

Abnormal Haematological Indices in Cirrhosis in a Tertiary Care Hospital

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Abstract

Background: The haematological changes are common in cirrhosis of liver the cause of which is multifactorial. It should be correlated by determining the underlying pathology accordingly. **Objective:** The objective of the study was to evaluate the pattern of change in Haematological indices in Cirrhosis of liver. **Methods:** This is a cross sectional prospective study conducted on purposely selected (non-probability) hospitalized patients admitted to Medicine, Gastroenterology and hepatology departments of Dhaka Medical College Hospital, Dhaka, Bangladesh. A total of 100 cases of cirrhosis were selected as per inclusion and exclusion criteria. After selection clinical history, meticulous physical examination and rational investigations were done. Data were collected as per a structured standard questionnaire and checklist. Data analysis was done using statistical software package SPSS 22.0 and was compared with other studies. **Results:** Anaemia was found in 81 cases out of 100 patients. Anaemia was morphologically normocytic in 46% patients which is the highest number in this study group. It was microcytic in 40% patients and macrocytic in 14%. Regarding Leukocyte count it was normal in 70(70%) patients, Leukopenia in 12(12%) and Leukocytosis in 18(18%) patients. Regarding platelet count it was normal in 46(46%), thrombocytopenia in 51(51%) but thrombocytosis in 3(3%) of cases. The average platelet count in thrombocytopenic patients was $90 \times 10^9 \pm 23 \times 10^9/L$. Lastly, pancytopenia was present in 14(14%) patients. Among them, 10 patients (71%) had splenomegaly. Iron Profile was done in all patients of microcytic anaemia and it revealed 68% of them were iron deficiency anaemia. Prothrombin time was done in all patients and it was prolonged in 54 (54%) and its average value was 16.13 ± 2.9 seconds. **Conclusion:** Haematological changes are common in cirrhosis of liver, the cause of which is multifactorial. Iron deficiency anaemia is the common type (68%). Prolong prothrombin time (54%) and thrombocytopenia (51%) are the common features.

Keywords: Haematological changes, Cirrhosis of liver, Anaemia, Platelet count.

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INTRODUCTION

Chronic liver disease in the clinical context is a disease process of the liver that involves a process of progressive destruction & regeneration of the liver parenchyma leading to fibrosis & cirrhosis [1]. Cirrhosis defined histopathologically and has a variety of causes,

clinical features and complication, that there is architectural distortion with the formation of regenerative nodules, which results in decreased liver function there is the development of liver fibrosis to the Heterogeneous studies of patients with varying stages of cirrhosis have shown a prevalence of abnormal HIS ranging from 6% to 77% [3]. To have abnormalities in the HI, defined as a

