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Procalcitonin/Albumin Ratio: Could it be a Novel Marker Indicating Severity of Inflammation in Pneumonia? A Retrospective Study in Elderly Patients with Community-acquired Pneumonia

Prokalsitonin/Albumin Oranı: Pnömoni Şiddetini Gösteren Yeni Bir Belirteç Olabilir mi? Toplum Kaynaklı Pnömonisi olan Hastalarda Yapılmış Retrospektif Bir Çalışma

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Amaç: Bu çalışmada; yoğun bakıma toplum kaynaklı pnömoni (TKP) nedeniyle yatırılan geriatrik yaş grubundaki hastalarda, prokalsitonin/albümin oranının pnömoni seyrini ve mortaliteyi göstermekteki etkinliği değerlendirilmiştir.

Gereç ve Yöntemler: Bu çalışma, geriatrik yaş grubundaki hastalarda, 1 Ocak 2016 - 31 Aralık 2018 tarihleri arasında TKP tanısı konularak, hastane yoğun bakım ünitesinde yatırılmış 490 hastadan çalışmaya dahil edilme kriterleri uyan 350'si ile tek merkezli ve retrospektif olarak yapılmıştır. Hastaların 162 (%46)'si kadın, 188 (%54)'i ise erkek idi. Hastaların yaş ortalaması 73,50±10,9 yıldı. Hastaların 30 günlük mortalite oranıyla; eşlik eden hastalıkları, yaş, cinsiyet, lenfosit, nötrofil ve trombosit sayısı, ortalama trombosit hacmi (MPV), C-reaktif protein (CRP), ürik asit, prokalsitonin ve albumin değerleri arasındaki ilişki değerlendirilmiştir. Hastaların biyokimya testleri, kan ve balgam kültürleri; yoğun bakıma yatırıldığı anda alınmıştır.

Bulgular: Yaşayan ve ölen hasta grupları arasında; yaş (p=0,005), prokalsitonin (p=0,001), MPV (p=0,001), CRP (p=0,002) ve prokalsitonin/albumin oranı (p=0,001) değerleri arasından anlamlı fark saptanmıştır. Otuz günlük takip sırasında; hastaların 166 tanesi yaşamını sürdürürken, 184 hasta yaşamını yitirmiştir. Prokalsitonin/albumin oranının eğri altında kalan alan (AUC) değeri, diğer parametrelerden anlamlı olarak fazla bulunmuştur (p=0,001).

Sonuç: Yoğun bakımda toplum kökenli pnömoni nedeniyle yatırılan hastalarda 30 günlük mortalite oranı ile yaş, CRP, MPV, prokalsitonin değerleri ve prokalsitonin/albumin oranının anlamlı olarak ilişkili olduğu saptanmıştır.

Anahtar kelimeler: Mortalite, pnömoni, prokalsitonin, prokalsitonin/albumin oranı, yoğun bakım

Aim: Community-acquired pneumonia (CAP) in elderly patients is a major health problem causing morbidity and mortality. Markers for determining the severity of disease are still insufficient. With this study conducted on geriatric age group patients treated in intensive care unit (ICU) with CAP; it was aimed to evaluate the importance and usability of procalcitonin/albumin ratio for predicting progression of disease or mortality.

Material and Methods: This retrospective study was conducted in a tertiary hospital, on geriatric age group patients who were hospitalized in ICU with diagnosis of community-acquired pneumonia, between January 1, 2016 and December 31, 2018. Total 490 patients were followed-up and 350 who met inclusion criteria were enrolled in the study. One hundred and sixty two patient (46%) were female and 188 (54%) were male, mean age was 73.5±10.9. On admission to ICU, blood tests, blood and sputum cultures has been obtained from all patients. Accompanying diseases, age, gender data has been recorded, complete blood count (leukocyte, platelet count, MPV), CRP, uric acid, procalcitonin and albumin has been studied.

Results: Age (p=0.005), procalcitonin (p=0.001), MPV (p=0.001), CRP (p=0.002) and procalcitonin/albumin ratio (p=0.001) were found to be significant between groups in survivors and fatalities. In 30-day follow up period, 166 patients survived, while 188 patients died. Area under curve (AUC) value for procalcitonin/albumin ratio was significant when compared to other parameters (p=0.001).

Conclusion: The relationship between thirty-day mortality in ICU and age, procalcitonin/albumin ratio, procalcitonin, CRP and MPV values were significant.

Keywords: Intensive care unit, mortality, pneumonia, procalcitonin, procalcitonin/albumin ratio.

