Performance of LENT Score in Hispanic Population with Malignant Pleural Effusion

Arturo Cortes-Telles*, Fernando Formento-Ceballos and Gary Kosai Vargas-Mendoza

Respiratory and Thoracic Surgery Department, Hospital Regional de Alta Especialidad de la Península de Yucatán, Yucatan, México

Abstract: *Background***:** Malignant Pleural Effusion (MPE) represents an advanced oncological disease. Overall survival ranges between 3 to 12 months depending on different factors. LENT score has emerged as the first validated instrument to predict MPE survival with significant better accuracy. There is no information regarding LENT score in Hispanic population. Therefore, the objective of this study is to analyze the performance of LENT score within a cohort of MPE patients from Mexico. *Methods***:** A retrospective observational study including 32 patients with a confirmed MPE was conducted. Stratification was according to LENT score (low-risk, moderate-risk, high risk). Overall survival was calculated from the date of diagnosis until death and differences between groups were analyzed. *Result*s: The median age was 61years (IQR 47-71) and 47% were women. Based on the stratification of LENT score, 6% was stratified as low-risk, 59% as moderate-risk and 34% as high-risk. Overall median survival time was 54 days (IQR 26-243), and considering the stratification, 227, 53 and 37 days for low, moderate and high-risk groups, respectively. The higher LENT score, the higher the risk of death (HR 2.26, CI 95%, 1.15-4.47, p=0.019). Pleural LDH, ECOG and NLR were the factors that provided greater accuracy to differentiate groups, (p=0.076, p=0.003 y p=0.015, respectively). *Conclusion***:** LENT score showed a good performance to identify patients with the most adverse prognosis and the highest risk of mortality in Hispanic population. Pleural LDH, ECOG and NLR provide the most valuable information in the identification of the cases.

Keywords: Malignant Pleural Effusion, Pleural Effusion, Survival, LENT Score.

INTRODUCTION

Malignant pleural effusion (MPE) can be developed in up to 50% of patients with metastatic malignancies with an overall survival time ranging between 3 and 12 months depending by tumor and histological characteristics, extent of the disease and clinical performance [1,2]. Currently, lung and breast cancer represents 50-65% of all MPE[3].

The estimated annual incidence of MPE is around 50,000-150,000 cases in the USA and UK, nonetheless, given the increase in diagnostic procedures, it is set to rise [1,4]. In Hispanic population from Europe, a study from Spain have reported a MPE prevalence of 27% in a group of patients with unilateral pleural effusion (PE)[5]. In Mexico, MPE is the second cause of medical attention in third-level reference centers specialized on respiratory diseases.[6-8] The quality of life in MPE patients is compromised by the severity of symptoms, however, up to 25% are asymptomatic[9]. Dyspnea is the most common symptom (more than 50% of patients), whilst thoracic pain, hemoptysis and cough are reported in a lesser proportion[10].

So far, treatment strategies are focused on palliative support, however, pleural and oncological therapeutic options are widely increasing; therefore, baseline prognostic evaluation might help to individualize treatment strategies[11]. Clive et al. have developed the LENT prognostic score to risk-stratify unselected patients with MPE[12]. LENT is a composite score integrated by the combination of pleural lactate dehydrogenase (LDH) levels, Eastern Cooperative Oncology Group (ECOG), serum neutrophil-to-lymphocyte ratio (NLR) and tumor type. It classifies patients into low, moderate and high-risk groups based on survival time. Clinical information regarding the LENT score in Hispanic population is null. To fill this gap of knowledge we sought to analyze the performance of LENT score in a group of patients from Yucatan, Mexico. The results may help to prioritize therapeutic options for patients with MPE.

STUDY DESIGN AND PATIENTS

This is an observational, retrospective study of cases nested in a cohort of patients evaluated with unilateral PE. All patients older than 18 years with a confirmed MPE diagnosis admitted to the Hospital Regional de Alta Especialidad de la Peninsula de Yucatán (HRAEPY) from January 2015 to December 2018 were included. Patients with insufficient information to define the MPE's etiology and with an unknown date of death were excluded. The present study was approved by local Research and Ethics Committee with the registration number 2018-037. At the time of unilateral PE approach, all patients signed an informed consent for the diagnostic procedure. All data were password protected in the computer of the principal researcher (ACT) and confidentiality was followed according to the Declaration of Helsinki[13].

*Address correspondence to this author at the Respiratory and Thoracic Surgery Department, Hospital Regional de Alta Especialidad de la Península de Yucatán, Yucatan, México; Email: dr_morenheim@hotmail.com; Tel: +52 (999) 9427600, ext 54302

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From each medical chart the following variables were obtained: age, gender, smoking status, comorbidities, symptoms, PE volume occupation, MPE diagnosis date, endopleural catheter placement (yes/no), pleurodesis (yes/no), in-hospital stay (days), lactate dehydrogenase pleural fluid levels (LDH in PF), ECOG, NLR, histopathologic report according to type of tumor and date of death.

