Original Article

Potential Novel Prognostic Factors in Malign Mesothelioma: Systemic Inflammatory Indices (SII) & Albumin-to-Globulin Ratio (AGR)

Malign Mezotelyomada Potansiyel Yeni Prognostik Faktörler: Sistemik İnflamatuar İndeksler (SII) ve Albümin-Globulin Oranı (AGO)

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ABSTRACT

Introduction: Malignant mesothelioma (MM) is rare with poor prognosis and often diagnosed at advanced stage. Systemic inflammatory indices (SII) may have prognostic value in cancer. Albumin is a negative acute phase reactant. We evaluated the prognostic significance of SII and albumin to globulin ratio (AGR) in MM followed-up at a single institute.

Methods: Fifty-six MM patients who met the inclusion criteria at our oncology cenrter were included in the study. Patients aged over 18 years with pathologically confirmed malignant pleural and peritoneal mesothelioma and no secondary malignancy followed up at our center were included in the study. Laboratory parameters for estimation of SII and AGR at diagnosis were obtained from database. Those with active infection, which might affect these parameters, those with a medical history of steroid use were excluded from the study.

Results: Median follow-up was 13.5 months. Most of the patients were female (58.9%). Median overall survival (OS) was 13 months. Median OS was 16 months in the pleural mesothelioma group and 9 months in the peritoneal mesothelioma group (p=0.982). Median OS was longer with lower platelet level, lower neutrophil to lymphocyte ratio (NLR) level and lower platelet to lymphocyte ratio (PLR) level (p1=0.001, p2=0.001 p3<0.001; respectively). On the other hand, median OS was longer with higher lymphocyte count, higher albumin level and higher AGR level (p1=0.032, p2=0.03, p3=0.003). Lymphocyte, Platelet count and AGR were determined as independent prognostic factors for OS according to multivariate cox regression analysis (p1=0.047, HR: 0.852; p2=0.011, HR: 2.502; p3=0.032, HR: 0.495, respectyively).

Discussion and Conclusion: It has been demonstrated that AGR, platelet and lymphocyte counts are independent prognostic factors for OS in MM.

Keywords: Malignant Mesothelioma, albumin, albumin-to-globulin ratio, systemic inflammatory indices (SII), NLR, PLR

ÖZET

Giriş ve Amaç: Malign mezotelyoma (MM) sıklıkla ileri evrede tanı alan kötü prognozlu nadir bir hastalıktır. Sistemik inflamatuar indeksler (SII) kanserde prognostik değerlere sahip olabilir. Albumin, negatif bir akut faz reaktanıdır. Sunulan calışmada MM takibinde SII ve albuminin globulin oranının (AGO) prognostik önemini değerlendirdik.

Yöntem ve Gereçler: Merkezimizde dahil edilme kriterlerini karşılayan 56 MM hastası calışmaya dahil edildi. 18 yaş üstü, patolojik olarak doğrulanmış malign plevral ve peritoneal mezotelyoma olan

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sekonder malignitesi olmayan hastalar calışmaya dahil edildi. Tanı anında SII ve AGR laboratuvar parametreleri veri tabanından retrospektif olarak kaydedildi. Bu parametreleri etkileyebilecek aktif enfeksiyonu olanlar, steroid kullaım öyküsü olanlar çalışma dışı bırakıldı.
Bulgular: Medyan takip süresi 13,5 aydı. Hastaların çoğunluğu (%58.9) kadındı. Medyan genel sağkalım (OS) 13 aydı. Median OS, plevral mezotelyoma grubunda 16 ay ve peritoneal mezotelyoma grubunda 9 aydı (p=0.982). Median OS, düşük trombosit seviyeleri, düşük nötrofil lenfosit oranı (NLR) seviyeleri ve düşük trombosit/lenfosit oranı (PLR) seviyelerinde daha uzundu (sırasıyla p1=0.001, p2=0.001 p3<0.001). Öte yandan, medyan OS yüksek lenfosit sayısı, daha yüksek albumin düzeyi ve daha yüksek AGR düzeyleriyle daha uzundu (p1=0.032, p2=0.03, p3=0.003). Lenfosit, trombosit sayısı ve AGR, multivariate cox regresyon analizine gore OS için bağımsız prognostik faktörler olarak belirlendi (p1=0.047, HR: 0.852; p2=0.011, HR: 2.502; p3=0.032, HR: 0.495, sırasıyla).
Tartışma ve Sonuç: Çalışmada AGO, trombosit ve lenfosit sayılarının MM'de OS için bağımsız prognostik faktörler olduğu gösterilmiştir.

