



ORIGINAL ARTICLE

Medicine Science 2021;10(2):539-44

Diagnostic role of complete blood count in pleural effusions

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Received 30 December 2020; Accepted 28 January 2021

Available online 26.04.2021 with doi: 10.5455/medscience.2020.12.264

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Abstract

Pleural effusion (PE) can be seen during the course and treatment of many malignant or benign diseases. Congestive heart failure and pneumonia are the most common causes of benign pleural effusion (BPE), while lung and breast cancer are the most common causes of malignant pleural effusion (MPE). MPE indicates that the disease is extensive or advanced and the average survival is 4-12 months. In this study, we aimed to investigate the changes in complete blood count parameters in patients with benign and malignant PE. Patients who underwent thoracentesis and pleural fluid analysis between January 1, 2015 and December 1, 2020 were included in the study. Demographic characteristics, pathological diagnoses, pleural fluid cell analysis, blood parameters of the patients were recorded. The patients were divided into two groups according to their MPE and BPE detection status. Complete blood count parameters, Systemic Inflammatory Index (SII), Platelet / Lymphocyte Ratio (PLR), Monosin / Lymphocyte Ratio (MLR), Eosinophil / Lymphocyte Ratio (ELR) and Neutrophil / Lymphocyte Ratio (NLR) values were found in both groups and were recorded and compared. 240 patients with PE and meeting the study criteria were included in the study. There were 154 (64.17%) patients with BPE and 86 (35.83%) patients with MPE. In patients with MPE, WBC (103 / mL) 10.22 (2.32-27.50) ($p = 0.001$), Neutrophil (103 / UL) 8 (0.48-24.25) ($p < 0.001$), Monocyte (103 / UL) 0.7 (0-1.9) ($p = 0.002$) were detected. In addition, SII 1868.54 (139.88-16862.63) ($p = 0.001$), NLR 6.68 (0.38-92.91) ($p = 0.001$), MLR 0.58 (0-4.46) ($p = 0.038$) were detected. All these values were statistically higher than the patients with BPE. SII, MLR and NLR values are cheap and easily applicable parameters that can help in the differentiation of malignant and benign pleural effusion, in predicting the prognosis of patients with MPE and in treatment planning.

Keywords: Malignancy, effusion, tumor, diagnosis

Introduction

The space between the thoracic wall and the lung parenchyma is called the pleural space. There may be 5-10 mL of transudate fluid in this space, and this is physiological. Both visceral pleura and parietal pleura play an important role in the homeostasis of the fluid in the pleural space. Pleural fluid is absorbed through the lymphatic vessels in the parietal pleura [3,4].

There is a balance between the systemic and pulmonary circulation and the pleural space in terms of hydrostatic and oncotic pressure differences.

Thanks to this, both production and absorption balance is provided [5]. This balance is disturbed due to increased production and / or decreased resorption. As a result of high pulmonary capillary pressure, low oncotic pressure, lymphatic obstruction, increased vascular permeability and decreased negative intrapleural pressure, fluid accumulates in the pleural space above the physiological limit. This situation is called pleural [6].

PE may develop due to infection, malignancy and other diseases of the lung and pleura, as well as due to extrapulmonary system pathologies such as cardiovascular system, gastrointestinal system, connective tissue diseases, and genitourinary system diseases [7].

In determining the etiology of PE, first of all, the distinction should be made between whether the fluid is transudate or exudate. For this, Light criteria are generally used. It should be kept in mind that Light criteria may give incorrect results in patients who receive diuretic therapy [8].

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Light criteria have a sensitivity of 99% and a specificity rate of 98% [9].

The most common pathologies that cause benign pleural effusion (BPE) are parapneumonic effusions and congestive heart failure and fluid transudate character. The most common pathologies that cause malignant pleural effusion (MPE) are lung and breast cancers. Symptomatic MPE can develop in 50% of patients with breast cancer, 25% of patients with lung cancer and more than 90% of mesothelioma patients during the disease and it has the character of liquid exudate [1]. MPE, diagnosed based on the presence of malignant cells in pleural fluid or pleural biopsy, is an indicator of high mortality and morbidity. It indicates an advanced malignant disease and ruins the patient's chances for curative treatment. Depending on the origin, histopathological type and stage of the patient's primary tumor, the mean survival time varies between 4-12 months in patients with MPE. Among the cancer patients with MPE, those with the shortest survival are those who have developed MPE due to lung cancer. This situation has been found to be important enough to cause revision in lung cancer staging [2].

