A Clinical, Radiographic and Laboratory Evaluation of Prognostic Factors in 363 Patients with Malignant Pleural Mesothelioma

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Key Words

Asbestos exposure • Malignant pleural mesothelioma • C-reactive protein

Abstract

Background: Malignant pleural mesothelioma (MPM) has a poor prognosis. **Objectives:** Only few studies in literature investigated the presence of pleural fluid and radiographic findings for the prognosis of MPM. **Methods:** We retrospectively investigated the hospital charts of 363 MPM patients who were diagnosed from January 1989 to March 2010. Survival time was calculated by the Kaplan-Meier method. Pre-treatment clinical, laboratory and radiographic features of each patient at the time of diagnosis were obtained from patients' charts. **Results:** The mean age of 363 patients (217 men, 146 women) was 50.6 ± 11.2 years (range 19–85) and the mean survival time was 11.7 ± 8.6 months (range 1–53). Histological types of MPM were epithelial (71.2%), mixed (15.9%) and sarcomatous type (4.9%). The frequency of disease stages were 31.4% for stage 1, 24.2% for stage 2, 28.6% for stage 3 and 15.8% for stage 4. The most frequent symptoms were dyspnea (82.1%), chest pain (68.3%) and weight loss (58.9%). Results of univariate and multivariate analyses revealed that a Karnofsky performance score ≤ 60 , a pleural fluid glucose level ≤ 40 mg/dl, a C-reactive protein level >50

mg/l, a serum lactate dehydrogenase level >500 U/l, the presence of pleural fluid, pleural thickening >1 cm and a platelet count of $>420 \times 10^3/\mu\text{l}$ were found to be associated with poor prognosis in MPM. **Conclusions:** Our data suggest that low pleural fluid glucose and high C-reactive protein, the presence of pleural fluid and pleural thickening were associated with poor MPM prognosis. Further prospective studies are needed to highlight prognostic factors more clearly.

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Introduction

Malignant pleural mesothelioma (MPM) is a cancer basically originating from the pleura, although the pericardium, peritoneum or tunica vaginalis may be affected. The strong relationship between asbestos exposure and MPM has been recognized in the early 1960s [1, 2]. It is generally caused by environmental and occupational asbestos exposure. Also, asbestos, erionite and natural fibrous zeolite, which can be found in volcanic tuffs, have been shown to induce mesothelioma. MPM due to environmental exposure to asbestos and erionite is a relatively common pleural cancer in some areas of Turkey [3–6].

MPM is a fatal malignancy resistant to most of the current therapeutic drugs. However, some patients may respond to chemotherapy, radiotherapy or immunotherapy, and fewer selected patients may obtain benefit from radical surgery and multimodality treatment [7, 8]. The median survival for MPM was reported to be about 1 year [9–12]. Current standard first-line chemotherapy in MPM treatment consists of cisplatin and pemetrexed [13]. In one multicenter trial, it was claimed that trimodality therapy with neoadjuvant pemetrexed plus cisplatin is feasible with a reasonable long-term survival rate, particularly for patients who completed all therapies [14].

Several studies on MPM epidemiology, clinical and radiological features were published. However, there is no study on prognostic markers of MPM in our region [15–17]. The southeastern region of Turkey has a volcano, Mount Karacadag, and thus, asbestos-related diseases are common in our region [15–17].

Patients can be divided based on prognostic features, including a good or poor prognosis group. Most patients with a poor prognosis survive <4 months after diagnosis. Two-year survival ranges between 0 and 10% in MPM patients [8, 18, 19].

In several studies, the effects of clinical and laboratory parameters on MPM prognosis have been well investigated, but the contribution of pleural fluid and radiologic features on MPM prognosis has not been studied well enough [3, 8, 11, 18–21].

In this study, we aimed to investigate the effects of various pretreatment clinical and laboratory characteristics on the survival of patients with MPM, which has not been examined previously in our region.

