Blood Neutrophil to Lymphocyte Ratio as a Prognostic Marker in Cirrhosis of the Liver

Dhabaleswar Meher[1], Kamalakhya Samantray[2], Niranjan Nayak[3], Rina Mohanty[4]

[1]Assistant Professor, Department of General Medicine, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, India
[2]Senior Resident, Department of General Medicine, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, India
[3]Assistant Professor, Department of General Medicine, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, India
[4]Professor, Department of General Medicine, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, India

Abstract:

Background: In this study, we wanted to correlate Neutrophil to Lymphocyte Ratio with development of complications in patients with cirrhosis of the liver in southern Odisha. We found out there is a statically significant association between Neutrophil to Lymphocyte Ratio and development of complications. Materials and Methods: This was a prospective observational study done between Sept. 2019 to Sep. 2021 in M.K.C.G. Medical College and Hospital, Berhampur, which is a tertiary care hospital in southern Odisha, India. Results: Out of 61% of alcoholic patients, 33% had elevated NLR, whereas 12% of total non-alcoholic patients had elevated NLR. This association was found to be statistically significant with p value of 0.022. 68% of patients who had elevated NLR developed complications either single or in combination. On the other hand, only 9% of patients having low NLR developed complications. Conclusion: Estimation of NLR is a cheap and easily available procedure which can be done in any hospital to monitor the development of complications in patients with cirrhosis of the liver.

Keywords: NLR, Prognosis, Cirrhosis, Mortality, Complications.

Introduction

Patients with cirrhosis develop immune dysfunction affecting both adaptive and innate immunity; develop systemic inflammation and immune deficiency. Persistence of systemic inflammation is associated with disease progression, complications and adverse outcomes.

Indicators which have been used for systemic inflammation in cirrhotic patients have limitations. The NLR is a systemic inflammatory response marker that has been developed as an independent marker of prognosis in patients with cirrhosis. It assesses two distinct pathways of the immune system: systemic inflammation by neutrophil count and immune regulation pathway by lymphocyte count. It has been studied in many liver diseases like NAFLD, Hepatitis B, and Hepatocellular carcinoma. But, data on NLR as a prognostic marker in cirrhosis of the liver is limited.

Hence, the present study Blood NLR as a prognostic marker in cirrhosis of the liver is planned to assess the role of NLR, a simple and easily available investigation as a predictor of complication in patients with cirrhosis of the liver, which will facilitate early detection and management of complications, thus improving quality of life and survival in these patients.

Objective:

To correlate NLR as a predictor of complication in patients diagnosed as cirrhosis of the liver without any history of decompensation and evaluate as prognostic marker in cirrhosis of the liver.

Methods

Source of study: Primary data collected by the principal investigator directly from the patients visiting the M.K.C.G.M.Ç.H, Berhampur.

Study design: Prospective observational study

Period of study: Two years (Sept. 2019 to Sept. 2021)

Sample size: 100 patients

Inclusion criteria

1. Patients diagnosed with Cirrhosis of the liver at M.K.C.G.M.C.H, Berhampur in the Dept. of Medicine and Gastroenterology OPD.
2. Age >18 years.

Exclusion criteria

1. Presence of secondary immunodeficiency states e.g. H.I.V. infection.
2. Hepatocellular cancer patients.
3. Patients on corticosteroids or cytotoxic drugs.
4. Patients with acute infection or inflammation.
5. Pregnancy or lactation.
6. Patients having chronic comorbidities like malignancy, CKD, stroke, A.M.I.
7. Patients not capable of giving consents.
8. Patients not willing to participate in the study.

Patients diagnosed as cirrhosis of the liver, not having prior history of hospitalization for acute decompensation and otherwise stable patients were included in the study after taking consent and fulfilling both inclusion and exclusion criteria. Alcoholics, patients with chronic hepatitis B or C infection complaining of fatigue, jaundice etc. are subjected to CBC, LFT, Serum albumin and globulin, RFT, Serum electrolytes, Tests for hepatitis B and C, USG, UGIE. Baseline NLR of cirrhotic patients has been calculated. They were followed up at 3 months, 6 months and 1 year for development of complications or hospitalization for acute decompensation. Then, the NLR, already calculated, was correlated for those who developed complications. Patients were followed up through review visits.

Investigations

Neutrophil to Lymphocyte Ratio: It is defined as the ratio of the absolute neutrophil count to absolute lymphocyte count.

