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# Role of Inflammatory Response Biomarkers, Monocytes, and Platelets as Prognostic Indicators in Lung Cancer Patients Presenting with Malignant Pleural Effusion

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## Abstract

**BACKGROUND/AIMS:** Malignant pleural effusion (MPE) patients do not have a good prognosis and are strongly associated with markers of systemic inflammation. The current research sought to investigate the association between systemic inflammation and prognosis in lung cancer patients with MPE.

**MATERIALS AND METHODS:** This retrospective analysis was carried out on cases of MPE and lung cancer which occurred between January, 2015 and December, 2019. The study also examined the association between prognosis and the hematological parameters recorded at the time of diagnosis.

**RESULTS:** This study enrolled 117 people with a median age of 63 years. Of the patients, ninety-two were male (78.6%), and 25 were female (21.4%). Following initial diagnosis, the patients were followed up on average for 12 months. Significantly higher levels of monocyte and platelet were observed in the group of deceased patients than in the group of living patients (monocyte 0.4±0.1 $10^3$/uL in living patients vs 0.6±0.5 $10^3$/uL in deceased patients, p=0.010, platelet 275.9±87.3 $10^3$/uL in living patients vs 339.1±113.010$^3$/uL in deceased patients, p=0.020). In the univariate model, survival time was strongly predicted by monocytes, neutrophils, platelets, C-reactive protein, albumin, and platelet/lymphocyte ratio values (p=0.012, p=0.038, p=0.004, p=0.040, p=0.011, p=0.022, respectively). Monocyte and platelet values were found to be independent risk factors for survival time, in the simplified multivariate model [monocyte heart ratio (HR): 1,382; 95% confidence interval (CI), 1,012-1,887, p=0.042, and platelet HR: 1,002; 95% CI, 1,001-1,004, p=0.009].

**CONCLUSION:** In cases of MPE accompanied by stage-4 lung cancer, high monocyte and platelet levels indicate a poor prognosis.

**Keywords:** Cancer, inflammatory markers, neoplasm

## INTRODUCTION

In cancer cells, systemic inflammation can be triggered by oncogenic alterations, and it contributes to the development of cancer. In addition, inflammation indicators may increase in many cancer-related conditions such as anorexia, cachexia, and pain. Cancer patients at high risk can be identified, and the progression of the illness can be predicted using systemic inflammatory signs. These indicators are affordable and simply calculated using regular laboratory data. Lung cancer, which has a high mortality rate, has a similar incidence in men and women.[1] It is widely known that white blood cell (WBC) subtype counts and WBC counts are involved in systemic inflammations or infections. Tumor formation and growth depend on monocytes

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and platelets. The immune system's regulation of tumor growth and metastasis is essential. Wculek and Malanchi[2] proposed that changed leukocyte levels in tumor-bearing hosts' tissues might have an impact on particular subgroups of invasive cancer cells. More specifically, it has been shown that leukocytes build up in the lung before cancer cells invade nearby tissues, and they multiply via the metastatic process.[2] Studies have proven that systemic inflammatory response can predict prognosis in a variety of malignancies.[3] The majority of lung cancer patients had metastatic diseases at the time of diagnosis. It has been shown that markers such as low serum albumin levels and high plasma C-reactive protein (CRP) play an important role in cancer development and progression.[4] It has been discovered that in cases with a range of malignancies, especially lung cancer, a poor outcome can be predicted by neutrophil/lymphocyte ratio (NLR), a systemic inflammatory marker.[5]

In determining survival and the course of the disease in patients with lung cancer, lymphocyte/monocyte ratio (LMR), NLR, and platelet/lymphocyte ratio (PLR) are easily detectable laboratory tests which can be very helpful. The current research aimed to explore the prognostic value of systemic inflammation markers such as LMR, NLR, and PLR in stage-4 lung cancer accompanied by malignant pleural effusion (MPE).

## MATERIALS AND METHODS

A retrospective analysis was carried out on cases diagnosed with stage-4 lung cancer from January, 2015 to December, 2019. The cases were examined in terms of LMR, NLR, PLR, and hematological systemic inflammation markers. Retrospective analyses were performed on age, sex, type of malignancy, hemogram, biochemical results, primary lesion, $SUV_{max}$ for pleural fluid, and overall survival (OS) (OS was described as the length of time from the diagnosis to the last follow-up or death). A comparison was made between the living and deceased patients.

In our research, it was discovered that elevated platelet and monocyte counts independently predicted poor prognosis in cases of lung cancer accompanied by MPE.

