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Association of Troponin, C-Reactive protein, Albumin and C-Reactive protein/Albumin Ratios with Mortality in Intensive Care Unit Patients with Community-acquired Pneumonia

Toplum Kökenli Pnömonisi olan Yoğun Bakım Hastalarında Troponin, C-Reaktif protein, Albumin ve C-Reaktif protein/Albümin Oranlarının Mortalite ile İlişkisi

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ABSTRACT

Aim: Parameters used to determine prognosis in community-acquired pneumonia (CAP) patients often have limited clinical value. This study aims to examine the efficacy of CRP, albumin, CRP/albumin ratio and troponin elevation in predicting 30-day mortality in patients hospitalized in the intensive care unit with CAP.

Material and Methods: In this study, 200 patients (85 females and 115 males) older than 18 years of age with a diagnosis of CAP who were followed up in the intensive care unit after emergency department admission between January 1, 2023 and January 1, 2024 were included. Patients who underwent chest radiography and biochemical analyses, including complete blood count, CRP and albumin, within the first 24 hours, were divided into two groups: those who died and those who survived. Troponin, CRP, albumin, and CRP/albumin ratios were compared between the groups about mortality.

Results: The findings obtained in our study were as follows: Troponin, CRP, albumin and CRP/albumin ratio values differed significantly in patients with mortality. When ROC analysis was performed to determine the power of troponin, CRP, albumin and CRP/albumin ratio to predict mortality in the emergency department, it was found that troponin value was the strongest marker in terms of sensitivity with 82.25%. In terms of specificity, low albumin was the most specific parameter, with 82.50% and CRP/albumin ratio followed albumin with 72.50%.

Conclusion: We believe that CRP, albumin, CRP/albumin and troponin are significant predictors of 30 day mortality in patients with CAP hospitalized in the intensive care unit.

Keywords: Pneumonia, Troponin, CRP/albumin, C-reactive protein, Albumin

ÖZ

Amaç: Toplum kökenli pnömoni (TKP) hastalarında prognozu belirlemek için kullanılan parametreler sıklıkla sınırlı klinik değere sahiptir. Bu çalışmanın amacı TKP tanısıyla yoğun bakıma yatırılan hastalarda 30 günlük mortaliteyi öngörmede CRP, albümin, CRP/albümin oranı ve troponin yüksekliğinin etkinliğini incelemektir.

Gereç ve Yöntemler: Bu çalışmaya 1 Ocak 2023- 1 Ocak 2024 yılları arasında acil servis başvurusu sonrası yoğun bakımda takip edilen TKP tanısı alan 18 yaşından büyük 85'i kadın, 115'i erkek olmak üzere toplam 200 hasta dahil edilmiştir. Çalışmada ilk 24 saat içinde akciğer grafisi çekilen, tam kan sayımı, CRP ve albumin dahil biyokimyasal analizleri yapılan hastalar, ölenler ve hayatta kalanlar olmak üzere iki gruba ayrıldı. Gruplar arasında troponin, CRP, Albumin, ve CRP/Albümin oranlarının mortalite ile olan ilişkisi karşılaştırıldı.

Bulgular: Çalışmamızda elde edilen bulgular şu şekildedir: Mortalite gerçekleşen hastalarda troponin, CRP, Albumin ve CRP/albumin oranı değerleri anlamlı şekilde farklılaşmıştır. Troponin, CRP, albumin ve CRP/albümin oranının acil serviste mortaliteyi öngörme gücünü belirlemek için ROC analizi gerçekleştirildiğinde %82,25 ile troponin değerinin sensitivite açısından en güçlü belirteç olduğu bulunmuştur. Spesifite açısından bakıldığında albümin düşüklüğü %82,50 ile en spesifik parametre olarak tespit edilmiştir ve CRP/albümin oranı %72,50 ile albümini takip etmektedir.

Sonuç: Yoğun bakıma yatan TKP hastalarında CRP, albümin, CRP/albümin ve troponin değerinin 30 günlük mortalite açısından anlamlı birer öngörücü olduğunu düşünüyoruz.

