A Study on Haematological Manifestations in Patients with Chronic Liver Disease in a Tertiary Care Hospital of North India

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ABSTRACT

BACKGROUND

Chronic liver diseases frequently are associated with haematological abnormalities. Anaemia occurs in about 75% of patients with chronic liver disease. The most common type of anaemia seen in liver cirrhosis is normocytic normochromic anaemia, due to the chronic inflammatory state, blood loss from oesophageal and rectal varices. The purpose of this study was to study the haematological manifestations in patients with chronic liver disease.

METHODS

A cross-sectional observational study was conducted at Sri Guru Ram Das Institute of Medical Sciences and Research (March 2019 - March 2020). Total of 90 patients with chronic liver disease were included in the study. The population was divided into 2 groups based on the model for end-stage liver disease (MELD) score and the various haematological abnormalities were assessed in these 2 groups. Similarly, haemoglobin (Hb) levels were assessed in 3 groups based on the Child-Turcotte-Pugh (CTP) classification.

RESULTS

There was a significant correlation between hemoglobina and CTP class ($P < 0.001$), with the lowest haemoglobin levels in CTP class C group. The correlation coefficient of MELD score and haemoglobin was -0.504 which was significant statistically. Thus, confirming the fact that haemoglobin levels decreases with the progress in the severity of liver cirrhosis. Of 39 patients with haemoglobin < 8 g/dl, 5 (12.8 %) had a MELD score of < 12, whereas 34 patients (87.2 %) had a MELD score of > 12 and was statistically significant ($P < 0.0001$). Leukocytosis was observed in 41 patients and leucopoenia in 14 patients. The mean prothrombin time was 20.4 seconds and 80 % of the patients had prothrombin time prolonged by more than 6 sec indicating liver damage alters coagulation profile.

CONCLUSIONS

We found an association between anaemia and indicators of advanced liver disease such as a higher MELD and CPS scores. This study inferred that levels of haemoglobin decrease as the severity of liver disease progresses. Thus, this measure can be used in the initial assessment of cirrhosis patients that needs urgent identification and correction to reduce morbidity and mortality.

KEYWORDS

Anaemia, Liver Cirrhosis, Model for End-Stage Liver Disease Score, Child-Turcotte-Pugh Class

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BACKGROUND

Liver plays a vital role in maintenance of blood homeostasis. Liver acts as the storage site for iron, B12 and folic acid which are necessary for maintaining the normal haematopoiesis. Liver also secretes thrombopoietin (regulates platelet production), clotting factors and the inhibitors of coagulation cascade. Thus, liver is the key regulator of haemostasis. Haematological parameter abnormalities are common in liver cirrhosis. The various causes of abnormal haematological indices (HIs) are hypersplenism induced sequestration, alterations of factors causing bone marrow stimulating, bone marrow suppression caused by various toxins and consumption or loss of coagulation factors. Liver failure results in a state of "rebalanced haemostasis" marked by a decrease in both pro-coagulation and anticoagulation factors.[1]

Chronic liver diseases frequently are associated with haematological abnormalities. Anaemia occurs in about 75 % of patients with chronic liver disease.[2] The most common type of anaemia seen in liver cirrhosis is normocytic normochromic anaemia, due to the chronic inflammatory state. Blood loss from oesophageal and rectal varices, portal hypertensive gastropathy and antral vascular ectasia can give rise to iron-deficiency anaemia (microcytic hypochromic anaemia).[3] Secondly, the functional and structural defects in membrane of red blood cells (RBCs) leads to acanthocytes and reduced life span. Another reason for anaemia in patient with chronic liver disease is hypersplenism and hepcidin deficiency. Another common haematological abnormality seen in chronic liver disease patients is macrocytosis. The cause of macrocytosis in liver cirrhosis is multifactorial.

