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Research Article

Does Platelet Count Affect Survival Outcomes in Patients with Malignant Pleural Mesothelioma?

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Abstract

Objectives: Malign mesothelioma arises from pleura, peritoneum, pericardium and tunica vaginalis of testis. It is a primary malignant tumor that originates from mesothelial cells. It is seen relatively low but has a high mortality rate.

Methods: In this study, we reviewed 41 (Malignant Pleural Mesothelioma) MPM patients who were admitted to Kocaeli University Department of Oncology between 2008 and 2014 retrospectively. Patient data were reviewed from medical records. We retrospectively analyzed the correlation between the clinical characteristics, complete blood count parameters and survival in patients with MPM.

Results: Overall survival (OS) of the entire population was 11.5 months (%95 CI; 5.86-17.19) In multivariate analysis we found a statistically significant correlation with platelet count and progression free survival (p=0.001). In our study overall survival was better in left pleura localized primary tumors, early staged tumors and patients with platelet count lower than 400.000 µl.

Conclusion: Early stage disease and low platelet count have a significant prognostic importance at the time of diagnosis.

Keywords: Mesothelioma, platelet, survival.

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Malignant mesothelioma arises from pleura, peritoneum, pericardium and tunica vaginalis of testis. It is a primary malignant tumor that originates from mesothelial cells. It is seen relatively low but has a high mortality rate. Most of cases arise from pleural surfaces (%90).[1] Two major risk factors for malign pleural mesothelioma (MPM) are asbestos and erionite.[1,2] Asbestos exposure can be found in %70-90 of all cases and varies in different series.[3,4] In industrial countries the risk increases with the heavy use of asbestos. In Turkey epidemiological data couldn't be counted except for some local datas. In Middle Anatolia asbestos exposure can be found in natural habitates.[5,6]

MPM is a locally growing and agressive tumor with low chemotherapy response rates and overall survival. Surgical procedures made progress in 1990's and response rates increased by the addition of radiotherapy to the treatment.[7] The most important factors that affect survival are T stage, lymph node status and histologic subtype. Median survival varies between 9 and 17 months and 5 year survival rate is less than %5.[8-10]

Leukocyte, lymphocyte and neutrophil counts and neutrophil-lymphocyte ratio (NLR) were examined to show systhemic inflamation. Cancer occurance and progression and these inflamatory markers have an established correlation.

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In the medical literature correlation between the inflamation and NLR was investigated in many cancer types.[11,12]

In our study, we retrospectively analysed the correlation between the clinical characteristics, complete blood count parameters and overall survival in patients with MPM.

Methods

In this study, we reviewed 41 MPM patients who were admitted to Kocaeli University Department of Oncology between 2008 and 2014 retrospectively. The study protocol was approved by the Kocaeli University School of Medicine Clinical Research Ethics Committee and written informed consent was obtained from all participants. Demographic characteristics such as age, sex, smoking, symptoms, leaving place, ECOG performance score, asbestos or erionit exposure, surgery, histopathologic subtypes, blood tests, adjuvant treatment, overall and disease free survival were reviewed.

Before treatment blood tests such as hemogram, hemotocrit, platelet, leukocyte, neutrophil, lymphocyte count and MPV and LDH were analysed. Median values of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (NLR) were calculated. NLR amount 5 and more is accepted as high less than 5 is accepted as low and 160 is the limit value for PLR.

Chemotherapy regimen was chosen by taking into consideration of ECOG score and other comorbitidies such as cardiac function and renal status. Chemotherapy was given to patients as neoadjuvant, adjuvant, second and third line and palliative purpose.

Treatment response and follow-up was assessed according to RECIST criteria. Briefly, complete response was defined as disappearance of disease and metastasis, while partial response was defined 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.[13]

Follow up visits were scheduled by 3 months intervals in the first 2 years, and 6 months intervals thereafter In every follow up visit physical examination, blood tests, thorax and abdominal CT scans as imaging modalities and PET-CT scan were done as necessary.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) for Windows version 22.0 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

There were 41 patients. Twenty-one (%51) of them were men and 20 (%49) were women. Median age at the time of diagnosis was 58 (27-86). Twelve (%29) patients had asbestos exposure. Erionit exposure was not known. Thirty-one (%75) patients had ECOG score 0-1 and 10 (%25) patients has ECOG score 2-4.

