CLINICAL STUDY ON HAEMATOLOGICAL PROFILE ABNORMALITIES IN ALCOHOLIC LIVER DISEASE PATIENTS IN A TERTIARY TEACHING HOSPITAL IN NORTH EAST INDIA

Achintya Narayan Ray1, Dilip Chandra Barman2, Narayan Pandit3

1Associate Professor, Department of General Medicine, Cooch Behar Government Medical College, West Bengal.
2Assistant Professor, Department of Pathology, North Bengal Medical College and Hospital, West Bengal.
3Associate Professor, Department of Radio-diagnosis, North Bengal Medical College and Hospital, West Bengal.

ABSTRACT

BACKGROUND
Alcoholic Liver Disease (ALD) is the cause of about 14 million premature deaths per year worldwide.1 Alcohol induced liver injury is the most prevalent cause of liver disease and affects 10–20% of the populations worldwide.2 Chronic alcohol consumption gives rise to various health hazards including liver disease, pancreatitis, central nervous system disorders, peripheral neuropathies and certain forms of cancer. Various haematological and biochemical changes are also seen in a chronic alcoholic patients that further worsen the clinical condition of the patient. The objective of the present study to evaluate clinical and haematological changes that occur in alcoholic liver disease patients and early identification of abnormalities in haematological indices.

METHODS
This observational, non-interventional hospital-based study was done at North Bengal Medical College and Hospital in the department of General Medicine for a duration of one year from March 2018 to February 2019. Total 200 cases diagnosed alcoholic liver disease patients were included in the study. Clinical history, examination, biochemical and haematological parameters, and USG of abdomen were studied.

RESULTS
Patients’ age ranged from 30 to 60 years and male to female ratio was 2:1. Majority of the patients were in the age group of 41 to 50 years (42%). Anorexia, abdominal pain, jaundice, ascites and splenomegaly were predominant symptoms and signs. Common haematological abnormalities were anaemia, thrombocytopenia and raised PT. Common types of anaemia were normocytic normochromic (58%) and macrocytic (58%).

CONCLUSIONS
Long duration excessive alcohol ingestion not only leads to acute and chronic liver disorder but also affect haematological indices. Pancytopenia, megaloblastic anaemia, increased PT, INR are some characteristic haematological abnormality in ALD.

KEYWORDS
ALD (Alcoholic Liver Disease), Cirrhosis of Liver, Haematological Abnormalities, PT/INR

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BACKGROUND
Alcoholic liver disease patients suffer from three major hepatic lesions like alcoholic fatty liver, alcoholic hepatitis and cirrhosis of liver. Patients who are binge drinkers have >90% fatty liver. Larger the amount and longer duration of drinking, there is more probability of development of alcoholic liver disease. About half of the patients who are chronic alcoholics, develop cirrhosis of liver and its complications, can lead to carcinoma liver also. Alcohol causes liver injury directly by producing protein-aldehyde, reducing equivalents and due to oxidative stress.

Pathophysiology of haematological abnormality in ALD may be multifactorial. In patients of alcoholic liver disease, different effect of alcohol may contribute to anaemia such as malabsorption, malnutrition, vitamin B12 deficiency or direct toxic effect on bone marrow, alteration in bone marrow stimulating factors, bone marrow suppression, hypersplenism induced sequestration, consumption, anaemia due to chronic disease, autoimmune haemolytic anaemia, iron and folic acid deficiency, aplastic anaemia, GI bleed etc. Liver is a site for extramedullary haemopoiesis and synthesis of coagulation proteins and the major storage site of iron, vitamin B12 and folic acid. Hence chronic liver disease frequently associated with a wide range of haematological abnormalities.

