PC	16 (%30.8)	36 (%69.2)	0.001**
HF	58 (%50)	58 (%50)	0.678**
Acute CVD	59 (%62.8)	35 (%37.2)	0.023**
Comorbidity			
COPD	94 (%58)	68 (%42)	0.074**
HF	116 (%55)	95 (%45)	0.277**
CVD sequelae	75 (%62)	46 (%38)	0.015**
CRF	77 (%59.2)	53 (%40.8)	0.063**
Hypertension	102 (%49.8)	103 (%50.2)	0.501**
DM	64 (%51.2)	61 (%48.8)	0.888**

AKI: Acute kindey injury , CVD: Cerebrovascular disease, HF: Heart failure, CRF:Cronic renal failure, DM:Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, PC: Postoperative complications, *Mann Whitney U test, ** Fisher'sexact test

Table 2. Characteristics of the patient groups

	Non-survival (n= 408)	Survival(n= 380)	p
Age(years),median (IQR)	82 (65-85)	76 (65-85)	<0.001*
Sex Male, n(%)	223 (54.7 %)	207 (54.5 %)	1.000**
APACHE II score, median (IQR)	22 (20-27)	18 (15-21)	<0.001*
SOFA score, median (IQR)	9 (7-10)	5 (4-6)	<0.001*
Inflammatory biomarkers, median (IQR)			
Procalcitonin (ng/mL)	1.24 (0.42- 5.45)	0.32 (0.09-1.19)	<0.001*
C-reactive protein (mg/dL)	106.11 (52.07-181.55)	55.52 (9.77- 126)	<0.001*
Neutrophil/lymphocyte ratios	11.95 (7.30-20.37)	8.81 (5.22 – 14)	<0.001*

*Mann Whitney U test, ** Fisher's exact test
APACHE II: Acute Physiology and Chronic Health Assessment II, SOFA: Sequential Organ Failure Assessment

Age, SOFA and APACHE II scores, PCT, CRP and neutrophil/lymphocyte levels were found to be associated with mortality as per the univariate cox regression analysis in our study, while only age, SOFA and APACHE II scores were determined to be the independent risk factors for mortality as per the multivariate Cox regression analysis. The P-value was P<0.001 for the PCT, P=0.887 for the CRP, and P= 0.014 for the NLR in the univariate analysis of Cox regression which was runned to examine the parameters affecting mortality. Moreover, the following p-calueswere yielded bythe multivariate Cox regression analysis:P=0.242, P=0.116, and P=0.523, respectively. High APACHE II 95% CI 1.03 (1.01-1.05)(P<0.003) and high SOFA score 95% CI 1.44 (1.37-1.52)(P<0.001) were obtained. The results of univariate and multivariate Cox regression analyses, which both were performed to examine the parameters affecting mortality, are presented in Table 3.

Table 3. Univariate and multivariate cox regression analysis for mortality

	Univariate			Multivariate		
Variables	**HR**	**%95 GA**	**P-value**	**HR**	**%95 GA**	**P-value**
Age	1.01	1.00-1.02	<0.001	1.01	1.00-1.02	<0.001
APACHE II score	1.13	1.11-1.15	<0.001	1.03	1.01-1.05	0.003
SOFA score	1.49	1.43-1.55	<0.001	1.44	1.37-1.52	<0.001
Procalcitonin	1.01	1.00-1.01	<0.001	1.00	0.99-1.00	0.242
C-reactive protein	1.00	0.99-1.00	0.887			
Neutrophil/lymphocyte ratios	1.00	1.00-1.00	0.014	0.99	0.98-1.00	0.523

HR, Hazardratio. APACHE II: Acute Physiology and Chronic Health Assessment II, SOFA: Sequential Organ Failure Assessment

In ROC analyzes for CRP, PCT, APACHE and SOFA score, NLR, Area Under The Curve(AUC) values were found to be between 0.881 and 0.615. The parameter with the highest AUC value was found to be the SOFA score.

Table 4. Optimal cut-off values and ROC analysis results for CRP, PCT, APACHE II and SOFA score and NLR

Risk factor	AUC(%95)	Cut off	p value	Sensitivity (%)	Specificity (%)
CRP	0.656 (0.613-0.692)	27.12	0.00	0.85	0.39
N/L rate	0.615 (0.573-0.653)	9.71	0.00	0.62	0.57
Prokalsitonin	0.684 (0.642-0.723)	0.64	0.00	0.65	0.66
APACHE score	0.781 (0.749-0.813)	20.50	0.00	0.68	0.74
SOFA score	0.881 (0.862-0.901)	6.51	0.00	0.80	0.78

APACHE II: Acute Physiology and Chronic Health Assessment II, SOFA: Sequential Organ Failure Assessment, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratios

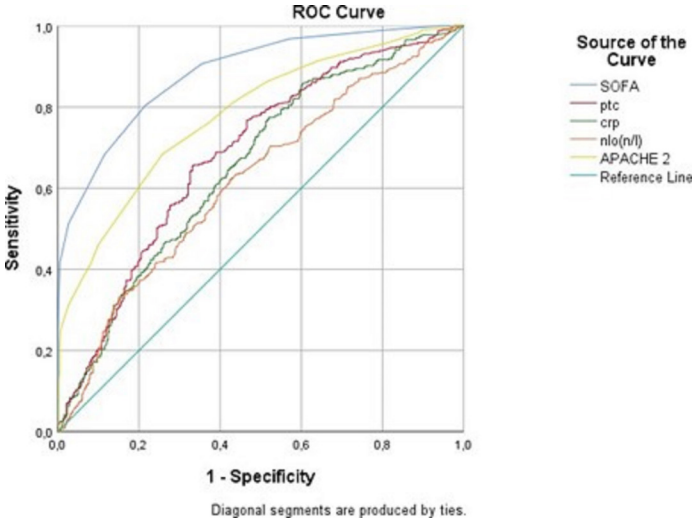

Figure 1. ROC analysis for CRP, PCT, APACHE II and SOFA score, NLR. APACHE II: Acute Physiology and Chronic Health Assessment II, SOFA: Sequential Organ Failure Assessment, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratios

DOI: 10.5455/medscience.2022.07.169

Discussion

The mortality rate in ICUs is affected by the level of the ICU, co-morbidities of the patients followed, age and many similar factors. In a study conducted in intensive care patients in England, intensive care mortality was reported as 24-41% [12]. Waheed et al. they evaluated the mortality rates of 4165 intensive care patients and found it to be 26.7% [13]. In their study in Turkey, Kaymak et al. reported the average mortality rate as 46.3% in the public, university and private hospital ICUs, while they reported the rate in public hospitals as 47.2% [14]. In our study, the mortality rate of 788 patients hospitalized in ICU of the public hospital was found to be 51.8%.

The SOFA and APACHE II scores are commonlyaddressed to predict hospital mortality and evaluate multiple organ functions while determining disease severity[15].The APACHE II score is a widely used scoring system. When the literature is examined, it is seen that there are studies that have a significant relationship between the mortality rate in the ICU and the APACHE II score [16].

The APACHE II score mean was reported as 17.9 (9.4) in the ICON study[17]. In the ICUs of our country; Kamis et al. found the APACHE II score to be 16.8±4.28 in the living group and 23.0±6.22 in the deceased group. Deceased patients had a significantly higher APACHE II score [18]. In the current study, the APACHE II mean score found to be 20(17-24) for all the patients, with 22 (20-27) in patients who died and 18 (15-21) in patients who were discharged. The study yielded statistically significant mean score difference between deceased patients and discharged patients groups($P<0.001$).

Huang et al., in their cohort study of the sepsis group patients in the ICU, stated that the SOFA value was 13 (10-15) in the patients who died, 6 (4-9) in the living group, and there was a statistical difference between the two groups [19]. In their study in which they evaluated sepsis patients in the ICU of our country, Balcan et al. reported that the average SOFA score of the deceased was 11.5 (±5.2), the sofa score of the survivors was 7 (±2.7), and that the mortality increased with the increasing SOFA score [20]. In our study, the SOFA score was 9(7-10) in the group of patients who died and 5(4- 6) in the group of patients who survived ($p<0.00$). We think that the reason why SOFA values were lower in both groups compared to the studies mentioned in our study was not only the sepsis group but also the heterogeneity of our patient population. No matter how heterogeneous our groups were, a significant difference was found between deceased and living patients' groups. Zou et al. reported the existence of association between both high APACHE II and SOFA scores and mortality [21].

Juan Jesus Rios-Toro et al. reported that changes in the SOFA and APACHE II scoring system were a more sensitive predictor of mortality compared to CRP and PCT in a study they conducted on patients including the sepsis group in the ICU [22].In their study, Izabela Kądziołka et al. reported that APACHE II and SAPS II discriminated better in intensive care, had better calibration and were more effective than SOFA as a mortality predictor. They stated that, contrary to the expected results between these scales, SOFA did not reach sufficient effectiveness [23].

The findings of the current study suggested that high SOFA and APACHE II scores might be seen asan independent risk factors for mortality.

CRP is a prognostic factor in many diseases and its relationship with mortality has been reported. Although it has been stated that CRP is associated with mortality, different results have been obtained in the literature regarding its mortality predictive power. While some studies support that CRP may be a good predictor for mortality, there are also studies reporting contrary results [24-25].

