

Evaluation of the Prognostic Value of the Pre-chemotherapy Platelet to Lymphocyte Ratio in Malignant Pleural Mesothelioma

Mira Canaan^{1,2}, Eman El-Sheikh¹, Ramy R. Ghali¹, Nada E. Eldin², Gehan Hamdy² and Wesam El-Ghamry¹

¹Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

²National Research Center, Cairo, Egypt

Abstract

Background: Malignant pleural mesothelioma is an aggressive disease. It is characterized with bad prognosis. We conducted this study to assess the prognostic significance of pretreatment PLR in patients with MPM.

Methods: We retrospectively reviewed 400 patients treated for MPM in Ain Shams University hospital, Clinical Oncology department between January 2013 and December 2017. Pre-treatment CBC was available for the 110 patients to calculate PLR.

Results: Out of 110 patients, age ranged from 28 to 70 years. Male: female was 5: 6. Epithelioid subtype represent 85%. Stages III, IV represent 48.2% and 35.5%. Median PFS and OS were 6.9 and 11.9 months. Using a cut-off value of 177.9. Low PLR was associated with better median PFS than high PLR (7.97 vs. 6.63), ($p=0.039$). For patients with low vs. high PLR, median OS was 15.07 vs. 10.4 months (P value= 0.063) 61.8% received platinum pemetrexed and 38.2% received platinum/gemcitabine as 1st line chemotherapy. Radiological response to first line therapy was SD, PR, PD and CR in 47%, 29%, 23% and 0.9% of patients respectively. There was no statistical significance in PFS and OS between patients who received platinum/pemetrexed versus platinum/Gemcitabine ($p=0.53$). The group who received platinum/pemetrexed had median OS 17.5 vs. 10.5 months ($P=0.108$) in low versus high PLR and median PFS 7.7 months vs. 5.03 months ($P=0.034$). The group who received platinum-gemcitabine had median OS 15.07 vs. 8.2 months ($P=0.264$) in low versus high PLR and median PFS 8.07 vs. 8.2 months ($P=0.332$).

Conclusion: The higher the PLR, the worse the prognosis. There was statistically significant difference in PFS between low vs. high PLR, and in PFS of both groups of PLR of the group who received platinum pemetrexed.

Keywords: Platelet to lymphocyte ratio • Malignant pleural mesothelioma • Prognostic factor

Introduction

Malignant pleura mesothelioma (MPM) is a rare aggressive cancer arising from serous surfaces due to asbestos inhalation. Pleura is the most common site (65%-70%), followed by peritoneum (30%), tunica vaginalis and pericardium (1%-2%) [1].

MPM is more common in men than in women (5:1) due to occupational exposure. The median age ranges vary from 45 to 85 years [2]. Mesothelioma global incidence as compared with other cancers is less than 1% [3].

The World Health Organization (WHO) recently estimated that ~107,000 people in the world die each year from asbestos-related diseases [4]. MPM is classified into 3 major sub-types based on histological basis: Epithelioid, sarcomatoid and mixed or biphasic. The epithelioid tumors are most common type representing 50% to 70% of all MPM diagnosed. It is less aggressive and responds to the treatment better [5].

Diagnostic procedures can be either non-invasive such as Chest X-ray, CT, FDG-PET or invasive such as image-guided (CT or US) pleural biopsy or laparoscopy. Video-assisted thoracoscopy is the best biopsy and cytology technique (accuracy of 98%), a reliable diagnostic tool for experienced cytopathologists, can offer additional tissue confirmation [6].

***Address for Correspondence:** Ramy R. Ghali, Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, Tel: +20-1227327330; E-mail: ramyghali@hotmail.com

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Received 01 October 2020; **Accepted** 21 October 2020; **Published** 29 October 2020

Immunohistochemistry helps in the diagnosis of MPM. Calretinin is the most commonly used antibody with a reported sensitivity of 71% and specificity of 95% [7]. Pleurectomy is considered as the best choice for the treatment of early stage disease. Two surgical techniques are available, Extended Pleurectomy/Decortication (EPD) and extrapleural pneumonectomy which is less tolerated [8]. Patients with malignant pleural mesothelioma have a poor prognosis, with estimated median survival times varying from 4 to 12 months [9].

