Original Article

The role of LENT and PROMISE scores in predicting survival in malignant pleural effusion

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ABSTRACT

Background: Malignant pleural effusion (MPE) is a condition, that can be seen in 15% of patients diagnosed with cancer. Because of the short overall survival, it is important to identify the appropriate treatment. In addition to the palliation of secondary symptoms due to MPE, it should also be decided in which cases a more aggressive treatment is to be followed. The purpose of the study was to evaluate the performance of LENT and clinical PROMISE scores in predicting survival in patients with MPE. **Methods:** Age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) score, cancer type, history of chemotherapy/radiotherapy, laboratory values, and pleural fluid lactate dehydrogenase were recorded. The LENT and the PROMISE scores were calculated and risk categories were determined. During the follow-up, blood tests and tomography controls were performed on the patients as routine. The overall survival was calculated as the period from the date of diagnosis of MPE to death or until December 31, 2019. **Results:** A total of 169 patients were included. The median age was 65 (26–86). In the single-variable analysis, there was a significant increase in mortality risk in the poor performance score and if the LENT risk group progressed from the low-to medium-/high-risk group or PROMISE categories A to B, A to C or A to D. In multivariate analysis, mortality risk in 1, 3, 6, and 12 months increased significantly in poor performance score, in PROMISE category B, C, and D. In high LENT risk-group, an increased mortality risk was shown in only 12 months of survival. **Conclusions:** Our data show that poor performance score (ECOG 3-4), PROMISE category B, C, and D significantly increase mortality risk and the LENT score is inadequate in predicting survival.

KEY WORDS: Eastern Cooperative Oncology Group, LENT, malignant pleurisy, PROMISE, survival

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INTRODUCTION

Malignant pleural effusion (MPE) is a condition that can be seen in 15% of patients diagnosed with cancer and often shows metastatic disease.[1,2] It is diagnosed by observing malignant cells in the pleura and/or pleural fluid.[3] It is most commonly observed in lung cancer and may also develop because of breast cancer, lymphoma, gynecological cancers, and malignant mesothelioma.[4,5] MPE can be seen at the time of diagnosis, especially in 15% of patients diagnosed with lung cancer.[6] MPE may also exist at the time of diagnosis of malignant disease or develop during the follow-up process, in both cases as an indication of poor prognosis.[5] High lactate dehydrogenase (LDH) levels, poor performance

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score (Eastern Cooperative Oncology Group [ECOG]: 3–4), elevated neutrophil/lymphocyte ratios, and low-pH in pleural fluid are indicators of poor prognosis in patients with MPE.[7] Overall survival after being diagnosed with MPE is on an average 3–12 months.[1]

Because of the short overall survival, it is important to identify the appropriate treatment protocol in patients with MPE. In addition to the palliation of secondary symptoms due to MPE, it should also be decided in which cases a more aggressive treatment is to be followed. The choice of proper treatment according to the expected survival of patients is a way to apply in everyday practice. In a study that examined the cost of treatment in patients with MPE, it was reported that more cost-effective treatments can be planned by using parameters that predict survival.[8] Recently, it has been suggested to use scoring systems instead of a single marker in studies on prognostic indicators that will determine survival in MPE patients. The LENT (pleural fluid LDH, ECOG, neutrophil/lymphocyte ratio, tumor type) scoring system was the first to be developed and was found to be superior in predicting survival compared with ECOG.[9] Another scoring system is the clinical and biological PROMISE scoring system, which was found to be superior in predicting survival compared to the ECOG and LENT scores.[10]

The purpose of the study was to evaluate the performance of LENT and clinical PROMISE scores in predicting survival in patients with MPE.

MATERIALS AND METHODS

The study was planned retrospectively. The medical data of the patients who were diagnosed with MPE cytologically/pathologically admitted to our clinic between January, 01, 2010, and December 31, 2019, were obtained from the hospital information management system. The MPE diagnosis was obtained with thoracentesis or closed pleural biopsy or video-assisted thoracic surgery, according to the patient's condition and the preference of the clinician. Closed pleural biopsy was done blind. These were the inclusion criteria:
1. Patients over the age of 18 diagnosed with MPE cytologically/pathologically
2. Sufficient clinical data in the hospital information management system
3. Presence of hemogram and C-reactive protein (CRP).

