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Research Article

A STUDY OF NEUTROPHIL LYMPHOCYTE-TO-ALBUMIN RATIO TO PREDICT SHORT-TERM MORTALITY IN ALCOHOL-RELATED LIVER DISEASE

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ABSTRACT

Aims and Objectives: The aims of this study were as follows: (1) to study neutrophil lymphocyte-to-albumin ratio (NLAR) in alcohol-related liver disease patients to predict 30-day mortality and (2) to determine the optimal cutoff value of the NLAR that maximizes sensitivity and specificity for predicting short-term mortality.

Methods: A prospective study conducted at our hospital for 18 months. A total of 46 males visiting the medicine OPD and IPD were included in the study. All patients underwent complete blood count (CBC), liver function tests (LFTs) including serum albumin. Neutrophil lymphocyte to albumin ratio was determined in all cases. Data was analyzed using appropriate inferential statistics.

Results: The majority of participants fall within the 31–40 age group (26.1%), followed by the 41–50 age group (23.9%). The majority of participants were diagnosed with cirrhosis of the liver (65.2%), while alcoholic hepatitis (AH) and fatty liver disease were both observed in 17.4% of the participants. The outcomes at 30 days a significant majority of the cases resulted in death (65.2%), with only 34.8% of the cases being followed up. We observe that for NLA, the cutoff value is observed to be 19.15 with a sensitivity of 100% and specificity of 100%. There is a significant mean difference observed for Hemoglobin, total count, neutrophil, lymphocyte, urea, INR, total protein, albumin, and NLA.

Conclusion: A cutoff value of 19.15 for the NLAR is identified as highly sensitive and specific, highlighting its clinical significance as patients with an NLA ratio above this threshold have a high probability of death within 30 days.

Keywords: Neutrophil lymphocyte-to-albumin ratio, Alcoholic liver disease, Cirrhosis, Mortality.

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INTRODUCTION

Alcoholic liver disease (ALD) comprises a clinical-histologic spectrum including fatty liver, alcoholic hepatitis (AH), and cirrhosis with its complications [1]. AH is an acute inflammatory condition characterized by hepatocellular injury mediated by alcohol-induced oxidative stress [2]. Cirrhosis is defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture with nodules. It is the leading cause of liver-related death in Asia-Pacific region and deaths due to cirrhosis in this region represented 54.3% of cirrhosis-related deaths globally in 2015 [3].

The progression of ALD can be divided into three primary stages, namely steatosis, AH, and cirrhosis. Steatosis, or fatty liver, is the initial stage and is characterized by the accumulation of fat within hepatocytes. This condition is usually asymptomatic and reversible with abstinence from alcohol. However, continued alcohol intake can lead to AH, a condition marked by inflammation and necrosis of liver cells. Clinically, this stage presents with jaundice, fever, and liver tenderness. The most severe stage of ALD is cirrhosis, where there is extensive fibrosis and scarring of the liver tissue, leading to impaired liver function. Cirrhosis can progress to liver failure and is often complicated by portal hypertension, ascites, hepatic encephalopathy, and variceal bleeding [4].

Biochemical derangements in ALD are reflective of both liver dysfunction and systemic inflammation. Patients with ALD typically exhibit elevated liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with an AST-to-ALT ratio often >2. Gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels may also be elevated [5]. Hypoalbuminemia has long been considered a cardinal feature of decompensated cirrhosis resulting from several events, such as reduced synthesis by hepatocytes, shorter total half-life attributable to increased catabolism, and dilution attributable to total plasma volume expansion. Low serum albumin concentration, measured by routine laboratory methods, has been consistently shown to be a good prognostic indicator of both mortality and morbidities in decompensated cirrhosis [6].