Prognostic factors for survival of MPM according to European Organization for Research and Treatment of Cancer (EORTC) scoring system included performance status, white blood cell (WBC) count, gender, histologic subtype [10].

Prognostic assessment methods that are easy to use, inexpensive, and effective are needed for those patients [11]. Studies have identified the neutrophil to-lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) as measures of systemic inflammation; they provide reproducible, early detected markers that may be of valuable prognostic factors in patients with MPM [12]. However, it is important to note that NLR can increase in many other non-malignant conditions [13].

PLR cut off value differs according to the affected organ. While PLR was found to be a prognostic factor for increased mortality in colorectal above 150 and above 160 in gastric cancer [14], the cutoff value for PLR in MPM was found to be 158 [15].

Pretreatment PLR was an independent risk factor for response to first-line chemotherapy in patients with NSCLC. An elevated PLR predicted a poor response to first-line chemotherapy and a poor prognosis [16]. Overall and disease-free survival were poorer in patients with high PLR score [17]. However, the prognostic value of PLR in MPM remains uncertain. Therefore, in this study, we aimed at investigating the prognostic significance of PLR in MPM patients.

Research Methodology

Study design and data selection

This study was collaboration between Oncology and Nuclear medicine department Ain Shams University and Internal medicine department in National Research Center in Egypt. At the department of clinical oncology, Ain Shams University, 400 patients with malignant pleural mesothelioma with all stages were identified in the period between January 2013 and December 2017.

The study included 110 patients with available prechemotherapy CBC, histologically confirmed malignant pleural mesothelioma, aged 18 years or above. We excluded patients with synchronous malignancies or pre-treatment infection or hematologic diseases that may affect blood cell counts. Clinicopathological data included: age, gender, ECOG, smoking, asbestos exposure (residence), presenting complaint, Type of biopsy, histopathological type of MPM.

Treatment

Surgery: All patients underwent thoraco abdominal CT scan before surgery. American Joint Commission on Cancer (AJCC) 7th edition 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 pemetrexed, pemetrexed 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 pemetrexed, pemetrexed or gemcitabine.

Blood samples: Pretreatment Platelet, white blood cell, neutrophil, lymphocyte was included to the analysis. PLR values were calculated from platelet and lymphocytes counts as ratio of platelets counts to lymphocyte count.

Follow-up: Treatment response was assessed according to modified RECIST (Response Evaluation Criteria In Solid Tumors) criteria [18].

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 imaging modalities including CT chest. Duration of follow-up was defined as time from date of CBC to last control visit in survivors and date of CBC to time of death in non-survivors. Survival parameters were calculated and defined as follow:

- i. **Progression free survival (PFS):** Time from date of CBC till progression or death from any cause.
- ii. **Overall survival (OS):** Time from date of CBC till death from any cause.
- iii. Baseline CBC with differential is done one month before chemotherapy, at clinical pathology department, Ain Shams University, using Colter LH to all the patients included.
- iv. The Colter LH is a stable machine. The staff does the Quality control daily to check its accuracy and precision. It is calibrated initially before to start using it in daily practice, when any modifications are done in the machine system, and regularly every six months.

Aim of study

- To evaluate the relation between the platelet to lymphocyte ratio and progression free survival (PFS) and overall survival (OS) of the study population.
- To compare between the PFS and OS in both groups of treatment: pemetrexed/cisplatin vs. Gemcitabine/ Cisplatin, and the predictive value of PLR for both groups.

Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS V20 for windows). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

- Mean, Standard deviation (\pm SD), Minimum and maximum values (range) for numerical data, Frequency and percentage of non-numerical data.
- Chi-Square test was used to assess the relationship between (PFS and OS).
- And subgroups of PLR, according to the median of PLR which was 177.9 in this study
- High PLR was defined as ≥ 177.9 , Low PLR was defined as < 177.9
- P-value: Statistical significance was defined as $p < 0.05$.