Twenty-four (%58) patients had a history of weight lost. Twenty-four (%58) patients were smokers. Twenty-nine (%70) patients had advanced stage disease at the time of diagnosis. Only 8 (%20) patients were sent to surgical procedures for diagnosis. Three (%7) patients underwent pleurectomy-decortication, 2 (%5) patients underwent extrapleural pneumonectomy.

Chemotherapy was planned for 37 (%90) patients, 4 patients couldn't receive chemotherapy because of poor performance score (ECOG score 4). Twenty-nine (%70) patients received cisplatin - pemetrexed, 4 (%10) patients received carboplatin - pemetrexed, 1 patient received pemetrexed alone and 3(%7) patients received other chemotherapy regimens as first line chemotherapy.

Three (%7) patients had complete response, 4 (%10) had partial response, 16 (%39) had stable disase and 8 (%20) had progression after first line chemotherapy. Two patients couldn't be assesed as well.

Only 17 (%41) patients could receive second line chemotherapy. Cisplatin, pemetrexed and gemcitabine agents were given in combination or solely as second line therapy. In the third line therapy, 2 patients received gemcitabine. 1 patient received pemetrexed-carboplatin and 2 patients received raltitrexed.

Eight (%20) patients underwent radiotherapy for palliation and 1 patient underwent radiotherapy for metastasis bone lesion.

Seven (%17) patients received trimodality treatment. (radiotherapy, chemotherapy and surgery)

This patient charecteristic were shown in Table 1 and 2.

Overall survival (OS) of the entire population was 11.53 months (%95 CI; 5.86-17.19). Progression free survival (PFS) was 8.67 months (%95 CI:5.81-11.53) (Figs. 1-2).

Table 1. Clinical characteristics of the patients

Characteristics	Patients (n=41) (%)
Gender	
Men	21 (51.2)
Women	20 (48.8)
Age (median)	
Men	60.1 (33-89)
Women	60.6 (42-87)
ECOG PS	
0-1	31 (75.6)
2-4	10 (24.4)
Weight loss	
< %10 in last 6 months	17 (41.4)
> %10 in last 6 months	24 (58.6)
Asbest exposure	
Yes	12 (29.3)
No	29 (70.7)
Smoking	
Previous/current	24 / (58.6)
No	17 / (41.4)
Hemitorax involvement	
Right hemithorax	20 (48.8)
Left hemithorax	21 (51.2)
Tumor stage	
I	1 (2.4)
II	7 (17.1)
III	10 (24.4)
IV	23 (56.1)
Pathology	
Epitheloid	28 (68.3)
Sarcomatoid	7 (17.1)
Mixt	6 (14.6)
Trimodal treatment	7 (17)
Surgery	
EPP	2 (4.9)
Pleurectomy/decortications	3 (7.3)
Biopsy	8 (19.5)
Radiotherapy	
Palyatif	8 (19.5)
Adjuvant	2 (4.9)
Metastasis bone	1 (2.4)
Chemotherapy	
Yes	37 (90.2)
No	4 (9.8)
First-line Chemotherapy	
Pemetrexet+cisplatin	29 (70.7)
Pemetrexet+carboplatin	4 (9.8)
The other	4 (9,8)
Second-line chemotherapy	
Pemetrexet+cisplatin	10 (24.4)
The other	7 (16.8)
Third-line chemotherapy	
Pemetrexet+carboplatin	1 (2.4)
Gemsitabin	2 (4.9)
Raltitrexet	2 (4.9)