The neutrophil-to-lymphocyte ratio (NLR) and albumin levels have emerged as important prognostic markers in various inflammatory and malignant conditions. In the context of ALD, the neutrophil lymphocyte-to-albumin ratio (NLAR) has been proposed as a novel marker to predict short-term mortality [7]. NLR is an indicator of systemic inflammation, with elevated neutrophil counts reflecting an acute inflammatory response and reduced lymphocyte counts indicating immune suppression. Albumin, a negative acute phase reactant, is decreased in chronic liver disease due to impaired synthetic function [8]. The combined measurement of these parameters into the NLAR provides a comprehensive index of both the inflammatory state and liver function. Studies have shown that a higher NLAR is associated with increased mortality in ALD patients, suggesting its utility as a prognostic tool [9].

METHODS

This was a prospective study conducted in the department of general medicine of a tertiary care medical institute. The duration of the study was 18 months extending from August 1, 2022, to January 31, 2024. Ethical clearance was taken from the Institutional Ethical Committee. A total of 46 patients attending the medicine OPD and IPD were included in this study on the basis of a predetermined inclusion and

exclusion criteria. Information was collected through prepared pro forma from each patient.

Demographic details such as age gender and socioeconomic status were noted in all cases. Detailed medical history, including comorbidities and previous episodes of hepatitis, was asked for and documented. A detailed clinical examination was done which included vital signs, general physical examination, and a thorough abdominal examination to detect signs of liver disease, such as hepatomegaly, ascites, and jaundice.

All patients underwent biochemical investigations including complete blood count to determine neutrophil and lymphocyte counts, liver function tests to measure levels of AST, ALT, bilirubin, ALP, GGT, and albumin, and coagulation profiles, including prothrombin time and international normalized ratio (INR). Serum electrolytes and renal function tests were performed to monitor associated metabolic disturbances. Ultrasound imaging of the abdomen was done to assess liver size, echotexture, and the presence of cirrhosis or ascites. Additional imaging studies, such as elastography or CT scan, may be performed for more detailed evaluation if indicated. Serial monitoring of these parameters was done to observe changes in NLAR and their correlation with clinical outcomes, particularly short-term mortality.

Statistical analysis was performed using SPSS version 22.0 software. Quantitative data, such as neutrophil counts, lymphocyte counts, albumin levels, and NLAR values, were presented as mean and standard deviation. Qualitative data, including the presence or absence of complications, were summarized in incidence and percentage tables. To analyze quantitative data, an unpaired t-test was employed. For qualitative data, the Chi-square test was used to evaluate associations. A p-value of < 0.05 was considered statistically significant, indicating a meaningful relationship between NLAR and short-term mortality in patients with alcohol-related liver disease.

Inclusion criteria

1. Patients diagnosed with alcohol-related liver disease
2. Age above 18 years
3. Those who gave informed and written consent of the study.

Exclusion criteria

1. Those who refused consent to be part of study
2. Age below 18 years
3. Patients with recent history of viral hepatitis
4. Known cases of autoimmune hepatitis, drug-induced hepatitis, Budd–Chiari syndrome, liver injury, hepatocellular carcinoma, or other malignancies
5. Pregnant or lactating women.

RESULTS

The analysis of gender distribution of the cases in this study showed that all patients were males (100%). No female patient was diagnosed with ALD during the study period. The analysis of the age distribution of the studied cases showed that the most common age interval was 31–40 years, with 12 individuals (26.1%). This was followed by the 41–50 age group which included 11 individuals (23.9%). Both the 21–30 and 51–60 age intervals had nines individuals each, both representing 19.6% of the cases. The least common age group was those over 60 years, with 5 individuals (10.9%). In total, 46 cases were analyzed, making up 100% of the study population (Table 1).

The analysis of the type of ALD in the studied cases showed that the most common diagnosis was cirrhosis of the liver, with 30 individuals (65.2%). Both AH and fatty liver were diagnosed in eight individuals each, representing 17.4% of the cases for each condition (Table 2).