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INTRODUCTION

Community-acquired pneumonia (CAP) is an important health problem worldwide (1). The morbidity and mortality of pneumonia, especially in older people, is high (2). Changes in the immune system with advancing age increase the risk of developing pneumonia (3). In older patients, prognosis of pneumonia differs from younger patients and it cannot be always easily diagnosed. Therefore, there is need for new biomarkers in CAP for diagnosis and determining severity and predicting complications (4). It has been shown that the clinical prognosis is worse in CAP when albumin is low (5). Albumin is an important marker of infection and the level in the blood decreases in acute infections (6). Procalcitonin has been shown to be a marker of bacterial infection and bacteremia and it has been found to be increased in severe pneumonia.

Procalcitonin serum level increases due to endotoxin release in bacterial infections in a short time; however, it may be elevated in non-infectious reasons (cirrhosis, burns and trauma, etc.) also and therefore the sensitivity of the procalcitonin test is high but the specificity is low (8). Procalcitonin follow-up has been reported to be beneficial in terms of prognosis and determining the duration of antibiotic treatment especially (9). CAP is more common in geriatric patients; nevertheless, this age group is often excluded from scientific studies due to the presence of many co-morbidities (10). The relationship between severity of pneumonia and high procalcitonin levels and low albumin levels has been reported in previous studies (5,9). In this study, unlike previous studies, the role of procalcitonin/albumin ratio in predicting the severity of pneumonia and predicting mortality was investigated in patients who were admitted to intensive care unit (ICU) for CAP in the geriatric age group.

MATERIAL AND METHODS

This study was a single center, retrospective study conducted in tertiary hospital with geriatric patient group. Between January 1, 2016 and December 31, 2018, 350 of 490 patients who met inclusion criteria and who were hospitalized in the ICU with CAP diagnosis were included in the study. Written informed consent was obtained from all patients included in the study or from their legal representatives.

Written informed consent was obtained from the patients included in the study or from their legal representatives. Ethics committee approval dated 15/10/2019 and numbered 2019/11 was taken from Lokman Hekim University Non-Interventional Research Ethics Committee for the study.

Definitions

Presence of newly developed infiltration on chest X-ray, existence of fever or hypothermia (> 38 ° C or <35 ° C), new onset of cough and dyspnea, changes in breathing sounds on physical examination which could not be explained by another causes were diagnosed as pneumonia (13).

Inclusion Criteria

Participants in geriatric age group (> 65 years) who were hospitalized in the ICU with diagnosis of CAP and who did not meet exclusion criteria were included in the study.

Exclusion Criteria

Participants who met following criteria were excluded from study; immunosuppression (HIV infections, patients receiving chemotherapy and patients having cancer), steroid treatment for at least two weeks for prednisolone 20 mg or equivalents, immunosuppressive drug usage, history of organ transplantation or splenectomy, admission to intensive care unit for trauma and surgical reasons and blood bilirubin levels over 40 mg/dl or triglycerides over 1000 mg/dl.

Obtaining data

Participants' co-morbidities [diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT) and coronary artery disease (CAD)], age, gender were recorded. Samples for lymphocyte, neutrophil and platelet count, mean platelet volume (MPV), C-reactive protein (CRP), uric acid, procalcitonin, albumin and blood, sputum cultures (endotracheal aspirate culture from intubated patients) were taken from all participants as they were admitted to the ICU. Procalcitonin/albumin ratio was calculated.

The cultures of the patients were evaluated on BD Phoenix 100 (USA). Uric acid, CRP and albumin were measured by Roche Hitachi Cobas 501 (Switzerland) with standard kits. Procalcitonin was measured immunochromatographically by Roche Hitachi Cobas 601 (Switzerland). Hemogram was examined with Sysmex XN-1000 (USA) as 22 parameters.

Expectations of the study

The primary expectation in this study is to show the role of procalcitonin/albumin ratio in predicting the severity of pneumonia and mortality in CAP. Other expectations are the investigation of the thirty-day mortality rates, and existence and effects of concomitant diseases and other inflammatory markers (lymphocyte, neutrophil and platelet counts, MPV, CRP and uric acid).

Statistical Analysis

Data were evaluated using the SPSS 25 program (SPSS Inc., Chicago, IL, USA).All variables were checked by Kolmogorov-Smirnov test, which showed normal distribution. Data are expressed as mean ± standard deviation. Significant differences between the groups were evaluated by One-Way ANOVA test. Student t test was used to evaluate the difference between the groups, and when $p < 0.05$, the results were considered statistically significant. In the Reciever Operator Characteristics Curve (ROC), the area under the curve was used to calculate the strength of the parameters relative to mortality.

