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Prognostic factors and the prognostic role of inflammation indices in malignant pleural mesothelioma

Malign plevral mezotelyomada prognostik faktörler ve enflamasyon indekslerinin prognostik rolü

Senar Ebinç, Zeynep Oruç, Ziya Kalkan, Oğur Karhan, Zuhat Urakçı, Mehmet Küçüköner, Muhammet Ali Kaplan, Işıkdoğan Abdurrahman

Department of Internal Medicine, Division of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

ABSTRACT

Background: In this study, we aimed to investigate the prognostic factors of malignant pleural mesothelioma and the prognostic value of inflammation indices in malignant pleural mesothelioma.

Methods: Between January 2002 and December 2019, a total of 132 patients (74 males, 58 females; mean age: 55 years; range, 31 to 79 years) diagnosed with malignant pleural mesothelioma were retrospectively analyzed. Patients' demographic data and laboratory results were recorded. The prognostic value of the following five inflammation indices was evaluated: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, advanced lung cancer inflammation index, C-reactive protein/albumin ratio, and prognostic nutritional index.

Results: Of all patients, 81% (n=107) were aged 65 or older and 61.4% (n=81) had an epithelioid histology. Of 12 variables examined in the multivariate analysis for their relationship with survival, age ≥65 years, non-epithelioid subtype, and prognostic nutritional index <40 were found to be poor prognostic factors. Based on the score constructed from these factors, the good prognostic group (score 0-1) had a median overall survival of 21 months and a one-year survival rate of 77.9%, while the poor prognostic group (score 2-3) had a median overall survival of nine months and a one-year survival rate of 29.7%.

Conclusion: Our study results indicate that age ≥65 years, prognostic nutritional index <40, and non-epithelioid histological subtype are poor prognostic factors of malignant pleural mesothelioma.

Keywords: Inflammation indices, malignant pleural mesothelioma, prognostic nutritional index, prognostic score.

ÖZ

Amaç: Bu çalışmada malign plevral mezotelyomanın prognostik faktörleri ve malign pleural mezotelyomada enflamasyon indekslerinin prognostik değeri araştırıldı.

Çalışma planı: Ocak 2002 - Aralık 2019 tarihleri arasında malign plevral mezotelyoma tanısı konan toplam 132 hasta (74 erkek, 58 kadın; medyan. yaş: 55 yıl; dağılım, 31-79 yıl) retrospektif olarak incelendi. Hastaların demografik bilgileri ve laboratuvar sonuçları kaydedildi. Şu beş enflamasyon indeksinin prognostik değeri araştırıldı: Nötrofil-lenfosit oranı, trombosit-lenfosit oranı, ileri akciğer kanseri enflamasyon indeksi, C-reaktif protein/albümin oranı ve prognostik nütrisyonel indeks.

Bulgular: Tüm hastaların %81'i (n=107) 65 yaş ve üzeri olup, %61.4'ünde (n=81) epiteloid histolojiye rastlandı. Çok değişkenli analizde sağkalım ile olan ilişkisi incelenen 12 değişken arasından ≥65 yaş, non-epiteloid alt tip ve <40 prognostik nütrisyonel indeksin kötü prognostik faktör olduğu tespit edildi. Bu faktörlerden oluşturulan skorlamada, iyi prognostik grupta (skor 0-1) medyan genel sağkalım 21 ay ve bir yıllık sağkalım %77.9 iken, kötü prognostik grupta (skor 2-3) medyan genel sağkalım dokuz ay ve bir yıllık sağkalım %29.7 idi.

Sonuç: Çalışma sonuçlarımız, malign plevral mezotelyomada ≥65 yaş, <40 prognostik nütrisyonel indeks ve non-epiteloid histolojik alt tipinin kötü prognostik faktör olduklarını göstermektedir.

Anahtar sözcükler: Enflamasyon indeksleri, malign plevral mezotelyoma, prognostik nütrisyonel indeks, prognostik skor.

Corresponding author: Senar Ebinç.

E-mail: senarebinc@gmail.com

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Malignant pleural mesothelioma (MPM) is an aggressive tumor of pleural surfaces. It becomes manifest years after asbestos exposure, which is an etiological risk factor.[1] The disease is difficult to treat, as many patients present at advanced stages. Median survival time is around one year and the five-year survival rate is approximately 10%. The chance of achieving cure is low.[2,3]

