

## A PROSPECTIVE CLINICAL STUDY OF HAEMATOLOGICAL DISORDERS IN CHRONIC LIVER DISEASE

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### ABSTRACT

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#### BACKGROUND

Liver plays a major role in maintaining the haematological parameters in normal and maintain the haemostasis. Liver is the storage site for iron, B12 and folic acid, which are necessary for the normal haematopoiesis. Liver also secretes the clotting factors and the inhibitors and keep the haemostasis in equilibrium. Hepatocellular failure, portal hypertension and jaundice may affect the blood picture. Chronic liver disease is usually accompanied by hypersplenism. Diminished erythrocyte survival is frequent. In addition, both parenchymal hepatic disease and cholestatic jaundice may produce blood coagulation defects. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood formation or coagulation add to complexity of the problem.

#### MATERIALS AND METHODS

To assess the haematological abnormalities in chronic liver disease, the prevalence study was conducted in Konaseema Institute of Medical Sciences, Amalapuram, during the period from June 2015 to August 2017. All blood investigations regarding haematological profile were done in clinical pathology laboratory in Konaseema Institute of Medical Sciences. Some investigations such as MCV, MCH and MCHC were done at outside lab, when the kit for testing was not available along with all other haematological profiles to have some control and to prevent the observers error if done separately.

#### RESULTS

The analysis of WBCs were done with the total count and the differential count. The total count of WBCs range from 1050/mm<sup>3</sup> to 16,100/mm<sup>3</sup>. Among 100 patients, only 14% had total proteins more than 6 gm% and only one patient had total protein <4 gm% and others in the middle group. 42% patients had protein in the range of 6-5 gm% and 43% had 5-4 gm% protein range.

#### CONCLUSION

According to this study conducted with a limited cases of 100 patients, we inferred many conclusive results regarding the haematological and haemostatic abnormalities in a decompensated chronic liver disease patients. In this study, more than 80% of the patients had total protein less than normal and almost 100% of patients had albumin-globulin ratio reversal.

#### KEYWORDS

Haematological Disorders, Liver Disease.

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#### BACKGROUND

Liver plays an important role in homeostasis. Any disease affecting the functions of liver will cause a breach in whole body homeostasis. Liver plays a major role in carbohydrate metabolism, lipid metabolism and protein metabolism. Its role in endocrine and haematological manifestations are important. Loss of liver function can

manifest as subtle metabolic abnormalities and derangements in haematological parameters, which can ultimately culminate in grave complications. Liver plays a major role in maintaining the haematological parameters in normal and maintain the haemostasis. Liver is the storage site for iron, B12 and folic acid, which are necessary for the normal haematopoiesis. Liver also secretes the clotting factors and the inhibitors and keep the haemostasis in equilibrium. Hepatocellular failure, portal hypertension and jaundice may affect the blood picture. Chronic liver disease is usually accompanied by hypersplenism. Diminished erythrocyte survival is frequent. In addition, both parenchymal hepatic disease and cholestatic jaundice may produce blood coagulation defects. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood

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formation or coagulation add to complexity of the problem. Spontaneous bleeding, bruising and purpura together with a history of bleeding after minimal trauma such as venepuncture are most important indications of a bleeding tendency in patients with liver disease than lab tests. The haematological abnormalities in a chronic liver disease adds morbidity to the primary pathology and increases the mortality. Hence, it becomes necessary to investigate the haematological abnormalities and haemostatic abnormalities to decrease the comorbidity. The study was conducted to assess the haematological abnormalities and haemostatic derangements and the nature of haematological abnormalities, so that the treatment can be done towards the line to decrease the morbidity.

### Aim of the Study

1. To assess the haematological abnormalities in a decompensated chronic liver disease patient.
2. To detect the abnormalities in RBCs in a cirrhosis patient.
3. To find the type of anaemia in a patient with chronic decompensated liver disease.
4. To assess the WBC abnormalities.
5. To detect the platelet abnormalities both quantitatively and qualitatively.
6. To assess the secretion and function of clotting factors in the patients with cirrhosis.

