

Role of Lent Score in Predicting Survival in Malignant Pleural Effusion

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Abstract:

Background: Malignant pleural effusions are a common clinical problem in patients with neoplastic disease and almost all malignancies have been reported to involve the pleura. In most studies, lung carcinoma has been the most common neoplasm, accounting for one-third of all malignant effusions. Breast carcinoma is next most common. Ovarian and gastrointestinal carcinomas are less commonly associated with malignant pleural effusions. No primary tumor is identified in 5 to 10% of malignant effusions. Although many factors predict prognosis in malignant pleural effusions including primary tumor, ECOG PS, Koronofsky score, pleural fluid LDH, pH and glucose levels, there is no validated prognostic scoring system that could stratify patients with malignant effusion. The present study is undertaken to evaluate the role of LENT Score in predicting survival in malignant pleural effusion.

Materials and Methods: This is a hospital based prospective study conducted on 30 patients with malignant pleural effusions who fulfilled the inclusion and exclusion criteria. The diagnosis of pleural effusion is done based on chest X ray and ultrasound chest. Patients baseline characteristics were noted and all necessary blood investigations were carried out and recorded in all subjects. Therapeutic aspiration and/or ICT insertion was done based on size of the effusions. Pleural fluid analysis including total count, differential count, AFB, ADA, LDH, Protein, Sugar, Cytology and cell block. LENT score is calculated based on pleural fluid LDH, ECOG prognostic scale, Neutrophil/Lymphocyte ratio, primary tumor. Based on LENT score, patients are divided into high, moderate and low risk and are followed up at 1, 3, 6 months or until death whichever is earlier. The primary outcome measure was survival time, calculated from date of diagnosis with malignant pleural effusion and date of death or final follow up.

Results: Out of 30 patients, 16 were male and 14 were female. 22 cases had primary in lung, 2 cases of cervical cancer and a single case of Breast, thyroid, esophagus, thymoma, osteosarcoma and mesothelioma. Adenocarcinoma is the most common histology in lung cancer (n=12) followed by squamous (n=7) and undifferentiated (n=3). Patients were classified based on LENT score, out of which 14 patients were in high risk group, 15 in moderate risk group and a single patient in low risk group. Median survival in the study is 45 days. The median survival in high risk group is 30 days and in moderate risk group is 75 days. In the high risk group survival rate at 1 month is 42% and none of the patients in high risk group survived at 3 months. Survival at 1, 3 and 6 months is 93%, 33% and 26% respectively in the moderate risk group.

Conclusion: The LENT prognostic score is a good prognostic factor in patients with malignant pleural effusions and can be used for risk stratification in this group of patients for planning therapy. The LENT scoring system is less subjective than ECOG PS and relies on readily available tests, allowing it to be rapidly calculated without additive costs.

Keyword: LENT; ECOG PS; Survival; Prognosis; Malignant pleural effusion

Date of Submission: 20-10-2022

Date of Acceptance: 04-11-2022

I. Introduction

Malignant pleural effusions are a common clinical problem in patients with neoplastic disease and were found in 15% of patients who died with malignancies and almost all neoplasms have been reported to involve the pleura. Lung carcinoma has been the most common neoplasm, accounting for approximately one-third of all malignant effusions. Breast carcinoma is the second most common. Lymphomas, including both Hodgkin's disease and non Hodgkin's lymphoma are also an important cause of malignant pleural effusions. Tumors less

commonly associated with malignant pleural effusions include ovarian and gastrointestinal carcinomas. In 5 to 10% of malignant effusions, no primary tumor is identified.