Informed consent was not necessary because of the retrospective character of this study.

### Study Population

The study population was selected consecutively from a patient group with MPE who had been histopathologically diagnosed with lung cancer at our medical center between 2015 and 2019. Patients who had malignant cells either in their tissue biopsy or pleural fluid cytology, patients with no other possible pleural effusion etiology, and patients who had suspected malignancy in pleural effusion pathologic examination together with massive or localized effusion causing ipsilateral lung volume loss were recruited. Between 2015 and 2019, 2,245 cases diagnosed in our hospital were screened. Of these, 302 had pleural fluid. The study enrolled 117 cases meeting the inclusion criteria.

The following criteria were the requirements for inclusion in this study: histologically confirmed lung cancer, proven MPE, and individuals who had been undergoing therapy for lung cancer.

The study's exclusion criteria were as follows: patients undergoing curative lung resection; a significant infection present at the time of cancer diagnosis; and having an underlying hematological illness.

### Ethical Considerations

The Ethics Committee of the University of Health Sciences Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital gave its approval for this investigation (2019/653).

### Statistical Method

The mean, standard deviation, frequency, ratio values median, lowest and highest values were calculated as descriptive statistics. The Kolmogorov-Smirnov test was used to examine the distribution of the variables. Mann-Whitney U test and t-test for independent samples were used to examine the quantitative data. The NLR, LMR, and PLR values were analyzed using the Mann-Whitney U test. When the Chi-squared test did not meet the criteria, Fisher's exact test was performed to examine qualitative data. Cox regression (univariate-multivariate) was used for survival analysis. The SPSS 27.0 application was used to analyze the data.

## RESULTS

The study enrolled a total of 117 patients. The median age was 63 years. Of the patients, 92 were male (78.6%), and 25 were female (21.4%). Distribution according to the histological lung cancer types was found as follows: adenocarcinoma (69.2%), squamous cell carcinoma (25.6%), and not otherwise specified (5.1%). Following their initial diagnosis, the patients had an average of 12 months of follow-up care. Table 1 includes the hematological, radiological, and pathological data of the 117 patients and their causes of MPE.

The deceased and the living patient groups did not significantly differ from each other in terms of their age or gender distribution ($p>0.05$). In addition, there was no significant difference between the groups' cell type distribution, tumor N stage distribution, tumor diameter, or tumor $SUV_{max}$ value ($p>0.05$). The percentage of positive biopsy results did not substantially differ between the groups ($p>0.05$). There was no difference in pleural effusion side distribution or pleural fluid cytology rate between the two groups ($p>0.05$) (Table 2).

There was no difference in lymphocyte, neutrophil, CRP, albumin, NLR, PLR, or LMR values between the deceased and living patient groups ($p>0.05$). The deceased patient group had significantly higher monocyte and platelet counts than the living patient group (Living patients' monocyte 0.4±0.1 vs Deceased patients' monocyte 0.6±0.5), (Living patients' platelets 275.9±87.3 vs Deceased patients' platelets 339.1± 113.0) ($p=0.010$, $p=0.020$ respectively) (Table 2).

In the univariate model, age, sex, cell type, tumor diameter, tumor $SUV_{max}$, T, tumor N stage, pleural fluid localization, pleural fluid cytology, pleural fluid FDG, pleural biopsy, lymphocyte, NLR, and LMR values were not statistically significant indicators of survival time ($p>0.05$). Monocytes [Heart ratio (HR): 1.420; 95% confidence interval (CI), 1.081-1.865, $p=0.012$], neutrophils (HR: 1.70; 95% CI, 1.23-2.35, $p=0.038$), platelets (HR: 1.002; 95% CI, 1.001-1.004, $p=0.004$), CRP (HR: 1.013; 95% CI, 1.001-1.025, $p=0.040$), albumin (HR: 0.666; 95% CI, 0.487-0.911, $p=0.011$), PLR (HR: 1.002; 95% CI, 1.000-1.004, $p=0.022$) values were found to be statistically significant in predicting survival time in a univariate model (Table 3).

Monocyte (HR: 1.382; 95% CI, 1.012-1.887, $p=0.042$) and platelet (HR: 1.002; 95% CI, 1.001-1.004, $p=0.009$) values were found as independent predictive factors in a reduced multivariate model (Table 3).

## DISCUSSION

A very important role in the pathogenesis and progress of cancer is played by systemic inflammation. Studies have highlighted the link between systemic inflammatory biomarkers and the development of several cancer types. We also planned to study the function of systemic inflammation biomarkers in advanced lung cancers complicated by MPE. In our study, we found that high platelet and monocyte levels were independent predictors of a poor prognosis in cases of lung cancer accompanied by MPE.

