RESEARCH ARTICLE

# Relationship Between Prognosis and Neutrophil: Lymphocyte and Platelet:Lymphocyte Ratios in Patients with Malignant Pleural Mesotheliomas

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## Abstract

**Background: It has been demonstrated that neutrophil:lymphocyte (NLR) and platelet:lymphocyte (PLR) ratios are associated with prognosis in cancer patients. The aim of this study was to investigate whether pretreatment white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet, basophil and eosinophil counts, LDH level, NLR and PLR are associated with prognosis in patients with malignant pleural mesothelioma (MPM). Materials and Methods: We retrospectively reviewed files of 50 patients who were managed with a diagnosis of MPM between 2005 and 2010. Demographic and clinical characteristics, treatments, response to treatment and prognostic factors were evaluated, along with relationships between pretreatment blood parameters and prognosis. Results: Overall, 38 men and 12 women were included to the study. Mean age was 61.5±9.4 years (range: 39-83 years). There was advanced disease in 86% (n=43) and the histological type was epithelial mesothelioma in the majority (82%). Of the cases, 17 (34%) received radiotherapy, while 42 cases underwent first- and second-line chemotherapy, with cisplatin plus pemetrexed as the most commonly used regimen. In the assessment after therapy, it was found that there was complete response in 4 cases (8%), partial response in 10 cases (20%), stable disease in 17 cases (34%) and progression in 19 cases (38%). Median follow-up was 10 months (range: 10 day-30 months). Median overall survival was found to be 20.7 months while median progression-free survival as 10 months. In univariate and multivariate analyses, it was found that factors significantly affecting overall survival included stage (p=0.030), response to treatment (p=0.026) and monocyte count (p=0.004), while factors affecting disease-free survival included NLR (p=0.018), response to treatment (p=0.001), and PLR score (p=0.003). Conclusions: Overall and disease-free survival was found to be better in cases with a WBC count<8.000, platelet count<300,000, and low NLR and PLR scores in malignant pleural mesothelioma.**

**Keywords:** Malignant pleural mesothelioma - survival - NLR - PLR - prognosis

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## Introduction

Malignant pleural mesothelioma is a tumor with aggressive course and limited therapeutic options which arises from serosal cells lining pleural cavity. It is estimated that there are annually 500-600 new MPM cases in Turkey and overall 30,000 MPM cases worldwide (Stahel et al., 2010; Utkan et al., 2013). It is rarely seen, although its incidence is tended to increase. The MPM incidence increases by age with male predominance. Asbestos and erionite are known causes in the etiology (Ibrahim et al., 2013). There is a widely accepted that MPM has no benefit from anti-tumor therapy and therapeutic options have no contribution to prognosis; in addition, no standard treatment protocol has been yet established. Many clinics consider that supportive therapy is sufficient. Currently used therapeutic approaches aren't curative. The fact that any treatment method alone isn't effective in MPM management brings forward novel combined treatment approaches. Today, recommended therapeutic approach is tri-modal treatment approach in selected cases, including extrapleural pneumonectomy followed by high-dose hemithorax irradiation and chemotherapy. Tri-modal treatment reduces local recurrence and improves mean survival (Stahel et al., 2010; Utkan et al., 2013). Majority of MPM cases are inoperable at the time of diagnosis; thus, they were managed by using chemotherapy and/or radiotherapy (Ibrahim et al., 2013). Mortality rate is high in MPM cases, with more than half of deaths resulting from local complications (Berk et al., 2013). In MPM, 5-years survival rate was lower than 5%. Median survival varies from 12 to 17 months (Edwards et al., 2000; Ibrahim

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et al., 2013).

White blood cell, neutrophil, lymphocyte and NLR are markers of systemic inflammation. It is suggested that inflammation plays role in all phases of cancer from development to progression. In the literature, relationship between inflammation and neutrophil has been widely investigated in cancer. It is shown that white blood cell and subtypes have predictive and prognostic value in many cancer types (Klinger and Welkmann 2002; Prete et al., 2011; Li et al., 2014).

To best of our knowledge, there is no study investigating prognostic features of NLR and PLR in MPM in the literature. In this retrospective study, it was investigated whether blood parameters measured at presentation have effect on prognosis in patients with MPM who were treated in our hospital.

