Hematological Parameters and Coagulation Profile in Patients with Chronic Liver Disease and its Correlation with Disease Severity

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ABSTRACT

Objective: To determine the haematological parameters and coagulation profile in patients with Chronic Liver Disease and to study their correlation with disease severity.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi Pakistan and Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Sep 2017 to Aug 2018.

Methodology: Hundred and eighty patients diagnosed with chronic liver disease were included in the study and compared with 60 normal healthy age and sex matched individuals. Haematologic parameters were assessed by automated haematology analyzer, peripheral blood films examined and coagulation studies were performed. These parameters were studied in association with disease severity.

Results: A total of 180 cases of Chronic Liver Disease were analyzed. Median age of patients was 42 years with a male to female ratio of 2.2:1. Anaemia and thrombocytopenia were prominently seen in chronic liver disease. The haemoglobin level and platelet count significantly decreased with increasing severity of disease. Prothrombin time and activated partial thromboplastin time were prolonged in majority of patients.

Conclusion: Haematologic parameters and coagulation profile are cost effective methods for assessing severity of chronic liver disease and monitoring for complications and prognosis.

Keywords: Anaemia, Chronic liver disease, Thrombocytopenia.

INTRODUCTION

Chronic liver disease (CLD) today is a commonly encountered cause of increasing morbidity and mortality worldwide.[1] CLD may be caused by a wide variety of etiological factors, all ultimately leading to a similar clinical presentation.[2] However, these patients have a varying disease course.[3] In developing countries like Pakistan, prevalence of chronic liver disease is on the rise. This is partly attributable to the increase frequency of hepatitis B and C infection in our population.[4] This in turn is due to lack of education and awareness, scarcity of resources, ineffective health policies and blood screening programs.[5]

A wide range of haematological abnormalities are seen in patients with chronic liver disease.[6] The reasons include hypersplenism, blood loss, bone marrow suppression and alteration in growth factors.[7] The liver has a significant role to play in the coagulation cascade and fibrinolytic system.[8] Haemostatic disorders are commonly encountered in patients of chronic liver disease and these have an important role in the assessment of severity of disease.[9] Assessment of these parameters can help in risk stratification and are also an integral part of predictive models.[10]

at every level is need of the hour. However, early diagnosis and risk stratification can help guide clinicians regarding prognosis and in tailoring treatment accordingly. Most of the data available is from Western studies. The present study was designed with an aim to evaluate the haematologic parameters and coagulation profile in chronic liver disease patients in our part of the country as so far there is lack of data on the haematologicaland coagulation parameters of CLD in our region. This will help to determine treatment protocols and prognosis.

METHODOLOGY

The cross sectional study was conducted at the Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi and Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from September 2017 to August 2018. Sample size was calculated by using WHO sample size calculator by keeping 95% confidence

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level, 5% error 13.5% prevalence of chronic liver disease. A total of one hundred and eighty patients were included by using non probability consecutive Sampling technique. These were patients presented to Gastroenterology Department, Military Hospital, Rawalpindi. The study included patients referred from different areas of Pakistan to Military Hospital, Rawalpindi and belonged to different ethnic groups. The sample was compared with 60 age and sex matched healthy controls.

Inclusion Criteria: Patients with confirmed diagnosis of Chronic Liver Diseasebased on clinical history and examination, biochemical testing andultrasonographic imaging were included in the study.

Exclusion Criteria: Patients taking any medication that may directly or indirectly affect the haematological parameters or the coagulation profile were excluded.

All subjects were elaborately apprised about the study and written informed consent was obtained. Specific etiology of chronic liver disease was determined and the patients were categorized according to Child Pugh Classification based on the presence or absence and severity of ascites and hepatic encephalopathy and laboratory values of bilirubin, albumin and prothrombin time. For assessment of haematologic parameters, 2.5ml peripheral blood was taken in EDTA. The CBC of each patient was done on 5-part SysmexXE-5000 automated haematology analyzer. Peripheral blood films were prepared and stained with Leishman's stain (Sigma-USA) to examine the RBC, WBC and platelet morphology.

Bleeding time was performed by Ivy's method. The bleeding time of each patient was recorded by giving two 1mm deep punctures 1-2 cm apart on the volar surface of the forearm followed by blotting on a filter paper at 30 second intervals. The time taken for bleeding to stop was noted. About 2ml peripheral blood was taken in sodium citrate for coagulation studies. The blood samples were centrifuged at 3000 rpm for 10min within 1 hour of collection to obtain platelet-poor plasma. Clotting based assays were performed on Sysmex CA-1500 automated coagulation analyzer for prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen levels. All abnormal samples were re-checked by manual conventional methods for PT and aPTT using PT and aPTT reagents (Helena Biosciences-Europe). Thrombin time was performed manually by conventional methods using thrombin reagent (Helena Biosciences-Europe).