The analysis of the 30-day outcomes based on age intervals showed that in the 21–30 age group, 22.2% (2 patients) died and 77.8% (7 patients) were followed up, totaling nine patients. In the 31–40 age group, 75.0% (9 patients) died while 25.0% (3 patients) were followed up, making a total of 12 patients. In the 41–50 age groups, all patients died, with 100.0% (11 patients) mortality and no follow-up cases, summing up to 11 patients. Among the 51–60 age groups, 55.6% (5 patients) died and 44.4% (4 patients) were followed up, totaling nine patients. For those over 60 years old, 60.0% (3 patients) died while 40.0% (2 patients) were followed up, making up a total of five patients. Overall, the total across all age groups showed that 65.2% (30 patients) died while 34.8% (16 patients) were followed up. There was a statistically significant association of age and outcome ($p<0.05$) (Fig. 1).

The analysis of diagnoses across age intervals showed that the most common diagnosis overall was cirrhosis of the liver (65.2%), followed by AH (17.4%) and fatty liver (17.4%). The 21–30 age group predominantly had fatty liver (55.6%), the 31–40 and 41–50 age groups primarily had cirrhosis of the liver (75.0% and 100.0%, respectively), and those over 60 had a significant prevalence of cirrhosis (60.0%) and fatty liver (40.0%). The differences in diagnoses across age groups were statistically significant (Chi-square statistic = 22.272, p=0.004) (Table 3).

The analysis of the distribution of cases according to diagnosis and outcome at 30 days showed that all patients with AH (100.0%, 8 patients) and fatty liver (100.0%, 8 patients) were followed up with no deaths reported in these groups. Conversely, all patients with cirrhosis of the liver (100.0%, 30 patients) died, with no follow-ups recorded. Overall, across all diagnoses, 65.2% (30 patients) died, while 34.8%

Table 1: Age distribution of the studied cases

Age interval	Frequency	Percent
21–30	9	19.6
31–40	12	26.1
41–50	11	23.9
51–60	9	19.6
>60	5	10.9
Total	46	100.0

Table 2: Type of alcoholic liver disease in studied cases

Diagnosis	Frequency	Percent
Alcoholic hepatitis	8	17.4
Cirrhosis of liver	30	65.2
Fatty liver	8	17.4
Total	46	100.0

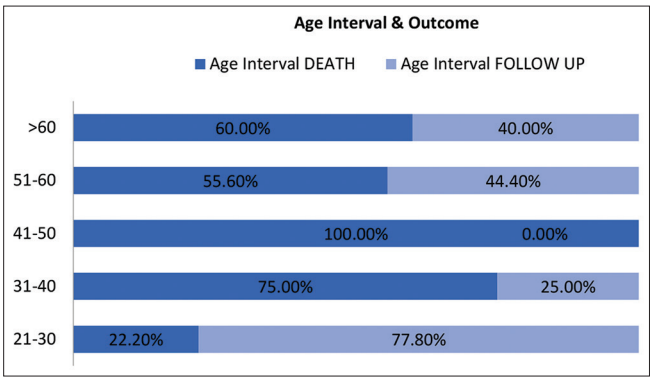

Fig. 1: Proportions of outcome among different age groups

(16 patients) were followed up. The Chi-square statistic is 46.00 with a p=0.000, indicating a statistically significant difference in outcomes based on diagnosis (Table 4).

Analysis of area under cure (AUC), its standard error, p-value, and confidence interval was done for determination of the overall accuracy of NLA in classifying death and follow-up groups. The test suggested that NLA has very high accuracy on classifying the case among death and follow-up (Table 5).

Gini's index test was used to classify the ability of the predictors as to how good the predictors have the ability to classify the measurements into the similar group. In this study, it was observed that for NLA, the cutoff value of 19.15 was having sensitivity as well as a specificity of 100% (Table 6).

The analysis of the correlation of various factors with mortality revealed several significant associations. Hemoglobin, total count, neutrophil count, lymphocyte count, urea, creatinine, INR, total protein, albumin, and the neutrophil lymphocyte-to-albumin ratio (NLA) all showed significant differences between the follow-up and deceased groups ($p<0.005$), indicating these parameters are strongly associated with mortality. Non-significant parameters included age, sodium, potassium, PT, direct bilirubin, indirect bilirubin, platelet count, SGOT, SGPT, ALP, and globulin, suggesting these factors did not show a strong correlation with mortality in this study ($P>0.05$) (Table 7).