Anahtar Sözcükler: Pnömoni, Troponin, CRP/albümin, C-reaktif protein, Albümin

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Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of morbidity and mortality worldwide. The clinical presentation of CAP ranges from mild pneumonia characterized by fever and cough with sputum to severe pneumonia characterized by respiratory distress and sepsis [1]. In patients with community-acquired pneumonia, traditional infection criteria based on clinical signs and symptoms, clinical scoring systems and general inflammatory markers (e.g., leukocytosis, fever, C-reactive protein (CRP) and blood cultures) are often of limited clinical value. They also have limited reliability regarding etiology, optimal treatment and prognosis [2]. Ideally, the management strategy for CAP and the nature of the intervention (including hospitalization and ICU (Intensive Care Unit) admission) should be tailored to the individual patient's severity of illness and risk of death. In our era of personalized medicine, it is important to minimize potential harm and maximize the effectiveness of each intervention through rapid diagnostic and treatment strategies based on unique patient characteristics [3]. Various biomarkers are used in the treatment, hospitalization, intensive care unit admission decision-making and prognosis of pneumonia patients [4].

Currently, the mechanism of severe pneumonia is unclear and not fully understood. Researchers' efforts aim to address the gaps in identifying the causes of CAP severity in patients with similar histories. For example, mixed viral-bacterial infections may be associated with an increased mortality risk [5]. In this context, supportive studies are needed to predict the severity and mortality risk of CAP. Currently, many studies aim to predict morbidity using parameters, such as CRP, albumin and troponin [6,7].

As in other infections, albumin synthesis in the liver is reduced in CAP infections. The severity of hypoalbuminemia reflects the severity of inflammatory stress in both acute and chronic conditions. Chronic conditions associated with hypoalbuminemia also complicate hospital management due to mechanisms described as the 'second strike' phenomenon. On the other hand, albumin levels have been found to be associated with mortality in diseases including CAP [8].

CRP, which is frequently used as a marker in patients with community-acquired pneumonia, is an acute-phase protein produced predominantly in the liver. In response to infection or tissue inflammation, CRP production is rapidly stimulated by cytokines, especially interleukin (IL)-6 [9]. As a new parameter, the CRP/albumin ratio has been shown to be more accurate than albumin and CRP alone in predicting the overall prognosis of certain clinical conditions [6,7]. Cardiac troponin may be elevated in patients with community-acquired pneumonia. Studies, especially in rodents and non-human primates, have shown that Streptococcus pneumoniae causes direct cardiac damage by invading the myocardium and forming microscopic lesions, ultimately leading to cardiac scar formation. A large proportion of patients hospitalized with CAP have elevated cardiac troponin levels. Hypoxemia, increased sympathetic activity, increased inflammatory activity within coronary atherosclerotic plaques and endothelial dysfunction are thought to cause elevated troponin levels in patients with CAP, suggesting that CAP is often complicated by myocardial injury, a phenomenon that can predict poor outcomes, and therefore troponin elevation may be a parameter that can be used to predict prognosis. [10]. However, we still do not have sufficient information about the subsequent cardiovascular effects of pneumonia.

For all these reasons, in our study, we aimed to investigate the role of CRP, albumin, CRP/albumin ratio, and the role of high levels of troponin in predicting 30-day mortality in patients admitted to the emergency department and hospitalized in the intensive care unit with a diagnosis of CAP.

Methods

Research Design

Between January 1, 2023 and January 1, 2024, a total of 200 patients diagnosed with CAP who were admitted to the emergency department and followed up in the intensive care unit were included in our retrospective study. This study was approved by the Non-interventional Clinical Research Ethics Committee of Erzurum City Hospital (Date 13.03.2024, Decision No: 2024/03-

56). It was conducted in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and its subsequent amendments. The diagnosis of pneumonia in the patients included in this study was based on the "Thoracic Society Guideline for the Diagnosis and Treatment of Community-acquired Pneumonia." The need for intensive care was also determined according to the same guideline.

Patients admitted to the emergency department and admitted to the intensive care unit with a diagnosis of pneumonia, who underwent chest radiography and/or thoracic computed tomography within the first 24 hours and biochemical analysis, including complete blood count, CRP and albumin were included in this study. In addition, the patients included in this study underwent cardiology consultation to determine whether the primary cause of troponin elevation was cardiac in origin. In conclusion, this study included 200 patients over the age of 18 years, in whom ACS and CHF were excluded and whose ECHO data were registered in the database of our hospital. Pregnant women, patients with active infections other than CAP, patients with ventilator-associated pneumonia, patients with hospital-acquired pneumonia, and patients with a history of chronic kidney disease, malignancy and connective tissue disease were excluded. Patients with severe congestive heart failure, myocardial infarction, direct cardiac injury, toxin exposure (adriamycin, 5-fluorouracil, trastuzumab, snake venom), viral myocarditis, pericarditis, cerebro vascular events, sepsis, tachyarrhythmias, lobarpneumonia and patients who refused to participate in this study were also excluded. Patients who were discharged were not included in this study if they were readmitted during the study. A data collection form was created for this study. Patient data were accessed using the hospital information management system. Patients were divided into two groups: patients who survived and patients who died within 30 days. Troponin, CRP, albumin, and CRP/albumin ratios were compared between the groups in relation to mortality.