Abnormalities in haematological indices are associated with increased risk of complications including bleeding and infection. Anaemia, leucopenia, thrombocytopenia and thrombocytopathy are common abnormalities responsible
for it. Causes of pancytopenia are hypersplenism, bone marrow suppression, consumptive coagulopathy, bleeding effect on granulocyte-macrophage colony stimulating factor, vitamin B12 deficiency etc. Megaloblasts are frequent finding in bone marrow. Reduced blood folate level is also seen in alcoholic. Our study was aimed to assess the haematological abnormalities.

More than 80% of patients with alcoholic liver disease have De Ritis Ratio (AST: ALT ratio) of 2 or more. This ratio is a valuable diagnostic marker of ALD. Hyperbilirubinemia is frequent in alcoholic liver disease. Tests for alkaline phosphatase, γ-glutamyl transpeptidase (GGT), serum albumin, and prothrombin time are also indicator tests of altered hepatic activity.

Aims and Objectives
1. To evaluate clinical and haematological profile in alcoholic liver disease patients.
2. To understand the pattern of haematological indices changes in ALD patients which may be associated with increasing morbidity and mortality in these patients.

METHODS

Study Design
Ethical committee approval taken from North Bengal Medical College Ethical Committee.

Study Type
Observational, non-interventional.

Source of Data
Department of Medicine, North Bengal Medical College & Hospital from February 2018 to January 2019.

Statistical Analysis
Done with SPSS Version 15.

Inclusion Criteria
All diagnosed cases of Alcoholic Liver Disease patients attended at medicine OPD and admitted in the indoor wards of department of Medicine.

Exclusion Criteria
1. Alcoholic Liver disease with other co-morbidities such as Diabetes mellitus and hypertension, thyroid disorders, hyperlipidaemias, vasculitis, malignancy or known primary hepatocellular carcinoma, COPD, heart failure, CKD were excluded.
2. Liver diseases due to Viral hepatitis, Drug induced hepatitis, NASH, Hemochromatosis.
3. Patients having history of hepatotoxic drug intake, acute hepatic failure was excluded.
4. Patients with primary coagulation disorder or primary abnormalities of haemostatic function were excluded.
5. Patients with pre-existing anaemia due to other causes were excluded.

Informed Consent
Informed written consent was taken from the patients or their attendants.

After fulfilling inclusion and exclusion criteria, a total of 200 cases with ALD who were attended at OPD and also admitted to medical wards were selected in this cross-sectional study. Majority of patients consuming >60 gm/24 hr of alcohol. History was obtained and clinical examination was done in all subjects. Detailed history of alcohol intake in amount and duration, diet, smoking, any previous or concomitant illness, past history of liver disease, socioeconomic status, drugs intake (from treatment record) were recorded if relevant.

We have divided our study population into ALD without cirrhosis and ALD with cirrhosis group for better evaluation. They underwent routine laboratory investigations including baseline radiographic and haematological, biochemical evaluation. Laboratory investigations included complete haemogram, biochemical parameters like liver function test, prothrombin time, INR. Folic acid and vitamin B12 level where indicated. Routine abdominal ultrasonography was also done. Alcoholic Liver Disease (ALD) was diagnosed with the help of clinical and biochemical and radiological findings.

Statistical Analysis
Data were analysed using the Statistical software SPSS version 15 (statistical packages for the social science, Chicago, IL). Microsoft word 2007 was used to generate tables. The continuous variables were expressed as mean and ± standard deviation, while categorical variables were expressed as percentages. A P-value <0.05 was considered as statistically significant. Descriptive statistics were used to interpret results.

RESULTS
A descriptive study to assess the haematological abnormalities in chronic liver disease was conducted. In the present study, 152 male and 48 female were included, majority of the patients were in the age group of 30-40 years (39%) and 41 to 50 years accounting for 42% cases. The 51 to 60 years age group contributed 19% cases. (Table 1).