Kaplan-Meier method was used to construct the Progression free survival and overall survival curves and their relationship with the platelet to lymphocyte ratio and compared via log-rank tests.

We also used the Kaplan Meier curves to compare between the PFS and OS in both groups of treatment: pemetrexed/cisplatin vs. Gemcitabine/ Cisplatin, and the predictive value of PLR for both groups.

Results

In the period between Jan 2013-Dec 2017, a total of 400 confirmed MPM cases presented to the thoracic malignancies unit at Ain shams university hospitals. Demographic data were found as follow in Table 1.

Table 1. Demographic data.

Demographic data	no.	%
Age (years) Mean=53.9, Median=54		
<54 years	53	48.2
≥ 54 years	57	51.8
Sex		
Male	50	45.5
Female	60	54.5
Performance status		
0	3	2.7
1	95	86.4
2	12	10.9
3	0	0
4	0	0
Residence		
Cairo	33	30
Kalyubia	68	61.8
Other	9	8.2
Smoking		
Smoker	46	41.8
Passive	5	4.5
Never smoking	59	53.6
Medical history		
No comorbidities	69	62.7
Diabetic patients	17	15.5
Hypertensive patients	14	12.7
HCV patients	8	7.3
SNL patients	5	4.5
Asthma	5	4.5
Cardiac patients	3	2.7
Renal disease patients	2	1.8

The most common symptom was dyspnea 67.3%, chest pain 23.6%, cough 22.7% and clinically relevant weight loss 6.4% (defined by unintentional unexplained loss of 5% for the last month or 10% for the last 6 months). The median duration of presenting symptoms was 2 months.

TNM staging system according to the American Joint Cancer Committee (AJCC) 7th edition was analysed using clinical and radiological data of the study population: T1, T2, T3, T4 4.5%, 43.6%, 32.7%, 19.1%. Lymph nodes metastasis N0, N1, N2, N3: 30.9%, 11.8%, 54.5%, 2.7%. M0:M1 is 80.9:19.1. Clinical stage I, II, III, IV 3.6%, 12.7%, 48.2%, 35.5%. 62 of the patients were right sided and 48 were left sided mesothelioma.

55.5% underwent thorascopic biopsy, 30% ultra sound guided, 10% CT guided and 4.5% by open biopsy. 94 were epithelioid type, 10 biphasic type and 6 sarcomatoid type. 20.1% underwent pleurodesis.

16 patients (14.5%) underwent surgery: 15 P/D once. One of the patients underwent P/D twice. No patients underwent EPP. 89 patients were not candidates for surgery, and 5 patients refused surgery.

Among the 110 patients with available pretreatment CBC platelet lymphocyte ratio (PLR) range was (31.1-1512.5) with median PLR of 177.9 and mean PLR was 234.4 with SD=198.26.

Median PFS 6.9 months with SE=0.78 with 95% CI (5.4-8.4) months.

Median OS 11.9 months and SE=1.06 with 95% CI (9.8-13.9) months.

All 110 patients received upfront platinum based chemotherapy. 61.8% (n=68) received platinum /pemetrexed and 38.2% (n=42) received platinum / gemcitabine.

32 patients demonstrated progression on 1st line, and received second line chemotherapy. 11 patients received third line chemotherapy.

All 110 patients received 1st line chemotherapy: 61.8% received platinum pemetrexed and 38.2% received platinum/gemcitabine. Radiological response to first line therapy was SD>PR>PD>PR, 47%, 29%, 23% and 0.9%.

The 42 patients who received platinum-Gemcitabine had median OS estimate 11.13 months and SE=1.6 months with 95% CI (7.9-14.3) while the 68 patients who received platinum-pemetrexed the median OS estimate was 12.7 with 95% and SE=1.8, with CI (9.06-16.39). The difference between OS in both groups of first line chemotherapy was found to be insignificant (p=0.532) (Figure 1).