These were the exclusion criteria:
1. Patients who did not have MPE diagnosed cytologically/pathologically
2. Patients admitted to MPE without cytological/pathological evaluation
3. Lack of adequate clinical data in the hospital information management system.

Age, sex, smoking history, ECOG score, cancer type, presence of pleural fluid during diagnosis or follow-up,

history of chemotherapy/radiotherapy, laboratory values (white blood cells, neutrophils, lymphocytes, hemoglobin, CRP), and pleural fluid LDH values of the patients were recorded. The ECOG scores of the patients were obtained from the records in the hospital information management system (i.e., physical examination, health board information). The LENT and the PROMISE scores were calculated and risk categories were determined. During the follow-up, blood tests and tomography controls were performed on the patients as routine. Overall survival was calculated as the period from the date of diagnosis of MPE to death or until December 31, 2019. Approval for this study was obtained from the hospital scientific evaluation board (01.11.2019-49109414-604.02).

The LENT score consists of 4 different variables [Table 1]. It predicts survival for 1, 3, and 6 months.[9] The PROMISE score includes two different scoring as clinical and biological and determines the risk of death of 3 months.[10] As the tissue inhibitor of metalloproteinase-1 (TIMP1), which is considered in the contents of the biological PROMISE score, cannot be carried out in our hospital, only the clinical PROMISE score was used in our study [Table 2].

Statistical analysis
The data obtained in the study were entered into the database that was created in SPSS version 18 (SPSS Inc. Chicago, IL, USA). The statistical analysis of the data was performed with the SPSS and MedCalc package programs. Categorical variables are presented as frequencies and percentages. The variables affecting survival were prepared in cross-tables and the diagnostic marker values were calculated. The Kaplan–Meier method was used in survival analysis, and intergroup survival comparisons were made with the log-rank test. The examination of factors that

Table 1: LENT score and risk category

	Variable	Score
L	Pleural fluid LDH level	
	<1500	0
	≥1500	1
E	ECOG performance score	
	0	0
	1	1
	2	2
	3-4	3
N	NLR	
	<9	0
	≥9	1
T	Tumor type	
	Mesothelioma-hematological cancer	0
	Breast-kidney-gynecological cancer	1
	Lung cancer and other cancer	2
Risk category		
Low risk: (score: 0-1)		
Moderate risk: (score: 2-4)		
High risk: (score: 5-7)		

‡It is an excerpt from the literature number 9.
NLR: Neutrophil/lymphocyte ratio, LDH: Lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group

Table 2: The clinic PROMISE score and risk category

Variable	Score
Chemotherapy	
No	0
Yes	4
Radiotherapy	
No	0
Yes	2
Hemoglobin (g/dL)	
>16	0
14-16	1
12-14	2
10-12	3
<10	4
White blood cell (10^9 cells/L)	
<4	0
4-6.3	2
10	4
10-15.8	7
>15.8	10
C-reactive protein (IU/L)	
<3	0
3-10	3
10-32	5
32-100	8
>100	11
ECOG performance status	
0-1	0
2-4	7
Cancer type	
Mesothelioma	0
Other cancer type	4
Lung cancer	5
Risk category	
Category A: <25% (score: 0-20)	
Category B: 25%-50% (score: 21-27)	
Category C: 50%-75% (score: 28-35)	
Category D: ≥75% (score: >35)	

†It is an excerpt from the literature number 10. ECOG: Eastern Cooperative Oncology Group

affected mortality was performed according to Wald value Cox regression analysis with backward step method. The first-type error share was determined as α: 0.05 in all tests and was tested in a bilateral way. The difference between groups was considered to be statistically significant if the value of $P < 0.05$.

RESULTS

A total of 183 patients with the diagnosis of MPE were admitted during the study period. Fourteen patients were excluded from the study because of inadequate laboratory data. Only 169 patients were included in the study after applying the inclusion and exclusion criteria. The median age was 65 (26–86) in the study group. A total of 115 (68%) patients were male and 54 (32%) were female. Among the 94 patients whose smoking status was learned, 72 (76.6%) were smokers (current or former) and 22 (23.4%) were never-smokers. The smoking status of 75 patients could not be obtained. In patients with a smoking history, the intensity of smoking was calculated as the median 45 (2–150) package/year. The primary tumor type of the patients diagnosed with MPE was lung

with 135 (79.9%) patients, mesothelioma with 16 (9.5%) patients, and breast with 9 (5.3%) patients. MPE was detected in 127 (75.1%) patients at the time of diagnosis and in 42 (24.9%) patients during follow-up. At the end of the 1-year data screening, 142 patients (84%) died and 27 (16%) patients are still alive. The demographic features were presented in Table 3.