A pleural effusion ipsilateral to the primary lesion is the rule in carcinoma of the lung. When the primary site of the cancer is elsewhere than the lung and with the possible exception of breast cancer, there seems to be no ipsilateral predilection and bilateral effusions are common. The presence of malignant effusions carry a poor prognosis, the survival depends on primary tumor with higher median survival for Breast carcinoma and Mesothelioma and low median survival for lung cancer. Although many factors predict prognosis in malignant pleural effusions including primary tumor, ECOG PS, Koronofsky score, pleural fluid LDH, pH and glucose levels but there is no validated prognostic scoring system that could stratify patients with malignant effusion. Several studies were undertaken to predict the survival in malignant pleural effusions and most of them used performance status (PS), cancer histology, primary site and biochemical parameters like pleural fluid pH, LDH and glucose. There are conflicting results regarding the prognostic value of pleural fluid pH, glucose levels and anatomic measures like extent of pleural carcinomatosis. Previous studies showed that poor ECOG PS is significantly associated with mortality.

The present study is undertaken to evaluate the role of LENT score in predicting survival in malignant pleural effusions.

II. Material and Methods

This is a prospective study conducted on patients with malignant pleural effusions in Department of Pulmonary Medicine at Government Hospital for Chest & Communicable diseases, Andhra medical college, Visakhapatnam from July 2021 to March 2022.

Study Design: Hospital based prospective observational study.

Study location: Government hospital for chest and communicable diseases, a teaching hospital of Andhra medical college, Visakhapatnam, Andhra Pradesh.

Study Duration: July 2021 to March 2022.

Sample size: A total of 30 patients presenting with malignant pleural effusion were enrolled in the study.

Subjects & Selection methods: The study population was selected from patients with malignant pleural effusion who got admitted in government hospital for chest & communicable diseases, Visakhapatnam.

Inclusion criteria:

- All patients aged >12 years with proved malignant effusions.

Exclusion criteria:

- HIV positive cases
- Co morbid diseases like end stage renal disease, LVF, IPF that likely influence the survival.

Procedure methodology:

- Patients baseline characteristics like age, sex, complete blood picture including Hb, TC, DC, AEC, ESR, HIV, HBsAg, Liver function tests, Renal function tests were done.
- The diagnosis of pleural effusion done based on chest x ray and ultrasound chest.
- Therapeutic aspiration and/or ICT insertion was done based on size of the effusions.
- Pleural fluid analysis including total count, differential count, AFB, ADA, LDH, Protein, sugar, cytology and cell block.
- A repeated cytology was done if initial report was negative.
- CECT chest done after draining of fluid.
- Histological diagnosis of the mass or nodular lesion found on CECT by ultrasound/CT guided FNAC/Biopsy.
- LENT score is calculated based on pleural fluid LDH, ECOG prognostic scale, Neutrophil/Lymphocyte ratio, primary tumor.

- **ECOG PS: Eastern Cooperative Oncology Group Performance Status** is determined as follows

GRADE	DESCRIPTION
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self care; confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry out any self care; totally confined to bed or chair

LENT SCORE CALCULATION:

	VARIABLE	SCORE
L	LDH level in pleural fluid (IU/L)	
	<1500	0
	>1500	1

E	ECOG PS 0 1 2 3-4	0 1 2 3
N	NLR <9 >9	0 1
T	Tumor type Lowest risk tumor types • Mesothelioma • Haematological malignancy Moderate risk tumor types • Breast cancer • Gynaecological cancer • Renal cell carcinoma Highest risk tumor types • Lung cancer • Other tumor types	0 1 2
RISK CATEGORIES	TOTAL SCORE	
Low risk	0-1	
Moderate risk	2-4	
High risk	5-7	

- Based on the LENT score, patients are divided into high, moderate and low risk and are followed up at 1, 3, 6 months or until death whichever is earlier.
- The primary outcome measure was survival time, calculated from date of diagnosis with malignant pleural effusion and date of death or final follow up.

Statistical analysis:

- Data was analysed using SPSS Version 20.
- Receiver operating characteristic curve (ROC curve) analysis comparing survival at 1, 3, 6 months is done using LENT score and ECOG performance status.