Patients who received platinum-Gemcitabine had median PFS estimate 8.07 and SE=0.8 months with 95% CI (6.4-9.6) while patients who received platinum-pemetrexed the median PFS estimate was 6.5 and SE=1.2 months with 95% CI (4.1-8.8)

The difference between PFS in both groups of first line chemotherapy was found to be insignificant (p = 0.381) (Figure 2). Correlation between PLR and patients characteristics: age, gender and ECOG were statistically insignificant. The correlation between PLR and Stage of tumor was statistically insignificant p=0.2.

The correlation between PLR and histological sub type:

- a. The mean PLR of patients with proven epithelioid MPM, biphasic, sarcomatoid was 223.5 ± 189.4, 316.5 ± 182.2 and 153.6 ± 86.1, respectively. It was statistically insignificant p=0.19
- b. Analysis of response to first line therapy is statistically insignificant between elevated PLR and worsening of outcome, in other words PLR failed to be of predictive of response, p=0.335 as shown in Table 2.

Analysis of response to first line therapy has shown no significant association between PLR and objective response rate (ORR) (which is defined as patients who achieved complete response and partial response) with P=0.47. Thirty three patients achieved ORR the mean of their PLR was 255.38 ± 267.07. Seventy seven patients who did not achieve ORR the mean of their PLR was 225.44 ± 161.46

The Median PFS of the whole population 6.93 months and SE=0.7 months with 95% confidence interval (5.4-8.46). For group of patients with PLR below 177.9 median PFS was 7.97 months (SE=1.1 with 95% CI 5.63-10.3) while for

patients with PLR above 177.9 median PFS was only 6.63 and SE=0.8 with 95% CI (4.9-8.2).

When PLR<177.9, it showed higher PFS than the group with PLR>177.9, and it was statistically significant. p=0.039 for correlation between PFS and PLR as shown in Figure 3. Median OS was 11.9 months (SE=1.06 months, 95% CI (9.8-13.9)). For patients with PLR<177.9 OS was 15.07 and SE=2.9 months with 95% CI (9.38-20.75) while for patients with PLR>177.9 estimated median OS was only 10.4 (SE=1.6, 95% CI (7.22-13.57)). The test of significance did not reach statistical significant p value=0.063 for shortening of OS with elevated PLR. In total, the survival increased with PLR<177.9, it was statistically significant with PFS but not with OS.

The group of patients who received platinum-pemetrexed in the first line chemotherapy with PLR <177.9 vs. >177.9 had median OS estimate 17.5 vs. 10.5 months but OS within platinum-pemetrexed group was found to be insignificant p=0.108

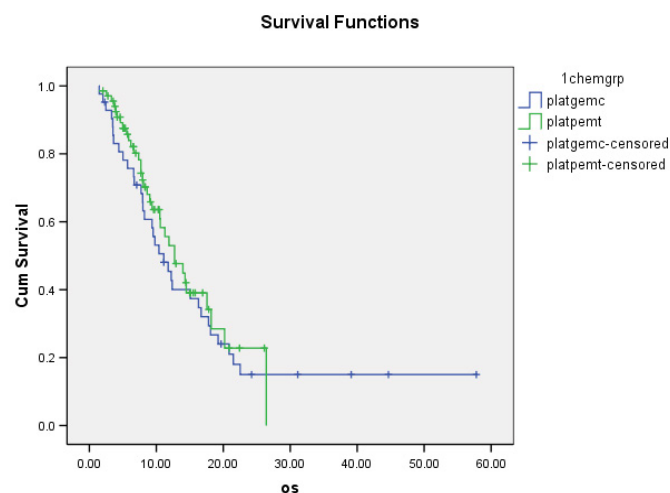


Figure 1. Illustrating overall survival in both groups of first line chemotherapy.