## Materials and Methods

*Patient group and demographic characteristics*

We retrospectively reviewed data of 50 patients with MPM who were managed at Kayseri Teaching Hospital between 2005 and 2010. In all patients included, demographic characteristics such as age, gender or smoking, asbestos exposure, presenting complaints, radiological studies, diagnostic procedures, histopathological diagnosis rates, blood tests, adjuvant treatments, overall and disease-free survivals and prognostic factors were reviewed. Patients with missing data and those not attending to controls were excluded.

*Treatments*

Surgery: chemotherapy and/or radiotherapy were selected according to age, performance status and comobid diseases. All patients underwent thoracoabdominal CT scan, MR imaging and/or PET-CT scan before surgery. Pleurectomy/decortication, extrapleural pneumonectomy (EPP) or thoracoscopic biopsy was performed in surgery. American Joint Commission on Cancer (AJCC) 2002 staging system was used for staging after surgery.

First-line chemotherapy: Chemotherapy was given to patients with ECOG (Eastern Cooperative Oncology Group) performance status 0-2, those having no severe cardiac problem, and those with normal renal and bone marrow functions. First-line chemotherapy regimens included one of the followings: cisplatin plus premetrexed, premetrexed or gemcitabine.

Second-line chemotherapy: Second-line chemotherapy was given to patients with progression and good performance status. Second line chemotherapy regimens included one of the followings: cisplatin plus premetrexed, premetrexed or gemcitabine.

Radiotherapy: Adjuvant radiotherapy was delivered to surgical scar and drain sites, whereas prophylactic radiotherapy was delivered to biopsy site to decrease recurrence and pain. In addition, palliative radiotherapy was delivered for symptom palliation. Radiotherapy involving macroscopic mass, surgical procedure site or painful sites was delivered with total dose of 3000-5600cGy in fractions of 200-300cGy per day by using Co 60/Linac (6 MC photon) device.

**Table 1. Patients' Characteristics**

| | | Patients n (%) or x̄±SD |
|---|---|---|
| Gender | Male | 38 (76) |
| | Female | 12 (24) |
| Age | (years) | 61.5±9.4 |
| | <65 | 29 (58) |
| | ≥65 | 21 (42) |
| Smoking | Yes | 20 (40) |
| | No | 15 (30) |
| | Unknown | 15 (30 |
| Asbestos exposur | No | 35 (70) |
| | Yes | 7 (14) |
| | Unknown | 8 (16) |
| The hometown | Nevsehir | 26 (52 |
| | Kayseri | 19 (38 |
| | The other | 5 (10) |
| Symptom | Chest pain | 20 (40) |
| | Dispne | 21 (42) |
| | Cough | 10 (20) |
| | Constitutional symptoms | 25 (50) |
| Hemithorax involvemen | Right hemithorax | 26 (52) |
| | Left hemithorax | 24 (48) |
| Tumor stage | I | 1 (2) |
| | II | 6 (12) |
| | III | 29 (58) |
| | IV | 14 (28) |
| Performance status | 0 | 12 (24) |
| | 1 | 37 (74) |
| | 2 | 1 (2) |
| Pathology | Epitheloid | 41 (82) |
| | Biphasic | 5 (10) |
| | The other | 4 (8) |
| Comorbidity | Yes | 19 (38) |
| | No | 27 (54) |
| | Unknown | 4 (8) |
| Surgery | EPP | 7 (14) |
| | Pleurectomy/decortications | 4 (8) |
| | Biopsy | 39 (78) |
| Chemotherapy | Yes | 42 (84) |
| | No | 8 (18) |
| Firstline chemotherapy | Platin+pemetrexed | 25 (50) |
| | Pemetrexed | 7 (14) |
| | The other | 10 (20) |
| Secondline chemotherapy | Platinum+pemetrexed | 6 |
| | Pemetrexed | 3 |
| | The other | 2 |
| Radiotherapy | Yes | 17 (34) |
| | No | 33 (66) |
| Response | Complete response | 4 (8 |
| | Partial response | 10 (20 |
| | Stable disease | 17 (34) |
| | Progressive disease | 19 (38) |
| Distant metastasis | Yes | 6 (12) |
| | No | 44 (88) |
| White blood cells, (x10$^3$ $\mu l^{-1}$) | | 7.6±2.0 |
| Neutrophil (x10$^3$$\mu l^{-1}$) | | 4.8±2.3 |
| Monocyte ($\mu l^{-1}$) | | 0.7±0.3 |
| Lymphocyte (x10$^3$ $\mu l^{-1}$) | | 1.5±2.4 |
| Hemoglobin (g/dl) | | 13.7±2.0 |
| Hematocrit (%) | | 41.1±6.0 |
| Platetelet (x10$^3$ $\mu l^{-1}$) | | 244.0±82.7 |
| LDH (U/L) | | 220±103 |
| NLR | | 2.9±7.1 |
| PLR | | 137±295 |
| NLR score | | 0.5±0.5 |
| PLR score | | 0.3±0.4 |

