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Prediction modeling using routine clinical parameters to stratify survival in malignant pleural mesothelioma patients complicated with malignant pleural effusion

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Abstract

Background: Malignant pleural effusion (MPE) is common in malignant pleural mesothelioma (MPM). The survival of patients with MPM and MPE is heterogeneous. The LENT and BRIMS scores using routine clinical parameters were developed to predict the survival of patients with unselected MPE and MPM, respectively. This study aimed to stratify the survival of selected MPM patients with MPE.

Methods: Data were collected from subjects diagnosed with MPM and MPE. The LENT and BRIMS scores were applied using a combination of clinical variables to stratify subjects and compare survival characteristics.

Results: In total, 101 patients with MPM complicated by MPE were included in the study. The median follow-up time was 71 months (interquartile range: 24–121 months). Overall median survival was 24 (interquartile range: 12–52 months). Based on the LENT score, the low-, moderate-, and high-risk groups accounted for 65.3% (66 cases), 34.7% (35 cases), and 0%, respectively. The cumulative survival rates of the two groups were statistically significant ($p = 0.031$). The area under the curve (AUC) of the LENT score was 0.662. Based on the BRIMS score, the first, second, third, and fourth risk groups accounted for 1.0% (1 case), 42.9% (35 cases), 28.7% (29 cases), and 19.4% (36 cases), respectively. Survival was significantly higher in patients in the risk groups 1 and 2 than in patients in the risk groups 3 and 4 ($p = 0.037$). The AUC of the BRIMS score was 0.605.

Conclusions: Using routinely available clinical variables, both LENT and BRIMS scores could stratify selected MPM and MPE patients into risk groups with statistically different survival.

KEYWORDS
BRIMS score, LENT score, malignant pleural effusion, malignant pleural mesothelioma, prognosis

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare malignant tumor originating from the pleural mesothelium, usually associated with asbestos exposure, and its incidence is currently increasing worldwide.[1] Previous studies have shown that the incidence of MPM with malignant pleural effusion (MPE) is approximately 80%–90%.[2,3] The lack of specificity in early clinical manifestations results in the majority of patients being diagnosed at an advanced stage; therefore, the overall prognosis is poor. However, patient survival is significantly heterogeneous.[4] The treatment of MPM combined with MPE remains a challenge, and predicting survival helps prioritize therapeutic options. For patients with limited

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survival, a more conservative treatment approach should be used to ensure good quality of life during end-stage disease.[5]

In 2014, Clive et al. reported the LENT score for predicting the prognosis of patients with MPE within 6 months of diagnosis,[6] recommended by the European Respiratory Society and major guidelines as a useful tool for predicting the survival of patients with MPE.[7,8] The LENT score is a composite score formed by the combination of pleural fluid lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group performance status (ECOG PS), serum neutrophil-to-lymphocyte ratio (NLR), and tumor type. It classifies patients into three risk groups based on the duration of survival for unselected subjects with MPE.

In May 2020, the European Respiratory Society, European Society of Thoracic Surgeons, European Association for Cardio-Thoracic Surgery, and the European Society for Radiotherapy and Oncology jointly published the guidelines for the management of MPM, which recommends the BRIMS score[9] for predicting the prognosis of patients with MPM within 18 months of diagnosis.[10] This model showed that the combination of clinical and pathological features, including weight loss, ECOG PS, hemoglobin, albumin, and sarcomatoid-containing histology, stratified unselected subjects with MPM into four different risk groups with significantly different median survival characteristics.

The aim of this study was to examine the performance of the previously described LENT and BRIMS scores using the same clinical variables in the selected population diagnosed with MPM complicated with MPE and undergoing nonsurgical treatments.

METHODS

Study population

Consecutive patients with newly diagnosed MPM at Beijing Chaoyang Hospital affiliated to Capital Medical University from June 1, 2010 to July 1, 2021 were enrolled in this study. The inclusion criterion included the histological confirmation of MPM combined with MPE undergoing nonsurgical treatment. The exclusion criteria were insufficient data. Based on the above criteria, eligible patients were selected from the electronic medical records system.