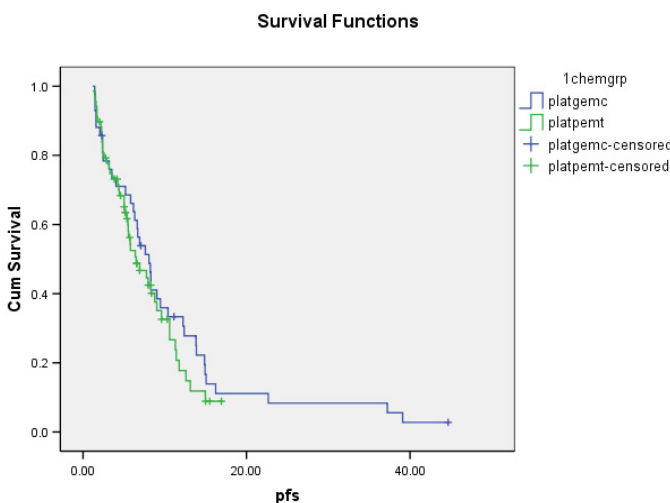


Figure 2. Graph illustrating progression free survival in both groups of first line chemotherapy.

Table 2. Different patterns of response among different PLR groups.

Variables	PLR group			Total	
	<177.9	>177			
1st chemo response	CR	0.9%	1	0	1
	PD	22.7%	9	16	25
	PR	29.09%	17	15	32
	SD	47.27%	28	24	52
Total		55	55	110	
%	100%	50%	50%	100%	

The group of patients who received platinum- gemcitabine in the first line chemotherapy with PLR <177.9 vs. >177.9 had median OS estimate 15.07 vs. 8.2 months. The OS within platinum- gemcitabine group was found to be insignificant p=0.264

The group of patients who received platinum-pemetrexed in the first line chemotherapy with PLR <177.9 vs. >177.9 had median PFS estimate 7.7 vs. 5.03 The PFS within platinum-pemetrexed group was found to be significant p=0.034 which means that the lower PLR<177.9 the better the prognoses, PLR is a good prognostic factor to detect PFS in platinum-pemetrexed group as illustrated in Figure 4.

The group of patients who received platinum- gemcitabine in the first line chemotherapy with PLR <177.9 vs. >177.9 had median PFS estimate 8.07 vs. 8.2. The OS within platinum gemcitabine group was found to be insignificant p=0.332

Discussion

In this study the median age was 54 an The male: female ratio was 5:6 in our study. In contrast to our study, a Surveillance, Epidemiology, and End Results (SEER) study of 14,228 patients. The SEER database was explored from 1973 to 2009 to identify all cases of pathologically-proven MPM. They had

a median age at diagnosis was 62 years which was an independent predictor factor in multivariate analysis [19]. This may be explained by the fact that asbestos was not banned in Egypt till 2004, combined with a latent period between exposure to asbestos and development of mesothelioma averaging 30-40 years [20].

In countries where people are exposed to asbestos through industrial practices, rates of MPM are generally higher in men than in women. However, in southeast Turkey, similar to Egypt, asbestos exposure is mostly environmental and begins at birth; it affects both sexes almost equally, because it is processed with water and people are exposed via inhalation, in home environments [21].

The Median PFS of our study population was estimated to be 6.9 months and overall was estimated to be 11.9 months. This is similar to the phase II study of the South West Oncology Group (SWOG 9810) which included 50 patients of advanced MPM. The median survival was 10 months and PFS was 6 months [22].

In our study, among the 110 patients with available pretreatment CBC platelet to lymphocyte ratio (PLR) range was (31.1-1512.5) with median PLR of 177.9 and mean PLR was 234.4 ± 198.26. This was comparable to the retrospective study performed by Cihan et al. [23], done to assess the prognostic value of PLR in patients with MPM. They reviewed the data of 50 patients with MPM who were managed at Kayseri Teaching Hospital between 2005 and 2010: platelet <3,00,000, and low PLR (<190) which was the median were identified to be good prognostic factors. Overall survival was found to be better those with low PLR scores; however, the difference didn't reach statistical significance, may be due small sample size.

It was also comparable to a retrospective study in Turkey done on 36 patients to assess the reliability of PLR as a parameter with prognostic value in MPM patients. PLR was found to be significant. The cutoff value for PLR is 158. But NLR was insignificant. Assessment of mortality according to PLR, the median of PLR of patients alive (75%) was 218 ± 13.45 (190.49). Patients dead were 25%, the median of their PR was 247 ± 140.62 (219.73) p=0.622 [11].