In the literature, it is stated that besides Light criteria, it can be used in biomarkers such as soluble urokinase plasminogen activator receptor [10] and N-terminal pro-brain natriuretic peptide (NT-proBNP) molecule in order to detect pleural fluid etiology [11]. Biomarkers such as the combination of serum platelets and lymphocyte / monocyte ratio [12] have also been studied.

In some meta-analysis studies conducted in recent years, it has been reported that the increase in serum NLR ratio negatively affects survival in many types of cancer, and there is a relationship between NLR and survival [13].

In this study, we compared the complete blood count parameters of patients with BPE and patients with MPE. We investigated the changes in PLR, MLR, Eosinophil / Basophil Ratio (EBR) and NLR values and the sensitivity and specificity of these values in malignant and benign effusions.

Material and Methods

Study population

This study was planned as a retrospective cohort study and conducted as a single center study.

Patients who underwent thoracentesis and pleural fluid analysis between 1 January 2015 and 1 December 2020 were identified. Radiology, pathology and blood results of the patients were accessed from the electronic database of our hospital.

Patients with hemothorax-like pleural effusion, whose pathology result could not be reached, whose pleural fluid was not analyzed and who had no definitive diagnosis were excluded from the study.

The study protocol was approved by the hospital's local ethics committee in accordance with the Declaration of Helsinki. Informed consent was not required due to the design of the study.

Data

Patients' demographic characteristics, pathological diagnoses based on clinical evaluation and interventional procedures, pleural fluid cell analysis, blood parameters and radiological findings were recorded.

The patients were divided into two groups as MPE and BPE according to their last diagnosis. All groups were compared according to complete blood count parameters, PLR, MLR, ELR and NLR values.

Definitions

Complete blood counts were measured by spectrophotometry / impedance. Venous blood samples were taken into ethylene diamine tetra acetic acid tubes and sent to the laboratory. Hemoglobin (g / dl), hematocrit (%), red blood cell distribution width standard deviation (RDW SD), platelet count (103 / UL), mean platelet volume (MPV), neutrophil count (103 / UL), lymphocyte count (103 / UL), monocyte count (103 / UL), basophil count (103 / UL), eosinophil count (103 / UL), SII, NLR, PLR, MLR and ELR results were recorded.

The SII value was calculated using the formula neutrophils × platelets / lymphocytes, the PLR value was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes, the MLR value by dividing the absolute number of monocytes by the absolute number of lymphocytes, the ELR value by dividing the absolute number of eosinophils by the absolute number of lymphocytes and the NLR by the absolute number of lymphocytes. These counts were obtained from the blood analysis of the patients. The diagnosis of MPE was made based on the malignant reporting of pleural biopsy and / or pleural fluid cytology results and the diagnosis of BPE as a result of benign reporting of pleural biopsy and / or pleural fluid cytology results.

Statistical analyses

SPSS program (SPSS v20; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean ± standard deviation, number of persons and percentages. Compliance of quantitative data to normal distribution was completed with Kolmogorov-Smirnov, Shapiro-Wilk test and graphical evaluations. Student's t-test was used to compare two groups of quantitative data with normal distribution and Mann-Whitney U test was used to compare two data groups with abnormal distribution. Pearson's chi-square test and Fisher's exact test were used to compare qualitative data. P <0.05 value was considered statistically significant. The "Receiver Operator Characteristic Curve" (ROC) analysis method was used to determine the specificity and sensitivity of SII, NLR, PLR, MLR and ELR parameters.

Ethical approval

The study was conducted according to good clinical procedures and the Helsinki Declaration. The study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University Medical Faculty Hospital (No: 2011- KAEK-2 2020/453).

Results

240 patients with pleural effusion were included in the study. There were 154 (64.17%) patients with benign fluid and 86 (35.83%) patients with malignant fluid. 57 (37.01%) of the patients with benign liquid were female and 97 (64.09%) were male. 35 (40.70%) of the patients with malignant liquid were female and 51 (59.30%) were male patients. The general mean age of the patients was 70.23 ± 14.48 . The mean age was 69.57 ± 15.69 in patients with benign fluid and 71.41 ± 12.09 years in patients with malignant fluid (Table 1).

