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Original Article

# Thrombocytopenia: Frequency and Severity in Patients with Chronic Liver Disease

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## ABSTRACT

***Objective:*** To determine the frequency and severity of thrombocytopenia in patients with chronic liver disease.
***Study design:*** Cross-sectional study
***Place and Duration of study:*** Department of General Medicine & Gastroenterology, Combined Military Hospital Rawalpindi, Pakistan, from Jul 24 to Mar 25.
***Methodology:*** This study included 248 patients aged 18 to 75 years, including both genders, diagnosed with a case of chronic liver disease. Platelet counts were measured, and thrombocytopenia was categorized as mild, moderate, and severe, and its association was analyzed with chronic viral hepatitis B and C, and severity of liver dysfunction and clinical staging of liver disease.
***Results:*** Among 248 patients, 138(55.6%) were male, and 110(44.4%) were female, with a mean age of 52.5± 11.48 years. Thrombocytopenia was present in 99(39.9%) patients, with 27(10.9%) mild, 47(19.0%) moderate, and 31(12.5%) severe thrombocytopenia. Of the 248 patients, 118(47.6%) had a disease duration ≤ 12 months, while 130(52.4%) had >12 months. Jaundice was present in 123(49.6%), splenomegaly in 157(63.3%), and ascites in 75 (30.2%). 109(44%) patients labeled as Child Pugh Class A, while 78(31.5%) as Child Pugh Class B and 61(24.6%) as Child Pugh Class C. Thrombocytopenia was more prevalent in patient with chronic hepatitis C [69 (47.58%)] than chronic hepatitis B [30 (29.12%)], and this difference was statistically significant (p = 0.003).
***Conclusion:*** Thrombocytopenia is frequently seen in patients with chronic liver disease, and it varies from mild to severe in chronic liver disease, from the compensated to the decompensated stage. It is significantly associated with viral causes of hepatitis.

**Keywords:** Ascites; Chronic Liver Disease; Hepatitis B; Hepatitis C; Thrombocytopenia

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## INTRODUCTION

Chronic liver disease is one of the main causes of mortality and morbidity worldwide. It accounted for 2.2% of deaths worldwide and 1.5% disability adjusted life years, making it the 11th largest cause of death and 15th major cause of morbidity according to a 2016 study.[1] Chronic liver disease (CLD) is characterized as a persistent decline in liver function that occurs due to inflammatory, infiltrative, immune-related, mechanical, or metabolic factors, that lasts for six months or more without complete resolution.[2] Two third of the global burden of liver cirrhosis is caused by Hepatitis B and Hepatitis C viruses. According to a 2017 WHO study, among the other causes, chronic hepatitis B (HBV) and hepatitis C (HCV) infections accounted for 96% of the 1.3 million deaths across the world due to hepatitis viruses in 2015, with about 720,000 of those deaths occurring during the stage of liver cirrhosis.[3]

Thrombocytopenia is the most common hematological consequence seen in patients with liver cirrhosis.4 It is defined by a platelet count of less than 150,000/µL. It is categorized into mild (100000/µL-150000/µL), moderate (50000/µL-100000/µL), and severe (< 50000/µL) thrombocytopenia. According to recent studies, its prevalence varies between 6% to 78%, and it increases progressively from the compensated stage of cirrhosis to the decompensated stage of liver cirrhosis, indicating poor prognosis.[5] Thrombocytopenia was recorded in 13% as moderate and 1% severe in patients with chronic liver disease.[6]

Research conducted in Pakistan reported that 22.6% of patients with chronic liver disease had thrombocytopenia, whereas another study reported a prevalence of 32.3%.[7] Thrombocytopenia in patients with cirrhosis has a complex pathogenesis, which can be broadly divided into three categories: splenic sequestration due to hypersplenism, immune-related increased platelet destruction, and decreased platelet production due to decreased thrombopoietin levels.[8]

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Chronic liver disease, particularly due to Hepatitis B and C infections, continues to be a severe health burden in developing countries, such as Pakistan. Thrombocytopenia is a common hematological consequence seen in patients with chronic liver disease, which increases the bleeding risks and delays treatment and invasive procedures. There is limited local data on the frequency and severity of thrombocytopenia and particularly its association with Chronic Hepatitis B and C infections. Therefore, this study seeks to fill the knowledge gap by assessing the frequency and severity of thrombocytopenia and analyzing its association with Chronic Hepatitis B and C.

