e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(9); 9-17

Original Research Article

Study of Haematological and Hemodynamic Disorders in Chronic Liver Disease Patients in Central Rajasthan

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Received: 15-06-2022 / Revised: 20-07-2022 / Accepted: 20-08-2022
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Conflict of interest: Nil

Abstract

Introduction: The liver plays an important role in homeostasis. Chronic liver disease including cirrhosis, hepatic failure, jaundice and portal hypertension may affect hemopoiesis. The abnormalities in RBC, WBC, and platelet functions in patients with CLD are well documented. It is thus important to detect and manage these abnormalities to reduce overall morbidity and mortality of patients with CLD.

Method: This is prospective study conducted for the period of 2 years at a tertiary care centre. A total of 100 patients of chronic liver disease were included and analysed for their haematological dysfunction and haemostatic abnormalities.

Results: In our study out of total 100 patients, there were 79 male and 21 female patients. The ages ranged from 20 years to 60 years. There were two patients with Wilson's disease, 61 of alcoholic liver disease, 15 patients were positive for HBsAg and one patient was positive for anti HCV antibody. Eight patients had severe anemia, 80 patients had anemia and only 12 patients had normal hemoglobin above 12 gm%. Fifty patients had normochromic normocytic anemia, 28 patients had microcytic anemia and 10 patients had macrocytosis. On account of WBC parameters, the TLC ranged from 1150/mm^3 to 16,100/mm^3. Forty-four patients had leukocytosis, out of which 12 patients had lymphocytosis. Eosinophilia was found in only 4 patients. Leucopenia was seen in 9% of patients. Thrombocytopenia was found in 42 patients. These patients had a history of at least an episode of hematemesis. Among the patients with severe thrombocytopenia 9 patients were found to have disseminated intravascular coagulation. Among the 58 patients with normal platelets level about 16 patients had mild splenomegaly and 12 patients had moderate splenomegaly. In 10 patients, splenomegaly was observed only on USG. In this study only 14% had total proteins more than 6 gm% and only one patient had total protein <4 gm% and others in the middle group. All the 100 patients had albumin globulin ratio reversal. Fifty-eight patients had prolonged prothrombin time. There was no correlation between the severity of jaundice and the prolongation of prothrombin time. Among the 58 patients with prolonged prothrombin time about 38 patients had history of at least one episode of hematemesis. Bleeding time was prolonged in 20 patients who had platelet counts less than 1,00,000/mm3.

Conclusion: This study reflects that all the chronic liver disease patients must be evaluated for hematological and hemostatic abnormalities and should be monitored for any complication. Early treatment to correct these comorbidities can decrease the mortality.

Keywords: Chronic Liver Disease, Hemostatic Disorder, Hematological Disorder, Cirrhosis of Liver

Introduction

Liver is an important organ which also help us maintain haemostasis. Any injury or disease that affects liver function will cause abnormalities in haemostatic system of our body. Liver stores iron, vitamin B12, and folic acid which are necessary for haematopoiesis. It also secretes the clotting factors and the inhibitors and keeps the hemostasis in equilibrium. The chronic liver disease involves recurrent and progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis [1].

Chronic liver disease including cirrhosis, hepatic failure, jaundice, and portal hypertension may affect hemopoiesis. Cholestasis and parenchymal liver diseases both can produce blood coagulation defects [2].

Patients usually present with spontaneous bleeding like epistaxis, purpuric rashes easy bruising etc. The haematological abnormalities add to overall morbidity and mortality in CLD cases. It is thus important to investigate and rule out haematological disturbance early for early management.

Pathophysiology of haematological disorders in CLD is multifactorial and mainly includes sequestration of blood cells, suppression of bone marrow due to toxins, viruses, and imbalance of BM stimulating factors.

Abnormalities in haematological indices are associated with an increased risk of bleeding & infection. Causes of anaemia in chronic liver disease are mainly deficiency of iron, vitamin B12 and folic acid, RBC destruction due to hypersplenism, anaemia of chronic disease, autoimmune haemolytic anaemia, aplastic anaemia, and as an adverse effect of the anti-viral drug.

Portal hypertension in CLD causes varices, gastrointestinal bleeding and hypersplenism which are also an important cause of anaemia in chronic liver disease. In patients with alcoholic liver disease, the different effects of alcohol may contribute to anaemia such as malabsorption, malnutrition, or direct toxic effect.