DISCUSSION

The aim of our study was to study NLAR in alcohol-related liver disease patients to predict 30-day mortality and to determine the optimal

Table 3: Correlation of age with type of liver disease

Age interval	Diagnosis			Total
	Alcoholic Hepatitis	Cirrhosis of liver	Fatty liver	
21–30	2	2	5	9
	22.2%	22.2%	55.6%	100.0%
31–40	3	9	0	12
	25.0%	75.0%	0.0%	100.0%
41–50	0	11	0	11
	0.0%	100.0%	0.0%	100.0%
51–60	3	5	1	9
	33.3%	55.6%	11.1%	100.0%
>60	0	3	2	5
	0.0%	60.0%	40.0%	100.0%
Total	8	30	8	46
	17.4%	65.2%	17.4%	100.0%

*Chi-square statistic=22.272, p=0.004 (significant)

Table 4: Distribution of cases according to diagnosis and outcome

Diagnosis	Outcome at 30 days		Total
	Death	Follow-up	
AH	0	8	8
	0.0%	100.0%	100.0%
Cirrhosis of liver	30	0	30
	100.0%	0.0%	100.0%
Fatty liver	0	8	8
	0.0%	100.0%	100.0%
Total	30	16	46
	65.2%	34.8%	100.0%

*Chi-square statistic=46.00, p=0.000 (significant)

Table 5: The following table shows the results obtained from ROC method

Area under the ROC curve					
Test Result Variable (s)	Area	SE	p-value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
NLA	1.000	0.000	0.000	1.000	1.000

a. Under the non-parametric assumption
b. Null hypothesis: true area=0.5

Table 6: Shows the overall model quality obtained by ROC method

Classifier evaluation metrics					
Test Result Variable (s)	Gini Index	K-S Statistics			
		Max K-S[a]	Cutoff[b]	Sensitivity	Specificity
NLA	1.000	1.000	19.1500	0.100	0.100

a. The maximum Kolmogorov–Smirnov (K-S) metric.
b. In case of multiple cutoff values associated with Max K-S, the largest one is reported

Table 7: Correlation of various parameters and mortality in studied cases

Study parameters	Mean±SD		Mean Diff.	Significance
	Follow-up (16)	Dead (30)		
Age	41.63±16.248	44.90±9.700	−3.275	0.396 NS
Hemoglobin	11.550±3.7635	8.180±2.1237	3.3700	0.000 HS
Total count	7706.25±2754.262	14971.67±9541.269	−7265.417	0.005 HS
Neutrophil	68.31±11.859	87.07±4.899	−18.754	0.000 HS
Lymphocyte	26.50±10.930	8.70±3.914	17.800	0.000 HS
Urea	17.325±8.9715	48.667±42.5784	−31.3417	0.006 HS
Creat	0.763±0.3181	1.537±1.2039	−0.7742	0.016 S
Sodium	136.25±6.465	133.93±6.848	2.317	0.271 NS
Potassium	4.088±0.8679	4.357±1.1449	−0.2692	0.416 NS
PT	20.050±10.3509	22.327±8.6649	−2.2767	0.432 NS
INR	1.356±0.3794	1.890±0.7586	−0.5338	0.012 HS
Direct	1.969±2.1303	6.717±10.2567	−4.7479	0.075 NS
Indirect bilirubin	1.269±0.9279	2.083±1.9403	−0.8146	0.121 NS
Platelet	1.9013±0.74274	1.6523±0.90663	0.24892	0.352 NS
SGOT	149.19±72.111	101.93±115.521	47.254	0.145 NS
SGPT	56.00±36.555	46.47±40.268	9.533	0.434 NS
ALP	167.00±103.764	139.10±51.756	27.900	0.228 NS
Total protein	7.256±0.8099	6.310±1.3466	0.9462	0.014 HS
Albumin	3.219±0.7626	2.347±0.5476	0.8721	0.000 HS
Globulin	4.038±0.8740	4.033±1.0739	0.0042	0.989 NS
NLA (Neutrophil lymphocyte-to-albumin ratio)	10.2431±4.79373	58.7833±47.38548	−48.54021	0.000 HS

*HS: Highly significance, S: Significance, NS: Not significance

cutoff value of the NLA ratio that maximizes sensitivity and specificity for predicting short-term mortality.

