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Blood Neutrophil to Lymphocyte Count as a Prognostic Marker in Liver Cirrhosis

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Abstract: ***Aim & Objectives: To evaluate the role of NLR as a prognostic marker in patients with liver cirrhosis. To identify early, the group of stable cirrhotic patients with likelihood of developing complications in the near future. Materials and Methods: The study that Blood Neutrophil to Lymphocyte ratio as a prognostic marker in Liver cirrhosis patients is conducted in Coimbatore Medical College Hospital in the period of study from July 2015 to June 2016. The blood sample of 100 cirrhosis patients satisfying the inclusion and exclusion criteria, were collected and analysed for Blood Neutrophil to Lymphocyte ratio. It is a Prospective Observational Study. Results: NLR ratio was calculated and found to be elevated [>2.72] in 38 patients and 62 patients had normal NLR [<2.72]. Out of the 38 patients with elevated NLR 32 developed complications and out of 62 patients with normal NLR 8 patients developed complications. Conclusion: We subjected the results to statistical analysis which revealed a P value of less than 0.05 which is hugely significant. This study reveals that cirrhosis patients with elevated NLR have a high likelihood of developing complications compared to patients with normal NLR. So we can infer that Blood Neutrophil to Lymphocyte Ratio is a prognostic marker in Liver Cirrhosis.***

Keywords: NLR ratio, Cirrhosis, Liver

1. Introduction

Liver is one of most important and fascinating organ of the human body. Human liver performs a lot of diverse functions, its functional heterogenicity is unmatchable and fascinating, and it is rightly known as the metabolic factory of the body. So on this background liver disease becomes a highly important area of concern for humans and it is one of the highly taxing disease to have of a person both physically, mentally and financially. Liver disease can be acute or chronic. Various causes of liver disease carry variable degree of mortality and morbidity.

Chronic liver disease can occur because of variety of reasons. Generally south east asia which includes our country is ,more prone for viral hepatitis ,and moreover alcoholism is becoming more and more prevalent in our country and our people are more prone to develop cirrhosis with comparatively lesser amount of alcohol intake and lesser duration when compared to the western population. This makes chronic liver disease of alcoholic cause more prevalent in our country. Next the new pandemic that is becoming more and more common is fatty liver, that is now identified as a part of metabolic syndrome, is leading to NASH, and finally to cirrhosis. Because of the above said reasons and also accounting for some of the rarer causes of liver disease, chronic liver disease and its complications have become more common in india.

In chronic liver disease when the patient is in a compensated state, his lifespan, mortality rate productivity etc.very good when compared to a decompensated state, when the chances of complications and mortality are very high. So if we can identify the particular group of patients who are more prone to get decompensated and prevent it, we can reduce the mortality and morbidity associated with decompensation. A tool that is simple, easily available, reproducible and more importantly cheap is the need of the hour. And one such tool, is the neutrophil to lymphocyte ratio. Neutrophil to lymphocyte ratio is one of the newly developed novel marker of inflammation , that can be used as a marker in stable cirrhosis patients to predict the occurrence of decompensation.

2. Aim and Objectives

Aim

Neutrophil-to-lymphocyte ratio (NLR) is a novel inflammation index that has been shown to independently predict poor clinical outcomes. The aim of the study is to evaluate the role of NLR as a prognostic marker in patients with stable liver cirrhosis

Objectives

To identify early, the group of stable cirrhotic patients with likelihood of developing complications in the near future.

3. Materials and Methods

Source of study

Data consists of primary data collected by the principal investigator directly from the patients visiting the Coimbatore Government Medical College Hospital.

Design of Study: Prospective Observational Study

Period of Study: One year, July 2015 - June 2016.

Sample Size: 100

Inclusion Criteria

1) Patients (Both Genders) diagnosed as Liver cirrhosis at Coimbatore Medical College Hospital.
2) Age above 18 yrs.