One study reported that CRP was associated with mortality in a single variant cox analysis for 28-day mortality in patients hospitalized in the ICU [25]. Wang et al. reported that CRP is an effective biomarker in predicting mortality in their study in unselected patient groups in the ICU. They stated that CRP is an independent risk factor from APACHE II, but it is more effective to evaluate both at the same time [26]. In another study in which they evaluated patients with sepsis, septic shock and SIRS in the ICU, they stated that CRP was not an effective biomarker in predicting hospital mortality [27]. In the current study, we found that CRP value is not an effective biomarker for mortality.

Huang et al. reported that the predictivity of the CRP value for 28-day mortality in the sepsis group in the ICU was AUC 0.656, its sensitivity was 85%, and the cut-off value was 105.4 mg/dL [19]. In our study, the ROC curve values of CRP were AUC 0.656, the sensitivity was 85%, and the cut-off value was 27.1 mg/dL.

Similar to CRP, the increase in PCT also shows the severity of the disease and can be associated with high mortality[28]. Based on the findings of the study investigated the effect of acute-phase reactants on survival in COVID 19 intensive care patients. Orhan et al. [29],suggested PCT level higher than 0.219 ng/mL as an independent risk factor for mortality ($P=0.017$). Jensen et al. [31], reported PCT as an independent risk factor in determining mortality in their study in which they examined PCT levels in the ICU, but they could not reach the same result for CRP. Zaccone et al. reported the area under the curve of PCT as 0.69 and its sensitivity as 64% in ROC analysis [31]. In our ROC analysis evaluation of our study, PCT was found to be 0.684 AUC and the sensitivity was 65% similar to other studies.

No relationship between CRP and PCT levels and mortality was found in our study. We think that the reason for the difference in results might be due to the heterogeneity of our patient group.

In the current study, patients'serum CRP and PCT values when

DOI: 10.5455/medscience.2022.07.169

they were admitted to the ICU were found to be significantly different between the groups (i.e.,deceased patients vs discharged patients). These findings are similar to findings of previously published studies in the literature[30- 32].Today, the NLR is accepted as a parameter that shows the negative effects of both high neutrophils reflecting acute inflammation and low lymphocyte levels reflecting physiological stress. It has been reported in the literature that NLR is an independent risk factor for mortality and morbidity in various conditions such as cancer and cardiovascular diseases. It is a useful biomarker not only in the case of a significant disease, but also in the detection of postoperative complications, monitoring of the traumatic process, identifying and predicting infectious and inflammatory conditions NLR values in healthy individuals have been reported to be between 0.78-3.53[33].

Heffernan et al. reported that neutrophil count increased and lymphocyte count decreased in SIRS and trauma patients [34]. In their study, Salciccioli et al. reported that the NLR they detected in the samples taken during ICU admission was associated with mortality, but it was not associated with mortality in their subgroups including the sepsis group[35]. In their prospective study, Akilli et al., reported a high rate of NLR in the group they included patients requiring intensive care admission. Their findings suggested it as an independent risk factor for hospital mortality and 6-month mortality [36].

Hwang et al. reported an association of NLR with 28-day mortality when admitted to intensive care. [37]. Martins et al. reported that NLR was an independent risk factor in mortality in their study in the sepsis group[38]. In our study, although the NLR level was higher in patients who died, its relationship with mortality could not be shown.

In their study evaluating the NLR and hospital mortality in patients with sepsis, Ni et al. reported the area under the ROC curve as 0.62 and the sensitivity as 54% [39].

Aygün et al., in their study with patients in the ischemic stroke group in the ICU; they expressed the NLR ratio, the area under the curve in ROC analysis as 0.57, and the sensitivity as 46.9%[40]. In our study, our ROC analysis evaluation; The NLR cut off value was 6.21, the NLR was 0.615, the AUC was drawn and the sensitivity was found to be 62%.

In our ROC analysis results, we found that the most valuable parameter was the SOFA score. Afterwards, they were APACHE II, CRP, PCT and NLR, respectively. Due to the heterogeneity of our patient groups, we could not achieve sufficient statistical performance from the biochemical parameters PCT, CRP and NLR. We believe that scoring systems in ICUs are more useful because they cover many diseases.

Limitations

The first limitation was that the study was single-centred and retrospective. The second limitation of the study was that there was no categorization performed on the patients according to their clinical diagnoses. This may have led to heterogeneity in our results. The third limitation of the study was shortness of follow-up period. It was not sufficient for evaluationof the patients' long-term prognosis. In the future, it would be beneficial to conduct multicenter prospective studies with a longer follow-up period.

Conclusion

Although inflammatory markers such as PCT, CRP, and NLR were high in patients who died, their relationship with mortality in the ICU could not be shown. The APACHE II and SOFA scores, used as mortality indicators in the ICU, have been determined to be independent risk factors for mortality in our study. It would be more appropriate to use the APACHE II and SOFA scores as an indicator of mortality in the ICU.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study was conducted following the Declaration of Helsinki, and patients gave their written consent. Approval for the study was granted by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (decision no:256, dated:2022)

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DOI: 10.5455/medscience.2022.07.169

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