Electronic information on medical cases was collected for all patients using their independent ID numbers. Data collected included age; sex; ECOG PS; history of asbestos exposure; side of pleural effusion; levels of serum LDH, serum protein, pleural LDH, and pleural protein; pleural fluid differential cell count; cytology; pleural biopsy result; and survival. The primary endpoint was death. All medical records were reviewed from the date of the first objective diagnosis of MPM either to the date of death or to the last medical follow-up record, whichever occurred earlier. This study was approved by the ethics committee of Beijing Chao-Yang Hospital, Capital Medical University (no. 2020-KE-512).

LENT score

The patients' baseline data for pleural fluid LDH, ECOG PS, serum NLR, and tumor type were collected. The LENT score was calculated for each patient according to the published literature, and the patients were grouped accordingly.[6] The type of MPM was scored as 0; a total score of 0–1 was classified as the low-risk group, 2–4 as the moderate-risk group, and 5–7 as the high-risk group.

BRIMS score

All variables required from the original model, including weight loss, hemoglobin concentration, ECOG PS, serum albumin concentration, histology, and overall survival were collected. The BRIMS score was divided for each patient according to previously published literature.[9] These risk groups were referred to as group 1 (best predicted outcome) and group 4 (poorest outcome).

Statistical analysis

Normally distributed measurement data are expressed as mean ± standard deviation, and non-normally distributed measurement data are expressed as median and interquartile range. Numerical data are expressed as frequencies and component ratios. Cox regression analysis was used to identify statistically significant differences between subgroups. The Kaplan–Meier survival curve was used to compare the overall cumulative survival rate, and the log-rank test was used to test the differences between the groups. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to assess the risk value of the LENT and BRIMS scores for predicting survival. All statistical tests were two-sided, and statistical significance was set at $p > 0.05$. All statistical analyses were performed using SPSS software (version 25.0; IBM). This study was reviewed by a professional epidemiologist.

RESULTS

Patient characteristics

In total, 101 consecutive patients diagnosed with MPM combined with MPE who underwent nonsurgical treatment were identified. There were no missing data for any of the variables. The 101 patients had a median age of 63.7 years, where 53 (52.5%) were male. Only 57 (56.4%) patients had never smoked, and 26 (25.7%) patients had a history of asbestos exposure. Weight loss was noted in 41 patients (40.6%). A total of 78.2% ($n = 79$) of the patients had an ECOG PS of 0 or 1 at the time of diagnosis, 37 (36.6%) patients had left-sided pleural effusion, 55 (54.5%) had right-sided pleural effusion, and nine (8.9%) had bilateral pleural effusion. Three (3.0%) patients

TABLE 1 Baseline demographic and clinical characteristics of the study population

Characteristic	Patients ($n = 101$) (%)[a]
Age ($\overline{x}\pm s$)	63.7 ± 10.2
Gender	
Male	53 (52.5)
Female	48 (47.5)
Smoking history	
Current and former	44 (43.6)
Never	57 (56.4)
Asbestos exposure	
Yes	26 (25.7)
No	75 (74.3)
Weight loss	
Yes	41 (40.6)
No	60 (59.4)
ECOG PS	
0	11 (10.9)
1	68 (67.3)
2	14 (13.9)
3	8 (7.9%)
WBC count (10^9/l) (median, IQR)	6.4 (5.0, 8.5)
Blood neutrophil lymphocyte ratio (median, IQR)	2.8 (2.1, 4.0)
Hemoglobin (g/l) ($\overline{x}\pm s$)	133.1 ± 1.8
Albumin (g/l) (median, IQR)	36.3 (33.5, 39.2)
Pleural fluid lactate dehydrogenase (median, IQR)	373.0 (263.2, 757.5)
Pleural fluid side	
Left	37 (36.6)
Right	55 (54.5)
Biphasic	9 (8.9)
Diagnostic methods	
Cell blocks from malignant pleural effusion	3 (3.0)
Ultrasound-guided percutaneous biopsy	16 (15.8)
Medical thoracoscopy	71 (70.3)
Video-assisted thoracoscopic surgery	11 (10.9)
Histology	
Epithelioid	63 (62.4)
Sarcomatoid	6 (5.9)
Biphasic	4 (4.0)
Not defined	28 (27.7)
Treatment	
Chemotherapy ± antiangiogenesis therapy	93 (92.1)
Best supportive care	8 (7.9)
LENT score	
0	9 (8.9)
1	57 (56.4)
2	24 (23.8)
3	8 (7.9)
4	3 (3.0)
BRIMS score	
Group 1	1 (1.0)
Group 2	35 (34.7)
Group 3	29 (28.7)
Group 4	36 (35.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.
[a]Data is presented as *n* (%), $\overline{x}\pm s$ or (median, IQR).

