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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Can some inflammatory parameters predict the survival of patients with malignant pleural effusion?

Enflamatuar parametreler malign plevral efüzyonlu hastaların sağkalımını öngörebilir mi?

Nur Dilvin Ozkan[1], Aynur Bas[2], Axel Scheed[3], Melanie Vogl[3], Tomas Bohanes[3], Elisabeth Stubenberger[3], Muhammet Sayan[4], Ismail Cuneyt Kurul[4], Ghanim Bahil[3], Ali Celik[4]

Institution where the research was done:
Department of Thoracic Surgery, Universitatsklinikum Krems, Krems an der Donau, Austria
Department of Thoracic Surgery, Gazi University School of Medicine, Ankara, Türkiye

Author Affiliations:
[1]Department of Thoracic Surgery, Milas State Hospital, Muğla, Türkiye
[2]Department of Thoracic Surgery, Başakşehir Çam Sakura City Hospital, İstanbul, Türkiye
[3]Department of Thoracic Surgery, Universitatsklinikum Krems, Krems an der Donau, Austria
[4]Department of Thoracic Surgery, Gazi University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Background: This study aimed to investigate whether there is a correlation between some serum inflammatory markers and the survival of patients with malignant pleural effusions (MPEs).

Methods: The prospective study included 125 patients (67 males, 58 females; median age: 62 years; range, 40 to 92 years) who underwent thoracentesis for pleural effusion between January 2020 and December 2021. An overall survival analysis was performed, and survival differences between the groups were investigated. The cutoff value of the inflammatory parameters associated with mortality was determined by receiver operating characteristic analysis.

Results: Median survival after detection of MPE was six months, and three- and five-year overall survivals were 16% and 4%, respectively. There was a significant correlation between the ECOG (Eastern Cooperative Oncology Group) score of the patients and the median survival. Serum C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), fluid albumin, and serum lactate dehydrogenase (LDH)-to-pleural LDH ratio and survival had a statistically significant relationship in receiver operating characteristic analysis. Threshold values were determined accordingly. Poor prognostic factors that were found to be statistically significant were high CRP (p=0.001), high NLR (p=0.001), high PLR (p=0.02), and high serum LDH-to-pleural LDH ratio (p=0.04).

Conclusion: Some serum inflammatory markers, including high CRP, high NLR, high PLR, and high serum LDH-to-pleural LDH ratio, can be a simple and inexpensive method in predicting prognosis in patients with MPE.

Keywords: Lymphocyte-to-monocyte ratio, malignant pleural effusion, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognosis.

ÖZ

Amaç: Bu çalışmada, bazı serum enflamatuar belirteçleri ile malign plevral efüzyonu (MPE) olan hastaların sağkalımı arasında bir ilişki olup olmadığı araştırıldı.

Çalışma planı: Prospektif çalışmaya Ocak 2020 - Aralık 2021 tarihleri arasında plevral efüzyon nedeniyle torasentez yapılan 125 hasta (67 erkek, 58 kadın; median yaş: 62 yıl; dağılım, 40-92 yıl) dahil edildi. Genel sağkalım analizi yapıldı ve gruplar arasındaki sağkalım farklılıkları araştırıldı. Mortalite ile ilişkili enflamasyon parametrelerinin kesim değerleri alıcı çalışma karakteristiği analizi ile araştırıldı.

Bulgular: Medyan sağkalım, MPE tespit edildikten sonra altı ay idi. Üç ve beş yıllık genel sağkalım sırasıyla %16 ve %4 idi. Medyan sağkalım ve hastaların ECOG (Eastern Cooperative Oncology Group) skoru arasında anlamlı bir ilişki vardı. Alıcı çalışma karakteristiği analizinde, sağkalım ve serum C-reaktif protein (CRP), nötrofil/lenfosit oranı (NLR), platelet/lenfosit oranı (PLR) ve serum laktat dehidrogenaz (LDH)/plevral LDH oranı arasında istatistiksel olarak anlamlı ilişki bulundu. Buna göre eşik değerler belirlendi. Yüksek CRP (p=0.001), yüksek NLR (p=0.001), yüksek PLR (p=0.02) ve yüksek serum LDH/plevral LDH oranı (p=0.04) istatistiksel olarak anlamlı kötü prognozla ilişkili faktörler idi.