Continuous variables were expressed as median with interquartile range (IQR) and categorical variables as frequencies with percentages. Based on LENT score, we stratify the groups in low, medium and high risk. Comparisons between-groups were examined using repeated measures one-way analysis of variance (ANOVA) followed by Bonferroni-adjusted post hoc comparisons when results were significant for the continuous variables. On the other hand, the between-groups differences in categorical variables were analyzed through the Kruskal-Wallis test. Survival time was calculated from the date of diagnosis of MPE to death. Overall survival analysis according to the LENT prognostic score was assessed using Cox proportional model and Kaplan-Meier survival curves. A p-value less than 5% (two-sided) was considered statistically significant. All analyses were performed using STATA software version 13 (Statacorp, College Station, Tx. USA).

RESULTS

A total of 32 patients with MPE diagnosis were identified. Baseline characteristics are detailed in Table 1. The median of age was 61 years (IQR 47-71), 53% were male and 31% had history of smoking with a median of 10 pack-years (IQR 5-40). The most frequent comorbidity was hypertension (25%). During baseline evaluation, the main symptom was dyspnea (97%) followed by weight loss (66%). Regarding the MPE treatment, 41% of patients required a chest tube placement with a median time of 7 days (IQR 6-8) and pleurodesis was performed in 16% of the cases using povidone-iodine solution. Finally, the median time of hospital stay was 13 days (IQR 6-19).

Overall survival according to the specific type of tumour is detailed in Table 2. Median survival time of the entire group was 54 days (IQR 26-243). There were non-between group differences regarding pulmonary vs extrapulmonary origin [56 days (IQR 39-298) vs 53 days (IQR 25-234), p=0.677].

LENT Score and Group Stratification

The median of pleural LDH was 575 IU/L (IQR 346.5-1629). At the time of diagnosis, 50% of patients had a functional performance of ECOG 2. The median of NLR was 6.05 (IQR 3-11.2). Finally, regarding tumour type, extrapulmonary tumours were the most predominant in our cohort (84%) and primary unknown cancer was the most prevalent (26%). MPE due to lung cancer have a prevalence of 16%.

Variables	**n=32**
Age, years	61 (47-71)
Female sex	15 (47%)
History of smoking	10 (31%)
Pack-Years	10 (5-40)
Comorbidities	
Diabetes Mellitus	1 (3%)
Hypertension	8 (25%)
Symptomatology	
Evolution, days	15 (6-43)
Cough	18 (56%)
Dyspnea	31 (97%)
Thoracic pain	14 (44%)
VAS	7 (7-8)
Fever	8 (25%)
Temperature	38.5 (38.4-38.8)
Phlegm	8 (25%)
Hyporexia	13 (41%)
Weight loss	21 (66%)
PE Volume Occupation	
1-25 %	2 (6%)
26-50 %	11 (34%)
51-75 %	9 (28%)
76-100 %	10 (31%)
Cell type, n (%)	
Pulmonary	5 (16%)
Extrapulmonary	27 (84%)
Chest tube insertion	13 (41%)
Chest tube duration, days	7 (6-8)
Pleurodesis	5 (16%)
Iodopovidone	5 (100%)
Hospitalization, days	13 (6-19)

Table 1: Demographic characteristics of the study population.

According to the LENT score, roughly 6 out of 10 patients were stratified into moderate-risk and nearly half of patients (44%) have a median survival time ranging from 0 to 30 days (Table 3).

Clinical Differences According to LENT Score

There were non-significant between group differences regarding age, sex, tobacco exposure and tumour type (Table 4). We observed a non-significant linear trend of pleural LDH, as higher the risk group the higher pleural LDH value (p=0.072). On the other hand, ECOG and NLR showed a gradual increase with the risk set by LENT score (p=0.003 y p=0.015, respectively). Finally, median survival time was 277 (IQR 103-351) for low-risk population, 53 for moderate-risk (IQR 26-256) and 37 for high-risk, however, without significant differences (p=0.298).

Variables	Median survival in days (IQR)	n (%)
Overall	54 (26-243)	32
Histopathological cancer type		
Lung	56 (39-298)	5 (16%)
Mesothelioma	351 (351-351)	1 (4%)
Gastric	68 (45-169)	4 (15%)
Breast	178 (54-605)	4 (15%)
Ovarian	136 (37-234)	2 (7%)
Cervical	1 (1-1)	1 (4%)
Haematological malignancy	203 (9-396)	2 (7%)
Pancreatic	8 (8-8)	1 (4%)
Hepatic	24 (24-24)	1 (4%)
Renal cell carcinoma	70 (26-277)	3 (11%)
Penile	26 (26-26)	1 (4%)
Primary unknown	46 (25-126)	7 (26%)

Table 2: Median survival according to histopathological cancer type.

