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A biomarker predicting unfavorable prognosis in malignant pleural mesothelioma: systemic immune–inflammation index

Hüsnü Baykal[1], Filiz Çimen[2]

[1]Department of Chest Disease, Ankara Atatürk Sanatoryum Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[2]Department of Chest Disease, Private Çankaya Life Hospital, Ankara, Turkey

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ABSTRACT

Aim: Malignant pleural mesothelioma (MPM) is an extremely mortal condition. Only a few prognostic biomarkers have been described for MPM. Our study looked into the association between patient survival and the Systemic Immune Inflammation Index (SII).

Material and Method: A total of 158 patients who were admitted to our hospital between January 2013 and December 2022, and had a histopathologically confirmed diagnosis of MPM were included in the study. Before treatment, hematological parameters and SII were determined. A Spearman's correlation analysis was performed to analyze the correlation of mean survival with hematological parameters.

Results: The study involved 158 patients in all. 70 patients had a history of smoking, the median age was 63 years, the mean survival time was 15.3 months, and 57.6% of the participants were men. The epithelioid type (84.2%) was the most prevalent histological subtype, and 29 patients had stage 4 illnesses. Of the participants, 84% had received chemotherapy, and 22% had received radiotherapy before. Among the 39 patients who had surgery, 5 had an extrapleural pneumonectomy. SII mean±sd was (1427.2±1207.3). The patients with stage 4 disease had significantly shorter survival (p=0.001). The patients who had surgery survived significantly longer (p=0.01). Hemoglobin (Hb) (r:0.21, p:0.01) and Hematocrit (Hct) (r:0.18, p:0.03) values showed weak positive correlations with mean survival. It was evident that mean survival got shorter as SII (r:-0.17, p:0.04) and neutrophil-lymphocyte ratio (NLR) (r:-0.19, p:0.02) values got higher. On the other hand, there was a strong positive association between mean survival and the lymphocyte-monocyte ratio (LMR) (r:0.21, p:0.01). When the parameters that had statistically significant differences among the groups were taken as control variables and the statistical analysis was re-performed, it was found that Hgb and Hct values as well as NLR and LMR ratios lost their significant correlations with survival. However, the SII ratio was still negatively correlated with survival (r:-0.16, p:0.04).

Conclusion: Pretreatment SII is a noninvasive and easy-to-calculate biomarker that predicts the prognosis of MPM. It is negatively correlated with mean survival regardless of the tumor stage and surgical management.

Keywords: Malignant pleural mesothelioma, systemic immune-inflammation index, prognosis, survival

This study was presented as an oral presentation at the 11th International Congress of Medical and Health Sciences Research (UTSAK) held on 24 - 25 - December 2022.

INTRODUCTION

Malignant mesothelioma (MM) is a fatal and extremely aggressive disease. Malignant pleural mesothelioma, which accounts for 80% of mesotheliomas, develops from the pleura (MPM) (1-3). Due to rising environmental contamination as well as occupational and environmental asbestos exposure, MPM incidence has recently been predicted to rise. Due to its lengthy latent period following exposure, MPM is frequently detected in later life. This period is about 20-40 years (3,4). MPM is an insidious disorder. The diagnosis is difficult due to non-specific symptoms and normal radiological findings early in the course of the illness.

Regardless of the tumor stage, MPM is resistant to treatment and has a median overall survival (OS) of 9–17 months (3). Malignant tumor formation and progression are highly dependent on tissue inflammation (5,6). Serum lymphocyte, monocyte, neutrophil, and platelet counts, are indicators of a systemic inflammatory response. These cell counts are used to determine the lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio, which are all directly associated with the prognosis of various cancers (7,8). The systemic immune-inflammation index (SII) is calculated based on lymphocyte (L), neutrophil (N),

Corresponding Author: Filiz Çimen, fhcimen@yahoo.com
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and platelet (P) values (SII=N×P/L). This parameter is correlated with prognosis in malignant tumors (9).