Table 2. Hemogram parameters of the patients

Laboratory	Mean (±SD)
White blood cells, (x10^3 μl^{-1})	8.4±3.6
Neutrophil (x$10^3 \mu l^{-1}$)	5.4±3.1
Monocyte (x10^3 μl^{-1})	0.79±0.5
Lymphocyte (x10^3 μl^{-1})	1.8±0.9
Hemoglobin (g/dl)	11.2±1.8
Platelet x10^3 μl^{-1})	407±177.8
MPV	7.9±1.2
LDH(u/l)	211±119.8
NLR	3.3±4.5
PLR	225±219
NLR score	5
PLR score	160

In univarite analysis, ECOG performance score, surgery, stage, platelet count and PFS was found statistically significant (p<0.05). Age, gender, smoke, asbestos exposure, NLR, PLR, LDH, monocyte count, leukocyte count, MPV, weight loss, primary localization of the disease, hemoglobin level and histological types and PFS was found statistically insignificant(p>0.05). Stage, ECOG performance score, surgery, platelet count and primary localization of the disease and OS was found statistically significant (p<0.05). Age, gender, smoking history, asbestos exposure, NLR, PLR, LDH, monocyte count, leukocyte count, MPV, weight loss, hemoglobin level and histological types and OS was found statistically insignificant (p>0.05) (Table 3).

In multivariate analysis platelet count was an independent prognostic factor for PFS. Also stage, platelet count and primary localization of the disease were independent prognostic factors for OS (p<0.05). Patients with platelet count > 400.000 µl had worse PFS and OS (Table 4, Fig. 3).

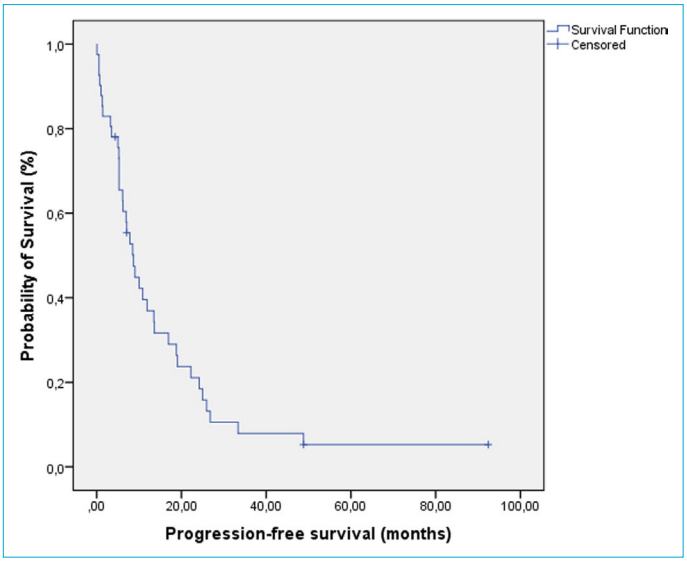

Figure 1. Progression free survival of the patients (PFS:8.67 months).

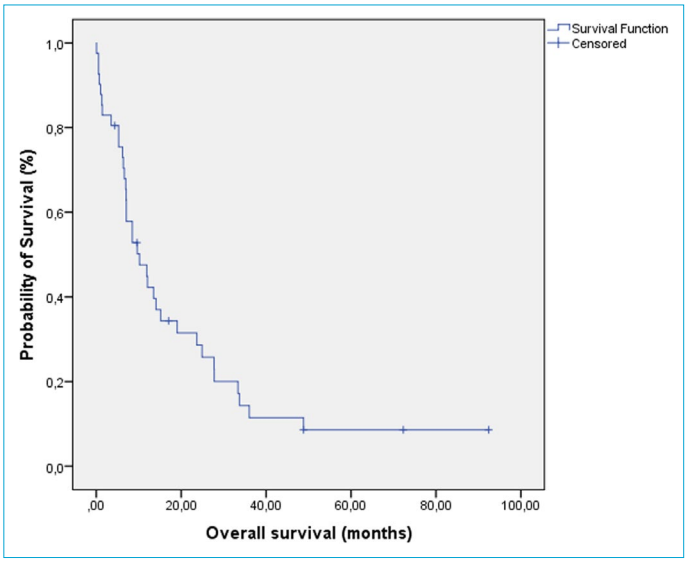

Figure 2. Overall survival of the patients (OS: 11.53 months).

