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"Clinical Correlates and Severity of Thrombocytopenia in Patients with Chronic Liver Disease Due to Hepatitis B and C"

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Abstract **Original Research Article**

Introduction: Chronic liver disease due to hepatitis B and C is common in our country, affecting over 10 million people. Globally, one in 12 people has hepatitis B or C. Thrombocytopenia, a frequent extrahepatic manifestation of CLD, can limit antiviral therapy by increasing bleeding risk. ***Aim of the study:*** The aim of this study was to assess the severity and clinical correlates of thrombocytopenia in chronic liver disease due to Hepatitis B and C. ***Methods:*** This cross-sectional observational study was conducted at Dhaka Medical College Hospital and Anwar Khan Modern Medical College from June to November 2011. In total 100 patients (79 patients of CHB and 21 patients of CHC) were enrolled on simple random sampling method from June 1 to 30 November 2011. All had full blood count with PBF, HBsAg /Anti-HCV by ELISA, abdominal ultrasound, upper GIT endoscopy and were assessed by Child-Pugh class. Thrombocytopenia was defined as platelet count below 150×10^9/L. ***Result:*** The thrombocytopenia was 35.44% in CHB and 42.86% in CHC. In CHB, males were more affected, while in CHC both sexes were equally affected. Thrombocytopenia was more common in patients >40 years and occurred early in CHC but usually in late-stage CHB. ***Conclusion:*** Thrombocytopenia is a common and important findings in CLD due to HBV and HCV.

Keywords: CLD, Thrombocytopenia, HBV, HCV.

INTRODUCTION

Chronic liver disease is the tenth leading cause of death in adults [1] with hepatitis B (HBV) and hepatitis C (HCV) virus infection being the most important underlying causes. [2] Approximately 350 million people worldwide have chronic HBV infection [3,4] and most of them live in the South-East Asia and Sub-Saharan Africa [5]. Hepatitis C Virus, first cloned in 1989, had been found to the major cause of chronic liver disease with around 130 million infected worldwide [6]. In Bangladesh, the most common cause of CLD is hepatitis B virus [7,8]. Extrahepatic manifestations are commonly observed in patients with chronic hepatitis C and also with advanced chronic hepatitis B. One of these manifestations is thrombocytopenia (TCP).

Haemostosis and hepatology are closely related. It is well known that patients with CLD show a marked decrease in liver synthesis of coagulation factors, which leads to a prolongation of the prothrombin time [9]. Less well studied, but equally important in the physiological process of clot formation, are the defects in primary haemostais in patients with liver disease. Blood platelets initiate the haemostatic process by interacting with the damaged vessel wall.[10] Platelets are the smallest cellular components of human blood, ranging in size from 2-4 microns.

Thrombocytopenia is a common clinical problem that is discovered in daily laboratory testing and often leads to further investigations. Thrombocytopenia is defined as the platelet count <150×10^9/L. [11] The most well-known causes of TCP are infectious diseases such as HIV infection and HCV, Cancer, toxic chemicals, drugs, pregnancy and autoimmune diseases.

Thrombocytopenia is considered as an indicator of advanced liver diseases [12,13]. HCV is strongly associated with thrombocytopenia which is correlated with hepatocellular damage and hepatic fibrosis. The prevalence of thrombocytopenia among anti-HCV positive subjects increases as the severity of liver disease increased and in HBsAg positive subjects, thrombocytopenia presents in those with advanced liver disease. Thrombocytopenia is highly associated in CLD patients, with older age, elevated serum ALT levels and abnormal sonography showing the severity of liver disease [14].

The pathophysiology of thrombocytopenia in patients with CLD due to chronic viral infection (HBV and HCV) is multifactorial [15]. These includes, sequestration of platelets in the enlarged spleen secondary to portal hypertension (Hypersplenism) [16,17], reduced hepatic production of thrombopoietin (TPO), which is mainly produced by liver [18,19] virus induced bone marrow suppression (HCV) [20-22], and increased platelet destruction mediated by immune mechanisms involving anti-platelet auto antibodies and platelet associated immune complexes [23-25]. TPO, the growth factor that primarily regulates megakaryocyte maturation and platelet formation, is produced by hepatocyte and is normally released at a constant rate into the circulation. However, in patients with cirrhosis production of TPO is reduced from hepatocyte.

