A STUDY ON HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE

Suresh Moothezhathu Kesavadas[1], Santhosh Kumar Thulaseedharan Saraswathy[2], Muhammed[3]

[1]Professor, Department of Internal Medicine, Government Medical College, Trivandrum.
[2]Assistant Professor, Department of Internal Medicine, Government Medical College, Trivandrum.
[3]Senior Resident, Department of Internal Medicine, Government Medical College, Trivandrum.

ABSTRACT

BACKGROUND

Liver plays an important role in normal erythropoiesis and synthesis of clotting factors. Chronic liver disease (CLD) patients are frequently associated with abnormalities in haematological parameters.

MATERIALS AND METHODS

This was an observational study conducted among diagnosed CLD patients over a period of 1 year from 2013 to 2014. Various haematological abnormalities in 75 CLD patients were studied. Relevant details were obtained in structured format.

RESULTS

The mean age of the study group 49.2 years. Male-to-female ratio was 5.8:1. Aetiologies of cirrhosis were alcoholism (61.3%), diabetes mellitus (26.7%) and dyslipidaemia (13%). 88% patients were anaemic with severe anaemia (Hb <8 gm%) observed in 33.3% patients with mean Hb being 8.76 gm%. Mean Hb in alcohol-related CLDs were lower than CLDs due to other aetiologies (8.62 gm% vs. 9.36 gm%). Most common anaemia observed was normocytic normochromic anaemia (40.9%). 26.7% had leucopenia and 88% had thrombocytopenia. Normal ferritin levels were observed in 6.7%, decreased in 16% and increased in the remaining cases of which a level of more than 900 ng/mL was observed in 18.7% cases. Mean CTP (Child-Turcotte-Pugh) score of the study group was 11.1. 80% of patients belong to child C. Patients with high ferritin levels had high CTP score (P-0.001). Platelet count decreases as CTP score increases (P-0.000) and as spleen size increases (P-0.001).

CONCLUSION

Most common haematological abnormalities observed were thrombocytopenia and anaemia. Severe anaemia was seen in males and alcoholics. Thrombocytopenia was more in those with advanced liver disease and large spleen. High serum ferritin level correlate well with advanced liver disease.

KEYWORDS

CLD- Chronic Liver Disease, DCLD- Decompensated CLD, LFT- Liver Function Tests, Hb- Haemoglobin, PT- Prothrombin time, CTP- Child-Turcotte-Pugh.

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BACKGROUND

Liver is the largest organ of the body weighing 1-1.5 kg, which is 1.5-2.5% of the lean body mass. It performs numerous and vital roles in maintaining homeostasis and health.

It plays major role in synthesis of proteins, regulation of nutrients, metabolism and conjugation of bilirubin and drugs, detoxification, production of bile and maintenance of immunity (Kupffer cells).

Right from being a primary site of haematopoiesis in foetal life to maintenance of haematological parameters in postnatal life, the liver has an extremely important role in maintenance of blood homeostasis.

It stores iron, folic acid and vitamin B12, secretes clotting factors and inhibitors. Hence, liver diseases cause wide range of abnormalities in haematological parameters.

Peripheral blood picture in chronic liver disease is influenced by the presence of jaundice, liver cell failure, portal hypertension and hypersplenism, reduced red cell half-life. Both cholestasis and hepatocellular failure can derange the coagulation system. Other problems seen were dietary deficiencies, bleeding, alcoholism and abnormalities in hepatic synthesis of proteins used for blood formation or coagulation.

Chronic Liver Disease (CLD) refers to disease of the liver, which had lasted more than six months. Disease process involves progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis.

CLD frequently associated with haematological abnormalities. These are associated with increased morbidity and mortality in these patients.

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Corresponding Author:
Dr. Santhosh Kumar Thulaseedharan Saraswathy,
PMRA B-72, Mangannurkonam Lane,
Pattom Palace P.O,
Trivandrum, Kerala-695004.
E-mail: ashasanthosh_ram@yahoo.com
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This study was undertaken to describe the haematological abnormalities in Decompensated Chronic Liver Disease (DCLD), so that measures could be taken to correct them and reduce morbidity.