Materials and Methods

Patients

A retrospective analysis was performed on the clinical, laboratory and radiological data of 363 patients with MPM who were registered and followed up in our hospital from January 1989 to March 2010. The local ethical committee approved the study protocol. Histological evaluation was performed on either surgical and/or necropsy material and patients with histologically proven MPM were included. Histochemical or immunohistochemical stains were used if necessary. Certain laboratory, clinical and radiographic variables were defined as potential prognostic factors and measured at the time of diagnosis.

After histopathological diagnosis, stage was determined. Chest, cranial and abdominal computed tomography (CT) was performed, and CT scan images were evaluated by a radiologist. Because some patients did not allow thoracoscopy, MPM staging was done according to the Butchart staging system [22].

Pleural effusion was evaluated at time of diagnosis and before pleurodesis was performed. All of the pleural fluids were exudates. We confirmed the presence of pleural fluid when pleural fluid was seen on chest radiography or when pleural fluid thickness was >0.5 cm on chest ultrasonography.

The following pretreatment characteristics were evaluated for prognostic evaluation. We registered clinical and laboratory characteristics, such as age (≤ 60 or >60 years), gender, asbestos exposure (yes or no), disease location (right, left, bilateral), histopathological subtype (epithelial or others), symptom duration (≤ 6 or >6 months), smoking history (yes or no), Karnofsky performance score (KPS, ≤ 60 or >60), stage (stage I–II or stage III–IV), presence of chest pain, dyspnea, weight loss ($>5\%$ in the last 3 months), pleural effusion, platelet count ($\leq 420,000$ or $>420,000/\mu\text{l}$), white blood cell (WBC) count ($\leq 11,300$ or $>11,300/\mu\text{l}$), hemoglobin concentration (<12.30 or ≥ 12.30 g/dl), levels of serum and pleural effusion lactate dehydrogenase (LDH, ≤ 500 or >500 U/l), serum alkaline phosphatase (ALP, ≤ 79 or >79 U/l), concentrations of pleural fluid glucose (≤ 40 or >40 mg/dl), C-reactive protein (CRP, ≤ 50 or >50 mg/l) level, and pleural thickening defined on the chest CT (measurement was done of thickest pleural area ≤ 1 or >1 cm). In this study, median values of laboratory measurements were used for statistical analysis.

Most of our patients had environmental asbestos exposure, were young and only 32 patients were >70 years of age. Therefore, the cut-off for age was set at 60 years. Pleural fluid was obtained from 330 patients.

Statistical Analysis

Mean values and standard deviation were calculated for continuous variables. The normality of the variables was analyzed by the Kolmogorov-Smirnov test. Duration of survival, median and mean event times with 95% confidence intervals (CIs) were estimated according to the Kaplan-Meier method. Duration of survival was defined as the period between the time of diagnosis and the time of death, or if patients were still alive, survival was defined as the period between the time of diagnosis and March 2010.

The proportional hazards regression model with stratification for the clinical trial was used for both univariate and multivariate analyses. Univariate analyses examined the prognostic importance of all factors mentioned above. The Cox proportional hazards model was used to examine variables. A 2-sided test was used, with a 0.05 level of significance. Comparisons for overall survival were made using 2-tailed log-rank tests. Only variables with p values <0.05 in univariate analysis were taken into the final model for multivariate analysis.

In the Cox regression analysis, the ‘backward conditional’ method was used. Significance was taken as $p < 0.05$. Of all patients, 26 were alive during this study. Statistical analyses were performed using SPSS statistical program version 11.

Results

Patient Characteristics

A total of 363 patients [217 (60%) men, 146 (40%) women] with a mean age of 50.6 ± 11.2 years (range 19–85) were included. Environmental asbestos exposure was de-

Fig. 1. Kaplan-Meier survival curves according to the presence of pleural fluid ($p < 0.001$; $n = 353$).

Fig. 2. Kaplan-Meier survival curves according to the presence of pleural thickening ($p < 0.001$; $n = 353$).