The median overall survival of all patients was calculated to be 4 months (95% confidence interval [CI], 2.97–5.03).

A total of 65 (38.5%) patients had ECOG scores of 3–4, and 104 (61.5%) had ECOG scores of 0-1-2. In the single-variable log-rank (Mantel-Cox) analysis that was made by using the ECOG score, the median survival of patients with ECOG 3–4 was found to be 1 month (95% CI, 0.89–1.10) and that of patients with ECOG 0-1-2 was found to be 8 months (95% CI, 5.05–10.94) $(P < 0.001)$ [Figure 1].

In the risk assessment made according to the LENT score, 15 (8.9%) patients were in the low-risk group, 86 (50.9%) patients were in the moderate-risk group, and 68 (40.2%) patients were in the high-risk group. According to the single-variable log-rank (Mantel-Cox) analysis that was made by using LENT score, the median survival of low-risk patients was found to be 27 months (95% CI, 24.03–29.96); the median survival of moderate-risk patients was 7 months (95% CI, 4.80%–9.19%) and the median survival of high-risk patients was 1 month (95% CI, 0.79–1.20) and survival decreased significantly as the risk increased according to LENT score $(P < 0.001)$ [Figure 1].

In the risk assessment that was made according to the PROMISE score, 66 (39.1%) patients were found to be in category A, 59 (34.9%) patients were in category B, 40 (23.7%) patients were in category C, and 4 (2.4%) patients were in category D. In the single-variable log-rank (Mantel-Cox) analysis that was made by using the PROMISE score, the median survival of patients with category A was found to be 11 months (95% CI, 7.82–14.18), the median survival of patients with category B was 2 months (95% CI, 0.75–3.25), the median survival of patients with category C was 1 month (95% CI, 0.77–1.22), and the median survival of patients with category D was 0.5 months (95% CI, 0.01%–0.99%) $(P < 0.001)$ [Figure 1].

The ECOG score, LENT risk categories and PROMISE categories were included in multivariate cox backward stepwise analysis, and the effect of the independent variables on survival at 1, 3, 6, and 12 months was investigated.

Poor performance score (hazard ratio (HR), 3.77; 95% CI, 1.94–7.33; $P = 0.000$), PROMISE category B (HR, 4.14; 95% CI, 1.39–12.39; $P = 0.011$), category C (HR, 5.81; 95% CI, 1.92–17.54; $P = 0.002$) and category D (HR, 31.97; 95% CI, 7.0–146.06; $P < 0.001$) caused increase in 1-month mortality risk. The LENT score did not have effects on 1-month life [Table 4].
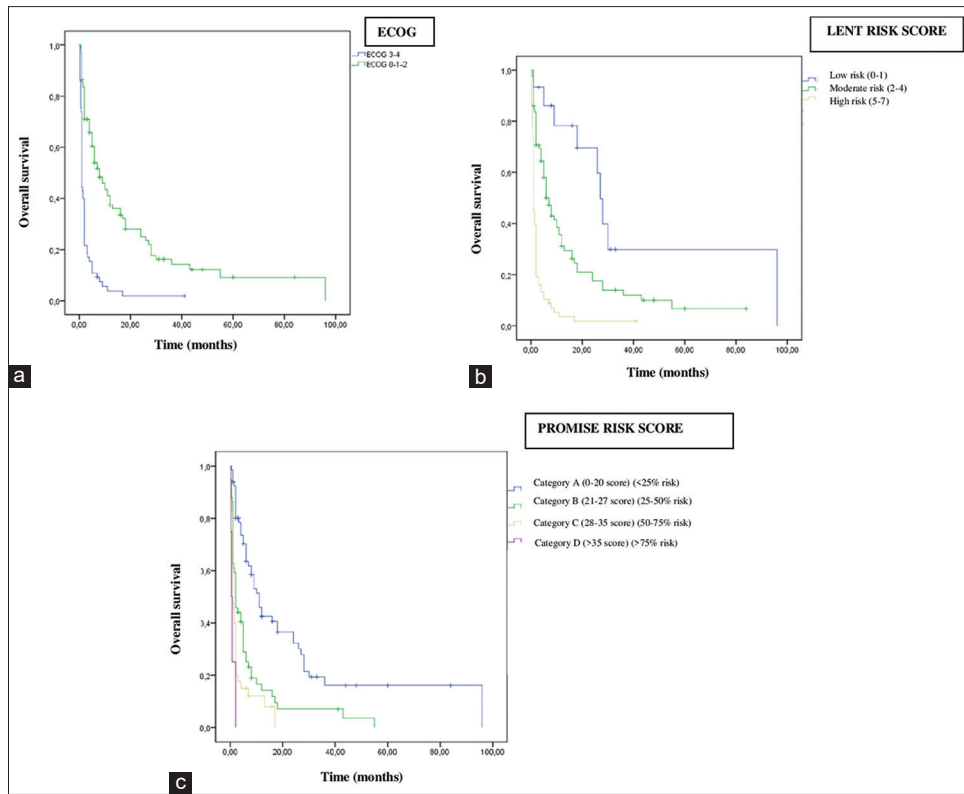
Figure 1: The role of Eastern Cooperative Oncology Group, LENT and PROMISE risk scores in patients with malignant pleural effusion. (a) Kaplan-Meier survival curves for Eastern Cooperative Oncology Group, (b) Kaplan-Meier survival curves for patients with low, moderate, and high LENT risk groups (c) Kaplan-Meier survival curves from patients classified into PROMISE categories for the clinical PROMISE score