Exclusion Criteria

1) Presence of secondary immunodeficiency states- HIV
2) Hepatocellular cancer patients,

3) Patients on corticosteroids or cytotoxic drugs
4) Patients with ongoing Infection
5) Pregnancy and lactation
6) Patients not capable of giving consent (psychiatric patients).
7) Patients not willing to participate in the study (who refused to consent).

Methodology

Patients attending the Medicine and Gastroenterology outpatient department, who are known cases of cirrhosis of liver inspite of aetiology, who full-fill the inclusion and exclusion criteria are involved in the study after obtaining informed consent from the patients.

Blood samples from these patients are taken and sent for investigations. The investigations includes, Complete blood count and their neutrophil to lymphocyte ratio is calculated.

All these patients where followed up over a period of one year, through follow-up visits, follow-up during inpatient admissions for various reasons and through phone.

Patients Who Got admitted where thoroughly evaluated with investigations that includes,

- Complete Blood Count
- Liver Function Tests
- Serum Proteins
- Serum Electrolytes
- Renal Function Test
- Ascitic Fluid analysis
- Ultrasound Abdomen

The patients in Follow-up, who got admitted in our GH where evaluated for development complications, and patients who got admitted elsewhere where also followed up, through subsequent visits and Phone. Among these patients, those who developed complications where identified and the correlation with the already calculated Neutrophil to Lymphocyte Ratio was done and the Results were analysed.

4. Results and Analysis

The study populations included 100 patients who have full filled the inclusion and exclusion criteria. Various characteristic patterns of the study population are analysed including age, sex distribution and alcohol consuming patterns.

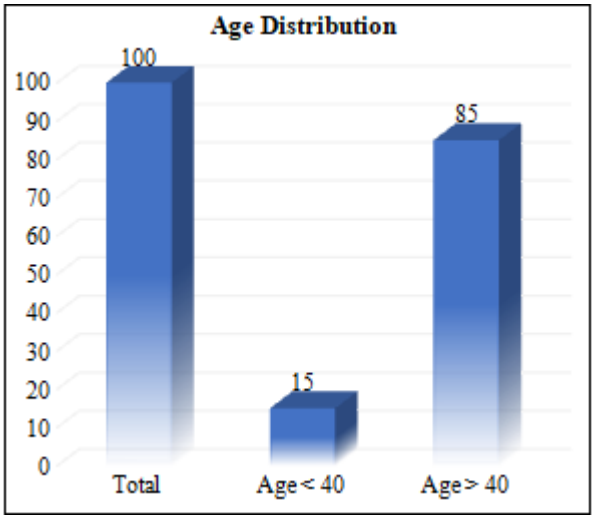

Chart 1: Age Distribution

Among the 100 patients, the study population predominantly consists of patients of age more than 40 years.

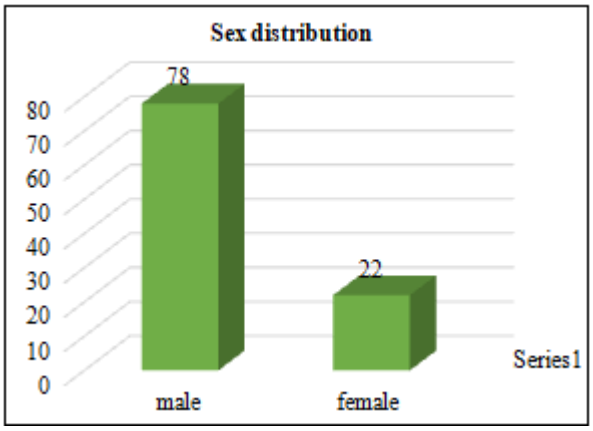

Chart 2: Sex Distribution

Among the study population, the predominant population is formed by males and a comparatively lesser population is formed by the females. This indicates the prevalence pattern of cirrhosis in general population.

Looking into the causes of such a distribution, alcoholism stands out as the prime factor that predisposes men to cirrhosis, as compared to their female counterparts.