### MATERIALS AND METHODS

To assess the haematological abnormalities in chronic liver disease, the prevalence study was conducted in Konaseema Institute of Medical Sciences, Amalapuram, during the period from June 2015 to August 2017. About one hundred patients were selected in random for this study. All of the cases in the study were admitted in the hospital ward and evaluated for chronic liver disease and for the study to assess the haematological abnormalities. Oral consent of the patients got for the clinical examination and for the lab investigations. Written consent also got for the special procedures such as liver biopsy, upper GI endoscopy and viral markers study. All the patients were interrogated regarding the presenting complaints, duration of illness, bleeding tendencies, abdominal distension, jaundice and oliguria. Past history regarding previous treatment history, any history of diabetes, hypertension, tuberculosis and coronary heart disease. History regarding past history of any trauma, blood transfusion, surgery needle pricks and contact with blood products. Personal history regarding alcoholism, smoking and high-risk behaviour also got. Family history of any liver disease in their family member was also noted. Then, the patient was subjected to general examination and systemic examination. Patients were submitted to a number of blood investigations. Blood samples obtained from the patients were personally handed over to laboratory. The results were got in person and was noted. Blood samples were anti-coagulated with EDTA. Patients were evaluated for chronic liver disease to

establish the diagnosis of cirrhosis. Liver biopsy with consent was done to confirm the diagnosis. In patients with defects in coagulation, i.e. increased prothrombin time or decreased platelet count, there is increased bleeding tendency during liver biopsy. So, in that case, diagnosis is established with ultrasound and CT scan abdomen. According to Schalm Sw, the diagnosis of cirrhosis J. Hepatol 1997;27:1118, ultrasound can pick up 87% of cirrhosis and should be confirmed by liver biopsy. In the setting of contraindication to liver biopsy, suspicious of cirrhosis with ultrasound is coupled with evidence of portal gastropathy or varices in upper GI endoscopy or with portal Doppler to gain more evidence of diagnosis. Above investigations were also supported with signs of liver cell failure to establish diagnosis. After establishing the diagnosis, patients were evaluated for haematological abnormalities. All blood investigations regarding haematological profile were done in clinical pathology laboratory in Konaseema Institute of Medical Sciences. Some investigations such as MCV, MCH and MCHC were done at outside lab when the kit for testing was not available along with all other haematological profiles to have some control and to prevent the observers error if done separately.

Similarly, prothrombin time and activated partial thromboplastin time were done at pathology laboratory or together in laboratory outside, which has same control test of PT and APTT as our pathology lab, when kits were not available in the pathology laboratory.

### To Assess RBC Abnormality

1. RBC count- RBC count are done in Neubauer's chamber using Hayem's fluid or autoanalyzer. Normal value- 4.5 to 6 million per mm<sup>3</sup>.
2. Haemoglobin estimation done by Sahli's method based on conversion of haemoglobin to acid haematin or acid analyser. Normal value- Male, 14 to 18 gm%; female, 12 to 16 gm%.
3. Packed Cell Volume (PCV)- It is done in autoanalyzer or using microhematocrit capillary method. Normal value- Male, 42 to 52%; female, 37 to 47%.
4. MCV, MCHC and MCH are estimated by autoanalyzer; MCV - 80 to 97 fl; MCH - 26 to 33 pg/dL; MCHC - 32 to 35 gm/dL.
5. Peripheral smear for blood picture using stains- Blood picture is examined with a lab microscope. Low power field examination- Quality of film number, distribution and staining of WBCs.  
RBCs examination- high-power field examination- Assess RBC's size and shape.  
Haemoglobin concentration, oil immersion examination- Assess atypical cells and inclusion bodies.
6. Reticulocyte count- Stain 1% brilliant cresyl blue, normal 0.2-2%.

**To Assess WBC Abnormality-**

1. Total WBC count done by QBC method or using Neubauer's chamber with Turk's fluid normal 3,800-9,000 cells per mm<sup>3</sup>.
2. Differential count assessed by QBC method or direct staining and visualising with lab microscope.