Sonuç: Yüksek CRP, yüksek NLR, yüksek PLR ve yüksek serum LDH/plevral LDH oranı dahil olmak üzere bazı serum enflamatuar belirteçleri MPE'li hastalarda prognozu tahmin etmede basit ve ucuz bir yöntem olabilir.

Anahtar sözcükler: Lenfosit/monosit oranı, malign plevral efüzyon, nötrofil/lenfosit oranı, platelet/lenfosit oranı, prognoz.

Corresponding author: Nur Dilvin Ozkan.
E-mail: dilvinozkan@gmail.com

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Malignant pleural effusions (MPEs) usually indicate end-stage malignant disease. The expected median survival in patients with MPE is between three and 12 months.[1] In these patients, the factors affecting survival were reported as the primary tumor, weight loss, ECOG (Eastern Cooperative Oncology Group) performance status, and hemoglobin and albumin levels.[2] The relationship between cancer and inflammation has been an issue of interest for a long time. Epidemiological research has demonstrated that chronic inflammation predisposes patients to develop several malignancies. Underlying infections and inflammatory reactions contribute to 15 to 20% of all cancer-related deaths globally.[3] Although some studies have shown the prognostic correlation between serum inflammation markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), and survival of lung cancer, studies on the effects of these markers in MPE are scarce.[4,5] Some studies concluded that high PLR and NLR in patients with MPE were indicators of poor prognosis. Moreover, the cytokine effect in malignant tumors increases neutrophils, which are crucial to tumorigenesis and angiogenesis. Another issue in tumor biology is that cancer cells are protected from phagocytosis by complexing with the platelet, indicating that there is a link between thrombocytosis and tumor aggressiveness. In addition, the anticancer effect of lymphocytes is well-known. Many studies have pointed out that a high lymphocyte count is associated with good survival in patients with cancer.[6] This study aimed to investigate the correlations between some serum inflammatory markers and the survival of patients with MPE.

PATIENTS AND METHODS

The two-center prospective cohort study was conducted with 125 patients having oncological diagnosis (67 males, 58 females; median age: 62 years; range, 40 to 92 years) who underwent thoracentesis for suspected MPE at the Universitatsklinikum Krems and Gazi University School of Medicine, Department of Thoracic Surgery between January 2020 and December 2021. Patients who underwent pleural fluid sampling catheter or tube thoracostomy due to MPE were included in the study. Patients whose follow-up records could not be obtained, those with empyema, those with chylothorax, those with transudative pleural fluid, those on corticosteroid medication, those with chemotherapy and thoracentesis date intervals shorter than two weeks, and patients with autoimmune disease were excluded from the study. The study protocol was approved by the Gazi University Clinical Research Ethics Committee (date 20.01.2020, no: 84). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood samples were taken from peripheral veins. For complete blood count, a sufficient blood sample was taken into a vacuum tube with EDTA (ethylenediaminetetraacetic acid). Analysis was performed using a Beckman Coulter UniCel machine (Beckman Coulter, Inc., Brea, CA, USA). Lactate dehydrogenase (LDH), albumin, and protein levels were assessed using the spectrophotometric method, and C-reactive protein (CRP) levels were assessed using the nephelometric method. The NLR, PLR, and LMR values were obtained from the serum complete blood count assay, and the ratios were calculated with albumin, protein, and LDH levels assessed simultaneously from serum and pleural fluid.