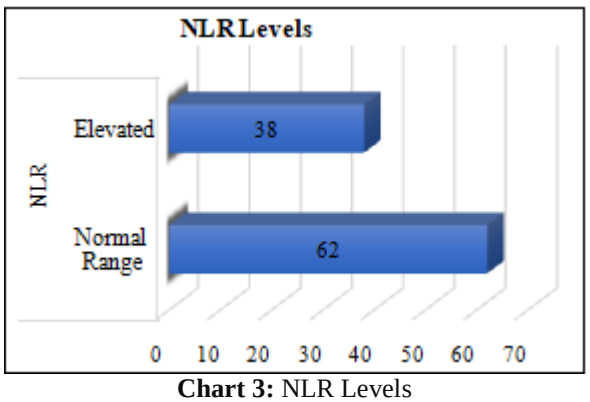

Chart 3: NLR Levels

NLR ratio is the ratio of absolute count of neutrophils to the absolute count of lymphocytes.

NLR ratio is calculated by dividing the absolute Neutrophil count by the absolute lymphocyte count.

The cut-off value of NLR is 2.72. The normal range group of patients have a NLR ratio of < 2.72 and the elevated group of patients have a NLR ratio of > 2.72.

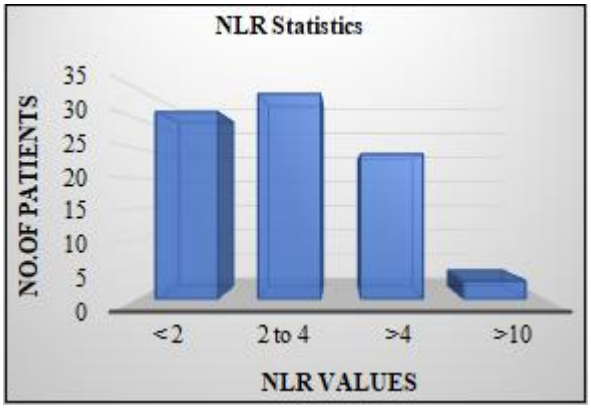

Chart 4: NLR Statistics

Table 5: NLR Distribution

NLR Levels	No. of Patients
<2	31
2 TO 4	34
>4	24
>10	3

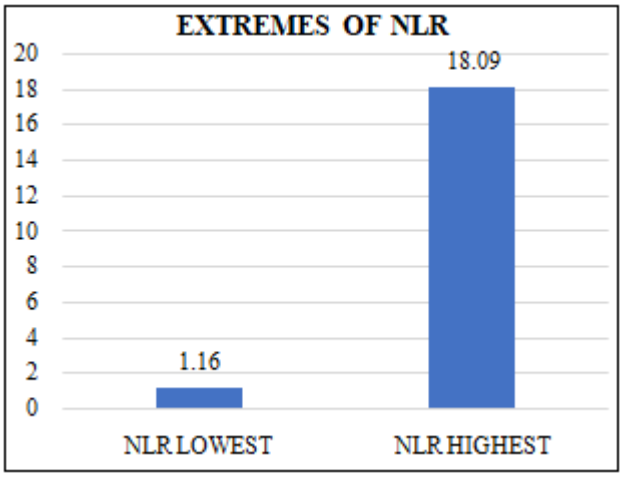

Chart 5: NLR Extremes

The highest number of study subjects fell in the NLR range of 2 to 4. 3 patients had an NLR ratio of more than 10 and all 3 of them had more than one complication. The lowest NLR recorded was 1.16 and the highest NLR obtained was 18.09.

