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Original Research Article

Hematological abnormalities in chronic liver disease and their association with severity and types of chronic liver disease

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ABSTRACT

Background: This study aimed to assess the hematological abnormalities in CLD patients and to study the association of hematological abnormalities with type and severity of CLD.
Materials and Methods: This study was conducted as a facility based cross-sectional study at tertiary care centre on confirmed cases of chronic liver disease. Detailed clinical history along with clinical examination findings were recorded. All patients were then subjected to investigations.
Results: Mean age of patients with CLD was 48.8±16.9 years and majority of patients were males (76%). Anemia was observed in 71% cases with CLD whereas leukocytopenia and thrombocytopenia were noted in 21% and 56% cases respectively. Mean MCV, MCH, serum bilirubin and iron were significantly higher in cases with alcoholic liver disease whereas TIBC was significantly lower in ALD cases as compared to NALD cases ($p<0.05$). Mean hemoglobin, platelet levels, MCV, albumin and iron levels were significantly lower in cases with severe liver disease (Child Pugh Class C). However, serum bilirubin, prothrombin time and TIBC levels increased significantly with increase in severity of CLD ($p<0.05$).
Conclusions: Hematological abnormalities particularly normocytic normochromic anemia and thrombocytopenia are common in cases with CLD, which might affect the prognosis of patients with CLD. Assessing the severity and type of anaemia is a useful tool for early initiation of the treatment in patients of CLD for reducing the morbidity and mortality. Early detection and treatment of haematological changes can prevent complications and reduce the mortality in CLD patients.

1. Introduction

Chronic liver disease is fourth leading cause of mortality among adults all over the world and is a pathogenic process of the liver characterized by progressive destruction and regeneration of parenchyma of liver causing fibrosis and cirrhosis.[1] Chronic liver disease may be secondary to certain viral infections such as (Hepatitis C and B), alcohol, and nonalcoholic steatohepatitis (NASH).[2] Liver is the largest organ which is involved in metabolism. Liver is an important site for erythropoiesis and synthesis of procoagulant as well as anticoaugulant proteins.[1,3] It is also a site for storage of vitamin B12, iron and folic acid.[4] Chronic liver disease irrespective of etiology is associated with haematological abnormalities and since liver is the major site for erythropoiesis, anemia of various etiologies is also one of the common finding, which can be observed in as high as three fourth cases.[5]

Hematological changes in CLD patients have also been attributed to portal hypertension induced sequestration, alteration in bone marrow stimulating factors, viral and toxin induced bone marrow suppression and

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consumption or loss.[6] Anemia in CLD patients may be due to hypersplenism, iron deficiency, folic acid deficiency, anaemia of chronic disease, autoimmune hemolytic anaemia, aplastic anaemia or secondary to anti-viral drug.[7] Anemia in CLD cases have been attributed to gatrointestinal hemorrhage, blood coagulation defect, thrombocytopenia etc. The anemia in cases with alcoholic liver disease may result from malabsorption, malnutrition or direct toxic effect. Thrombocytopenia is also one of the common hematological finding in cases with CLD, and is due to alteration in thrombopoetin, splenic sequestration associated with portal hypertension, suppression of bone marrow, increased blood loss or consumptive coagulopathy.[8]

Chronic liver disease is also associated with changes in WBC, reduced synthesis of plasma proteins from the liver leading to low circulating of blood clotting factors, resulting in prolongation of prothrombin time.[3] With the above background, we conducted this study to assess the hematological abnormalities in CLD patients and to study the association of hematological abnormalities with type and severity of CLD so that treatment can be initiated toward reducing the morbidity and mortality of patients.

2. Materials and Methods

This study was conducted as a facility based cross sectional study at Gajara Raja Medical College (GRMC), Gwalior Madhya Pradesh during the study period of 12 months i.e. from 1^{st} June 2019 to 31^{st} May 2020. All confirmed cases of chronic liver disease by clinical, biochemical and radiological evaluation belonging to more than 15 years of age were included whereas patient on drugs which cause defect in haematological parameters (such as glucocorticoid, synthetic estrogen, aspirin, tamoxifen, methotrexate, OCP etc.), patients with malignancy, pregnancy or previous history of haematological and coagulation disorder other than CLD were excluded from the study.

