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REGULAR ARTICLE

Prognostic value of the lymphocyte-to-monocyte ratio and other inflammatory markers in malignant pleural mesothelioma

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Abstract
Objectives Inflammation plays a role in malignant pleural mesothelioma (MPM) prognosis and symptoms. We investigated the roles of the new and old inflammatory indexes and markers in MPM prognosis.
Methods Two hundred and ninety-two MPM patients (167 male and 125 female) were included in this retrospective study. Demographic parameters were collected from the patients' files. Kaplan–Meier curves and multivariate Cox regression analyses were used for the analysis of prognosis.
Results The mean age of the patients was 58.4 years. The mean survival time was 14.6 ± 13.0 months. Twenty-four potential prognostic factors associated with a poor outcome were calculated in the univariate analysis, and 16 potential prognostic factors were associated with a poor prognosis. These 16 potential prognostic factors were also analyzed in multivariate analysis. Multivariate analysis showed that increased age, stage 3–4 disease, the non-epithelial type, a low Karnofsky performance score, a high white blood cell count, and a low lymphocyte-to-monocyte ratio (LMR) were associated with a poor prognosis. The results of the multivariate analysis showed that a decreased LMR was associated with poor survival. Patients with LMR ≤2.6 had poor survival compared with those with LMR >2.6 (mean 9.6 vs. 17.0 months, respectively; $p = 0.004$).
Conclusions LMR is an independent marker of prognosis in patients with MPM and is superior to the other inflammation-based markers. The inexpensive nature and easy reproducibility of the hemogram should encourage the use of the LMR in clinical practice.

Keywords Lymphocyte-to-monocyte ratio · Inflammation · Malignant mesothelioma · Prognosis

Introduction

Malignant pleural mesothelioma (MPM) is a rare aggressive tumor originating from the pleural mesothelium that is associated with poor survival, and there is limited knowledge concerning its natural history [1]. Due to environmental asbestos exposure, MPM is commonly seen in the southeast region of Turkey [2–4]. MPM has a poor prognosis, and the mean survival time has been reported to be approximately 12 months [4–6].

The European Organization for Research and Treatment of Cancer (EORTC) and Cancer and Leukemia Group B (CALGB) devised two prognostic scoring systems for use in patients with mesothelioma [7, 8]. However, these scoring systems are not routinely used for MPM prognosis because they are time-consuming and require costly equipment.

Identification of parameters that are useful, easy, and inexpensive to measure for predicting MPM prognosis is needed. Furthermore, these parameters may be useful for estimating the occurrence of malignant mesothelioma (MM) after asbestos exposure and predicting treatment options and results.

Inflammation plays an important role in the development of MPM. Moreover, during the mesothelioma period,

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patients show signs of increased inflammatory responses such as fever, sweats, and weight loss [9, 10].

Recent studies have identified the neutrophil–lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) as a measure of systemic inflammation; they are relatively inexpensive and readily obtainable reproducible markers that serve as independent prognostic factors in MM patients [3, 11–14]. One study showed that the derived NLR (dNLR) is a prognostic factor for colon cancer [15].

The red cell distribution width (RDW) is a parameter that measures the variability in the size of circulating erythrocytes [16]. It is a routinely measured hemogram. The mean platelet volume (MPV) reflects the platelet size, which is correlated with platelet function and activation. A high MPV predicts platelet activity and the intensity of inflammation [17].

Lymphocytes act as tumor suppressors by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration [18]. Lymphocyte infiltration into cancer tissue has been associated with a better prognosis in various malignancies [19]. The important role of monocytes and macrophages in cancer, including thoracic cancer, has recently been uncovered [20]. The combined index, the lymphocyte-to-monocyte ratio (LMR), has been demonstrated to be an independent prognostic factor in MPM patients, and the LMR is superior to other inflammation-based prognostic scores [21].