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platelet count of less than or equal to $150 \times 10^9/L$, WBC count of less than or equal to $4 \times 10^9/L$ or haemoglobin level less than or equal to 135 g/L for men and 115 g/L for women, in a recent analysis of homogenous patients with compensated Child-Pugh class A/B cirrhosis, 84% were found [4]. By toxins like alcohol, hepatitis B and C causes of leukopenia are portal hypertension-induced splenic granulocyte macrophage-colony stimulating factor, bone marrow suppression mediated and splanchnic sequestration, alterations in granulocyte-colony stimulating factor [4]. Causes of anaemia in cirrhosis are portal hypertension-induced splenic sequestration, alterations in erythropoietin, bone marrow suppression mediated by toxins like alcohol, hepatitis B and C, increased blood loss like haemorrhage, haemolysis [4]. In the portal hypertension-induced enlarged spleen is defined as hypersplenism, red blood cells (RBCs) splenic sequestration and destruction of platelets, white blood cells (WBCs) [5]. In patients with cirrhosis, thrombopoietin stimulates the production and differentiation of megakaryocytes into mature platelets, circulating platelet mass located in the enlarged spleen. By liver, kidney, muscle and bone marrow, there is a redistribution of platelets, with up to 90% of the thrombopoietin is produced and its synthesis is mainly dependent on hepatic function [6]. Differentiation of megakaryocytes into mature platelets Thrombopoietin is produced by liver, kidney, muscle and bone marrow [7]. Because alterations in hepatic perfusion may alter either the synthesis or release of the hormone the liver is one of the major organs that produces thrombopoietin [8]. By the kidney but also by the liver, thrombopoietin levels correlated with spleen size but not platelet count, report concluded that increased thrombopoietin degradation in the portal hypertension-congested spleen may contribute to the thrombocytopenia of cirrhosis [9] erythropoietin is produced predominantly. It protects RBCs from apoptosis and enhances the development of precursor RBCs [10], Granulocyte colony stimulating factor (G-CSF), or Granulocyte macrophage colony stimulating factor (GM-CSF) By the immune cells to stimulate the bone marrow to produce and release granulocytes and stem cells into the circulation these factors are produced. They also have a role in the function of mature neutrophils and differentiation. Study have shown that GM-CSF treatment for seven days in patients with cirrhosis and leukopenia resulted in an increase in the WBC count [11]. Peripheral blood studies, including determination of volumetric data and corpuscular constant will be carried out according to methods described by Wintrobe [12]. It can produce awareness among all level of medical practitioners, minimizing diagnostic hazards and thereby reducing both mortality and morbidity among the population of this country as well as the world and also there is a message for the health policy makers about importance of timely diagnostic and therapeutic interventions.

OBJECTIVES

General objective:

To evaluate the pattern of changes in

Haematological indices in Cirrhosis of liver.

Specific objectives:

- To detect the prevalence of anemia with type of anemia in study population.
- To evaluate the demographic parameters of study group.

MATERIALS AND METHODS

This was a observational, cross sectional study, conducted from March 2015 to August 2015. The patient of both sexes diagnosed as cirrhosis admitted in department of Medicine, Gastroenterology, Hepatology in Dhaka Medical College and Hospital, Dhaka, Bangladesh, were suffering cirrhosis of liver recruited as study population. The cirrhosis was diagnosed by patient's history, clinical examination, ultrasound evidence of small and coarse echotexture of liver with or without ascites, low serum albumin, endoscopic evidence of esophageal varices and liver biopsy in selected cases. Haematological changes were diagnosed by history and clinical examination and were verified by laboratory investigations. Morphological pattern of anaemia was diagnosed by red cell indices. Some special investigations were also done. In case of microcytic anaemia, iron profile was done to find out whether the etiology was iron deficiency or not. Changes of WBC and platelet were also noted. To detect any coagulation defect and also for detection of decompensation of cirrhosis prothrombin time was done in all patients. 24 hour's urinary copper estimation was done for suspected Wilson's disease. Extra sheet of paper was tagged to the questionnaire whenever it demanded accommodation of elaborate write-up of any of the relevant structured variables. All information including history, physical findings and laboratory investigations were collected by using a preset questionnaire accordingly and recorded systematically

Inclusion Criteria

Patient attending outpatient department of Medicine, Gastroenterology, Hematology and admitted in department of Medicine, Gastroenterology, Haematology and in Dhaka Medical College and Hospital, Dhaka, Bangladesh, at or above the age of 18 years who are diagnosed as case of cirrhosis of liver by liver function test, viral marker, biochemical test, ultrasonography and others relevant investigation and give consent voluntarily.

Data Analysis

Statistical analysis was carried out by using the statistical package for social sciences version 20.0 for windows (SPSS Inc., Chicago, Illinois, USA), A descriptive analysis was performed for all data. The mean values were calculated for continuous variables. The quantitative and qualitative observations were indicated by frequencies, percentage. Chi-square test with 95% Ci was used to analyze the categorical variables and was shown with cross tabulation. Independent t-test was used to analyze the continuous variable. A p-value will be considered to be statistically non-significant if >0.05

and significant if <0.05 .