Malignant pleural mesothelioma has three main subtypes, which are epithelioid, sarcomatoid and biphasic. Epithelioid histology has better survival outcomes than the other subtypes.[4] Despite poor survival outcomes, long survival times have been achieved in some patients. Accordingly, several factors that can predict the prognosis have been investigated to date. In line with this aim, the prognostic factors in MPM were mainly researched in studies by the European Organization for Research and Treatment of Cancer (EORTC) and Cancer and Leukemia Group B (CALGB).[5,6] In the study by the EORTC, multivariate analysis determined five risk factors to be associated with a poor prognosis: high white blood cell (WBC) count, probable/possible histological diagnosis instead of a definitive histological diagnosis, sarcomatoid subtype, and male sex. Based on the risk score constructed of these five parameters, the one-year survival rate was found to be 40% in the good risk group and 12% in the poor risk group.[5] Meanwhile, the CALGB study attempted to predict the prognosis by forming six groups based on the parameters of WBC count, hemoglobin level, chest pain, and weight loss and median survival was reported to vary between 1.4 and 13.9 months across the groups.[6] Recently, the prognostic role of the neutrophil-lymphocyte ratio (NLR) has been examined in various cancers. Several studies have proposed that NLR can be an independent prognostic factor in MPM.[7,8] In a study investigating the prognostic nutritional index (PNI), it was reported to be an effective factor predicting survival in MPM.[9] A C-reactive protein (CRP)/albumin (CRP/ALB) ratio of ≤0.58 was also shown to be associated with improved survival in patients diagnosed with MPM.[10] Although the advanced lung cancer inflammation index (ALI) has not been studied in MPM patients, ALI has been shown to be an independent prognostic factor, particularly in lung cancer.[11] Another factor to influence survival in MPM is the platelet-lymphocyte ratio (PLR).[12] Some studies have reported that fluorodeoxyglucose positron emission tomography (PET)-computed tomography (CT) parameters may also play a prognostic role in mesothelioma.[13] This may also be an indirect indicator of inflammation.

To the best of our knowledge, there is no study comparing inflammation indices in MPM. In the present study, we, therefore, aimed to investigate the potential prognostic factors of MPM, as well as the prognostic value of inflammation indices for survival, and develop a useful score from the identified factors. We also aimed to examine the correlations between inflammation indices in MPM.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dicle University Faculty of Medicine, Medical Oncology Clinic between January 2002 and December 2019. Patients diagnosed with MPM were screened. A total of 132 patients (74 males, 58 females; mean age: 55 years; range, 31 to 79 years) who met the inclusion criteria were included.

Demographic data and laboratory results were retrieved from the hospital archive system. Age at the time of diagnosis, sex, disease stage at presentation, Eastern Cooperative Oncology Group performance status (ECOG PS), mesothelioma subtype, type of surgical intervention if performed (extrapleural pneumonectomy [EPP]/pleurectomy-decortication [P/D]), radiotherapy and treatment intent (adjuvant/palliative), and systemic treatments and treatment intent (adjuvant/palliative) were recorded. Also, weight and height, WBC, total lymphocyte, total neutrophil, platelet counts, hemoglobin, serum albumin and CRP values at the initial presentation were recorded.

Definitions and formulae

All indices were based on the clinical and laboratory parameters from patients' initial diagnosis. The indices were computed using the following formulae: body mass index (BMI); weight/height^2 (kg/m^2), NLR; absolute neutrophil count (count/mm^3)/absolute lymphocyte count (count/mm^3), PLR; absolute platelet count (count/mm^3)/absolute lymphocyte count (count/mm^3), ALI; BMI × serum albumin/NLR, CRP/ALB; CRP (mg/dL)/serum albumin (g/dL), PNI: [(10 × serum albumin (g/dL)) + (0.005 × absolute lymphocyte count (count/mm^3))].

Variables

In the light of literature data, parameters previously reported to have a prognostic value in MPM were categorized according to the relevant studies. In this context, age (years) (<65/≥65), sex (female/male), ECOG PS (0-1/≥2), histological subtype (epithelioid/non-epithelioid), baseline WBC (×10^9/L) (<8.3/≥8.3), baseline platelet count (×10^9/L) (≤400/>400) and hemoglobin level (g/dL) (<10/≥10) were classified.

The relationships of these variables that have been previously reported in the literature and the variables investigated in our study, which included the PNI, ALI, NLR, PLR, CRP/ALB indices, with overall survival (OS) were evaluated with univariate and multivariate analyses. Also, the relationships of these five indices with each other were analyzed using the Spearman correlation test. For PNI, which was an index determined to be associated with survival, a cut-off value (<40/≥40) was identified with 72% sensitivity and 64% specificity, and introduced to the analysis (area under the curve [AUC]: 0.643 [0.544-0.741], p=0.007). A prognostic score was constructed using the three parameters that were determined to be associated with survival; age (<65/≥65), histological subtype (epithelioid/non-epithelioid), and PNI (≥40/<40). A score of 1 was added for each of the following parameters: age ≥65, non-epithelioid type, and PNI <40. The score was calculated as 0 for age >65, epithelioid type and PNI ≥40. Although there was a numerical difference between the survival of patients with a score of 0 and 1 in the Cox regression analysis, those with a score of 0-1 were considered as the good prognostic group based on the absence of a statistically significant difference. Similarly, those with a score of 2-3 were accepted as the poor prognostic group, since there was no statistically significant difference between those with a score of 2 and 3 in terms of survival.

Statistical analysis

Statistical analysis was performed using the PASW for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and frequency for categorical variables. The Student t-test was used for normally distributed numeric variables, and the Mann-Whitney U test was used for the analysis of non-normally distributed or non-parametric variables.