Aims and Objectives

- To assess the haematological abnormalities in decompensated chronic liver disease.
- To determine severity, morphology and most common type of anaemia in chronic liver disease.
- To correlate ferritin levels with the severity of liver disease.
- To assess the PT/INR in patients with decompensated chronic liver disease.
- To assess correlation between spleen size as well as CTP score with thrombocytopenia.

MATERIALS AND METHODS

Study Design- Descriptive study involving decompensated chronic liver disease patients.

Study was conducted among patients admitted to medical wards of Internal Medicine Department, Medical College Hospital, Trivandrum.

Sample Size

Calculated using the formula N = 4 PQ/D^2.
N = Sample size.
P = Prevalence from previous studies.
Q = 100 - PD = allowable error (5-20% of P).

According to a study on spectrum of anaemia associated with chronic liver disease by Rosario Gonzalez-Casas et al showed anaemia of diverse aetiology occurs in upto 75% of cases of chronic liver disease. As anaemia was the most important parameter studied in this study, its prevalence was taken as P.

So, P = 75, Q = 25 (100-75); D was taken as 10 (13.33% of P).

Thus, N = 4 x 75 x 25/10 x 10 = 75.

Study Population

Patients with decompensated chronic liver diseases admitted to medical wards of Internal Medicine Department, Medical College Hospital (MCH), Thiruvananthapuram.

Inclusion Criteria

1. The study subjects included all cases of DCLD admitted to medicine wards of Internal Medicine Department of MCH, Thiruvananthapuram.
2. All patients with liver disease whose symptoms and signs persists for more than 6 months were classified as CLD. Diagnosis was supported by Ultrasonography (USG) of abdomen.
3. CLD patients with 1 or more features of decompensation in the form of ascites, jaundice, hepatic encephalopathy or bleeding varices were included. Cirrhosis with Child-Pugh score of 7 or more also included as DCLD.
4. The study included only those cases in which an informed consent can be obtained from either the patient themselves or from the nearest of kin if the clinical condition of the patient does not allow consent to be elicited from him.

Exclusion Criteria

1. Patients with primary coagulation disorder or primary abnormalities of haemostatic function were excluded.
2. Patients with preexisting anaemia due to other causes were excluded.
3. Patients suffering from end-stage medical diseases like chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease and cardiac failure were excluded.
4. Those with history of recent transfusion (within 3 months) with blood or blood products were excluded from the study.

METHODOLOGY

After ethical clearance, permissions were obtained from Head of the Department of Internal Medicine. History, physical examination, blood investigations, radiographic assessment and endoscopy help in establishing a diagnosis of CLD. Those found to have DCLD by above assessment were informed about the study in native language. After satisfying the exclusion criteria and getting informed consent, the structured proforma was filled with respective data. Patients were evaluated for haematological abnormalities.

Data Analysis

Data analysis was done in SPSS 15. Various haematological abnormalities of DCLD patients were analysed and compared.

Factor	1 Point	2 Points	3 Points
Total bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT/INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild	Moderate-to-severe
Hepatic encephalopathy	None	Grade I or II	Grade III or IV

Table 1. Child-Pugh Score

Chronic liver disease is classified into child class A, B and C based on Child-Pugh score. Score 7 or more classified as DCLD.

RESULTS

Age	Count	Percent
30-40	12	16
41-50	30	40
51-60	21	28
>60	12	16
Mean ± SD	49.2 ± 8.6	

Table 2. Percentage Distribution of the Sample According to Age

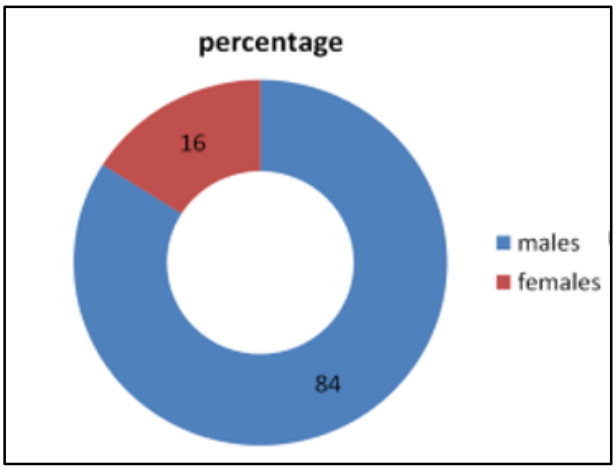

Figure 1. Percentage Distribution of Sample

Aetiology	Count	Percent
Alcoholism	46	61.3
Alcohol + viral hepatitis	6	8
Hepatitis B	5	6.7
Hepatitis C	4	5.3
NASH	4	5.3
Autoimmune	2	2.7
Biliary cirrhosis	2	2.7
Wilson's disease	4	5.3
Cryptogenic	2	2.7