Very few biomarkers have been identified for MPM. There is no specific algorithm for the management of MPM. There are few prospective and retrospective studies on MPM patients' prognostic variables, as well as the effectiveness and tolerability of antineoplastic therapy. The objective of this study was to retrospectively examine how systemic inflammation affected MPM patients' prognoses.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.01.2023, Decision No: 2012-KAEK-15/2624). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective analysis was performed on patients who were admitted to our hospital between January 2013 and December 2022 and who had a histological MPM diagnosis. The patients' demographic, laboratory, therapeutic, clinical, and survival information was documented. The readings from the laboratory used for the analysis were those at the time of diagnosis and before therapy. Demographic, clinicopathological, therapeutic, and prognostic data were systematically analyzed. Asbestos exposure, TNM stage, histopathological subtype, SUV max value on PET, chemotherapy and radiotherapy data, surgical treatment history, life expectancy, hemoglobin (Hb), hematocrit (Hct), neutrophil, monocyte, lymphocyte, and platelet (PLT) count, white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and systemic immune-inflammation index (SII) were determined, calculated, and recorded. NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count and LMR was calculated as absolute lymphocyte count divided by absolute monocyte count. Systemic immune-----inflammation index (SII) (SII=N×P/L), known as systemic immune–inflammation index, is calculated on neutrophil (N), platelet (P), and lymphocyte (L) count. The staging of malignant mesothelioma was performed using the tumor–node–metastasis (TNM)-based on The International Mesothelioma Interest Group (IMIG) Staging System.

Overall survival (OS) and survival were reported (OS was defined as the interval between diagnosis and death or last follow-up). The informed consent of the participants was not obtained due to the retrospective nature of the study.

Study Population

The patients who were admitted to our hospital between January 2013 and December 2022 and histopathologically diagnosed with MPM were reviewed retrospectively.

Inclusion criteria are (1) a histopathological diagnosis of MPM in our hospital between January 2013 and December 2022; (2) age ≥ 18 years; (3) the presence of clinical and follow-up data; and (4) not having received any anti-neoplastic treatment before the definitive diagnosis.

Exclusion criteria are (1) the patients with benign mesothelioma or tumor origin elsewhere other than pleura; (2) having an anti-neoplastic treatment before the definitive diagnosis; (3) the patients with inflammatory or autoimmune disorders (4). In addition, those with any viral infections (HBV, HCV, HIV, etc.), autoimmune disorders, including systemic lupus erythematosus, leukemia, any other hematological disorders, inflammatory disorders, or solid organ (liver, spleen, etc.) conditions.

Statistical Method

The SPSS 23 package application for Windows was used to conduct all statistical analyses. The percentiles in the descriptive data of the variables were calculated using cross-tabs. Mann-Whitney U test was used to compare the means. To analyze the relationship of survival with age and hematologic variables, the Spearman correlation test was employed in the case of continuous data that did not fit the normal distribution. In the comparison of the groups, the stage and the presence of a surgical procedure, which are thought to affect survival, were used as control variables, and the parameters found to be correlated in the Spearman correlation test were re-evaluated with partial correlation analysis. Results were considered statistically significant when the p-value was less than 0.05.

RESULTS

The study involved 158 patients in all. The average lifespan was 15.3 months, with a mean age of 63. Among the participants, 57.6% were men, and 70 patients had a history of smoking. A history of asbestos contact was evident in 123 participants. The most common histopathologically subtype was the epithelioid type (84.2%), 29 patients had stage 4 tumors. 84% of the participants had chemotherapy, and 22% had radiotherapy. While the surgery was performed on 39 patients in total, 5 had an extrapleural pneumonectomy. **Table 1** displays the means for hematological parameters and demographic information. A comparison of the mean survival of the groups showed significantly shorter survival in patients with stage 4 tumors compared to other stages (p=0.001). The mean survival was 6.5