Table 3: Demographic characteristics of patients

	n (%)
The number of the patients	169
Median age	65 (26-86)
Male/female	115 (68)/54 (32)
Smoking history (+/−)	72 (76.6)/22 (23.4)
The intensity of smoking (package/year)	45 (2-150)
The primary tumor type	
Lung carcinoma	135 (79.9)
Mezothelioma	16 (9.5)
Breast cancer	9 (5.3)
Gynecological cancer	6 (3.6)
Gastric cancer	1 (0.6)
Hematological cancer	1 (0.6)
Malignant melanoma	1 (0.6)
Presence of pleural fluid	
At diagnosis	127 (75.1)
During follow-up	42 (24.9)
ECOG	
0	36 (21.3)
1	29 (17.2)
2	39 (23.1)
3-4	65 (38.5)
Chemotherapy	
Yes	104 (61.5)
No	65 (38.5)
Radiotherapy	
Yes	57 (33.7)
No	112 (66.3)

ECOG: Eastern Cooperative Oncology Group

Poor performance score (HR, 3.38; 95% CI, 2.07–5.50; $P < 0.001$), PROMISE category B (HR, 2.37; 95% CI, 1.21–4.61; $P = 0.011$), category C (HR, 4.07; 95% CI, 2.07–7.99; $P < 0.001$), and category D (HR, 17.07; 95% CI, 5.47–53.30; $P < 0.001$) increased 3 months mortality risk. The LENT score did not have effects on 3 months life [Table 4].

Poor performance score (HR, 2.84; 95% CI, 1.85–4.36; $P < 0.001$), PROMISE category B (HR, 2.10; 95% CI, 1.23–3.60; $P = 0.006$), category C (HR, 3.15; 95% CI, 1.79–5.55; $P < 0.001$), and category D (HR, 13.06; 95% CI, 4.40–38.77; $P < 0.001$) caused increase in 6 months mortality risk. The LENT score did not have effects on 6 months life [Table 5].

Poor performance score (HR, 2.71; 95% CI, 1.81–4.05; $P < 0.001$), PROMISE category B (HR, 1.95; 95% CI, 1.22–3.10; $P = 0.005$), category C (HR, 2.76; 95% CI, 1.65–4.61; $P < 0.001$), and category D (HR, 11.21; 95% CI, 3.86–32.59; $P < 0.001$) increased 12 months mortality risk. A high LENT risk group was shown to increase only the 12 months mortality risk (HR, 4.42; 95% CI, 1.04–18.90; $P = 0.045$) [Table 5].