Semi-quantitative determination of D-dimers was done by using Atlas D-Dimer latex test (Atlas Medical-UK).

Collected data was entered and analyzed using IBM SPSS software (Statistical Package for Social Sciences, version 20, IBM, Armonk, NY, USA). Quantitative variables i.e. age, haemoglobin and platelet count have been presented by mean and SD). Qualitative variables like gender and etiologies have been presented by frequency and percentage. For comparison chi square and t test was used. A *p*-value ≤0.05 considered significant

RESULTS

A total of 180 patients diagnosed with chronic liver disease were included in the study. Mean age of the patients was 42±2.6 years (range 28-72 years). Hundred and twenty-four (68.9%) patients were males while 56(31.1%) were females. The etiology specific distribution of our patients is summarized in figure-1.The patients were classified into three groups according to Child Pugh Scoring system in order to determine the severity of disease of our patients. Twenty-nine (16.1%) patients were in Child Pugh class A while majority of the patients 95(52.7%) of our study group were in Child Class Pugh 56(31.1%) patients were in Child Pugh Class C.
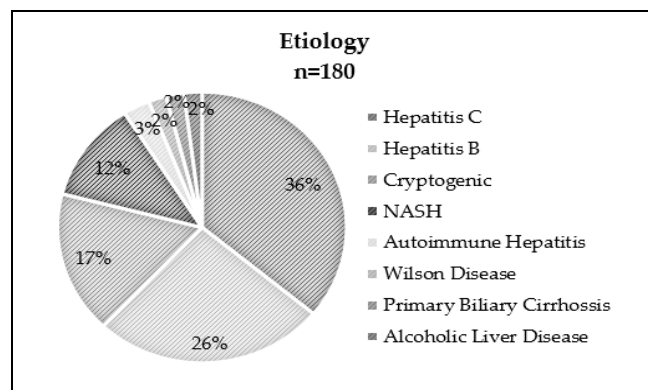
NASH (Non-alcoholic staeatotic hepatitis)
Figure: Etiology specific profile of Chronic Liver Disease Patients (n=180)

The haematological parameters including WBC count, haemoglobin levels, platelet count as well as the RBC indices were noted and compared with normal control group as shown in Table-I. Thrombocytopenia and anaemia were prominent in patients with chronic liver disease. The median WBC count, haemoglobin level and platelet counts of patients in each Child Pugh Class is shown in figure-2. Distribution of the study group based on mean corpuscular volume is shown in Table-II.

Table-I: Comparison of Hematological Parameters and Coagulation Profile in Chronic Liver Disease Patients with the Control Group (n=180)

|	Chronic Liver Disease	Control Group	p-value
WBC (x10⁹/l)	4.1±0.3	6.8±1.3	<0.001
Hb (g/dl)	9.1±2.4	12.4±3.9	<0.001
Platelet (x 10⁹/l)	124±5.2	248±6.7	<0.001
MCV (fl)	85.3±10.1	86.2±12.7	0.57
MCH (pg)	28.7±4.5	29.8±6.8	0.15
MCHC (g/dl)	32.1±6.2	32.9±8.69	0.43
Coagulation Profile			
Bleeding Time	4 min 2 sec	2 min 0 sce	<0.001
PT (Sec)	13.24±2.53	14.32±0.89	<0.001
APTT (Sec)	37.64±1.92	32.31±2.01	<0.001
TT (Sec)	19±1.29	18±1.5\	<0.001
Fibrinogen (mg/dl)	189±7.86	265±30.41	<0.001
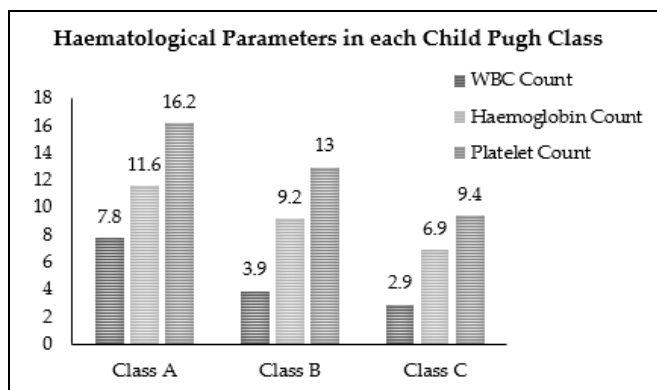
Figure-2: WBC count (x10⁹/l), hemoglobin level (g/dl) and platelet counts (x10¹⁰/l) of patients in each Child Pugh class (n=180)

Table-II: Distribution of the Study Group based on Mean Corpuscular Volume (n=180)

MCV (fl)	Male	Female
<80	31(17.2%)	13(7.2%)
80–100	63(35%)	38(21.1%)
>100	30(16.7%)	20(2.8%)

Peripheral film examination was done and revealed normocytic normochromic anaemia in majority of the patients. Comparison of patterns of peripheral blood film findings based on RBC morphology in both the study population as well as the control group shown in Table-III.