Table 1. Baseline characteristics of the patients

	n	%	Median	Range
Age (year)			55	31-79
<65	107	81		
≥65	25	19		
Sex				
Female	58	43.9		
Male	74	56.1		
ECOG PS				
0-1	109	82.6		
≥2	23	17.4		
Histologic subtypes				
Epitheloid	81	61.4		
Non-epitheloid	51	38.6		
Stage at diagnosis				
I-II	42	31.8		
III-IV	90	68.2		
Type of surgery				
EPP	5	3.8		
P/D	37	28		
No	90	68.2		
Radiation therapy				
Adjuvant	23	17.4		
Palliative	37	28		
No	72	54.6		
No of treatment line (adjuvant or palliative)				
1	132	100		
2 or more	55	41.6		

ECOG PS: Eastern Cooperative Oncology Group performance status; EPP: Extrapleural pneumonectomy; P/D: Pleurectomy-decortication.

Table 2. Baseline characteristics based on prognostic nutritional index groups

	All patients		PNI <40		PNI ≥40		
	n	%	n	%	n	%	*p**
Age (year)							0.10
<65	107	81	37	74	70	85.4	
≥65	25	19	13	26	12	14.6	
Sex							0.15
Female	58	43.9	18	36	40	48.8	
Male	74	56.1	32	64	42	51.2	
ECOG performance status							0.27
0-1	109	43.9	39	78	70	85.4	
≥2	23	17.4	11	22	12	14.6	
Histologic subtypes							0.08
Epitheloid	81	61.4	26	52	55	67.1	
Non-epitheloid	51	38.6	24	48	27	32.9	
Stage at diagnosis							0.46
I-II	42	31.8	14	28	28	34.1	
III-IV	90	68.2	36	72	54	65.9	
Primary surgery							0.97
Yes	42	31.8	16	32	26	31.7	
No	90	68.2	34	68	56	68.3	
Radiation therapy							0.53
Yes	60	45.5	21	42	39	47.6	
No	72	54.5	29	58	43	52.4	

PNI: Prognostic nutritional index; ECOG: Eastern Cooperative Oncology Group; * Chi-square test.

Normally distributed variables were analyzed using the Pearson correlation analysis and non-normally distributed variables were analyzed using the Spearman correlation analysis. The Kaplan-Meier method was used for survival analysis. The log-rank *p* value was used. In survival analyses, Cox regression analysis was used for univariate and multivariate analyses. The enter method was used in univariate analysis, and the backward stepwise likelihood ratio method was used in multivariate analysis. The receiver operating characteristic (ROC) curve analysis was performed to identify a cut-off value for the inflammatory index that was found to be associated with survival in the multivariate analysis. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Patient demographics and outcomes

The majority of the patients (81%, n=107) were aged 65 years or older. There were 61.4% (n=81) patients with epithelioid histology and 38.6% (n=51) patients with non-epithelioid histology. At the time of diagnosis, 31.8% (n=42) of the patients were Stage I-II, while 68.2% (n=90) had Stage III-IV disease. The ECOG PS was assessed as ≥2 in 17.4% (n=23) patients. Of the patients, 31.8% (n=42) underwent a surgical procedure (EPP=5, 3.8%, P/D=37, n=28). The rate of patients receiving radiotherapy was 45.5% (n=60) (adjuvant=23, 17.4%, palliative=37, 28%). All patients received at least one line of chemotherapy, while 41.6% (n=55) patients received two or more lines of chemotherapy. Details regarding the baseline characteristics are reported in Table 1. Baseline characteristics were also compared between the PNI groups. Patients with PNI <40 and PNI ≥40 showed a similar distribution in terms of general characteristics (Table 2).

Potential prognostic factors

Of the seven variables (age, sex, ECOG PS, histological subtype, WBC count, platelet count, and hemoglobin level) investigated in the univariate analysis with regard to their relationship with OS, two (age: <65/≥65 and histological subtype: epithelioid/non-epithelioid)

were found to be associated with survival. In the multivariate analysis, being aged ≥65 (hazard ratio [HR=1.87; 95% CI: 1.18-2.96, p=0.007) and non-epithelioid histology (HR=1.79; 95% CI: 1.23-2.59, p=0.002) were found to be associated with poor survival outcomes. These two variables, which showed a significant relationship with survival in the univariate analysis, were determined to be independent prognostic factors in the multivariate analysis. Median OS (mOS) was 19 months in patients younger than 65 years, while it was 11 months in patients aged ≥65 (Figure 1). Patients with an epithelioid histology had a mOS of 22 months, while it was 11 months in non-epithelioid histology (Figure 2). There was no statistically significant relationship between OS and these parameters that were included in the analyses in our study. Details regarding the univariate and multivariate analysis of the variables predicting OS are provided in Table 3.

Prognostic role of indices and PNI

The associations of the five inflammation indices with OS were investigated in the univariate analysis: PNI, ALB/CRP ratio, NLR, PLR and ALI. Of these indices, PNI had a statistically significant relationship with OS (p=0.002). In the multivariate analysis, PNI <40 (HR=1.62; 95% CI: 1.11-2.36, p=0.012) was found to be associated with poor survival outcomes and to be an independent prognostic factor in predicting survival. The mOS was 21 months in patients with PNI >40 and 12 months in patients with PNI ≤40 (Figure 3). Other indices including ALB/CRP ratio, NLR, PLR, and ALI did not have a statistically significant relationship with survival (Table 3).