In one study, the dNLR was found to be associated with poor cancer prognosis [22]. This association was not investigated in MPM patients. Zhang et al. [23] showed that the preoperative platelet count and neutrophil–lymphocyte ratio (COP–NLR) can predict the prognosis of patients with lung cancer. In one study, the authors demonstrated that the neutrophil–platelet score (NPS) predicted survival in various common cancers [24].

Based on our knowledge, this is the first study that compares the NPS, COP–NLR, and dNLR, as well as other inflammatory markers, with respect to their effect on MPM prognosis. The aim of this study was to investigate the relationship between potential inflammatory prognostic indicators, such as the NPS, COP–NLR, NLR, dNLR, PLR, MPV, LMR, and RDW, and MPM prognosis.

Materials and methods

This retrospective study included 338 MPM patients who were diagnosed and treated at Dicle University Hospital between May 2005 and December 2015. The local ethics committee approved the study protocol. Forty-six patients were excluded from the study due to a lack of data and active infection. Two hundred and ninety-two patients were included in the study.

MPM was confirmed by histopathological examination in all of the patients. Histochemical or immunohistochemically staining was used if necessary. Demographic data, asbestos exposure type and time, histopathological subtype of MPM, and basic laboratory parameters were obtained from the patients' files. We used the Butchart staging system in our patients because we could not perform thoracoscopy on all patients [25]. Details on the potential prognostic parameters measured at the time of diagnosis were also obtained from the patients' files.

Approximately half of our MPM patients were received chemotherapy, one of four were received surgical treatments and one of four were received best supportive care treatment.

Blood samples were taken at diagnosis time. Hemogram parameters [including the white blood cell (WBC), hemoglobin, platelet, neutrophil, monocyte and lymphocyte counts] were measured using Cell-Dyn 3700 (Abbott Diagnostics, Lake Forest, IL, USA). The complete blood cell count was measured using a Cell-Dyn 3700 (Abbott Diagnostics).

Assays were performed within 1 h of collection, after centrifugation at 1500*g* for 10 min at room temperature of the paired specimens. The inflammatory indexes were defined for MPM patients based on parameters from patients' files that were obtained at the time of diagnosis.

The NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was determined by dividing the absolute platelet count by the absolute lymphocyte count. The LMR was determined by dividing the absolute lymphocyte count by the absolute monocyte count. The dNLR neutrophil count was calculated as WBC count − neutrophil count [22].

NPS was defined according to the system proposed by Watt et al. [24]:

NPS 0 neutrophils $\leq 7.5 \times 10^9$/L and platelets $\leq 400 \times 10^9$/L

NPS 1 neutrophils $>7.5 \times 10^9$/L or platelets $>400 \times 10^9$/L

NPS 2 neutrophils $>7.5 \times 10^9$/L and platelets $>400 \times 10^9$/L

COP–NLR was calculated as follows:

COP–NLR 0 NLR ≤ 3 and platelets $\leq 300 \times 10^9$/L

COP–NLR 1 NLR >3 or platelets $>300 \times 10^9$/L

COP–NLR 2 NLR >3 and platelets $>300 \times 10^9$/L

The following potential prognostic parameters were used, and the mean value of the biochemical parameters was used for prognostic calculations (Table 1). Some of these parameters were age ≥ 60 and <60 years, gender, male or female gender, histopathological subtype, epithelial or non-epithelial, stage 1–2 or 3–4 disease, pleural fluid

Table 1 Demographic features of mesothelioma patients

Features	*n*	%
Number of patients	292	100
Mean age of patients	58.4	
Gender		
Male	167	57.2
Female	125	42.8
History of exposure of asbestos	174	59.6
Sub-type of MM		
Epithelial	201	68.8
Mixed	16	5.6
Unidentified	67	22.9
Sarcomatous	8	2.7
Mean value of WBC ($\times 10^9$/L) ($n = 292$)	9102	
Mean value of neutrophil ($\times 10^9$/L) ($n = 285$)	6.2	
Mean value of lymphocyte ($\times 10^9$/L) ($n = 285$)	1.9	
Mean value of monocyte ($\times 10^9$/L) ($n = 283$)	0.7	
Mean value of platelet ($\times 10^9$/L) ($n = 292$)	340.4	
Mean value of hemoglobin (g/L) ($n = 289$)	13.5	
Mean value of sodium (mmol/L) ($n = 273$)	138.4	
Mean value of RDW (%) ($n = 285$)	15.9	
Mean value of MPV (fL) ($n = 284$)	8.7	
Mean value of albumin (g/dL) ($n = 278$)	3.3	
Mean value of CRP (mg/L) ($n = 208$)	46.8	
Mean value of NLR ($n = 285$)	3.7	
Mean value of PLR ($n = 285$)	196.0	
Mean value of LMR ($n = 283$)	5.0	