*x̄±SD: Aritmethic mean±Standart Deviation

*Blood samples*

Pretreatment hemoglobin, hematocrit, platelet, white blood cell, neutrophil, lymphocyte, eosinophil, monocyte and LDH values were included to the analysis. NLR and

PLR values were calculated from neutrophil, platelet and lymphocytes counts as ratio of neutrophil and platelets counts to lymphocyte count, respectively. Due to skewed distribution, median values were used for NLR and PLR. The patients were stratified according to median NLR and PLR values as follows: NLR<3 as low or NLR≥3 as high and NLR<190 as low or NLR≥190 as high.

*Follow-up*

Treatment response was assessed according to World Health Organization criteria. Briefly, complete response was defined as disappearance of disease and metastasis, while partial response as regression by 50% or more in measurable lesions or lack of newly developed lesions. Stable disease was defined as regression by less than 25% or no change for at least 4 weeks in the size of lesions while progression as growth by more than 25% in measurable tumor areas or onset of new lesions. Follow-up visits were scheduled by 3-months intervals during first 2 years after treatment; and by 6-months intervals thereafter. In the follow-up visits, all patients were assessed by physical examination, blood tests including complete blood count and hepatic and renal function tests, and imaging modalities including thorax and abdomen CT scans or PET-CT scan. Duration of follow-up was defined as time from diagnosis to last control visit in survivors and time from diagnosis to time of death in non-survivors. Overall survival time was calculated as time from diagnosis to time of death due to any reason while disease-free survival was calculated as time from diagnosis to time of death due to recurrence (local-regional recurrence or distant metastasis) or cancer.

*Statistical analysis*

SPSS (Statistical Package for the Social Sciences) for Windows version 15.0 was used in data analyses. Kaplan-meier analysis was used to calculate overall cumulative probability of survival. Log-rank test was used to assess survival differences. Univariate analysis was performed to assess association between several prognostic factors and survival. Prognostic factors found to be significant in univariate analysis were included to Cox proportional hazard model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess strength of associations between predictors and survival. $p<0.05$ was considered as statistically significant.

## Results

Table 1 presents clinical characteristics and blood parameters evaluated including mean, minimum and maximum values. There were 38 men and 12 women with a mean age of 61.5±9.4 years (range: 39-83 years). Majority of the cases (52%) were referred from Cappadocia region. There was history of exposure to asbestosis in 7 cases (14%). The most common presenting complaints were shortness of breath and chest pain. There was advanced disease in 43 (86%) of the cases. Hemithorax location of lesions was similar for both sides (26/24). Majority of the cases were inoperable with advanced disease. Histological type was epithelial mesothelioma in vast majority of the cases (82%). First-line chemotherapy was given to 42 cases, including cisplatin/carboplatin plus premetrexed (50%), premetrexed alone (14%) and other chemotherapy regimes. For first-line chemotherapy, It was found that there was complete response in 4 cases (8%), partial response in 10 cases (20%), stable disease in 17 cases (34%) and progression in 19 cases (38%). Second-line chemotherapy was given to 10 cases with progression and good performance status, including one of the followings: premetrexed alone, gemcitabine, cisplatin plus premetrexed or cisplatin plus gemcitabine. Palliative radiotherapy was delivered to 17 (34%) of the cases. No severe radiotherapy-related complication was observed. Median follow-up was 10 months (range: 10 days-30 months). Overall and progression-free survivals were found to be 20.7 and 10 months, respectively. One-year overall survival rate was 68% while 2-years overall survival rate was 41%. Six-months, 1-years and 18-months disease-free survival rates were found as 67%, 42% and 28%, respectively (Figure 1 and 2).