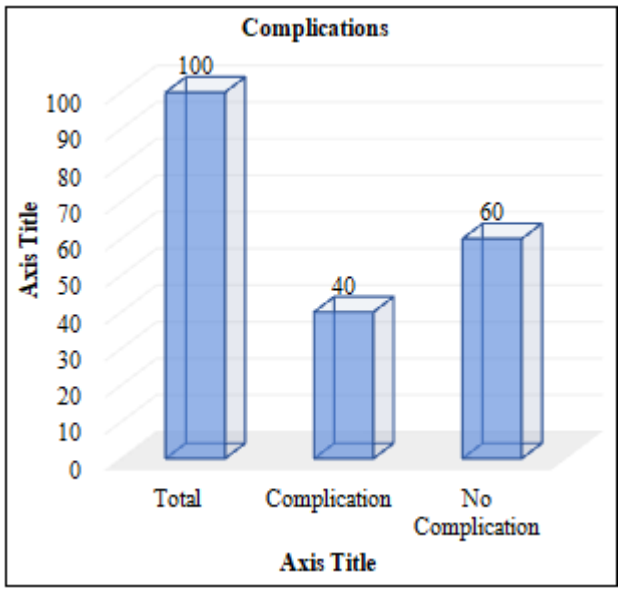

Chart 6: Complication Prevalence

Among the total of 100 patients taken up for this study, 40 patients developed complications, in the due course of the study ie, 1 year.

The complication was more prevalent in the elevated NLR group as compared to the normal NLR group. The complications encountered include Upper gastrointestinal bleeding, Ascites and Hepatic Encephalopathy.

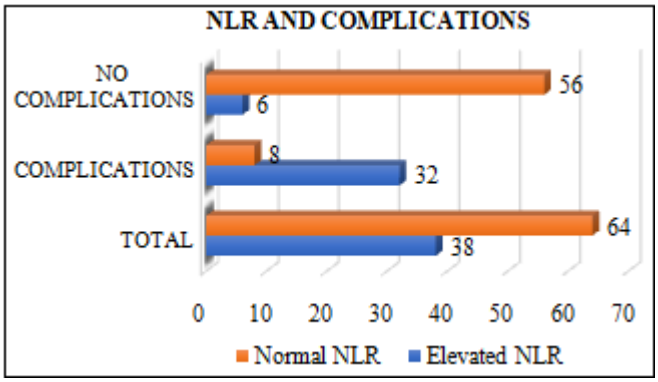

Chart 7: NLR and Complications

Among the 38 patients who had an elevated NLR ratio 32 developed complications and only 8 patients with normal NLR developed complications. We compared both the sample groups statistically.

Table 6: NLR and Complications

	High NLR	Normal NLR
Total	38	62
Complication	32	8
No Complications	6	54

Results

Table 7: p Value Calculation

Difference	24%
95% CI	6.8126 to 41.9109
Chi-squared	9.468
DF	1
Significance level	P = 0.0021

The results show a P value of 0.0021 which is less than 0.05 and hence statistically highly significant.

Hence this indicates High NLR is associated with higher incidence of development of complications.

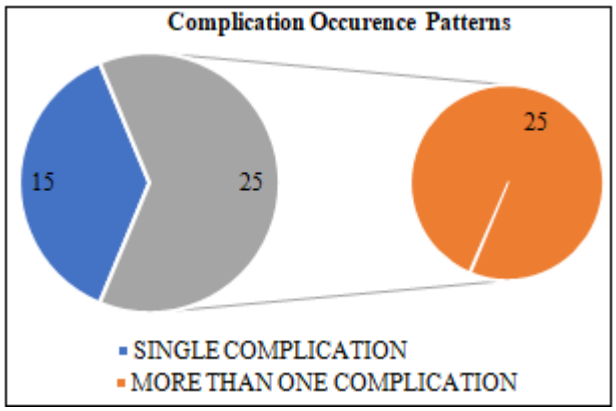

Chart 8: Complication Occurrence Patterns

Among the study population the prevalence of complications was variable. A part of the population had a single complication, but a major part of the patients had a combination of the above said complication.