The analysis of age groups of the patients showed that the majority of the patients belonged to 31–40 age group (26.1%) and the 41–50 age group (23.9%). Cirrhosis of the liver was the most common diagnosis (65.2%), followed by AH and fatty liver disease (both 17.4%). A high mortality rate of 65.2% was observed, with significant associations found between age and outcome (Chi-square=14.138, p=0.007) and between age and diagnosis (Chi-square=22.272, p=0.004). The 41–50 age groups had a 100% death rate, while the 21–30 age group had the highest follow-up rate (77.8%). All cases of cirrhosis resulted in death, contrasting sharply with AH and fatty liver cases, which had 100% follow-up rates (Chi-square=46.00, p=0.000). The neutrophil lymphocyte-to-albumin (NLA) ratio demonstrated perfect classification ability, with an AUC, Gini index, and K-S statistic all at 1.000 and a cutoff value of 19.15, achieving 100% sensitivity and specificity.

Jeong *et al*. conducted a retrospective study to identify predicting factors for mortality in alcoholic liver cirrhosis (LC) patients visiting the emergency department (ED) [10]. For this purpose, the authors undertook a study comprising 433 patients with alcoholic LC who visited an ED between November 2017 and June 2021. Baseline characteristics, LC complications, model for end-stage liver disease (MELD) score, and laboratory values including lactate were assessed. The study found that the in-hospital mortality rate was 15.9%. Univariate regression analyses identified MELD score, lactate, platelet count, INR, bilirubin, creatinine, albumin, and CRP as predictors of in-hospital mortality. Multivariate regression showed MELD score, lactate, albumin, and CRP significantly associated with mortality. On the basis of these findings, the authors concluded that MELD score, lactate, albumin, and CRP predicted mortality in alcoholic LC patients visiting the ED. Similar factors related to mortality in cases of ALD were also reported by the authors such as Orrego *et al*. [11] and Forrest *et al*. [12].

Zhang *et al*. conducted a retrospective study to evaluate the role of the NLR and other biomarkers in predicting short-term mortality in alcoholic cirrhosis patients [13]. For this purpose, the authors undertook a study comprising 459 male alcoholic cirrhosis patients, 345 of whom completed follow-up. Data on demographic, clinical, and biochemical features were collected for analysis. The study found that prognostic scores, including NLR, MELD, MDF, and i-MELD, were significantly higher in no surviving patients. Logistic regression showed albumin, NLR, and i-MELD correlated with 30-day mortality. ROC analysis revealed that NLR had an AUROC of 0.72. A new biomarker, NLA, had the best prognostic value with a cutoff of 19.6. On the basis of these findings, the authors concluded that the NLR and NLA are robust predictors of 30-day mortality in alcoholic cirrhosis patients. The cutoff prognostic value of NLAR in this study was found to be similar to our study. Similar cutoff values were also reported by the authors such as Du *et al*. (19.5) [14]. However, authors such as Omar YA *et al*. reported the cutoff value of NLA ratio to be lower than our study (12.3) [15].

CONCLUSION

This study highlights significant demographic and clinical findings among participants, including a predominance in the 31–40 age group and a high prevalence of cirrhosis of the liver. Mortality rates at 30 days were notably high, with further analysis indicating a critical cutoff value for NLAR as a sensitive and specific predictor. Patients with alcohol-related liver disease were predicted to have a high probability of death within 30 days if their NLAR was more than 19.15. In addition, substantial mean differences were observed in several hematological and biochemical parameters, underscoring the severity and complexity of liver diseases examined in this cohort.

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