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Neutrophil-Lymphocyte Ratio in Serum and Pleural Fluid as Prognostic Factors in Malignant Pleural Effusion

Dr Athira Krishna Sugesh[1],Dr R.Sunil kumar M.D[2],
Dr S.Praveena M.D[3], Dr V Vijayakumari M.D[4]

[1](Department of Respiratory Medicine, GHCCD, Andhra Medical College, Visakhapatnam, NTRUHS, India)
[2](Department of Respiratory Medicine, GHCCD, Andhra Medical College, Visakhapatnam, NTRUHS, India)
[3](Department of Respiratory Medicine, GHCCD, Andhra Medical College, Visakhapatnam, NTRUHS, India)
[4](Department of Respiratory Medicine, GHCCD, Andhra Medical College, Visakhapatnam, NTRUHS, India)

Abstract:
Background*: In lung cancer as well as metastatic carcinoma, presence of malignant pleural effusion indicates advanced stage of cancer and hence poor prognosis.Many studies have shown that the neutrophil-to-lymphocyte ratio in the serum(sNLR) can be used as a cost effective and a useful prognostic factor in different types of cancer. In this study we investigated the clinical impact of serum NLR (sNLR) and NLR in pleural fluid(mNLR) as prognostic factors in malignant pleural effusion (MPE) and thereby decide the appropriate therapy for the patients.*
Materials and Methods*:In this study we retrospectively reviewed 12o patients with age 18 years or above, who were diagnosed with malignant pleural effusion.12 patients were excluded due to paramalignant effusion and lack of pleural fluid hemogram reports. Hence a total of 108 patients were analysed. Serum NLR and pleural fluid NLR were calculated for each patient. The relationship between sNLR and mNLR value with survival in these patients was investigated.*
Results*: Patients with mNLR value ≥0.41(p value<0.001) and/or sNLR value ≥4.68(p value <0.024) had a shorter survival. Multivariate analysis showed that survival was significantly related to mNLR ≥0.41(Odds ratio 5.93 95% CI p value 0.027) and sNLR ≥ 4.68(Odds ratio 6.73 95% CI p value 0.017).*
Conclusion*: mNLR and sNLr act as simple and cost effective prognostic factors in MPE. Also these results maybe helpful to carry out further research into the mNLR in the future. This information will help clinicians to determine the survival of patients with MPE at presentation and determine the appropriate therapy for them.*
Key Word*: Malignant pleural effusion, sNLR, mNLR, Prognostic factors*

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I. Introduction

In lung cancer as well as metastatic carcinoma, malignant pleural effusion indicates advanced stage of cancer and it usually indicates that mortality is likely to occur in a few months after identification.[1,2]The frequency of malignant pleural effusion ranges from 7% to 23% in lung cancer patients[3].The median survival periods range between 3 and 12 months.[4] Due to this, the prognosis stage category for lung cancer with malignant pleural effusion was upgraded from T4 to M1a.[5]There are many treatment modalities one can opt to relieve respiratory symptoms due to malignant pleural effusion. Based on the predicted survival ,one can select less invasive to more invasive modalities. If expected survival is shorter,less invasive procedures are performed[2,4,6,7]

Some factors might be useful in predicting survival in patients with malignant pleural effusion. One such predictor is serum neutrophil-lymphocyte ratio(sNLR). A meta-analysis consisting of an analysis of 100 studies showed that elevated serum neutrophil-to lymphocyte ratios (sNLR), are associated with adverse Overall Survival (OS) for many solid tumor types as a several systemic inflammatory indicator. Therefore, the sNLR may be used as a useful and cost-effective survival time prognostic factor.[8] Clinical effects of NLR as a predictive tool in MPE (mNLR) was studied by Lee et al and he developed a new scoring system in lung cancer patients that uses sNLRs and mNLR, known as the smNLR score [9], which suggest that the mNLR (and also the sNLR) may be used as a new predictive factor of survival in MPE patients.

This study is intended to investigate the ability of sNLR and mNLR in estimating survival times in a patient presenting with malignant pleural effusion.

II. Material And Methods

It is a retrospective observational study carried out in hospitalized patients with malignant pleural effusion in Department of Respiratory Medicine at Government Hospital for Chest & Communicable diseases, Andhra medical college, Visakhapatnam from June 2018 – June 2020. A total of 120 patients(both males and females) of age ≥ 18 years were studied.