Thrombocytopenia is common in CLD. Thrombocytopenia is mainly due to PHTN associated splenic sequestration, alteration in thrombopoietin, bone marrow suppression, consumptive coagulopathy, and increased blood loss. Thrombocytopenia is associated with an increased bleeding tendency in CLD patients, so early detection of thrombocytopenia is important and helpful for decreased mortality and morbidity.

Changes in WBC may be associated with CLD; it is mainly due to PHTN-induced splenic sequestration, changes in mainly reduced production of colony stimulating factors like GCSF and GMCSF, bone marrow suppression, and infection.

This study was conducted at our institute to assess the haematological and haemostatic abnormalities associated with chronic liver disease and the nature of haematological abnormalities so that appropriate modifications in the management of patients of chronic liver disease and reduce morbidity and mortality of patient.

Materials and Methods

This is a prospective study conducted in J.L.N. Medical College, Ajmer (Raj.), for

the period of two years from Sep. 2018 to August 2020. Patients were selected with random sampling. We included a total of 100 patients of age range between 18 yrs and 80 years of both genders.

Inclusion Criteria

- Patients with signs and symptoms of chronic liver disease of duration of more than 6 months.
- All patients were included, who on initial workup were diagnosed with Alcoholic liver disease, storage diseases like Wilson's disease and hemochromatosis, post-necrotic cirrhosis and other caused of CLD.

Exclusion Criteria

- Patients with history of primary hepatocellular carcinoma or metastatic carcinoma.
- Patients with pre-existing anaemia or haematological disorders.
- Patients with acute hepatic failure and patients suffering from end stage diseases like COPD, CAD, and Cardiac failure. CKD were excluded.

Methodology

Initially on admission, detailed current, family, and past history was recorded. H/o previous jaundice and other systemic illness recorded. H/o chronic alcoholism was recorded as per the proforma.

All the patients were submitted to all initial blood investigations. Patients with indications for liver biopsy, upper GI endoscopy for detection of varices and CT scan abdomen were also conducted. All initial investigations were supported with signs of liver failure, to establish diagnosis.

Assessment of RBCs

1. RBC count (Normal value taken as 4.5-6 million / mm^3),
2. Haemoglobin estimation (Normal value: In males 14-18 gm / dl and in females 12 -16 gm / dl) was done using automated 5 part haematology analyser.
3. Packed cell volume (PCV) (Normal value, in males 41 to 51% and in females: 36 to 46 %). was done with auto-analyser or using microhematocrit capillary method.
4. RBC indices (MCV, MCHC, MCH) are estimated by 5-part haematology autoanalyzer. Normal values taken as MCV - 80-97 fl, MCH – 26-33 pg/dl, MCHC - 32-35 gm/dl.
   Peripheral smear for blood picture was done for typing of anaemia.

Assessment of WBCs:

Total WBC count was done by hematology 5-part analyser. Manual TLC and DLC was also done by peripheral blood smear examination by a Pathologist. Normal value taken 3,800-9,000 cells per mm3

To assess haemostasis

1. Platelet count – by hematology 5 part auto analyser.
2. Prothrombin time (Normal 10-14 sec.) and Partial thromboplastin time (Normal 24-34 sec) and D – dimer was done by Stago STA Max coagulation auto analyser.

Upper GI endoscopy

UGI endoscopy was done at medical gastroenterology department wherever required.

Results

In our study out of the total 100, there were 79 males and 21 female patients. The ages ranged from 20 years to 60 years. History of chronic alcoholism was present in 6 patients and all were males. Thirty two patients had past history of jaundice, out of which 15 patients were reported positive for HBsAg and one patient for anti HCV antibody.

There were two patients with Wilson's disease and in remaining 22 patients with all signs and lab evidence of CLD, no definitive underlaying cause was reported and grouped as patients with unknown etiologies. Eighty-six patients had raised

bilirubin level and 14% were with normal bilirubin level.