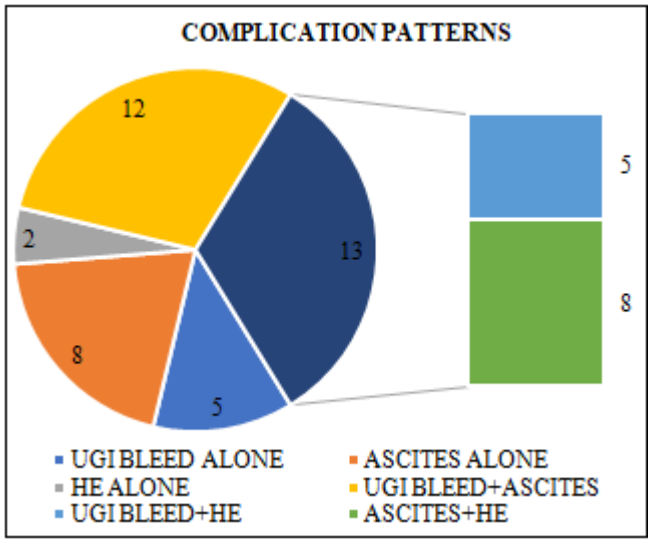

Chart 9: Complications Distribution

The occurrence of complications in the study populations had a variety of combinations. Part of them had a single complication and a majority of them had a combination, like Upper Gastrointestinal bleeding with Ascites, Ascites with Hepatic Encephalopathy and Upper Gastrointestinal Bleeding with Hepatic Encephalopathy.

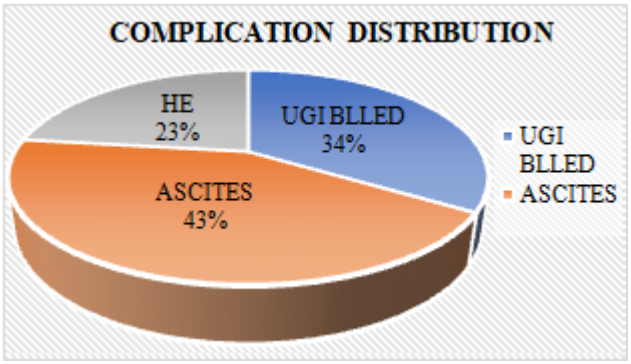

Chart 10: Complication Percentage Distribution

Taking into consideration both the individual and combination occurrence of the complications, Ascites was the most Prevalent of the complication followed by UGI Bleed. The least prevalent of the complications was Hepatic encephalopathy compared to other complications in the study population.

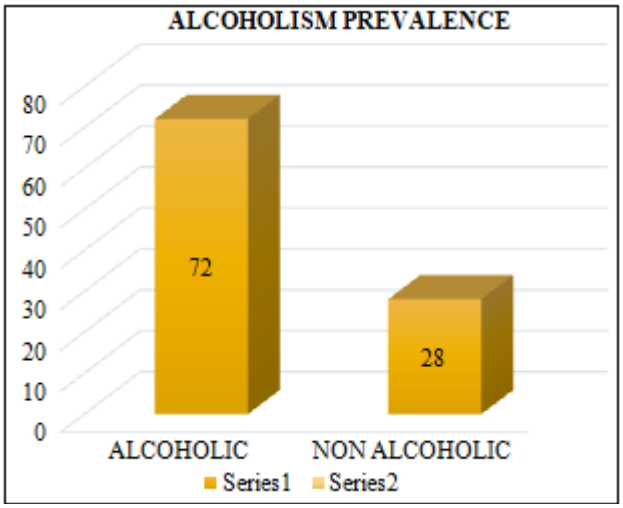

Chart 11: Alcoholism Prevalence

Alcoholism prevalence among the study population was high. Alcoholism is a very important factor because it itself can cause cirrhosis as an isolated cause and also can be an important co factor when it occurs with other causes of cirrhosis such as viral infections as it accelerates the process of the hepatic cirrhosis.

When compared to the western population, south-east Asians, especially the Indians more easily develop cirrhosis with relatively lesser amount of alcohol intake and with lesser duration of alcohol intake.