According to duration of alcohol intake frequency and percentage of patient are shown in table-2. Majority of the patients (56.6%) patients had history of consuming >60 gm/24 hr of alcohol. 24.4% patients had history of consuming between 50-60 gm/24 hours of alcohol and only 19% consumed <50 gm alcohol in 24 hours. Urban and rural distribution of study population are shown in table 3. When we studied various clinical features anorexia, abdominal pain, fever, upper gastrointestinal haemorrhage, pedal oedema, Jaundice, hepatomegaly, splenomegaly, signs of liver failure were the predominant features in both ALD without cirrhosis and ALD with cirrhosis group of patients, shown in table- 4. In the present study (Table-5), when we noted that percentage of haemoglobin, total number of RBC and WBC were found to be significantly decreased (p<0.05) in both group but it is more predominant in cirrhosis group. Among the study subjects mean haemoglobin in noncirrhotic...
ALD patients groups was 10.43 ± 1.8 g/dl and in alcoholic cirrhosis study population was 7.8 ± 2.6 g/dl. WBC count were found to be significantly decreased, but mean corpuscular volume (MCV, p<0.05) significantly increased in both group but it is more predominant in cirrhotic group. Mean leucocyte count of the population was 4600 ± 540 cells per mm³ in non-cirrhotic patients’ groups and 3500±640 cells/mm³ in cirrhotic patient group. Average mean corpuscular volume (fl/l) was 101.6 ± 5.5 & 110 ± 8.4 in non-cirrhotic and cirrhotic patient groups respectively. Packed cell volume (PCV) was found marginally decreased in n mean corpuscular volume (mcv) in both group of patients. Mean platelet count in both group of patients. Mean platelet count among the study subjects were 130.0 ± 15 ×10³/mm³ in our study was reduced but mean corpuscular volume (MCV, p<0.05)) significantly in both groups but more in cirrhotic group. Pattern of changes are narrated in table 5.

**Table 5. Haematological Parameters among ALD Patients with Cirrhosis and without Cirrhosis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total</th>
<th>ALD without Cirrhosis (n=110)</th>
<th>ALD with Cirrhosis (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (%)</td>
<td>4,59±0.28</td>
<td>3,3±0.24</td>
<td>2,7±0.1.8</td>
</tr>
<tr>
<td>Eosinophil (%)</td>
<td>47±13±0.16</td>
<td>49±0.6</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>14/75±0.10</td>
<td>12/32±30</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6. Types of Anaemia among Alcohol Liver Disease Patients with Cirrhosis and without Cirrhosis**

**Table 7 & Table 8 respectively.**

**Table 8. INR Value in Study Population (n=200)**

In our study normocytic normochromic anaemia (58%) and macrocytic anaemia (25.5%) was predominant in both groups. Microcytic-hypochromic anaemia and dimorphic anaemia were seen in 12% and 4.5% cases respectively. (Table 6). Prothrombin time and INR are increased in both groups but more in cirrhotic group. Pattern of changes are narrated in table 7 & table 8 respectively.

### DISCUSSION

Alcoholic liver disease (ALD) is one of the leading causes of morbidity and mortality associated with alcohol ingestion in developed as well as developing countries. Changes in haematological indices are common in patients with alcoholic liver disease. Excess alcohol intake itself causes both direct and indirect effects on the bone marrow. Direct effects of alcohol on bone marrow suppression leading to toxic effects on the blood cell lines. Indirectly, it affects the nutritional biology of the patient resulting in production of functionally immature cells. Alcohol related abnormalities in

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haematological indices increases the risk of bleeding and infection, further augmenting the rate of morbidity and mortality in alcoholic patients.

In the present study 152 patient (76%) were male and 48(24%) were female. Similar study on drinking patterns among men and women conducted by Assanangkornchai, S. et al27 across the developing country, was similar to our study. In a study done in Nepal by Om K Pathak et al (2009)18 181 patients of ALD was analysed out of which 146 males (80.66%) and 35(19.33%) are female. Our study is also close to same geographical area had almost similar results. Majority of the patients with ALD were in the age group of 40-49 years of age(42%) with mean age 43.45 ± 8.65 which corroborates with the study done by Ardhendu Kumar Sen et al. 2017,9 where the mean age 45.91±10.34 and Swati Hegda et al. 201510 where the mean age at presentation was 45.18 years. In the present study anorexia noted in 60% and 86.66%, pain abdomen in 52.72% and 73.33% in non-cirrhotic and cirrhotic group of patients respectively. Pedal oedema 65.55% and ascites 91.11% noted in cirrhotic group of patients respectively but none of non-cirrhotic group.