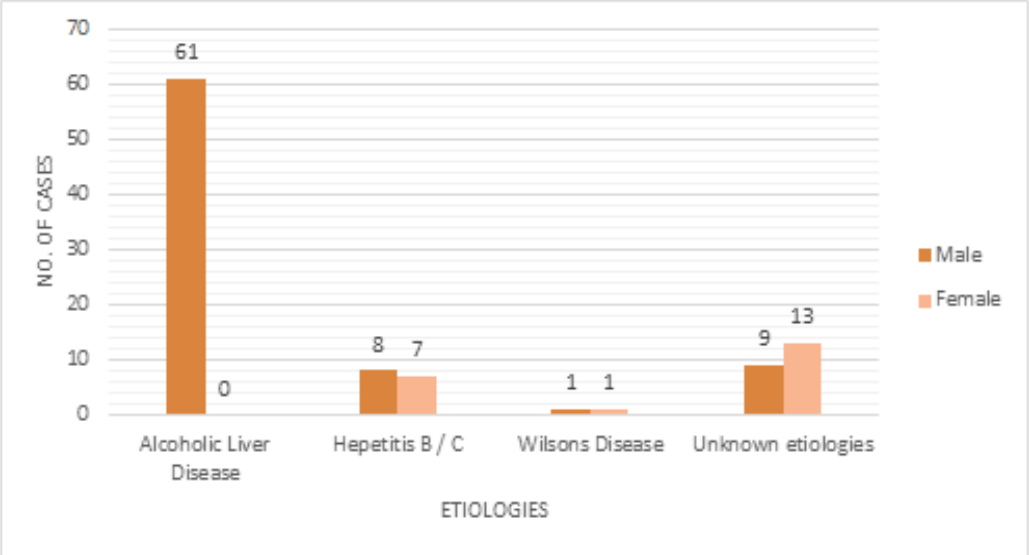

Figure 1: Distribution of cases according to cause of CLD

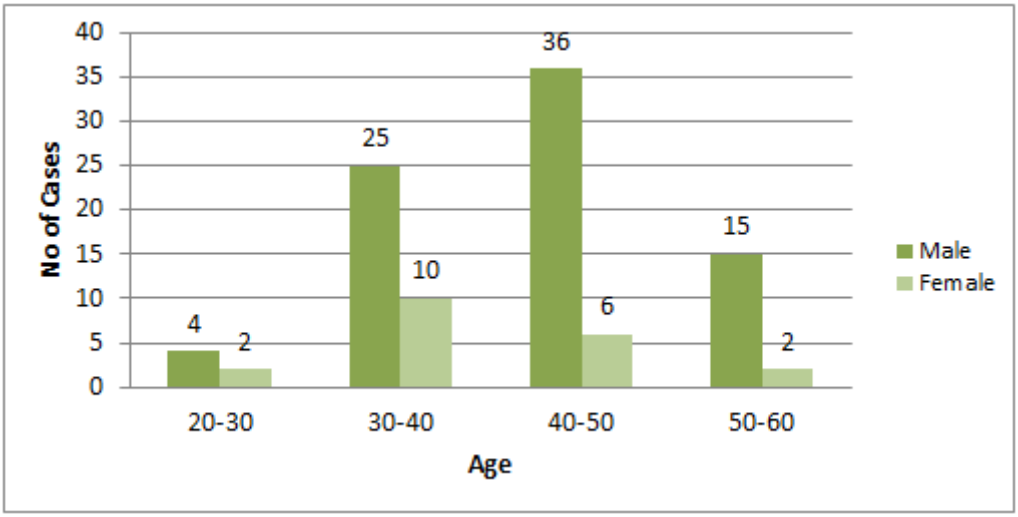

Figure 2: Age of patients

Hematological Profile of P

Table 1: Haematological profile in patients with CLD

	No. of Cases	Percent
Hemoglobin gm%		
<8	8	8%
8.1 to 12	80	80%
12.1 to 18	12	12%
Total RBC count		
25 to 3 million/mm3	13	13%
3.0 to 4.5	74	74%
> 4.5	13	13%
Total leucocyte count in Cells/mm^3		
<4000	9	9%
4000-11000	47	47%
>11000	44	44%

Platelet count cells/mm^3		
<50,000	13	13%
50,000 - 1,00,000	29	29%
1-2.5 lakhs	32	32%
>2.5 lakhs	26	26%

Table no. 1 shows the haematological characteristics of the study group. Severe anaemia with haemoglobin <8% was reported in 8 patients, eighty patients had anaemia with Hb% ranged between 8.1 gm% to 12 gm% and only 12 patients had normal haemoglobin of >12 gm%. On PBF examination, 50 patients had normochromic normocytic anaemia, 28 patients had microcytic hypochromic anaemia and 10 patients had macrocytosis. On analysing WBC parameters, the TLC ranged from 1150/mm^3 to 16,100/mm^3. Forty-seven patients had WBCs in normal physiological range, 44 patients had leucocytosis, out of which 18 patients had neutrophilic leucocytosis, 12 patients had lymphocytosis and Eosinophilia was found in only 4 patients. Leucopoenia was seen only in 9% of patients.