**To Assess Haemostasis**

1. Platelet count manually is done by Rees-Ecker method, i.e. with staining with brilliant cresyl blue dye or by autoanalyzer.1.
2. Prothrombin time- Normal 10-14 seconds.
3. Activated partial thromboplastin time- Normal 24-34 seconds.

**Liver Biopsy-** Liver biopsy is done with Menghini's needles under the guidance of ultrasound.

**Upper GI Endoscopy-** UGI endoscopy was done at Medical Gastroenterology Department.

**Inclusion Criteria**

1. All liver disease patients whose symptoms and signs persists more than 6 months.
2. Alcoholic and post infective, metabolic causes of liver diseases are taken for study.

**Exclusion Disorder**

1. Patients with known GIT malignancy or known primary hepatocellular carcinoma.
2. Patients with primary coagulation disorder.
3. Acute liver cell failure.

**RESULTS**

This study regarding assessment of haematological profile and haemostasis was conducted among 100 inpatients in Medical Department at Konaseema Institute of Medical Sciences. Out of 100 patients in this study, there are 80 male patients and 20 female patients. The age of patients in this study were in the range from 20 to 60.

Age in Years	Male	Female	Total	Percentage
20 to 30	4	2	6	6%
30 to 40	25	10	35	35%
40 to 50	36	6	42	42%
50 to 60	15	2	17	17%

**Table 1. Age of Patients**

Most of the patients in the study were in the middle age group and only 6% were in younger age.

**Alcoholism-** Among 20 female patients, none gave history of alcoholism, and among the 80 male patients, 62 patients were found to be alcoholic.

**Past History of Jaundice-** Among 100 patients, only 32 patients had past history of jaundice. Later serology investigation for HBV-Ag, anti-HCV antibody shows 12 patients were positive for HBsAg and only one shows positive for anti-HCV antibody.

**Serum Proteins**

Total Proteins gm%	Number of Patients	Percentage
>6	14	14%
6 to 5	42	42%
5 to 4	43	43%
<4	1	1%

**Table 2. Serum Proteins in CLD**

Among 100 patients, only 14% had total proteins more than 6 gm% and only one patient had total protein <4 gm% and others in the middle group. 42% patients had protein in the range of 6-5 gm% and 43% had 5-4 gm% proteins range. All the 100 patients had albumin-globulin ratio reversal, which is again towards the diagnosis of CLD.

**Analysis of RBCS**

Patients in the study were analysed for the presence and absence of anaemia and the characteristics of anaemia when present. Eighty-eight patients had anaemia and only twelve patients had normal haemoglobin above 12 gm%. About 32 patients had severe anaemia less than 8 gm%.

Haemoglobin gm%	Cases	Percentage
<6	3	3%
6 to 8	29	29%
8.1 to 10	44	44%
10.1 to 12	12	12%
12.1 to 18	12	12%
>18	Nil	-

**Table 3. Anaemia in CLD**

Total RBC Count	Cases	Percentage
2.5 to 3 million/mm <sup>3</sup>	18	18%
3 to 3.5	28	28%
3.5 to 4	32	32%
4 to 4.5	10	10%
>4.5	12	12%

**Table 4. RBC Count in CLD**

Type of RBCs	Patients with Anaemia	Patients with Normal Haemoglobin
Normocytic	52	12
Microcytic	19	
Macrocytic	16	
Dimorphic	1	

**Table 5. Type of Anaemia**

**WBC Abnormalities-** The analysis of WBCs were done with the total count and the differential count. The total count of WBCs range from 1050/mm<sup>3</sup> to 16,100/mm<sup>3</sup>. Among the 100 patients, leucocytosis were observed in 22 patients with lymphocytosis were observed in 12 patients. Eosinophilia was found in only two patients. Leucocytosis were observed in patients with fever due to secondary infection of ascites due to repeated paracentesis and four patients had leucocytosis due to spontaneous bacterial peritonitis. Leucopenia is present in 5% of patients. Lymphocytosis is seen in 12% of patients and eosinophilia in 2% of patients.