III. Result

Out of 30 patients, 16 were male and 14 were female. The mean age in the present study is 59.5 years. The majority of patients are in the age group of 50-70 (n=20). In the age group <50, female patients are more than male, 6:3. (table 1)

Table no 1: shows Age distribution

AGE GROUP	MALE	FEMALE	TOTAL
10-30	0	2	2
30-50	3	4	7
50-70	12	8	20
>70	1	0	1

Pleural effusions are common on right side. Right:Left:Bilateral = 17:12:1. Left side effusions are common in female patients. In patients with Carcinoma lung, the side of effusion was on the side of mass/nodular lesion.(table 2)

Table no 2: Side of effusion

SIDE OF EFFUSION	MALE	FEMALE	NUMBER OF PATIENTS
RIGHT	13	4	17
LEFT	3	9	12
BILATERAL	0	1	1

The malignant etiology was established by pleural fluid cytology and/or cell block. In present study blind pleural biopsy was done only in one patient. In patients with two samples of pleural fluid cytology reported negative for malignancy, diagnosis is made based upon the pleural fluid characteristics like colour (hemorrhagic), ADA, lymphocyte predominant effusions with a histologically proven malignancy.(table 3)

Table no 3: Mode of diagnosis of effusion

MODE OF DIAGNOSIS	NO.
CYTOLOGY/CELL BLOCK	21(70%)
PLEURAL BIOPSY	1(3%)
UNEXPLAINED PLEURAL EFFUSION WITH PROVEN MALIGNANCY	8(27%)

7 patients had pleural fluid LDH levels >1500, majority of the patients had their LDH levels between 500-1000.(table 4)

Table no 4: LDH levels

LDH(IU)	NUMBER OF PATIENTS
>1500	7
1000-1500	3
500-1000	17
<500	3

In the present study, 24 patients had a ECOG score of 2 or more.(table 5)

Table no 5: ECOG PS

ECOG PS	NO. OF SUBJECTS
0	1
1	5
2	9
3-4	15
5	0

In this study, only 1 patient had a N/L ratio of >9, although 16 patients had neutrophilia they didn't reach the cutoff value.

Of 30 subjects, carcinoma lung is diagnosed in 22 and 8 had primary outside the lung. (table 6)

Table no 6: Primary malignancy

PRIMARY TUMOR	NO. OF PATIENTS
CARCINOMA LUNG	22
CERVIX	2
BREAST	1
MESOTHELIOMA	1
THYMOMA	1
THYROID	1
ESOPHAGUS	1
OSTEOSARCOMA	1

In the present study, 14 patients were in high risk group based on LENT score (score of 5-7), 15 patients in moderate risk group (score of 2-4) and only one patient in low risk group. (table 7)

Table no 7: LENT score risk groups

SEX	HIGH RISK(5-7)	MODERATE RISK(2-4)	LOW RISK(0-1)
MALE	7	8	1
FEMALE	7	7	0
TOTAL	14	15	1

Overall median survival in the study is 45days. (table 8)

Table no 8: Median survival

GROUP	MEDIAN SURVIVAL(DAYS)
OVER ALL (n=30)	45
HIGH RISK (n=14)	30
MODERATE RISK (n=15)	75
LOW RISK (n=1)	210

In the high risk group (n=14), 42% (n=6) were alive at 1 month. In the moderate risk group (n=15), the survival at 1, 3, 6 months was 93%, 33% and 26% respectively. (table 9)

Table no 9: Survival rate at 1, 3, 6 months

RISK GROUP	SURVIVAL AT 1 MONTH	SURVIVAL AT 3 MONTHS	SURVIVAL AT 6 MONTHS
HIGH (n=14)	42% (n=6)	0	0
MODERATE (n=15)	93% (n=14)	33% (n=5)	26% (n=4)
LOW (n=1)	100% (n=1)	100% (n=1)	100% (n=1)

Receiver operating characteristic curve (ROC Curve) using ECOG PS:

- For survival at 1 month with associated criterion of ECOG PS >2 has AUC (area under curve) of 0.855 and p value < 0.0001
- For survival at 3 months with associated criterion of ECOG PS >1 has AUC of 0.938 and p value < 0.0001
- For survival at 6 months with associated criterion of ECOG PS >1 has AUC of 0.976 and p value < 0.0001
- Above findings suggest that ECOG is a statistically significant prognostic factor.