A study which included 101 lung cancer cases with MPE found that the cytology exam of pleural fluid was positive in 60.4% of the cases. The authors underline pleural fluid cytology's sensitivity in MPE.[6] Another study involving 165 patients with pathologically proven MPE identified positive pleural cytology and positive histology as independent predictive factors for survival but found no significance in Cox regression.[7] Similarly, in our study, positive pleural cytology was found to have no significant effect on mortality or survival.

Biomarkers of an inflammatory response, such as LMR, PLR, and NLR, have frequently been cited in recent studies on lung cancer prognosis. Xu et al.[8] found that, apart from N3, PLR had a significant independent relationships with the T stage and N stage. NLR and PLR were found to be potential biomarkers for Non-small-cell lung cancer (NSCLC) in

**Table 1. Demographic, radiological and pleural fluid characteristics**

| | | Min.-Max. | Median | Mean ± SD/(n, %) |
|---|---|---|---|---|
| Age (years) | | 37.0-77.0 | 63.0 | 62.5±7.5 |
| Sex | Female | - | - | 25 (21.4%) |
| | Male | - | - | 92 (78.6%) |
| Cell type | Adeno | - | - | 81 (69.2%) |
| | SCC | - | - | 30 (25.6%) |
| | NOS | - | - | 6 (5.1%) |
| Tumor N | I | - | - | 9 (7.7%) |
| | II | - | | 74 (63.2%) |
| | III | - | | 34 (29.1%) |
| Pleural | Biopsy (+) | - | - | 26 (22.2%) |
| | Biopsy (-) | - | | 14 (12.0%) |
| | No biopsy | - | | 77 (65.8%) |
| Pleural fluid FDG | >2.5 | - | - | 57 (48.7%) |
| | <2.5 | - | | 60 (51.3%) |
| Pleural fluid localization | Right | - | - | 61 (52.1%) |
| | Left | - | | 56 (47.9%) |
| Pleural fluid cytology | (+) | - | - | 64 (54.7%) |
| | (-) | - | | 53 (45.3%) |
| Tumor diameter (cm) | | 2.0-12.0 | 5.0 | 4.9±2.2 |
| Tumor $SUV_{max}$ | | 2.9-32.0 | 11.4 | 12.4±5.4 |
| Lymphocyte ($10^3$/uL) | | 0.6-3.9 | 1.7 | 1.8±0.7 |
| Monocyte ($10^3$/uL) | | 0.1-4.8 | 0.5 | 0.6±0.5 |
| Neutrophil ($10^3$/uL) | | 2.1-16.7 | 6.1 | 6.6±2.7 |
| Platelet ($10^3$/uL) | | 127.0-667.0 | 303.0 | 331.0±111.8 |
| CRP (mg/dL) | | 0.1-98.2 | 4.1 | 8.0±13.5 |
| Albumin (mg/dL) | | 2.3-5.1 | 3.8 | 3.8±0.6 |
| NLR | | 0.9-15.5 | 3.4 | 4.1±2.7 |
| PLR | | 65.1-561.6 | 180.0 | 209.1±106.0 |
| LMR | | 0.2-12.3 | 3.6 | 4.0±2.3 |
| Following time (months) | | 1.0-67.0 | 12.0 | 17.3±15.5 |
| Alive | | - | - | 15 (12.8%) |
| Deceased | | - | - | 102 (87.2%) |

Min.: Minimum, Max.: Maximum, SD: Standard deviation, SCC: Squamous cell carcinoma, NOS: Not otherwise specified, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio

its early stages and could be useful in predicting stages 3 and 4. In both surgical and non-surgical NSCLC patients, elevated PLR was found to be strongly related to poor OS in a meta-analysis evaluating 5,314 patients from 13 studies, with a cut-off value of 160 for PLR; however, the same relationship was not discovered in the case of small cell lung cancer (SCLC).[9]

LMR was connected to both OS and disease-free survival (DFS) in another study of NSCLC patients.[10] Decreased progression-free survival and OS after systemic therapy were linked to higher NLR before treatment, according to a meta-analysis by Wang et al.[11] (chemotherapy, immunotherapy, and targeted therapy). In their retrospective study, Wang et al.[12] defined the inflammatory response biomarker (IRB) scores with 3 parameters, namely NLR, PLR, and LMR, and found that an IRB score of 2 or above was an independent predictive factor for poor OS and DFS.

