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The Prognostic Significance of the Neutrophil-to-Lymphocyte Ratio in Patients with Multiple Myeloma: A Pilot Study

Multiple Miyelom Hastalarında Nötrofil Lenfosit Oranının Prognostik Önemi

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ABSTRACT

Objective: The neutrophil-to-lymphocyte ratio(NLR) is a biomarker for systematic inflammation. It is also thought that the NLR can be used as a new biomarker by clinicians in predicting the prognosis of patients with multiple myeloma(MM). This study, aimed to retrospectively investigate the prognostic significance of pretreatment NLR in patients with MM, based on the hypothesis that elevated pretreatment NLR is a biomarker indicating worse survival in patients with MM.
Materials and Methods: Patients aged >18 years with MM diagnosed, follow-up, and treated between January 2011 and December 2017 in the department of internal and geriatric medicine at Istanbul Faculty of Medicine were enrolled into this study. We retrospectively collected the data of 40 patients from the medical records. The relationship between NLR and baseline characteristics, laboratory parameters, prognosis, and survival outcome was analyzed.
Results: The study showed that the mean NLR was 2.84±2.62 (0.1-14.8) in the whole blood count. No significant correlation was found between NLR and mortality (p=0.965). A significant relationship was found between higher stage and mortality (p=0.035). In addition, anemia, low albumin level, and elevated lactate dehydrogenas (LDH) level indicated poor survival time in patients with MM (p=0.022; p=0.031; p=0.023).
Conclusion: Our study showed no relationship between NLR and both mortality and overall survival (OS). The above result can be explained by the fact that our study had some limitations such as the use of retrospective data from a single-center and the small sample size.
Keywords: Multiple myeloma, neutrophil-lymphocyte ratio, overall survival

ÖZ

Amaç: Nötrofil-lenfosit oranı (NLR), bir sistematik inflamasyon biyobelirtecidir. Multipl miyelomlu (MM) hastalar için de NLR'nin prognozu öngörmede yeni bir biyobelirteç olarak klinisyene yardımcı olabileceği düşünülmektedir. Bu çalışmada, tedavi öncesi NLR'nin MM hastalarında daha kötü bir sağkalım biyobelirteci olduğu hipotezine dayanarak, MM'lu hastalarda tedavi öncesi NLR'nin prognostik önemini retrospektif olarak araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmaya, İstanbul Tıp Fakültesi İç Hastalıkları ve Geriatri Anabilim Dalı'nda Ocak 2011 - Aralık 2017 tarihleri arasında tanı, takip ve tedavi gören 18 yaş üstü MM hastaları alındı. 40 hastanın verileri tıbbi kayıtlardan retrospektif olarak toplandı. NLR ile temel özellikler, laboratuvar parametreleri, prognoz ve sağkalım arasındaki ilişki analiz edildi.
Bulgular: Mevcut çalışma, tam kan sayımında ortalama NLR'nin 2,84±2,62 (0,1-14,8) olduğunu gösterdi. NLR ile mortalite arasında anlamlı bir ilişki bulunmadı (p=0,965). Yüksek evre ile ölüm arasında anlamlı bir ilişki vardır (p=0,035). Ayrıca anemi, düşük albümin düzeyi ve yüksek laktat dehidrogenaz (LDH) düzeyi MM'lu hastalarda kötü sağkalım süresine işaret ediyordu (p=0,022; p=0,031; p=0,023).
Sonuç: Çalışmamız NLR ile mortalite ve genel sağkalım (OS) arasında bir ilişki olmadığını gösterdi. Çalışmamızda NLR ile mortalite ve OS arasında bir ilişkinin olmamasının nedeni, çalışmamızın tek merkezden geriye dönük verilerin toplanması ve küçük örneklem büyüklüğü gibi bazı sınırlılıklara sahip olması olabilir.
Anahtar Kelimeler: Multipl miyelom, nötrofil-lenfosit oranı, genel sağkalım

INTRODUCTION

Multiple myeloma (MM) is a plasma cell cancer characterized by the accumulation of neoplastic plasma cells in the bone marrow, which produce excess immunoglobulin. MM is the second most common hematological malignancy that accounts for 1% of all tumors in adults and approximately 15% of all hematological malignancies (1). Patients with MM may present clinical manifestations during the course of the disease, including bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections (2).