Study Design: Hospital-based retrospective observational study

Study Location: This was a tertiary care teaching hospital based study done in Department of Respiratory Medicine, at GHCCD, Andhra Medical College, Visakhapatnam, Andhra Pradesh

Study Duration: June 2018 to June 2020

Sample size:120 patients

Sample size calculation:A total of 120 consecutive patients presented with malignant pleural effusion during the study period were included in the study

Subjects & selection method: The study population was drawn from malignant pleural effusion patients who got admitted in Government Hospital for chest &communicable diseases, Visakhapatnam during the study period.12 patients were excluded due to paramalignant effusion and lack of pleural fluid hemogram reports. Hence a total of 108 patients were analysed in the study with mean age of 55±10 years

Inclusion criteria:

1.Patients with pleural effusion in which malignant cells were confirmed in the pleural fluid or pleural biopsy.
2.Patients ≥18 years.

Exclusion criteria:

1. Patients with paramalignant pleural effusion,in whom malignant cells were not identified in pleural fluidand/or pleural biopsy
2.Patients who did not have pleural fluid hemogram analysis values
3.Patients <18 years.

Procedure methodology:

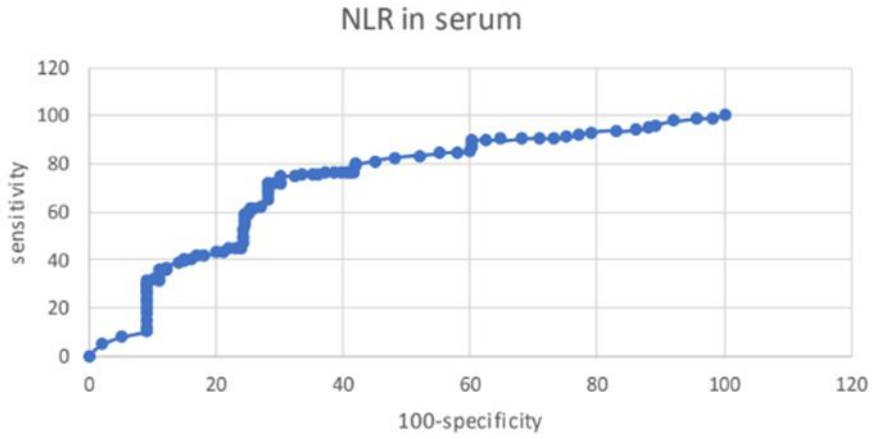
Clinical and laboratory data were collected from hospital medical records which included age, gender, and complete blood count, pleural fluid hemogram reports. NLRs were obtained by dividing absolute neutrophil count by lymphocyte count in complete blood count at diagnosis and in total cell count of malignant pleural effusion after diagnostic thoracocentesis. A follow up period of 2 years from the time of diagnosis was selected. Survival times were obtained from hospital records and by direct information from patient family members.

Statistical analysis:

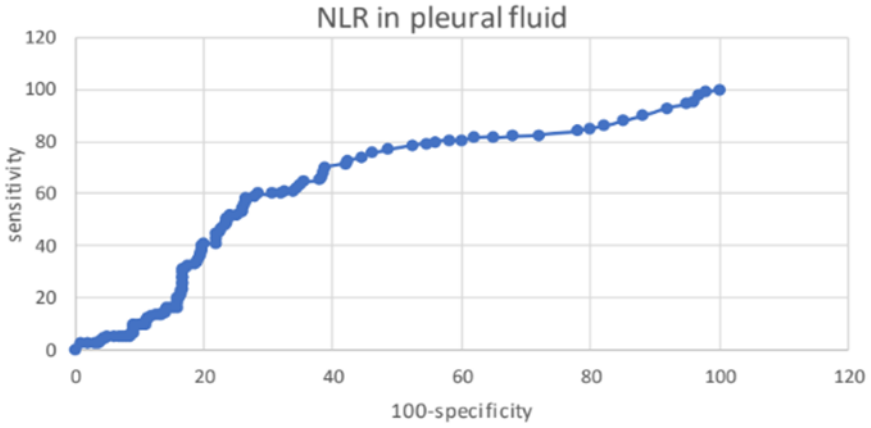
Statistical analysis was performed using SPSS. The compliance of continuous variables to normal distribution was tested. Receiver Operating Characteristic (ROC) analysis was performed for variables sNLR and mNLR and the most appropriate cut-off value was determined by the Youden index.A cut off of 0.41 was obtained for mNLR and 4.68 for sNLR. Overall survival (OS) curves were produced using Kaplan-Meier methods and the survival difference between groups was assessed by the log-rank test. Cox regression analysis was used to develop the multivariate models describing the association of the independent variables with OS.$p<0.05$ was considered to have statistical significance; and 95% Confidence Interval was identified for each parameter.