Table 1. Demographic features of MPM patients

Features	n	%
Patients	363	100
Gender		
Male	217	60
Female	146	40
Asbestos exposure	309	85.1
Primary site of disease		
Right	220	60.6
Left	119	32.7
Bilateral	24	6.7
Symptoms at diagnosis		
Dyspnea	298	82.1
Chest pain	248	68.3
Weight loss	214	58.9
Current smokers ($n = 363$)	160	44.1
Positive cytology in pleural effusion ($n = 312$)	102	32.7
Type of MPM		
Epithelial	258	71.2
Mixed	58	15.9
Unidentified	29	7.9
Sarcomatous	18	4.9
Stage of disease		
Stage 1	114	31.4
Stage 2	88	24.2
Stage 3	104	28.6
Stage 4	57	15.8

tested in 85.1% of the patients, and the mean exposure duration was 32.5 ± 14.9 years. Histological types of MPM were epithelial in 71.2% of patients, mixed type in 15.9% and sarcomatous type in 4.9%. The primary site of disease was right in 60.6%, left in 32.7% and bilateral in 6.7% of patients. The frequency of disease stage was as follows: stage 1 in 31.4%, stage 2 in 24.2%, stage 3 in 28.6% and stage 4 in 15.8% of patients. The most frequent symptoms were dyspnea (82.1%), chest pain (68.3%) and weight loss (58.9), and the mean duration of symptoms was 5.5 ± 4.8 months. The mean KPS was 62.8 (range 50–80) (table 1).

Diagnostic methods were closed pleural biopsy in 250 (70.8%) patients and open pleural biopsy in 103 (29.2%). The mean erythrocyte sedimentation rate was 69.7 ± 21.9 mm/h.

Peritoneal invasion was detected in 12 and pericardial invasion in 2 patients. The mean survival time was 11.7 ± 8.6 months (range 1–53).

Univariate Analyses

Twenty-two parameters that we expected to be associated with prognosis were used in univariate analysis. Significant poor prognostic factors were nonepithelial histological subtype, positive smoking history, $KPS \leq 60$, disease stage III–IV, presence of chest pain, platelet count $>420,000/\mu\text{l}$, WBC count $>11,300/\mu\text{l}$, level of hemoglobin <12.30 g/dl, serum and pleural LDH >500 U/l, serum ALP >79 U/l, CRP >50 mg/l, pleural fluid glucose ≤ 40 mg/dl, presence of pleural effusion, and pleural thickening.

Table 2. Result of univariate analysis for potential prognostic patient characteristics

Variable	O/N ¹	%	Median survival months	95% CI	p value	Variable	O/N ¹	%	Median survival months	95% CI	p value
Age						Hemoglobin					
≤60 years	245/262	0.95	11.8	13.02–14.98	0.158	>12.30 g/dl	193/200	0.96	11.00	10.07–11.93	0.319
>60 years	92/101	0.93	8.8	6.98–11.02		≤12.30 g/dl	144/163	0.92	8.00	6.69–9.31	
Gender						Platelet count					
Male	203/217	0.95	9.30	8.03–10.97	0.328	≤420 × 10 ³ /μl	150/162	0.97	14.00	13.21–14.79	0.000
Female	134/146	0.93	10.00	8.53–11.47		>420 × 10 ³ /μl	187/201	0.92	7.00	6.26–7.74	
Asbestos exposure						WBC count					
Present	290/309	0.95	10.00	9.02–10.98	0.172	≤11,300/μl	238/259	0.94	11.00	9.70–12.30	0.019
Absent	47/54	0.90	10.00	6.59–13.41		>11,300/μl	99/104	0.94	9.00	7.24–10.76	
Smoking						ALP					
Never	150/159	0.96	10.50	8.54–12.46	0.007	≤79 U/l	144/157	0.92	14.00	13.03–14.97	0.000
Ever	187/204	0.93	9.00	7.53–10.47		>79 U/l	193/206	0.96	8.00	7.28–8.72	
Stage						Pleural fluid glucose level					
I–II	179/202	0.90	14.00	13.07–14.92	0.000	≤40 mg/dl	183/189	0.97	8.00	7.51–8.49	0.000
III–IV	158/161	0.99	7.00	6.29–7.71		>40 mg/dl	126/141	0.89	14.00	12.53–15.47	
KPS						Pleural fluid pH					
<60	167/173	0.98	7.00	6.40–7.60	0.000	>7.2	157/169	0.97	14.00	12.99–15.01	0.000
≥60	170/190	0.91	15.00	13.95–16.05		≤7.2	152/161	0.92	7.00	6.30–7.70	
Histopathological type						Pleural thickening on thoracic CT					
Epithelial	241/258	0.93	11.00	9.88–12.12	0.018	≤1 cm	138/150	0.93	17.00	15.37–18.63	0.000
Others	96/105	0.96	8.00	6.13–9.87		>1 cm	199/213	0.95	7.00	6.42–7.58	
Pleural fluid cytology						CRP					
Positive	98/102	0.99	9.00	7.47–10.53	0.212	≤50 mg/l	114/134	0.87	17.00	15.20–18.80	0.000
Negative	239/261	0.92	11.00	9.53–12.47		>50 mg/l	223/229	0.98	8.00	7.36–8.64	
Duration of symptoms						Pleural effusion					
≤6 months	204/216	0.96	10.00	8.67–11.33	0.955	Yes	310/330	0.94	9.00	8.02–9.98	0.000
>6 months	133/147	0.92	11.00	9.29–12.71		No	27/33	0.98	20.00	16.18–23.82	
Chest pain						Serum LDH level					
Ever	234/248	0.95	8.1	9.15–12.85	0.013	≤500 U/l	93/101	0.97	13.00	12.11–13.89	0.000
Never	104/115	0.91	9.5	8.77–11.23		>500 U/l	244/262	0.93	6.00	5.31–6.69	
Dyspnea						Pleural fluid LDH					
Ever	274/298	0.93	10.00	8.90–11.10	0.086	≤500 U/l	116/126	0.89	13.50	12.52–14.48	0.000
Never	63/65	0.98	12.00	9.89–14.12		>500 U/l	193/204	0.97	8.00	7.51–8.49	
Weight loss											
Ever	207/214	0.98	10.00	8.83–11.17	0.065						
Never	130/149	0.88	11.00	9.55–12.45							