DISCUSSION

In single-variable analysis in the group of patients with MPE, there was a significant increase in mortality risk in poor performance score and if the LENT risk group progressed from low to medium/high-risk group or PROMISE category A to B, A to C, or A to D. According to

Table 4: Multivariate cox backward stepwise analysis of Eastern Cooperative Oncology Group, LENT score and PROMISE categories for 1 and 3 months survival

	1 month		*P*	3 months		*P*
	HR	95% CI		HR	95% CI	
ECOG						
3-4 versus 0-2	3.77	1.94-7.33	0.000	3.38	2.07-5.50	0.000
PROMISE category						
B versus A	4.14	1.39-12.39	0.011	2.37	1.21-4.61	0.011
C versus A	5.81	1.92-17.54	0.002	4.07	2.07-7.99	0.000
D versus A	31.97	7.0-146.06	0.000	17.07	5.47-53.30	0.000
LENT score						
Moderate versus low	0.59	0.06-5.76	0.647	2.67	0.34-20.76	0.347
High versus low	0.62	0.05-7.69	0.711	4.63	0.49-43.68	0.180

ECOG: Eastern Cooperative Oncology Group, CI: Confidence interval, HR: Hazard ratio

Table 5: Multivariate Cox backward stepwise analysis of Eastern Cooperative Oncology Group, LENT score and PROMISE categories for 6 and 12 months survival

	6 months		*P*	12 months		*P*
	HR	95% CI		HR	95% CI	
ECOG						
3-4 versus 0-2	2.84	1.85-4.36	0.000	2.71	1.81-4.05	0.000
PROMISE category						
B versus A	2.10	1.23-3.60	0.006	1.95	1.22-3.10	0.005
C versus A	3.15	1.79-5.55	0.000	2.76	1.65-4.61	0.000
D versus A	13.06	4.40-38.77	0.000	11.21	3.86-32.59	0.000
LENT score						
Moderate versus low	2.82	0.66-12.11	0.163	3.26	0.99-10.72	0.051
High versus low	3.88	0.72-20.94	0.115	4.42	1.04-18.88	0.045

ECOG: Eastern Cooperative Oncology Group, CI: Confidence interval, HR: Hazard ratio

multivariate analysis results, mortality risk in 1, 3, 6, and 12 months increased significantly in poor performance score, in PROMISE category B, category C, and category D. In high LENT risk group, an increased mortality risk was shown in only 12 months of survival.

The LENT score was first developed by Clive *et al*. in 2014 as a prognostic scoring system used to predict survival in patients with MPE.[9] In a study conducted with 789 patients, the primary tumor types were lung cancer, breast cancer, and mesothelioma, which was similar to our study. The average age was similar to our study (66.3). The majority of patients were male, which was also similar to our study. In the 1, 3, and 6 months mortality analyses, the LENT score showed more significant results in predicting survival based on the ECOG score (*P* = 0.005, *P* < 0.001, *P* = 0.001, respectively).[9] Similar results were obtained in single-variable analyses in our study; however, multivariate 1, 3, and 6 months analyses showed that the LENT score was not effective in predicting survival. It was shown that a high LENT risk group increased the mortality risk by 4 times in only 12 months of survival.

There may be some reasons why the LENT score predicted mortality risk in only 12 months of survival in our study. When it is considered that the average survival after being diagnosed with MPE is 3–12 months, sensitivity to

chemotherapy is one of the most important factors affecting survival. Even when lung cancer is considered alone, different histological types may have different responses to treatment. In addition, improvements in palliative care opportunities in end-stage cancer patients increase the life comfort of patients and prolong survival. For this reason, the period in which the LENT score was most successful in predicting survival might have been determined to be 12 months.

Jeba *et al*.[11] evaluated the relationship between the LENT score and the prognosis of 48 patients with MPE. The LENT prognostic score could be calculated in 15 patients. Similar to our study, most patients had lung cancer (41.7%) and were in adenocarcinoma histology (44.7%). Survival was significantly lower with poor ECOG performance status (*P* = 0.002), bilateral effusion (*P* < 0.001) and no oncological treatment after MPE diagnosis (*P* < 0.001).[11] The median survival in the moderate- and high-risk LENT groups was 6 and 3 months, respectively (*P* = 0.16).[11] The number of patients in our study was quite high compared to that in this study. Although we had similar results regarding the role of the LENT score in predicting prognosis, our study results can be considered more valid.