After obtaining ethical clearance, all the chronic liver disease patients attending the study centre during the study period were screened and enrolled. Written consent was obtained from all the study participants. A detailed history was elicited from all patients with emphasis on symptomatology and history of presenting & past illness; personal & family history; drug & addiction history is taken. Detailed clinical evaluation including history including questioning about risk factors for chronic liver disease ,history of hepatitis, alcohol consumption, diabetes mellitus, use of illicit drugs (by injection or inhalation), transfusions, family history of liver disease, travel, and the presence of autoimmune diseases (including inflammatory bowel disease, rheumatoid arthritis and thyroid disease). The review of systems including questioning related to fatigue, easy bruisability, lower extremity edema, fever, weight loss, pruritus, increasing abdominal girth, and confusion or sleep disturbance (possibly indicating encephalopathy). Clinical signs including spidernaevi, gynaecomastia, anemia, low grade fever, white opaque nails, clubbing of nails, foetor hepaticus, jaundice, ascitis, encephalopathy, Prominent veins over abdomen, caput medusa, hepatomegaly, splenomegaly. Patients were classified on disease severity on basis of Child Pugh Turcotte Score.[9]

All patients were then subjected to investigations such as routine hemogram, liver function tests, FBS and PPBS, renal function tests, Serum electrolyte, Anaemia typing with reticulocyte count, Serum iron, TIBC, Ascitic r/m, Upper GI endoscopy, Chest x-ray, Ultrasonography of abdomen etc.

2.1. Statistical methods

Data was compiled using MsExcel and analysed with the help of statistical software namely SPSS 22.0. Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups and chi square test has been used to analyse the data having ordinal variables. A p value of <0.05 was considered as significant.

3. Results

The present study included a total of 100 patients with chronic liver disease who were admitted at the study area during the study period.

Mean age of patients with CLD was 48.8±16.9 years and majority of patients belonged to 51 to 60 years of age (48%). Male predominance was observed for CLD (76% males and 24% females). Non alcoholic cause of CLD was noted in 54% cases. Most common clinical feature was abdominal distension (71%). However, hematemesis and Malena were noted in 15% and 12% cases respectively. About 3% cases had altered sensorium. Splenomegaly was noted in 43% cases. Severity of CLD was assessed using Child Pugh score. Majority of cases belonged to Child Pugh score of B (56%), followed by class C (23%).Table 1

Above table represents hematological abnormalities in cases with CLD. Anemia was observed in 71% cases with CLD whereas leukocytopenia and thrombocytopenia were noted in 21% and 56% cases respectively. Serum bilirubin was 3.9±1.3 mg/dl whereas albumin was 3.09±0.61 g/dl. Mean prothrombin time was 18.5±3.9 seconds. About 25% cases had microcytic normochromic anemia. Serum iron and TIBC were 96.4±16.3 μg/dL and 292.46±38.9 mg/dL respectively.Table 2

Mean MCV, MCH, serum bilirubin and iron were significantly higher in cases with alcoholic liver disease whereas TIBC was significantly lower in ALD cases as compared to NALD cases ($p<0.05$). Incidence of microcytic anemia was higher in NALD cases and macrocytic anemia

Table 1: Distribution according to baseline variables

Baseline variables		Frequency (n=100)	Percentage
Age (years)	≤40	19	19
	41-50	31	31
	51-60	48	48
	>60	12	12
Gender	Male	76	76
	Female	24	24
Cause of CLD	ALD	46	46
	NALD	54	54
Clinical features	Abdominal Distension	71	71
	Fever	17	17
	Jaundice	42	42
	Abdominal Pain	31	31
	Pedal Edema	49	49
	Hematemesis	15	15
	Malena	12	12
	Altered Sensorium	3	3
	Splenomegaly	43	43
Child Pugh Score	A	21	21
	B	56	56
	C	23	23

Table 2: Hematological abnormalities in CLD

Hematological abnormalities			
CBC	Hemoglobin (gm/dl)	<8	71 (71%)
		>8	29 (29%)
		Mean	8.01±2.6
	TLC (cells/mm^3)	<4000	21 (21)
		4000-11000	57 (57)
		>11000	22 (22)
		Mean	7512±2891.9
	Platelets (Lakh/μL)	<1.5	56 (56)
		1.5-4	41 (41)
		>4	3 (3)
		Mean	1.33±0.76
	MCV (fl)		88.6±11.8
	MCH (pg)		26.9±5
	MCHC (%)		29.8±3.5
	PCV (fl)		26.5±9.4
LFT	Bilirubin (mg/dl)		3.9±1.3
	SGOT (U/L)		97.44±60.31
	SGPT (U/L)		59.16±20.8
	Albumin (g/dL)		3.09±0.61
Coagulation	Prothrombin time (sec)		18.5±3.9
Peripheral smear	Normocytic Normochromic		59 (59)
	Microcytic Hypochromic		25 (25)
	Macrocytic		14 (14)
	Dimorphic		2 (2)
Iron studies	Serum iron (μg/dL)		96.4±16.3
	TIBC (mg/dL)		292.46±38.9