When the patients' 12-month survivals were considered (patients surviving ≤12 months 35.6%, n=47,

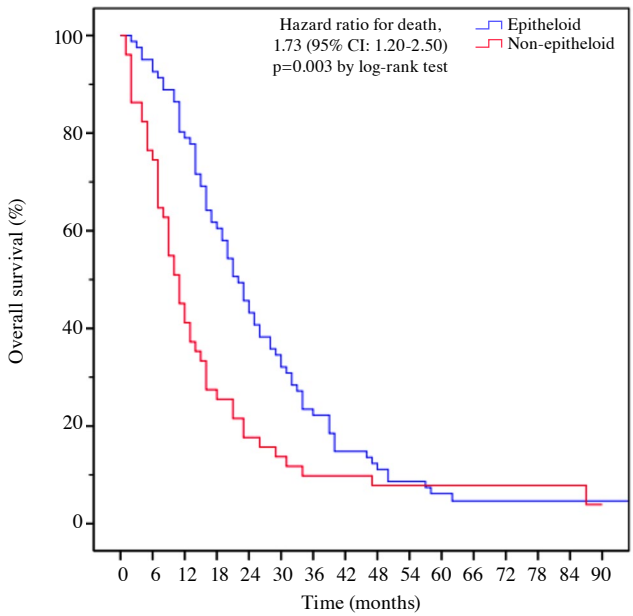

Figure 2. Overall survival outcomes according to histological subtypes.
CI: Confidence interval.

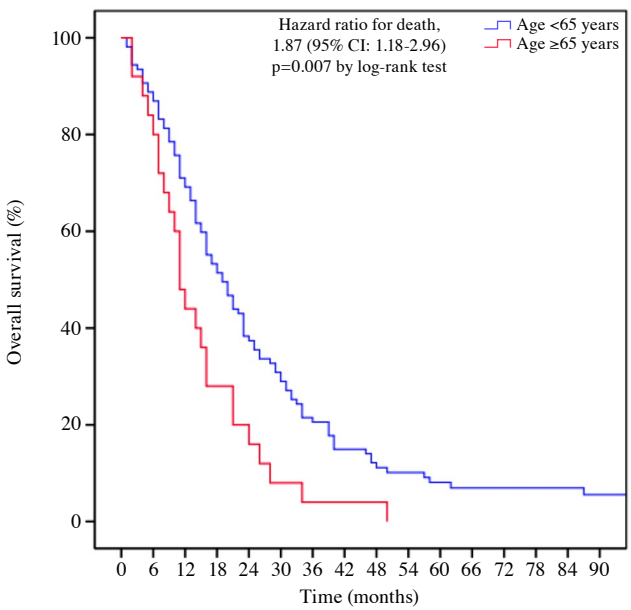

Figure 1. Overall survival outcomes according to age of patients.
CI: Confidence interval.

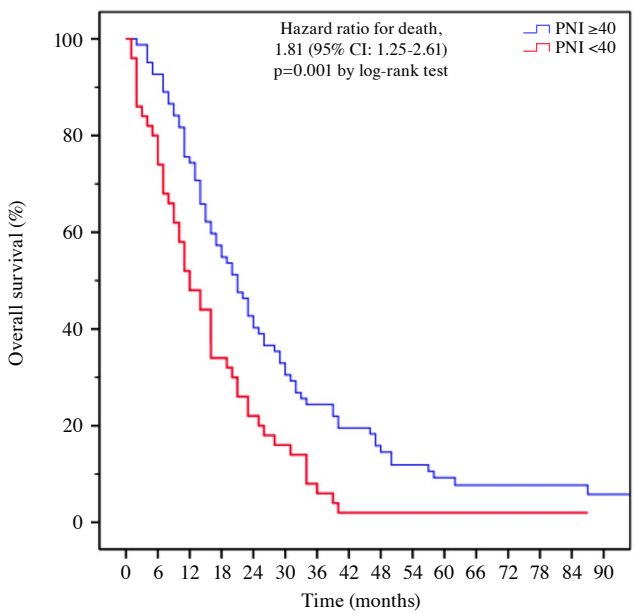

Figure 3. Overall survival outcomes according to prognostic nutritional index.
CI: Confidence interval; PNI: Prognostic nutritional index.