When the complete blood count parameters of patients with MPE and BPE were compared, the number of WBC ($10^3 / \text{mL}$) in

patients with MPE was $10.22 (2.32-27.50)$ ($p = 0.001$), Neutrophil ($10^3 / \text{UL}$) number $8 (0.48 -24.25)$ ($p < 0.001$), Monocyte ($10^3 / \text{UL}$) count $0.7 (0-1.9)$ ($p = 0.002$), SII $0.626 (0.553-0.699)$ ($p = 0.001$), NLR $6.68 (0.38-92.91)$ ($p = 0.001$), MLR was determined as $0.58 (0-4.46)$ ($p = 0.038$) and a statistically significant higher was found in patients with BPE.

MPV (fL) value 10.05 ± 1.29 ($p = 0.016$), eosinophil count ($10^3 / \text{UL}$) $0.12 (0-2.15)$ ($p < 0.001$) and ELR value $0.09 (0-2.09)$ ($p < 0.001$) in patients with BPE. These results were statistically higher than in patients with MPE. No statistically significant difference was observed in terms of Hemoglobin (g / dl), Hematocrit (%), RDW SD (fL), PDW (fL), Lymphocyte ($10^3 / \text{UL}$), Basophil ($10^3 / \text{UL}$), PRL values (Table 2).

Table 1. General characteristics of the patients

	Benign Pleural Effusion (N = 154)	Malignant Pleural Effusion (N = 86)	Total (N=240)
Gender			
Female N (%)	57 (%37.01)	35 (%40.70)	92 (%100)
Male N (%)	97 (%64.09)	51 (%59.30)	148 (%100)
Age	69.57 ± 15.69	71.41 ± 12.09	$*70.23 \pm 14.48$

*overall age average

Table 2. Laboratory data of patients

Laboratory Parameters	Benign Pleural Effusion (N=154)	Malignant Pleural Effusion (N=86)	Average	p value
Hemoglobin (HGB) (g/dL)	12.08 ± 2.19	11.73 ± 2.26	11.95 ± 2.22	0.264
White Blood Cell (WBC) ($10^3/\text{mL}$)	$8.08(0.76-43.27)$	$10.22(2.32-27.50)$	$8.51(0.76-43.27)$	0.001
Hematocrit (%)	37.91 ± 6.99	36.95 ± 7.05	37.56 ± 7.01	0.327
Red Cell Distribution Width (RDW SD) (fL)	15.75 ± 2.44	16.25 ± 2.74	15.93 ± 2.56	0.167
Platelet ($10^3/\text{UL}$)	258.15 ± 119.15	286.36 ± 123.06	268.30 ± 121.08	0.093
Platelet Distribution Width (PDW) (fL)	13.58 ± 2.85	14.01 ± 3.37	13.73 ± 3.04	0.301
Mean Platelet Volume (MPV) (fL)	10.05 ± 1.29	9.61 ± 1.36	9.89 ± 1.33	0.016
Neutrophil ($10^3/\text{UL}$)	$5.60(0.43-42.04)$	$8(0.48-24.25)$	$6.22(0.43-42.04)$	<0.001
Lymphocytes ($10^3/\text{UL}$)	$1.18(0.04-4.21)$	$1.27(0.11-6.70)$	$1.38(0.4-6.70)$	0.732
Monosite ($10^3/\text{UL}$)	$0.56(0.01-11.20)$	$0.7(0-1.9)$	$0.61(0-11.20)$	0.002
Basophil ($10^3/\text{UL}$)	$0.03(0-0.45)$	$0.03(0-2.84)$	$0.03(0-2.84)$	0.491
Eosinophil ($10^3/\text{UL}$)	$0.12(0-2.15)$	$0.06(0-1.40)$	$0.1(0-2.15)$	<0.001
Systemic Inflammatory Index (SII)	$1098.88(129.00-64679.92)$	$1868.54(139.88-16862.63)$	$1351.45(129.00-64679.92)$	0.001
Neutrophil Lymphocyte Ratio (NLR)	$4.34(0.72-254.7)$	$6.68(0.38-92.91)$	$4.84(0.38-254.7)$	0.01
Platelet Lymphocyte Ratio (PLR)	$188.54(20.18-2150.00)$	$228.33(26.12-847.83)$	$205.71(20.18-2150)$	0.341
Monosit/ Lymphocyte Ratio (MLR)	$0.40(0.03-14.93)$	$0.58(0-4.46)$	$0.48(0-14.93)$	0.038
Eosinophil / Lymphocyte Ratio (ELR)	$0.09(0-2.09)$	$0.04(0-0.72)$	$0.0729(0-2.09)$	<0.001

When the ROC analysis was performed according to the SII value, the confidence interval was determined as 0.626 (0.553-0.699) cut off value 1512.08. Its sensitivity was 62% and specificity 38%, and it was statistically significant ($p = 0.001$) (Figure 1).