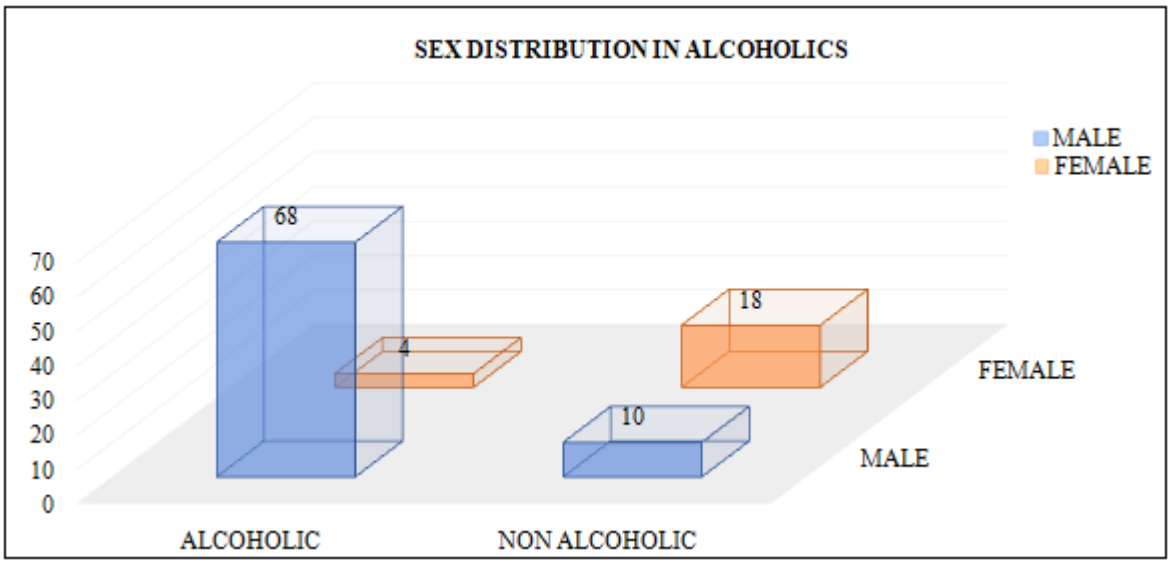

Chart 12: Sex Distribution in Alcoholics

Alcoholism was more prevalent in the study population. It was more prevalent among the males. Among the Females though the prevalence was very low compared to the males, alcoholism was also found as the cause in a subset of females in the study population.

It is a very significant factor in females because when compared to males females don't tolerate alcoholism and develop cirrhosis, earlier and with comparatively lesser amount of alcohol consumption when compared to males.

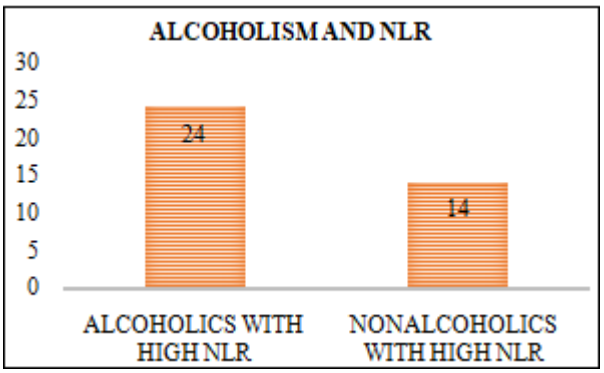

Chart 13: Alcoholism and NLR

Among the study population, the prevalence of High NLR was studied, that showed a statistically insignificant prevalence of higher NLR among the Alcoholics.

In the study population, the subjects included were already known cases of cirrhosis due to a variety of causes. But in general population, in persons who are not cirrhotics, the prevalence of Higher NLR in Alcoholics when compared non alcoholics need to be studied.

Table 8: Alcoholism and NLR

	Alcoholic	Non-Alcoholic
Total	72	28
Elevated NLR	24	14
Normal NLR	48	14

Table 9: Calculation of P Value

Difference	10%
95% CI	-10.5373 TO 25.3290
Chi-Squared	1.195
DF	1
Significance Level	P = 0.2744

The P value obtained was 0.2744, which is more than 0.05, and so statistically insignificant. Thus Alcoholism is not significantly related to the raised NLR ratio in our study group of patients

5. Discussion

Liver Cirrhosis is a common end point of various causes of chronic liver diseases. Pathologically cirrhosis liver consists of widespread fibrosis with nodular regeneration. The rate at which chronic liver disease transforms into Hepatic cirrhosis is highly unpredictable and it varies depending upon a lot of factors, the most important of them being the cause of the chronic liver disease.