Several researchers have described the absolute lymphocyte count as a surrogate biomarker of tumor-infiltrating lymphocyte, reflecting systemic host immunity, and absolute neutrophil count as the host inflammatory response to cancer. In addition, the absolute counts of inflammation parameters and the NLR have been proposed as a simple and inexpensive marker to assess clinical outcomes in various types of cancers. Recently, the NLR has been shown to be a new independent prognostic factor in patients with MM, and a meaningful relationship has been found between NLR and the accepted prognostic markers (4-6). Further, an elevated NLR may predict worse clinical outcomes in patients with MM (4-7). In this study, we aimed to evaluate the possible association between NLR and clinical parameters, prognosis, and survival in patients with MM.

MATERIALS AND METHODS

Study Objectives

Recently, several investigators have suggested that the NLR is an easily available and inexpensive marker for assessing clinical outcomes in MM patients. However, the relationship between NLR and prognosis in patients with MM has not yet been clearly demonstrated. This study aimed to evaluate the prognostic significance of NLR in patients with MM (3-5,7).

Study Population

Male and female patients aged 26 to 87 years with MM, diagnosed, follow-up, and treated between January 2011 and December 2017 in the department of internal and geriatric medicine at Istanbul Faculty of Medicine were included in this study.

Inclusion and Exclusion Criteria

Male and female patients older than 18 years at the time of diagnosis with a definite MM were included in the study. Patients without sufficient data in the medical record and regular follow-up were excluded from the study.

Methods

Since this was a pilot study, no sample size/power calculation was performed. We enrolled 43 patients with MM by a retrospective review of the medical record of patients.

A total of 40 patients with MM were eligible, including 21 female and 19 male patients. The data of these patients were extracted from the hospital automation systems in the department of internal and geriatric medicine at the Istanbul Faculty of Medicine.

The patients were classified according to the International Staging System (ISS) criteria. Dates of death were obtained from the death notification system of the Turkish Statistical Institute. Overall survival (OS) was defined as the period between the date of diagnosis and date of death from any cause.

Statistical Considerations and Data Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for data analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum and maximum) were used to evaluate the study data. Shapiro Wilk test and graphical analysis were used to determine if the quantitative data were normally distributed. The student t-test was used to make comparisons between two groups of normally distributed quantitative, while the Mann Whitney U test for comparison between two groups of non-normally distributed quantitative variables. Pearson chi-square test and Fisher Freeman Halton test were used to compare the qualitative data. OS was analyzed using Kaplan Meier curves. Comparisons of survival between the different groups were made using the log-rank test. Statistical significance was considered as $p<0.05$. For visualization of the collected data and resulting prevalence values and relationships, pie charts, bar charts, and tables were used.

Data Protection

All patients were coded with a consecutive number and pseudonymized for further evaluation. Only authorized persons had access to the original data.

Risk-Benefit Assessment

The included patients had no direct benefit from the study. However, since this study was only a retrospective analysis of their data, no patient risk was expected. The only possible risk of the disclosure of sensitive patient data was minimized by the pseudonymization and access restriction.

RESULTS

Statistical Analysis

A total of 40 patients with MM, including 21 females (52.5%), and 19 males (47.5%) were included in the pilot study. The baseline characteristics of the MM patients in this study are shown in Table-1.

Regarding the type of multiple myeloma M protein, the largest group consisted of 7 (20.0%) with IgG lambda, followed by 5 (14.3%) patients IgG kappa. In addition, 4 (11.4%) patients had IgA lambda, 3 (8.6%) IgA kappa, 8 (22.9%) light chain kappa, and

Table 1. Distribution of demographic data of patients with MM

Multiple Myeloma (n=40)		Cases (n)	Percent (%)	Min-Max (Median)	Mean±SD
Age (years)				26-87 (61)	61.20±11.20
	Female			43-87 (64)	63.4±11.0
	Male			26-75 (60)	58.9±11.2
Gender	Female	21	52.5	-	-
	Male	19	47.5		
Subtype (n=35)	IGA kappa type	3	8.6	-	-
	IGA lambda type	4	11.4		
	IGG kappa type	5	14.3		
	IGG lambda type	7	20.0		
	IGM kappa type	1	2.9		
	IGM lambda type	1	2.9		
	Kappa type	8	22.9		
	Lambda type	4	11.4		
	Smoldering type	2	5.7		
ISS Staging (n=36)	Stage I	9	25.0	-	-
	Stage II	7	19.4		
	Stage III	20	55.6		
Symptoms	Weight loss	11	27.5	-	-
	Weakness	22	55.0		
	Paleness	10	25.0		
	Night sweats	1	2.5		
	Fever	9	22.5		
	Paresthesia	2	5.0		
	Bone pain	31	77.5		
	Shortness of breath	2	5		
	Spinal cord compression	1	2.5		
Organomegaly (n=39)	No	29	74.4	-	-
	Yes	10	25.6		
	Hepatomegaly	10	25.6	-	-
	Splenomegaly	4	10.3		
Palpable Lymphadenomegaly (n=39)	No	37	94.9	-	-
	Yes	2	5.1		
Pleural Effusion (n=39)	No	33	84.6	-	-
	Yes	6	15.4		
Extra Plasmacytoma (n=39)	No	30	77.0	-	-
	Yes	9	23.0		
Lytic Lesions (n=37)	No	16	43.2	-	-
	Yes	21	56.8		