The occurrence of thrombocytopenia in patients with chronic liver disease may have significant clinical implications. It may be a limiting factor when considering invasive procedures such as liver biopsy (<80×10^9/L), paracentesis, dental, endoscopic or surgical procedures [26]. Thrombocytopenia determines a reduction in antiviral drug dosage of pegylated interferon (PEG-IFN) and this may eventually be associated with lower sustained virological response. [27,28] During treatment with interferon, platelet count should monitor to avoid any serious complications of thrombocytopenia. The study aims to assess the severity, and clinical correlates of thrombocytopenia in patients with chronic liver disease due to HBV and HCV infection.

OBJECTIVES

The main objective was to assess the severity and clinical correlates of thrombocytopenia in chronic liver disease due to Hepatitis B and C.

METHODOLOGY & MATERIALS

This cross-sectional observational study was conducted in the Department of Medicine, Dhaka Medical College Hospital and Anwar Khan Modern Medical College, Dhaka, Bangladesh, from June 2011 to November 2011.

A total of 100 consecutive patients with chronic liver disease due to Hepatitis B or Hepatitis C infection of more than six months' duration were included, based on predefined selection criteria. All diagnosed cases of chronic liver disease with serological evidence of HBsAg or Anti-HCV positivity, and patients or legally accepted guardians who provided informed consent were included in the study. Patients with chronic liver disease due to other causes (e.g., alcohol, drugs), evidence of acute viral infection or febrile illness (e.g., dengue), hematological disorders (e.g., ITP, leukemia, aplastic anemia), history of cytotoxic/myelotoxic drug intake, or unwillingness to participate were excluded. The main outcome measures included platelet count, age, sex, and Child-Pugh classification. Data collection involved detailed history-taking and clinical examination, with emphasis on hepatobiliary system findings and features of thrombocytopenia, followed by laboratory investigations (complete blood count with peripheral smear, viral serology, liver function tests, serum albumin, prothrombin time), ultrasonography of the whole abdomen, and upper gastrointestinal endoscopy. Patients were subsequently classified by Child-Pugh score, and stratified into Group A (<40 years) and Group B (>40 years). Written informed consent was obtained after full explanation of the study, and ethical approval was secured from the Ethical Review Committee of Dhaka Medical College. Confidentiality and voluntary participation were ensured throughout the study.

Statistical Analysis:

All data were recorded systematically in a preformed data collection form. Quantitative data were expressed as mean ± standard deviation, and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences) Version 16. A p-value <0.05 was considered statistically significant. Confidentiality was strictly maintained.

RESULT

Table 1: Baseline Characteristics of Study Population (N=100)

Variable		Frequency	Percentage
Age	<40	64	64%
	≥40	36	36%
Mean Age (years)		42.35 ± 11.40	
Sex	Male	72	72%
	Female	28	28%
Compensation status	Compensated CLD	24	24%
	Decompensated CLD	76	76%
Etiology	HBV	79	79%
	HCV	21	21%
Mean Platelet count (41-409´10^9/L)		184.89 ± 82.29	
Mean S. ALT (28-150 U/L)		51.33 ± 21.29	

Table 1 shows that the baseline characteristics of the respondents. The study showed that 64% of patients were younger than 40 years, while 36% were aged 40 years or older. The mean age of the study population was 42.35 ± 11.40 years. In terms of sex distribution, the majority were male (72%), and 28% were female. Regarding disease compensation status, only 24% had compensated CLD, whereas the majority, 76%, had decompensated CLD at presentation. Considering etiology, HBV was the predominant cause (79%) of CLD in this cohort, while HCV accounted for 21%.

Laboratory parameters indicated a mean platelet count of 184.89 ± 82.29 × 10^9/L, which falls within the reference range (41–409 × 10^9/L). The mean serum ALT level was 51.33 ± 21.29 U/L, also within the normal laboratory range (28–150 U/L).