SGOT (AST): It was measured in serum by the Reitman and Frankel method.

Normal value: 5-40 IU/ml

SGPT (ALT): It was measured in serum by the Reitman and Frankel method.

Normal value: 5-40 IU/ml

Alkaline phosphatase: It was measured by King, Abdul Fade and Walker method

Normal value: 33-96 U/l

Serum bilirubin: It was estimated by the Evelyn and Malloy method.

Normal value: Total bilirubin: 0.2 to 0.6 mg/dl

Conjugated bilirubin: < 0.3 mg/dl

Serum protein: It was estimated by the Biuret method.

Normal value: 6.7 to 8.6 gm/dl

Prothrombin Time: It was calculated by Quick's One-stage method

Normal value: 12 to 16 seconds. Prothrombin time is abnormal when it is >2 seconds longer than control time.

Observation

The majority of patients were > 50 years of age, followed by patients within 41-50 years of age. Only 10 patients were in the 20-40 years age group.79 patients were male, whereas 21 were female. So, Cirrhosis is more common in males than in females. History of alcohol intake is present in 61% of patients. So, the major aetiology of cirrhosis in our community is alcohol intake. Alcohol intake is more frequent in male patients compared to their female counterparts.

The majority of patients had INR less than 1.5. Only 10% of patients had INR between 1.5-2. Whereas, only 2% patients had INR more than 2. During follow-up, 64 patients developed complications and 36 patients did not develop any complications. Complications included in the study were ascites, upper GI bleeding and hepatic encephalopathy.60% of patients had serum bilirubin less than 2 mg/dl, 32% of patients had serum bilirubin between 2-3 mg/dl.

Only 8% of patients had serum bilirubin more than 3 mg/dl. 15% of the patients had elevated AST level, whereas 10% of the patients had elevated ALT. 10% of the patients had both AST and ALT levels elevated. 15% of the patients had serum albumin 3.5-5 g/dl, 30% of the patients had serum albumin between 3-3.5 g/dl. 55% of the patients had serum albumin level less than 3 g/dl.

When the patients were assessed for CTP score, 68% of the patients belonged to Child-Pugh class A and 32% of the patients belonged to Child-Pugh class B. Out of 3 complications studied, 33 patients (30-male, 3-female) developed ascites.

Whereas UGI Bleeding occurred in 15 patients (14-male, 1-female). Hepatic encephalopathy developed in 6 patients only (5-male, 1-female). So, the major complication developed was ascites, followed by UGI bleeding and Hepatic encephalopathy.

Out of total patients who developed complications, 68% developed ascites, 31% developed UGI bleeding and 12% developed Hepatic encephalopathy. Out of 3 complications, some patients developed more than 1 complication.

Table 1: Frequency of complications

Sl. No.	Complication	Frequency	Percentage
1	No Complication	64	64%
2	One Complication	19	19%
3	Two Complications	16	16%
4	Three Complications	1	1%
5	Total	100	100

64 patients developed only one complication during follow up, whereas only 1 patient developed all the 3 complications. In the study conducted by Biyik et al [3] involving stable cirrhosis patients having NLR>2.72 had significant mortality. So, the cut off NLR was taken as 2.72. Patients having NLR >2.72 were categorized as having elevated NLR and patients having NLR <2.72 were categorized as normal NLR.

The incidence of complication in patients having high NLR and in patients having normal NLR was calculated. Then it was statistically analysed to estimate the significance of association.

Table 2: Statistical Analysis of High NLR with Complication

Sl. No.	Complication	High NLR	Low NLR	Total
1	Any Complication	31	5	36
2	No Complication	14	50	64
3	Total	45	55	100

Patients with high NLR (>2.72) were found to have more complications, which is highly statistically significant.

Table 3: Association of Alcoholism with NLR

Sl. No.	Alcoholic Status	NLR		Total
		High	Low	
1	Alcoholic	33	28	61
2	Non-Alcoholic	12	27	39
3	Total	45	55	100

Patients who are alcoholic had elevated NLR compared to those who are not alcoholic.

Discussion

In this study, 79% of the patients were male and 21% were female. 48 patients were > 50 years, constituting the major group. Patients 41-50 years of age were 42. Only 10 patients are of < 40 years of age. Alcohol was the major cause of cirrhosis found in this study. Alcohol intake was more in males compared to females. 36% of patients developed complications during the course of 1 year. 64% of the patients did not develop any complication.