ROC Curve using LENT Score:

- For survival at 1 month with associated criterion of LENT score >4 has AUC of 0.760 and p value < 0.0001
- For survival at 3 months with associated criterion of LENT score >4 has AUC of 0.889 and p value < 0.0001
- For survival at 6 months with associated criterion of LENT score >3 has AUC of 0.920 and p value < 0.0001
- Above findings implies that LENT score can significantly predict survival in all risk groups.

IV. Discussion

Malignant cells in pleural fluid and/or parietal pleura signifies disseminated or advanced disease and a reduced life expectancy in patients with cancer¹. Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer and longest in ovarian cancer.

Several studies were undertaken to know the role of various factors like ECOG PS, koronofsky, pleural fluid pH, glucose, LDH, N/L ratio, primary site of malignancy in predicting survival in malignant pleural effusions. Studies revealed variable results with above factors with ECOG PS consistently being the best predictor of prognosis and thereby guiding the treatment plan.

Evaluating treatment strategies in malignant pleural effusion suggest that clinicians are inaccurate at predicting survival in this population. In the TIME 2 trial, 36/106 participants (34%) died within 3 months of trial entry (despite an exclusion criteria for trial entry of predicted survival of <3 months) and 58/340 (17%) of patients died within 30 days of trial entry to the Dresler et al study (who only included patients with a predicted survival of >2 months)^{2,3}. This highlights that clinical judgement alone is imprecise at estimating patient survival. In addition, the ECOG performance status of patients with malignant pleural effusion may vary as the effusion is managed and hence solely relying only on this to predict prognosis may be suboptimal.

O Clive et al developed and validated LENT score and demonstrated that it has a better performance than ECOG alone⁴. Present study is a prospective study conducted in patients with malignant pleural effusion, to evaluate the role of LENT score. The median age in the present study is 60 years with majority are in 50-70 years age group. It is comparable to other studies by O clive et al, Burrows et al, Zamboni et al^{4,5,6}. The sex distribution is comparable to O clive et al in which male were 48% and female were 42%⁴. In the present study, right side effusions were more common which is similar to other studies like O clive et al⁴.

The etiological diagnosis of the effusion is established by cytology and/or cell block in 73% of the patients which is comparable to study by O clive et al in which cytological diagnosis is obtained in 68-81% in different study cohorts⁴. Lung cancer is the most common primary (n=22) in the present study which is similar to other studies like O clive et al. The number of extra pulmonary primary tumors are low owing to low sample size in the present study. Adenocarcinoma was the most common histological pattern reported in lung malignancy with pleural effusion. Similar results were obtained in studies by Kato et al.

The overall median survival in the present study is 45 days. Survival in studies on malignant pleural effusion, O clive et al was 4.3 months⁴, Biesla et al 5.4 months⁷, Heffner et al 4 months⁸, Burrows et al 3.3 months⁵, Zamboni et al 5 months⁶. The lower median survival in present study compared to other studies is attributed to low sample size and the predominant lung cancer patients.

Higher LDH levels were associated with worsened survival of patients. LDH level of >1500 was seen in only 7 patients. Present study showed that with LDH alone there is no significant association with survival. Martinez-Moragon et al reported that LDH concentration >600 U/L was a significant predictor of poor survival

(6months vs. 10months, $P<0.01$). However, in a multivariate study by Amiz Z et al showed that LDH is not a significant predictor of mortality⁹.