Total Count in Cells/mm <sup>3</sup>	Number of Patients	Percentage
<3,000	5	5%
3,000-6,000	13	13%
6,000-9,000	32	32%
9,000-12,000	28	28%
>12,000	22	22%

**Table 6. WBC Count in CLD**

### Platelet Abnormalities

Platelet Count Cells/mm <sup>3</sup>	Number of Patients	Percentage
<50,000	8	8%
50,000-1,00,000	12	12%
1-1.5 lakhs	26	26%
1.5-2 lakhs	28	28%
>2 lakhs	26	26%

**Table 7. Platelet Count in CLD**

### DISCUSSION

The study involving 100 patients done at Government General Hospital has thrown light over the haematological abnormalities of chronic liver disease. The results of this study confirms with previous published reports.

**RBC Abnormalities-** In the study, we inferred that 88% of the total patients had anaemia, and among them, 32% of cases had severe anaemia. According to studies by Kimber C, Deller DJ and Lander H., the mechanism of anaemia in CLD 1965 and Sheehy W and Berman A, the anaemia of cirrhosis, anaemia occurs in up to 75% of patients with chronic liver disease. It is characteristically of moderate severity and is either normochromic, normocytic or moderately macrocytic.<sup>1,2</sup>

In our study, 32 patients had severe anaemia less than 8 gm%. In uncomplicated cirrhosis, it is rare to have such low level of haemoglobin as anaemia in cirrhosis mostly due to-

- i. Haemodilution.
- ii. Decreased erythropoietin level as per the study Siciliano.
- iii. Hepatol 1995 who showed decreased erythropoietin level in cirrhosis patients with anaemia when compared with patients with chronic anaemia due to iron deficiency. Cirrhosis without anaemia is not associated with low erythropoietin levels (Pirsi, J Hepatol 1994).<sup>3,4</sup>
- iv. Chronic inflammation in cirrhosis leads to increased levels of serum inflammatory cytokines such as TNF- $\alpha$ , IL-1 suppress the bone marrow.

**Serum Proteins-** The plasma proteins produced by the hepatocyte are synthesised on polyribosomes bound to the rough endoplasmic reticulum from which they are discharged into the plasma. According to Tavill AS, fall in concentration usually reflect decreased hepatic synthesis.<sup>5</sup> In our study, 86% of cases had decreased albumin and total protein level and all the 100 patients had albumin-

globulin ratio reversed. The hypoproteinemia was also contributed by poor socioeconomic status of the patients who got admitted at the government hospitals.

In a study done by Barle H. Myberg B, Essen P, et al, the fractional synthetic rate of albumin is approximately 6% per day compared with 25% for total liver proteins.<sup>6</sup> About 10 gm of albumin is synthesised by normal liver, whereas with cirrhosis, it synthesis only about 4 g.

**Characteristics of Anaemia-** According to Sheila Sherlock and Oxford Textbook of Hepatology, most common anaemia seen in cirrhotic patients is normochromic and normocytic anaemia.<sup>7</sup> It is well proven in our study too. The incidence of normochromic normocytic anaemia in our patients is 52%, whereas in some studies, there are varied results. The incidence of macrocytosis in our patients was 16%, macrocytosis in cirrhosis is mostly due to the toxic of alcohol on RBC production in the bone marrow and deficiency of B12 and folic acid.<sup>8</sup> About 19 patients in our group and microcytic hypochromic anaemia, bleeding from oesophagitis, peptic ulceration or oesophageal varices compounded by the haemostatic defects of chronic liver disease occurs in up to 70% of patients with liver disease or per the study conducted by Kimber, Philips, et al microcytosis in cirrhosis.

**Abnormalities of RBCs-** Target cells are also thin macrocytes found in cholestatic jaundice and hepatocellular jaundice. They have increased resistance to osmotic lysis. They are particularly prominent in cholestasis where a rise in bile acids may contribute by inhibiting Lecithin-Cholesterol Acyltransferase (LCAT) activity,<sup>9</sup> which was proved by the study conducted by Cooper RA, Arner EC. It is seen in 2% of patients in our study.