¹ Observed death number/total patient number.

ing >1 cm ($p < 0.05$ for each variable). Variables with $p < 0.05$ in univariate analysis were taken into the final model for multivariate analysis (table 2).

No associations were found between MPM prognosis and age, gender, asbestos exposure, pleural fluid cytology, duration of symptoms, presence of dyspnea, weight loss and level of hemoglobin ($p > 0.05$ for each variable) (table 2).

Multivariate Analyses

According to multivariate analysis results, a KPS ≤60 increased poor prognosis 2.25 times, pleural fluid glucose level ≤40 mg/dl 1.73 times, CRP >50 mg/l 1.56 times,

serum LDH >500 U/l 2.24 times, presence of pleural fluid 2.90 times, pleural thickening >1 cm 2.15 times and platelet count >420 × 10³/μl 1.33 times in MPM patients (table 3). Our data and those of previous studies that investigated prognostic factors in MPM are shown in table 4.

The survival curves of the patients for the presence of pleural effusion, pleural thickening, serum CRP level and pleural effusion glucose level are presented in figures 1–4.

Fig. 3. Kaplan-Meier survival curves according to the presence of the CRP level ($p < 0.001$; $n = 353$).

Fig. 4. Kaplan-Meier survival curves according to the pleural glucose level ($p < 0.001$; $n = 320$).

Discussion

In an asbestos-containing area, exposure to environmental asbestos and erionite starts at birth. Therefore, occupational cases of MPM are seen among an older population. The mean age is around 60–65 years in patients with occupational exposure [23–25].

In our region, asbestos exposure is mostly environmental [15–17] and begins at birth. Therefore, MPM is detected at earlier ages. In one study performed in this region, the mean age of patients was 52.4 years [15]. The mean age of MPM patients in our study is relatively low, probably as a result of regional environmental asbestos exposure.

In spite of several available treatment regimens, MPM still is a disease with a poor prognosis. The mean survival time of MPM patients is 6–12 months [18–21, 24, 26, 27], and in our study, 12 months.

The Cancer and Leukemia Group B and the European Organization for Research and Treatment of Cancer have analyzed large numbers of patients enrolled in MPM trials and have identified the following poor prognostic factors for MPM [28]: nonepithelioid histology, poor performance status, chest pain, age >75 years, male gender, $WBC \geq 8.3 \times 10^9/l$, platelet number $>400,000/\mu l$, and $LDH >500 IU/l$.