Table 3. Univariate and multivariate analysis results in terms of overall survival

				Univariate analysis			Multivariate analysis		
	n	%	Median OS (months)	HR	95% CI	*p***	HR	95% CI	*p****
Age (year)				1.84	1.18-2.88	**0.007**	1.87	1.18-2.96	**0.007**
<65*	107	81	19						
≥65	25	19	11						
Sex				1.33	0.93-1.90	0.12			
Female*	58	43.9	20						
Male	74	56.1	16						
ECOG PS				1.45	0.91-2.31	0.11			
0-1*	109	82.6	17						
≥2	23	17.4	13						
Histologic subtypes				1.73	1.20-2.50	**0.003**	1.79	1.23-2.59	**0.002**
Epitheloid*	81	61.4	22						
Non-epitheloid	51	38.6	11						
Baseline white blood cell count ($\times10^9$/L)				1.12	0.78-1.62	0.51			
<8.3*	80	60.6	18						
≥8.3	52	39.4	16						
Baseline platelet count ($\times10^9$/L)				1.19	0.81-1.74	0.37			
≤400*	92	69.7	18						
>400	40	30.3	16						
Hemoglobin level (g/dL)				0.72	0.41-1.27	0.26			
<10*	14	10.6	14						
≥10	118	89.4	17						
PNI				1.81	1.25-2.61	**0.002**	1.62	1.11-2.36	**0.012**
≥40*	82	62.1	21						
<40	50	37.9	12						
CRP/albumin	132	100		1.11	0.99-1.25	0.06			
ALI	132	100		0.99	0.99-1.01	0.45			
NLR	132	100		1.01	0.99-1.03	0.09			
PLR	132	100		1.01	0.99-1.02	0.24			

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; PNI: Prognostic nutritional index; CRP: C-reactive protein; ALI: Advanced lung cancer inflammation index; NLR; Neutrophil-to-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; * Reference category; ** Cox regression analysis Enter method; *** Cox regression analysis Backward stepwise likelihood ratio method.

patients surviving >12 months 64.4%, n=85), there was a statistically significant difference between the mean PNI of the two groups. Those who demonstrated a survival of 12 months or shorter had a lower mean PNI than those who survived longer than 12 months (39.7±7.5 *vs*. 43.4±8.1, p=0.013). The one-year survival rate was 74.4% in those with PNI ≥40 as opposed to 48% in patients with PNI <40 (p=0.002). Mean values of the ALB/CRP ratio, PLR and ALI did not show a statistically significant difference between these two groups (Table 4). In the correlation analysis, a moderate negative correlation was found between PNI-NLR, PNI-PLR and PNI-CRP/ALB and a strong positive correlation was found between PNI-ALI (r=0.733, p<0.001). A strong negative correlation between PLR-ALI (r=-0.671, p<0.001) and ALI-NLR (r=-0.920, p<0.001), and a strong positive correlation between PLR-NLR (r=0.657, p<0.001) were found (Table 5).

Prognostic scoring

Age, histological subtype, and PNI were included in the scoring system after showing a strong association with survival in the multivariate analysis. Age ≥65 years, non-epithelioid histology, and PNI <40 were found to be associated with a poor prognosis. A score of 1 was assigned to each of these characteristics; those with a score of 0-1 were considered as the good prognostic group

Table 4. The effectiveness of inflammation indexes in predicting one-year survival

	Survival ≤12 month (n=47)	Survival >12 month (n=85)	
	Mean±SD	Mean±SD	*p*
Prognostic nutritional index	39.7±7.5	43.4±8.1	0.013*
Advanced lung cancer inflammation index	35.2±32.4	37±26.8	0.78**
C-reactive protein/albumin	1.36±1.58	0.94±1.21	0.06**
Neutrophil-to-lymphocyte ratio	5.8±15.1	3.2±2.2	0.19**
Platelet-lymphocyte ratio	198±113	210±115	0.38**

SD: Standard deviation; * Independent samples t-test; ** Mann-Whitney U test.

Table 5. The relationship between inflammation indexes

	CRP/ALB	NLR	PNI	ALI
NLR				
r	0.187	-	-	-
p	0.032	-	-	-
n	132	-	-	-
PNI				
r	-0.409	-0.558	-	-
p	<0.001	<0.001	-	-
n	132	132	-	-
ALI				
r	-0.289	**-0.920**	**0.733**	-
p	0.001	**<0.001**	**<0.001**	-
n	132	132	132	-
PLR				
r	0.165	**0.657**	-0.582	**-0.671**
p	0.059	**<0.001**	<0.001	**<0.001**
n	132	132	132	132

CRP/ALB: C-reactive protein/albumin; NLR: Neutrophil-to-lymphocyte ratio; PNI: Prognostic nutritional index; ALI: Advanced lung cancer inflammation index; PLR: Platelet-to-lymphocyte ratio; Spearman's correletion.

[no statistically significant difference between those with a score of 0 and 1 (HR=1.2, 95% CI: 0.81-1.89, p=0.30)] and those with a score of 2-3 were considered as the poor prognostic group [no statistically significant difference between those with a score of 2 and 3 (HR=0.74, 95% CI: 0.28-1.91, p=0.53)]. The mOS was 21 months in the good prognostic group (score=0-1) as opposed to nine months in the poor prognostic group (score=2-3) (HR=3.09, 95% CI: 2.05-4.65, p<0.001) (Figure 4). Details concerning the scores are presented in Table 6. When the one-year survival times of the patients were inspected with respect to the prognostic groups, the one-year survival rate was 77.9% in the good prognostic group versus a rate of 29.7% in the poor prognostic group.

DISCUSSION

In the present study, we investigated the prognostic roles of different inflammation indices in MPM, as well as the prognostic factors that have been previously studied in this disease. We evaluated the effectiveness of the prognostic factors associated with survival in predicting the prognosis in the framework of a scoring system.

