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RESEARCH

RELATIONSHIP BETWEEN MORTALITY AND THE LABORATORY VALUES AT ADMISSION TO PALLIATIVE CARE UNIT IN GERIATRIC PATIENTS WITH NO DIAGNOSIS OF MALIGNANCY

ABSTRACT

Introduction: With a global rise in the elderly population, the need for palliative care units (PCU) is also increasing. Moreover, it is important to determine the prognosis in these patients. Thus, the present study aimed to evaluate the relationship between mortality and the biomarkers at admission to PCU, in the geriatric patients with no diagnosis of malignancy.

Materials and Method: Medical records of the patients hospitalised in the Isparta City Hospital PCU, between 01.03.2017 and 31.03.2018, were retrospectively reviewed. Age, gender, neutrophil, lymphocyte and platelet counts, mean platelet volume and the C-reactive protein and albumin values, at admission to the PCU, were evaluated.

Results: The median age of the patients was 81 years (interquartile range: 73–87 years), and 58.5% (n=76) of the patients were female. The mortality rate of the patients was 21.5% (n=28). An albumin value <3.5 g/dL (odds ratio 35.40, 95% confidence interval (CI)=4.86-257.65 and p<0.001) was determined as an independent risk factor. The cut-off for the mean albumin value according to the receiver operating characteristic analysis, performed to predict the mortality rate, was 3.5 g/dL, with sensitivity and specificity values as 89% and 92%, respectively. The positive and negative predictive values and the positive and negative likelihood ratio values were 0.75, 0.96, 11.38 and 0.12, respectively (area under the curve=0.937 and 95% CI=0.880–0.994, p<0.0001).

Conclusion: Albumin values may effectively predict the prognosis of geriatric PCU patients, not diagnosed with malignancy.

Key words: Palliative Care; Geriatrics; Mortality; Serum Albumin.

ARAŞTIRMA

MALİGNİTE TANISI OLMAYAN GERİATRİK HASTALARIN PALYATİF BAKIM ÜNİTESİNE YATIŞ LABORATUAR DEĞERLERİ İLE MORTALİTENİN İLİŞKİSİ

Öz

Giriş: Yaşlı popülasyonda küresel bir artışla birlikte, palyatif bakım üniteleri (PBÜ) ihtiyacı da artmaktadır. Ayrıca, bu hastalarda prognozun belirlenmesi önemlidir. Bu nedenle, bu çalışmada malignite tanısı olmayan geriatric hastalarda PBÜ'ye giriş sırasındaki biyobelirteçler ile mortalite arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 01.03.2017 ve 31.03.2018 tarihleri arasında Isparta Şehir Hastanesi PBÜ'de yatan hastaların tıbbi kayıtları retrospektif olarak incelendi. Üniteye giriş sırasındaki yaş, cinsiyet, nötrofil, lenfosit ve trombosit sayısı, ortalama trombosit hacmi ve C-reaktif protein ve albümin değerleri değerlendirildi.

Bulgular: Hastaların ortalama yaşı 81 (çeyrekler arası aralık: 73-87) idi ve hastaların % 58.5'i (n=76) kadındı. Hastaların mortalite oranı % 21.5 (n=28) idi. <3.5 g/dL'lik bir albümin değeri (Odds oranı=35.40, %95 güven aralığı (CI)=4.86–257.65 ve p<0.001) bağımsız bir risk faktörü olarak belirlenmiştir. Mortalite oranını tahmin etmek için yapılan ROC çözümleme analizine göre albümin cut-off değeri, sırasıyla% 89 ve% 92 olarak duyarlılık ve özgüllük değerleri ile 3,5 g / dL idi. Pozitif ve negatif prediktif değerler ve pozitif ve negatif olabilirlik oranı değerleri sırasıyla 0.75, 0.96, 11.38 ve 0.12 idi (eğri altındaki alan=0.937 ve% 95 CI=0.880-0.994, p<0.0001).

Sonuç: Albumin değerleri, malignite tanısı olmayan geriatric PBÜ hastalarının prognozunu etkili bir şekilde öngörebilir.