months in stage 4 patients, while this value was 17.3 months in the patients with tumors in other stages. The survival was 20.4 months in the surgery group, it was significantly longer than the no-surgery group, which had 13.6 months of survival (p =0.01). **Table 2** provides a detailed comparison of the groups' survival rates. The correlation of mean survival with hematological parameters was analyzed with the Spearman correlation test. Age and survival did not significantly correlate with one another (p=0.22). Hemoglobin (r:0.21, p:0.01) and hematocrit (r:0.18, p:0.03) values showed weak positive correlations with mean survival. It was observed that the mean survival decreased as the systemic immune-inflammation index (r:-0.17, p:0.04) and NLR (r:-0.19, p:0.02) values increased. On the other hand, mean survival and lymphocyte-monocyte ratio had a significant positive correlation (r:0.21, p:0.01). When the parameters that had statistically significant differences among the groups were taken as control variables and the statistical analysis was re-performed, it was found that hemoglobin and hematocrit values as well as neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio ratios lost their significant correlations with survival. However, the Systemic immune-inflammation index ratio was still negatively correlated with survival (r:-0.16, p:0.04).

Table 1. Demographic data (n=158)

Average age	63.97±9.15
Male	91 (57.6)
Smoking	70 (44.3)
History of asbestos	123 (77.8)
Stage	
1,2,3	129 (81.6)
4	29 (18.4)
Histological type	
Epithelioid	133 (84.2)
Sarcomatosis	5 (3.2)
Biphasic	20 (12.7)
Chemotherapy	132 (83.5)
Radiotherapy	35 (22.2)
Surgical	39 (24.7)
Extrapleural pneumonectomy	5 (3.2)
Hgb	13.1±1.9
Hct	39.7±5.9
Lymphocyte	10.23±11.3
Monocyte	3.69±4.1
Neutrophıl	35.9±36.2
PLT	327.8±118.4
SII	1427.2±1207.3
NLR	4.29±3.2
PLR	123.7±134.6
LMR	3.20±1.71
Survey months	15.3±12.9

(%) Column percentages Mean±sd, Hgb: Hemoglobın, Hct: hematocrit, PLT: platelet, SII: systemic immune-inflammation index, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio.

Tablo 2. Comparison of average life expectancy with demographic data

n=158		**p**
Gender		0.24
Male	91±15.1	
Female	67±15.6	
Smoking		0.30
Yes	14.1±9.2	
No	16.3±15.2	
History of asbestos		0.10
Yes	14.4±12.6	
No	18.5±13.4	
Stage		0.001*
1,2,3	17.3±13.2	
4	6.5±6.5	
Histological type		0.17
Epithelioid	16.1±13.1	
Sarcomatosis	12.0±19.7	
Biphasic	10.6±7.9	
Chemotherapy		0.34
Yes	15.8±11.8	
No	12.4±17.4	
Radiotherapy		0.08
Yes	18.3±11.2	
No	14.4±13.3	
Surgical		0.01*
Yes	20.4 ±14.4	
No	13.6±11.9	
Extrapleural pneumonectomy n=39		0.12
Yes	32.8±20.1	
No	18.7±12.9	

*p < 0.05

Table 3. Relationship between hematological values and mean survival

	Spearman correlation analysis		**Partial correlation analysis**	
	Correlation coefficient	**p**	**Correlation coefficient**	**p**
Age	-0.09	0.22		
Hgb	0.21	0.01*	0.15	0.05
Hct	0.18	0.03*	0.13	0.08
Lymphocyte	0.06	0.43		
Monocyte	-0.07	0.36		
Neutrophıl	-0.08	0.31		
PLT	-0.07	0.42		
SII	-0.17	0.04*	-0.16	0.04*
NLR	-0.19	0.02*	-0.15	0.05
PLR	-0.06	0.43		
LMR	0.21	0.01*	0.15	0.05

*p < 0.05, Control variables:Stage and surgical

DISCUSSION

There are few studies on mesothelioma since it is less frequent than lung cancers. Numerous cancer types have been researched to determine the connection between inflammation and cancer. We investigated the systemic immune-inflammation index (SII) in this study's individuals who had been diagnosed with mesothelioma.