Ethical Measures

Prior to the commencement of this study, the research protocol was approved by the Dhaka Medical College Ethical Review committee. The aims and objective of the study along with its procedure, risk and benefits was explained to the patients in easily understandable local language and then informed written consent was taken from each patient for all the patients of study intending enlisting.

RESULTS

A total of 100 subjects with cirrhosis of liver were studied. Among them 65% were male and 35% were female. Majority of the patients were belonged to age group 60-69 years. Regarding demographic pattern most of the patients belong to poor socioeconomic Status(59%). Educational level of the patients reveals a majority (42%) of them belongs to primary level. Among the patients 63 patients presented with abdominal distention which is the most common presentation followed by ankle edema (37%) and yellow discoloration Ascites is the most common physical findings (84%). 60% and 47% patients

found to have anemia and splenomegaly respectively. most of the patents (53%) presented with different type of complications. Among them hematemesis and melena were most common (30%). Apart from unknown etiology (38%) Hepatitis B Virus is the most common cause of cirrhosis of liver Other causes were Hepatitis C virus, Wilson's Disease and alcoholism. ultrasonography of whole abdomen revealed that 87% patients had ascites, 48% patients have splenomegaly. Endoscopy of upper GIT revealed that 21% patients had grade 2 oesophageal varices. Mean Serum Bilirubin 3.15 ± 3.2 mg/dl & 81% patients had above normal level of serum bilirubin. 92% patients had their SGPT (U/L) level above normal range. Whereas 79% patients had low Serum albumin level and 4% patients had 24-hour urinary copper more than 100 micrograms. Regarding pattern of anemia 39% patients had mild anemia, 26% had moderate anemia and 16% had severe anemia Most of the patients (46%) had normocytic anemia. Prolonged Prothrombin time (>4 seconds) was found in 54% patients and Thrombocytopenia ($<150 \times 10^9/L$) in 51% patients. Mean Platelet count in thrombocytopenic patients was $90 \times 10^9 \pm 23 \times 10^9/L$.

Table 1: Distribution of study population by age (N=100)

Age group (in year)	n	%
<20 yrs.	4	4.0
20-29 yrs.	8	8.0
30-39 yrs.	11	11.0
40-49 yrs.	23	23.0
50-59 yrs.	21	21.0
60-69 yrs.	27	27.0
>70 yrs.	6	6.0