On account of platelet parameters, thrombocytopenia was found in 42 patients. Patients with severe thrombocytopenia (<50,000 cells/mm^3) also had enlarged spleen >8cms on palpation also give positive history of massive hematemesis. Features of disseminated intravascular coagulation were present in 9 patients with severe thrombocytopenia, which was later confirmed by the raised PT / aPTT values and with D dimer estimation. Among the 58 patients with normal platelets level about 16 patients had mild splenomegaly and 12 patients had moderate splenomegaly. In 10 patients, splenomegaly was observed only on USG.

Serum Protein Levels of Patients

Table 2: Serum Protein levels in CLD patients

Total proteins gm%	No. of patients	Percent
< 4	1	1%
41.-5	43	43%
5.1-6	42	42%
>6.1	14	14%

In the present study maximum patients had serum total protein between 4.1 gm% to 6 gm%. Fourteen percent patients had total proteins more than 6.1 gm%, and one patient with proteins less than 4 gm%.

All the 100 patients in our study group had albumin globulin ratio reversal, which points towards the diagnosis of CLD.

Abnormalities in Coagulation

Out of 100 patients, prolonged prothrombin time was reported in 58 patients.

We did not find any correlation between the severity of jaundice and the prolongation PT. Out of 58 patients with prolonged PT, 38 patients had at least one episode of hematemesis. Bleeding time was prolonged in 20 patients with platelet counts <1,00,000/mm^3.

Discussion

Our study included 100 patients of chronic liver disease admitted at a tertiary care Government Teaching Hospital and has evaluated the importance of investigating the haematological abnormalities in chronic liver disease.

Haematological Profile in Patients with CLD

In our study, we inferred that 88% of the total patients had anemia and among them, 8% of cases had severe anaemia. Sheehy TW and Berman A [3] in their study reported that the anemia of cirrhosis occurs in up to 75% of patients with chronic liver disease. It is mainly moderate in severity and is either normochromic normocytic or moderately macrocytic. As described by Siciliano M *et al* [4] in their study, the cause of anaemia in CLD is mainly due to hemodilution, decreased erythropoietin level and chronic inflammation in cirrhosis leading to increased cytokines such as TNF- α, IL-1 which in turn suppress the bone marrow. In developing countries like India, nutritional anemia due to iron and B12 /folic acid deficiency has a very high prevalence, which along with cirrhosis leads to severe anaemia. Female patients are affected more when compared with males.

As mentioned in Oxford Textbook of Hepatology by Sherlock [5] normochromic and normocytic anaemia is the most common type of anaemia seen in CLD. Our results is in concordance with maximum number of anaemic patients had normochromic normocytic anaemia with 52% cases. Malhotra *et al* (1951), reported an incidence of 90% which is in contrast with our study.

This may be due to the difference in general characteristics of the study population like age group and gender. Whereas Bhatia (1961) and Mishra *et al*., (1982) reported an incidence of normocytic normochromic anaemia as 59% and 79% respectively [6] which is again in concordance with our study.

The incidence of macrocytosis in our study group was 16%, which is in contrast of study done by Kimber C. *et al*. [8] who reported 43% of patient with macrocytosis. The main cause of macrocytosis in patients with CLD is vitamin B12 and folic acid deficiency either due to direct toxic effect of alcohol or decreased hepatic functions. There is also suppression of bone marrow due to chronic inflammatory response causing macrocytic anaemia [7].

Microcytic hypochromic anaemia was reported in 19 patients in our study group. Blood loss from oesophageal varices is the main cause of microcytic anaemia in CLD. Other factors are peptic ulceration, haemostatic defects and thrombocytopenia in chronic liver disease. Kimber C [8] in their study, described that microcytosis in CLD is mainly due to decreased TIBC, serum transferrin, RBC destruction due to splenomegaly, deranged lipid profile, or intra-corpuscular defects.

In the present study, TLC was reported in the range of 1150 - 16,100 / mm^3. Leucocytosis was reported in 44 patients, which was mostly because of community-acquired infection, hospital acquired infection due to prolonged hospitalization, spontaneous bacterial peritonitis, and secondary peritonitis due to repeated peritoneal tap. Most of the patients with leucocytosis had h/o repeated hospital admissions and had repeated peritoneal taps.