RDW red cell distribution width, *WBC* white blood cell, *MPV* mean platelet volume, *PLR* platelet-to-lymphocyte ratio, *NLR* neutrophil–lymphocyte ratio, *CRP* C-reactive protein, *LMR* lymphocyte to monocyte ratio

cytology positive or negative, and Karnofsky performance score (KPS >60 or ≤60). The NLR was taken as ≤3 and >3 from previous studies [3, 14].

Receiver operating characteristic (ROC) curve analysis was performed to select the most appropriate cut-off point for the WBC, neutrophil, lymphocyte, monocyte, albumin, LMR, PLR, RDW, dNLR, MPV, and sodium values to predict poor prognosis in patients with MPM. The score with the maximum sensitivity and specificity was selected as the best cut-off value. Survival results were dichotomized by survival (alive vs. death) in the ROC analysis.

Statistical analysis

The mean values and standard deviation were calculated for the continuous variables. For continuous variables, we used the independent *t* test; for categorical variables, we used the chi square test. The duration of survival and the median and mean event times with 95 % confidence intervals were estimated according to the Kaplan–Meier method. The duration of survival was determined as the period between the time of diagnosis and the time of death. If patients were still alive, survival was defined as the period between the times of diagnosis until December 1, 2015.

The proportional hazards regression model with stratification for the clinical trial was used for both the univariate and multivariate analyses. The univariate analyses examined the prognostic importance of all of the aforementioned factors. The Cox proportional hazards model was used to examine the variables. A two-sided test was used, with a 0.05 level of significance. Comparisons of overall survival were made using two-tailed log-rank tests. Only variables with p values <0.1 in the univariate analysis were included in the final model for the multivariate analysis.

In the Cox regression analysis, the "backward conditional" method was used. A p value <0.05 was considered to indicate statistical significance. In the study group, 32 were alive at the time of this study. Statistical analyses were performed using SPSS statistical program version 15 (SPSS® Inc., Chicago, IL, USA).

Results

Two hundred and ninety-two MPM patients met the inclusion criteria and were included in this study. The mean age of the MPM patients was 58.4 ± 12.2 (22–87) years. One hundred and sixty-seven (57.2 %) patients were male and 125 (42.8 %) were female. Two hundred and one (68.8 %) patients showed the epithelial-type histopathological subtype (Table 1). The mean survival time was 14.6 ± 13.0 months in all of the MPM patients. The mean value of NLR was 3.7, and the mean value of LMR was 5.0 (Table 1).

Twenty-four potential prognostic factors associated with a poor outcome were calculated in the univariate analysis, and 16 potential prognostic factors were associated with a poor prognosis (Table 2). These 16 potential prognostic factors were also analyzed in multivariate analysis.

The results of multivariate analysis showed that an increased age, stage 3–4 disease, the non-epithelial type, a low KPS, a high WBC count, and a low LMR were associated with a poor prognosis. The results of multivariate analysis demonstrated that an LMR ≤2.6 was associated with a poor prognosis of MPM patients. Patients with an LMR ≤2.6 had a 1.8-fold increased mortality rate (Table 2). Figure 1 shows the association between LMR and MPM prognosis. Figure 2 shows the association between dNLR and MPM prognosis. The results of the