Statistical analysis

Analyses were made with IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Overall survival was calculated in months based on the date of pleural effusion detection, the date of death for patients who died, and the date of study for patients who were alive. Categorical data were expressed as frequency and percentage. The distribution normality of numerical data was investigated with histogram and Kolmogorov-Smirnov tests. Variables with normal distributions were presented as mean ± standard deviation (SD), and nonparametric distributions were expressed as median (min-max). The correlation between the inflammation parameters of the patients and mortality status was investigated by receiver operating characteristic (ROC) analysis. Specific cutoff values were determined for significant factors according to the sensitivity and specificity points in the ROC curve. Overall survival analysis was performed by the Kaplan-Meier method, and survival differences between the groups were investigated by log-rank and Cox regression tests. Survival analyses were performed at a 95% confidence interval (CI), a two-sided p-value was calculated, and a p-value <0.05 was considered statistically significant.

RESULTS

The most common primary malignancy was lung cancer (n=33, 26.4%), followed by breast cancer (n=13, 10.4%). The most common ECOG score was 3 (n=44, 35.2%). The macroscopic view of the pleural fluid of most patients was serous (n=67, 53.6%). The most common drainage method was catheter thoracostomy

Table 1. The characteristics of patients (n=125)

	n	%	Median	Range
Age (year)			62	40-92
Sex				
Male	67	53.6		
Female	58	46.4		
Primary malignancy				
Thorax				
Lung cancer	33	26.4		
Mesothelioma	5	4.0		
Trachea	1	0.8		
GIS				
Colorectal Ca	3	2.4		
Gastric Ca	9	7.2		
Liver	3	2.4		
Cholangiocellular Ca	4	3.2		
Esophagus	3	2.4		
Pancreas	6	4.8		
GUS				
Bladder	4	3.2		
Renal	6	4.8		
Endometrium	3	2.4		
Adnexal	1	0.8		
Over	5	4.0		
Vulva	1	0.8		
Prostate	2	1.6		
Cervix	1	0.8		
Krukenberg	1	0.8		
Hematologic	9	7.2		
Endocrine				
Breast	13	10.4		
Parotid gland	1	0.8		
Thymic	2	1.6		
Thyroid	1	0.8		
Unknown	3	2.4		
Other	5	4		
ECOG PS				
0	13	10.4		
1	16	12.8		
2	30	24.0		
3	44	35.2		
4	22	17.6		
Macroscopic view				
Serous	67	53.6		
Bloody	8	6.4		
Serohemorrhagic	39	31.2		
Yellow	11	8.8		
Drainage method				
Catheter thoracostomy	82	65.6		
Tube thoracostomy	24	19.2		
Both	16	11.2		
Thoracentesis	5	4.0		

GIS: Gastrointestinal system; Ca: Cancer; GUS: Genitourinary system; ECOG PS: Eastern Cooperative Oncology Group Performance Scale.

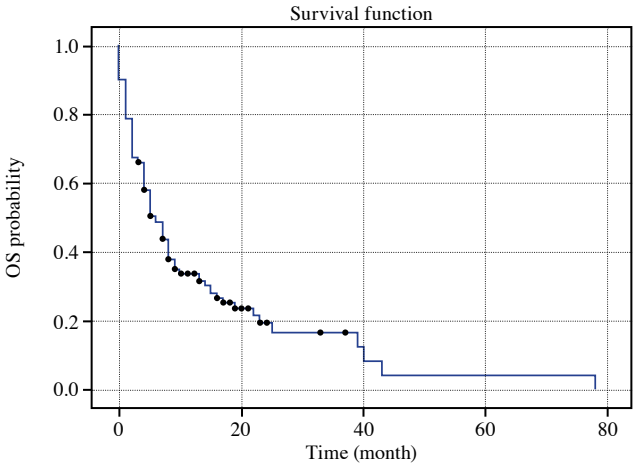

Figure 1. The median survival was six months after malignant pleural effusion was detected in a patient with an oncological diagnosis (95% CI, 4.1-7.8 months).

(n=82, 65.6%). The characteristics of the patients are given in Table 1.