III. Result

108 patients were included.60 patients were males and 48 were females. The mean age of the patients was 55±10 years. The follow up period was 2 years. The optimal cut off values for sNLR and mNLR were obtained from receiver operating curves(ROC) and sNLR ≥ 4.68 and mNLR ≥ 0.41 were considered cut off.



ROC showing the cut off value for serum NLR(sNLR).Area under the curve(AUC) value of 0.72 was obtained using sNLR as a prognostic factor and sensitivity and specificity were 71.5% and 67.2% respectively at a cut off level of ≥4.68

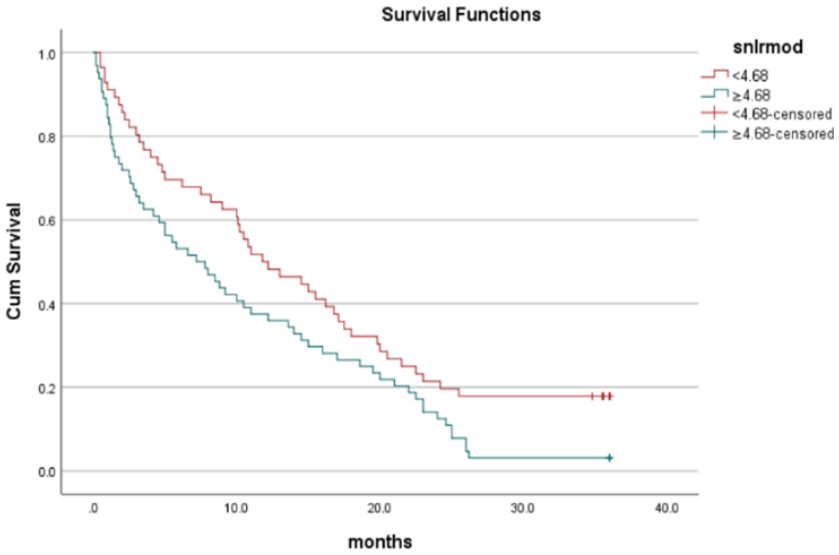


ROC showing the cut off value for pleural fluid NLR(mNLR).Area under the curve(AUC) value of 0.62 was obtained using mNLR as a prognostic factor and sensitivity and specificity were 70.2% and 58% respectively at a cut off level of ≥0.41

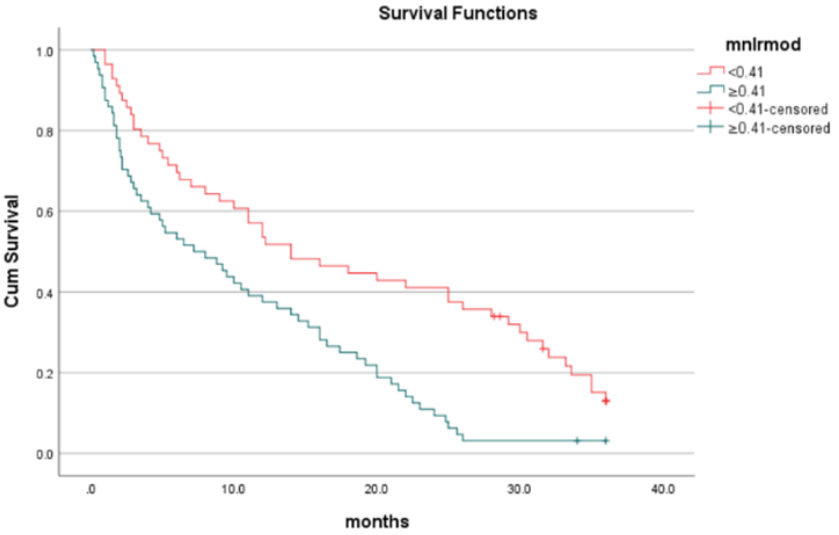
Table no 1 Shows sensitivity and specificity of cut off values obtained for sNLR≥4.68 and mNLR≥0.41

	Sensitivity	Specificity
sNLR≥4.68	71.5%	67.2%
mNLR≥0.41	70.2%	58%

Overall survival curves were produced using Kaplan-Meier method.