Table 2 Univariate and multivariate analysis of parameters

Variable	Univariate analysis			Multivariate analysis		
	O/*N**	Survival[a]	*p*	HR	95 % CI	*p*
Age (years) ($n = 292$)						
>60	128/162	12.1	**<0.001**	1.5	(1.1–2.0)	**0.011**
≤60	120/130	16.6				
Gender ($n = 292$)						
Male	145/167	13.1	**0.040**	1.1	(0.8–1.6)	0.45
Female	103/125	16.6				
Butchart stage ($n = 271$)						
1–2	151/184	17.1	**0.000**	1.7	(1.2–2.3)	0.002
3–4	80/87	9.9				
Pleural fluid cytology ($n = 224$)						
Negative	130/150	15.6	0.60			
Positive	63/74	14.0				
Pathological type ($n = 292$)						
Epithelial	167/201	13.0	**0.003**	1.5	(1.1–2.0)	0.011
Others	81/91	12.1				
KPS ($n = 280$)						
≤60 %	48/48	9.4	**0.000**	2.2	(1.5–3.2)	>0.001
>60 %	189/232	15.9				
Platelet count ($n = 292$) ($\times 10^9$/L)						
≤300	111/130	15.5	0.54			
>300	137/162	13.9				
WBC count ($n = 292$) ($\times 10^9$/L)						
≤8100 K/UL	100/120	17.5	**0.009**	1.4	(0.9–2.3)	**0.2**
>8100 K/UL	148/172	12.7				
Hemoglobin ($n = 289$) (g/L)						
≤13.2 U/L	133/151	15.3	0.85			
>13.2 U/L	112/138	13.8				
Albumin ($n = 278$) (g/dL)						
≤3.5	138/154	11.9	**0.000**	1.3	(0.96–1.8)	0.09
>3.5	101/124	17.8				
CRP ($n = 208$) (mg/L)						
≤14.7 U/L	44/64	13.8	0.21			
>14.7 U/L	124/144	13.9				
NA ($n = 273$) (mmol/L)						
≤138.5	120/138	14.5	0.68			
>138.5	112/135	14.7				
NLR ($n = 285$)						
≤3	106/127	17.2	**0.001**	1.1	(0.6–1.9)	0.8
>3	135/158	12.0				
Derived NLR ($n = 285$)						
≤1.8	78/96	17.1	**0.01**	1.2	(0.7–1.9)	0.5
>1.8	163/189	13.0				
PLR ($n = 285$)						
≤144	83/97	17.0	**0.034**	1.4	(0.9–2.3)	0.1
>144	158/188	12.9				
MPV ($n = 284$) (fL)						
≤7.8	110/137	14.1	0.62			
>7.8	130/147	14.6				

Table 2 continued

Variable	Univariate analysis			Multivariate analysis		
	O/*N**	Survival[a]	*p*	HR	95 % CI	*p*
RDW ($n = 285$) (%)						
≤14.6	78/102	14.6	0.13			
>14.6	163/183	14.2				
Neutrophil count ($n = 285$) ($\times 10^9$/L)						
≤5.3	101/122	16.8	**0.015**	1.4	(0.8–1.7)	0.2
>5.3	140/163	12.4				
Lymphocyte count ($n = 285$) ($\times 10^9$/L)						
≤2.0	134/158	13.2	0.094			
>2.0	107/127	15.8				
Monocyte count ($n = 283$) ($\times 10^9$/L)						
≤0.55	94/116	16.6	**0.015**	1.2	(0.8–1.7)	0.3
>0.55	145/167	12.7				
LMR ($n = 283$)						
≤2.6	91/104	9.6	**0.000**	1.8	(1.2–2.7)	**0.004**
>2.6	148/179	17.0				
CRP/albumin ($n = 201$)						
≤7.5	67/89	13.7	0.48			
>7.5	97/112	14.1				
Combine platelet NLR ($n = 285$)						
0	53/59	17.8	**0.006**	1.3	(0.6–2.7)	0.5
1	110/138	15.0				
2	78/88	11.0				
NPS ($n = 285$)						
0	134/162	16.4	**0.05**	1.7	(0.9–3.3)	0.1
1	87/100	11.6				
2	20/23	11.7				