When the LENT score is considered, the evaluation of Murray *et al*. was important, which shows that the LENT score was more of a scoring system that could show prognosis in MPE due to lung cancer and since other cancer types (i.e., hormone receptor-positive breast cancer, and hematological cancer) can respond well to chemotherapy, and the use of this score was not correct.[12] Since 79.9% of the patients in our study were lung carcinoma patients and 9.5% of them had malignant mesothelioma diagnosis, it can be said that the response rates of our patient group to chemotherapy were low. This increases the reliability of our results.

By evaluating this criticism, Abisheganaden *et al*. evaluated 70 patients who had malignant pleural effusions that developed only because of lung adenocarcinoma[6] and reported that 55.7% of patients received tyrosine kinase inhibitor (TKI) treatment and 44.2% received standard chemotherapy.[6] Considering that those receiving TKI treatment had longer survival, the "T" score in the LENT score was given 0 instead of 2, and three groups were formed: *The Entire Group, TKI Group,* and *Standard Chemotherapy Group*.[6] Although all three groups had similar LENT scores (*P* = 0.44), survival was significantly higher in the group that received TKI treatment (*P* = 0.003).[6] As a result of the study, it was reported that the LENT score could not be used safely in pleural effusion because of lung adenocarcinoma and the LENT score needed modification to be used in different patient groups.[6] Because of the small number of patients included in our study, no analyses could be performed according to histological/pathological type for lung cancer.

Since there are different ideas about the LENT score, Psallidas *et al*. published the PROMISE score by using

more comprehensive data.[10] A total of 17 different biological markers were tested and gelsolin, macrophage migration inhibitory factor, versican, and TIMP 1 were found to be used to predict survival.[10] Considering the risk of 3 months mortality, patients were divided into 4 different categories according to clinical or biological PROMISE scores to determine the mortality risk.[10] The LENT score and clinical and biological PROMISE scores were calculated for 192 patients, and survival analysis was performed. Kaplan–Meier survival analysis showed that mortality risk increased according to LENT score from low to moderate ($P = 0.001$) and from low to high ($P \leq 0.001$).[10] According to the clinical PROMISE score, the mortality risk increased from risk categories A to B ($P < 0.0001$), from A to C ($P < 0.0001$), and from A to D ($P < 0.0001$).[10] In addition, the PROMISE score was argued to be a better prognostic indicator than the LENT score.[10] In our study, the risk of mortality in 1-month survival increased 4 times in category B, 6 times in category C, 31 times in category D; in 3 months survival, 2 times in category B, 4 times in category C, and 17 times in category D; in 6 months survival, 2 times in category B, 3 times in category C, and 13 times in category D; and in 12 months survival, 2 times in category B, 3 times in category C, and 11 times in category D in multivariate analyses. In all analyses, the PROMISE score was found to be a better prognostic indicator than the LENT score. Although the PROMISE score was shown to provide a prediction for mortality risk for 3 months, our results show that the PROMISE score can also be used safely in determining the mortality risk in the 1, 6 and 12 months periods. Because the mortality risk in PROMISE category A is 25%, all necessary efforts can be made for the treatment of patients, and in PROMISE category D, the mortality risk is 75%, and only palliative treatments can be considered.

Finally, Grendelmeier and Rahman[13] published an article on the proper scoring system in patients with MPE. It was reported that the LENT score was strong in predicting survival; however, generalization could not be made for some groups of patients (clinically questionable MPE or paramalignant effusion). In addition, more prospective studies are needed to plan treatment decisions according to the LENT score.[13] The PROMISE score is an important step for personalized MPE treatment and can be used in everyday practice and specifying the risk of mortality by category is an important advantage over the LENT score.[13]

Although the number of patients in our study was similar to the studies in the literature and adequate, there are some limitations in our study. Only patients who were certainly diagnosed with MPE were included in our study and suspected MPE or paramalignant effusion cases were excluded. In addition, the fact that separate survival analyses were not performed for different oncological diagnoses due to primary tumors and the effect of treatment differences even in the same cancer types were not considered on outcomes in the evaluation were among the limitations of our study. On the other hand, the fact that the majority of our patients were diagnosed with MPE due to lung cancer was one of the most important points that can affect the results of the study in a positive way and our study results indicate that criticisms on LENT score are correct.

CONCLUSIONS

A poor performance score (ECOG 3-4), PROMISE category B, category C, and category D significantly increased mortality risk, and the LENT score was inadequate in predicting survival.

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Conflicts of interest
There are no conflicts of interest.

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