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Assessment Prevalence of thrombocytopenia in chronic hepatitis B and C

Ali Kareem Durib[1], Zainab ahmad Hassan[2], Zorkin Michael Viktorovich[3]

[1,2]Middle Technical University, Baghdad, Iraq (MTU)

[3]Ogarev Mordovia State University

***** Correspondence: ali_kareem37@yahoo.com

Abstract: Thrombocytopenia is a common complication in chronic liver disease characterized by a low platelet count, which is lower than the normal platelet count < 150 X10 9. The condition had variable incidence, regarding viral hepatitis and is more common in hepatitis C than B.
Aim of the study: Assess the prevalence of thrombocytopenia (lower than normal platelet count) in patients proved to have hepatitis B and C by RNA testing. Cross sectional study included 50 viral hepatitis patients (HCV and HBV diagnosed previously), all patients were evaluated for complete blood count and liver function test. Males were forming 68% of all participant, 58% were HBV patients and 42% were HCV patients. The overall prevalence of Thrombocytopenia was 46%. The mean platelet level in HCV was177.43 ± 18.19 with higher prevalence of thrombocytopenia (60.9% vs 39.1%) in hepatitis C than B, with no association between gender and liver functions. Thrombocytopenia one of common complications in viral hepatitis, despite that both HCV and HBV had lower platelet count in comparison to normal person, the count is much more lower in HCV patients with higher prevalence of thrombocytopenia in compare to HBV that is more common in male gender.

Keywords: CLD, HCV, HBV, Thrombocytopenia

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Introduction

The phrase "chronic liver disease" (CLD) describes a protracted process wherein the liver's ability to produce clotting factors and other proteins, detoxify harmful metabolic products, and excrete bile is compromised. Chronic liver disease (CLD) is a continuous process that causes inflammation in the liver parenchyma in addition to destruction and regeneration, which results in cirrhosis and fibrosis (Kim et al., 2018).

There are many different causes of chronic liver disease, such as autoimmune disorders, long-term alcoholism, infections, toxins, and anomalies in metabolism. The final stage of chronic liver disease, known as cirrhosis, is marked by extracellular matrix deposition, vascular reconfiguration, neo-angiogenesis, widespread nodules, and deformation of the liver's architecture (Sharma & Nagalli, 2023).

One of the most common causes of chronic liver disease (CLD) and a major global cause of morbidity and mortality is hepatitis viruses. The World Health Organization (WHO) estimates that 1.4 million people die

from viral hepatitis each year, with hepatitis B or C accounting for the majority of these (Liu et al., 2020).

Hepatitis B, C, and D virus (HBV, HCV, and HDV) infections have been prevented and treated with great success; but, chronic hepatitis brought on by these viruses continues to be the leading cause of cirrhosis and hepatocellular carcinoma (HCC). (El-Serag, 2020).

Common causes of clinical hepatitis and abrupt liver failure include the hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Despite its rarity, the latter condition poses a serious risk to life (Torre et al., 2021).

Despite being underdiagnosed, hepatitis C is the most often reported blood-borne infection in the US. It is brought on by HCV, a single-strand RNA virus belonging to the Hepacivirus genus and family of Flaviviridae that was identified in 1989 by Michael Houghton and associates. Humans are the only known host for HCV, which is transmitted through the bloodstream. Eight viral genotypes have been found to date (Shashidhar & Nallagangula, 2019).

Acute hepatitis is caused by HCV infection in 15% of instances, while chronic infection affects about 80% of infected individuals; within 25 years, 20% of patients with chronic infection develop cirrhosis, and 25% of cirrhosis patients develop HCC and/or decompensated liver disease (Borgia et al., 2018) (Freeman et al., 2001).

Numerous variables influence the frequency of HCV infection nowadays, including: the quantity of individuals who currently have a chronic HCV infection, which is shown by detectable HCV RNA at least six months after an acute infection (Falla et al., 2018).

Elevated transaminases are a sign of acute HCV infection, which typically goes unnoticed until six to eight weeks after exposure (Vogel et al., 2018). After six months, about 30% of people with HCV infection are able to recover from the infection on their own. On the other hand, chronic infection—which is characterized by the presence of anti-HCV antibody in the blood and HCV-RNA persistence for at least six months—occurs in between 60% and 70% of infected patients. Transaminases can be normal, but they are typically significantly increased (Hofmeister et al., 2019) (Dunn et al., 2022).