Survival analysis curves were drawn according to sNLR with the cut off of 4.68



Survival analysis curves were drawn according to mNLR with the cut off of 0.41

Table 2 Shows means and medians for survival time using sNLR cut off as 4.68. A mean survival time of 10.5 months and median survival time of 7.2 months was obtained for patients witrh sNLR≥4.68. A mean survival time of 14.9 months and median of 11.8 months was obtained for patients with sNLR<4.68.

MEANS AND MEDIANS FOR SURVIVAL TIME								
SNLR	MEAN				MEDIAN			
	ESTIMATE	STD ERROR	95% CI		ESTIMATE	STD ERROR	95% CI	
			LOWER BOUND	UPPER BOUND			LOWER BOUND	UPPER BOUND
<4.68	14.995	1.592	11.874	18.115	11.8	2.494	6.911	16.689
≥4.68	10.522	1.222	8.1127	12.917	7.2	1.9	3.476	10.924
overall	12.609	1.009	10.631	14.587	10	1.18	7.688	12.312

Table 3 Shows assessment of survival difference between two groups by log rank test.Chi square value is 5.07 and there is a significant difference in survival between the two groups(p value 0.024)

	CHI SQUARE	SIGNIFICANCE
LOG RANK(MANTEL COX)	5.07	0.024

Table 4 Cox regression model showing significant association between survival and sNLR values.p value 0.017 and Exp(B) – adjusted Odds ratio was 6.739

Variables in the equation									
		B	STD ERROR	WALD	df	sig	Exp(B)	95% CI for Exp(B)	
Step 1a	sNLR	1.908	0.799	5.707	1	0.017	6.739	1.409	32.243
	constant	1.526	0.349	19.13	1	0	4.6		

Table 5 Shows means and medians for survival time using mNLR cut off as 0.41. A mean survival time of 10.4 months and median survival time of 7.2 months was obtained for patients witrh mNLR≥0.41. A mean survival time of 17.9 months and median of 14 months was obtained for patients with mNLR<0.41.

MEANS AND MEDIANS FOR SURVIVAL TIME								
mNLR		MEAN			MEDIAN			
	ESTIMATE	STD ERROR	95% CI		ESTIMATE	STD ERROR	95% CI	
			LOWER BOUND	UPPER BOUND			LOWER BOUND	UPPER BOUND
<0.41	17.901	1.791	14.391	21.412	14	3.739	6.671	21.329
≥0.41	10.469	1.177	8.162	12.776	7.2	2.25	2.79	11.61
overall	13.94	1.097	11.789	16.091	10.5	1.461	7.637	13.363

Table 6 Shows assessment of survival difference between two groups by log rank test.Chi square value is 14.14 and there is a significant difference in survival between the two groups(p value 0.00)

	CHI SQUARE	SIGNIFICANCE
LOG RANK(MANTEL COX)	14.147	0

Table 7 Cox regression model showing significant association between survival and mNLR values.p value 0.027 and Exp(B) – adjusted Odds ratio was 5.936

Variables in the equation									
		B	STD ERROR	WALD	df	sig	Exp(B)	95% CI for EXP(B)	
Step 1a	mNLR	1.781	0.805	4.891	1	0.027	5.936	1.225	28.773
	constant	1.653	0.364	20.638	1	0	5.222		

sNLR was significantly associated with shorter survival with p value 0.017 and OR of 6.73 and mNLR was significantly associated with shorter survival with p value 0.027 and OR 5.93.