were diagnosed with pleural effusion cell wax block, 16 (15.8%) patients had undergone ultrasound-guided pleural biopsy, 71 (70.3%) patients had undergone medical thoracoscopy, and 11 (10.9%) had undergone video-assisted thoracoscopic surgery (VATS). According to the 2015 WHO classification criteria,[11] this MPM cohort of 101 cases included the epithelioid subtype (62.4%; $n = 63$), sarcomatoid subtype (5.9%; $n = 6$), biphasic (4.0%; $n = 4$), and undefined type (27.7%; $n = 28$). A total of 92.1% ($n = 93$) of the patients underwent chemotherapy either alone, or in combination with, antiangiogenesis therapy; some patients were supposed to undergo surgical treatment but refused for a variety of reasons. Eight (7.9%) patients received the best supportive care, including traditional Chinese medicine treatment, and 69 patients (68.3%) had died at the time of censoring (Table 1).

LENT score

The median follow-up time for all patients was 71 (interquartile range: 24–121) months, and median survival was 24 (interquartile range: 12–52) months. In the subgroup analysis, the low-risk group accounted for 65.3% (66 cases) of the patients, with a median survival of 37 (interquartile range: 10–72) months. The moderate-risk group accounted for 34.7% (35 cases) of the patients, with a median survival of 22 months (interquartile range: 12–30 months). There was no high-risk group. Using Cox regression on a complete data set, survival was found to be significantly higher in patients in the moderate-risk group than in those in the low-risk group ($p = 0.034$) (Table 2). Kaplan–Meier analysis demonstrated that there was a significant difference in prognosis according to the log-rank test ($p = 0.031$) (Figure 1). The AUC of the LENT score was 0.662 (95% CI: 0.554–0.771) (Figure 2).

BRIMS score

After assigning the risk groups according to the variables, the patients were divided into four major risk groups, with 1.0% (1 case) in risk group 1, 34.7% (35 cases) in risk group

TABLE 2 Comparison of median survival time based on LENT score

LENT score	Patients	Survive time (median, IQR)	HR(95%CI)	*p*-value
Low risk (LENT 0–1)	66	37 (10–72)	1	
Moderate risk (LENT 2–4)	35	22 (12–30)	1.687 (1.036, 2.746)	0.034

TABLE 3 Comparison of median survival and survival rate based on BRIMS score

BRIMS score	Patients	Survive time (median, IQR)	HR (95% CI)	*p*-value
Group 1 and 2	36	35 (12, 98)	1	
Group 3 and 4	65	24 (12, 52)	1.763 (1.022, 3.040)	0.039