Acute liver failure caused by HCV infection is a rare occurrence. Hepatomegaly and splenomegaly can be discovered through a physical examination. Chronic HCV infection can cause fibrosis in the liver, which can lead to cirrhosis, decompensation, and HCC. According to the research

population and numerous risk factors, such as male gender, alcohol intake, older age at the time of infection, and coinfection with other viruses as HIV, the proportion of individuals who develop liver cirrhosis after 20 years of infection varies greatly, ranging from 2% to 51% (Dunn et al., 2022),(Beasley et al., 1982).

Infection with the hepatitis B virus is a severe global health issue. The hepatitis B virus causes a potentially life-threatening liver infection (HBV). The infection is caused by DNA HBV that has 8 genotypes (A–H) which are associated with moderate differences in response to therapy (Terrault et al., 2018), (Kowdley et al., 2012).

About 240 million individuals are affected by chronic HBV; 15%–40% of infected patients will get severe liver disease, and up to 1.2 million people will die annually as a result (Ocama). In addition to the indigenous people of Alaska, Northern Canada, Greenland, Australia, and New Zealand, chronic HBV is endemic in Southeast Asia, China, sub-Saharan Africa, Micronesia, and Polynesia. Over 7% of people live in these high-prevalence areas and the majority of illnesses occur in early life (Kowdley et al., 2012), (Burns & Thompson, 2014), (Ocama et al., 2005), (Saiyed et al., 2020).

The natural progression of the illness can be categorized into four phases: immunological tolerance, immune clearance, immune control, and immune escape. These phases are dictated by the interaction between the host immune system and virus reproduction (Saiyed et al., 2020).

An abnormally low platelet count, which is less than the adult normal range of 150 x 10 9 /L to 450 x109 /L, is the hallmark of thrombocytopenia. When platelet counts are less than 20x109/L, a condition known as severe thrombocytopenia occurs (not induced by injury). Making clinically significant decisions with confidence requires obtaining trustworthy platelet counts since neglecting a severe thrombocytopenia can have major effects for the patient.However, getting precise platelet counts is a difficult issue for the laboratory, especially when working with samples that have thrombocytopenic characteristics (Jahangiri, 2022).

Aside from hepatic problems, chronic viral hepatitis is linked to a number of extra-hepatic symptoms, including thrombocytopenia. The fact that individuals with CLD frequently require diagnostic and/or therapeutic invasive procedures emphasizes the importance of thrombocytopenia. Thrombocytopenia also has a negative impact on CLD treatment, since it increases the risk of bleeding and the need for blood transfusions, delaying

surgical procedures and potentially raising treatment expenses (Peck-Radosavljevic, 2017), (Yoshida et al., 2022).

Patients with CLD have a prevalence rate of thrombocytopenia of 15–70%; this percentage is higher in those with end-stage liver disease and lower in those with compensated CLD. In contrast, patients with cirrhosis or fibrosis have a prevalence rate of 64–84% (Huang et al., 2022).

TCP is said to be more common among populations with high rates of advanced cirrhosis. Understanding TCP is critical because it might raise the risk of problems during invasive diagnostic or therapeutic procedures, necessitate the use of interferon (IFN) medication, and affect how patients on waiting lists for orthotropic liver transplantation are managed (Mitchell et al., 2016). It may increase the risk of bleeding esophageal varices, hematological malignancies, chemotherapy-induced solid tumors, and surgical procedures. Major bleeding is linked to Plt levels below 10*109/L, and bleeding risk rises when levels fall below 50*109/L. However, additional parameters including Plt function, the existence of anti-Plt antibodies, and levels of coagulation factors may also be involved, so Plt counts alone may not always represent bleeding (Omar et al., 2014), (Gotlieb et al., 2020).

Studies indicate that HCV may produce secondary immunological thrombocytopenia (ITP), and that patients with HCV may experience more severe thrombocytopenia than those with HBV. HCV-ITP has been connected to deterioration of immunity. There aren't many studies on the immunological relationships between HBV and platelet count for HBV-TP (Scharf, 2021).