Table 2: Distribution of thrombocytopenia according to etiology of CLD across Child-Pugh classes

Child-Pugh Class	All CLD (n=100)	HBV (n=79) – with TCP n (%)	HCV (n=21) – with TCP n (%)
A	24	0 / 18 (0.0)	1 / 6 (16.7)
B	43	1 / 33 (3.0)	3 / 10 (30.0)
C	33	27 / 28 (96.4)	5 / 5 (100.0)
Total TCP	37	28 / 79 (35.4)	9 / 21 (42.86)

Table 2 shows the distribution of Child-Pugh classes and thrombocytopenia prevalence. A total of 24 CLD patients were in Class A, 43 in Class B, and 33 in Class C. Thrombocytopenia was rare in Class A and Class B but extremely common in Class C, with 96.4% of HBV and 100% of HCV Class C patients presenting with thrombocytopenia. Thrombocytopenia occurred in 35.4% of HBV and 42.86% of HCV patients overall.

Table 3: Clinical Correlates of Thrombocytopenia in All CLD (n=100)

Variable	Subgroup	TCP Present n (%)	TCP Absent n (%)	Total	p-value
Sex	Male	27 (37.5%)	45 (62.5%)	72	0.776 (NS)
	Female	10 (35.7%)	18 (64.3%)	28	
Age	<40 yrs	16 (25.0%)	48 (75.0%)	64	0.003 (S)
	≥40 yrs	21 (58.3%)	15 (41.7%)	36	
Splenomegaly	Present	32 (43.2%)	42 (56.8%)	74	0.036 (S)
	Absent	5 (19.2%)	21 (80.8%)	26	
Ascites	Present	31 (40.8%)	45 (59.2%)	76	0.292 (NS)
	Absent	6 (25.0%)	18 (75.0%)	24	
Varices	Present	34 (44.2%)	43 (55.8%)	77	0.020 (S)
	Absent	3 (13.0%)	20 (87.0%)	23	

Table 3 shows the clinical correlates of thrombocytopenia in CLD patients. Thrombocytopenia was slightly more common in males (37.5%) than females (35.7%), but this difference was not statistically significant (p=0.776). Age ≥40 years was significantly associated with thrombocytopenia (58.3% vs. 25.0% in <40 years, p=0.003). Patients with splenomegaly had a higher prevalence of thrombocytopenia compared to those without (43.2% vs. 19.2%, p=0.036). Similarly, the presence of varices was significantly associated with thrombocytopenia (44.2% vs. 13.0%, p=0.020). Ascites

was not significantly associated with thrombocytopenia (40.8% vs. 25.0%, p=0.292).

Table 4: Clinical Correlates of Thrombocytopenia in HBV-related CLD (n=79)

Variable	Subgroup	TCP Present n (%)	TCP Absent n (%)	Total	p-value
Sex	Male	24 (36.9%)	41 (63.1%)	65	0.738 (NS)
	Female	4 (28.6%)	10 (71.4%)	14	
Age	<40 yrs	12 (23.1%)	40 (76.9%)	52	**0.005 (S)**
	≥40 yrs	16 (59.3%)	11 (40.7%)	27	
Splenomegaly	Present	25 (43.1%)	33 (56.9%)	58	**0.042 (S)**
	Absent	3 (14.3%)	18 (85.7%)	21	
Ascites	Present	24 (39.3%)	37 (60.7%)	61	0.268 (NS)
	Absent	4 (22.2%)	14 (77.8%)	18	
Varices	Present	26 (43.3%)	34 (56.7%)	60	**0.031 (S)**
	Absent	3 (13.0%)	20 (87.0%)	23	

Table 4 shows the clinical correlates of thrombocytopenia in HBV-related CLD patients (n=79). Thrombocytopenia was slightly more common in males (36.9%) than females (28.6%), but this difference was not statistically significant (p=0.738). Age ≥40 years was significantly associated with thrombocytopenia (59.3% vs. 23.1% in <40 years, p=0.005). Patients with splenomegaly had a higher prevalence of thrombocytopenia compared to those without (43.1% vs. 14.3%, p=0.042). Similarly, the presence of varices was significantly associated with thrombocytopenia (43.3% vs. 13.0%, p=0.031). Ascites was not significantly associated with thrombocytopenia (39.3% vs. 22.2%, p=0.268).