Anahtar sözcükler: Palyatif bakım; Geriatri; Mortalite; Serum Albumin



INTRODUCTION

The elderly population is rising globally. In the United States, the population over 65 years of age was 9% in the year 1960, while it is expected to reach 20% by 2050 (1). Likewise, the elderly population is increasing in our country. In the last census in our country, the population of the elderly was found to be 8.3% (2). Life expectancy in Turkey is 75.3 years for men and 80.7 years for women (3). With the increase in life expectancy, the burden of chronic diseases in patients over 65 years of age also increases (4). Chronic diseases increase with the ageing population. As a result, the need for palliative care units (PCUs) is increasing (5). According to the data of Turkish Public Hospitals Authority (October 2016), Turkey has a total of 2,220 beds in 197 PCUs, the number being much lower than the required (6).

PCUs are intended to improve the quality of life of people with chronic illnesses, by preventing and relieving symptoms (7). In Turkey, palliative care, intensive care, geriatric care and home care services are nested case. In this way, it is aimed to provide the necessary care to patients in every environment.

A better definition of the profile of patients in PCUs and the factors affecting the duration of stay will contribute to the efficient use of existing palliative care beds. For this reason, it is essential to determine the clinical characteristics of the patients in PCU and examine the factors associated with the prognosis. Studies investigating the factors, affecting the duration and prognosis of palliative care patients, are limited (8).

The aim of this study was to evaluate the relationship between mortality and the biomarkers at admission to PCU, in geriatric patients with no diagnosis of malignancy. When selecting the biomarkers evaluated, it is intended to be used in relatively new markers such as C-reactive protein/Albumin Ratio as well as classical markers such as neutrophil, lymphocyte, platelet count, neutrophil

to lymphocyte ratio, C-reactive protein and albumin.

MATERIALS AND METHOD

In this study, medical records of the patients hospitalised in the Isparta City Hospital PCU, between 01.03.2017 and 31.03.2018, were retrospectively reviewed, after obtaining the approval of the local ethics committee (Ethical Committee approval date & number: 27.06.2018 & 2018/250). Patients with a diagnosis of malignancy, lack of medical records and under the age of 65 years were excluded from the study. Furthermore, patients with recurrent admissions were not included in the study. Patients with hemodynamic instability and infection were also excluded. The following variables during the admission to the PCU were recorded: age, gender, accompanying illnesses, neutrophil, lymphocyte and platelet counts, mean platelet volume (MPV) and the C-reactive protein (CRP) and albumin values. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and CRP/albumin ratio were calculated from these values. Furthermore, the length of stay and survival were also recorded. Survival data were collected over three months, after the end of the study and the survival was determined from the date of initial admission at the PCU.

Data were statistically analysed using the SPSS Version 22.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Data were tested for normality with Kolmogorov–Smirnov (with Lilliefors correction) and Shapiro–Wilk tests. Descriptive statistics were performed in both the patient groups; numerical data were expressed as median [the interquartile range (IQR)], while categorical data as percentages. Patients were classified according to the PCU outcomes (dead or survived), as survivor and the non-survivor groups. Patient features were compared using the Chi-Square or Fisher's Exact test for categorical

variables and Mann–Whitney U-test for numerical variables. A p value < 0.05 was accepted as statistically significant. To identify any independent risk factor associated with mortality, among the significant parameters of univariate analysis, the ones which were not associated with each other were subjected to multivariate linear regression analysis. Receiver operating characteristic (ROC) analysis was performed.

RESULTS

Two hundred and twenty-one patients were admitted to the PCU during the study period,

and 130 of them met the criteria for inclusion and analysis of data. The general characteristics of the patients included in the study are presented in Table 1. The median age of the patients was 81 years (IQR: 73–87 years), and 58.5% (n=76) of the patients were female. The median length of stay was 14 days (7–42 days). The mortality rate of the patients was 21.5% (n=28).

The patient characteristics in terms of mortality are shown in Table 2. In the survivor group, the neutrophil count (p=0.009), MPV (p=0.004), CRP (p=0.015) and CRP/albumin ratio (p<0.001) were lower, whereas albumin was higher (p<0.001), than the non-survivor group.

Table 1. General Characteristics of Patients.