Several studies have been conducted on the evaluation of prognostic factors in MPM before. Each study assessed different prognostic factors.[14-18] Due to the hypothesis implicating long years of inflammation in the etiology of MPM, the focus of the search for a prognostic biomarker has shifted to inflammation markers.[19,20] In the present study, we

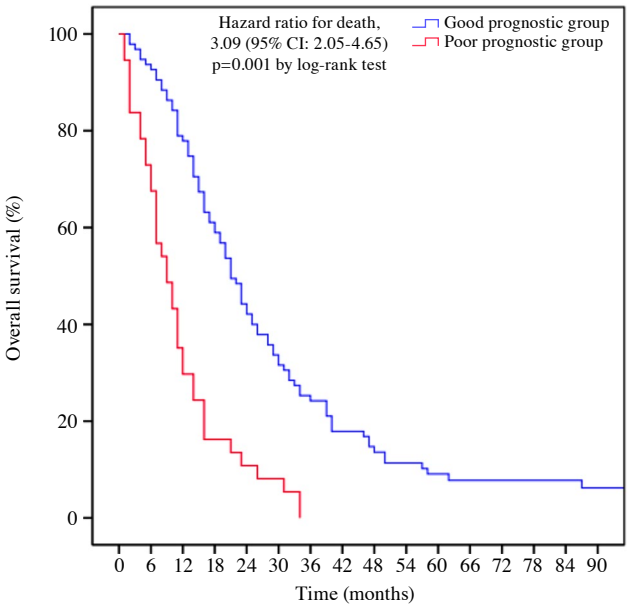

Figure 4. Overall survival outcomes according to good and poor prognostic scores.
CI: Confidence interval.

investigated PNI, NLR, PLR, CRP/ALB and ALI, which are inflammation indices that have previously been researched in MPM or other types of cancer. In addition to inflammation indices, seven other factors that have been identified as prognostic factors in various studies, which included age, sex, ECOG PS, histological subtype, WBC count, platelet count and hemoglobin level at diagnosis, were also incorporated into the analyses.

In a study by Kao et al.,[8] the importance of NLR in predicting the prognosis in MPM was emphasized. The multivariate analysis of this study showed that epithelioid histology and NLR <5 were associated with a good prognosis. The one-year survival rate was reported as 60% for NLR <5 and 26% for NLR ≥5. In another study, phosphatase and tensin homolog (PTEN), NLR and PLR were found to be associated with survival in epithelioid MPM.[21] Tural Onur et al.[22] investigated NLR and PLR as prognostic markers in MPM. In this study, PLR had a prognostic value in MPM, while no significant relationship was found between NLR and the prognosis. In our study, NLR and PLR did not have a statistically significant contribution to the prediction of MPM prognosis. Based on one-year survival analysis, there was no statistically significant difference between the mean NLR and PLR values. On the other hand, NLR showed a strong positive correlation with PLR. In addition, both NLR and PLR showed

Table 6. Comparison of survival times by prognostic score

	n	%	Median OS (month)	95% CI	HR	95% CI	*p*
Score							<0.001*
0	48	36.4					
1	47	35.6					
2	32	24.2					
3	5	3.8					
Good prognostic group (0-1)	95	72	21	17.8-24.1			<0.001*
Poor prognostic group (2-3)	37	28	9	5.4-12.5			
Score							
0					Reference		**<0.001**†
1					1.24	0.81-1.89	0.30†
2					3.31	2.06-5.33	**<0.001**†
3					4.47	1.73-11.51	**0.002**†
3					Reference		**<0.001**†
2					0.74	0.28-1.91	0.53†
1					0.27	0.10-0.71	**0.008**†
0					0.22	0.08-0.57	**0.002**†
Prognostic groups							
Good (0-1)					Reference		
Poor (2-3)					3.09	2.05-4.65	**<0.001**†

OS: Overall survival; CI: Confidence interval; HR: Hazard ratio; * Log Rank P; † Cox regression analysis Enter method.

a strong negative correlation with ALI. Considering that NLR is influenced in the early stages of acute inflammation, we can expect it to differ across studies in the prediction of the prognosis. In the literature, studies examining the prognostic role of PLR in MPM were conducted with a low number of patients. In some of these studies, important factors such as the histological subtype and patient age were not included in the analyses.

Takamori et al.[10] reported the CRP/ALB ratio was an independent prognostic marker in MPM. In their study, the cut-off value for CRP/ALB was determined as ≤0.58 and >0.58, respectively. They reported survival to be more favorable in MPM patients with CRP/ALB ≤0.58. In our study, CRP/ALB was not a predictor for the prognosis. Based on one-year survival analysis, there was no statistically significant difference between those who survived shorter than one year and those who survived longer than one year in terms of mean CRP/ALB. When the relationship of the CRP/ALP ratio with the other inflammation indices was examined, there was a moderate negative correlation with PNI. However, there is not a sufficient number of studies investigating the CRP/ALB ratio as a prognostic factor in MPM for comparison.