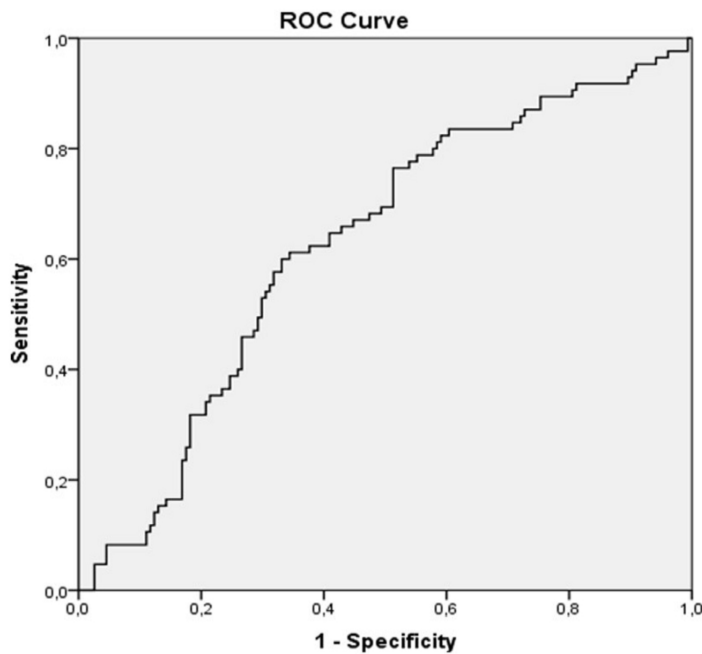


Figure 1. SII ROC table

When the ROC analysis was performed according to the NLR value, the confidence interval of 0.601 (0.526-0.675) was found to be 5.156. Its sensitivity was 60.4% and specificity was 40%, and it was statistically significant ($p = 0.01$) (Figure 2).

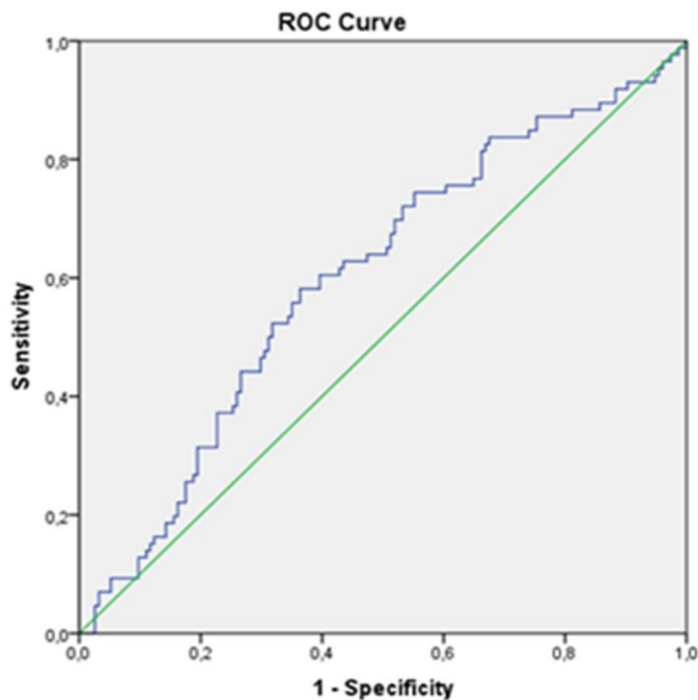


Figure 2. NLR ROC table

When the ROC analysis was performed according to the PLR value, the confidence interval of 0.537 (0.463-0.611) was found to be 211.28. Its sensitivity was found to be 57% and specificity 43% and it was not statistically significant ($p = 0.341$) (Figure 3).