Alcohol is a common aetiologic factor of chronic liver disease. It causes direct bone marrow toxicity. Alcoholics often develop secondary malnutrition, which may lead to anaemia caused by vitamin B12 and folate deficiency. In some patients, hepatitis-associated aplastic anaemia, characterized by pancytopenia and hypocellular bone marrow is observed. Anaemia is also a known complication of treatment of chronic hepatitis C with interferon and ribavirin; anaemia in these patients is predominantly caused by haemolysis due to ribavarin.[4] In cirrhosis liver, decreased synthesis of plasma proteins causes reduced levels of several clotting factors. Haemorrhage may occur as a complication of chronic liver disease because of a lack of these clotting factors, thrombocytopenia, and/or functional defect in platelets. Such patients can present with haemorrhage from oesophageal or gastric varices secondary to portal hypertension.[2]

In chronic liver disease and cirrhosis, alterations in primary platelet haemostasis (platelet adhesion, activation and aggregation) occur along with changes in secondary haemostasis (coagulation). An increased platelet pooling and breakdown in spleen along with decreased platelet production from liver are the most important determinants of decrease platelet count. Regarding the functional change, there is a decreased aggregability caused by defective (trans-membrane and intracellular) signalling, a storage pool defect and an aggravation of the inhibitory pathways.[5] The model for end-stage liver disease score which is a scoring system to assess the severity of chronic liver disease patients and includes three variables i.e. serum bilirubin, serum creatinine and international normalized ratio (INR).

The presence of anaemia is associated with higher MELD scores and a poor prognosis.[6] Various consequence of anaemia in chronic liver disease includes higher CTP score and increased risk of developing hepatic encephalopathy and hepatorenal syndrome (HRS). Thus, these haematological alterations increase the morbidity and mortality in chronic liver disease patients

We wanted to study the haematological manifestations in chronic liver disease patients and the relationship between anaemia and the severity of liver disease.

METHODS

A cross sectional analytical study was conducted in which a total number of 90 patients attending the Department of Medicine in SGRDIMSR, Sri Amritsar from march 2019 to March 2020, satisfying the inclusion and exclusion criteria were included in the study. Study was conducted after obtaining clearance from institutional ethics committee. Informed and written consent of cases was taken during the study. A detailed history, clinical examination and relevant investigations were done on the participating subjects. The observations and interpretations were recorded and the results obtained were statistically analysed**.**

Inclusion Criteria

1. Patients within age group of 18 to 75 years.
2. All proven cases of liver cirrhosis irrespective of the cause.
3. All patients with liver cirrhosis whose symptoms and signs persisted for more than 6 months

Exclusion Criteria

1. Patients who were known case of primary hepatocellular carcinoma or any other malignancy.
2. Patients who were on treatment for anaemia or had blood transfusion in last 3 months.
3. Patients on drugs causing bone marrow suppression.
4. Patients suffering from end stage medical diseases like heart failure, chronic kidney disease (CKD) and those who were chronic smokers were excluded.

Liver cirrhosis was defined on the basis of clinical examination and ultrasound findings. All patients were asked about the presenting complaints and the duration of illness. History regarding bleeding from any site, jaundice, pedal oedema, abdominal distension and oliguria was taken. Significant past history regarding diabetes, hypertension, tuberculosis was also taken from the patient. History of any previous trauma, blood transfusion, surgery, needle pricks and contact with blood products was taken from the patients. Various complications of cirrhosis such as portal hypertension, ascites, spontaneous bacterial peritonitis,

hepatic encephalopathy, hepatorenal syndrome and upper gastro intestinal (GI) bleeding were recorded. Personal history regarding alcohol intake, smoking and intravenous drug abuse was taken. Family history of liver disease was also noted. Then general examination and systemic examination of patients was done.

Under all aseptic precautions, blood samples were collected and were analysed for complete blood count, peripheral blood film, prothrombin time (PT)/INR, blood urea, serum creatinine, random blood glucose, serum sodium, liver function tests (LFTs), urine complete examination, hepatitis B and hepatitis C serology. Ultrasound abdomen was done for echo texture of liver, splenomegaly, presence of ascites and kidney size to rule out CKD. In those patients who had ascites on physical examination or on ultrasonography (USG), ascitic fluid analysis was done. Under all aseptic precautions, ascitic fluid sample of about 10 ml was withdrawn for analysis including: cytology, biochemistry and adenosine deaminase (ADA). Upper gastrointestinal (UGI) endoscopy was done in patients who were hemodynamically stable.