Data Collection Form

A form was created to record the information obtained from the electronic environment for this study. Age, gender, comorbid diseases, vital signs (blood pressure, pulse rate, saturation, respiratory rate), duration of intensive care unit stay, total length of stay, whether they were intubated or not, and mortality status of the patients were recorded on this form. Blood parameters (White blood cell (WBC), RDW (red blood cell distribution volume), platelet, neutrophil, lymphocyte, lactate, troponin, BUN (blood urea nitrogen), creatinine, glomerular filtration rate, albumin, C-reactive protein, d-dimer) were added to the form. CRP/albumin ratio was calculated and recorded on the form.

Statistical analysis

Data were analyzed using the SPSS 23.0 program. Before the analysis of the data, a general screening was performed for missing and outlier data, and while no missing data were observed in categorical variables, 260 missing data were detected in five variables: systolic blood pressure, diastolic blood pressure, pulse, saturation and respiratory rate. These are were follows: systolic blood pressure 52, diastolic blood pressure 52, pulse 52, saturation 45 and respiratory rate 59. Little's MCAR test was used to determine whether these missing data were random to not distort the analyses. Based on a chi-square value of 19.39 and a significance value of 0.08, it was determined that the missing data did not distort the analyses ($p>0.05$), and they were replaced with the means of the relevant variables. Following this step, the data were analyzed descriptively and interpretatively. Descriptive statistics were reported as frequency and percentage for categorical variables and as the mean and standard deviation for continuous variables depending on the normality of the data, if the data were normally distributed, and median and IQR (interquartile range) otherwise. Interpretative statistics were reported by checking the necessary assumptions before conducting the analyses. When the necessary assumptions for the tests were not met, the alternative non-parametric tests were applied. Accordingly, comparisons of independent groups were performed with the independent sample t-test or Mann-Whitney U test, depending on whether the assumptions were met. In addition, ROC analysis was performed to determine the predictive level of Troponin, CRP, albumin, and CRP/albumin variables for mortality, to calculate the AUC, sensitivity and specificity

predictive values, and to find the optimal cut-off point if a significant predictive value was detected. Youden'sindex (sensitivity + 1-specificity) was used for the optimum threshold levels of the parameters. In all statistical analyses, 0.05 was taken as the significance level.

Results

A total of 200 patients, 85 women and 115 men, were included in this study. When the entire patient group was analyzed in terms of comorbidities, chronic obstructive pulmonary disease (COPD) stood out as the most common chronic disease. The average duration of total hospitalization was 12 days. Among the patients included in this study, 110 were intubated, and 80 patients died in the whole patient group. Demographic data of the patients are given in detail in Table I.

In this study, it was examined whether Troponin, CRP, albumin and CRP/albumin ratio values differed significantly according to mortality status in the hospital. Troponin rank scores (MeanRank) were 115.14 in the mortality group and 90.74 in the survivor group and were significantly different (U=3629 p<0.00). The findings showed that CRP was higher in the deceased group (t(198)=-2.49; p=0.013), albumin was higher in the survivor group (t(198)=4.72; p=0.000) and CRP/albumin ratio was higher in the deceased group (t(198)=-3.32; p=0.001) and these variables were significantly differentiated according to mortality.

ROC analysis was performed to determine the predictive power of troponin, CRP, albumin and CRP/albumin ratio for mortality in the emergency department. Details of the analysis findings and ROC Curve are given in Table 3 and Figure 1. Youden's method was used to determine the cutoff values for the variables. The findings revealed that the variables were statistically significantly predictive of mortality at the 0.05 level for CRP (p=0.014) and at the 0.01 level for troponin (p=0.002), albumin (p=0.000) and CRP/albumin (p=0.001). The cut-off values for troponin, CRP, albumin and CRP/albumin were >19.27, >124.93, <=31, and >4.16, respectively. This showed that all of these variables were significant parameters in predicting mortality.

As a result of the ROC analysis of the predictive power of tropin, CRP, albumin, and CRP/albumin ratio for mortality, troponin value was the most powerful marker in terms of sensitivity with 82.25%. In terms of specificity, low albumin was the most specific parameter with 82.50% and CRP/albumin ratio followed albumin with 72.50% (Table 3).