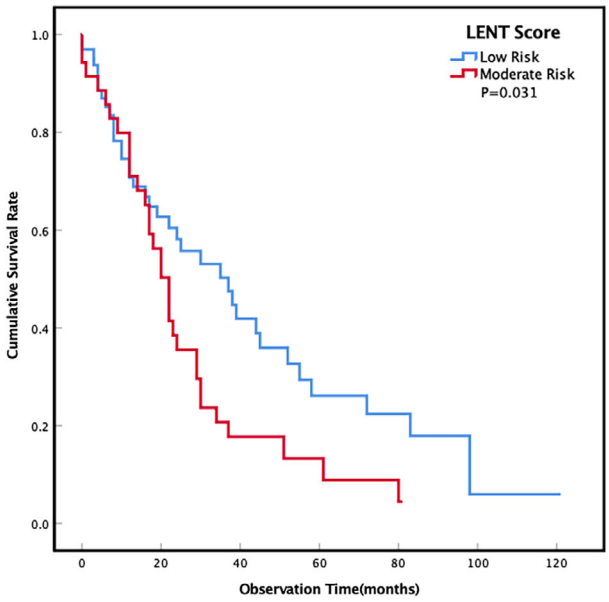

FIGURE 1 Comparison of overall survival between the low and moderate risk of LENT risk score using Kaplan–Meier curves survival analysis ($p = 0.031$)

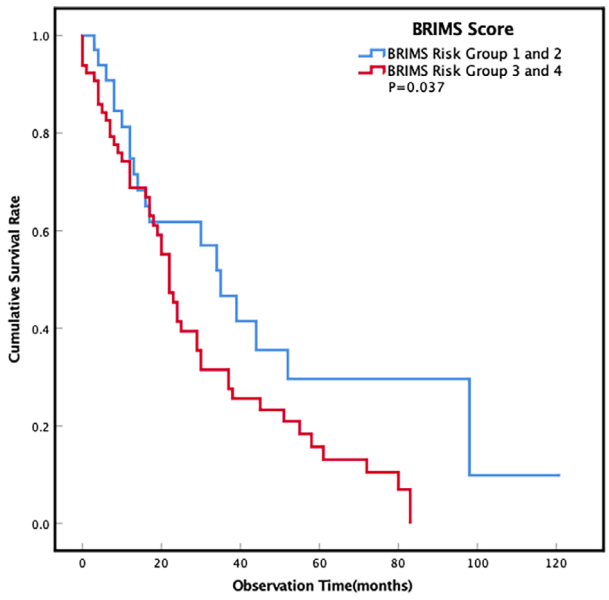

FIGURE 2 ROC curve of the LENT and BRIMS scores

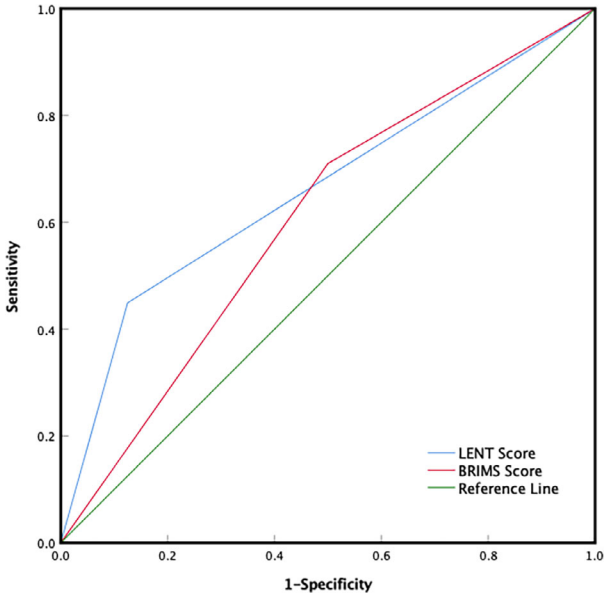

FIGURE 3 Comparison of overall survival among different risk groups of BRIMS using Kaplan–Meier curves survival analysis ($p = 0.037$)

2, 28.7% (29 cases) in risk group 3, and 35.6% (36 cases) in risk group 4. The median survival for all patients was 24 months (interquartile range, 12–52 months). In the subgroup analysis, patients in risk groups 1 and 2 and risk groups 3 and 4 had median survival times of 35 (interquartile range: 12–98) months and 24 (interquartile range: 12–52) months, respectively. Using Cox regression on a complete data set, survival was significantly higher in patients in risk groups 1 and 2 than in patients in risk groups 3 and 4 ($p = 0.039$) (Table 3). Kaplan–Meier analysis demonstrated that there was a significant difference in prognosis according to the log-rank test ($p = 0.037$) (Figure 3). The AUC of the BRIMS score was 0.605(95%CI 0.484–0.726) (Figure 2).