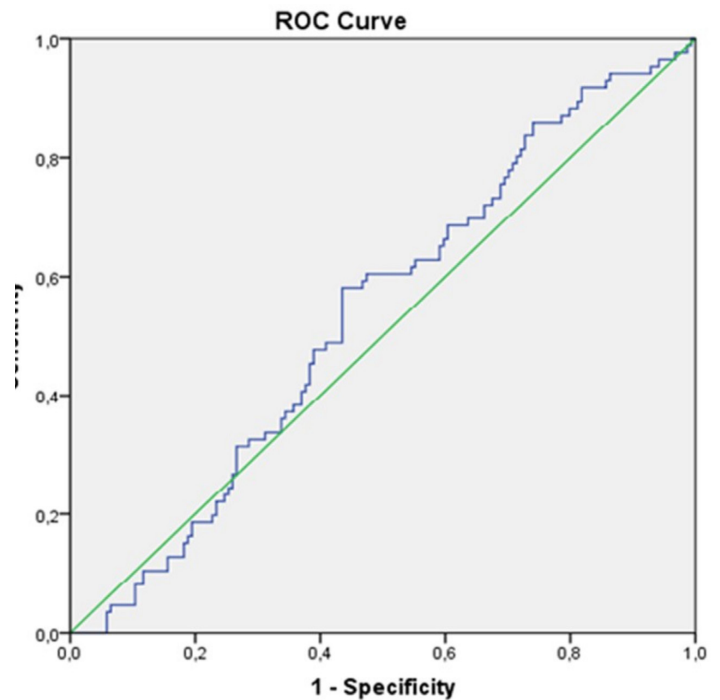


Figure 3. PLR ROC table

When the ROC analysis was performed according to the MLR value, the confidence interval of 0.581 (0.504-0.657) was found to be 0.5. Its sensitivity was 59.3% and specificity was 39.6% and it was statistically significant ($p = 0.038$) (Figure 4).

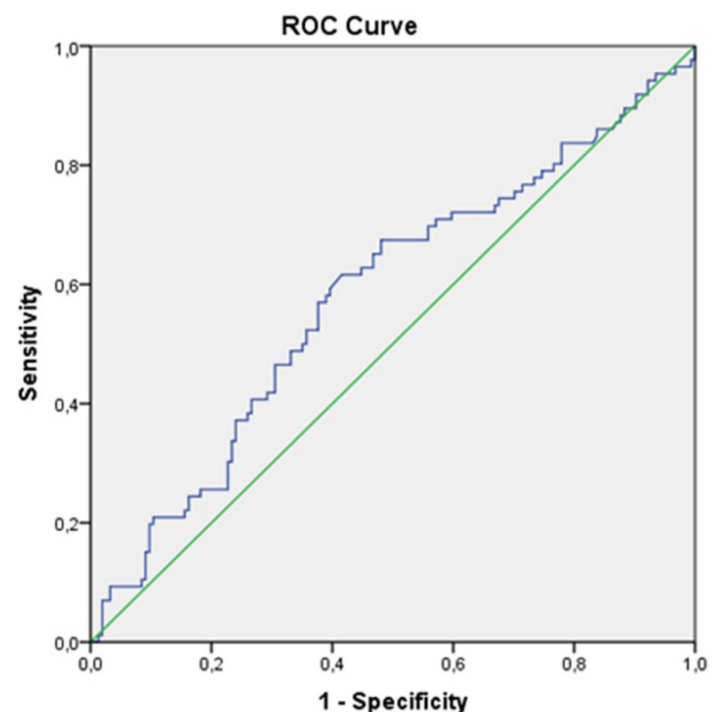


Figure 4. MLR ROC table

When the ROC analysis was performed according to the ELR value, the confidence interval of 0.358 (0.286-0.430) was determined as the cut off value 0.067. Its sensitivity was found to be 38% and specificity 61% and it was statistically significant ($p < 0.001$) (Figure 5).