Another retrospective study done with 171 patients with a histologically proven diagnosis of MPM presenting to the Imperial College NHS Healthcare Trust between 1993 and 2011. A PLR greater than 300 was seen in 60 patients (35%). Univariate analysis variables that predict for poor OS PLR ≥300 (p =0.03) and reached statistical significance for shortening of OS with high PLR [24].

Similarly, a cohort study done to investigate the prognostic value of Platelet-to-Lymphocyte Ratio (PLR) in patients with Malignant Pleural Mesothelioma (MPM) undergoing Extrapleural Pneumonectomy (EPP). 85 patients who underwent EPP over 10 years at Toronto General Hospital, 65 patients whose blood test results before initial therapy were available were retrospectively analyzed as a training cohort to identify and develop a prognostic score. In univariate analyses, PLR <215 (p=0.030) was a predictor of favorable survival. Multivariate analysis confirmed that PLR (P=0.049) as independent predictor of OS. Median OS in the cohort stratified by PLR was 37.0 and 20.0 months for PLR <215 and ≥215 respectively (p=0.014) [25]

Radiological response to 1st line chemotherapy was: CR (0.9%), PR (29.1%), SD (47.3%), PD (22.7%). A prospective study done on 33 eligible patients with pathologically proven advanced MPM between August 2008 and July 2011, for assessment of the combination of Gemcitabine / Cisplatin in MPM patients at Ain Shams Hospitals, Department of Oncology and nuclear medicine. Regarding response rate according to modified RECIST criteria of response, the responders constituted 57.5% (n=19) representing one complete response (3%) and 18 partial responses (54.5%) while non responders constituted 42.5% (n = 14) including 12 stable diseases (36.4%) and 2 progressive diseases (6.1%) [26].

A cohort study performed on 68 epithelioid MPM patients from Ain Shams University Hospitals, department of Clinical oncology and nuclear medicine and El-Nasr hospital for health insurance in Helwan to find new predictors to platinum-based regimens response in MPM patients No difference was observed between patients treated with platinum in combination with gemcitabine or patients treated with platinum in combination with pemetrexed in terms of PFS (p=0.81) or OS (p=0.47) [27].

Survival Functions

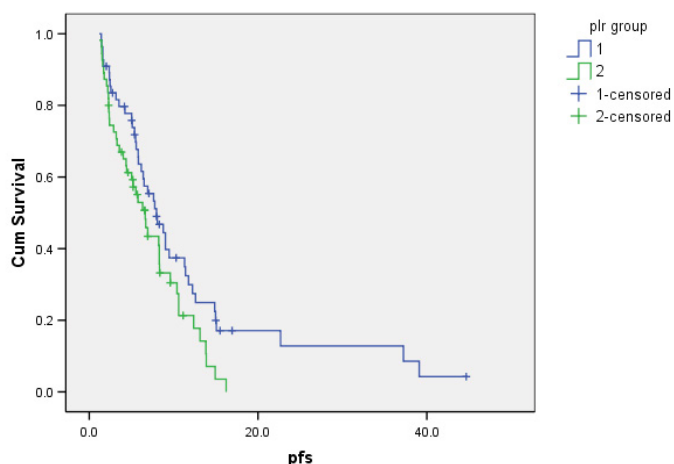


Figure 3. Kaplan-Meier curve illustrating the relationships between PFS and different PLR, Groups: Group 1=PLR<177.9, Group 2=PLR>177.

Survival Functions

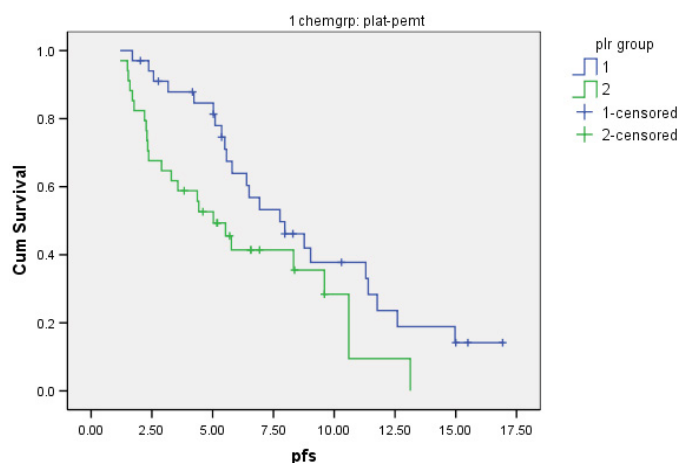


Figure 4. Graph illustrating PFS within the platinum-pemetrexed. Group 1 PLR<177.7, Group 2 PLR>177.7.