The survival percentage of patients with cirrhosis declines with the progression of years, for example in one study the survival at the end of one year was 67% and it declined to 11% at ten years.

In patients with compensated stage of Liver cirrhosis the, most common reason for mortality was progression to decompensated state of liver cirrhosis. Development of complications in the form of upper gastrointestinal bleeding, ascites, Hepatic encephalopathy significantly reduces the chances of survival of the cirrhosis patients.

A mortality and survival rate in Cirrhosis patients, despite the state of the disease is also influenced by the associated co-morbid conditions. Presence of Co morbid conditions accelerate the progression of cirrhosis and also the predispose the patients for decompensation which significantly decreases the survival benefit and the mortality rates in the group of patients with co-morbid conditions, when compared to liver cirrhosis patients of the same stage of the disease without complications.

In Indian population, there are a lot of co-morbid conditions; the chief cause among them is alcoholism, among others. The Rate of transformation of compensated cirrhosis to a decompensated state is highly variable and it mainly depends upon the cause of cirrhosis. For example the rate of progression is slow, around 4% for Hepatitis C virus associated cirrhosis when compared to hepatitis B virus associated cirrhosis, which has a rate of around 10% progression to Decompensated state.

Development of renal failure, concurrent infections of various aetiology, concurrent consumption of alcohol are all associated with rapid progression of compensated liver disease to decompensated liver disease.

So the prevention of progression of compensated liver cirrhosis by effectively management and early identification of such a progression greatly reduces the rate of mortality and increase the survival benefit.

Effective management of compensated liver cirrhosis includes effective management of the causative factor of the cirrhosis. Other measures include screening for the development of oesophageal varices, by upper gastro-intestinal endoscopy periodically, screening for the development of hepatocellular carcinoma every six months, stopping alcoholism, losing weight and life style modification.

All these above said factors make the early prediction of progression of compensated state to decompensated state very important as timely intervention at this state has a significant impact in prevention of the development of a decompensated state and also significantly reduces the mortality rate and improves the survival benefit and duration of survival of compensated liver cirrhosis patients.

Now these things make tools that helps to predict early the progression of compensated to decompensated state. Many such markers are being invented. Neutrophil to lymphocyte ratio is one such tool, that is cheap, easily available and easily reproducible.

Our study is conducted at the Coimbatore medical college Hospital Regarding NLR ratio as a predictor of Prognosis in Liver Cirrhosis Patients.
Samples which were collected from the patients were analysed with strict confidentiality and the results were also kept confidential.

Among the patients studied, the majority [78%] is formed by males. Female form only 22% of the study population. The predominance of male patients in the study can be directly correlated to the higher prevalence of alcoholism in males compared to the females.

Among the study population only 15% is constituted by age group less than 40. A major group of the study population is formed by the age group 40 to 60. As mentioned in various studies cirrhosis affects the important productive phase of an individual. A minor group of patients only fall in an age group of more than 60. As also the prevalence of cirrhosis below the age of 30 in the study population is nil. So from this we can infer cirrhosis except rarely don't occur in the extremes of the age group and it occurs exclusively in the middle aged people from 30 to 60, which is the most productive phase of an individual's career in all aspects, which makes cirrhosis of liver a huge burden both for the society and for the family of the patient.

NLR ratio is calculated from the blood samples collected from the study subjects by dividing the absolute Neutrophil count by the absolute Lymphocyte count. The samples collected were analysed in coulter principle machine cell counter and the total cell count, differential cell count of the WBC were obtained.

The calibration of the cell counter a machine were absolute up-to date and was verified. The samples were processed in the Laboratory of Coimbatore medical college hospital. There was no inter observer variability as the samples were analysed by automated machines.

The NLR ratio normal value is 2.72 as in numerous previous studies involving NLR ratio. The NLR ratio calculated and found out to be higher than the reference value in 38 subjects. In the other 62 patients the NLR ratio is in the normal range. NLR ratio was less than 2 in 31% of the patients. It was between 2 to 4 in 34% patients. It was more than 4 in 24% of the patients. It was more than 10 in 3% of the patients.