Table I. Clinical characteristics of the surviving and deceased patients

	All Patient	Deceased	Surviving	p value
Age (years)	73.50±10.9	75.31±11.08	71.78±10.59	**0.005**
Male/Female (%)	54/46	58/42	49/51	0.080
Diabetes Mellitus	121	63	58	0.910
Hypertension	185	98	87	0.910
CAD[1]	167	86	81	0.910
COPD[2]	94	41	53	0.051
Lymphocytes (10^3 /µl)	1375±137	1433.42±121.32	1312.03±77.43	0.410
Neutrophils (10^9 g/L)	13578±2367	14851.14±1338	12159.63±2225	0.290
Thrombocytes (10^3 /µl)	228.56±12.53	217.55±9.76	240.76±9.01	0.840
Albumin (g/dl)	3.09±1.53	2.94±1.9	3.26±0.56	0.060
Uric acid (mg/dl)	6.05±2.84	6.77±3.2	5.61±2.4	0.420
MPV[3] (^{3} µm)	10.71±1.18	10.98±1.10	10.40±1.09	**0.001**
CRP[4] (mg/L)	162.94±14.11	185.27±10.73	137.85±10.24	**0.002**
Procalcitonin (ng/ml)	10.20±2.32	14.11±1.98	5.87±1.34	**0.001**
Procalcitonin/Albumin	3.94	5.53	1.99	**0.001**

[1] Coronary Artery Disease
[2] Chronic Obstructive Pulmonary Disease
[3] Mean Platelet Volume
[4] C-Reative Protein

RESULTS

The 30 day mortality rate was significantly associated with age (p=0.005), procalcitonin (p=0.001), MPV (p=0.001), CRP (p=0.002) and procalcitonin/albumin ratio (p = 0.001) in patients who were admitted to ICU with CAP.

Demographic data of the patients included in the study were; 162 (46%) of participants were female and 188 (54%) were male. The mean age of the participants included in the study was 73.50 ± 10.9 years. The mean age of the females was 75.31 ± 11.08, while the mean age of males was 71.94 ± 10.64 years. At the end of the 30-day follow-up, 184 patients died and 166 survived. Of the patients who died, 77 (42%) were female and 107 (58%) were male. In 83 patients, none of the four diseases (DM, HT, COPD, and CAD) investigated for mortality was available. Forty-four of the surviving patients and 39 of the deceased patients did not have these diseases. In the patients, the most common concomitant disease was hypertension. Co-morbidities, demographic data, laboratory characteristics, and investigated parameters of the surviving and deceased patients were reported in Table I. In 185 (52%) of patients microorganisms were reproduced in cultures. In 106 (57%) of the patients who died and in 79 (47%) of the surviving patients, culture was positive. Microorganisms reproduced in culture are shown in Table II.

In order to demonstrate the effectiveness of biomarkers in predicting 30 day mortality rates, ROC analysis were performed with CRP, albumin, procalcitonin, MPV and procalcitonin/albumin ratio parameters in CAP. The AUC value of procalcitonin/albumin ratio was significantly higher than other parameters (p = 0.001). The values obtained from the ROC analysis are shown in Table III. In the ROC curve, albumin value was below 0.5 and above other values (Figure 1). The cut-offs with maximum sensitivity and specificity were 83 mg / L for CRP, 9,950 10^9g/L for neutrophils, 0.75ng/ml for procalcitonin, and 0.22 for procalcitonin/albumin ratio.

Table II. Microorganisms reproduced in culture

Microorganisms	**Number of patients (%)**
Klebsiella pneumoniae	40 (21%)
Escherichia coli	33 (18%)
Acinetobacter baumannii	32 (18%)
Streptococcus pneumoniae	30 (16%)
Pseudomonas aeruginosa	18 (10%)
Staphylococcus aureus	8 (4%)
Other (Proteus mirabilis, Pantoea agglomerans, Serratia plymuthica, etc.)	24 (13%)

Table III. The values obtained from the ROC analysis

Variables	Area under curve (95% confidence interval)	p value
Procalcitonin/albumin	0.700 (0.643-0.757)	0.001
Procalsitonin	0.689 (0.632-0.748)	0.001
MPV[1]	0.631 (0.571-0.692)	0.001
CRP[2]	0.614 (0.559-0.682)	0.001
Albumin	0.306 (0.252-0.356)	0.001

[1] Mean Platelet Volume
[2] C-Reative Protein

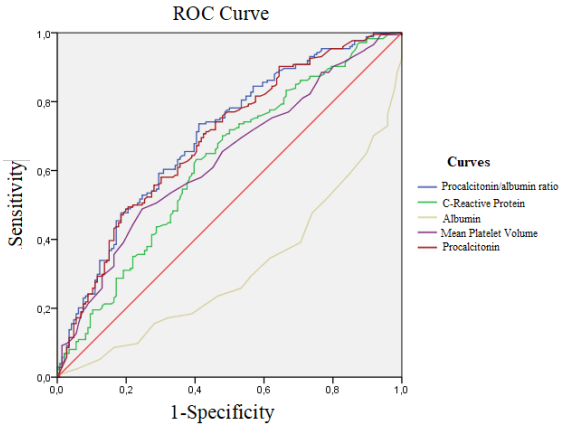

Figure 1. ROC Curves of albumin, procalcitonin, procalcitonin/albumin ratio, CRP and MPV