These results were similar to our results. This means there was no statistical significance in PFS or OS in patients who received platinum gemcitabine or platinum pemetrexed as first line chemotherapy, which has a socioeconomic value in Egypt, as pemetrexed is more expensive, and gemcitabine is more available.

Currently, the best known clinical prognostic scoring systems for MPM patients are from European Organization for Research and Treatment of Cancer (EORTC) and Cancer and Leukemia Group B (CALGB) [28]. However, these scoring systems are not routinely used in MPM prognosis because they are time consuming to perform [29].

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 [30].

Platelets are part of the inflammatory response and thrombocytosis is common in patients with solid tumors. The level of platelets is a parameter that indicates severity of inflammation [31].

Platelets are known to have protumor effect. They interact with tumor cells directly and contain factors that contribute to tumor growth, invasion and angiogenesis. Platelets can contribute in tumor metastasis by two mechanisms: they protect tumor cells from NK-cell mediated lysis and also the megakaryocytes release vascular endothelial growth factor for angiogenesis [26].

Increased platelet aggregation was included as a negative prognosticator in the CALGB and EORTC scoring systems, with cut-off values of $400 \times 10^9/L$ and $350 \times 10^9/L$, respectively [27].

In contrast to platelets, lymphocytes have been associated with antitumor effects, based on the concept of 'cancer immune-surveillance'. T-cells secrete cytokines and induce acute inflammation, which result in a tumor environment that enhances cytotoxic T cells and tissue destruction. Natural killer (NK) cells also have antitumor effects through direct cytolytic activity and the production of cytokines [28].

In various types of cancer, increased infiltration of tumor-infiltrating lymphocytes (TILs) is associated with a good prognosis and favorable responses to anticancer therapy [29]. With the recognition that low lymphocyte counts may also be associated with shorter survival, the platelet to lymphocyte ratio (PLR) has been studied as a prognostic biomarker. It has been hypothesized that an increased PLR is indicative of an increased host inflammatory response associated with more aggressive tumor characteristics [30].

Studies have identified the neutrophil to-lymphocyte ratio (NLR) and the platelet to-lymphocyte ratio (PLR) as measures of systemic inflammation; they are relatively inexpensive to perform and provide readily obtainable (and reproducible) markers that may be prognostic factors in patients with MPM [31].

Platelets and lymphocytes are seen on the routine complete blood count (CBC) with from differential white blood cells WBC count that is routinely performed at presentation. Platelet/lymphocyte ratio (PLR) is calculated, by dividing the number of platelets by the number of lymphocytes. PLR is a global inflammation marker that has a prognostic value in solid organ tumors that has been detected early [32-34].

Considering the different studies in the literature, the prognostic situation of either the NLR or PLR scores remains controversial. For this reason, although these markers are easy to use and are inexpensive methods, it is too early to replace multiple prognostic survey indicators such as EORTC and CALGB [11].

Limitations of our study are: Small sample size, and its retrospective nature.

Conclusion

PLR is a prognostic marker in patients with MPM. Further prospective studies with larger sample size are required for validation, generalization of results on wider scale population and future utilization of this simple, cheap and available prognostic marker in daily management of MPM patients.

Conflicts of Interest

There are no conflicts of interest.

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How to cite this article: Mira Canaan, Eman El-Sheikh, Ramy R. Ghali and Nada E. Eldin, et al. "Evaluation of the Prognostic Value of the Prechemotherapy Platelet to Lymphocyte Ratio in Malignant Pleural Mesothelioma." *J Cancer Sci Ther.* 12 (2020). 12:649