ECOG PS scale evaluates disease progression and quantifies the extent to which the disease affects the daily living abilities of the patient. In our study, 90% of the patients with a PS of 2 or less were alive at 1 month and 25% with a score of 3 or more were alive at 1 month. 91.67% of the patients with score of 1 or less were alive at 3 months, whereas 83.33% patients with a score of 2 or more were dead by 3 months. Patients with a score of 2 or more has 100% mortality at 6 months. Above findings suggest that ECOG is a statistically significant prognostic factor. The disadvantage of ECOG PS is its subjective nature and inter personal variation in assessment of score¹⁰. Findings in the present study are in accordance with those of Zamboni et al and Anevlavis et al¹¹. Both of them found that Performance Scale scores were predictive of survival in patients with malignant pleural effusion. The limitations of using ECOG PS are poor reliability, variable levels of interobserver agreement, subjective nature, poor concordance between patient recorded and physician recorded PS.

Systemic inflammation play an important role in cancer progression, and a high neutrophil to lymphocyte ratio (NLR) has been reported to be a poor prognostic indicator in several malignancies. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells and natural killer cells. Neutrophils and macrophages have been reported to secrete tumor growth promoting factors thus likely contribute to a stimulating tumor microenvironment. N/L ratio cutoff in LENT score is 9, in our study only one patient had a N/L ratio of >9 , although 16 patients had neutrophilia they didn't reach the cut off value. The prognostic effect of NLR was highest in mesothelioma, followed by pancreatic cancer, renal cell carcinoma, colorectal carcinoma, gastroesophageal cancer, non small cell lung cancer, cholangiocarcinoma and hepatocellular carcinoma^{12,13}.

Many studies evaluated the primary site of malignancy as a prognostic marker in malignant effusion. Studies showed that the median survival in malignant pleural effusion depends on the primary tumor with carcinoma lung having poor and breast, gynecological tumors having the best prognosis. The median survival among lung cancer group in the present study is 37 days which is similar to studies by O clive et al and Biesla et al.

Lent Score calculated from LDH, ECOG PS, N/L ratio and the primary tumor. In present study ($n=30$), the no. of high, moderate risk cases are 14, 15 and their median survival are 30 days and 75 days respectively. There is only one patient under low risk category who survived for 210 days. In study by O clive et al, low risk, moderate risk and high risk groups gave median survivals of 319 days, 130 days and 44 days respectively. In present study high risk group, only 42% survived 1 month and none beyond 3 months compared to 65% of patients with a high risk LENT score survived 1 month and just 3% survived 6 months in study by O clive et al and 1 and 6 month survival was 89% and 44% in study by Psallidas et al¹⁴.

Receiver operating characteristic curve (ROC curve) using LENT score for survival at 1, 3, 6 months with associated criterion >4 LENT score for 1, 3 months and >3 for 6 months gave p value of <0.0001 , thus implying that LENT score can significantly predict survival in all risk groups. Similar results were produced by O clive et al and Psallidas et al. ROC Curve analysis of survival at 1, 3, 6 months using LENT and ECOG PS showed that ECOG PS has a good level of accuracy in predicting survival in malignant pleural effusion better than LENT score, although the difference between them is statistically insignificant. ROC analysis of survival at 1, 3, 6 months using both LENT and ECOG PS showed that they both had statistically significant association with survival.

On the other hand LENT score is only partially subjective and its consideration of other variables which are readily available makes it potential option for risk stratification and prognosis of the patient.

The limitations of the study are low sample size and less number of extra pulmonary malignancies or low risk tumors. This is the likely cause of low mortality in our study when compared to other previous studies. Future studies are required which employ larger sample size with both high and low risk malignancies.

V. Conclusion

- The LENT prognostic score is a good prognostic factor in patients with malignant pleural effusions and can be used for risk stratification in this group of patients for planning therapy.
- ECOG PS is also a significant predictor of mortality and there is no statistically significant difference between ECOG PS and LENT in predicting prognosis.
- The LENT scoring system is less subjective than ECOG PS and relies on readily available tests, allowing it to be rapidly calculated without additive costs.

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Dr G.Lavanya, et. al. "Role of Lent Score in Predicting Survival in Malignant Pleural Effusion."
IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), 21(11), 2022, pp. 13-19.