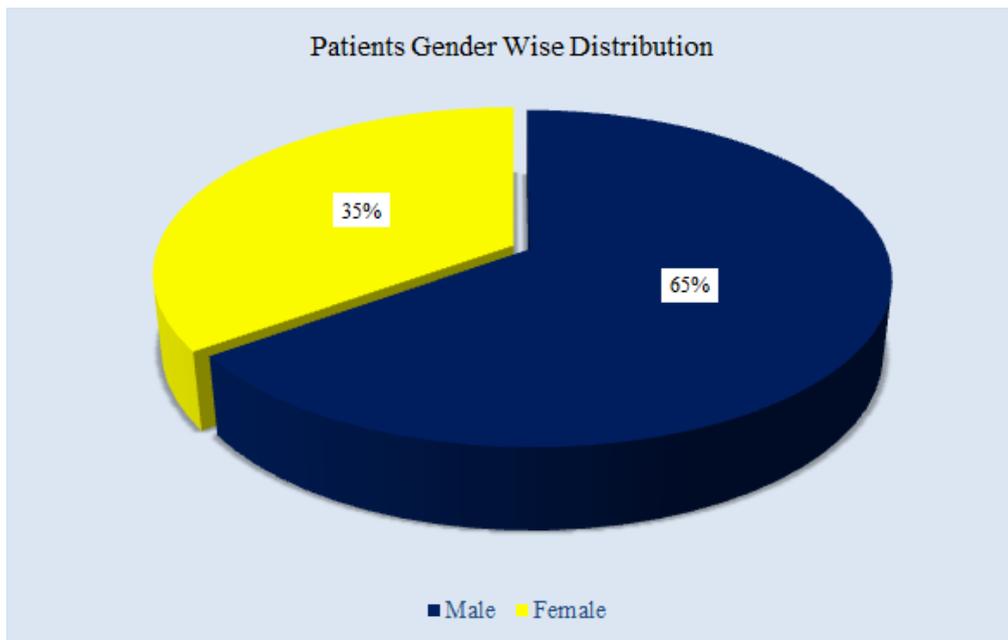


Figure I: Patient Gender Wise Distribution (N=100)

Table 2: Distribution of study population by history, (N=100)

Variables	n	%
Abdomen distention	63	63.0
Ankle edema	37	37.0
Yellowish discoloration of eye	35	35.0
Hematemesis/ Melena	30	30.0
Alcoholism	8	8.0
Fever	20	20.0
History of blood transfusion	11	11.0
Loss/ altered consciousness	13	13.0

Table 3: Physical examination findings, (N=100)

Examination findings	n	%
Anaemia	60	60.0
Jaundice	14	14.0
Clubbing	9	9.0
Leukonychia	21	21.0
Koilonychia	4	4.0
Palmar erythema	21	21.0
Vascular spider	14	14.0
Testicular atrophy	16	16.0
Gynecomastia	12	12.0
Parotid swelling	1	1.0
Flapping tremor	8	8.0
Kayser fleischer ring	3	3.0
Ascites	84	84.0
Caput medusa	15	15.0
Hepatomegaly	10	10.0
Splenomegaly	47	47.0
Hemorrhoids	5	5.0

Table 4: Complications of Cirrhosis at presentation, (N=100)

Complication	n	%
Hepatic encephalopathy	10	10.0
Hematemesis/ melena	30	30.0
Renal failure	7	7.0
Spontaneous bacterial peritonitis	2	2.0
Other infections	4	4.0

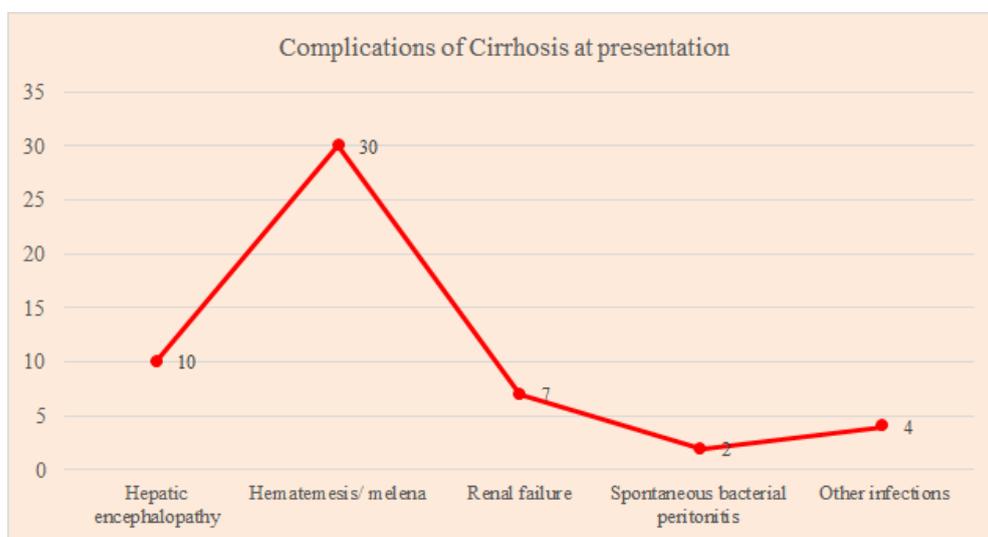


Figure II: Complications of Cirrhosis at Presentation, (N=100)