Spur cells or acanthocytes, which are associated with advanced liver disease are bad prognostic sign. They are not found in our study groups. They form because of an interaction with the abnormal HDL found in liver disease.<sup>10</sup>

**Abnormalities of WBCs-** According to Sheila Sherlock, leucopenia and thrombocytopenia are commonly found in cirrhotics. But, according to Oxford Textbook of Hepatology, leucocyte abnormalities in liver disease may be due to the underlying disease or its therapy and range from neutrophilia to neutropenia and lymphopaenia. In patients with cirrhosis and systemic inflammatory response syndrome, leucocyte activation is evident from measurement of leucocyte adhesion molecule expression and there is elevation of serum IL-6 evident by the study of Rosenbloom, JAMA.<sup>11</sup>

In our study group, all the 100 patients, WBC total count are in the range of 1,000 to 16,000 cells per mm<sup>3</sup>. About 22 patients had leucocytosis, which was mostly due to infections due to community-required infection, nosocomial infection, spontaneous bacterial peritonitis and secondary peritonitis due to repeated peritoneal paracentesis.

In our study group, in patients with leucocytosis,  $>12,000/\text{mm}^3$  of blood, most of the patients had history of repeated hospital admissions and had repeated paracentesis. About 50% of patients with leucocytosis had high-grade fever and all patients with leucocytosis had increased cell count mostly of polymorphs in ascitic fluid analysis, which suggests the presence of peritonitis in this group of patients.

**Immunoglobulins and Liver Disease-** Cirrhosis maybe associated with a state of generalised hyperactivity perhaps as a result of a defect of immune regulation. Berger et al found that peripheral blood mononuclear cells from cirrhosis with hypergammaglobulinemia had a normal proportion of B cells, but that IgG and IgA hypergammaglobulinemia synthesis was markedly increased. The ESR is not raised by inflammation, infection or neoplasia to the extent that one would expect is largely due to lower fibrinogen level found in cirrhotics and to the lower kininogen level.<sup>12</sup>

In our study, almost all patients had hypergammaglobulinemia and all the 100 cases had albumin-globulin ratio reversal. The ratio reversal is also contributed by lower albumin concentration due to decreased synthesis.

**Platelets Abnormalities-** Defects of platelet number and function are well documented in patients with chronic liver disease contributing significantly to their haemostatic abnormalities. Alcoholic liver disease is associated with additional abnormalities, which are probably a consequence of the toxic effect of alcohol on platelet production.

In our study, the above findings are evident, and out of 100 patients, 13 patients had thrombocytopenia  $<1,00,000/\text{mm}^3$  and 29 patients are i.e. the range of mild thrombocytopenia 1.5 lakhs/ $\text{mm}^3$ . All the patients with count less than one lakh had history of bleeding tendencies, and among them, two patients had severe thrombocytopenia  $<50,000/\text{mm}^3$ . Among the patients, four patients diagnosed to have DIC, which also contributed to the very low platelet count in cirrhotics.

All the patients with platelet count less than one lakh had increased bleeding time. Qualitative platelet abnormalities assessed by template bleeding times and platelet aggregation studies may correlate with severity of chronic liver disease.

Liver plays a major role in regulating haemostasis, synthesising most of the clotting factors and coagulation inhibitors, as well as some proteins of the fibrinolytic activated enzymes of the clotting and of the fibrinolytic systems.

As per the studies, Manner EJ, 1992, and Colman RW and Rubier R.N. blood coagulation 1988, clotting factors may be decreased even before any other evidence of liver damage. In hepatocellular failure, factor VII is earlier to be decreased due to its short half-life, then followed by factors II and X. Factor IX is usually the last to be affected.<sup>12,13</sup>

These are vitamin K dependant proteins synthesised in liver. If these deficiencies are unresponsive to parenteral administration of vitamin K, it can be assumed that the hepatic synthesis of clotting factors is impaired.<sup>14</sup>

**Prothrombin Time Abnormalities-** In our study, 60 patients had elevated prothrombin value, which is evident of clotting factor deficiency. They were also treated with vitamin K injection for a period of one week and the prothrombin time was repeated. Some show, decrease in the prothrombin value.<sup>15,16</sup>

Factor V synthesised in liver independent of vitamin K and decreased level of factor V along with factors II, VII, IX and X is an indicator of hepatocellular failure.