Table 2 presents results of univariate and multivariate analysis of risk factors for overall survival. In univariate analysis, it was found that factors significantly affecting overall survival were stage, response to treatment

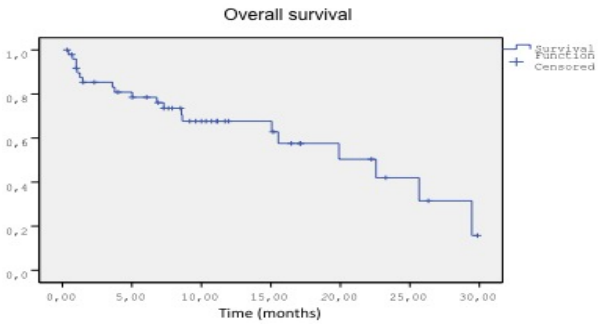


**Figure 1. Kaplan-meier Overall Survival**

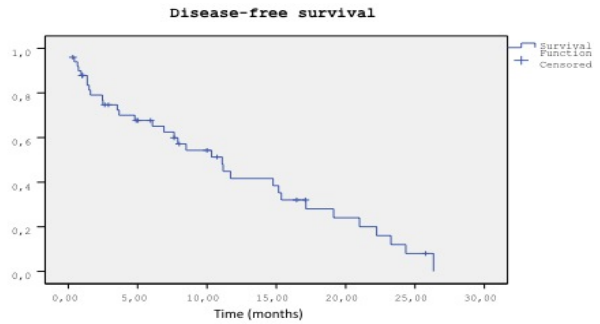


**Figure 2. Kaplan-meier Disease-free Survival**

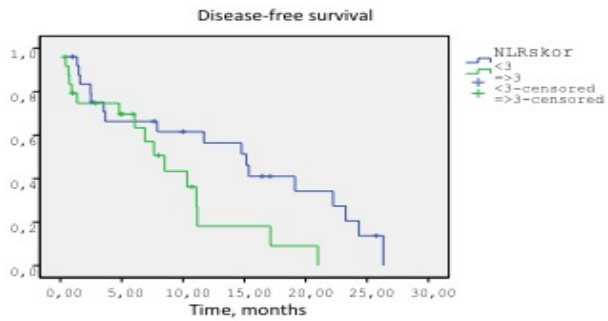


**Figure 3. The Disease-free Survival According to Neutrophil to Lymphocyte Ratio**

**Table 2. Overall and Disease-Free Survive and p value According to Characteristics of Patients (CI: Confidence Interval)**