Variable	Total Patients (n= 130) Median (IQR), n (%)
Age, year	81.00 (73.00-87.00)
Gender, (M/F) n (%)	54 (41.5) / 76 (58.5)
Accompanying Illnesses, n (%)	
Diabetes	20 (15.4)
Hypertension	38 (29.2)
Neurological Diseases	74 (56.9)
Organ Failure	18 (13.8)
Nutritional Disorder	85 (65.4)
Length of Stay, day	14.00 (7.00-42.00)
Neutrophil count, (109 /L)	5.79 (4.41-8.27)
Lymphocyte count, (109 /L)	1.34 (1.02-1.78)
Platelet count, (109 /L)	261000 (210000-355000)
Mean Platelet Volume, fl	8.4 (7.90-9.00)
Neutrophil to lymphocyte ratio	4.71 (2.81-7.63)
Platelet to lymphocyte ratio	197.57 (147.36-279.14)
C-reactive protein, mg/L	3.67 (1.71-8.46)
Albumin, g/dL	3.50 (3.47-3.82)
C-reactive protein/Albumin Ratio	1.09 (0.46-2.59)

IQR: Inter Quantile Range, M: Male, F: Female.



The parameters with significant results according to univariate analysis were evaluated with multivariate analysis. Among these parameters, only albumin < 3.5 g/dL [odds ratio (OR) 35.40, 95% confidence interval (CI)=4.86–257.65, $p < 0.001$] was determined as an independent risk factor. Albumin < 3.5 [OR 157.2, 95% CI=4.3–5709.8, $p = 0.006$] was determined as an independent risk factor (Table 2).

The ROC analysis for the prediction of mortality and cut-off values in the survivor group versus non-survivor group was performed. The mean albumin values based on ROC analysis are shown in Table 3. The cut-off value of mean albumin values according to the ROC analysis was found as 3.5 g/dL (Figure 1). The sensitivity and specificity values for the albumin cut-off value of 3.5 g/dL were 89% and 92%, respectively.

Table 2. The patient characteristics in terms of mortality.

	Univariate analysis			Multivariate analysis	
	Mortality		P	OR	P
	Survivor (n= 102) Median (IQR), n (%)	Non-Survivor (n= 28) Median (IQR), n (%)			
Age, year	80.50 (72.00-87.00)	83.00 (76.25-86.25)	0.505		
Gender, (M/F) n (%)	42 (41.2) / 60 (58.8)	12 (42.9) / 16 (57.1)	0.873		
Accompanying Illnesses, n					NS
Diabetes	19 (18.6)	1 (3.57)	0.038		
Hypertension	33 (32.35)	5 (17.85)	0.101		
Neurological Diseases	60 (58.82)	14 (50.00)	0.267		
Organ Failure	13 (12.74)	5 (17.85)	0.337		
Nutritional Disorder	63 (61.76)	22 (78.57)	0.074		
Length of Stay, day	14.50 (7.00-52.25)	12.00 (4.25-34.00)	0.145		
Neutrophil count, mm ³ ^a	5.58 (4.14-7.93)	6.80 (5.47-9.55)	0.009		NS
Lymphocyte count, mm ³	1.38 (1.03-1.85)	1.15 (0.97-1.38)	0.060		
Platelet count, mm ³	259000 (210750-355000)	274500 (209250-357000)	0.937		
Mean Platelet Volume, fl ^a	8.40 (7.90-8.90)	8.65 (8.10-9.37)	0.004		NS
Neutrophil to lymphocyte ratio	3.84 (2.58-7.46)	6.32 (4.75-8.01)	0.161		
Platelet to lymphocyte ratio	187.16 (137.86-267.77)	253.81 (167.31-317.84)	0.090		
C-reactive protein, mg/L ^a	3.27 (1.59-7.36)	7.17 (2.80-9.22)	0.015		NS
Albumin, g/dL	3.60 (3.50-3.92)	2.32 (2.12-3.01)	<0.001	35.40 (4.86-257.65)	<0.001
C-reactive protein/Albumin Ratio ^a	0.89 (0.39-2.08)	2.32 (0.94-4.01)	<0.001		NS

The parameters in bold indicates the significant ones in univariate and multivariate analysis. ^a Marked parameters which were significant in univariate analysis and not associated with each other were included in the multivariate analysis. IQR: Inter Quantile Range, OR: Odds Ratio, M: Male, F: Female.

Figure 1. Receiver Operating Characteristic (ROC) curve for mean Albumin Value.