Table 1. Continued

Proteinuria (n=31)	No Yes	14 17	45.2 54.8	-	-
Renal Involvement (n=40)	No Yes	35 5	87.5 12.5	-	-
Hemoglobin (g/dl)	>10	15	37.5	5.4-13.9 (9.3)	9.63±2.05
	≤10	25	62.5		
PLT (µL)	>375000	3	7.5	45400-512500 (192500)	205482.50± 94934.06
	155000-375000	25	62.5		
	<155000	12	30		
Beta 2 Microglobulin (mg/dl)	>2,2	31	91.2	1.7-80.1 (5.9)	10.21±14.39
	≤2,2	3	8.8		
Albumin (g/dl)	>3,5	19	50	1.82-5.6 (3.54)	3.45±0.80
	≤3,5	19	50		
ESR (mm/h)	>40	33	86.8	26-155 (92)	89.45±34.78
	≤40	5	13.2		
CRP (mg/l)	>5	25	67.6	0-126 (8)	18.51±30.07
	≤5	12	32.4		
LDH (U/L)	>250	25	62.5	113-998 (292.5)	324.45±158.28
	≤250	15	37.5		
Neutrophil/lymphocytes ratio				0.1-14.8 (2)	2.84±2.62
Survival status	Alive	21	52.5	-	-
	Death	19	47.5		
Survival time (months)				1-73 (13)	22.9±22.0

4 (11.4%) light chain lambda. Two patients (5.7%) had the smoldering type *(Figure 1)*.

The mean age of the patients was 61.20±11.20 years, and the age range was between 26 (male) and 87 (female) years. According to sex, the mean age of the female patients was 63.4±11.0, and that of the males was 58.9±11.2.

Clinically, at the time of diagnosis, 9 (25.0%) patients were diagnosed as stage I, 7 (19.4%) patients as stage II, and 20 (55.6%) patients as stage III on the basis of the ISS- staging *(Figure 2)*.

We found that 52.5% (n=21) of the patients were still alive. The median and mean survival times of the patients were obtained. The follow-up period ranged from 24 to 88 months, and mean survival was 22.9±22.0 months *(Figure 3)*.

In the whole blood count, the mean HGB level was 9.63±2.05 (5.4-13.9) g/dL, mean PLT was 205482.50±94934.06 (45400-512500) µL, mean CRP was 18.51±30.07 (0-126) mg/L, mean ESR was 89.45±34.78 (26-155) mm/h, mean beta-2 micro-

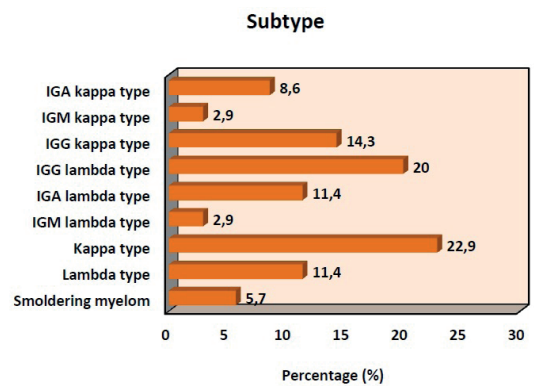

Figure 1. MM population by subtype.