| Variables | | Patients No. | Overall Survival | | Disease-free Survival | |
|---|---|---|---|---|---|---|
| | | | Survival month mean (95% CI) | p value | Survival month mean (95% CI) | p value |
| Age | <65 | 29 (58 | 18.0 (13.1-22.7) | 0.838 | 12.1 (8.3-16.0) | 0.590 |
| | ≥65 | 21 (42) | 15.9 (11.9-19.8) | | 10.9 (7.2-14.3) | |
| Gender | Female | 12 (24) | 24.0 (18.5-31.1) | 0.099 | 12.2(9.1-15.3) | 0.663 |
| | Male | 38 (76) | 16.5 (12.6-20.5) | | 11.6 (8.8-14.3) | |
| Smoking | Yes | 20(40) | 17.8 (12.0-23.6) | 0.867 | 9.6 (5.3-13.9) | 0.058 |
| | No | 15 (30) | 19.2 (12.4-26.1) | | 15.4 (10.1-20.7) | |
| | Unknown | 15 (30) | 13.0 (9.8-16.1) | | 8.9 (5.5-12.4) | |
| Asbestos exposure | No | 35 (70) | 16.1 (12.1-20.2) | 0.399 | 10.6 (7.6-13.7) | 0.257 |
| | Yes | 7 (14) | 11.9 (6.6-17.1) | | 8.6 (3.1-14.1) | |
| | Unknown | 8 (16) | 24.0 (18.2-29.8) | | 11.6 (8.8-14.3) | |
| Hemithorax involvement | Right | 26 (52) | 19.5 (14.0-24.9) | 0.552 | 11.7 (7.8-15.5) | 0.967 |
| | Left | 24 (48) | 16.3 (12.0-20.7) | | 15.5 (7.6-15.4) | |
| Tumor stage | II | 6 (12) | 22.0 (14.4-29.7) | 0.035 | 14.7 (7.7-21.6) | 0.172 |
| | III | 29 (58) | 19.6 (15.1-24.1) | | 12.3 (8.6-16.0) | |
| | IV | 14 (28) | 9.2 (5.9-12.6) | | 7.5 (3.9-11.1) | |
| Performance status | 0 | 12 (24) | 20.5 (14.6-26.4) | 0.433 | 13.3. (6.4-20.2) | 0.387 |
| | 1 | 37 (74) | 17.1 (12.6-21.6) | | 10.8 (8.8-14.5) | |
| Comorbidity | Yes | 19 (38) | 17.5 (12.3-22.7) | 0.407 | 12.2 (7.2-17.2) | 0.034 |
| | No | 27 (54) | 18.9 (14.5-23.4) | | 12.8 (9.3-16.3) | |
| | Unknown | 4 (8) | 5.3 (1.9-8.6) | | 3.7 (0.1-7.3) | |
| Pathology | Epitheloid | 41 (82) | 16.3 (12.3-20.3) | 0.407 | 10.2 (7.5-12.9) | 0.096 |
| | Biphasic | 5(10) | 24.8 (14.3-35.3) | | 19.2 (10.2-28.2) | |
| | The others | 4 (8) | 21.4 (13.1-29.7) | | 11.6 (8.8-14.3) | |
| Response | Complete response | 8 (8) | 22.0 (13.4-30.6) | 0.009 | 22. 7( 15.6-29.7) | 0.001 |
| | Partial response | 10 (20) | 22.8 (15.8-29.9) | | 17.0 (10.6-23.4) | |
| | Stable disease | 17 (34) | 18.5 (14.8-22.2) | | 13.2 (9.4-16.9) | |
| | Progressive disease | 19 (38) | 8.4 (4.7-12.1) | | 4.3 (1.9-6.7) | |
| Radiotherapy | No | 33 (66) | 16.3 (11.8-20.8) | 0.174 | 11.1 (7.7-14.6) | 0.609 |
| | Yes | 17 (34) | 19.8 (14.8-24.8) | | 12.7 (8.3-17.0) | |
| NLR score | <5 (low) | 25 (50) | 19.4 (14.8-24.1) | 0.569 | 12. 1(9.1-15.1) | 0.467 |
| | ≥5 (high) | 25 (50) | 17.2 (11.3-23.1) | | 8.1 (3.6-12.5) | |
| PLR score | <190 (low) | 31 (62) | 18.2 (13.4-23) | 0.907 | 8.5 (5.5-11.5) | 0.042 |
| | ≥190 (high) | 19 (38) | 17.6 (11.8-23.4) | | 13.7 (9.6-17.7) | |
| Chemotherapy | Yes | 42 (84) | 18.0 (14.0-21.9) | 0.779 | 10.1 (6.4-13.9) | 0.360 |
| | No | 8 (16) | 12.8 (8.4-17.2) | | 12.4 (8.6-16.1) | |
| White blood cells, ($x10^3 \mu l^{-1}$) | <8 | 29 (58) | 20.2 (15.9-24.4) | 0.131 | 12.9 (9.5-16.3) | 0.287 |
| | ≥8 | 21 (42) | 13.6 (8.0-19.2) | | 9.7 (5.1-14.3) | |
| Platetelet ($x10^3 \mu l^{-1}$) | <300 | 36 (72) | 20.2 (15.9-24.5) | 0.065 | 12.4 (9.0-15.8) | 0.217 |
| | ≥300 | 14 (28) | 12.5 (7.0-17.9) | | 9.6 (4.9-14.3) | |

and monocyte count (p=0.035; p=0.009 and p=0.008, respectively). It was found that these factors remained to be significant in multivariate analysis (p<0.001 for stage; p=0.001 for response to treatment and p=0.001 for monocyte count). Mean overall survival was found to be 22 months for stage 2 (6 patients), 19.6 months for stage 3 (29 patients) and 9.2 months for stage 4 (14 patients). When mean overall survival was assessed according to response to treatment, it was found as 22 months for complete response (8 patients), 22.8 months for partial response (10 patients), 18.5 months for stable disease (17 patients) and 8.4 months for progressive disease (19 patients). Overall survival was found to be better in non-smokers, those without asbestosis exposure, those with good performance status, those without comorbid disease, those received radiotherapy and chemotherapy and those with low NLR and PLR scores; however, the difference didn't reach statistical significance.