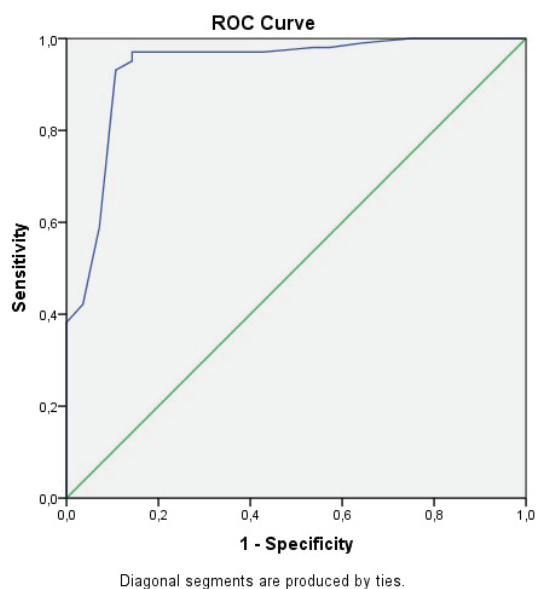


Table 3. Receiver operating characteristic analysis for the prediction of mortality. Cut-off for Survivor group versus Non-Survivor group mean Albumin based on ROC analysis.

	AUC	p value	Asymptotic 95 % confidence intervals lower bound -upper bound	Cut off value
Mean Albumin	0.937	<0.0001	0.880-0.994	<3.5
Outcome: Death				
		Yes	No	Total
Mean Albumin< 3.5	Yes	25	8	33
	No	3	94	97
	Total	28	102	130
95 % confidence intervals				
Sensitivity		0.89		0.72-0.97
Specificity		0.92		0.85-0.96
Predictive value of positive test		0.75		0.61-0.86
Predictive value of negative test		0.96		0.91-0.98
Positive likelihood ratio		11.38		5.78-22.41
Negative likelihood ratio		0.12		0.04-0.35

ROC: Receiver operating characteristic; AUC: Area Under The Curve.



Positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio values were found as 0.75, 0.96, 11.38 and 0.12, respectively (the area under the curve (AUC) was 0.937 and 95% CI=0.880–0.994, $p < 0.0001$) (Table 3).

DISCUSSION

The concept of PCU is the newly defined in Turkey and the PCU capacity is not enough yet. Due to the growing elderly population throughout the world, the need for PCUs is increasing. Therefore, effective use of PCU is important. PCU-related studies are limited in the literature and are mostly related to the duration of stay and the factors affecting cost (8). Moreover, the PCU-related studies are more related to patients with malignancy, who constitute the majority of the PCU patients. In the literature, there are limited studies on the factors that affect the prognosis in PCUs and in the patients with no malignancy admitted to the PCUs.

In the present study, the relationship between mortality and the laboratory values at admission to PCU was evaluated in geriatric patients with no diagnosis of malignancy. In the present study, it was shown that only the albumin levels influenced the mortality rate. The literature assessing the factors affecting the prognosis of patients in PCUs is limited. In addition, the inclusion of patients with malignancy in these studies further complicates the situation. Many laboratory values have been evaluated for the evaluation of prognosis in various patient groups, especially in the intensive care units (ICUs). However, the studies evaluating the effect of these parameters on the prognosis in PCUs are not enough.

Albumin is an acute phase protein, synthesised by the liver and has several basic functions. It is the primary serum binding protein responsible for the transport of various substances, has anti-thrombotic effect and is responsible for maintaining normal plasma colloid oncotic pressure (9).

Normally, albumin has a long half-life (15–19 days), but rapid declines are seen in critically ill patients (9). Albumin is primarily a binding protein. This is particularly important in the elderly, because the concentration of circulating free drugs increases in hypoalbuminemia and an increased bioavailability may cause adverse effects (10). Hypoalbuminemia has previously been associated with short-term mortality, hospital stay, and complications (9, 11). A large prospective study of emergency patients showed that patients with hypoalbuminemia had a shorter-term mortality, three times higher than the patients with normal albumin (9). Jellinge et al. found hypoalbuminemia to be associated with 30-day all-cause mortality in acutely admitted medical patients (12). In patients with normal albumin levels at admission, a 2% mortality was determined (13). Mortality was determined as 12% in patients with mild hypoalbuminemia and 34% in patients with marked hypoalbuminemia. This rate was found to be 0.3% in patients with hyperalbuminemia (13). In addition, there was a significant increase in long-term and short-term survival in patients who had hypoalbuminemia at the time of admission, but normalised albumin levels during the stay in the hospital (13).

The prognostic role of albumin in patients with severe comorbidity has increased. However, its value as a marker of mortality in PCU patients is still unclear. The effect of albumin and creatinine levels at the time of admission on survival was evaluated in PCU patients and albumin values lower than 3.1 g/dL were shown to be associated with poor survival (14). In the present study, it was shown that the only parameter with prognostic importance in geriatric patients in the PCU, without a diagnosed malignancy, was albumin. Albumin values lower than 3.5 g/dL were shown to be associated with poor survival.