In other studies, the prognostic factors associated with MPM were older age [20, 21, 28], male gender [18, 19, 21], advanced stage [18], nonepithelioid histology [18, 19, 21, 26], thrombocytosis [18, 29], higher serum LDH level [20],

Table 3. Multivariate stepwise model

Variable	Hazard ratio	95% CI	p value
KPS			
≥60	1	1.623–3.118	0.001
<60	2.25		
Pleural fluid glucose level			
>40 mg/dl	1	1.222–2.451	0.002
≤40 mg/dl	1.73		
CRP			
≤50 mg/l	1	1.139–2.105	0.005
>50 mg/l	1.56		
Serum LDH level			
≤500 U/l	1	1.585–3.168	0.001
>500 U/l	2.24		
Pleural effusion			
No	1	1.869–4.527	0.001
Yes	2.90		
Pleural thickening on chest CT			
≤1cm	1	1.520–3.025	0.001
>1cm	2.15		
Platelet count			
≤420 × 10 ³ /μl	1	1.009–1.757	0.043
>420 × 10 ³ /μl	1.33		

higher WBC count [18, 19], lower hemoglobin level [18] and poor performance status [18–20, 26] (table 4). Prognostic parameters, such as a lower KPS, a higher serum LDH level and thrombocytosis accepted in literature, were also considered to be prognostic factors in this study.

Table 4. Suggested prognostic factors for MPM in the present and previous studies

	This study	Metintaş et al. [20]	Curran et al. [19]	Herndon et al. [28]	Edwards et al. [18]	Montanaro et al. [21]	Borasio et al. [27]	Gorini et al. [26]	Spirtas et al. [29]	Manzini et al. [31]
Patients	363	100	204	337	142	4,100	394	381	1,475	80
Age	–	+	–	+	–	+	–	–	+	–
Gender	–	–	+	–	+	+	–	–	+	–
Stage	–	+	–	–	–	Ø	Ø	Ø	+	+
Smoking	–	–	Ø	–	Ø	Ø	–	Ø	Ø	Ø
Histological type	–	–	+ (sarco- matous)	+ (non- epithelial)	+ (non- epithelial)	+	+ (non- epithelial)	+	Ø	+
Dyspnea	–	–	Ø	–	Ø	Ø	Ø	Ø	Ø	–
Symptom time	–	Ø	Ø	–	Ø	Ø	– (4 months)	Ø	Ø	–
Platelet count	+	–	–	+	–	Ø	+	Ø	+	–
Pleural fluid glucose	+	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
Serum LDH	+	+ (>500 U/l)	–	+ (>500 U/l)	Ø	Ø	Ø	Ø	Ø	Ø
Hemoglobin	–	–	–	–	+ (<14 g/dl)	Ø	Ø	Ø	Ø	Ø
Chest pain	–	–	Ø	+	–	Ø	–	Ø	Ø	–
Weight loss	–	–	Ø	–	–	Ø	–	Ø	Ø	–
Performance status	+ (KPS <60)	+ (KPS <70)	+ (ECOG)	+ (ECOG)	+ (ECOG)	Ø	+ (KPS <80)	Ø	Ø	–
Presence of pleural fluid	+	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	– ¹
CRP level	+	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	–
Pleural thickening	+	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	–
Pleural LDH level	–	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	–
Pleural fluid cytology	–	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	– (ECOG)
Serum ALP level	–	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
WBC count	–	Ø	+	–	+	Ø	Ø	Ø	Ø	Ø
Pleural fluid pH	–	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
Primary site of tumor	Ø	–	Ø	Ø	Ø	Ø	–	Ø	Ø	–
Asbestos exposure	–	–	–	–	–	–	–	–	Ø	Ø

+ = Significant; – = not significant; Ø = not studied; ECOG = Eastern Cooperative Oncology Group.

¹ Presence of pleural fluid and pleural fluid cytology were studied together.