MM most frequently involves the pleura (73-85%), followed by the peritoneum (7-18%). MM is more frequent in men (male: female ratio: 5:1) (10-11). Treatment options for MPM are systemic chemotherapy, radiotherapy, and surgery. Systemic chemotherapy is the preferred treatment modality in cases of an un-resectable tumor, in patients with tumor recurrence, and in those who do not prefer surgery. Preoperative or postoperative radiotherapy aims to relieve local symptoms (12).

If MPM is a tumor at an operable stage, tri-modal management including surgery, chemotherapy, and radiotherapy is preferred (13). Surgical treatment has been independently correlated with a favorable prognosis in operable cases (stages I, II, and III). The prognosis is often miserable, as most patients diagnosed with mesothelioma have inoperable tumors at the time of diagnosis. The surgical options are pleurodesis, pleurectomy/decortication, and extrapleural pneumonectomy (EPP) in the treatment of mesothelioma if the tumors are suitable for surgery (14). Patients who have surgery have been reported to have improved OS, which is consistent with our findings (15).

It has been known that inflammation may increase the tumor risk, triggering the genetic mutation mechanisms, and promoting tumor formation, metastasis, and progression (16). Studies have shown that hemoglobin levels are directly related to survival and tumor development in cancer patients (17). In our study, the Hgb and Hct values showed weak positive correlations with mean survival.

An essential component of the tumor microenvironment is inflammation, which has been linked to a poor prognosis in several tumor forms. It is possible to forecast the prognosis of malignancies using variables like neutrophil, lymphocyte, monocyte, and platelet counts, which may indicate the immunological condition of the host. A high inflammatory response generally indicates a worse prognosis (18-19). The onset and development of cancer are significantly influenced by systemic inflammation. Hematological parameters including serum lymphocyte, monocyte, neutrophil, and platelet counts, and NLR, LMR, and PLR calculated using these cell counts are prognostic parameters for malignancies (2,20,21). Recent studies have shown that certain blood markers, such as the ratio of neutrophils to lymphocytes (NLR), the ratio of platelets to lymphocytes (PLR), and the ratio of lymphocytes to monocytes (LMR), represent inflammatory changes in the tumor microenvironment (22).

It has been shown that lymphocytes, and particularly T cells, are associated with prognosis (23). Depending on their subgroup, monocytes can perform a variety of functions, including promoting blood vessel formation and secreting tumoricidal mediators. In conclusion, LMR calculated using two parameters may be a better prognostic parameter in non-small cell lung cancer. High NLR and PLR as well as a slow LMR predict shorter survival (24-26). In our investigation, it was found that the mean survival decreased as the NLR values increased; however, there was a statistically significant positive association between the mean survival and the LMR value.

The development of tumors is significantly influenced by inflammation.SII is a systematic indicator of inflammatory response that can be calculated by the following formula: neutrophil (N) count× platelet (P) count/lymphocyte (L) count. Pre-treatment SII may better reflect the inflammatory and immune status of the body. In many cancer types, previous studies have shown that pre-treatment SII is a significant prognostic parameter. These cancers include lung, stomach, bladder, cervix, breast, and hepatocellular carcinoma (27-31). Our research demonstrated a link between a high pre-treatment SII and a poor prognosis for MPM. SII is a noninvasive and inexpensive prognostic parameter for MPM. These findings are extremely valuable for the clinics that follow up on patients with MPM. These values may help clinicians establish treatment plans and follow-up with the patients.

Studies on the prognostic role of the pretreatment SII on MPM are limited. In our study, a negative correlation was found between the pre-treatment SII ratio and the mean survival, irrespective of tumor stage and surgical treatment.

Our study does have certain limitations. It might not be suitable to apply these findings to the general population because the first study had a single-center single-center design and a small sample size. The study is also retrospective.

CONCLUSION

This study was performed on patients with histo-pathologically proven MPM in our hospital. Hematological parameters may be easily obtained before treatment. These biomarkers may be easily incorporated into routine clinical practice. SII is a noninvasive and easily calculable biomarker in MPM. High SII is an independent negative prognostic factor in MPM. Regardless of the stage of the tumor and the performance of surgery, the SII ratio is negatively correlated with mean survival.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.01.2023, Decision No: 2012-KAEK-15/2624).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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