Anahtar Kelimeler: Malign Mezotelyoma, albumin, albumin globulin oranı, sistemik inflamatuar indeksler, NLR, PLR

Introduction

Malignant mesothelioma (MM) is a rare neoplasm of serous membranes such as pleura, peritoneum, pericardium, and tunica albuginea [1]. It has poor prognosis with a median overall survival (OS) of around one year (range: 6-12 months) [2]. The incidence of pleural MM is approximately 10 to 30 fold higher than peritoneal MM [3]. The incidence is increasing worldwide, mainly due to occupational asbestos exposure [4]. There is a strong positive correlation between asbestos exposure and MM development at any localization. Respiratory exposure to asbestos has been reported as the main cause of pleural MM that accounts for approximately 70% of pleural MM cases who were documented for asbestos exposure [5].

Major histological subtypes are epithelioid, sarcomatoid, and biphasic (mixed) MM. Sarcomatoid MM has worse prognosis than epitheloid subtype [6]. 60% of MM patients present with stage III or IV disase at diagnosis [7]. In the literature, some factors including blood hemoglobin level and white blood cell count, Eastern Cooperative Oncology Group (ECOG) performance score and baseline symptoms have been reported to have prognostic significance [8,9]. However, their role as prognostic factors in MM are not so clear since most of clinical data are based on retrospective series in the literature because of its rarity and geographical distribution. Turkey, especially some regions such as Tuzköy and its nearby localizations tend to have relatively higher risk for MM because of erionit and others similar to asbestos structure in that region that may have role in development of MM [10]. Therefore, we should focus on MM in Turkey in terms of prognostic and predictive factors in MM.

In recent years, numerous studies, which have been conducted with inflammation-based markers, have obtained promising outcomes for revealing the prognosis in various cancers [11]. It has been demonstrated that systemic inflammation is associated with poor survival in many cancer types [12]. Inflammatory cells in the tumor microenvironment were shown to have significant effects on tumor development, and systemic inflammation blood markers may provide considerable information in predicting the prognosis [9]. Albumin and globulin are proteins that are the main component of serum. Albumin is a negative acute phase reactant which also reflects the nutritional status and systemic inflammatory response in cancer patients [13]. Globulin, the other main protein component of serum, has crucial roles in immunity and

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inflammation [14]. Lower serum albumin level accompanied with higher globulin level may reflect inflammatory response in tumors. Recently, albumin to globulin ratio (AGR) has been reported to have prognostic value in various cancers [15]. However, its role has not been well studied in relatively rare tumors including MM. Therefore, we considered that AGR may have prognostic role in MM, besides other systemic inflammatory indeces such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR).

Hence, this study was planned to determine the prognostic factors which impact OS, by assessing the retrospective data of patients with MM at our center, who had been followed up in a single center, in the light of the literature.

Material Methods

Upon retrospectively reviewing the data of 102 MM patients who were followed up in our cancer center between 2011 and 2020, 56 patients met the inclusion criteria for our study were included. Patients aged over 18 years with pathologically confirmed malignant pleural and peritoneal mesothelioma without any secondary malignancy were enrolled. Laboratory parameters for SII and AGR at diagnosis were obtained from the patients' database. Those with active infection or a medical history of steroid use, which might affect these parameters, were excluded from the study. The demographic data of the patients and their clinical characteristics were noted down from the patient files. During the study follow-up, disease-free survival (DFS) and progression-free survival (PFS) were calculated based on the recurrence in patients with early-stage and progression in patients with advanced stages. Moreover, OS was calculated by using the central record, according to the dates of the deaths (death notification form). NLR, PLR and AGR were calculated with the formula: Neutrophil count (/μL) / Lymphocyte count (/μL); Platelet count (10^9/L) / Lymphocyte count (/μL) and Albumin value (g/dl) / Globulin value (g/dl). The study was approved by the local ethics committe, ethical approvel number 2021-04/1125; approvel date:21/04/2021.

Statistical Analysis

Statistical analyzes were performed via the software of SPSS 25.0 (SPSS, Chicago, IL, USA). Mann-Whitney U test was used for comparison of nonparametric data, and Student T-test was used for comparison of parametric data. Chi-Square or Fisher's Exact test was used for comparison of categorical data. Optimum cut-off values that can be used to determine the prognostic significance of NLR, PLR, AGR, lymphocyte count and platelet count were determined by receiver operating characteristic (ROC) analysis. Kaplan–Meier method was used for survival analysis, and the Log-Rank test was used for the comparisons between groups. Prognostic factors affecting overall survival were determined by conducting multivariate analysis with the Cox proportional hazards model. Variables with a p value under 0.20 as a result of univariate analysis were evaluated in the cox-regression model. The results were considered statistically significant at $p<0.05$.