DISCUSSION

This study showed that routinely collected clinical data could be used to stratify selected patients with newly

diagnosed MPM and MPE into distinct prognostic groups with different survival characteristics. This provided further validation for the previously described LENT and BRIMS scores with a fair-to-good performance of the model for discrimination of survival.

Since LENT score was developed for a diverse unselected population including various kinds of tumors, this study was performed to assess the performance of LENT score in the "selected" population of MPM compliment with MPE. The results of the present study suggested that the LENT score was useful in the prognostic risk stratification of patients, which is consistent with the results of another study.[12,13] By analyzing the reasons for its application, it was inferred that each risk factor of LENT score was significantly correlated with the prognosis in our study, including ECOG PS, pleural fluid LDH level, and serum NLR. These findings are supported by the results of previous reports.[14–18] However, the selected MPM population was different from the "all-comers" design of the LENT score cohort, which may affect the efficacy of its evaluation.

This study demonstrated that the BRIMS score might be useful in prognosis risk stratification of patients, which was similar to a previous study.[19] The strongest predictive variable in the BRIMS score was weight loss, which is controversial.[20,21] In this study, the median time from the discovery of pleural effusion to the diagnosis of pleural mesothelioma was 60 days, and 81.2% of the patients were diagnosed using thoracoscopy, which reduced the time of diagnosis. Thus, at the time of diagnosis, 40.6% had weight loss, 78.2% had an ECOG PS of 0–1, and the median values of indices such as hemoglobin and serum albumin concentrations were within the normal ranges. The good physical status of patients provided the option for subsequent treatment after diagnosis. Therefore, the median survival of 24 months in this cohort was better than that reported in previous studies.[12] Moreover, previous studies have shown that the prognosis of patients with epithelial mesothelioma was better than that of sarcomatoid mesothelioma.[22] Most of the patients in this study had epithelial mesothelioma; systemic chemotherapy combined with antiangiogenesis therapy has been shown to increase survival by a few months.[23,24]

Interestingly, we saw that the two risk groups began to separate after 18 months of follow-up in the Kaplan–Meier curve, regardless of the LENT or BRIMS score. A potential explanation for this phenomenon may be related to the composition of the patients in this study. The patients in our cohort were predominantly epithelial and generally in good condition at the time of diagnosis. Treatment was well tolerated and overall survival was good. In particular, patients in the low-risk group had more treatment opportunities after 18 months, and the survival period was further prolonged than in the higher-risk group. However, the conjecture that the prediction performance of LENT and BRIMS scores for MPM combined with MPE patients after 18 months is better still needs to be further prospectively verified by a larger cohort.

This study had the limitation of a single-center experience with a retrospective observational design. However, its main strength is that it was conducted on a homogenous population of MPM complicated with MPE; thus, this increased the precision with which it could be applied to this group of patients. In addition, a greater proportion of patients with MPM with MPE were eligible for platinum-based chemotherapy, either alone or in combination with antiangiogenesis therapy. Hence, based on our findings, the LENT and BRIM scores may impact most patients with MPEs from MPM undergoing nonsurgical treatments.

In conclusion, the individual survival of patients with MPM combined with MPE varied greatly. Both LENT and BRIMS scores could help stratify the survival risk of patients with MPM complicated by MPE with fair-to-good performance. More effective predictive models should be established in adequately designed prospective studies.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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