Complete blood counts were estimated through automated analyser. Peripheral blood film was done to determine the type of anaemia. Blood urea level and random blood glucose were estimated using enzymatic methods and creatinine by the Jaffe method. Viral Markers (hepatitis B, hepatitis C) were estimated using enhanced chemiluminescence method. Diagnostic criteria for severity of anaemia as per haemoglobin levels was determined according to world health organization (WHO) guidelines.[7]

Population	Non Anaemia	Mild Anaemia	Moderate Anaemia	Severe Anaemia
Females (≥ 15 years age)	≥12	11.0-11.9	8.0-10.9	< 8
Males (≥ 15 years age)	≥13	11.0-12.9	8.0-10.9	< 8

Table 1. WHO's Diagnostic Criteria for Severity of Anaemia According to Haemoglobin Values (g/dL)

Cut offs for mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were derived from the reference values of the local laboratory.[8] Thrombocytopenia was defined as a platelet count < 1.5 lacs/mm^3 and leukopenia as white blood cell count < 4000 cells/cumm, respectively.[9,10] The severity of the disease was evaluated according to the Child-Pugh classification and MELD score. Child Turcotte-Pugh score was calculated based on parameters like serum bilirubin, serum albumin, prothrombin time, ascites, encephalopathy and score varies from 5 - 15 points.

MELD score was calculated using the formula 9.57 × loge (creatinine mg/dL) + 3.78 × loge (bilirubin mg/dL) + 11.2 × loge (INR) + 6.43, where 6.43 is the constant for liver disease aetiology.[11,12]

Statistical Analysis

The patients were classified according to the grading of anaemia and further sub classified according to their MELD score and CTP class. Associations of MELD score and CTP score with Hb levels was done using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test and the results were taken as significant statistically if the P - value was < 0.05.

RESULTS

In our study, 78 (86.6 %) out of the 90 patients were males and 12 (13.3 %) patients were females. The mean age was 52.67 years. Alcohol was the most common aetiology of cirrhosis in 52 patients (57.8 %), followed by hepatitis C in 16 patients (17.8 %), both alcohol and hepatitis C virus (HCV) in 10 patients (11.1), Hepatitis B in 6 patients (6.6 %), other aetiologies in 6 patients (6.6 %). Various signs and symptoms on presentation were fatigue, abdominal distention, abdominal pain, fever, upper gastrointestinal haemorrhage, pedal oedema, jaundice, hepatomegaly, and splenomegaly. Abdominal distention (92.8 %) and fatigue (88.8 %) were the most common presenting symptoms. The mean Hb level was 8.8 g/dl. Out of the 90 patients, 12 patients were having Hb in the normal range (13.3 %), 10 patients had mild anaemia (11.1 %), 29 patients had moderate anaemia (32.2 %) and 39 patients had severe anaemia (43.3 %).

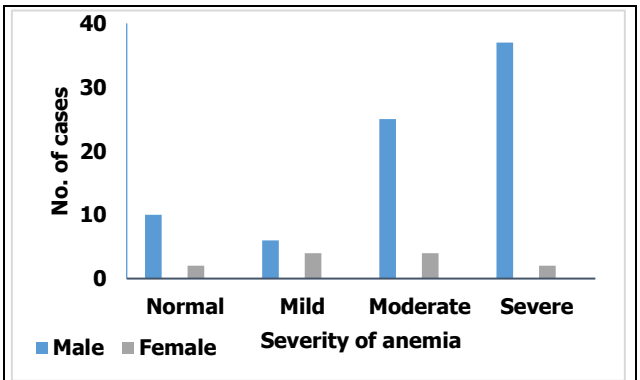

Figure 1. Distribution of Cases According to Severity of Anaemia

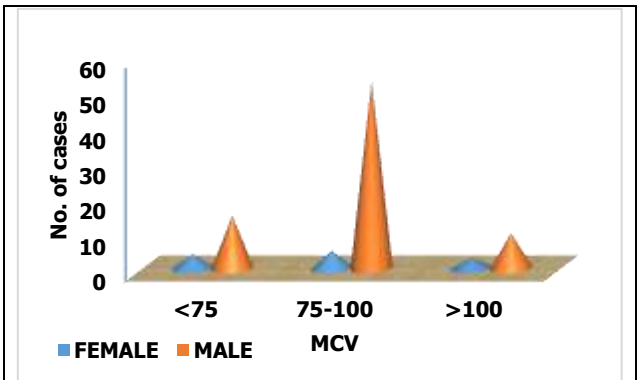

Figure 2. Distribution of Cases According to the MCV Values

The patients were divided into 3 categories according to the MCV values. 19 patients (21.1 %) had MCV of < 75 fl indicating the presence of microcytic anaemia. Maximum number of patients 58 (64.4 %) had MCV in normocytic range i.e. 75 - 100 fl. Mean MCV was 84.95 fl. Mean MCH and MCHC was 28.91 pg and 31.52 gram % respectively.