Table 3 presents results of univariate and multivariate analysis of risk factors for disease-free survival. In univariate analysis, it was found that factors significantly affecting overall survival were comorbidity, response to treatment, NLR score and NLR (p=0.034; p=0.001 and p=0.008, respectively). It was found that these factors remained to be significant in multivariate analysis (p=0.018 for NLR; p=0.001 for response to treatment, p=0.003 for NLR score). It was found that mean disease-free survival was 12.2 months in patients with comorbid disease, whereas 12.8 months in those without. When mean disease-free survival was assessed according to response to treatment, it was found as 22.7 months for complete response, 17 months for partial response, 13.2 months for stable disease and 4.3 months for progressive disease. Mean disease-free survival was found as 13.7 months in patients with NLR score<3 whereas 8.5 months in those with NLR score≥3 (Figure 3).

Disease survival was found to be better in women younger than 65 years, non-smokers, those with early disease, those with good performance status, those with epithelioid type, those received radiotherapy and chemotherapy, those with WBC count<8,000, those with platelet count<300,000, and those with low NLR and PLR scores; however, the difference didn't reach statistical significance.

**Table3. Univariate Analysis of Risk Factors for the Overall and Disease-Free Survival**

| Risk factors | | Overall Survive Univariate Analysis | | Disease-free Survive Univariate Analyis | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p value | OR (95% CI) | p value |
| Age | <65 | Ref | | Ref | |
| | ≥65 | 0.91 (0.35-2.36) | 0.838 | 0.8(0.4-1.6) | 0.590 |
| Gender | Female | Ref | | Ref | |
| | Male | 3.3 (0.8-14.3) | 0.118 | 0.8 (0.3-1.8) | 0.663 |
| Smoking | Yes | Ref | | Ref | |
| | No | 0.8 (0.3-2.2) | 0.614 | 0.3 (0.1-0.9) | 0.028 |
| | Unknown | 0.9 (0.3-3.1) | | 0.8 (0.3-1.9) | 0.675 |
| Asbestos exposure | Yes | Ref | | Ref | |
| | No | 2.2 (0.5-8.7) | 0.229 | 2.1 (0.8-5.7) | 0.133 |
| | Unknown | 2.9 (5.2-16.3) | 0.218 | 2.6 (0.6-10.5) | 0.162 |
| Hemithorax involvement | Righ | Ref | | Ref | |
| | Left | 0.7 (0.3-1.8) | 0.554 | 1.0 (0.5-2.0) | 0.967 |