Table 3: Association of hematological abnormalities with type of CLD

Hematological abnormalities		Alcoholic liver Disease (n=46)	Non alcoholic liver disease (n=54)	P value
CBC	Hemoglobin (gm/dl)	7.7±2.1	8.09±2.9	0.35
	TLC (cells/mm^3)	7601.2±4017.3	7049.2±3912.5	0.85
	Platelets (Lakh/μL)	1.47±0.61	1.50±0.70	0.96
	MCV (fl)	93.1±16.3	80.1±10.2	**0.001**
	MCH (pg)	27.5±3.3	24.3±5.1	**0.03**
	MCHC (%)	30.2±3.1	29.01±4.6	0.08
	PCV (fl)	25.9±10.3	26.01±8.4	0.85
LFT	S.Bilirubin (mg/dl)	4.2±1.2	1.97±1.2	**0.001**
	SGOT (U/L)	100.4±49.2	86.2±40.6	0.20
	SGPT (U/L)	64.1±20.2	58.3±16.4	0.55
	Albumin (g/dL)	3.1±0.72	3.14±0.55	0.58
Coagulation	Prothrombin time (sec)	17.6±2.8	19.1±7.02	0.21
Peripheral smear	Normocytic Normochromic	25	34	0.89
	Microcytic Hypochromic	10	15	**0.001**
	Macrocytic	10	4	**0.001**
	Dimorphic	1	1	1.0
Iron studies	Serum iron (μg/dL)	145.5±50.7	74.6±46.2	**0.001**
	TIBC (mg/dL)	271.2±45.3	336.7±35.9	**0.001**

Table 4: Association ofhematological abnormalities with severity of CLD

Hematological abnormalities		Child Pugh Score A	B	C	P value
CBC	Hemoglobin (gm/dl)	9.3±3.9	8.5±3.1	7.6±2.01	**0.001**
	TLC (cells/mm^3)	8019.2±2789.2	7623.1±3319.4	7312.5±2674.3	0.292
	Platelets (Lakh/μL)	1.71±0.80	1.32±0.56	1.10±0.45	**0.03**
	MCV (fl)	91.5±11.7	88.3±10.3	83.1±10.01	**0.02**
	MCH (pg)	28.1±4.6	27.5±5.1	26.2±3.4	0.549
	MCHC (%)	31.4±6.6	28.4±6.1	27.1±6.02	0.374
	PCV (fl)	27.3±10.5	26.6±9.2	25.3±8.9	0.451
LFT	S.Bilirubin (mg/dl)	1.44±0.41	3.3±1.02	3.9±1.3	**0.001**
	SGOT (U/L)	87.14±59.12	92.3±60.4	99.21±61.1	0.39
	SGPT (U/L)	50.2±18.4	55.8±12.3	59.3±10.9	0.567
	Albumin (g/dL)	3.71±0.85	3.2±0.5	2.6±0.34	**0.03**
Coagulation	Prothrombin time (sec)	16.7±6.9	18.6±7.7	22.8±4.7	**0.03**
Peripheral smear	Normocytic Normochromic	14	29	16	0.28
	Microcytic Hypochromic	4	14	7	**0.04**
	Macrocytic	2	12	0	0.34
	Dimorphic	1	1	0	0.67
Iron studies	Serum iron (μg/dL)	340.2±40.5	309.5±45.3	273.7±35.4	**0.001**
	TIBC (mg/dL)	80.3±25.6	103.4±40.3	128.7±50.6	**0.001**

was higher in alcoholic liver diseases (p<0.05).Table 3

Mean hemoglobin, platelet levels, MCV, albumin and iron levels were significantly lower in cases with severe liver disease (Child Pugh Class C). However, serum bilirubin, prothrombin time and TIBC levels increased significantly with increase in severity of CLD (p<0.05).Table 4

4. Discussions

Hematological abnormalities are common in patients with chronic liver disease and various factors have been observed to be associated with hematological abnormalities in CLD patients.[6] Our study aimed to assess the hematological abnormalities in CLD patients and to observed their association with severity and types of liver diseases. A total of 100 cases with mean age of 48.8±16.9 years were enrolled. About three fourth of cases with CLD were males.