MELD Score and Severity of Anaemia

Of the 90 patients, 32 patients had a MELD score of < 12 (35.6 %), 58 patients had a MELD score of > 12 (64.4 %). Of the 32 patients who had a MELD score of < 12, 11 patients had normal Hb (34.4 %), 8 patients had mild anaemia (25.0 %), 8 patients had moderate anaemia (25.0 %) and 5 patients had severe anaemia (15.6 %). Of the 58 patients who had a MELD score of > 12, one patient had normal Hb (1.7 %), 2 patients had mild anaemia (3.4 %), 21 patients had moderate anaemia (36.2 %) and 34 patients had severe anaemia (58.6 %). This was statistically significant (P < 0.001). The Pearson correlation between Hb and MELD score was also significant (P < 0.001).

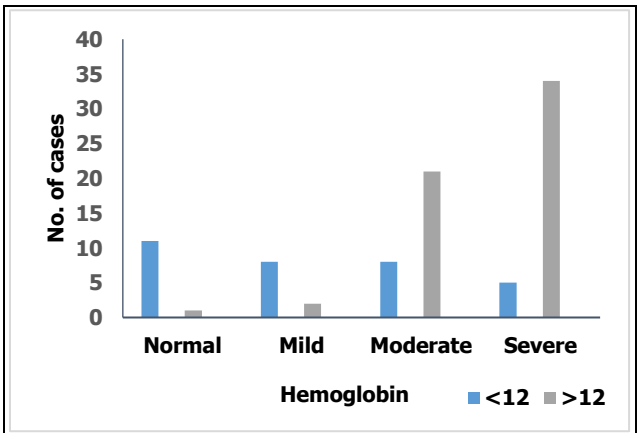

Figure 3. Patients in Meld Group and Its Correlation with Severity of Anaemia

	Parameter	Number of Patients	Percentage
Haemoglobin (g/dL)	≥ 12	12	13.3
	11.9 - 11	10	11.1
	10.9 - 8	29	32.2
	< 8	39	43.3
	Mean ± SD	8.80 ± 3.05	
TLC (cells/cumm)	4000 - 11000	35	38.9
	➢ 11000	41	45.6
	< 4000	14	15.6
	Mean ± SD	11445.96 ± 8591.30	
MCV (fl)	< 75	19	21.1
	75 - 100	58	64.4
	> 100	13	14.4
	Mean ± SD	93.54 ± 12.97	
Platelet count (lac/cumm)	< 1.5	53	58.9
	1.5 - 4.5	36	40.0
	➢ 4.5	1	1.1
	Mean ± SD	151900.00 ± 87779.22	
INR	1.0	10	11.1
	➢ 1.0	80	88.9
	Mean ± SD	1.41 ±0.33	

Table 2. Distribution of Cases According to Platelet Count and INR

In our study, we observed that MCV increases with a rise in MELD score. The mean serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total bilirubin were 95.6 (IU/L), 85.3 (IU/L), 3.5 (mg/dl), respectively. The mean serum albumin was 2.48 g/dl. Serum albumin of < 3.5 gm/dl was found in 78 % of the patients.

The mean serum sodium, blood urea and serum creatinine were 134.8 mEq/L, 29.16 mg/dL, and 1.69 mg/dL, respectively. Hyponatremia (< 130 mEq/L), hypernatremia (>145 meq/l), raised blood urea (> 20 mg/dL), and creatinine (> 1.5 mg/dL) were present in 44 %, 3 %, 48 %, and 45 % of the patients, respectively.

CTP Score and Severity of Anaemia

Of the 90 patients, 25 patients were in Child Pugh Class A, 34 patients in Child Pugh Class B and 31 patients in Class C respectively. Out of 25 patients in CPS class A, 11 patients had normal Hb (44.0 %), 7 patients had mild anaemia (28.0 %) and 7 patients had moderate anaemia (28.0 %). Among the 34 patients in CPS class B, 1 patient had normal Hb (2.9 %), 3 patients had mild anaemia (8.8 %), 20 patients had moderate anaemia (58.8 %) and 10 patients had severe anaemia (29.4 %).

Out of 31 patients in CPS class C, 2 patients had moderate anaemia (6.5 %), 29 patients had severe anaemia (93.5 %). There was a statistically significant correlation between Hb and CTP class (P < 0.001).