Although there is no study regarding ALI in MPM patients in the literature, ALI is included among the prognostic inflammation indices researched in non-small cell lung cancer.[22] These studies have suggested that ALI <18 is associated with a poor prognosis. In our study, ALI could not be demonstrated to have a role in predicting the prognosis of MPM (p=0.45). Mean values of ALI were also not different in terms of the one-year survival outcomes (p=0.78). When its relationship with the other inflammation indices was analyzed, there was a strong positive correlation with PNI and a strong negative correlation with NLR and PLR.

In the study of Zhou-Hong et al.,[9] the prognostic role of PNI was investigated in MPM. In this study, the cut-off value was reported as 44.6. The mOS and one-year survival rate were 18 months and 72.3%, respectively in patients with PNI <44.6 as opposed to 11 months and 45.5% in patients with PNI ≥44.6. In our study, PNI was found to be a strong prognostic marker for the prediction of survival. It predicted survival in both univariate (HR=1.81, 95% CI: 1.25-2.61, p=0.002) and multivariate analyses (HR=1.62, 95% CI: 1.11-2.36, p=0.012). Moreover, PNI was also shown to have a role in the prediction of one-year survival. The one-year survival rate was 74.4% in those with PNI ≥40 versus 48% in patients with PNI <40 (p=0.002). When the relationship of PNI with the other inflammation indices was analyzed, there was a strong positive correlation with ALI in particular. In our study, the cut-off value for PNI was found to be 40. The prognosis was poorer in those with PNI <40. The prognostic role of PNI in our study is consistent with the literature.

In the CALGB study, 337 MPM patients were evaluated between 1984 and 1994, and survival times were investigated by constructing six different groups based on hemoglobin, WBC count, age, performance status, weight loss and chest pain.[6] In this study, survival times ranged between 13.9 and 1.4 months. On the other hand, the EORTC study evaluated 204 patients between 1984-1993, and of the factors included in the analysis, a non-definitive diagnosis, sarcomatoid histology, WBC count, and male sex were found to be poor prognostic factors in the multivariate analysis. In the risk groups constructed based on the poor prognostic factors in the EORTC study, one-year survival was 40% in the good prognostic group and 12% in the poor prognostic group.[5] Of the seven factors included in our study besides the inflammation indices based on the results of other studies in the literature (age, sex, ECOG PS, histological subtype, WBC count, platelet count and hemoglobin level at diagnosis), only two (age and histological subtype) were determined to have a statistically significant relationship with survival. Sex, ECOG PS, WBC count, platelet count and hemoglobin level at the time of diagnosis did not have a statistically significant relationship with the prognosis. Age was associated with the prognosis in both univariate (HR=1.84, 95% CI: 1.18-2.88, p=0.007) and multivariate analyses (HR=1.87, 95% CI: 1.18-2.96, p=0.007). Age ≥65 was identified as a poor prognostic factor. Similarly, histological subtype was associated with the prognosis in both univariate (HR=1.73, 95% CI: 1.20-2.50, p=0.003) and multivariate analysis (HR=1.79, 95% CI: 1.23-2.59, p=0.002). Non-epithelioid histology was identified as a poor prognostic factor in our study.

In our study, the good prognostic group (score=0-1) had a median survival time of 21 months and a one-year survival rate of 77.9% as opposed to a median survival time of nine months and one-year survival rate of 29.7% in the poor prognostic group (score=2-3). There was a statistically significant survival difference between the two groups in terms of the mOS (HR=3.09, 95% CI: 2.05-4.65, p<0.001). In this study, we found these parameters to have an

association with the prognosis in multivariate analysis (PNI <40, ≥65 years and non-epithelioid histology) to be important predictors of survival in MPM.

In the literature, there is no other study comparing these five inflammation indices in MPM patients. There are also no studies including inflammation indices and conventional prognostic factors in a prognostic score in MPM. Therefore, this is the first study to compare inflammation indices in MPM and their inclusion in the prognostic score.

The main limitations to our study are its single-center, retrospective design, the heterogeneity of the patient groups, and the relatively low number of patients aged ≥65 years.

In conclusion, our study results indicate that prognostic nutritional index <40, age ≥65 years, and non-epithelioid histology are poor prognostic factors. There is also a significant difference in survival between the good-risk group and the poor-risk group based on the prognostic scores. This score may serve as a simple and useful scoring system in the prediction of malignant pleural mesothelioma prognosis in clinical practice.