The mean age of patients with CLD in a study of Radicheva et al was 49.90±12.2 years and 104 out of 160 cases were males.[10] Kumar et al reported CLD in 70% males and 30% females in their study.[11] Mean age of patients was 52.08±13.11 years in a study of Pathak et al and majority of patients were males.[12]

All the cases with CLD in our study had anemia and majority of cases hemoglobin level below 8 gm/dL. Gonzalez-Casas et al reported almost all types of anemia in CLD patients and their underlying pathophysiological mechanism in cases with chronic liver disease, explaining the findings of our study.[13] Our study findings were also supported by findings of Sambyal et al in which thrombocytopenia was reported in 48.7% cases along with derangement of INR.[14] Jha et al observed anemia in 88% cases with CLD, of them, 24$ cases were severely anemic.[1] Anemia in CLD patients could be due to multiple factors such as heamodilution, decreased erythropoietin levels, upper or lower GI hemorrhage, micronutrient deficiency, anemia of chronic disease, splenic sequestration of RBC, aplastic anemia etc.[7] Peripheral smear revealed Normocytic Normochromic anaemia as predominant form of anemia followed by microcytic hypochromic. Similar findings were reported by Kumar et al, in which more than half of CLD patients had normocytic normochromic anemia followed by microcytic anemia.[11] Jha et al also documented normocytic normochromic anemia as the most common anemia in CLD cases[1]

In our study, more than half of the cases had thrombocytopenia and this could be associated with reduced levels of thrombopoetin in CLD, splenic sequestration, consumptive coagulopathy and bone marrow suppression.[8] Our study findings were concordant with the findings of Jha et al, in which thrombocytopenia was reported in 64% cases.[1] Similarly, Sambyal et al also reported thrombocytopenia in 48.7% cases.[14]

In our study, mean MCV and MCH were significantly higher in alcoholic CLD cases as compared to non alcoholic cases, which could be attributed to folic acid and other vitamin deficiency in alcoholic CLD, precursor cells has maturation defect leading to large immature and non functioning cell called megaloblast which accumulates in bone marrow and blood stream and also contributes to anaemia.[15] Das et al also observed findings concordant to our study, i.e. MCV was significantly higher I alcoholic CLD cases as compared to non Alcoholic CLD cases.[16] Tanriverdi et al in their study also observed highest MCV and MCH in alcoholics as compared to non-alcoholics.[17] We also observed that the incidence of normocytic normochromic anaemia was common in both group but in alcoholic CLD, Macrocytic anemia was higher than non alcoholic. Also, microcytosis and iron derangement was predominantly associated with non alcoholic liver disease. This could be due to folic acid and other vitamin deficiency in alcoholic CLD, precursor cells cannot divide properly and large immature and non functioning cell called megaloblast accumulate in bone marrow and blood stream and also contributing macrocytic anaemia in alcoholic CLD.[16] Our study findings were concordant with the findings of Erhabor et al in which alcoholic liver disease was significantly associated with macrocytic anemia.[18] Barik et al also reported macrocytosis to be associated with chronic alcoholism supporting our observation also.[19]

Bilirubin may be normal in compensated CLD. However, it rises as the disease progress and more in decompensate stage. Aminotransferase may increase with progress of disease but normal aminotransferese do not preclude diagnosis of chronic liver disease. SAP was usually elevated but <2-3 times of normal. Albumin level fall as synthetic function of liver declines with disease progress. In CLD because of decreased ability of synthesizing clotting factor, patients had Increase PT. We observed bilirubin to be significantly raised in alcoholic liver disease than non-alcoholic CLD which was comparable with previous study of Pathak et al.[12]

Increasing severity of liver disease further compromise the liver function reflecting hematological abnormalities to be proportional to severity of chronic liver disease. Iron might be important for progression of liver fibrosis in CLD. In present study, hemoglobin, platelet, MCV, albumin and iron levels significantly reduced whereas serum bilirubin, prothrombin time and TIBC levels increased significantly with increase in severity of CLD ($p<0.05$).

5. Conclusions

Hematological abnormalities particularly normocytic normochromic anemia and thrombocytopenia are common in cases with CLD, which might affect the prognosis of patients with CLD. Assessing the severity and type of anaemia is a useful tool for early initiation of the treatment in patients of CLD for reducing the morbidity and mortality. Early detection and treatment of haematological changes can prevent complications and reduce the mortality in CLD patients.

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None.

7. Conflict of Interest

None.

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