In our series, median survival after detection of MPE was six months (95% CI: 4.1-7.8), and three- and five-year overall survivals were 16% and 4%, respectively (Figure 1). Due to the histopathological type of primary malignancy, the best median survival was 12 months in the breast cancer group, while the worst survivals were three months in the gastrointestinal system malignancies and primary malignancy unknown group. There was no significant correlation between age (p=0.1), sex (p=0.8), and pleural fluid drainage method (thoracentesis, tube thoracostomy, or catheter thoracostomy; p=0.1) and survival. There was a significant correlation between the ECOG score of the patients and the median survival separately for each category. The median survival was 22 months for the ECOG 0 group and 4 months for the ECOG 4 group (p=0.002). Although fluid albumin levels, serum CRP, NLR, PLR, and serum LDH-to-pleural LDH ratio were significant in survival by ROC analysis, LMR, serum protein-to-pleural protein ratio, and serum albumin-to-pleural albumin ratio were not significant (Table 2). The ROC curves were created according to the significant values, and cutoff values were determined (Figures 2, 3). Poor prognostic factors that were found to be statistically significant by the log-rank method were as follows: high CRP (p=0.001), high NLR (p=0.001), high PLR (p=0.02), and high serum LDH-to-pleural LDH ratio (p=0.04; Figures 4-7).

DISCUSSION

This study demonstrated some serum inflammatory markers that could predict the survival of patients with MPE. Histopathology of primary malignancy of patients with MPE is an important indicator for survival. Related studies in

Table 2. Areas under the curve calculated by receiver operating characteristic analysis

Variables	AUC (%)	SE	*p*	Cut-off value
Serum CRP	69	0.074	0.010	51.2
Serum LDH	57	0.070	0.306	
Serum albumin	35	0.074	0.055	
Serum CEA	63	0.064	0.075	
Serum NLR	70	0.069	0.005	6.81
Serum PLR	69	0.068	0.009	275.08
Serum LMR	41	0.071	0.222	
Fluid LDH	36	0.064	0.059	
Fluid albumin	31	0.073	0.013	1.46
Albumin_ratio*	59	0.074	0.194	
Protein_ratio†	61	0.071	0.133	
LDH_ratio‡	71	0.060	0.004	1.42

AUC: Area under the curve; SE: Standard error; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; *Serum albumin-to-pleural fluid albumin ratio; † Serum protein-to-pleural fluid protein ratio; ‡ Serum LDH-to-pleural fluid LDH ratio.

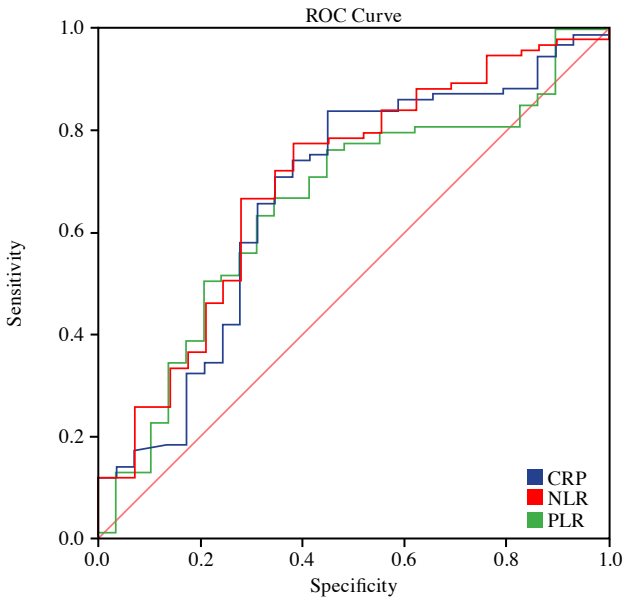

Figure 2. Receiver operating characteristic curves were created according to some significant values (CRP, NLR, and PLR), and cutoff values were determined.

CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

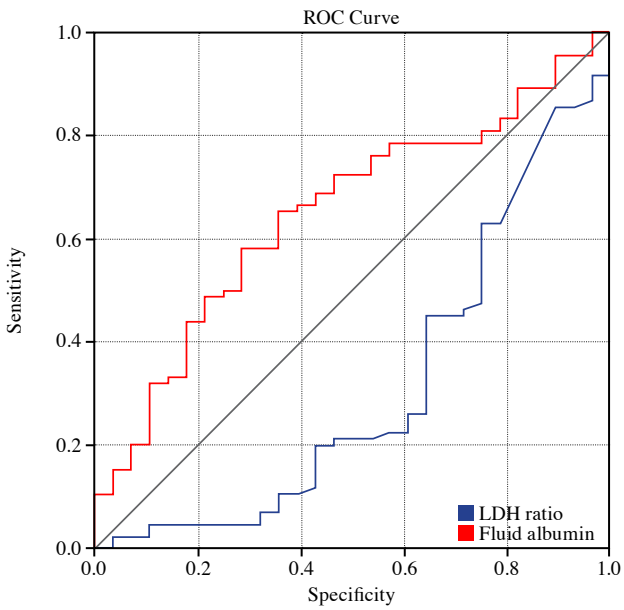

Figure 3. Receiver operating characteristic curves were created according to the serum LDH and fluid albumin levels, and cutoff values were determined.

CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; LDH: Lactate dehydrogenase.

the literature reported that the median survival was better in patients who developed MPE due to breast cancer.[7] In our study, the best median survival

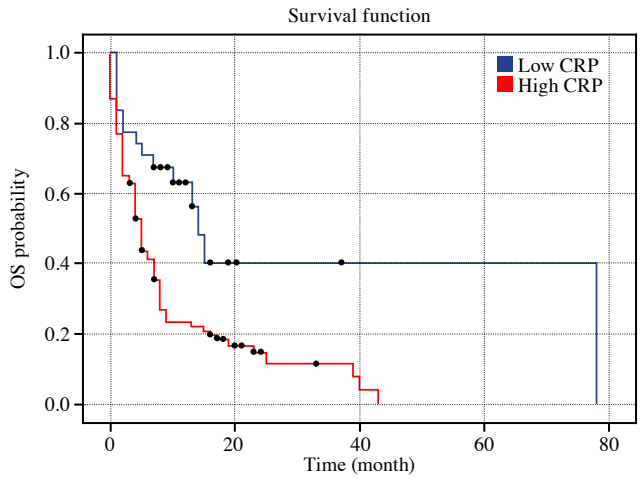

Figure 4. The graph shows that a high serum CRP level is a poor prognostic factor (p=0.001).

CRP: C-reactive protein.

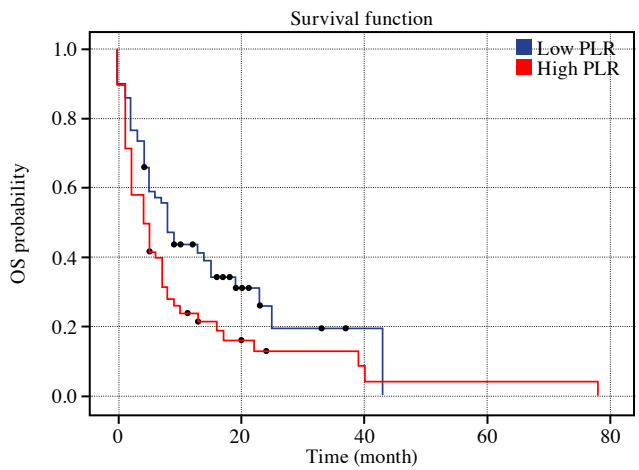

Figure 5. The graph shows that a high PLR is a poor prognostic indicator (p=0.02).