Results

Thirty-three (58.9%) of 56 patients in the study were female. Median age of the patients was 65 years (18-77). While 37 (66.1%) patients had pleural mesothelioma, 19 (33.9%) patients were diagnosed with peritoneal mesothelioma. The demographic and clinical characteristics of the patients are summarized in Table-1. At the time of diagnosis, 18 patients (32.1%) were operable, 34 patients (60.7%) were unresectable, and 4 patients (7.1%) were medically inoperable. Pathologically, 40 patients (71.4%) had epithelioid MM while 9 patients (16.1%) had

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Table 1: Summary of Patient Characteristics

Characteristics		
Gender		
	Female	33 (58.9%)
	Male	23 (41.1%)
Median Age		65 (18-77)
Tumor Location		
	Plevra	37 (66.1%)
	Periton	19 (33.9%)
Asbest Exposure		
	No	16 (28.6%)
	Yes	16 (28.6%)
	Unknown	24 (42.9%)
Smoker		
	No	39 (69.6%)
	Yes	17 (30.4%)
ECOG PS		
	<2	33 (58.9%)
	≥2	23 (41.1%)
Symptoms at diagnosis		
	Localized pain	39 (69.6%)
	Dyspnea	32 (57.1%)
	Weight loss	11 (19.6)
	Fatigue	28 (50%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status

biphasic MM and 7 patients (12.5%) had sarcomatoid MM subtypes. Grade 3-4 adverse effects related to chemotherapy occurred in 17 patients (30.4%). Five pleural MM patients (8.9%) received adjuvant radiotherapy. Pathological, surgical and medical treatment characteristics of the patients are summarized in Table-2.

Median follow-up period was 13.5 months. In the study, median OS was 13 months (95% CI =9.85-16.14). Median OS was 16 months (95% CI=10.04-21.95) in the pleural MM group while it was 9 months (95% CI = 6.38-11.61) in the peritoneal MM group and there was no significant difference for OS between these two groups (p=0.982). Median DFS of 18 patients who recurred after surgery was 12 months (95% CI=4.16-19.84). In 38 non-operated patients, median PFS was 7 months (95% CI=4.93-9.06) following first line treatment. Median PFS was 8 months (95% CI = 4.04-11.98) for pleural MM group, and it was 6 months (3.41-8.58) for peritoneal MM group, as well. (p=0.159) (Table-3).

Table 2: Baseline Characteristics of Surgery Pathology and Therapy

Characteristics	
Operation	
Operable	18 (32.1%)
Inoperable	34 (60.7%)
Medical Inoperable	4 (7.1%)
Type of Operation	
Pleurectomy/Decortication (Pleural)	8 (14.3%)
Debulking (Peritoneal)	10 (17.9%)
HIPEC	4 (7.1%)
Pathology	
Epithelioid	40 (71.4%)
Sarcomatous	9 (16.1%)
Biphasic	7 (12.5%)
IHC Staining	
Kalretinin	56 (100 %)
WT-1	43 (75.57%)
Cytokeratin 5/6	33 (58.9%)
Chemotherapy at Adjuvant in Operable Patients	
Platin + Pemetrexed	14 (77.8%)
Platin+Pemetrexed+Bevacizumab	1 (5.6%)
Not Received	3(16.7%)
Chemotherapy at First Line in Inoperable Patients	
Platin + Pemetrexed	23 (60.5%)
Platin+Pemetrexed+Bevacizumab	5 (13.2%)
Platin + Gemcitabine	1 (2.6%)
Not Received	3(7.9%)
Unknown	6(15.8%)
Chemotherapy at Relapse in Operable Patients	
Pemetrexed	2 (28.5%)
Vinorelbine	1 (14.2%)
Gemcitabine	3 (42.8%)
Not Received	1 (14.2%)
Chemotherapy at Progression in Inoperable Patients	
Gemcitabine	13 (46.4%)
Platin + Gemcitabine	1 (3.5%)
Pemetrexed	2 (7.14%)
Vinorelbine	1 (3.5%)
Not Received	11(39.2%)
Adjuvant Radiotherapy	5 (8.9%)