| Tumor stage | II | Ref | | Ref | |
| | III | 0.1(0.0-1.0) | 0.049 | 0.4 (0.1-1.2) | 0.104 |
| | IV | 0.3 (0.1-0.9) | 0.040 | 0.5 (0.2-1.1) | 0.121 |
| Performance status | 0 | Ref | | Ref | |
| | 1 | 0.6 (0.2-1.9) | 0.436 | 0.7 (0.3-1.6) | 0.390 |
| Comorbidity | Yes | Ref | | Ref | |
| | No | 0.4 (0.0-2.0) | 0.265 | 0.2 (0.0-0.8) | 0.028 |
| | Unknown | 0.4 (0.0-1.7) | 0.200 | 0.2 (0.8-0.8) | 0.019 |
| Pathology | Epitheloid | Ref | | Ref | |
| | Biphasic | 2.5 (0.3-19.5) | 0.364 | 2.6 (0.6-11.5) | 0.185 |
| | The others | 1.1 (0.1-13.4) | 0.891 | 0.7 (0.1-5.2) | 0.755 |
| Response | Complete response | Ref | | Ref | |
| | Partial response | 0.1 (0.0-0.7) | 0.022 | 0.0(0.0-0.3) | 0.004 |
| | Stable disease | 0.1 (0.0-0.7) | 0.019 | 0.1 (0.0-0.3 | 0.001 |
| | Progressive disease | 0.2 (0.7-0.7) | 0.013 | 0.2 (0.1-0.5) | 0.001 |
| Radiotherapy | No | Ref | | Ref | |
| | Yes | 2.1 (0.7-6.3) | 0.184 | 1.2 (0.6-2.5) | 0.609 |
| Chemotherapy | Yes | Ref | 0.780 | Ref | 0.470 |
| | No | 1.2 (0.2-5.4) | | 0.7 (0.2-1.8) | |
| White blood cells (x$10^3$ $\mu l^{-1}$) | | 1.1 (0.92-1.3) | 0.238 | 1.0 (0.9-1.2) | 0.215 |
| White blood cells (x$10^3$ $\mu l^{-1}$) | <8 | Ref | | Ref | |
| | ≥8 | 0.4 (02-1.2) | 0.119 | 0.8 (0.4-1.8) | 0.692 |
| Neutrophil (x$10^3\mu l^{-1}$) | | 1.1 (0.9-1.3) | 0.334 | 1.1 (0.9-1.3) | 0.080 |
| Monocyte ($\mu l^{-1}$) | | 6.5 (1.6-4.7) | 0.008 | 1.3 (0.3-4.7) | 0.655 |
| Lymphocyte (x$10^3$ $\mu l^{-1}$) | | 1.0 (0.9-1.2) | 0.345 | 0.8 (0.5-1.2) | 0.370 |
| Hemoglobin (g/dl) | | 1.0 (0.8-1.3) | 0.968 | 1.0 (0.9-1.3) | 0.309 |
| Hematocrit (%) | | 1.0 (0.9-1.0) | 0.994 | 1.0 (0.9-1.0) | 0.372 |
| Platetelet (x$10^3$ $\mu l^{-1}$) | | 1.0 (1.0-1.0) | 0.249 | 1.0 (1.0-1.0) | 0.264 |
| Platetelet (x$10^3$ $\mu l^{-1}$) | <300 | Ref | | Ref | |
| | ≥300 | 0.4 (0.1-1.1) | 0.108 | 0.6 (.03-1.2) | 0.148 |
| LDH (U/L) | | 1.0 (1.0-1.0) | 0.247 | 0.8 81.0-1.0) | 0.835 |
| NLR | | 1.0 (0.9-1.1) | 0.696 | 1.0 (1.0-1.1) | 0.005 |
| NLR score | <3 | Ref | | Ref | |
| | ≥3 | 0.7 (0.3-1.8) | 0.571 | 0.4 (0.2-1) | 0.047 |
| PLR | | 1.0 (1.0-1.0) | 0.602 | 1.0 (1.0-1.0) | 0.203 |
| PLR score | <190 | Ref | | Ref | |
| | ≥190 | 1.0 (0.4-2.6) | 0.907 | 0.7 (0.3-1.4) | 0.363 |