PLR: Platelet-to-lymphocyte ratio.

was in the breast cancer group, compatible with the literature, and the worst median survival was in the gastrointestinal cancer group. Although a significant correlation between serum inflammatory markers and prognosis in lung and other cancers has been demonstrated, such studies in patients with pleural effusion are rare.[5] In studies, high neutrophil and platelet levels in serum were associated with increased inflammation, cancer aggressiveness, and poor prognosis.[8,9] A meta-analysis published by Zhang et al.[10] showed that high NLR and low LMR were associated with lower overall survival in patients with multiple myeloma. Neutrophils are

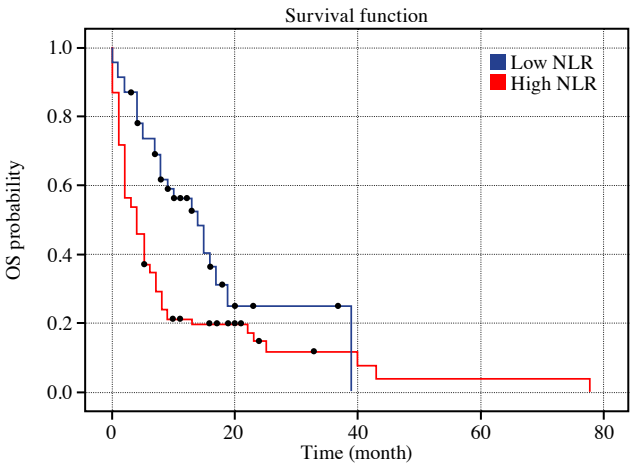

Figure 6. The graph shows that a high NLR level is a poor prognostic factor (p=0.001).
NLR: Neutrophil-to-lymphocyte ratio.

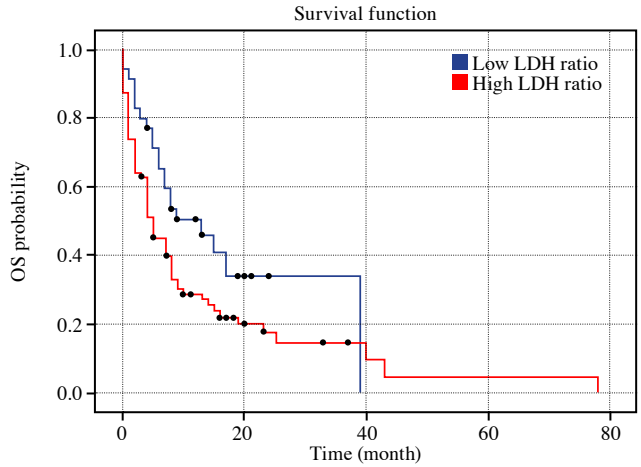

Figure 7. The graph shows that a high LDH ratio is a poor prognostic factor by the log-rank method (p=0.04).
LDH: Lactate dehydrogenase.

the frontline cells in inflammatory disorders in the body. In recent years, the role of neutrophils has been proven to be complex in tumor development and progression. All stages of tumor development, including tumor initiation, metastasis, and immunosuppression, can be influenced by neutrophil infiltration. Therefore, poor survival in a variety of solid tumors in advanced stages is correlated with high peripheral blood NLR levels.[11] Another study conducted by Gayaf et al.[5] demonstrated the poor prognostic impact of high serum NLR, which is an item of the LENT (serum LDH, ECOG performance score, blood NLR, and tumor type) score. Besides encouraging cancer cell proliferation, tumor angiogenesis, and metastasis, platelets also have been demonstrated to enhance several stages of cancer development and tumor growth.[12] In their study of patients with soft tissue sarcomas, Que et al.[13] showed that high preoperative PLR was an independent risk factor for survival in extensive radical surgery patients. Similarly, survival was found to be significantly worse in the high NLR and PLR groups in our study. In some studies, high lymphocyte levels have been reported as a good prognostic factor due to anticancer characteristics of lymphocytes.[14,15] Lymphopenia has been observed in patients with advanced cancer and linked to poor outcomes.[14-16] The lower LMR state can indicate an active inflammation. In recent years, LMR has been established as an independent prognostic factor in hematologic and solid tumors, including colorectal cancer, pancreatic cancer, multiple myeloma, and diffuse large B-cell lymphoma.[16] The monocytes are also important immune cells in cancer. Due to their recruitment into tumors, they can change the tumor's microenvironment and promote cancer growth through local immune suppression and angiogenesis. Solid tumor patients with higher monocyte counts have been shown to have a poor prognosis.[17] Therefore, the higher the LMR (the absolute lymphocyte count divided by the absolute monocyte count), the better the prognosis.[17] In a study by Hutterer et al.[18] on nonmetastatic clear cell renal cell carcinoma patients, low LMR was found as an independent prognostic factor by multivariate analysis. In our study, those with high LMR levels had a good prognosis when the cutoff value was calculated according to the median value, but no significant cutoff value was obtained in the ROC analysis.