DISCUSSION

According to the results of this study, 30 day mortality rate was significantly associated with age, CRP, MPV, procalcitonin and procalcitonin/albumin ratio in patients admitted to ICU with CAP. The most significant of these associations is the

procalcitonin/albumin ratio. In the guidelines (11,12), two scoring systems recommended to evaluate severity of pneumonia are CURB-65 (confusion, uremia, respiratory rate, hypotension, and age greater than 65 years) and pneumonia severity index (PSI). In these two scoring systems, ages of the patients are being taken into account but, presences of DM, HT, CAD and COPD are not. In addition, these guidelines do not include leukocyte, lymphocyte and platelet counts and uric acid values in demostrating the severity of pneumonia. In this study, it was shown that mortality rate was higher in older patients. However, gender, leukocyte, lymphocyte and platelet counts, uric acid levels and existence of DM, HT, COPD and CAD were not correlated with 30-day mortality which may be reported as concordant with guidelines. Malnutrition due to infections will impair liver function, cause an increase in inflammatory mediators and a decrease in albumin synthesis (13). Albumin is thought to improve outcome of infection due to its antioxidant, anti-inflammatory effects and its protective role in regulating hemostasis and microcirculation (14). In a study conducted in Spain, albumin value was found to be associated with mortality in CAP (15). In this study, it was found that albumin levels were lower in the group who died compared to survivors. However, the difference was not statistically significant ($p = 0.06$). This was thought to be caused by demographic properties of participants who had multiple co-morbidities (77% of total participants). In a Korean study, it was shown for the first time that the severity of pneumonia was associated with MPV in inpatients. (16). Current reported study is one of the few studies showing the association of MPV with the severity of pneumonia in ICU patients. MPV value was associated with mortality rate in pneumonia. Infections cause production of large platelets which have higher thrombogenic activity. Elevated MPV reflects increased inflammatory response and hypercoagulability, leading to higher mortality (17).

As reported in previous studies, CRP testing may be used in the diagnosis of sepsis and infection, but early CRP testing may be insufficient in diagnosis of infections (18). In geriatric patients CRP levels may be higher due to co-morbidities, thus, it is less effective in showing the severity of pneumonia (19). In this study, CRP value was studied to demonstrate severity of pneumonia, but due to the aforementioned factors, it was not considered sufficient lonely. In addition to CRP, the researchers needed to use other parameters to demonstrate the severity of pneumonia. In this study, similar to many other studies (20), CRP was found to be concordant with mortality. In a meta-analysis, it has been shown that high procalcitonin level is related with mortality rate in CAP (21). In a study conducted by Akagi et al., there was no relationship between procalcitonin level and 30-day mortality in geriatric patients (10). Deterioration of procalcitonin response to microorganisms in geriatric patients due to various reasons was shown to be the reason for this. Procalcitonin level may also increase for non-infectious reasons. Procalcitonin level may also increase for non-infectious reasons (8) and its specificity is low, so it is considered that it may not adequately reflect the risk of mortality in pneumonia. The use of procalcitonin and albumin parameters together (procalcitonin/albumin ratio) yields a better marker of sensitivity and specificity in infections. The role of this ratio in determining the prognosis in infections was previously examined in two studies. In a study conducted in China, it was demonstrated that procalcitonin/albumin ratio was better than CRP and leukocyte count in differentiating urinary tract infection and urosepsis diagnosis (18). In another study by Deng et al., albumin/procalcitonin ratio was evaluated inversely as a ratio. Lower values of this ratio has been thought to be an indicator of an early sign of a nasocomial infection in patients with cerebral hemorrhage (22). Procalcitonin/albumin ratio can be used in early diagnosis of bacterial infection. Among

the parameters examined in this study, the procalcitonin/albumin ratio revealed the strongest relationship with mortality, therefore it was considered to be useful in predicting the prognosis of infection and predicting mortality. One of the limitations of this study is that it was performed retrospectively. Although the number of cases may be statistically significant, prospective studies with larger cohorts are needed to support such an important determination. Another limitation of this study is that there are not yet many studies supporting and / or opposing the results of the present study in the current literature.

CONCLUSION

There was a significant relationship between 30-day mortality and age, CRP, MPV, procalcitonin and procalcitonin/albumin ratio in CAP. This study showed that procalcitonin/albumin ratio could be used as an indicator of mortality in the early stage of CAP.

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Conflict of interest and funding

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