Ascites developed in the maximum number of patients. 33 patients developed ascites. Out of this, 30 were males and 3 were females. UGI bleeding developed in 15 patients, including 14 males and 1 female. Hepatic Encephalopathy developed in 6 patients, including 5 males and 1 female. Hence the development of complication was also more in males compared to females. Some patients develop multiple complications.

The NLR was calculated for all patients. Majority of patients had NLR in the range of 2 to 4. 19 patients had NLR more than 4. The cut off value for NLR was based on similar studies done before. Accordingly, patients with NLR >2.72 were labelled as having elevated NLR and patients with NLR <2.72 were labelled as normal NLR. 45 patients were found to have elevated NLR and 55 numbers of patients had normal or low NLR. Out of 45 patients who had elevated NLR, 31 patients had an abnormal LFT profile.

Only 5 patients, out of 55 patients having low NLR had abnormal LFT profile. So, patients having high NLR have the risk of having abnormal LFT. Majority of patients had INR <1.5. 10% of the patients had INR in the range of 1.5 to 2. Only 2% of patients had INR more than 2. Out of 45 patients who had elevated NLR, 31 patients developed complications either single or in combination. On the other hand, only 5 patients having low NLR developed complications.

Complications included in the study were ascites, UGI bleeding and Hepatic Encephalopathy. This was analysed statistically and the p value was calculated. The p value was <0.001, which is highly significant. We also studied the association of alcoholism with elevated NLR. Out of 61 alcoholics, 33 were found to have elevated NLR. Whereas, out of 39 non-alcoholics, only 12 had elevated NLR. The p value for this association was < 0.022, which is also statistically significant. So, patients who drink alcohol tend to have elevated NLR, so are at higher risk of developing complications. In a study conducted by Kalra et al [1], found elevated NLR

was associated with liver-related death, independent of MELD and cirrhosis.

They also found high NLR may aid in determining risk for cirrhotic decompensation, need for increasing monitoring, and urgency for expedited liver transplantation in candidates with low MELD. In a study conducted by Leithead et al [2], NLR increased with increasing severity of ascites (P <0.001). A higher neutrophil count (P <0.001) and lower lymphocyte count (P=0.001) were predictors of wait-list death.

They observed NLR is an independent predictor of mortality in patients with liver failure listed for liver transplantation. Zhang W et al [5] studied association of NLR with mortality in decompensated cirrhosis patients undergoing TIPS. They found that elevated NLR independently predicts 30-day and 90-day mortality. In patients with a MELD ≤15, NLR is a better prognostic factor than MELD or MELD-Na in predicting short-term mortality. Popoiag RE et al [6] studied predictors of SBP in Romanian adults with liver cirrhosis focusing on NLR. Multivariate analysis identified ESR and NLR as predictive factors in the occurrence of SBP. Deng Y et al [7] studied the prognostic impact of NLR in cirrhosis. Subgroup analysis showed that NLR >8.9 was an independent risk factor of 90-day mortality regardless of age, gender, CTP or MELD score.

Maccali C et al [4] evaluated the prognostic role of NLR in cirrhotic patients and its relation with inflammatory cytokines (IL-6, IL-10 and IL-17). NLR evaluated at 48 hours of hospitalization and its early increase after admission were independently associated with short-term mortality in patients hospitalized for acute decompensation of cirrhosis. Sun J et al [8] studied 494 HBV-ACLF patients, enrolled in 4 tertiary academic hospitals in China with 90-day follow up. They observed the prognostic value of NLR is superior to that of lactate in predicting mortality risk in cirrhotic and non-cirrhotic patients with HBV-ACLF.

Summary

100 patients with stable cirrhosis were included in the study and followed up for two years for development of complications. The complications under study were ascites, UGI bleeding and Hepatic encephalopathy. Around 48% of patients were above 50 years of age, 42% were 40 to 50 years of age. Only 10% of patients were below 40 years of age. Males constituted 79% of patients and females constituted 21% of patients.

This shows that cirrhosis mainly develops in the 4th to 5th decade of life and is more common in males compared to females. History of alcohol intake was present in 61% of patients. Alcohol intake is also more common in males than females. 57% of male patients were alcoholic compared to only 4% of female patients. Alcohol was found to be the major cause of cirrhosis in this study. Around 36% of patients developed complications during follow up. Ascites was the major complication which developed in 68% of patients. 31% developed UGI bleeding and 12% developed Hepatic encephalopathy. Around 16% developed 2 complications whereas only 1% developed all the 3 complications.