The pathophysiology of thrombocytopenia in chronic liver disease is multifaceted and intricate. Hypersplenism has been linked to CLD-related thrombocytopenia, which is brought on by increased platelet pooling and quick splenic destruction as a result of portal hypertension (Moore, 2019), (Houot et al., 2016). In patients with CLD, decreased production of thrombopoietin, which is mostly generated in the liver and is involved in megakaryocyte development and platelet formation, can lead to thrombocytopenia. Furthermore, certain underlying etiologies of liver illness may limit platelet synthesis in the bone marrow (Meintker & Krause, 2020), (Rawi & Wu, 2020).

Aim of the study: assess the prevalence of thrombocytopenia (lower than normal platelet count) in patients proved to have hepatitis B and C by RNA testing.

Materials and Methods

Patients:

Study design and data setting:

Cross sectional study that included 50 hepatitis patients (diagnosed by PCR and CT) who admitted to al Yarmouk teaching hospital from the duration of July 2020 to August 2021, both gender from different age group (adult) was included. ethical committee approval was obtained.

Inclusion criteria:

1- Irrespective of age and sex.

2- Laboratory evidence of chronic hepatitis as proved by viral RNA testing.

3-Laboratory evidence of low platelet count.

4- Clinical evidence of chronic liver disease.

Exclusion criteria:

1-malignancy on chemotherapy.

2-aplastic anemia or other hematological malignancy.

Results and Discussion

The current study is a cross sectional study included 50 patients with CLD due to viral hepatitis. Regarding patient's gender, 68% of them were males and 32% were female. Regarding viral type 29 out of 50 (58%) were HBV patients and 21 out of 50 (42%) were HCV patients. The gender distribution according to viral type show that 62.1% of HBV were male and 37.9% were females in compare to 76.2% of HCV were male and 23.8% were females. Result revealed that 46% of all included patients had thrombocytopenia, as presented in table 3-1 and figure 1.

the association between development of thrombocytopenia and gender of included patients regardless the viral type.

Result show that 19 out 34 males didn't develop thrombocytopenia and 15 out of 34 (44.1%) had thrombocytopenia. Regarding female gender, 50% didn't develop thrombocytopenia and 50% had thrombocytopenia. There was no statistical significant association between development of thrombocytopenia and gender, p-value 0.65, as presented in table 2.

The complete blood count (CBC) was for all included patients, result revealed that HCV patients has a statistical lower mean platelet count (177.43 ± 18.19) in compare comparison to HBV patients (249.38 ± 21.99), p-value 0.02. No statistical significant difference in mean level of HB, RBC, WBC in HBV patients (13.35 ± 0.40, 4.26 ± 0.16, 6951.72 ± 351.72) in compare

to mean level in HCV patients (13.58 ± 0.46, 4.31 ± 0.18, 6809.52 ± 453.97), p-value was 0.71, 0.83 and 0.8, respectively. As presented in table 3.

Liver function test was assessed for all included patients, result revealed no statistical significant differences in mean level of TSB, AST, ALT, ALP, PT, PTT and albumin in HBV patients (1.29 ± 0.12, 44.45 ± 4.19, 48.03 ± 4.48, 79.48 ± 5.59, 12.64 ± 0.16, 27.79 ± 0.77, 3.95 ± 0.09) in compare comarison to HCV patients (1.38 ± 0.12, 45.52 ± 3.91, 47.19 ± 4.45, 84.57 ± 5.87, 12.58 ± 0.21, 28.92 ± 0.84, 4.28 ± 0.22), p-value was 0.65, 0.85, 0.89, 0.54, 0.81, 0.33 and 0.13, respectively.

Both groups show normal mean level of PT, PTT and albumin (HCV group only), however, regarding TSB, AST and ALT mean level, both groups show higher TSB mean level in compare comparison to normal population, as presented in table 4.

The mean difference in CBC and liver function parameters were assessed according to presence or absence of thrombocytopenia. Result revealed thrombocytopenic patients had statistically lower mean low level of platelet count (140.17 ± 8.82) in compare comparison to non-thrombocytopenic patients, p-value 0.000.

Regarding CBC parameters, the mean level of HB, RBC and WBC mean level in non-thrombocytopenic patients (13.88 ± 0.44, 4.39 ± 0.18, 6566.67 ± 337.58) had a non-statistical significant difference from the thrombocytopenic patients (12.94 ± 0.37, 4.16 ± 0.16, 7273.91 ± 446.87), p-value 0.12, 0.36 and 0.2, respectively.