## METHODOLOGY

This Cross-sectional study was carried out at the Department of General Medicine & Gastroenterology, Combined Military Hospital (CMH), Rawalpindi, Pakistan, from Jul 24 to Mar 25 after obtaining approval from the Institutional Ethical Review Committee letter 854, dated 17 April 2024. Sample size was calculated using the WHO sample size calculator, with a confidence level of 95% and precision of 6%; the sample size came out to be 248 patients. In a previously published observational study, the overall prevalence of Thrombocytopenia was found to be 36.3% in 190 patients.[7] All patients were selected by a non-probability consecutive sampling technique. This sampling method was acknowledged as a limitation of the study.

**Inclusion Criteria:** All the patients of chronic liver disease, including both males and females, aged 18 to 75 years, confirmed diagnosis of chronic hepatitis B(HBV) and chronic hepatitis C (HCV) by serological testing, and all the patients of any grade of severity of liver cirrhosis based on clinical, laboratory, and Ultrasound findings.

**Exclusion Criteria:** Patients with hepatitis D or HIV co-infection, patients taking interferon therapy or undergoing chemotherapy, any malignancy affecting the platelet counts (e.g., Aplastic anemia), patients with a history of splenectomy, recent history of blood transfusion within 7 days, pregnant women, and patients with incomplete laboratory records.

Written informed consent was obtained from all participants before enrollment in the study. Patients visiting the outpatient department or admitted to the Gastroenterology/Medicine wards of CMH Rawalpindi were screened for eligibility, and those participants who fulfilled the inclusion criteria were enrolled. All the participants underwent a detailed and relevant clinical history, which was recorded on a structured proforma, and a clinical examination was performed. A 5cc blood sample was collected after informed consent under aseptic measures and sent to the Armed Forces Institute of Pathology (AFIP) laboratory for analyzing platelet counts using an automated hematology analyzer. Reports were collected through keeping a record of the patient's hospital ID. The reference range of Platelet counts in the laboratory at AFIP is 150-400 x 109/L. A patient with platelet counts less than 150,000/mm$^3$ was labeled as having thrombocytopenia. (Figure)

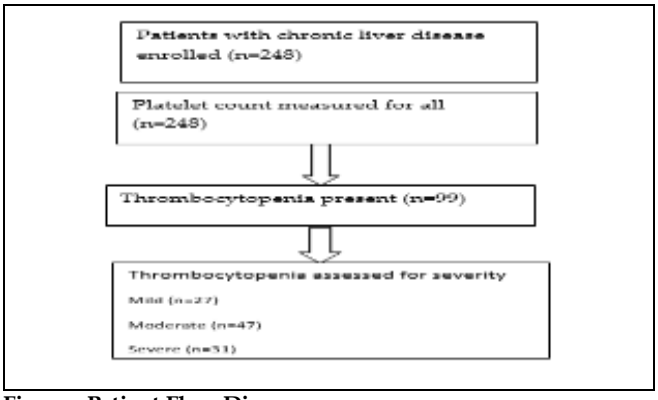


**Figure: Patient Flow Diagram**

Chronic liver disease was defined as progressive deterioration of liver functions lasting more than 6 months, leading to liver fibrosis and cirrhosis. Thrombocytopenia was defined as platelet count less than 150,000/mm3. Severity of Thrombocytopenia was assessed as follows: Mild thrombocytopenia was labeled as platelet counts of 100,000 to 150,000 /mm$^3$, while moderate thrombocytopenia was labeled as platelet counts of 50,000 to 100,000/mm3, and severe thrombocytopenia was labeled as platelet counts of less than 50,000/mm$^3$

The structured proforma comprised of demographic details by asking the patient relevant clinical questions and obtaining laboratory records, such as age, gender, BMI, duration of disease, platelet counts, hepatitis B and C status, jaundice, presence or absence of splenomegaly, presence or absence of ascites, liver enzymes, coagulation profile to label the Child Pugh Class (A, B, C) to assess the severity of chronic liver disease. The score of 5-6 was labeled as Class A, 7-9 as Class B, and score of 10-15 as Class C.

The primary outcome was frequency and severity of thrombocytopenia in chronic liver disease, and the secondary parameters included association of

thrombocytopenia with Hepatitis B and C, severity of liver dysfunction, and clinical staging of liver disease.

The statistical analysis of the study was done using Statistical Package of Social Sciences (SPSS) version 24. Mean and standard deviation (SD) were calculated for continuous variables, including age and BMI. Frequencies and percentages were computed for categorical variables such as gender, duration of disease, presence of jaundice, splenomegaly, ascites, hepatitis type, Child-Pugh class, and severity of thrombocytopenia. The independent-sample t test was applied to compare mean values of continuous variables (e.g., age, BMI) between patients with and without thrombocytopenia. The chi-square test was used to assess associations between thrombocytopenia and categorical variables such as gender, hepatitis type, disease duration, splenomegaly, and ascites. A *p*-value of <0.05 was considered statistically significant.