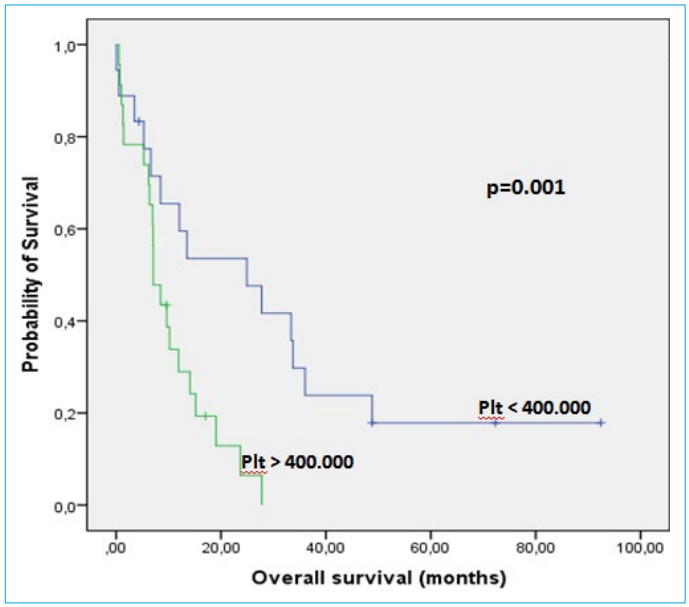

Figure 3. Relationship between platelet count and overall survival of the patients.

Discussion

In MPM mean age is nearly 60 years (45-83) according to Chapman et al. MPM has a higher rate of men and usually occurs in the fifth or sixth decades.[14] In our study median age was 58±11.8 and majority of patients were male (%51).

In large series overall survival ise between 6-17 months and median survival is nearly 12 months or less.[15] In our study we found the overall survival 11,53 months in consistent with the literature.

In some studies inflamation markers were found as an independent prognostic factor and emphasised the importance of chronic inflammation especially in gastric, pancreas, breast, lung and kidney cancers.[11-17] Tumor aggressiveness and ability to metastasis depends on the tumors own cell character and environmental factors. Tumor cells mediates a inflammatory reaction by the migration of inflamatory cells.[18] Prognostic and predictive effects of leukocyte subtypes are shown in the early studies.[19] There are not much studies about the relationship between MPM and platelet, leukocyte counts and its subtypes.[20-22] In this study, we evaluated the clinicopathologic characteristics of complete bood count parameters.

One of the prognostic factors is performance score at the time of diagnosis. Patients whom performance score were 0-1 had a better overall survival as expected.[23] In univariate analysis relation between our patients' ECOG performace score and overall survival was statistically significant (p=0.025).

Surgery can be curative in MPM in addition to diagnostic and palliative significance. Even though it has a important morbidity, surgery can be used for the analgesia and for the relief of dyspnea. It is known as a fact that surgical resection is a major part of aggressive multimodal therapy. In other studies, few patients underwent surgery because of older age and other comorbidities.[24,25] In our study, we found no benefit with the use of surgery on progression free survival and overall survival (p>0.05).

Platelet and neutrophil counts are found high in malignancies. Although the pathogenesis is unknown, inflammation is found to be associated with the tumor progression. Myeloid growth factors and various cytokines are released from tumor cells and mediate leukocyte and platelet pro-

Table 4. The multivariate analysis between patient clinopathological characteristics and OS and PFS.

	Progression-free survival			Overall survival		
Variables	**Hazard ratio**	**95% CI**	**p**	**Hazard ratio**	**95% CI**	**p**
Tumor site*	0.89	0.381-0.842	0.063	0.74	0.280-0.830	0.028
Platelet count	0.72	0.271-0.825	0.028	0.72	0.296-0.826	0.026
Stage	0.86	0.495-0.840	0.054	0.80	0.373-0.854	0.034

* primary localization of the disease.