Parameter	CTP Class			F-Value (P - Value)
	Class A (N=25)	Class B (N=34)	Class C (N=31)	
Hb (g/dL)	12.40 ± 1.61*	8.82 ± 1.82	5.88 ± 1.48	0.001
Platelet count	180600.00 ± 70538.4	183058.82 ± 106978.3	94580.65 ± 33281.4*	0.001
MCV	93.71 ± 9.45	92.40 ± 11.32	94.63 ± 16.85	0.788
TLC	8921.20 ± 4890.3	9676.47 ± 9245.2	15422.77 ± 8978.5*	0.005
INR	1.24 ± 0.16	1.32 ±0.27	1.62 ±0.37*	0.001

Table 3. Correlation between Average Haemoglobin (HB) and Child-Turcotte-Pugh Class

* Statistically significant group on Post hoc Bonferroni's test compared to the rest of two groups

The mean total leukocyte count (TLC in mm3) and mean platelet counts (×10 3/µL), were 11445 and 151 respectively. Among the 90 patients, leukocytosis was observed in 41 patients (45.6 %) and leukopenia in 14 (15.6 %) patients. The mean prothrombin time was 20.4 seconds. 0ut of 90 patients, 80 % of the patients had prothrombin time prolonged by more than 6 sec with the mean INR of 1.40. INR was > 1.5 in 77.8 % of patients.

DISCUSSION

In this study out of the 90 patients included, 86.6 % (78) patients were males and 13.3 % patients were females. This was in concordance with study conducted by Pathak O K et al. in which 80.7 % among 181 patients were males.[13] The mean age was 52.67 years. Similar results were seen in a study conducted by Nagarajaiah RB et al. on cirrhosis liver in which the mean age of patients was 50.7 years.[14] In our study involving 90 patients of chronic liver disease, we inferred that 86.6 % of the total patients had anaemia and among them 43.3 % had severe anaemia.

A study conducted by Khan F et al. in the year 2015 -16 observed that anaemia was present in 109 (94.8 %) out of 115 patients.[15] A study by Rosario Gonzale Z et al. showed that 75 % of CLD patients were anemic.[16] In our study, 39 patients had Hb less than 8 gm/dl. Hegde et al. in their study also found that severe anaemia was present in 43 % of cases.[17] Anaemia in liver cirrhosis is multifactorial and is the most frequently encountered complication, occurring due to:

1. Haemodilution
2. Decreased erythropoietin level

3. Raised serum inflammatory cytokines such as TNF- α, IL-1 suppressing the bone marrow.

In patients with alcoholic liver disease, the iron is not incorporated into the haemoglobin molecules. Instead, it is converted into the storage form i.e., ferritin, which can accumulate in RBC precursors, forming granules around the nucleus producing functionally immature cells.[18] Megaloblasts are frequently seen in the bone marrow of alcoholic patients affecting up to one-third of these patients. These alcoholics generally have reduced folic acid levels in their RBC's mostly due to dietary deficiency of folic acid. In addition, alcohol ingestion aggravates this by altering the absorption of folic acid from food[19]

Mean MCV and MCH were 84.9 fl and 28.91 pg respectively with 58 patients (64.4 %) had MCV in normocytic range i.e. 75 – 100 fl indicating that normocytic normochromic anaemia was the most common type seen in our study. According to Sherlock's and Oxford text book of Hepatology most common type of anaemia seen in cirrhosis is normocytic normochromic.[20] Similar results were observed in previous studies by Selvamani et al. Among the 100 patients, 52 patients had normochromic and normocytic anaemia, 30 patients had microcytic anaemia and 16 patients had macrocytosis.[21]

We observed a progressive fall in haemoglobin levels in association with the increase in MELD score. A study conducted by Jain et al. showed similar findings where 88 patients with alcoholic liver cirrhosis were divided into 5 groups on basis of their MELD scores. It was found that prevalence of anaemia and leukopenia, were more common in the higher MELD score group.[22] With agreement to our study, Qamar et al. concluded that anaemia is a poor prognostic factor in patients with liver cirrhosis, and the severity of anaemia increases with the stage of liver disease.[23] In our study, MCV was raised in patients with higher MELD score and this was statistically significant. A similar relation was observed by Yang et al. in 463 patients. In their study patients with macrocytic anaemia had higher MELD scores (10.8 ± 6.6) than those with normocytic (8.0 ± 5.5) or microcytic anaemia (6.3 ± 5.1).[24] In our study, there was a significant correlation between CTP class and Hb. Patients with CTP class C had lowest Hb levels.