All the 3% patients who had more than 10 value of NLR had more than one complication.

The lowest NLR value in our study population was 1.16 and the highest value was 18.09.

Of the 38 % of patients who had an elevated NLR 32% developed complications in the form of Upper gastrointestinal bleeding, Ascites or Hepatic encephalopathy either in single or in complication.

Of the 62% of the study population who had a normal NLR, only 8% developed complications and the rest of 54% didn't develop any complications. The two sample groups were compared and the P value was calculated.

In the calculation, the P value is found to be 0.0021 which is highly significant. This shows us that elevated NLR is associated with higher incidence of complications in cirrhosis patients and is a useful marker in predicting the occurrence of complications in the future.

Alcoholism is highly prevalent among our study subjects, so study was done to see whether there can be alcohol is contributing factor.

The observed P value was 0.2744 which is more than 0.05, and thus is statistically insignificant. So alcoholism doesn't have a significant impact in our study group.

6. Summary

Liver cirrhosis is one of the leading causes of mortality and morbidity. Liver cirrhosis is due to a variety of reasons of

which viral hepatitis and alcoholism are the leading causes in India.

Liver cirrhosis usually occurs in the most productive age group of a person and so adds to significant financial burden to both the family and country. The life expectancy is significantly lower and mortality rate is significantly higher in the decompensated Liver disease compared to compensate liver cirrhosis, which has a better survival rate and less mortality.

The progression of a patient from compensated to decompensated occurs due to a number of factors, the main being the cause of liver disease and the associated co-morbid conditions.

So a marker that can predict the occurrence of decompensated state and complications liken UGI bleed, ascites and HE can help in early identification of such subset of compensated liver cirrhosis patients who are more likely to develop these complications.

Early intervention in this subset of patients can prevent them from progression to a decompensated state and also prevents complication related mortality and improves significantly the life expectancy.

Neutrophil to lymphocyte ratio is a cheap, easily available, less complicated and easily reproducible marker to assess the prognosis of liver cirrhosis patients.

100 selected patients of liver cirrhosis who fulfilled the inclusion and exclusion criteria were included in the study. Blood samples were collected and Neutrophil to lymphocyte ratio was calculated for all subjects and they were followed up for a period of one year.

Among the study subjects 78 were males and 22 were females. Of these 72 were alcoholics and 28 were non-alcoholics. In the study population 38 subjects had elevated NLR ratio [> 2.72] and 62 had normal NLR ratio [< 2.72]. Among the study population 40 patients developed complications in the form of UGI bleed, ascites and HE either single or in combination.

In the High NLR group of 38 patients 32 developed complications and in Normal NLR group of 62 patients 8 developed complications in the course of the follow up. We analysed the results of the study by chi square test and the p value was less than 0.05 which is statistically very significant.

So we conclude that Blood neutrophil to Lymphocyte ratio is highly significant and can be used as a prognostic marker in liver cirrhosis to detect the likelihood of development of complications and progression from a compensated to a decompensated state.

7. Conclusion

The study that Blood Neutrophil to Lymphocyte ratio as a prognostic marker in Liver cirrhosis patients is conducted in Coimbatore Medical College Hospital in the period of study from July 2015 to June 2016.

The blood sample of 100 cirrhosis patients were collected and analysed for Blood Neutrophil to Lymphocyte ratio. NLR ratio was calculated and found to be elevated [>2.72] in 38 patients and 62 patients had normal NLR [<2.72]. Out of the 38 patients with elevated NLR 32 developed complications and out of 62 patients with normal NLR 8 patients developed complications.

We subjected the results to statistical analysis which revealed a P value of less than 0.05 which is hugely significant. This study reveals that cirrhosis patients with elevated NLR have a high likelihood of developing complications compared to patients with normal NLR.

So we can infer that Blood Neutrophil to Lymphocyte Ratio is a prognostic marker in Liver Cirrhosis.

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