Variables	n=32
LDH level in pleural fluid, IU/L	575 (346.5-1629)
ECOG	
0	1 (3%)
1	12(38%)
2	16 (50%)
3	3 (9%)
4	0 (0%)
Neutrophil-to-Lymphocyte Ratio	6.05 (3-11.2)
Tumor type	
Lowest risk tumor types - Mesothelioma - Haematological malignancy	3 (9%)
Moderate risk tumor types - Breast cancer- Gynaecological cancer - Renal cell carcinoma	10 (31%)
Highest risk tumor types - Lung cancer - Other tumor types	19 (60%)
LENT Score	
Risk categories	
Low Risk (0-1)	2 (6%)
Moderate Risk (2-4)	19 (59%)
High Risk (5-7)	11 (34%)
Survival	
0 to 1 months	14 (44%)
1 to 6 months	9 (28%)
6 or more months	9 (28%)

Table 3: LENT score of the study population.

Variable	Low (n=2)	Risk categories Moderate (n=19)	High (n=11)	p value
Age, years (IQR)	45 (37-54)	64 (37-72)	60 (48-80)	0.530
Female (%)	1 (50%)	8 (42%)	6 (55%)	0.849
Smoking (%)	2 (100%)	6 (32%)	4 (36%)	0.593
Cell type, n (%)				
Pulmonary		3 (60%)	2 (40%)	NS
Extrapulmonary	2 (7.5%)	16 (59%)	9 (33.5%)	NS
LDH level in pleural fluid, IU/L (IQR)	375 (250-501)	445 (307-1029)	1587 (676-2049)	0.072
ECOG	0 (0-1)	2 (1-2)	2 (2-3)	0.003
Neutrophil-to-Lymphocyte Ratio (IQR)	2.45 (1.61-3-28)	5.22 (2.83-7.05)	12.9 (8.33-23.92)	0.015
Survival				0.355
0 to 1 months	0 (0%)	8 (42%)	6 (55%)	
1 to 6 months	1 (50%)	4 (21%)	4 (36%)	
6 or more months	1 (50%)	7 (37%)	1 (9%)	
Overall survival, days (IQR)	227 (103-351)	53 (26-256)	37 (2-82)	0.298

Table 4: Clinical differences according groups stratification by LENT Score.

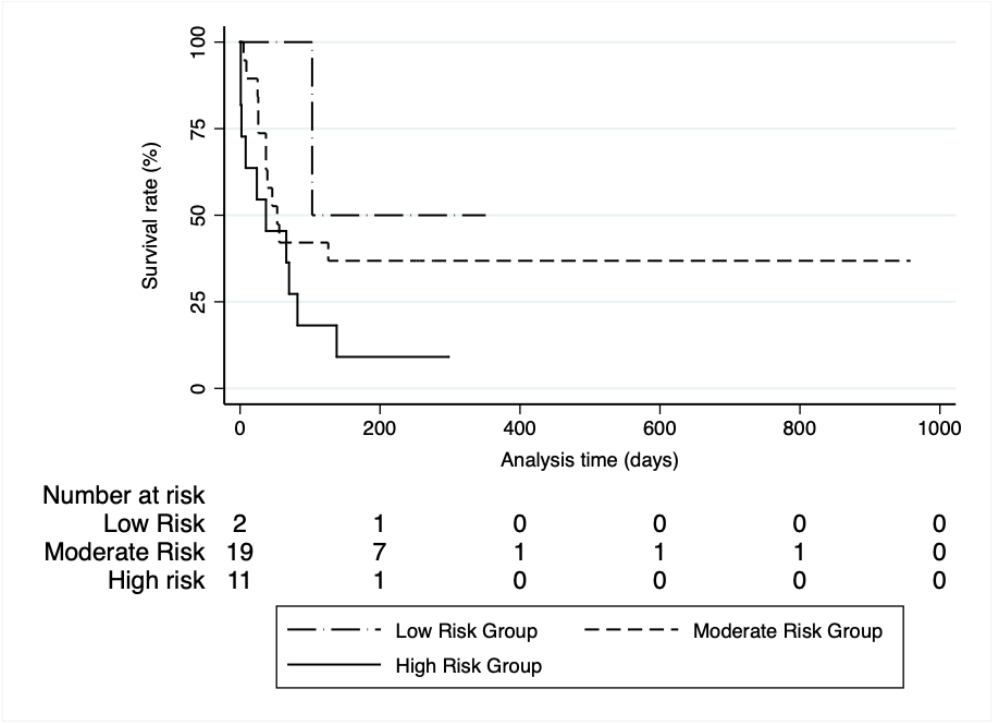

Figure 1: LENT score mexican population.