Table 3. Percentage Distribution of the Sample According to Aetiology

Comorbidities	Count	Percent
Nil	30	40
DM	20	26.7
HTN	4	5.3
DLP	13	17.3
CAD	4	5.3
DVT lower limb	5	6.7
UTI	3	4
Cellulitis leg	4	5.3
Sepsis	2	2.7
SBP	3	4
AIHA	2	2.7
Haemorrhoids	1	1.3
HCC	2	2.7
HRS	1	1.3
Psychiatric illness	1	1.3

Table 4. Percentage Distribution of the Sample According to Comorbidities

	Among All CLD Patients	Alcoholic CLD	Alcohol Plus Hepatitis-Related CLD	Other CLD Groups
Mean	8.76	8.62	7.63	9.36
Minimum	4.1	4.1	5.5	6.5
Maximum	13.3	13.2	11.8	13.3

Table 5. Mean HB Based On Different Aetiologies

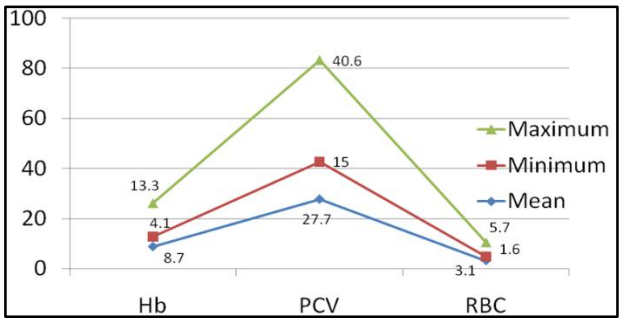

Figure 2. Mean, Minimum and Maximum Values of HB, PCV and RBC Count

P. smear	Count	Percent
Dimorphic	3	4.5
Hypochromic microcytic	17	25.8
Macrocytic	19	28.8
Normocytic normochromic	27	40.9

Table 6. Morphology of Anaemia Based on Peripheral Smear

S. Ferritin	Mean	SD	N	F	p
Below normal	10.9	2.2	12	22.74**	0.001
Normal	8.6	0.5	5		
Above normal up to 900	10.6	1.2	44		
>900	13.4	0.9	14		