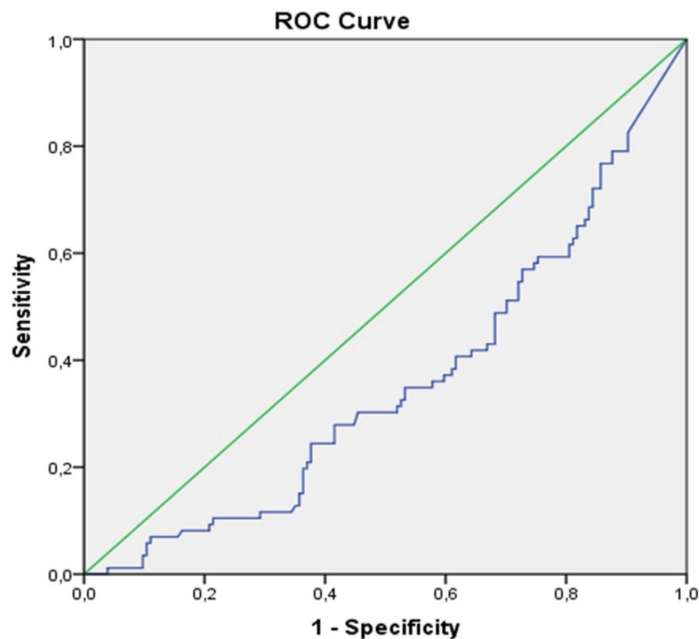


Figure 5. ELR ROC table

AUC: Area Under the Curve SII: Systemic inflammatory index
 NRL: Neutrophil / Lymphocyte ratio PLR: Platelet / Lymphocyte ratio
 MLR: Monocyte / Lymphocyte ratio ELR: Eosinophil / Lymphocyte ratio

This study showed that the sensitivity and specificity rates of the NRL and MLR values are close to each other and the specificity ratio of ELR values is higher than the NRL, PRL and MLR values in the distinction between MPE and BPE (Table 3).

Discussion

It has been reported that inflammation plays an important role in different stages of cancer development [14]. In recent years, many studies have investigated the prognostic effects of C-reactive protein, leukocytes and cytokines which are the most commonly used markers of systemic inflammatory response [15]. Some studies have shown a relationship between neutrophil and lymphocyte counts and the degree of systemic inflammatory response in cancer patients.

In addition, a parameter calculated by using complete blood count parameters, called the systemic immune inflammation index and calculated by the formula of neutrophils \times platelets / lymphocytes, was developed. This parameter has been stated to be a potential marker of inflammation. It has been argued that SII elevation is an indicator of poor prognosis in cancer patients [16].

It has been demonstrated that high NRL has a negative effect on overall survival in various types of cancer [7].

Additionally, there are publications reporting that tumor-infiltrating lymphocytes have a positive effect on the survival of cancer patients. When the results obtained are evaluated together, it suggests that the prognostic effect of SII and NRL may depend on the relationship between inflammation and them [18].

In our study, in line with the results of previous studies, the SII value was significantly higher in cancer patients with MPE, at

the same time, it was the biomarker with the highest sensitivity in cancer patients with MPE. In addition, SII, neutrophil and monocyte levels were significantly higher in patients with MPE compared to BPE patients. There was no significant difference in lymphocyte levels.

Platelets are the source of various proangiogenic and anti-angiogenic proteins [12]. It causes cancer metastasis and tumor cell invasion by secreting vascular epidermal growth factor (VEGF), transforming growth factor beta (TGF- β) and platelet-derived growth factor (PDGF) [19]. For these reasons, it has been argued that platelets have an important role in tumor activity and thrombocytosis and PLR are indicators of poor prognosis in advanced lung cancers [20,21].

In our study, no significant difference was found between the platelet counts in patients with BPE and MPE. Platelet counts were within normal limits in both groups. There was no significant difference in PRL values between the two groups.

Monocytes are precursor cells of macrophages. Macrophages, on the other hand, play a role in tumor growth through tumor angiogenesis [22] and metastasis [2]. The migration of macrophages to the tumor region is associated with a poor prognosis in various cancers and MRL is important in the prognosis of cancer [24].

In our study, in accordance with the literature, the MRL value in patients with MPE was found to be significantly higher than those with BPE.

As a result; SII, NRL, MRL values, neutrophil and monocyte counts were found to be high in cancer patients with MPE, consistent with the literature.

This study limitations

This study is a single center study. This situation causes limitations in generalizing our study results. Many more patients and study series are needed to increase the accuracy of the results. In addition, the result of cytological and / or closed pleural biopsy of pleural fluid in PE varies between 40% and 87% (25) and this situation causes some patients not to be diagnosed.

Conclusion

Neutrophil, monocyte counts and SII, NRL, MLR values can be easily calculated by complete blood count in patients with advanced stage cancer with PE, cheap and highly reliable parameters. It can also help predict short survival in patients, determine the treatment protocol and minimize inappropriate and unnecessary aggressive treatment practices.

Conflict of interests

The authors have no conflicts of interest to declare

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

The study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University Medical Faculty Hospital (No: 2011- KAEK-2 2020/453).

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