Survival curves allowed us to identify that during the first 100 days there is a marginal significant difference in moderate and high-risk cases compared to low risk ones (log rank p=0.055, figure 1). Finally, compared to low-risk score, patients with a moderate and high-risk score have a higher risk of mortality (HR 2.26, 95% CI, 1.15-4.47, p=0.019).

DISCUSSION

To the best of our knowledge, this is the first report analyzing the performance of LENT score in Hispanic/Latin-American population. There are different reports focused on the prognosis definition and survival of patients with MPE; amongst the factors that have shown a consistent accuracy are the functional state at the time of diagnosis (Karnofsky, ECOG), type of primary tumour, and the PE biochemical components (pH, glucose, LDH, etc.)[11]. Clive et al. developed the LENT score, considered as the first validated system for prognosis identification in MPE. Moderate-risk patients have a median of survival of 130 days (IQR 47–467), furthermore, 81% survives 1-month and 47% can reach a 6-month survival. On the other hand, when LENT score defines a high-risk patient, the median of survival time is 44 days (IQR 22–77) and their probabilities for surviving 1 and 6 months were 65% and 3% respectively[12]. In our report was evident that patients with a moderate-risk LENT score have a lower median of survival time compared with previous reports (53 days, IQR 26-256); also, we identified a lower prevalence of survival at 1- and 6-months (58% and 37%). Possible explanations of this differences might be related with a delay to prompt diagnosis. On the other hand, patients who were stratified as high-risk showed a median of survival time of 37 days (IQR 2-82) which was similar to previous reports. Therefore, our findings are in order to state that LENT score could stratify the risk and prognosis in Hispanic population and might allowed to generate the best therapeutic strategies available at each hospital center.

Anecdotical risk stratification groups using only ECOG performance as the only variable to predict prognosis in MPE might be suboptimal. Even though, Abrao et al. [14] reported that patients with ECOG 2 and MPE diagnosis had a survival average of 245 days, they did not consider the relevance of biomarkers such as pleural fluid LDH and NLR which have showed a better performance in overall survival of these patients. Both are indicative of poor prognosis due to necrosis and cell death within pleural cavity as well as systemic inflammation. To reinforce these findings, Lee et al., documented that patients with a diagnosis of MPE due to lung cancer, presenting a NLR ≥ 3.85 and higher levels of pleural LDH have the lower survival rate with an average of 3.6 months.[2,12] We identified an overall median survival time in our population of 54 days and was lower in comparison with other reports who have showed survival ranges from 3 to 12 months; possible explanations for these difference might include the type of tumour prevalence, timely interventions to diagnosis and access to treatments.[3]

Regarding MPE related tumour type, we documented that the main cause in our population was primary unknown cancer (26%), followed by lung cancer (16%) and breast and gastric cancer in third place (15% each). It was noteworthy that MPE due to lung cancer have a lower prevalence in our center

comparing to other centers in Mexico who have reported a prevalence of MPE due to lung cancer between 32.6 - 33.5%.[5-7] Possible explanations is that our center is not exclusive for cancer patient's diagnosis and treatment. We have, nonetheless, previously reported the largest cohort of pleural effusions in our region, and MPE was identified in 19% of the population.[8] Therefore our results might be considered in a case-by-case analysis of tumour type possibilities. This contrast provides us a reflection of the disease's clinical expression in different regions and strengthen our findings to analyze the regional presentation of the disease, by providing a landscape regarding the etiology and medical actions to perform.

Estimation of survival time in MPE patients should orientate the optimal treatment strategy, particularly in those patients with an unfavorable prognosis. Options for ambulatory care, including therapeutic pleural aspiration could be considered to avoid prolonged hospital stay.[15] Recently, the AMPLE study reported that patients treated with a pleural catheter had shorter hospital stays compared with the employment of chemical pleurodesis with powder through chest tube and less subsequent pleural interventions.[16]

Our study has the limitation of being a single center study with retrospective observational design, although the total of patients included were consecutive and systematically approached with a complete diagnosis. Second, the sample size, even though, our hospital is a third-level reference center, is not exclusive for oncological nor respiratory (pleural disease) diseases. Despite the limitations, this is the first report analyzing the performance of LENT score in Mexican or Latin-American population.

CONCLUSION

The performance of LENT score in Hispanic patients from Mexico was acceptable. It identifies patients with the worst prognosis and higher risk of mortality. LDH, ECOG and NLR were the strongest variables to define the risk in MPE patients. Subsequent studies are needed in order to reinforce our findings.

Conflict of Interest

The authors declare to have no conflict of interest.

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