Chavan et al11 reported nausea and vomiting as an important symptom in 89% of the alcoholics, pain in abdomen (68%) and fluid retention in (66%). In Leiber’s study12 ascites was present in 87% patients with cirrhosis but none of the patients with fatty liver and hepatitis. Their reports are similar with our study.

In the present study jaundice and hepato-splenomegaly were found to be the most commonly observed clinical findings. On ultrasound, hepatomegaly was seen in 96.36% and 10% cases of non-cirrhotic and cirrhotic group, splenomegaly in 14.54% and 88.88% cases of non-cirrhotic and cirrhotic group respectively. Jaundice in 50.9% and 85.55% cases of non-cirrhotic and cirrhotic group respectively. Upper GI bleeding, hepatic failure and fever were other common clinical findings. In the study of Leiber et al.12 jaundice was seen in 35% of patients with fatty liver, 60% patients with alcoholic hepatitis and 81% with cirrhosis, hepatomegaly was present in 75%, 95% and 67% in fatty liver, hepatitis and cirrhosis respectively which is similar to the finding of our study except hepatomegaly in cirrhosis which is lower in our study. Ray et al.13 in their study showed splenomegaly was present in 8% patients of alcoholic hepatitis and 92% patients of cirrhosis which also close to our results. In our study, we observed a progressive fall in haemoglobin levels with the increase in the chronicity of the disease, where we found mean Hb (gm/dl) were 10.43±1.8 and 7.84±2.6 in non-cirrhotic and cirrhotic group of patients respectively.

While in study by Halleys Kumar and Colleagues (2014).14 58% of cases were having Hb<9.0 gm/dl. Because of defect in iron utilization of haemoglobin molecule may cause functional immaturity of RBCs in ALD patient. MCV was noted higher in our study. Mean MCV 101±5.5 and 110±8.4 in non-cirrhotic and cirrhotic group of patients respectively. One study by Ozgur Tanriverdda et al (2008),15 MCV in alcoholic was 94.6 ± 11.9 and in non-alcoholic was 89.2 ± 2.72. In our study we found different pattern of anaemia like normocytic normochromic (58%), macrocytic (25.5%), microcytic hypochromic (12%) and dimorphic (9%) in ALD patient. According to Shellsherslock.16 and Oxford textbook of hepatology,17 most common anaemia in seen in cirrhotic patients was normocytic and normochromic anaemia. In study done by Bhatia and Mishra et al (1982) incidence was 59%. Their findings were almost similar with our results. Cause of normocytic normochromic and microcytic hypochromic anaemia may be related to nutritional deficiency and chronic GI blood Loss respectively in alcoholic patients. One striking finding in our study was macrocytic anaemia (25.5%). The study done by Shigeo Maruyama in Japan (2001)18 showed that macrocytosis was a major finding in alcoholic liver disease patients. Another studies done by Shivam Khare et al.19 and Erhabor Osaro et al,20 showed macrocytosis was 28.88% and 20.0% respectively in alcoholic patients, supporting our observation also. Macrocytosis in alcoholic cirrhosis is mostly due to the toxicity of alcohol on RBC production in the bone marrow and deficiency of B12 and folic acid.14 It can affect up to one-third of these patients.

In our study mean Leukocyte was 4600 ± 540 and 3500 ± 640 in non-cirrhotic and cirrhotic group of patients respectively. Study done by Jain D et al.21 also showed decreased WBC count with increasing MELD score. The observed neutropenia may be related to impaired neutrophil development in the bone marrow due to toxic effect of alcohol which are more prominent in advanced ALD. Neutrophenia can be again due to hypersplenism causing decreased cell count.