## RESULTS

After the application of inclusion and exclusion criteria, 248 patients were included in the study. Table-I showed that out of 248 patients, 138(55.6%) were male and 110 (44.4%) were female, with a mean age of 52.5± 11.5 years, and the mean Body mass index (BMI kg/m$^2$) was 23.9± 4.0 kg/m$^2$. 103(41.5%) patients had Hepatitis B, while 145(58.5%) had Hepatitis C. Thrombocytopenia was found in 99(39.9%) patients: 27(10.9%) had mild, 47(19.0%) had moderate, and 31(12.5%) had severe thrombocytopenia. 118(47.6%) had disease duration ≤12 months, while 130(52.4%) had disease duration > 12 months. Jaundice was observed in 123(49.6%), splenomegaly in 157(63.3%), and ascites in 75(30.2%). On Child-Pugh classification, 109(44%) patients were labeled as Child Pugh Class A, while 78(31.5%) were labeled as Child Pugh Class B and 61 (24.6%) were labeled as Child Pugh Class C. Association between thrombocytopenia and clinical variables is presented in Table-II. Thrombocytopenia was also strongly associated with longer disease duration ($p$=0.01), presence of splenomegaly ($p$<0.001), presence of ascites ($p$<0.001), and advanced Child-Pugh class ($p$<0.001). Severity of thrombocytopenia stratified by hepatitis type is shown in Table-III. Thrombocytopenia was significantly more common in patients with Hepatitis C (69/145, 47.6%) compared with Hepatitis B (30/103, 29.1%) ($p$=0.003).

## DISCUSSION

In this study, 248 patients were enrolled; males, 138 (55.6%), outnumbered the females 110 (44.4%), with the majority (55.6%) of the patients in their 4th or 5th decade of life. Mean age was 52.5± 11.5 years. The mean Body mass index (BMI kg/m$^2$) was 23.9±4.04 kg/m$^2$. Out of 248 patients, 118(47.6%) had a disease duration <12 months, while 130(52.4%) had a disease duration >12 months. Thrombocytopenia was present in 39.9%, while mild thrombocytopenia was present in 10.9%, moderate thrombocytopenia 19.0%, and severe thrombocytopenia in 12.5%. The prevalence of thrombocytopenia has been reported in the literature as 36.3%, and a high prevalence of thrombocytopenia was reported as 61.4%.[9] Nawaz *et al.*, reported a prevalence of thrombocytopenia 64% in cirrhosis patients. The results showed a higher prevalence compared to this study.[10]

**Table-I: Baseline characteristics of patients (n=248)**

| Variable | Values |
|---|---|
| Age (years) | 52.5±11.5 |
| BMI(kg/m2) | 23.9±4.04 |
| Gender | |
| Male, n (%) | 138(55.6%) |
| Female, n (%) | 110(44.4%) |
| Hepatitis | |
| B, n (%) | 103(41.5%) |
| C, n (%) | 145(58.5%) |
| Thrombocytopenia | |
| Yes, n (%) | 99(39.9%) |
| No, n (%) | 149(60.1%) |
| Duration of illness | |
| ≤ 12 months | 118(47.6%) |
| > 12 months | 130(52.4%) |
| Splenomegaly | |
| Yes, n (%) | 157(63.3%) |
| No, n (%) | 91(36.7%) |
| Ascites | |
| Yes, n (%) | 75(30.2%) |
| No, n (%) | 173(69.8%) |
| Jaundice | |
| Present, n (%) | 123 (49.6%) |
| Absent, n (%) | 125(50.4%) |
| Child Pugh Class | |
| A, n (%) | 109(44.0%) |
| B, n (%) | 78(31.5%) |
| C, n (%) | 61(24.6%) |

**BMI – Body Mass Index*

A study conducted by Bano *et al.*, indicated that the prevalence of thrombocytopenia was 43.3% among patients with Hepatitis C. These findings are similar to those of this study, indicating that hepatitis C is the most common cause in patients with chronic liver disease.[11] Rauber *et al.*, found that the prevalence of thrombocytopenia in Hepatitis C infection was 32%. Thrombocytopenia was present in 53% in Hepatitis C infections. [12]. A total of 157(63.3%) patients had

splenomegaly, while 91 (36.7%) had no splenomegaly. This finding was like the study conducted by Yoshuji *et al.*, which reported the presence of splenomegaly up to 60%.[13]