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

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Table-3: Survival Rates

	OS (month)
All patients (n:56)	13 (9.85-16.14)
Pleural	16 (10.04-21.95)
Peritoneal	9 (6.38-11.61)
	DFS (month)
Recurrence after surgery (n:18)	12 (4.16-19.84)
	First Line PFS (month)
Non operated patients (n:38)	7 (4.93-9.06)
pleural	8 (4.04-11.98)
peritoneal	6 (3.41-8.58)

The patients with better ECOG-PS at diagnosis had longer OS. Median OS was 22 months (95% CI=16.56-27-44) for the patients with an ECOG-PS <1 at the time of diagnosis whilst it was 7 months (95% CI=3.79-10.22) for the others with ECOG-PS >2 and the difference between these two groups was statistically significant (p=0.002). While median OS was 22 months (95% CI =7.53-36.46) in the operated patients, it was 11 months (95% CI=6.97-15.02) in the non-operated patients (p=0.014). Of the patients who had progression with first line treatment, 17 patients were followed-up with best supportive care (BSC) whereas 6 patients had second line chemotherapy. When these subgroups were compared for PFS, those who had second line chemotherapy had numerically longer PFS, however, the difference was not statistically different (6 months versus 3 months, p=0.141).

Optimum cut-off values for NLR, PLR, AGR, albumin, lymphocyte count, and platelet count which predicting OS were 3.0, 200, 1.07, 3.5, 1500, and 350, respectively. Median OS was 22 months (95% CI = 7.43-36.56) for the patients with lower NLR level while it was 9 months (95% CI = 4.00-13.99) for the patients with higher NLR level (p=0.001). Median OS was 26 months (95% CI = 11.66-40.33) for the patients with lower PLR level while it was 9 months (95% CI = 4.01-13.98) for the patients with higher PLR level (p<0.001). Median OS was 9 months (95% CI= 4.15-13.84) for the patients with lower AGR level while it was 22 months (95% CI =13.33-30.66) for the patients with higher AGR level (p=0.003). OS was significantly longer in the patients with higher albumin level (>3.5 g/dL). Median OS was 19 months (95% CI = 11.21-26.78) for the patients with an albumin value of >3.5g/dL, while it was 9 months (95% CI = 6.24-11.75) for the patients with an albumin value of ≤3.5 g/dL (p=0.03). OS was significantly longer in the patients with higher lymphocyte level (18 vs 10 months, respectively; p=0.032) while it was significantly shorter in the patients with higher platelet level (10 vs 28 months, respectively; p=0.001).

Multivariate cox regression analysis was performed with lymphocyte, AGR, albumin, NLR, PLR and Platelet. Lymphocyte, Platelet count and AGR were determined as independent prognostic factors for OS according to multivariate cox regression analysis [p=0.047, HR: 0.852 (95% CI= 0.674 –0.986) for lymphocyte count; p=0.011, HR: 2.502 (95% CI =1.233 – 5.076) for platelet count; p=0.032, HR: 0.495 (95% CI =0.260–0.942) for AGR, respectyively].

Discussion

In this study, in which 56 patients with malignant pleural and peritoneal MM were investigated retrospectively in a single cancer center, it was demonstrated that lymphocyte, AGR values and platelet count at the time of diagnosis are independent prognostic factors for OS. Median age of was 65 years, and when the literature was reviewed, it was found to be higher compared to other studies that have been conducted in Turkey [1,16].

Median OS was 13 months for all population. It increased to 16 months in the pleural MM subgroup and whereas it decreased to 9 months in the peritoneal MM group. It is well-

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known that OS varies depending on the clinical characteristics of the patients with MM, such as stage at diagnosis, operability and pathological subgroups. In the series in which Dogan et al. examined patients with pleural and peritoneal MM, median OS was 22 months, while in a large series of 910 patients in which only patients with pleural MM were evaluated, median OS was determined to be 10 months [1,17]. Besides, in a study conducted on patients with peritoneal MM, median OS was determined as 11 months [18].

In the present study, the patients who were operated had a significant survival advantage when compared to those who were not operated (22 months vs. 11 months). It is well-documented that median OS in patients with pleural MM who underwent extrapleural pneumonectomy is 18 months and that a substantial number of patients achieve long-term survival [19]. In a study in which 27 patients with peritoneal MM were given intraperitoneal chemotherapy in addition to cytoreductive surgery, the 3-year survival was determined to be 67% [20]. Unlike this study, in presented study 10 out of 19 peritoneal MM patients were operated and only 4 received intraperitoneal chemotherapy.