The development of complications was also more in males compared to females. 30% male patients developed ascites compared to 3% female patients. 14% male patients developed UGI bleeding, whereas only 1% female patients developed the same. 5% male patients developed Hepatic encephalopathy whereas 1% of female patients developed this complication. The NLR was calculated for all patients and correlated to the development of complications. Majority patients had NLR in the range of 2 to 4. Only 19% patients had NLR more than 2.72, the cut off value in previous similar studies. Out of 45% of patients having elevated NLR, 36% developed complications, whereas only 5% patients having low NLR developed complications.

This was analysed statistically and the value came out as highly significant with p value of < 0.001. So, we can confirm that patients having elevated NLR had more complications. Out of 61% of alcoholic patients, 33% had elevated NLR, whereas 12% of total non-alcoholic patients had elevated NLR. This association was also found to be statistically significant with p value of 0.022. Hence, alcoholic cirrhosis patients have a higher NLR and consequently higher chance of developing complications.

Conclusion

Cirrhosis of the liver is a major cause of morbidity and mortality. Identifying cases of cirrhosis of the liver by screening of at-risk patients and taking measures to delay or prevent progression and subsequent complications is an important goal in the management of such patients. Estimation of NLR in these patients which is an important marker in development of life-threatening complications is very useful in preventing these complications. As NLR is a cheap and easily available procedure, this can be done in any hospital and patients with cirrhosis can be monitored for better outcome. However, more studies with an increased number of patients are required to further validate the findings of this study.

Abbreviations

- NLR -Neutrophil to Lymphocyte Ratio
- CRP -C-Reactive Protein
- ACLF- Acute on Chronic Liver Failure

- NAFLD -Non-Alcoholic Fatty Liver Disease
- OPD -Out Patient Department
- H.I.V. -Human Immunodeficiency Virus
- CKD -Chronic Kidney Disease
- A.M.I.- Acute Myocardial Infarction
- UGI- Upper Gastro-Intestinal
- AST- Aspartate Aminotransferase
- ALT- Alanine Aminotransferase
- MELD- Model For End-Stage Liver Disease
- CBC- Complete Blood Count
- LFT -Liver Function Test
- RFT- Renal Function Test
- USG- Ultrasonography
- CTP- Child-Turcotte-Pugh

References

1. Kalra A et al. NLR correlates with proinflammatory neutrophils and predicts death in a low model for end-stage liver disease patients with cirrhosis. PMID: 28006875 PMCID: PMC5 529041 DOI:10.1002/lt.24702
2. Leithed JA et al. NLR predicts mortality in patients listed for liver transplantation. Liver Int. 2015 Feb; 35(2):502-9. doi: 10.1111/ liv.12688. Epub 2014 Oct 7. PMID: 25234369
3. Biyik M et al. Blood NLR independently predicts survival in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2013 Apr; 25(4):435-41. doi:10.1097/MEG.0b0 13e32 835c2af3. PMID: 23249602
4. Claudia M et al. NLR predicts short-term mortality in patients hospitalized for acute decompensation of cirrhosis. Arq Gastroenterol. 2021 Apr-Jun; 58(2):131-138. Doi: 10.1590/S0004-2803.202100000-23. PMID: 34287528.
5. Zhang W et al. Prognostic value of NLR in cirrhosis patients undergoing trans jugular intrahepatic portosystemic shunt. Eur J Gastroenterol Hepatol. 2022 Apr 1;34(4):435-442.doi: 10.1097/MEG.0000000000002295. PMID: 34750323.
6. Popoiag RE et al. Predictors of spontaneous bacterial peritonitis in Romanian adults with liver cirrhosis: Focus on the NLR. Exp Ther Med. 2021 Sep; 22(3):983. doi: 10.3892/ etm.2021.10415. Epub 2021 Jul 12. PMID: 34345265
7. Deng Y et al. Prognostic impact of NLR in cirrhosis: A propensity score matching analysis with a prespecified cut-point. Liv Int. 2019 Nov; 39(11):2153-2163. doi: 10.1111/ liv.14211. Epub 2019 Aug 29.PMID: 31408916
8. Sun J et al. A NLR based prognostic model to predict mortality in patients with HBV-related acute-on-chronic liver failure. BMC Gastroenterol. 2021 Nov 10; 21(1):422. doi: 10.1186/ s12876-021-02007-w. PMID: 34758747.