Table 5: Clinical Correlates of Thrombocytopenia in HCV-related CLD (n=21)

Variable	Subgroup	TCP Present n (%)	TCP Absent n (%)	Total	p-value
Sex	Male	3 (42.86%)	4 (57.1%)	7	1.000 (NS)
	Female	6 (42.86%)	8 (57.1%)	14	
Age	<40 yrs	4 (33.3%)	8 (66.7%)	12	0.387 (NS)
	≥40 yrs	5 (55.6%)	4 (44.4%)	9	
Splenomegaly	Present	7 (43.8%)	9 (56.2%)	16	1.000 (NS)
	Absent	2 (40.0%)	3 (60.0%)	5	
Ascites	Present	7 (46.7%)	8 (53.3%)	15	0.639 (NS)
	Absent	2 (33.3%)	4 (66.7%)	6	
Varices	Present	8 (47.1%)	9 (52.9%)	17	0.540 (NS)
	Absent	3 (13.0%)	20 (87.0%)	23	

Table 5 presents the clinical correlates of thrombocytopenia in HCV-related CLD patients (n=21). The prevalence of thrombocytopenia was identical in males and females (42.86%), with no significant difference (p=1.000). Age, splenomegaly, ascites, and varices were also not significantly associated with thrombocytopenia (p>0.05 for all), though thrombocytopenia tended to be higher in patients aged ≥40 years (55.6% vs. 33.3%) and in those with varices (47.1% vs. 13.0%).

Table 6: Distribution of the respondents according to severity of Thrombocytopenia

Severity (Platelet count)	All CLD (n=100)	HBV (n=79) – with TCP n (%)	HCV (n=21) – with TCP n (%)
Mild (<150 × 10^9/L)	19 (19.0%)	17 (21.5%)	2 (9.5%)
Moderate (<100 × 10^9/L)	15 (15.0%)	9 (11.4%)	6 (28.6%)
Severe (<50 × 10^9/L)	3 (3.0%)	2 (2.5%)	1 (4.8%)
Total TCP	37 (37.0%)	28 (35.4%)	9 (42.86%)

Table 6 shows the distribution of thrombocytopenia severity among CLD patients. Overall, 37% of patients had thrombocytopenia, with the majority being mild (19%) or moderate (15%), and a small proportion severe (3%). Among HBV-related CLD, most cases were mild (21.5%), while moderate thrombocytopenia was more common in HCV-related CLD (28.6%). Severe thrombocytopenia was uncommon in both groups.

DISCUSSION

Thrombocytopenia is one of the most important extra hepatic complications of chronic liver disease. In CLD due to HBV, it is more common when disease severity progresses. In CLD due to CHC, it may present even in the absence of cirrhosis. Older age, disease duration, advanced hepatocellular damage i.e. high

S.ALT level and male gender are more frequently associated with thrombocytopenia. The several mechanisms are implicated for thrombocytopenia; increase portal hypertension (hypersplenism), reduced thrombopoietin production by liver, virus induced (HCV) bone marrow suppression and auto antibodies production against platelet. In general, thrombocytopenia is defined as a condition where there is subnormal number of platelets in the circulating blood. In this study, thrombocytopenia was defined as platelet count less than 150×10^9 /L. The results of this study show that etiological causes of CLD, 79% due to HBV and 21% due to HCV. This result is similar to other study done in Bangladesh [7,8]. In CLD due to HBV, thrombocytopenia prevalence was 35.4%. Thrombocytopenia was more prevalent in the older age group (≥40 years, 59.3%) compared to the younger age group (<40 years, 23.1%). TCP was slightly higher in males (36.9%) than in females (28.6%). Regarding Child-Pugh class, thrombocytopenia was most common in class C, with 27 out of 28 patients (96.4%) affected (Table-4).