Table 1. Demographic and clinical characteristics of the patients

Variables *	Total Patients (n = 200)
Gender	
Female, n (%)	85 (42,5)
Male, n (%)	115 (57,5)
Age, years old x (sd)	74,22 (14,93)
Comorbidities n (%)	
HT	79 (39,5)
DM	37 (18,5)
CAD	24 (12)
COPD	86 (43)
CHF	26 (13)
Malignancy	26 (13)
CVD	18 (9)
CRF	17 (8,5)
Vital signs	
SBP, mmHg x̄ (sd)	116,52 (21,17)
DBP, mmHg x̄ (sd)	70,47 (62 - 76)
Pulse /min median, (IQR)	101,89 (92 -110)
SpO2 % median x̄ (sd)	81,25 (8,78)
Respiration Rate /min, x̄ (ss)	25,26 (4,77)
Troponin, ng/ml median, (IQR)	35,11 (15,29 – 149,34)
CRP, mg/dl x̄ (sd)	121,49 (99,58)
Albumí n, g/dl x̄ (sd)	33,63 (6,16)
CRP/Albumin, x̄ (sd)	3,89 (3,37)
Total Duration of Hospitalization, median, (IQR)	12 (7 – 29,50)
Duration of ICU stay, median, (IQR)	9 (4,25 - 22)
Intubation, n (%)	
Yes	110 (55)
No	90 (45)
Mortality, n (%)	
Yes	80 (40)
No	120 (60)

Note: DM, Diabetes mellitus; HT, Hypertension; CRF, Chronic renal failure; CAD, Coronary artery disease; CHF, Congestive heart failure; CVD, Cerebrovascular disease; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SpO2, Oxygen saturation ICU, Intensive care unit; IQR, interquartilerange; x̄, mean; sd, standard deviation

Table 2. Comparison of Troponin, CRP, Albumin and CRP/Albumin ratio according to mortality

	Mortality		p
	Yes (n=80, %40)	None (n=120, %60)	
Troponin, median (IQR)	69,33 (22,88 – 209,09)	26,73 (12,31 – 107,81)	[b]0,00**
CRP, x̄ (sd)	142,67 (102,84)	107,28 (95,17)	[a]0,01*
Albumin, x̄ (sd)	31,23 (6,27)	35,33 (5,57)	[a]0,00**
CRP/Albumin, x̄ (sd)	4,83 (3,60)	3,25 (3,07)	[a]0,00**

Note: b, mann-whitney U-test; a, independent sample t-test; **, p<0,01; *, p<0,05; CRP, C-reactive protein

Table 3. ROC analysis findings regarding the predictive power of tropin troponin, CRP, albumin and CRP/Albumin ratio for mortality

	Troponin	CRP	Albumin	CRP/ Albumin
AUC	0,62	0,60	0,69	0,63
95% CI	0,55-0,69	0,53 – 0,67	0,62 - 0,75	0,55 – 0,70
P Value	<0,00**	0,014*	<0,00**	<0,00**
Youden index J	0,24	0,24	0,325	0,27
Cut-off Pointa	>19,27	>124,93	<=31	>4,16
Sensitivity [CI]	82,25	55,00	50,00	55,00
Specificity [CI]	43,33	69,17	82,50	72,50
Positive Predictive Value [CI]	48,9 [44,2 – 53,6]	54,3 [46,0 – 62,4]	65,6 [54,9- 74,8]	57,1 [48,4 – 65,5]
Negative Predictive Value [CI]	77,6 [67,8 – 85,1]	69,7 [63,8 – 75,1]	71,2 [66,2 – 75,8]	70,7 [64,9 – 75,9]

Note: CRP, C-reactive protein; a, Youden index method; **, p<0,01; *, p<0,05; AUC, Area under curve

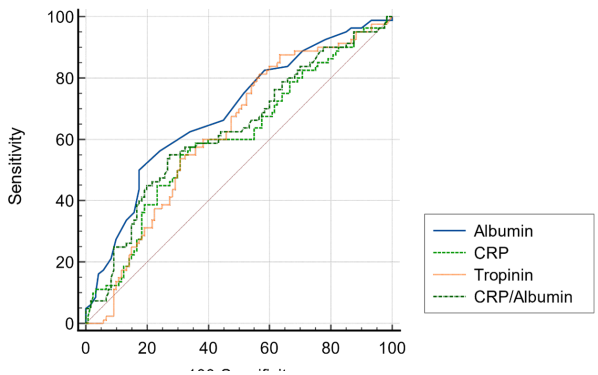

Figure 1. ROC analysis curves to measure the predictive value of laboratory tests for mortality

Discussion

Considering patients' demographic data and clinical characteristics of the, the in-hospital mortality rate was higher in our study, which is different from the literature. In a meta-analysis of 127 studies evaluating the mortality rate associated with CAP in adults, in which medical outcomes of more than 33,000 patients were reported, the mortality rate was reported as 5.1% for outpatients and hospitalized patients, 13.6% for inpatients and 36.5% for patients admitted to the intensive care unit [11]. Our study shows that mortality occurred in 40% of patients with pneumonia hospitalized in the intensive care unit. We attribute the higher mortality rate compared to the literature to our clinicians' more accurate use of intensive care hospitalization criteria when admitting patients to the ICU.