**Table-II: Association of Different Pathological Variables and Thrombocytopenia (N=248)**

| Variables (n) | | Thrombocytopenia | | *P*-value |
|---|---|---|---|---|
| | | Present n (%) | Absent n (%) | |
| Hepatitis B (n=103) | | 30(29.1%) | 73(70.9%) | 0.003 |
| Hepatitis C (n=145) | | 69(47.6%) | 76(52.4%) | |
| Duration of liver disease | ≤12 m (n=118) | 57(48.3%) | 61(51.7%) | 0.01 |
| | >12 m (n=130) | 42(32.3%) | 88(67.7%) | |
| Splenomegaly | Present (n=157) | 98(62.4%) | 59(37.6%) | <0.001 |
| | Absent (n= 91) | 1(1.1%) | 90(98.9%) | |
| Ascites | Present (n= 75) | 72(96.0%) | 3(4.0%) | <0.001 |
| | Absent (n=173) | 27(15.6%) | 146(84.4%) | |
| Child Pugh Class | A (n=109) | 5(4.6%) | 104(95.4%) | <0.001 |
| | B (n=78) | 34(43.6%) | 44(56.4%) | |
| | C (n=61) | 60(98.4%) | 1(1.6%) | |

**Table-III: Association between hepatitis type and severity of thrombocytopenia (n=248)**

| Hepatitis (n) | Thrombocytopenia | | | | *p*-value |
|---|---|---|---|---|---|
| | Absent n (%) | Mild n (%) | Moderate n (%) | Severity n (%) | |
| Hepatitis B (n=103) | 72(69.9%) | 6(5.8%) | 16(15.5%) | 9(8.7%) | 0.008 |
| Hepatitis C (n=145) | 71(49.0%) | 21(14.5%) | 31(21.4%) | 22(15.2%) | |

Another study by Fierro *et al.*, found 68% prevalence of hypersplenism. Many factors, such as splenic sequestration, decreased activity of hematopoietic growth factor thrombopoietin (TPO), cirrhotic coagulopathy, bone marrow suppression by chronic HCV infection, anti-cancer agents, and anti-viral treatment with interferon (IFN) based therapy, can cause thrombocytopenia.[14] Platelet sequestration in the spleen and decreased hepatic synthesis of TPO in patients with chronic liver disease are two primary causes, as reported by Desai *et al*.[15] It has been believed that thrombocytopenia results from increased platelet pooling in an enlarged spleen. There is a negative relationship, which has been observed between the platelet count and splenic size.[15] In this study, 248 patients were scored on the Child-Pugh scoring system, with the highest number of patients in Class A, 109(44%), while 78(31.5%) were in Class B and 61 (24.6%) in Class C. These findings are like the study conducted by Miller at al.[16]

Saab *et al.*, concluded that there are several other drugs in the research pipeline at various stages of development, including a new class of monoclonal antibodies that can bind to and activate TPO-receptor agonists. The outlook for treatment choices for thrombocytopenia in patients with liver disease is promising.[17]

There is a need for a thoughtful approach to manage bleeding risk in patients with cirrhosis undergoing procedures, with the consideration of a comprehensive hemostatic profile, the severity of portal hypertension, and the complexity of the invasive procedure to guide decisions regarding transfusions or use of TPO receptor agonists.[18]

This study signified that in patients with liver cirrhosis, the degree of thrombocytopenia is a helpful indicator of poor prognosis of the disease. It was also noted that chronic liver disease was strongly associated with thrombocytopenia. The duration of the disease is prolonged in cases of splenomegaly and Hepatitis C.

## LIMITATION OF STUDY

This study was conducted in a single tertiary-care center with consecutive non-probability sampling, which limits the diversity of the patient population. Another was a cross-sectional design, due to which we cannot determine whether thrombocytopenia causes disease worsening.

## CONCLUSION

In our study, the frequency of thrombocytopenia was found to be 39.9%. Most of the patients belonged to the 4th and 5th decades. It was frequently seen in male patients compared to females. It was significantly associated with duration of disease more than 12 months, presence of splenomegaly, and chronic Hepatitis C. This emphasizes the need for early screening of platelet counts for prompt management and to decrease the bleeding risks.

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**Authors' Contribution**

Following authors have made substantial contributions to the manuscript as under:

SS & MNQ: Data acquisition, data analysis, critical review, approval of the final version to be published.

FAS & SA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AR & LS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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