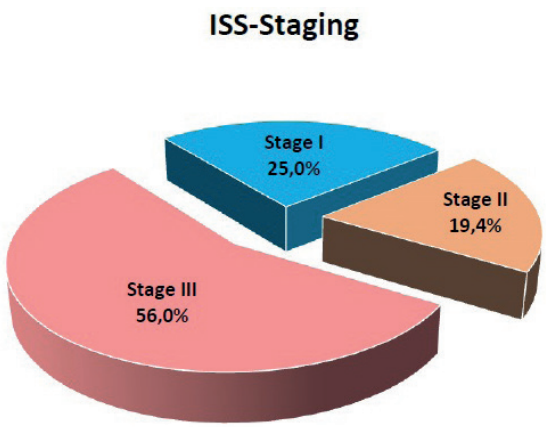

Figure 2. MM patients by ISS-staging.

globulin was 10.21±14.39 (1.7-80.1) mg/L, mean LDH was 324.45±158.28 (113-998) U/L, mean NLR was 2.84±2.62 (0.1-14.8) and mean albumin was 3.45±0.80 (1.82-5.6) g/dL. Based on the laboratory reference range, 25 (62.5%) patients had low hemoglobin levels, 12 patients (30.0%) low PLT levels, and 19 patients (50%) low albumin levels; CRP was found high in 25 (67.6%) patients, ESR in 33 (86.8%) patients, LDH levels in 25 (62.5%) patients, and beta-2 microglobulin in 31 (91.2%) patients.

Figure 3. MM population by mortality.

The demographic assessments of the MM patients by mortality are shown in Table 2.

Regarding the relationship between mortality and clinical parameters in the patients with MM, no significant correlation was found between age, gender, pathological subtype, and mortality (p=0.951, p=0.987, p=0.622, respectively).

There was a statistically significant relationship between ISS-staging and mortality (p=0.035; p<0.05).

Table 2. Demographic assessments of MM patients by mortality

Multiple Myeloma (n=40)		**Mortality**		**p values**
		Death (n=19)	**Alive (n=21)**	
Age	Min-Max(Median) Mean±SD	26-74 (63) 61.32±11.46	43-87 (60) 61.10±11.23	[a]0.951
Gender	Female Male	10 (47.1) 9 (47.4)	11 (42.9) 10 (52.6)	[b]0.987
Subtype (n=35)	IGA kappa type IGA lambda type IGG kappa type IGG lambda type IGM kappa type IGM lambda type Kappa type Lambda type Smoldering type	2 (66.7) 3 (75) 3 (60) 2 (28.6) 0 (0) 1 (100) 3 (37.5) 2 (50) 0 (0)	1 (33.3) 1 (25) 2 (40) 5 (71.4) 1 (100) 0 (100) 5 (62.5) 2(50) 2 (100)	[c]0.622
ISS Staging (n=32)	Stage I Stage II Stage III	1 (11.1) 4 (51.1) 12 (60.0)	8 (88.9) 3 (42.9) 8 (40.0)	[c]0.035*
Albumin g/dl	>3.5 ≤3.5	7 (35.0) 12 (66.7)	13 (65.0) 6 (33.3)	[b]0.023*
HGB (g/dl)	Min-Max(Median) Mean±SD	6.1-12.6 (8.9) 8.9±1.55	5.4-13.9 (10.5) 10.33±2.23	[a]0.022*
PLT (µL)	Min-Max(Median) Mean±SD	72000-512500 (189300) 200100±115483.4	45400-397000 (200000) 210352.4±74290.8	[d]0.336
NLR	Min-Max(Median) Mean±SD	0.4-14.8 (2.05) 3.06±3.2	0.1-9.5 (2) 2.64±2.04	[d]0.965
LDH (U/L)	Min-Max(Median) Mean±SD	163-998 (315) 378.4±185.9	113-509 (240) 275.6±111.7	[d]0.031*
Beta 2 Microglobulin (mg/dl)	Min-Max(Median) Mean±SD	2-29 (6.7) 10.40±8.71	1.7-80.1 (4.5) 10.04±18.3	[d]0.129
ESR (mm/h)	Min-Max(Median) Mean±SD	26-155 (107.5) 95.8±38.6	26-133 (84) 81.0±32.6	[d]0.230
CRP (mg/l)	Min-Max(Median) Mean±SD	0-126 (9) 25.74±38.5	1-203 (5) 16.5±28.4	[d]0.378

[a]Student t Test, [b]Pearson Chi-Square Test, [c]Fisher Freeman Halton Test[d]Mann Whitney U Test, *p<0.05

In addition, the frequency of ISS-Stage III was higher in dead patients (60.0%) compared to patients who were still alive (40.0%) *(Figure 4)*.

Regarding the relationship between mortality and laboratory parameters in the patients with MM, there was a statistically significant relationship between HGB, LDH, and albumin measurements and mortality (p=0.022, p<0.05; p=0.031, p<0.05; p=0.023, p<0.05).