## Discussion

The relationship between cancer and inflammation has begun to be discussed in 19th century. Preliminary studies showed that inflammation could be an important marker for cancer development. It was reported that chronic inflammation is involved in gastric, hepatic, intestinal, pulmonary, pancreatic, esophageal cancers and in the cancers of bladder and biliary tract (Klinger and Welkmann 2002; Cedres et al., 2012; Li et al., 2014). Although etiology and underlying mechanisms are unknown, it is suggested that toxic granules in the cytoplasm of neutrophils accounts from inflammation in neoplastic tissues by activating monocytes (Prete et al., 2011). In subsequent studies, it was shown that subtypes of white blood cells can be important markers for cancer prediction. It was reported that subtypes of white blood cells were increased in bladder, endometrial, lung, prostate, colorectal, and ovary cancers (Cihan et al., 2013). Detection of inflammation in MPM as a primary component raised the question whether inflammation plays role in the pathogenesis of mesothelioma. There is limited number of studies investigating association between white blood cells and subtypes in MPM (Edwards et al., 2000). The aim of this study was to investigate prognostic value of pretreatment blood parameters in patients with MPM.

In our study, overall and disease-free survivals were found to be shorter in patients with WBC count >8,000, platelet count >300,000/$\mu$l or high PLR score, but the difference didn't reach statistical significance. It was found that disease-free survival was significantly worse in patients with high NLR score. Overall survival was found to be shorter in patients with high NLR score, but the difference didn't statistical significance. It is apparent

that cancer has an impact on peripheral leukocytes, erythrocytes, and platelets. Although neutrophilia and thrombocytosis are frequently observed, pathogenesis isn't fully elucidated. It has been proposed that tumor cells secrete myeloid growth factors, several cytokines and chemokines which induce proliferation of leukocytes and platelets. In addition, it is suggested that many factors released from cancer cells such as interleukin-6 and tumor necrosis factor are also involved. Among these mediators, most attracting one is CD40 which is a transmembrane glycoprotein belonging to receptors of tumor necrosis factor released from active platelets. CD40 serves as a strong mediator among several cell types including smooth muscle cells, macrophages, T cells and platelets. Platelets enhance maturation of dendritic cells and functions of B and T cells. The relationship between platelets and cancer isn't fully understood yet. Thrombocytosis occurs as a result of megakaryocyte stimulation by pro-inflammatory mediators such as IL-1, IL-2 and IL-6. The level of platelets is a parameter that indicates severity of inflammation (Klinger and Welkmann 2002; Alexandrakis et al., 2003; Prete et al., 2011; Li et al., 2014). It was reported that survival was shorter in cases with neutrophilia and thrombocytosis (Edwards et al., 2000; Alexandrakis et al., 2003; Kwon et al., 2012). There is no consensus on the idea that neutrophil is associated with poor prognosis. Increased neutrophil counts are found to be associated with good prognosis in patients with gastric and pancreatic cancer, while it was found to be associated with increased mortality in patients with bronchoalveolar cancer, renal cell cancer and malign melanoma (Suzuki et al., 2004; Schmidt et al., 2005; Yamanaka et al., 2007; Cedres et al., 2012). In a study on patients with MPM by EORCT, leukocytosis (leukocyte count>8400/mm3) was reported as poor prognostic index (Edwards et al., 2000). In a study by Cancer Leukemia Group B (CALGB), it was suggested that serum LDH>500 IU/L, poor performance status, chest pain, low hemoglobin values, non-epithelial histology, age>75 years and platelet count>400,000/$\mu$L were poor prognostic actors (Edwards et al., 2000; Stahel et al., 2010; Ibrahim et al., 2013; Utkan et al., 2013). Together, these findings clearly indicate that neutrophilia and thrombocytosis are prognostic factors. In our study, mortality was found to be higher in patients with neutrophilia and thrombocytosis in agreement with CALGB and EORTC studies.

As there is considerable number of evidence indicating role of neutrophil in cancer pathophysiology, comprehensive understanding regarding already known roles of neutrophil becomes increasingly attractive. It was found that PLR and NLR are closely related to mortality rate and response to treatment and it was reported that they could be predictive factors (Alexandrakis et al., 2003; Suzuki et al., 2004; Schmidt et al., 2005; Yamanaka et al., 2007; Cedres et al., 2012; Kwon et al., 2012; Wang et al., 2013). Currently, NLR is accepted as a parameter that indicates negatives effects of both increased neutrophil count representing acute inflammation and decreased lymphocyte count representing physiological stress at the same time. NLR and PLR are readily available biomarkers. On contrary to other inflammatory markers and biochemical analysis, NLR and PLR can be easily calculated from differential WBC count that is routinely performed at presentation. In many studies, it was reported that NLR and PLR were prognostic indices in demonstration of response to treatment and survival in patients with cancer. Patients with colorectal, ovary and lung cancer were preoperatively stratified according to NLR as those with NLR>5 and those with NLR<5. It was reported that cancer-related mortality was significantly higher in patients with NLR>5 (Sarraf et al., 2009; Chua et al., 2011). In a study on patients with colorectal cancer, Kishi et al. reported that mortality was higher in patients with high NLR who had liver metastasis and received neo-adjuvant chemotherapy. Authors suggested that NLR could be an important marker to monitor early response to chemotherapy and prognosis. It was reported that increase in PLR (>150) was an independent risk factor for increasing mortality in patients with colorectal or pancreas cancer (Kishi et al., 2009; Smith et al., 2009; Kwon et al., 2012).

In conclusion, in our study, overall and disease-free survival were poorer in patients with WBC count>8,000, platelet count>300,000 and high PLR score, but the difference didn't reach statistical significance. This could be attributed to small sample size. The most important limitations of this study are retrospective design and limited number of patient. To best of our knowledge, our study found shorter disease-free survival in patients with high NLR for the first time in literature. It was shown that NLR was increased in patients with disease progression and that it was associated with increased mortality. It could be suggested that NLR and PLR are inexpensive and readily available parameters in the assessment of inflammatory process when compared to other parameters in patients with MPM.

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