It is well-established that the ECOG performance score is a prognostic factor in various cancers [21]. In a Taiwan study, which was conducted on patients with pleural MM, it was revealed that patients with an ECOG performance score of ≥2 had a poor prognosis [22]. Consistent with the literature, patients with low ECOG performance scores had a shorter OS in the presented study (22 months vs. 7 months). These differences in survival outcomes might be related to the heterogeneity of the studies, including the fact that some of them are retrospective, the number of patients, ECOG performance scores, pathological subtypes, operation status, whether intraperitoneal chemotherapy is given in peritoneal mesothelioma, and the difference in the chemotherapy protocols.

In the study, when the albumin levels > 3.5 and AGR >1.07 by using the ROC curve, the median OS was statistically significant at high albumin and AGR levels. Also, AGR was independent prognostic factors for OS. It is well-known that serum albumin level, which is simple, inexpensive, and widely available, is a negative acute phase reactant and decreases as inflammation increases [23]. Furthermore, as malnutrition is very common in cancer patients, serum albumin level is often used to assess malnutrition status [24]. It has been demonstrated in a study, which was conducted on various cancers, that serum albumin level is an independent predictive marker indicating malnutrition [25,26]. Total serum protein and albumin show the absorption, synthesis, and decomposition of body proteins. Moreover, albumin has anti-tumor activity and can reflect immune system functions into practice [27]. Globulin, which is the other major protein component of serum may rise in serum as a result of the accumulation of acute-phase proteins which are involved in inflammation [28]. Studies have found out that increased cytokines in cancers are associated with a rise in immunoglobulin. This situation corroborates the thesis that an elevated level of globulin may be associated with apoptosis inhibition and cancer progression [29]. Hence, the AGR derived from albumin and globulin could be used as a factor indicating cancer progression [28]. Considering these data, it was found out that increasing serum AGR before treatment in patients with malignant mesothelioma were associated with better survival, additionally AGR was also an independent prognostic factor for OS. Consistent with the presented study, pre-treatment low AGR was reported to be significantly associated with poorer OS, increased 5-year mortality rates besides higher relaps and progression rates in a meta-analysis of 15356 patients diagnosed with

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various cancer types such as gastric cancer, colorectal cancer, breast cancer, larynx carcinoma, and hepatocellular cancer [15]. Moreover, the studies including many solid tumor types at different stages demonstrated that basal AGR at diagnosis was associated with a better OS, DFS and PFS [30,31,32].

It is well-documented that hypoalbuminemia is a poor prognostic factor in many cancers [33,34]. In the presented study, a significant OS difference was determined between the patients with a serum albumin level of >3.5g/dL and those with a level of ≤3.5 g/dL (22 months vs. 9 months). In paralel to this data, pre-treatment serum albumin level was defined as an independent prognostic factor for OS in pleural MM [25]. Consistent with the presented study, studies performed in the patients with peritoneal MM also revealed poorer overall survival as the serum albumin value decreased [18, 24].

In the study, when the cut-off values for NLR, PLR, platelet and lymphocyte were taken using the ROC curve, the median OS was statistically significantly lower at high NLR, PLR and platelet levels, while the median OS was statistically significant at high lymphocyte levels. Besides platelet and lymphocyte markers were independent predictive factors for prognosis. The efficacy of these blood inflammatory parameters has been reported in numerous studies conducted on patients with MM. In a meta-analysis of 1533 pleural MM patients, it was revealed that increased NLR was associated with poorer survival rates [9]. In another study, PLR was also determinned to have prognostic significance [35]. It is well-known that platelets have a crucial role in inflammation and have a prognostic significance [36]. In a meta-analysis, pre-treatment high platelet count was shown to be associated with a poorer OS [37]. Lymphocytes act as tumor suppressors by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration [38]. Tumor-infiltrating lymphocytes can activate an effective antitumor cellular immune response [39]. Thus, as demonstrated in the presented study, increased lymphocyte counts may be associated with better survival outcomes.

This study has some limitations. It was retrospective, and a prospective multicenter study would be much better in terms of evaluating the prognostic factors of malignant mesothelioma. In this study, there is a risk of bias in some results due to the lower number of patients and missing data.

Conclusions

In this study, it has been demonstrated that AGR, platelet and lymphocyte counts are independent prognostic factors in MM. Higher albumin levels and AGR are associated with better survival. Large prospective clinical trials will provide better information and could reduce the possibility of bias.

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