Bold values indicate better results

O observed death number, *N* total patient number, *HR* hazard ratio, *RDW* red cell distribution width, *MPV* mean platelet volume, *PLR* platelet-to-lymphocyte ratio, *NLR* neutrophil–lymphocyte ratio, *WBC* white blood cell, *CRP* C-reactive protein, *LMR* lymphocyte to monocyte ratio, *NA* sodium, *KPS* Karnofsky performance status, *NPS* the neutrophil–platelet score

[a] Mean survival (months)

multivariate analysis demonstrated a more significant relationship between LMR and poor MPM prognosis than other inflammatory parameters (NLR, PLR, dNLR, NPS and COP–NLR).

Discussion

Previous studies focused on developing a parameter that could accurately predict MPM prognosis. Several models were defined, using measurements that included: symptoms, pathologic factors, stage and some blood parameters; unfortunately, none were considered to be ideal.

EORTC and CALGB analyzed large numbers of patients enrolled in MPM studies and identified the following poor prognostic factors for MM [7, 8]: non-epithelioid histology, bad performance status, presence of chest pain, age older than 75 years, male gender, WBC 8.3×10^9/L or greater, platelet number over 400,000/μL, and an LDH level >500 IU/L.

Similarly, we found that the prognostic factors of increased age, stage 3–4 disease, the non-epithelial type, a low KPS, and a high WBC count were associated with a poor survival.

In our previous study, our results indicated that pleural fluid cytology was not associated with mesothelioma prognosis [4]. In the present study, pleural fluid cytology was associated with mesothelioma prognosis in univariate but not in multivariate analysis.

Hypoalbuminemia is associated with poor prognosis of MM. In one study, albumin <3.5 g/L was independently associated with a decrease in survival [26]. PLR was

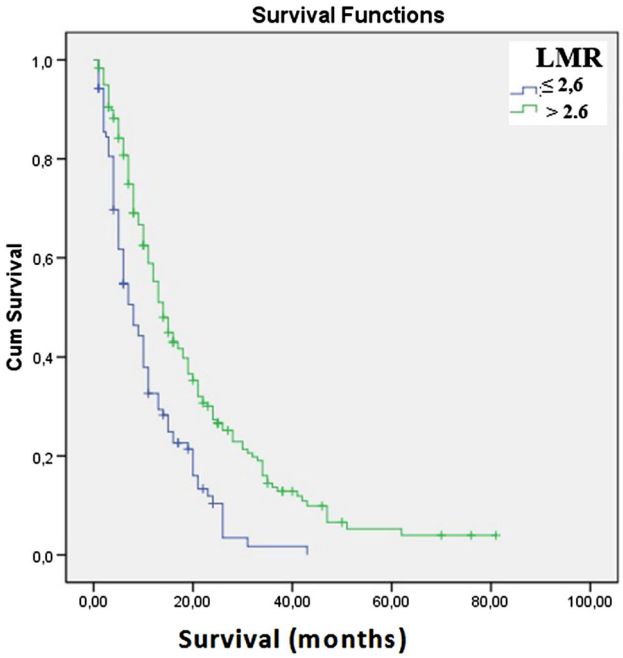

Fig. 1 Kaplan–Meier survival curves according to LMR ($p < 0.001$) ($n = 283$)