High NLR and PLR levels were discovered to be linked to a worse OS in a study of 389 individuals with advanced-stage NSCLC taking chemotherapy, and a similar significant relationship was also identified for total lymphocyte count.[13] The results of our study contradict all this literature data, but this may be due to our smaller sample size when compared to the biomarker studies in the literature.

Previous studies determined that thrombocytosis before treatment was a poor indicator of prognosis in malignant mesothelioma, cervix, colon, and non-small cell carcinoma.[14,15] By generating growth and angiogenic factors, tumor-associated macrophages are known to promote angiogenesis, encourage the development of tumor cells, and facilitate invasion and metastasis.[16] According to Hamilton et al.[17], circulating tumor cells (CTC) interact with macrophages composed of monocytes. In SCLC, aggressive invasion of CTC as well as cytokines, chemokines, and growth factors are seen. As a result, a high monocyte count

**Table 2. Data comparison between the living and the deceased group**

| | | Living | | Deceased | | p-value |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Median | Mean ± SD | Median | |
| Age (years) | | 61.1±8.1 | 61.0 | 62.7±7.4 | 63.0 | 0.456 |
| Sex | Female | 2 (13.3%) | - | 23 (22.5%) | - | 0.416 |
| | Male | 13 (86.7%) | - | 79 (77.5%) | - | |
| Cell type | Adeno | 12 (80.0%) | - | 69 (67.6%) | - | 0.503 |
| | SCC | 3 (20.0%) | - | 27 (26.5%) | - | 0.526 |
| | NOS | 0 (0.0%) | - | 6 (5.9%) | - | 1.000 |
| Tumor N | I | 1 (6.7%) | - | 8 (7.8%) | - | 0.931 |
| | II | 9 (60.0%) | - | 65 (63.7%) | - | |
| | III | 5 (33.3%) | - | 29 (28.4%) | - | |
| Pleural | Biopsy (+) | 2 (50.0%) | - | 24 (66.7%) | - | 0.601 |
| | Biopsy (-) | 2 (50.0%) | - | 12 (33.3%) | - | |
| | No biopsy | 11 | - | 66 | - | |
| Pleural fluid $SUV_{max}$ | >2.5 | 8 (53.3%) | - | 49 (48.0%) | - | 0.702 |
| | <2.5 | 7 (46.7%) | - | 53 (52.0%) | - | |
| Pleural fluid localization | Right | 10 (66.7%) | - | 51 (50.0%) | - | 0.228 |
| | Left | 5 (33.3%) | - | 51 (50.0%) | - | |
| Pleural fluid cytology | (+) | 6 (40.0%) | - | 58 (56.9%) | - | 0.221 |
| | (-) | 9 (60.0%) | - | 44 (43.1%) | - | |
| Tumor diameter (cm) | | 4.9±2.4 | 5.0 | 4.9±2.2 | 5.0 | 0.843 |
| Tumor $SUV_{max}$ | | 12.3±7.2 | 10.4 | 12.4±5.1 | 11.9 | 0.441 |
| Lymphocyte ($10^3$/uL) | | 1.6±0.6 | 1.6 | 1.9±0.7 | 1.8 | 0.274 |
| Monocyte ($10^3$/uL) | | 0.4±0.1 | 0.4 | 0.6±0.5 | 0.5 | ***0.010*** |
| Neutrophil ($10^3$/uL) | | 5.8±2.9 | 5.7 | 6.7±2.6 | 6.2 | 0.242 |
| Platelet ($10^3$/uL) | | 275.9±87.3 | 252.0 | 339.1±113.0 | 310.0 | ***0.020*** |
| CRP (mg/dL) | | 8.0±19.8 | 2.4 | 8.0±12.5 | 4.5 | 0.122 |
| Albumin (mg/dL) | | 3.8±0.6 | 4.0 | 3.8±0.6 | 3.8 | 0.701 |
| NLR | | 3.7±2.1 | 3.4 | 4.2±2.8 | 3.4 | 0.680 |
| PLR | | 184.3±91.0 | 162.6 | 212.8±108.0 | 185.2 | 0.340 |
| LMR | | 4.6±1.7 | 4.2 | 3.9±2.3 | 3.5 | 0.082 |
| [t]t-test /[m]Mann-Whitney U test/[χ²] | | Chi-squared test | | | | |

Bold and italic indicate significant values: p<0.05., SD: Standard deviation, SCC: Squamous cell carcinoma, NOS: Not otherwise specified, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio

**Table 3. Patient data in the univariate and multivariate model**

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Age (years) | 1.016 | 0.988-1.044 | 0.270 | - | - | - |
| Sex | 1.129 | 0.703-1.812 | 0.616 | - | - | - |
| Cell type | 1.094 | 0.790-1.513 | 0.589 | - | - | - |
| Tumor diameter (cm) | 1.054 | 0.960-1.156 | 0.269 | - | - | - |
| Tumor $SUV_{max}$ | 0.997 | 0.964-1.032 | 0.874 | - | - | - |
| Tumor N stage | 1.130 | 0.800-1.597 | 0.488 | - | - | - |
| Pleural biopsy | 1.079 | 0.855-1.362 | 0.522 | - | - | - |
| Pleural fluid $SUV_{max}$ | 1.223 | 0.826-1.810 | 0.315 | - | - | |
| Pleural fluid localization | 1.059 | 0.713-1.571 | 0.777 | - | - | - |
| Pleural fluid cytology | 0.815 | 0.549-1.210 | 0.311 | - | - | - |
| Lymphocyte ($10^3$/uL) | 1.148 | 0.854-1.545 | 0.361 | - | - | - |
| Monocyte ($10^3$/uL) | 1.420 | 1.081-1.865 | ***0.012*** | 1.382 | 1.012-1.887 | ***0.042*** |
| Neutrophils ($10^3$/uL) | 1.075 | 1.004-1.151 | ***0.038*** | - | - | - |
| Platelet ($10^3$/uL) | 1.002 | 1.001-1.004 | ***0.004*** | 1.002 | 1.001-1.004 | ***0.009*** |
| CRP (mg/dL) | 1.013 | 1.001-1.025 | ***0.040*** | - | - | - |
| Albumin (mg/dL) | 0.666 | 0.487-0.911 | ***0.011*** | - | - | - |
| NLR | 1.060 | 0.987-1.137 | 0.108 | - | - | - |
| PLR | 1.002 | 1.000-1.004 | ***0.022*** | - | - | - |
| LMR | 0.905 | 0.814-1.005 | 0.062 | - | - | - |
| Cox regression (forward LR) | | - | - | - | - | - |

Bold and italic indicate significant values: p<0.05. HR: Heart ratio, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio

may contribute to tumor progression. In support of these findings, monocyte and platelet counts were discovered to be independent predictors of OS duration in our research.

### Study Limitations

In our study, it was discovered that elevated platelet and monocyte levels are independent predictors of poor prognosis in cases of lung cancer accompanied by MPE. This suggests that more rapid and aggressive treatment should be applied to lung cancer patients with increased monocytes and platelets. In addition to conventional chemotherapy, developing adjunct therapies for monocyte and platelet functions (targeting monocyte-platelet receptors and the chemokines, cytokines, and the growth factors secreted from them) may facilitate the management of these patients and favorably influence their survival.

## CONCLUSION

Patients with MPE generally have a poor prognosis. A correlation between prognosis and systemic inflammation marker levels has been emphasized in a number of previous studies in this patient group. This study showed a positive and independent correlation between high thrombocyte and monocyte levels and a poor prognosis in lung cancer patients with MPE. These are simple, widespread, and low-cost diagnostic tests which can help provide foresight toward future outcomes. In cases of advanced lung cancer with MPE, patients with high levels of thrombocytes and monocytes are subject to a poor prognosis.

## MAIN POINTS

- Survival of patients with malignant pleural effusion is generally poor.
- In lung cancer patients, Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio and advanced lung cancer inflammation index show a strong correlation with prognosis.
- One hundred and seventeen patients were included in the study.
- Monocyte and platelet values were significantly higher in the deceased patients' group than in the living patients' group (p=0.010, p=0.020).
- High monocyte and platelet counts reflect poor prognosis in advanced-stage lung cancer cases with malignant pleural effusion.

## ETHICS

**Ethics Committee Approval:** The Ethics Committee of the University of Health Sciences Türkiye, Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital gave its approval for this investigation (2019/653).

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Concept: F.Ç., M.A., Ş.A., Design: F.Ç., Data Collection and/or Processing: F.Ç., M.A., S.D., A.Ş., Analysis or Interpretation: F.Ç., M.A., S.D., A.Ş., Literature Search: F.Ç., M.A., S.D., A.Ş., Ş.A., Writing: F.Ç., M.A.

**DISCLOSURES**

**Conflict of Interest:** No conflict of interest was declared by the authors.

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