Scheiner B et al. study also observed strong association between presence of anaemia and CTP score and MELD, where anaemic patients showed a higher MELD (12 ± 4 vs. 9±3; $P < 0.001$) and incidence of anaemia was more observed in CTP class C.[25] Ozgur et al. compared the mean corpuscular volume levels of 46 patients diagnosed with alcoholic liver disease (Group 1) and 51 patients diagnosed as having hepatitis B and hepatitis C cirrhosis (Group 2).When the relationship between the Child-Pugh Classification and the MCV level was investigated in adrenoleukodystrophy (ALD) patient group (Group 1), it was determined that MCV level was statistically significantly higher in Child class C patients. ($p < 0.01$).[26]

In our study group of 90 patients, 15.6 % had leukopenia and 45.6 % had leukocytosis. Leukocytosis is mostly due to community acquired infections, nosocomial infections, spontaneous bacterial peritonitis or secondary peritonitis due to repeated peritoneal paracentesis. Leukopenia in chronic liver disease may be due to: Direct influences of alcohol on bone marrow, chronic inflammatory cytokines suppressing the bone marrow, hypersplenism or Infections. Similar results were seen in a study by Gupta et al. in which leukocytosis was seen in 30 % of patients, thrombocytopenia was seen in 58.33 % of patients.[27]

There are multiple causes of thrombocytopenia in cirrhosis patients: Hypersplenism causing platelet sequestration, reduced thrombopoietin production, decreases half-life of platelets caused by the auto antibodies, folate and B12 deficiency, and alcohol causing bone marrow suppression, disseminated intravascular coagulation (DIC) caused by various infections or drugs. In our study, thrombocytopenia was seen in 58.9% of patients (< 1 lakh). The results were in accordance with study conducted by Tanushree Maitra et al. who observed thrombocytopenia in 78 % patients and INR > 1 in 82 % patients among 200 patients.[28] Rajkumar Solomon et al. in their study, found 50 % of the patients had thrombocytopenia (< 1 lakh).[29]

A deranged coagulation system is very common in chronic liver disease. In our particular study as much as 88.9 % of patients had a prolonged PT-INR, which is an evidence of clotting factor deficiency. Out of 90 patients, 70 % had raised INR with the mean of 1.40. Similar results were seen in study by Suthar et al. in which the mean prolongation of prothrombin time was 5.6 sec. 72 % of patients had prolonged prothrombin time by > 6 sec. The mean INR was 1.92.[30] The mean serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total bilirubin were 95.6 (IU/L), 85.3 (IU/L), 3.5(mg/dl), respectively. In the study by Suthar et al. the mean SGPT and SGOT levels were 56.1 IU/L and 134 IU/L respectively. Average serum bilirubin in this study was between 3.17 ± 1.81 mg/dl.[30] Hypoalbuminemia is commonly observed in patients with chronic liver disease. In our study mean albumin was 2.4 g/dl. This finding was similar Nand et al. where mean albumin levels were 2.79 ± 0.62 g/dL and severe hypoalbuminemia was seen in 65 %.[31] Our present findings of kidney profile comprising of slightly elevated blood urea and serum creatinine in later stages of cirrhosis are quite similar to earlier reports of Das et al.[32]

CONCLUSIONS

In countries like India, alcoholic cirrhosis is common. Another common cause of cirrhosis in our study was Hepatitis C. 86.6 % of the patients had anaemia in any one of the forms, the most common type being normocytic normochromic type. A significant negative correlation was observed between MELD and haemoglobin levels. MELD score can be used effectively to predict haematological complications in such patients. Haemoglobin levels were significantly lower in CTP class C patients as compared to class A and B. This difference was statistically significant. Leukopenia is found to be rare as per the study and leukocytosis is more common in patients. Thrombocytopenia is present in more than 58.9 % of patients.

Many haematological alterations are present in cirrhosis patients that need to be identified and corrected as early as possible to decrease the morbidity and mortality. However, large group studies are still required to assess whether haemoglobin should be used as a marker for the severity of liver disease. The cause of anaemia in individual patients was not studied extensively which could further improve the management of patients and improve the prognosis.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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