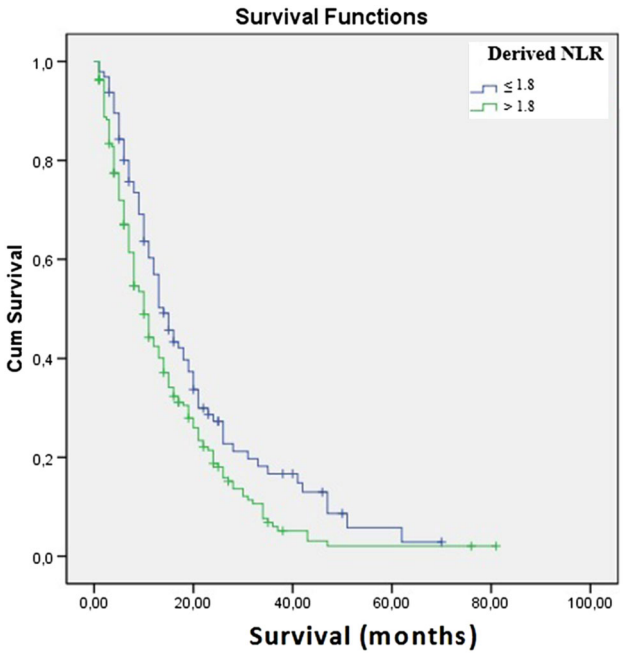

Fig. 2 Kaplan–Meier survival curves according to dNLR ($p = 0.01$) ($n = 285$)

associated with poor prognosis [13]. We found that hypoalbuminemia and high PLR were associated with a poor prognosis in univariate analysis but not in multivariate analysis.

The pathological role of chronic inflammation in the development of MPM is already known [27]. Based on our results, inflammatory-based biomarkers may be predictive of survival, and the AMI may be viewed as an inexpensive predictor of MM prognosis at the time of diagnosis.

Many investigations have presented the role of inflammatory parameters such as the NLR and PLR in the prognosis of MPM [11–13, 28]. These studies have reported that the mortality is increased patients with an NLR ≥3 [12, 28]. One study showed that dNLR is a prognostic factor for colon cancer [15]. The dNLR was not studied in MPM patients. In univariate analysis, we found that the NLR and dNLR were associated with poor survival in MPM patients. A possible explanation for this finding is that MPM patients with more advanced disease at the time of diagnosis may have a more excessive systemic inflammatory response and therefore a higher NLR and dNLR.

The newly investigated inflammatory marker COP–NLR was capable of predicting the prognosis of patients with lung cancer [23]. In another study, the authors demonstrated that NPS predicted survival in various common cancers [24]. These two inflammatory prognostic scores included a high platelet level and were not studied in mesothelioma patients. Platelets can secrete cytokines and growth factors, such as vascular endothelial growth factor, platelet-derived growth factor, TGF-β, and FGF [29, 30], which, in turn, contribute to cancer progression, including angiogenesis, cell migration and proliferation, and the epithelial to mesenchymal transition [31]. In many studies, a similar high platelet count was associated with mesothelioma prognosis [4, 7, 8]. In this study, the platelet count was not significant. However, the COP–NLR and NPS were associated with MPM prognosis in univariate analysis.

The LMR was found to be an independent prognostic marker for survival in patients with MPM, and the LMR is superior to other inflammation-based prognostic scores [21]. In this study, patients with an LMR <2.74 exhibited a median survival was 5.0 months, while those with an LMR ≥2.74 had a median survival of 14.0 months ($p = 0.000$) [21]. Also, in this study, the NLR and PLR were not associated with MPM prognosis in multivariate analysis [21]. Similarly, we found that the LMR was the only associated inflammatory prognostic factor in multivariate analysis. The LMR was also demonstrated to be an independent predictor of survival in various patients with lung cancer [32].

A potential limitation of this study is that it is a retrospective and single-center study. Additionally, the treatment regimens and outcomes were not investigated in this study. However, this investigation demonstrated that the LMR is an independent marker of prognosis in patients

with MPM and is superior to the other inflammation-based markers (e.g., NLR, dNLR, NPS, and COP–NLR).

LMR is easily assessed using a simple complete blood count test and is both technically and financially feasible to predict the patients' clinical outcomes in routine practice. The LMR is a useful marker, given the high prevalence and the prognostic importance of increased levels. The inexpensive nature and easy reproducibility of the hemogram should encourage its use in clinical practice. Despite our findings, this index must be validated in a large, prospective study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Dicle University Ethics Committee obtained ethical approval.

Informed consent Informed consent was obtained from all individual participants included in the study.

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