Ethics Committee Approval: The study protocol was approved by the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date: 15.12.2021, no: 10). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape province. Br J Ind Med 1960;17:260-71. doi: 10.1136/oem.17.4.260.
2. Mazurek JM, Syamlal G, Wood JM, Hendricks SA, Weston A. Malignant mesothelioma mortality - United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2017;66:214-8. doi: 10.15585/mmwr.mm6608a3.
3. Musk AW, Olsen N, Alfonso H, Reid A, Mina R, Franklin P, et al. Predicting survival in malignant mesothelioma. Eur Respir J 2011;38:1420-4. doi: 10.1183/09031936.00000811.
4. Howel D, Arblaster L, Swinburne L, Schweiger M, Renvoize E, Hatton P. Routes of asbestos exposure and the development of mesothelioma in an English region. Occup Environ Med 1997;54:403-9. doi: 10.1136/oem.54.6.403.
5. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: The European Organization for Research and Treatment of Cancer experience. J Clin Oncol 1998;16:145-52. doi: 10.1200/JCO.1998.16.1.145.
6. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998;113:723-31. doi:10.1378/chest.113.3.723
7. Chen N, Liu S, Huang L, Li W, Yang W, Cong T, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with malignant pleural mesothelioma: A meta-analysis. Oncotarget 2017;8:57460-9. doi: 10.18632/oncotarget.15404.
8. Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van Zandwijk N, et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin Cancer Res 2010;16:5805-13. doi: 10.1158/1078-0432.CCR-10-2245.
9. Yao ZH, Tian GY, Wan YY, Kang YM, Guo HS, Liu QH, et al. Prognostic nutritional index predicts outcomes of malignant pleural mesothelioma. J Cancer Res Clin Oncol 2013;139:2117-23. doi: 10.1007/s00432-013-1523-0.
10. Takamori S, Toyokawa G, Shimokawa M, Kinoshita F, Kozuma Y, Matsubara T, et al. The C-reactive protein/albumin ratio is a novel significant prognostic factor in patients with malignant pleural mesothelioma: A retrospective multi-institutional study. Ann Surg Oncol 2018;25:1555-63. doi: 10.1245/s10434-018-6385-x.
11. Ozyurek BA, Ozdemirel TS, Ozden SB, Erdoğan Y, Ozmen O, Kaplan B, et al. Does advanced lung inflammation index (ALI) have prognostic significance in metastatic non-small cell lung cancer? Clin Respir J 2018;12:2013-9. doi: 10.1111/crj.12768.
12. Cihan YB, Ozturk A, Mutlu H. Relationship between prognosis and neutrophil: Lymphocyte and platelet:lymphocyte ratios in patients with malignant pleural mesotheliomas. Asian Pac J Cancer Prev 2014;15:2061-7. doi: 10.7314/apjcp.2014.15.5.2061.
13. Yenigün BM, Kahya Y, Soydal Ç, Ata Tutkun N, Kocaman G, Koçak EM, et al. The prognostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography parameters in patients with malignant pleural mesothelioma. Turk Gogus Kalp Dama 2021;29:92-100. doi: 10.5606/tgkdc.dergisi.2021.20432.

14. Antman K, Shemin R, Ryan L, Klegar K, Osteen R, Herman T, et al. Malignant mesothelioma: Prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965-1985. J Clin Oncol 1988;6:147-53. doi: 10.1200/JCO.1988.6.1.147.
15. Spirtas R, Connelly RR, Tucker MA. Survival patterns for malignant mesothelioma: The SEER experience. Int J Cancer 1988;41:525-30. doi: 10.1002/ijc.2910410409.
16. Ruffie P, Feld R, Minkin S, Cormier Y, Boutan-Laroze A, Ginsberg R, et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: A retrospective study of 332 patients. J Clin Oncol 1989;7:1157-68. doi: 10.1200/JCO.1989.7.8.1157.
17. De Pangher Manzini V, Brollo A, Franceschi S, De Matthaeis M, Talamini R, Bianchi C. Prognostic factors of malignant mesothelioma of the pleura. Cancer 1993;72:410-7. doi: 10.1002/1097-0142(19930715)72:2<410::aid-cncr2820720216>3.0.co;2-g.
18. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, Ledoray V. Thoracoscopy in pleural malignant mesothelioma: A prospective study of 188 consecutive patients. Part 2: Prognosis and staging. Cancer 1993;72:394-404. doi: 10.1002/1097-0142(19930715)72:2<394::aid-cncr2820720214>3.0.co;2-5.
19. Vogl M, Rosenmayr A, Bohanes T, Scheed A, Brndiar M, Stubenberger E, et al. Biomarkers for malignant pleural mesothelioma-A novel view on inflammation. Cancers (Basel) 2021;13:658. doi: 10.3390/cancers13040658.
20. Hillegass JM, Shukla A, Lathrop SA, MacPherson MB, Beuschel SL, Butnor KJ, et al. Inflammation precedes the development of human malignant mesotheliomas in a SCID mouse xenograft model. Ann N Y Acad Sci 2010;1203:7-14. doi: 10.1111/j.1749-6632.2010.05554.x.
21. Liang Y, Zheng G, Yin W, Song H, Li C, Tian L, et al. Significance of EGFR and PTEN expression and PLR and NLR for predicting the prognosis of epithelioid malignant peritoneal mesothelioma. Gastroenterol Res Pract 2019;2019:7103915. doi: 10.1155/2019/7103915.
22. Tural Onur S, Sokucu SN, Dalar L, Iliaz S, Kara K, Buyukkale S, et al. Are neutrophil/lymphocyte ratio and platelet/lymphocyte ratio reliable parameters as prognostic indicators in malignant mesothelioma? Ther Clin Risk Manag 2016;12:651-6. doi: 10.2147/TCRM.S104077.