Table 7. Comparison of CTP Score vs. Serum Ferritin

Mean	4.3
SD	1.7
Median	4
Minimum	1
Maximum	8

Table 8. Size of Spleen in CLD Patients

PT/INR	Count	Percent
<1.7	10	13.3
1.7-2.3	15	20
>2.3	50	66.7

Table 9. Percentage Distribution of the Sample According to PT/INR

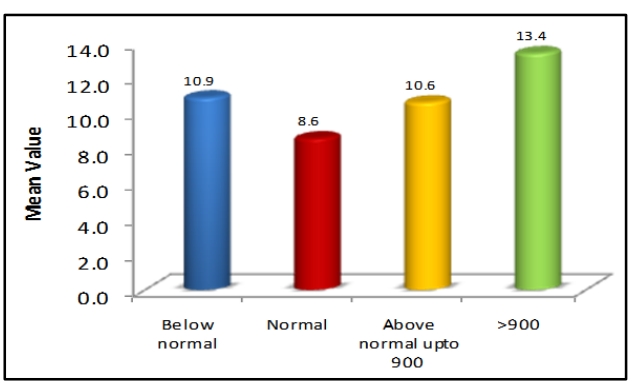

Figure 3. CTP Score Vs. Serum Ferritin Levels

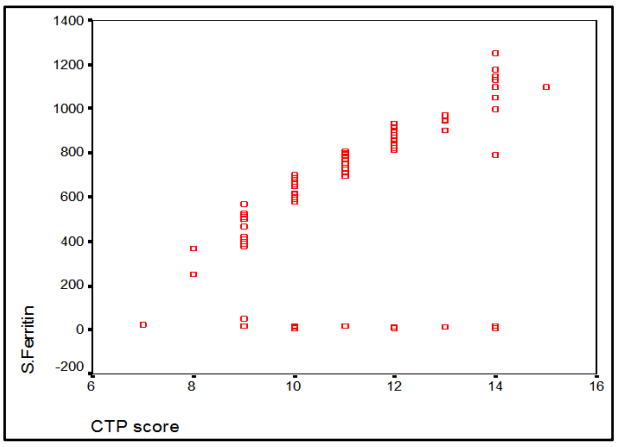

Figure 4. Scatter Diagram Comparing CTP Score Vs. Ferritin Levels

DISCUSSION

In this study, 64 patients were males and 11 were females. This study was comparable to a study done by Anbazhagan et al[1] in which 88% were males and 12% were females. Mean age of the study population in our study was 49.2 with 40% patients belong to 41-50 years of age. 44% patients belong to more than 50 years of age and 16% patients were 40 years or younger. Most common aetiology found in our study was alcoholism seen in 61.3% of patients followed by alcohol plus viral hepatitis (in 8% cases). Viral hepatitis observed in 12% cases (hepatitis B in 6.7%, hepatitis C in 5.3%) and NASH-related CLD in 5.3% of cases. These observations were comparable to the study by Gautam Ray et al.[2]

They showed alcohol as the most common aetiology for the CLD (in 42% cases) followed by viral hepatitis (in 31% cases- 21% cases were hepatitis B and 10% cases were hepatitis C) and cryptogenic causes (in 25% cases) and mean age of alcohol-related CLD was 48.4 years.

Comorbidities were present in 60% cases. Most common comorbid condition noted was Diabetes Mellitus (DM) in 26.7% cases followed by Dyslipidaemia (DLP) in 13% cases. DVT of lower limb noted in 6.7% cases; coronary artery disease, hypertension and cellulitis lower limb were observed in 5.3% cases each. 2.7% patients had Hepatocellular Carcinoma (HCC). This was comparable to a study by Garcia Compean et al,[3] which showed diabetes in 30%. According to a study by Ali M et al,[4] 1.8% of admitted CLD patients had venous thromboembolism, but in our study, DVT was observed in 6.7% cases. HCC observed in 11% of patients with cirrhosis in a study by Kalaitzakis et al,[5] but in our study only 2.7% cases were diagnosed to have HCC.

88% of patients had anaemia. Severe anaemia (Hb <8 gm%) was observed in 33.3% patients. Mean Hb of the study group was 8.76 gm%. Mean Hb in males were lower than females (8.45 gm% vs. 10.45 gm%). Mean Hb was less in alcohol-related CLD when compared to CLDs (8.62 gm% vs. 9.36 gm%) due to other aetiologies. It was lowest in alcohol plus viral hepatitis-related CLD (7.6 gm%). Anbazhagan et al[1] found out 80% of the study population were anaemic and in 30% cases Hb was less than 6 gm%. A study by Rosario Gonzalez-Casas et al[6] showed that anaemia due to various aetiologies occur in 75% cases of CLD patients. E. Halleys Kumar et al[7] observed 86% cases were anaemic with 16% of patients had Hb of less than 6 gm%. These results were comparable with our study.

Alcoholics are at more risk of anaemia by various mechanisms[6] maybe the reason for low Hb in alcoholic CLDs observed in this study. Most of the CLDs in this study group were alcoholics and all were men. This maybe the reason for low mean Hb observed in men compared to females in our study.

Most common anaemia observed was normocytic normochromic anaemia (40.9%). 28.8% had macrocytic anaemia, 22.7% had hypochromic microcytic anaemia and in 4% cases. Dimorphic blood picture was observed. This was comparable to a study done by Anbazhagan et al.[1] In that study, most common anaemia observed was normocytic normochromic (in 62.5% cases), microcytic anaemia in 25% cases, macrocytic anaemia in 10% cases and dimorphic anaemia in 2.59% cases. A study by E. Halleys Kumar et al[7] also showed normocytic normochromic anaemia as the most common anaemia (52.3%) followed by microcytic anaemia (27.9%), 17.44% anaemia's had macrocytic blood picture. Haemolysis observed in 4 cases of which one had autoimmune-related CLD, second case had Wilson's disease, third case had hepatitis C and fourth case had Zieve's syndrome.