Most (50%) of the patients with leucocytosis presented with or developed high-grade fever during hospital stay. On peripheral blood film examination, maximum number of patients had increased polymorphs in blood and also in ascitic fluid examination.

Leucopoenia was observed in only a few patients with 9% incidence in our study, which may be due to direct influences of alcohol on bone marrow, suppression of bone marrow, hypersplenism, and Infection.[9] Eosinophilia was reported in 4% of cases in our study and most cases were due to mostly due to parasitic infection. E. Krithiga et. al [10] reported that leucocytosis was more common than leucopoenia which is in concordance with our study.

Most of the patients in their study had ascites and had undergone paracentesis

which might have contributed to leucocytosis. They also inferred that spontaneous bacterial peritonitis may be the other possible explanation. Another study done by Berman *et al* in 1949 on the blood and bone marrow of cirrhotic patients suggested that some patients may present with normal leucocyte count, while others experience leucocytosis after paracentesis, infections, or surgical procedures [11].

Thrombocytopenia was reported in 42 patients, out of which 13 had severe thrombocytopenia and 29 patients had moderate thrombocytopenia (platelet count 50000-100,000 / mm^3). Nine patients were diagnosed with DIC, which further reduce platelet count in CLD. Similar results were also reported by studies of Miller JB *et al* [12], and Alawad *et al* [13].

Serum Proteins in Patients with CLD

Increased globulin is a well-documented feature of CLD. [5] Berger *et al* [9] described that there was normal proportion of B lymphocytes in peripheral blood but IgG and IgA synthesis was markedly increased. The raised ESR is not due to neoplastic process, inflammation or infection but mainly due to lower fibrinogen levels found in cirrhosis and lower kininogen levels.

In the present study, almost all patients had hypergammaglobulinemia and all 100 cases had albumin globulin ratio reversal. The ratio reversal is also contributed by lower albumin concentration due to decreased synthesis. Decreased serum albumin, and serum total proteins was reported in 86% cases and all the patients had the albumin globulin ratio reversed. Hypoproteinaemia was also found to be associated with poor socioeconomic status of the patients in our study.

In cirrhosis, there is a chronic progressive inflammatory response in the body, which causes elevated cytokines levels such as IL-1, IL-6, and TNF- α which in turn hampers with the synthesis of albumin and transferrin by the liver. As reported by Barle H. & Nyberg B [14] the fractional synthetic rate of albumin is approximately 6% per day compared with 25% for total liver proteins.

Patients with CLD also show low levels of serum transferrin. Which may also contribute to iron deficiency anaemia in CLD.?

Prothrombin Time Abnormalities

Elevated prothrombin time (PT) was reported in 58% patients in our study. This shows deficiency of clotting factor. The PT was also repeated after administration of vitamin K in such patients. Factor V synthesized by liver is independent of vitamin K levels in blood. Reduced factor V along with factors, II, VII, IX and X further indicated hepatocellular dysfunction [15].

Disseminated Intravascular Coagulation

In our study, 9 patients were found to have DIC and it was confirmed with prolongation of PT and APTT along with severe thrombocytopenia and was confirmed by estimation of D- dimer.

These patients were found to have septicaemia, and they are culture positive showing gram negative organisms. As described by Green FG *et al* [16]. on evaluation of thrombin-antithrombin complexes, soluble fibrin and fibrinogen degradation products (D-dimer, D-monomer), it is evident that low grade DIC is a component of coagulopathy in some patients with liver disease. The mechanism stimulating this are thought to include impaired clearance of activated clotting factors and endotoxemia.

Thus, after analysis the results of our current study and review of literature for similar studies, it is inferred that many of the haematological abnormalities are likely to occur in patients suffering from a chronic liver disease. Conditions like severe anaemia, leucocytosis, and disturbance in albumin globulin ratio add s to the morbidity in patients of CLD through increased inflammation response.

Thrombocytopenia and coagulation disorders lead to bleeding tendency and further deteriorate the clinical condition of patients. Early identification of these disorders and timely correction may improve the prognosis and survival of patients of CLD.

Conclusion

This prospective study reflects that all the patients presented with signs of chronic liver disease must be thoroughly evaluated for complete blood and coagulation profile to detect haematological abnormalities and should be monitored for any complication. Early initiation of treatment can decrease the overall mortality in these patients.

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