The mean HGB concentration was 8.9±1.55 (6.1-12.6) g/dL in the death patients and 10.33±2.23 (5.4-13.9) g/dL in patients who are still alive; the HBG levels of the dead MM patients were found to be lower than those of the patients who were still alive *(Figure 5)*.

The mean LDH level was 378.4±185.9 (163-998) U/L in the death patients and 275.6±111.7 (113-509) U/L in patients who were still alive; the LDH levels of the dead MM patients were higher than those of the patients who were still alive *(Figure 6)*

The patients were divided into two categories as ≥3.5 g/dL albumin level and <3.5 g/dL albumin level, and the mortality rate in patients with albumin <3.5 g/dL (66.7%) was found to be higher compared to patients with albumin ≥3.5 g/dL (35%) *(Figure 7)*.

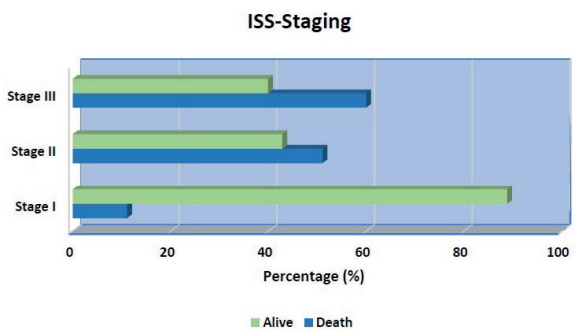

Figure 4. The ISS-Staging distributions of MM patients by mortality.

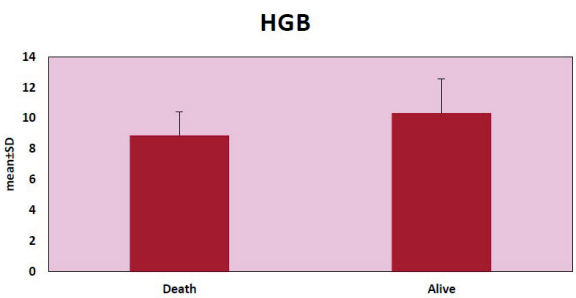

Figure 5. The HGB distributions of MM patients by mortality.

No significant correlation was found between PLT, beta-2 microglobulin, ESR, CRP levels, NLR, and mortality (p=0.336, p=0.129, p=0.230, p=0.378, p=0.965, respectively). It is noteworthy that the ESR measurements of the dead patients were higher than those of the patients who were still alive (p>0.05).

We found a higher OS in patients with albumin ≥3.5 g/dL compared to patients with albumin <3.5 g/dL (p=0.028, p<0.05) *(Figure 8)*.

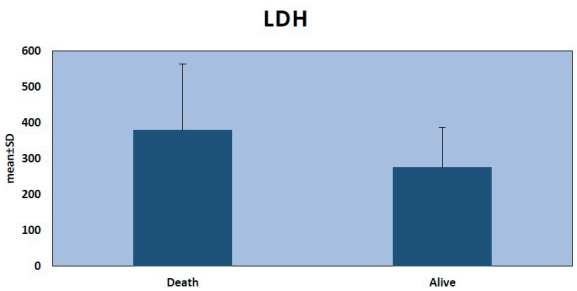

Figure 6. The LDH distributions of MM patients by mortality.

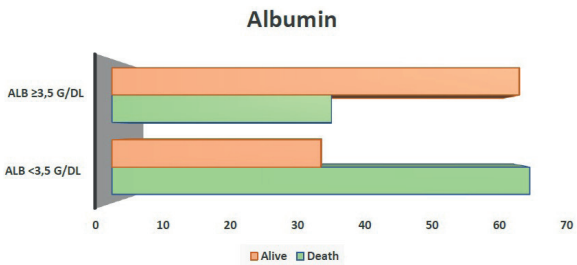

Figure 7. The albumin distributions of MM patients by mortality.

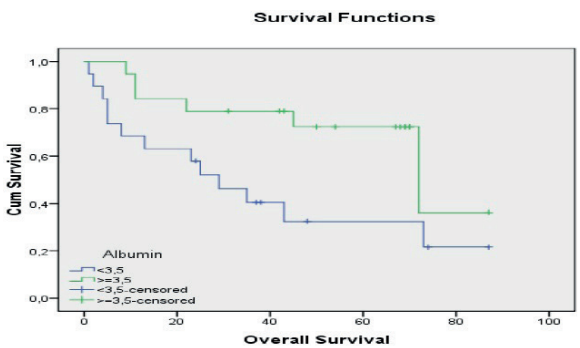

Figure 8. Survival rate correlation with albumin level.