Table 5 Etiological pattern of cirrhosis (N=100)

Etiology	n	%
HBsAg positive	34	34.0
Anti-HCV positive	16	16.0
Alcoholism	8	8.0
Wilson's disease	4	4.0
Unknown	38	38.0

Table 6: Clinical evaluation etiology of anemia in patients with cirrhosis, (N=100)

Examination findings	n	%
Bleeding	14	17.3
Coexisting other diseases	18	22.2
Nutritional deficiencies	29	35.8
Alcoholism	8	9.9
Unknown etiology	12	14.8

Table 7: Non Haematological Investigations findings, (N=100)

Investigations	n	%
HBsAg positive	34	34.0
Positive anti HCV	16	16.0
Ultrasonography		
Cirrhosis	25	25.0
Hepatosplenomegaly	20	20.0
Splenomegaly	48	48.0
Ascites	87	87.0
Endoscopy of upper GIT		
Grade 1 varices	7	7.0
Grade 2 varices	21	21.0
Grade 3 varices	19	19.0
Serum bilirubin (mg/dl)		
More than normal level	81	81.0
Mean \pm SD	3.60 \pm 1.63	
SGPT (UL)		
More than normal level	92	92.0
Mean \pm SD	499.35 \pm 165.17	
Albumin (gm/d)		
Less than normal level	79	79.0
Mean \pm SD	2.89 \pm 1.55	
Urinary copper (micro gm/24 hour)		
More than 100	4	4.0
Mean \pm SD	518.75 \pm 55.43	

Table 8: Pattern of anemia in study population, (N=100)

Investigations	n	%
Severe anemia	16	16.0
Moderate anemia	26	26.0
Mild anemia	39	39.0
Normocytic	37	37.0
Microcytic	33	33.0
Macrocytic	11	11.0
Red cell indices		
MCV	83.55 \pm 15.70	
MCH	29.22 \pm 2.69	
MCHC	28.74 \pm 2.95	

Table 9: Leukocyte count in study population, (N=100)

Leukocyte count	n	%
Normal	70	70.0
Leukopenia	12	12.0
Leukocytosis	18	18.0

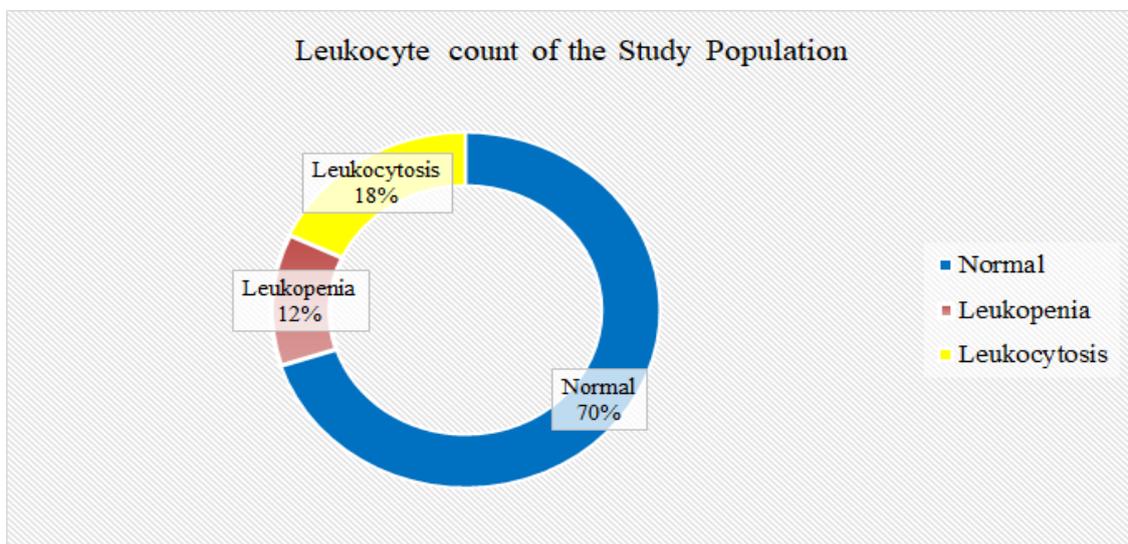


Figure III: Leukocyte count in study population (N=100)