Overall, other studies have not detected any significant correlation between prognosis of MPM and duration of symptom time and symptoms (table 4). In this study, no significant correlations between the prognosis of MPM and the duration of symptom time, dyspnea, weight loss and chest pain were found.

Factors that have not been taken into consideration in earlier prognostic studies and which we thought could have potential effective prognostic value, such as serum ALP level and pleural fluid cytology, did not show any prognostic value.

Previously, a positive pleural fluid cytology was detected in about one third of MPM patients, similar to our results. However, contrary to our study, in other studies, tumor cells in pleural fluid had not been considered a prognostic factor [30].

The prognostic parameters determined to be significant or insignificant as well as their comparison with other large MPM studies are shown in table 4. As can be seen

in our study results, the presence of pleural fluid, a high CRP level and pleural thickening were shown to be poor prognostic factors for the first time.

In our study, the presence of pleural fluid was established as a prognostic factor, in contrast with previous studies. We think that the presence of pleural fluid shows invasion of pleural surface by MPM cells, and thus, expansion of this disease into the pleural cavity. In one study, the presence of pleural fluid with mesothelial cells but without neoplastic cells was found to be a favorable prognostic factor. However, in that study, the presences of pleural fluid and pleural fluid cytology were studied together [31]. We believe that the presence of pleural fluid especially with a positive cytology is associated with a poor prognosis.

In a Turkish study on pleural fluid parameters of 71 MPM patients, a lower pleural fluid glucose level was found to be associated with poor prognosis [32]. In another study, performed on 26 patients, to evaluate pleural

fluid parameters, it was reported that the pleural fluid glucose level and pleural fluid pH were associated with MPM prognosis [33]. In our study, we found that a lower pleural fluid glucose level was also associated with a poor prognosis of MPM. On the other hand, we could not find any significant relationship between prognosis and pleural fluid pH and pleural LDH level. MPM cells are using pleural glucose for their metabolic activity. Therefore, in our opinion, lower pleural fluid glucose levels lead to higher activity of MPM and this reflects a poor prognosis.

CRP is an acute-phase reactant, and it is increased in inflammatory cases. In our study, a higher CRP level was correlated with a poor prognosis of MPM. In several prognostic studies carried out on lung cancer patients, a significant relationship was detected between a higher CRP level and a poor prognosis of lung cancer, suggesting that the CRP level could be used as a prognostic marker of lung cancer patients [34, 35]. To our knowledge, this is the first study to investigate the relationship between CRP and MPM prognosis. The CRP test is inexpensive and can be used for the follow-up of prognosis.

For pulmonary and pleural abnormalities, the most commonly used imaging method is chest CT. In MPM, pleural thickening is the most frequently detected abnormality on chest CT, seen in variable types and sizes [37, 38]. Pleural thickening of more than 1 cm is a specific MPM finding on chest CT [30]. In this respect, we investigated pleural thickening to find out how it affects MPM survival and found it to be significant. As shown in sev-

eral studies, pleural thickening appears to be a remarkable finding of MPM, and an increase in thickening raises the tumor burden in the pleural area. As a result, patients with a thicker pleura have a poorer survival. In one MPM study, an association between the degree of pleural involvement and MPM prognosis was detected during thoracoscopy [27].

One limitation of our study is its retrospective nature. Another limitation is that some markers were not studied. Soluble mesothelin-related peptide, osteopontin and megakaryocyte potentiating factor have been studied for mesothelioma prognosis [39]. These and other promising markers can be studied in new clinical trials.

In conclusion, MPM still is a disease with poor prognosis. We have very few parameters to estimate MPM prognosis, such as pleural fluid glucose, platelet count and WBC counts. The number of studies that have investigated the effect of pleural fluid and radiographic findings on the prognosis of MPM is very limited. In this study, new parameters that could have an effect on MPM prognosis were discussed. Significant predictors of survival include KPS, platelet count, pleural fluid glucose level, serum CRP and LDH level, the presence of pleural fluid and pleural thickening. Understanding the importance of these markers for MPM prognosis should allow targeted treatments to be developed.

Therefore, we believe that studies of large series are needed to investigate the relationship between prognostic markers and treatment regimens.

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