DISCUSSION

MM accounts for 1% of all cancers and approximately 15% of hematological cancers. Thus, it is the second most common hematological cancer. MM

occurs more frequently in men than in women, and the cause is unknown (3). In our study, 47.5% males and 52.5% females were diagnosed with MM. The male-to-female ratio was found to be 0.90, and therefore, the ratio in our study was not consistent with the worldwide literature. The median age at diagnosis is 65 years in Europe, and 69 years in the USA, and it is rarely diagnosed under 40 years (3,10). The median age in our study was 61.2 yr. Accordingly, our population was still younger compared with the literature. We found no significant association between age and survival.

The previous studies reported that gender had no statistically significant effect on prognosis and OS in MM patients (8,13,16,17). In our study, similar to the literature, no significant correlation was found between gender and both mortality and OS.

Studies have demonstrated that higher stages of the disease tend to correlate with a poor prognosis (6,8,9,12). In our study, consistent with the previous results, there was a statistically significant correlation between the ISS stage and mortality.

According to the study by Zhou et al. the IgD subtype was shown to be an independent risk factor for prognosis, and it was associated with a poor OS (11). In our study, the majority of the study population also had IgG.

Pleural effusion (PE) is a poor prognosis factor in patients with MM. In our study, the incidence of PE was as high as 15.4%. The reason for the high incidence of PE in our study may due to the small number of cases.

Osteolytic lesions are one of the most common clinical manifestations of MM. In our study, more than half of the patients had bone lesions at the time of diagnosis.

Anemia is considered to be a poor prognostic factor in MM patients (14).In our study, the mean Hb concentration was 9.63, and 62.5% of patients had <10 mg/dL HGB level. Our findings were similar to those in the literature. Anemia in MM patients was associated with a worse outcome in the literature (13,14,20,21). In our study, similar to the literature, there was a statistically significant relationship between hemoglobin level and mortality.

Recent studies showed that a decreased PLT level predicts poor prognosis in MM patients (6,8,9,22). In our study, no significant correlation was found between PLT level and both mortality and OS in patients with MM. However, similar to our study, some studies reported no significant relationship between the PLT level and OS (5,15).

Recently, it has been suggested that the NLR can be used to predict prognosis in patients with MM. It has been reported in previous publications that an elevated NLR was associated with shortened OS in MM patients (4-6,23). In our study, there was no relationship between the NLR and both mortality and OS in patients with MM. However, similar to our study, no significant correlation between NLR and mortality and OS was demonstrated in other studies (9,15).

Serum beta-2 microglobulin and LDH are the most important markers for estimating the proliferative activity and invasive potential of MM (16). In our study, a high level of beta-2 microglobulin was found in 91.2% patients, while 62.5% of patients in our study had a high LDH level. We found no significant correlation between beta-2 microglobulin level and mortality and OS. The elevated LDH level has been frequently shown to indicate an unfavorable prognosis (8,17,18,19,23). Similar to previous studies, our study found a statistically significant relationship between LDH level and mortality.

A relationship between low albumin level and poor outcomes of MM patients has been demonstrated in the literature (8,24,25,26). In addition, similar to the literature, our study found a statistically significant relationship between albumin level and both mortality and OS, and the patients with low albumin levels had a poor survival.

CONCLUSION

Our study retrospectively evaluated the correlation between clinical and laboratory parameters and mortality and OS in patients with MM. The current study showed that there is a significant relationship between higher stages of the disease and mortality. In addition, anemia, low albumin levels, and elevated LDH levels indicated poor survival time in patients with MM.

In summary, our study showed no relation between NLR and both mortality and OS. The reason for this could be that our study had some limitations such as the use of retrospective data from a single-center and the small sample size.

Hakem Değerlendirmesi: Dış bağımsız.

Peer Review: Externally peer-reviewed.

Etik Komite Onayı: Bu calışma icin etik komite onayı İstanbul Universitesi İstanbul Tıp Fakultesi Etik Kurulu'ndan alınmıştır. (20.12.2018 tarihli, 1743 sayılı).

Ethics Committee Approval: This study was approved by the Ethical Committee of the Istanbul University Istanbul Faculty of Medicine (Date: 20.12.2018, Number: 1743).

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Informed Consent: Written consent was obtained from the participants.

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