It was previously established that cancer prognosis was correlated with the concentration of LDH in the pleural fluid. Prognosis worsens with higher LDH levels in serum. A study showed that an LDH concentration >600 U/L was a significant predictor of poor survival.[19] Although the serum LDH-to-pleural effusion LDH ratio is diagnostically important for effusions and high LDH is known as a poor prognostic factor, no studies have demonstrated the effect of this ratio on the prognosis in patients with MPE. In our study, survival was worse in those with a high serum LDH-to-pleural LDH ratio. Considering the tumor-related pleural thickening and the presence of malignant cells in the pleural fluid, LDH level of the pleural fluid is expected to be higher; this creates an uxpected situation. Contrary to expectations,

prognosis worsens as the serum LDH value increases due to the transition from pleural fluid to serum. Our results can be interpreted as high serum LDH level is a better indicater of tumor aggressiveness than high pleural fluid LDH. In a study, it was observed that the pleural effusion LDH isoenzyme pattern was successful in predicting the presence of malignancy and the type of malignancy.[20] The pleural LDH level may vary depending on the malignancy type and the number of malignant cells in the pleural fluid.

The LENT score is the only validated prognostic scoring system for MPEs.[21] Pleural effusion LDH level, ECOG performance status, NLR, and tumor type are the accepted prognostic factors on the scale. The prognostic factors we revealed in our study to predict the survival in patients with MPE are compatible with LENT.

Inflammation is linked to all phases of cancer development, and patients with solid tumors who have higher levels of systemic inflammation have worse prognosis. C-reactive protein is a hepatocyte-produced acute-phase serum protein, markedly elevated in inflammatory diseases. It is associated with the prognosis of various cancer types. The relationship between serum CRP levels and cancer prognosis could be explained by the fact that carcinogenesis causes an increase in CRP and a tendency to tumor growth. Tumor growth and invasion cause inflammation of the tissue and increase CRP levels, initiating a vicious cycle.[22] Adachi et al.,[23] in their study of head and neck cancer patients receiving chemotherapy, found that the three-year survival was statistically significantly better in those with normal CRP levels than those with high CRP levels. In our study, survival was worse in the high CRP group as mentioned before. As suggested in the literature, we thought that the high serum CRP levels were correlated with high cancer aggressiveness.

The study had some limitations. The number of patients included was relatively low, and the variety of the types of malignancy was limited. Therefore, the relationship between inflammatory parameters according to the type of malignancy could not be clearly determined. Furthermore, it was impossible to perform a pleural biopsy to confirm the diagnosis of MPE in every patient. Determining the relationship between tumor mutation status and inflammatory parameters could offer a different perspective.

In conclusion, some serum inflammatory markers, including a high C-reactive protein, high neutrophil-to-lymphocyte ratio, high platelet-to-lymphocyte ratio, low lymphocyte-to-monocyte ratio, and high serum lactate dehydrogenase-to-pleural lactate dehydrogenase ratio, present a simple and inexpensive way to predict prognosis in patients with malignant pleural effusion.

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

Author Contributions: Idea/concept, design, control/supervision, critical review: N.D.O., A.B., A.S., M.V., T.B., E.S., M.S., I.C.K., B.G., A.C.; Data collection/processing: N.D.O,. A.B., A.S., M.V., T.B., E.S.; Analysis/interpretation, references/fundings: N.D.O., M.S.; Literature review: N.D.O., M.S., A.C.; Writing the article: N.D.O., M.S., B.G., A.C.; Materials: N.D.O.

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