Survival analysis according to combined NLR with sNLR≥4.68 and mNLR ≥0.41

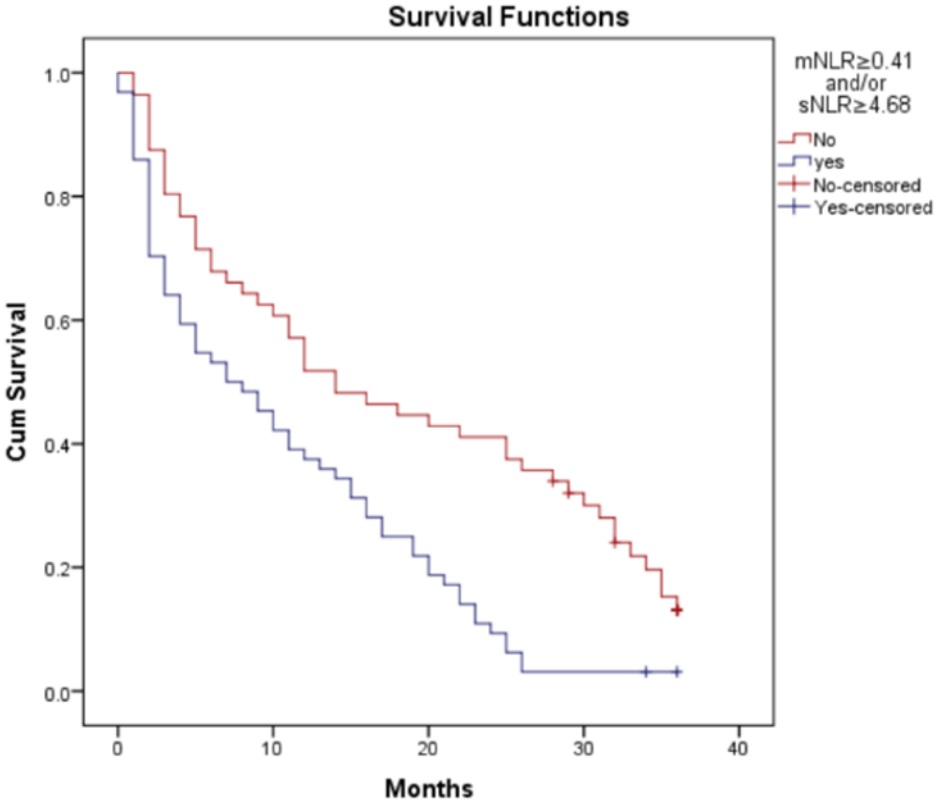


Table 8 Shows means and medians for survival time using both sNLR cut off as 4.68 and mNLR cut off as 0.41. A mean survival time of 10.5 months and median survival time of 7 months was obtained for patients with sNLR and mNLR above cut off. A mean survival time of 17.9 months and median of 14 months was obtained for patients with sNLR and mNLR below cut off.

MEANS AND MEDIANS FOR SURVIVAL TIME								
	MEAN				MEDIAN			
			95% CI				95% CI	
mNLR≥0.41 and/or sNLR ≥4.68	ESTIMATE	STD ERROR	UPPER BOUND	LOWER BOUND	ESTIMATE	STD ERROR	UPPER BOUND	LOWER BOUND
No	17.960	1.790	14.451	21.468	14.000	3.739	6.671	21.329
Yes	10.563	1.172	8.255	12.870	7.000	2.182	2.724	11.276
overall	14.017	1.097	11.867	16.166	11.000	1.563	7.937	14.063

The estimated median survival time was 7 months when pleural fluid NLR and/or serum NLR values were above cut-off values.
The estimated median survival time was longer 14 months when sNLR and mNLR were less than cut-off values. Also multivariate analysis showed that survival was significantly related to mNLR ≥ 0.41(OR:5.93 95%CI p value-0.027) and sNLR ≥ 4.68(OR 6.73 95%CI p value 0.017)

IV. Discussion

In our study, it was found that sNLR and mNLR are significant predictive factors for overall survival times in patients with malignant pleural effusion. Therefore, evaluation of both the sNLR and mNLR values together is useful and cost-effective in estimating overall survival in malignant pleural effusion.The sNLR and mNLR values together made up a more accurate prognostic tool than mere sNLR,which was first reported as a prognostic factor in various cancer patients.[10,11,12] Also, differential leukocyte counts, especially neutrophil and lymphocyte count, are objective parameters that can evaluate the severity of systemic inflammatory response in cancer patients[10,11,13] These studies suggested that elevated sNLR levels make up a good predictor of shorter overall survival times in solid tumor patients of various stages.

A recent study showed that the sNLR is a significant prognostic factor to predict survival in MPE patients. Anevlavis et al. suggested that prognostic factors that affected survival in MPE patients were ECOG PS, primary tumor histology, and NLR[14]

V. Conclusion

mNLR and sNLr act as simple ,useful ,readily available and cost effective prognostic factors in malignant pleural effusion. Both combined can be used to estimate the overall survival.Also these results prompt us to carry out further research into the mNLR in the future. This information will help clinicians to determine the survival of patients at presentation and determine the appropriate therapy for them.

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