Table 10: Prothrombin time & Platelet count in patients with cirrhosis. (N=100)

Investigations	n	%
Prolonged Prothrombin time (>4 seconds)	54	54.0
Thrombocytopenia (<150x10 ⁹)	51	51.0
Prothrombin time Mean ±SD	16.14±2.02	
Platelet count in thrombocytopenic patients Mean ±SD	90.17±23.95	

DISCUSSION

In this study attempt has been made to find out haematological changes in patients with cirrhosis in our population and to enrich the existing statistics of this kind both in home and abroad. The mean age of the study population was 51.6 years with and SD of ±21.30 years from the age distribution of the patients. it was found that the highest number of patient i.e. 27(27%) patients are in the age group of 60-69 years. Gender characteristics of the study population showed that 65% are males and 35% females. This result is consistent with previous study findings where considerable gender differences seen in cirrhosis of liver [13]. On the occupational background the highest number of patient's 25(25%) were housewife, 24% were Businessmen, only 5% patients were service holder. The current study shows that the underprivileged people of different occupations are more subjected to the development of cirrhosis regarding clinical history 63% patients presented with history of abdominal swelling. This result implicates that abdominal swelling is almost universal for cirrhosis of liver. History of hematemesis and/or melena was present in 30% patients. Only 8% patients had history of chronic alcoholism. Low incidence of alcoholism clearly reflects the overall picture: of Bangladesh where majority of people refrain from taking alcohol by virtue of their This result showed that etiology of cirrhosis of liver found in 62 patients out of

100. Among them 34% patients were HBsAg positive, 16% patients were anti-HCV positive. 8% patients were chronic alcoholic and only 4% patients had Wilson's disease. 38% patients had no definite etiology. This result is similar to other study of Bangladesh in this regard [14, 15]. Among the investigated patients 16% were severely anaemic while 26% were moderately anaemic. These laboratory results are no clear disagreement with that of clinical grading of anaemia on physical examination. Morphological types of anaemia were done by red cell indices. Anaemia as called hypochromic microcytic for mean corpuscular volume (MCV) values below 80 fl and the mean corpuscular haemoglobin (MCH) values below 27 picogram: normocytic normochromic anaemia for MCV values between 80 and 100 fl and MCH between 27 and 31 Picograms. Macrocytic anaemia for a value of greater than 100 fl MCV. Anaemia was morphologically normocytic in 37 (46%) patients which is the highest Number in this study group. It was microcytic in 33 (40%) patients and macrocytic in 11(14%) patients. Hence it is obvious that the pattern of anaemia that is the most common in the study in people of cirrhosis of liver is normocytic anaemia and above. The prevalence of anaemia in our study is higher than that of more [16] in Nigeria and lower than that of denies *et al.*, [17] in France. Normochromic normocytic anaemia of cirrhosis could be explained by hypersplenism frequently found in

cirrhosis [18] in the present study, the 2nd most common pattern of anemia is microcytic hypochromic anaemia. Iron profile was done in all patients of microcytic anaemia and it revealed that the major cause of microcytic anaemia was Iron deficiency anaemia They were observed at rates below those of traores' in Nigeria [16] and above those of Denies *et al.*, [17] in France. The hypochromic microcytic anaemia of cithosis are due to:

a. gastrointestinal bleeding: those are a frequent and serious complication of cirrhosis indeed, 62% of patients with a microcytic hypochromic anaemia had gastrointestinal bleeding. Besides clinically obvious, important sources of iron loss, about 10 to 20mL of blood per day can easily pass unnoticed by the patient [19]. B. Chronic inflammation: cirrhosis resulting in hyposideremia involves the diversion of iron to the inflammatory zone. The iron is taken up by cells of the reticuloendothelial system and microcytic hypochromic anaemia not explained by iron deficiency always. Bruno *et al.*, [20] showed that there was increased production of erythropoietin in patients with iron deficiency anaemia in cirrhotic patients as anaemic. They conclude that the increase of erythropoietin in patients with cirrhosis is detectable only when the haemoglobin falls below 12 gm/dl and that this increase is lower than that observed during iron deficiency anaemia and not adapted to the degree of anemia. [20] Macrocytic anaemia is the third prevalent pattern. Denies et Al. [20,21] in France found macrocytic anaemia in 48% of their patients. Alcoholic cirrhosis had cleared majority in France [22] Classically responsible for macrocytic anaemia [23]. These macrocytic anaemia are secondary to: Complex abnormalities in folate metabolism and vitamin B12 on their capture and storage. However, these vitamins lead to hyperhomocysteinaemia. Thus in addition to its role in atherogenesis and thrombogenesis makes it a cardiovascular risk factor, hyperhomocysteinaemia is a risk factor for cirrhosis. Nacuolna EW et al. in their study on types of anaemia in patients with cirrhosis found that overall prevalence of anaemia was 74.5%. All types of anaemia were observed by them Normochromic normocytic anaemia was observed in 43.3%. They also described that the microcytic hypochromic anaemia observed in 20% cases is not exclusively linked to blood loss or iron deficiency [24]. In the current study, the predominance of normocytic anaemia may be of multifactorial, interdependent or confounding etiology which calls for a larger scale study for in-depth understanding of causal relationship as well as focused appreciative prediction of multi-diverse expressions of anaemia in cirrhotic patients. In this study it was found that 51% of patients with cirrhosis of liver had thrombocytopenia. A study from Taiwan reported only 10.2% had thrombocytopenia in patients with positive anti-HCV antibody. It was a community based study. Due to their definition of thrombocytopenia the low Compared with other study the higher frequency of thrombocytopenia in this study may be due to it was a hospital based study and most patients had advanced disease. In case of WBC majority of patients Leukocyte

count were normal, only 14(14%) patients had leukopenia the reason behind this is hypersplenism or bone marrow suppression due to the effect of anti-viral medications. Again 19% had leukocytosis, this might be due to SBP or other concomitant infections [25]. The prothrombin time was prolonged in majority (54%) of patients. The average value of prothrombin mean time was 16.13 ± 2.9 seconds. Thrombocytopenia was present in 51% patients. The average platelet count in thrombocytopenic patients was $90 \times 10^9 \pm 23 \times 10^9/L$. Thrombocytopenia and prolonged prothrombin time give rise to increase incidence and severity of variceal bleeding.

LIMITATIONS OF THE STUDY

Although sample size was calculated statistically, sample size was relatively small in relation to huge number of population. Confounding variables couldn't be fully eliminated. Abnormality in Haematological indices in different stage of cirrhosis couldn't be elicited properly.

RECOMMENDATIONS

In this study, it is observed that anaemia, leukopenia, thrombocytopenia and prolonged prothrombin time is common in cirrhosis patients, even in all stage of cirrhosis. So it is recommended to check the above haematological parameters during follow up of cirrhosis patients and take corrective measures accordingly. Multicenter long term case control studies can be done to consolidate the findings of the study.

CONCLUSION

Majority of patients in this study were in advanced stage. Etiological causes of Cirrhosis revealed that HBV is more common than HCV. The prevalence of Normocytic normochromic anemia is most prevalent among anaemic patients. The prevalence of leukopenia, thrombocytopenia and prolonged prothrombin time are more common in patients of cirrhosis of liver.

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