In this low Hb values goes in parallel with low PCV value and RBC count in most of the cases, mean PCV value is 27.7% (mean Hb 8.76 gm%), mean RBC count was 3.1 million/cmm and mean reticulocyte count was 1%. According to a study by David Bessman et al[8] states anaemia of chronic disease associated with low reticulocyte count.

Leucopenia was observed in 26.7% patients, leucocytosis in 18.7% patients and rest had normal WBC count. It was observed that leucopenia is seen in half of cirrhosis patients.[9] Thrombocytopenia was found out in 88% of patients in our study.

Platelet count of most of the patients ranges between 0.5 to 1 lakh/cmm. In our study, thrombocytopenia observed in 88% cases probably because most of the patients were having advanced liver disease.

Most of the patient in our study were having advanced liver disease as evidenced by mean CTP score of 11.1. 80% of patients belong to child C class (CTP score 10 or more) and 20% belong to child B class (CTP 7 to 9). Platelet count decreases as CTP score increases (p 0.001). This implies that patients with more advanced end-stage disease tend to have a higher degree of thrombocytopenia than those with less advanced CLDs.[10]

Serum ferritin level assessment in this study showed that normal ferritin observed in 6.7%, decreased in 16% and increased in the remaining cases of which a level of more than 900 was observed in 18.7% cases. All patients with low ferritin level had upper or lower GI bleed. Tan TC et al[11] in his study showed that serum hepcidin level was decreased in CLD patients compared to non-liver disease patient controls and was lowest in those with cirrhosis. Low hepcidin

results in increased iron absorption, so as liver disease progresses to cirrhotic or end-stage liver disease, serum ferritin level increases. This was observed in our study that as CTP score increases serum ferritin level also increases (0.001). Mean CTP score of normal ferritin group patients was 8.6, score was 10.6 in high ferritin group up to a level of 900 ng/mL and the score was 13.4 in those with ferritin level >900 ng/mL. These observations were comparable with studies done by Elizabeth et al[12] and Jacobs and Worwood et al.[14]

Thrombocytopenia was compared with splenomegaly in our study, which showed that as spleen size increases, severity of thrombocytopenia increases. Mean spleen enlargement below costal margin is 5.1 cm in those with platelet count of <1 lakh/cmm. It was 3.3 cm in those with platelet count ranging between 1 to 1.5 lakh/cmm and it was 2.4 cm in those patients with platelet count above 1.5 lakh/cmm. This is probably due to pooling of platelets in spleen. A study by Aster RH et al[13] showed that as spleen size increases pooling of platelets in spleen increases. Normally, one third of platelets concentrated in the spleen. In splenomegaly, this pooling increases to 50 to 90%.

86.7% patients had PT/INR value more than or equal to 1.7. Despite of high PT/INR, upper GI bleed occurred only in 26% of patients. Among patients with upper GI bleed, 4 had PT/INR values less than 1.5. DVT lower limb noted in 6.7% of patients despite elevated PT/INR. These observations state PT/INR alone cannot predict the bleeding risk in CLD patients. This was supported by studies done by Caldwell et al[15] and Tripodi et al,[16] which showed PT/INR is a poor marker for bleeding risk in patients with CLD.

CONCLUSION

1. Most common haematological abnormalities observed were anaemia and thrombocytopenia (in 88% cases each).
2. 33.3% cases of anaemias were severe and 50% of patients with thrombocytopenia had platelet count <1 lakh/cmm.
3. Males had worse mean Hb than females and alcoholic CLDs had low, mean Hb than non-alcoholic CLDs.
4. Most common anaemia observed was normocytic normochromic anaemia.
5. High serum ferritin levels correlate well with severity of liver disease in CLD patients.
6. High ferritin level CLD patients are at high risk for HCC.
7. Platelet count decreases as CTP score and spleen size increases.
8. PT/INR is a poor predictor of coagulopathy and bleeding in CLD patients.

Limitations of the Study

1. Patients with recent upper GI bleed were not excluded from the study, which can contribute to anaemia.
2. Only serum ferritin levels were estimated. Other iron studies not performed.
3. Vitamin B12 and serum folate estimation not done.
4. Other coagulation parameters such as APTT, BT, CT were not done.

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