A study in the literature showed that clinicians used different criteria in making hospitalization decisions for adults with CAP, which led to serious differences in the appropriate care of their patients, and that clinicians often overestimated the short-term mortality risk of patients, even in low-risk patients [12].

Accurate prognosis is particularly crucial in critically ill patients and many biochemical markers can reflect the severity of their illness. CRP, albumin and troponin are some of these biochemical markers. Many scoring systems, such as PSI and CURB-65, and many parameters, such as CRP, Procalcitonin and albumin are used to determine the severity of CAP [13,14].

CRP is an acute phase reactant and non-specific marker used in the diagnosis of various conditions, such as infectious diseases, autoimmune and rheumatologic disorders. Elevated CRP levels are associated with the prognosis of various diseases, such as coronary artery disease, ischemic stroke, sepsis and cancer [15,16]. Albumin is a negative acute phase reactant associated with mortality in critically ill patients. When we look at the literature, Reinhardt et al. reported that 25% mortality occurred in patients with serum albumin concentrations below 34 g/L for 30 days, and the same study reported that mortality increased to 62% when serum albumin concentrations fell to 20 g/L or less during hospitalization [17]. Min Hyung

Kim et al. found the CRP/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock in a study on severe sepsis patients in which mortality was investigated within 180 days [18]. In another study in which patients over 65 years of age were retrospectively analyzed, and 811 patients were included in this study, it was found that low albumin and CRP/albumin ratio during admission to the emergency department were associated with all-cause in-hospital mortality in patients over 65 years of age [19]. In our study, CRP, albumin, and CRP/albumin ratio values were compared between the group with in-hospital mortality and the group that survived, and these parameters were found to differ significantly between the two groups. Also, albumin levels were low and CRP and CRP/albumin ratios were high in the deceased patient group consistent with the literature.

Troponin is an enzyme found mainly in the heart muscle and is released into the bloodstream in cardiac damage. However, blood troponin levels are also increased in many other diseases and this is thought to have an effect on prognosis. For example, Orly Efros et al. showed that high troponin levels have a significant effect on prognosis in patients hospitalized for pneumonia. In addition, a meta-analysis by Francis Bessière et al. showed that high troponin was significantly associated with all-cause mortality [20,21]. In our study, in addition to the literature, troponin rank scores were significantly higher in the deceased patient group than in the survivors. Our study showed that high troponin levels have a significant effect on prognosis in patients hospitalized in the intensive care unit for pneumonia, which supports very few literature studies. Previous studies have shown that myocardial injury is associated with prolonged hospitalization, multiple organ failure and increased short-term mortality. However, it is not yet clear whether the poor prognosis is due to the myocardial injury itself or whether it is a sign of a severe disease.

In our study, ROC analysis was also performed to determine the predictive power of Troponin, CRP, albumin, and CRP/albumin ratio for mortality. As a result of the analysis, the troponin value was the strongest marker in terms of sensitivity with 82.25%. In terms of specificity, low albumin is the most specific parameter with 82.50%. In the literature, there are studies showing that the predictive power of CRP/albumin ratio for mortality has higher AUC values than CRP [22-24].

There are very few studies on the ability of troponin to predict mortality in patients with pneumonia. However, Vestjens et al. showed that cTnT combined with PSI had higher AUC values than cTnT alone in predicting 30-day mortality in a study of patients with pneumonia. [25].

Limitations

Our study indicated that prospective, multicenter studies are needed to further evaluate the prognostic significance of troponin levels in patients hospitalized for pneumonia.

Conclusion

To our knowledge, our study is the first to report that troponin value is a significant predictor of one-month mortality in intensive care unit patients with CAP. In this study, CRP, albumin, CRP/albumin and troponin values were significant predictors of one-month mortality in patients with CAP.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Ethics Committee Approval: This study was approved by the Erzurum Training and Research Hospital Ethics Committee with Approval No: 2024/03-56.

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