Table-III: Comparison of patterns of Peripheral Blood Film findings based on RBC Morphology in both the study population and the control group (n=180)

Peripheral Blood Film	Chronic Liver Disease n(%)	Control Group n(%)	p-value
Normocytic normochromic	101(56.1)	42(70)	0.207
Microcytic hypochromic	44(24.4)	14(23.3)	
Macrocytic	29(16.1)	4(6.7)	
Dimorphic	6 (3.4)	-	

DISCUSSION

Patients with Chronic Liver Disease have a highly variable clinical course ranging from a chronic, symptomatic disease to a rapidly progressive one with high mortality.[11] The Child-Pugh score relies on two clinical and three laboratory parameters to assess the prognosis of these patients and predict their survival.[12] Another predictive tool is the Model for End Stage Liver Disease. It is based on etiology of disease and laboratory values for serum bilirubin, serum creatinine and international normalized ratio (INR). Itpredicts the severity of disease, predicts prognosis and helps in prioritizing patients fortreatment decisions like liver transplant.[13]

Management of these patients focuses on symptomatic management, correction of laboratory abnormalities as well as efforts to slow or reverse the progression of disease and prevent complications.[14] Definitive treatment, however, is liver transplant but liver transplant facilities are offered only in few centers in Pakistan. Also, liver transplant has its own risks and affordability is also an important issue in a country like Pakistan.[15]

Chronic liver disease is increasing in our country.[16] Prevention. Chronic liver disease, a chronic debilitating disease, is a significant cause of morbidity and mortality in many countries of the world. Early diagnosis can help prevent complications and improve the quality of life. In developing and resource-constraint countrieslike Pakistan with poor socioeconomic status of patients, basic laboratory investigations like haematologic parameters and coagulation profile can serve as a guide to assess the severity of disease and are cost effective methods for monitoring for risk of complicationsand disease progression.

Alterations in haematological parameters are seen in patients of chronic liver disease. Leukopenia, anaemia and thrombocytopenia are the prominent features.[7] The clinical relevance of these indices is of paramount importance in determining the risk of several complications like infections and bleeding which may in turn lead to increased morbidity and mortality. Anaemia in chronic liver disease is multifactorial. Anaemia of chronic disease is seen in many patients. In others, blood loss may lead to iron deficiency anaemia presenting with a microcytic hypochromic blood picture. Bone marrow suppression as well as alterations in growth factors may lead to aplastic anaemia. Hypersplenism and haemolysis coupled with vitamin B12 and folate deficiency can

lead to megaloblasticanaemia. Macrocytosis is also seen in patients with alcoholic liver disease.[6]

Basic laboratory tests of coagulation can help in risk stratification of patients with chronic liver disease. These tests are readily available and can help assess the severity of liver disease as most coagulation factors are synthesized by the liver.[9] The clinical significance of these parameters is of paramount prognostic importance and are known to predict the bleeding risk, particularly in the gastrointestinal tract.[10] The coagulation profile can also serve to guide the requirement of transfusion support in these patients. In patients of chronic liver disease there is an increased risk of bleeding due to several factors including thrombocytopenia and decrease in coagulation factors. However, at the same time these patients are at risk of thrombosis and this risk increases with the severity of disease.[8]

In our study, the median age of the patients was 42 years with a range of 28-72 years. A study on the burden of chronic liver disease patients conducted by Khan *et al*.[5] has reported a median age of 49 years. Our study population had a male to female ratio of 2.2:1 while Varnika *et al*.[17] has reported a much higher male to female ratio of 3.6:1 in his study.

Reduced haemoglobin and platelet levels were observed in patients presenting with more severe disease in our study. Median haemoglobin of 11.6g/dl and platelet count of 162x10^9/l in Child Pugh Class-A patients versus haemoglobin 6.9g/dl and platelet count 94x10^9/l in Child Pugh Class-C.These findings are in concordance with studies done by Chauhan *et al*.[18] and Shivam *et al*.[19] which have confirmed increasing anaemia and thrombocytopenia with advanced disease. Findings of prolonged PT and aPTT in patients of chronic liver disease are in conformity to findings of Rai *et al*.[17] In our study population, fibrinogen levels were normal or near-normal. Low fibrinogen levels were seen in only 19.4% of our patients. Al-Ghumlas *et al*.[20] in his study has confirmed fibrinogen levels to be normal or increased in CLD patients owing to the fact that fibrinogen is an acute phase reactant.

CONCLUSION

Chronic liver disease is an increasing cause of morbidity and mortality today. Haematologic parameters and the coagulation profile are significantly affected in chronic liver disease. While alterations in haematologic indices and prolongation of conventional coagulation screening tests can help in assessing the severity of disease, at the same time regular monitoring of these parameters may help to see for disease progression and any complications.

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