CRP is a classical acute phase protein that shows a rapid and significant increase in plasma concentration in response to acute inflammation (15). The CRP level has been reported to be a

good prognostic marker in patients with advanced stage cancer (15).

Anamo et al. have demonstrated the relationship between CRP levels with symptoms and activities of daily living in advanced stage cancer patients receiving palliative care and that CRP levels may be a good biomarker in these patients (16). In the present study, although CRP values were 2 times higher in the non-survivor group, it was shown that they had no effect on mortality.

Recently, the CRP/albumin ratio, a combination of markers for systemic inflammation and nutritional status, has been extensively studied as an independent prognostic marker in patients with infection, malignancy and other diseases (17). However, there is no study focusing on patients in the PCUs. The increased CRP/albumin ratio in the ICUs is an independent risk factor for mortality (18). In addition, the CRP/albumin ratio among patients receiving parenteral nutrition is closely related to morbidity and mortality (19). Since the CRP/albumin ratio effectively reflects both inflammation and malnutrition, it can be a useful biochemical marker to predict prognosis among the critically ill patients. In a retrospective study evaluating the clinical benefit of CRP/albumin ratio in predicting 30-day mortality in critically ill patients, an elevated CRP/albumin ratio was an independent risk factor for the 30-day mortality, and the predictive value of CRP/albumin ratio was lower than that of the albumin alone, APACHE (Acute Physiology and Chronic Health Evaluation) II score and Charlson Comorbidity Index (20).

In the study performed by Park et al., high CRP/albumin ratio was shown to be associated with increased mortality in the ICU patients (21). However, the sensitivity and specificity of the CRP/albumin ratio were not enough high for mortality estimation. In the present study, although the CRP/albumin ratio was higher in the non-survivor group, it was found to have no effect on mortality.

The NLR which can be easily obtained by

automated blood count devices has been evaluated for the clinical effects of many types of cancer (22). It was stated that, elevated NLR was an independent prognostic factor for poor survival in patients with terminal cancer (23).

In the studies performed in ICU patients, the effect of NLR on prognosis could not be demonstrated (24). In addition, these studies showed that the neutrophil and platelet counts, MPV and CRP did not have any significance in terms of prognosis in the ICU patients, similar to the results of the present study.

Apart from all these laboratory values, accompanying illnesses of the patients have an effect on mortality. Although there is not enough literature about this subject in PCU patients, there is a wide literature about ICU patients. Already, the basis of many scoring systems routinely used in ICUs is based on organ failure and accompanying illnesses. One of the most important scoring systems, Sequential Organ Failure Assessment (SOFA) score, was used to clearly define the relationship between organ failure and mortality in ICU patients (25,26). The highest SOFA score in the first and first few days of entry to ICU was reported to be strong prognostic indicators (27). Although there is not enough information about the effects of organ failure on the mortality and morbidity of PCU patients, the effect of a serious medical condition such as organ failure on mortality should be considered as a natural outcome. However, our study revealed that organ failure in PCU patients is not an independent risk factor for mortality. We believe that the inclusion of patients without a diagnosis of malignancy was the reason for this result.

It has been shown that the duration of ICU stay and mortality are increased in patients with nutritional disorders (28). As a natural consequence of this condition, changes in laboratory values such as albumin are expected in patients with nutritional disorders. In the present study, although the rate of nutritional disorders was high in the Non-Survivor



group, no statistically significant difference was found. However, we think that significant decrease in albumin in Non-Survivor group is a clinical indicator of this condition.

In a study in which the clinical features of the PCU patients were evaluated for the duration of hospital stay and prognosis, it was stated that the advanced pressure wound was the most important factor to prolong hospital stay (29). In addition, it was shown that the use of opioid and malignancy were the most important factors for prognosis. Unlike the present study, malignancy patients were also included in that study and laboratory values were not studied.

This study had some limitations, the first being its retrospective nature and the other being a single-centred work. And also, it can be seen as a limitation that no scoring system was used during PCU admission.

Thus, to predict the prognosis of geriatric PCU patients, without a diagnosis of malignancy, the albumin values at admission to PCU may be effective.

CONFLICT OF INTEREST

All authors state that there is no conflict of interest.

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