In CHB, thrombocytopenia is usually present in advanced-stage disease, and this is also true for the present study. In this study, thrombocytopenia was more prevalent in patients who had splenomegaly. Splenomegaly is a common feature in patients with chronic liver disease. It is usually asymptomatic but may cause hypersplenism. The spleen normally contains approximately one-third of the total platelet mass, leaving the remaining two-thirds evenly distributed in the circulation. In normal subjects, approximately 37% of platelets are sequestered in the spleen and 24% in the liver. In patients with splenomegaly in the present study, 43.1% of HBV patients with splenomegaly had thrombocytopenia. In Akyuz *et al.,*[29] study, the spleen is inversely correlated with the platelet count. The survival time of platelets increases by 47% after splenectomy. Thus, splenic sequestration due to splenomegaly is one of the main factors for the thrombocytopenia. In a study from Iran, [30] the prevalence of thrombocytopenia in CHB was reported as 17.7%. The lower frequency in their study was likely due to the exclusion of cirrhotic patients, as they only included patients with chronic active hepatitis B. In contrast, in the present study, most of the patients had cirrhosis, which explains the higher prevalence of thrombocytopenia observed.

In CLD due to HCV, the frequency of thrombocytopenia was 42.86%. Older age groups (≥40 years) had more thrombocytopenia (55.6%) compared to younger age groups (<40 years, 33.3%), while there was no sex difference (42.86% in both males and females). Regarding Child-Pugh class, 1 patient from Class A, 3 from Class B, and all patients in Class C (n=5) had thrombocytopenia (Table-5). The frequency of thrombocytopenia of 40% and 33.3% in this study, after exclusion of patients with splenomegaly and esophageal varices, suggests that portal hypertension has a major contribution, but a direct viral effect and impaired thrombopoietin production by the liver are also important factors in CLD due to HCV. A study from Pakistan reported, [31] the prevalence of thrombocytopenia in CLD due to HCV was 32.2%. They defined thrombocytopenia as $<150\times10^9$/L and most of the patient in their study were Child-Pugh A (66.5%) but in this study most of the patient were in Child-Pugh class B (47.62%). A study from Taiwan reported 10.2% had thrombocytopenia ($<100\times10^9$/L) in patients with positive anit-HCV antibody.[14] It was a community-based study. The low frequency of thrombocytopenia in their study could be due to their definition of thrombocytopenia ($<100\times10^9$/L) used. The authors also reported frequency of thrombocytopenia 20.3% among those with chronic hepatitis and 31.8% among those with advanced liver disease including liver cirrhosis.

Another community based large-scale study from Taiwan reported 25.5% had thrombocytopenia, using platelet threshold ($<150\times10^9$/L). [32] The higher frequency of thrombocytopenia (42.86%) in this study may be due to the hospital-based nature of the study, where most patients had advanced disease, i.e., Child-Pugh Class C, and were in the older age group (>40 years). The Child-Pugh classification is a well-validated system for assessing hepatic function in patients with cirrhosis. The prevalence of thrombocytopenia in CLD due to HBV and HCV infection increases in patients with older age, advanced Child-Pugh class, splenomegaly, and esophageal varices. The higher frequency of thrombocytopenia in the older age group compared to the younger age group indicates that the likelihood of liver injury, subsequent inflammation, and consequent fibrosis increases as patients grow older.

LIMITATIONS OF THE STUDY

There are some limitations of this study. Firstly, the viremic status of patients was not evaluated by HBV DNA or HCV RNA assays. Additionally, this was a hospital-based, cross-sectional study with a small sample, mostly including patients with advanced disease, which may limit generalizability. Only HBV- and HCV-related CLD were studied, and long-term follow-up was not performed, limiting assessment of progression and outcomes.

CONCLUSION

Due to inadequate surveillance, lack of medical knowledge, and low health consciousness, patients with chronic liver disease in our country are prone to report late. In the present study, most patients were far advanced in the stage of disease. Among the etiologic causes, HBV was more common than HCV. Thrombocytopenia was more frequent among HCV patients even at early stages, while in HBV it was observed more in advanced disease. Increased age, higher Child-Pugh class, and presence of portal

hypertension were the best predictors of thrombocytopenia in CLD due to HBV and HCV.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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