Table 3. The univariate analysis between clinopathological characteristics of the patient group and OS and PFS

Variables	overall survival Median(months)	p	disase free survival median(months)	p
Gender		0.84		0.60
Men	19.05		8.67	
Women	11.53		8.41	
Histopathology		0.31		0.22
Epitheloid	14,65		8.64	
nonepitheloid	10,84		7.85	
Smoking		0.35		0.39
yes	9.92		6.20	
no	19.05		13.50	
Performance score		0.014		0.025
0-1	15.17		10.02	
2-4	3.35		1.41	
Age		0.077		0,53
< 60	15.17		8.67	
> 60	8.83		6.20	
Hemithorax involvement		0.013		0,095
Right hemitorax	6.30		5.29	
Left hemitorax	24.08		10.02	
Surgery		0.039		0.005
Yes	24.08		18.82	
No	8.83		7.09	
Stage		0.001		0.007
I-II	33.84		22.20	
III-IV	7.22		6.96	
Weight loss		0.51		0.87
Last 6 months < %10	8.83		7.09	
Last 6 months > %10	15.17		9.03	
Platetelet ($x10^3$ μl^{-1})		0.001		0.001
Plt 407>	27.95		22.20	
Plt 407<	8.83		6.96	
White blood cells, ($x10^3$ μl^{-})		0.14		0.09
8.4>	15.17		10.02	
8.4<	10.84		6.96	
NLR score(3)		0.56		0.57
3>	12.38		10.87	
3<	10.9		6.96	
LDH(U/L)		0.71		0.46
211>	11.53		10.02	
211<	19.12		6.14	
Hemoglobin		0.62		0.32
11>	7.09		6.20	
11<	24.08		11.89	
PLR score(160)		0.79		0.21
160>	11.53		10.02	
160<	7.22		6.96	

liferation. Proinflamatory parameters such a IL-1, IL-2 and IL-6 mediate megakaryocyte stimulation and causes trombocytosis.[11,22] In our study, also we found a statistically significant relation with platelet and progression free survival and overall survival ($p<0.05$).

The relationship between cancer pathophysiology and leukocyte subtypes especially neutrophils was demonstrated in early studies. It was demonstrated that NLR and PLR have a close relation with mortality and the therapy

response. These parameters were accepted as predictive factors.[26-28] NLR and PLR are easily measured parameters. It was published that mortality was higher in preoperative NLR<5 group than NLR>5 group.[29,30] A prognostic role for NLR in MPM was reported in a number of retrospective series. The first report was a cohort of patients receiving systemic therapy, and further reports by the same group included surgically treated patients and patients receiving compensation for asbestos-related disease.

Therefore, NLR was proposed as a potential biomarker for stratification in clinical trials and for use in clinical practice. [31-33] In our study no significant relationship was found between NLR, PLR and PFS and OS (p>0.05).

Early tumor stage in MPM is also one of the major factors affecting survival. M. Metintas et al. demonstrated that patients with advanced stage disease, older than 75 years of age and with poor performance score had worse prognosis.[34] In our study median survival was 33.8 months at early stages (stage1-2) and 7.2 months in advanced staged patients. In multivariete analyses we found statistically significant relationship with overall survival and stage (p<0.05) in consistent with other early studies.

Our study has several limitations. The main weaknesses are the retrospective nature of the study and the limitations of collecting data and the low volume.

In conclusion, MPM has poor prognosis and expected overall survival is approximately 1 year. Multiple parameters were studied as predictive markers. We demonstrated that early stage and overall survival has a significant correlation. We found platelet count as an independent prognostic factor for progression free survival and overall survival. In our study patient with high platelet count had a worse prognosis. There was no correlation between leukocyte count, NLR score and PLR score. We need longer, prospective and randomized studies to understand the nature of the disease and to evaluate the diagnosis, treatment and prognosis of MPM.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Kocaeli University School of Medicine Clinical Research Ethics Committee and written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – K.U.; Design – O.A.; Supervision – A.S.; Materials – O.A., A.S.; Data collection &/or processing – O.A., A.S.; Analysis and/or interpretation – O.A.; Literature search – O.A., A.S.; Writing – O.A.; Critical review – K.U.

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