**APTT Abnormality-** APTT is prolonged in all coagulation defects including platelet activity and thromboplastic prolonged APTT is found into-

1. Vitamin K deficiency.
2. Liver disease.
3. Presence of circulating anticoagulants.
4. DIC disease.

In our study, four patients had found to have DIC and they have significant prolongation in APTT along with increased PT with severe thrombocytopenia. Other patients with history of bleeding tendencies had found to have moderately increased APTT.

According to Oxford Textbook of Haematology, APTT may be found to be moderately to highly prolonged according to the degree of liver failure. In case of moderate deficiencies of factor II, IX, X and V associated with a high level of factor VIII, the APTT will be normal.

### Disseminated Intravascular Coagulation

According to Sheila Sherlock, the complex changes found in coagulation proteins, inhibitors and protein fragments usually associated with DIC could have been attributed to chronic liver diseases. According to studies by Bakkar CM, Knot EAR, Stibbe J., et al, thrombin antithrombin complexes, soluble fibrin and fibrinogen degradation products (D-dimer, D-monomer) suggest that low-grade DIC is a component of coagulopathy in some patients with liver disease.<sup>14,17</sup>

The mechanism stimulating this are thought to include impaired clearance of activated clotting factors and endotoxaemia.

In our study, four 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.

Thus, with the above studies, we inferred that many of the haematological abnormalities are to be noticed in a chronic liver disease patient, so that the comorbidity, which causes increased mortality can be decreased.

From the above study, we noted that the severe anaemia present in increased proportion in women than men and is not correlated with severity of disease as evident by serum bilirubin and hypoalbuminaemia. Instead, it is related with history of bleeding tendency.

The character of anaemia depends upon the various factors such as bleeding tendencies, dietary deficiency, alcoholism and haemolytic syndromes. But, normochromic, normocytic anaemia is most commonly found and mostly due to the primary pathology leads to haemodilution and chronic inflammation suppressing the bone marrow.

Macrocytosis is less common in females where the incidence of alcohol is less common.

Among the leucocyte abnormalities, leucopenia, which are found in cirrhosis as per the western literature is uncommon in our study. The leucocytosis is associated with infections mostly of secondary peritonitis due to repeated paracentesis and spontaneous bacterial peritonitis.

Platelet abnormalities as assessed by thrombocytopenia and increased bleeding time had no correlation with the severity of liver cell failure best associated in patients with large spleen and is more common in patients with bleeding tendencies, a consequence of platelet defect.

Similarly, prothrombin time and APTT are prolonged in more than 50% patients, which can be correlated with the liver disease and there is significant rise in APTT along with severe thrombocytopenia is seen in patients with DIC.

## CONCLUSION

According to this study conducted with a limited cases of 100 patients, we inferred many conclusive results regarding the haematological and haemostatic abnormalities in a decompensated chronic liver disease patients. In this study, more than 80% of the patients had total protein less than normal and almost 100% of patients had albumin-globulin ratio reversal. Almost, 80% of the patients had anaemia in any one of the form. Most common anaemia in cirrhosis is normochromic, normocytic anaemia as inferred from the study. Microcytic anaemia is most common among women and macrocytosis is rare. Macrocytosis is almost common with alcoholics, abnormal red cells such as microcytes, macrocytes, target cells and anisocytosis are found to be common in cirrhosis. Leucopenia is found to be rare as per the study and leucocytosis are more common in patients with spontaneous bacterial peritonitis and secondary peritonitis. Thrombocytopenia is present in more than 30% of patients and is commonly present in the patients with splenomegaly and with the history of bleeding tendencies. Prothrombin time and activated partial thromboplastin time are prolonged in more than half of the patients. A significant rise in APTT with severe thrombocytopenia is found in DIC patients.

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