Our study also showed platelet abnormality where mean platelet count was 130±15(x 109/mm3) and 95±12 (x 109/mm3) in non-cirrhotic and cirrhotic group of patients respectively. In study by Shivam Khare et al.,19 showed mean platelet 1,46,000±62000, this results also close to our study. Low platelet counts can be the result of decreased platelet production, enhanced splenic sequestration or platelet consumption. Most authors agree on a decrease in platelet count in relation to the severity of cirrhosis.22 According to an interesting article by Jody L Kujovich MD - "Haemostatic defects in end stage liver disease"; Critical care clinics 21(2005) - mild to moderate thrombocytopenia occurs in 49 to 64% of patients with DCLD.

In our study, we observed that 52.72% and 35.55% patients had PT level between 10- 20 followed by 31.81% and 62.22% PT level between 21 to 30 seconds in non-cirrhotic and cirrhotic group of patients respectively. PT levels >30 seconds in 32.22% of patients of cirrhotic groups noted. INR value is also deranged, it is between 1.6 to 2.0 respectively in non-cirrhotic and cirrhotic groups. In study by Ardhendu Kumar Sen et al 2015,9 found mean PT was 17.30±4.65 s, and study done by Naveen et al.(2017),23 found that mean PT was 19.25±5.25 s. Liver is site for synthesis of blood clotting factors except factor VII. Bleeding tendency in ALD is also related to it. Serum PT which collectively measures factor II, V, VII and X is an useful marker for both diagnosis
and assessing the prognosis of acute and chronic parenchymal liver disease.

CONCLUSIONS
Long-term alcohol consumption leads to alcoholic fatty liver disease, alcoholic hepatitis and liver cirrhosis. Alcohol has direct toxic effect on bone marrow which interferes with various physiological, biochemical and metabolic processes involving the blood cell production and maturation affecting the production and functioning of virtually all types of blood cells. The medical consequences of these adverse effects can be severe which include anaemia, increased risk of serious bacterial infections and impaired blood clotting and fibrinolysis which increase with the severity of the disease. Types of anaemia can sometimes be an indicator of alcoholic liver disease. Assessing the severity and type of anaemia is a useful tool for early initiation of the treatment in patients of CLD for reducing the mortality and morbidity. From our clinical experiences we have to come in contact with the miserable life of these patients particularly when they develop cirrhosis and turn into decompensated states and its complications. Associated haematological alterations that are frequent in ALD again threaten the life of these patients. They should be identified and corrected early to reduce morbidity and mortality.

Limitations
Number of patients and duration of study is less. This zone has residents of different religious people like Hinduism, Muslim, Buddhism, Christian and people from others states and countries like Nepal, Bhutan and, Bangladesh. So, little variations in results from other studies may be related to this. Only patients with alcoholic liver disease have been considered in the present study. Studies are needed to compare results in patients having end stage liver disease due to other causes with larger population.

Abbreviations
- ALD- Alcoholic Liver Disease.
- USG- Ultrasonography.
- HB- Haemoglobin.
- PT- Prothrombin Time.
- INR- International Standardization Rate.
- GI- Gastrointestinal.
- UGI- Upper Gastro-Intestinal.
- RBC- Red Blood Cell.
- WBC- White Blood Cell.
- CLD- Chronic Liver Disease.
- PHTN- Portal Hypertension.
- OPD- Out Patient Department.
- COPD- Chronic Obstructive Pulmonary Disease.
- CKD- chronic kidney disease.
- NASH- Non-Alcoholic Steatohepatitis.
- MCV- Mean Corpuscular Volume.
- PCV- Packed Cell Volume.
- ESR- Erythrocyte Sedimentation Rate.
- DCLD- Decompensated Chronic Liver Disease.

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REFERENCES