The mean level of TSB, AST, ALT, ALP, PT, PTT and Albumin in non-thrombocytopenia group (1.33 ± 0.12, 47.19 ± 4.32, 49.96 ± 4.68, 80.81 ± 5.66, 12.51 ± 0.18, 27.81 ± 0.79, 4.08 ± 0.16) had a non-statistical significant difference from the thrombocytopenic patients (1.32 ± 0.13, 42.22 ± 3.79, 45.00 ± 4.21, 82.57 ± 5.90, 12.73 ± 0.18, 28.80 ± 0.82, 4.10 ± 0.14), p-value 0.95, 0.40, 0.44, 0.83, 0.42, 0.39 and 0.96, respectively.

Both groups had normal mean level of HB, RBC, WBC, ALP, PT, PTT and albumin, but a higher mean level of TSB, AST, ALT in compare comparison to normal population reference, as presented in table 5. PT

The result of studied parameters was classified according to being normal, increased or decreased, and distributed according to viral type and development of thrombocytopenia.

A statistical significant association between HCV and development of thrombocytopenia, p-value 0.02, 60.9% of HCV had thrombocytopenia in compare to 39.1% of HBV patients.

No statistical significant association between viral type and PT, PTT, ALT, AST, ALP, ALB and platelet result, p-value 0.79, 0.48, 0.66, 0.75, 0.10, 0.31 and 0.06, respectively.

Those who had normal PT, 59% were HBV and 41% were HCV, while those who had prolonged PT 54.5% were HBV and 45.5% were HCV, 66.7% of HBV and 33.3% of HCV have prolong PTT, patients who had ALT level >45IU/L 54.5% were HBV and 45.5% were HCV, patients had ALP < 30 IU/L, 66.7% were HBV and 33.3% were HCV. Those who had AST level > 35IU/l, 48.3% were HBV and 51.7% were HCV patient. 64.3%of HBV and 35.7% of HCV patients had albumin level< 4 μg/L.

Patients who had platelet count < 150 *109/L, 57.1% of them were HCV patients and 42.9% were HBV, as presented in table 6.

TT, ALT, AST, ALP, Albumin, p-value 0.52, 0.73, 0.52, 0.65, 0.41 and 0.94, respectively.

Those who had prolonged PT 54.5% were thrombocytopenic and 45.5% were non-thrombocytopenic patient, 41.7% were thrombocytopenic and 58.3% were non-thrombocytopenic patient had prolong PTT, patients who had ALT level >45IU/L 40.9% were thrombocytopenic and 59.1% were non-thrombocytopenic patient, patients had ALP < 30 IU/L, 33.3% were thrombocytopenic and 66.7% were non-thrombocytopenic patient. Those who had AST level > 35IU/l, 41.1% were thrombocytopenic and 58.9% were non-thrombocytopenic patient. 45.5% of thrombocytopenic and 54.5% of non-thrombocytopenic patient had albumin level< 4 μg/L, as presented in table 7.

Discussion:

The abrupt bleeding episodes that can lead to death and increase the overall mortality rate in medical wards, thrombocytopenia is one of the most important factors in hepatitis C and hepatitis B patients. Thrombocytopenia is common complication in CLD due to HBV and HCV. The current study included patient of HBV and HCV and investigate the presence of thrombocytopenia in them. Gender, viral hepatitis type with thrombocytopenia:

Most of included patients 68% were males and 46% of included patients had thrombocytopenia. No association between gender and development of thrombocytopenia, however, most thrombocytopenic patients were males. Regarding gender distribution according to viral type, 62.1% of HBV were males and 72.2% of HCV were males. The gender distribution may be related to the lower susceptibility of female to viral

infection due to owning more intense immune response, hormonal causes in addition to humoral and cell-mediated.

No statistical significant difference in mean level of liver function tests, HB, WBC count, RBC count and albumin between HCV and HBV patients, but, a statistical significant difference in mean level of platelet count, HCV patients had a statistical significant lower platelet count (177.43 ± 18.19) in compare to HBV patients (249.38 ± 21.99).

Acute liver hepatitis is associated with marked elevation in transaminase enzymes, elevation in ALP is more common due to cholestasis cause either intrahepatic or extrahepatic not common in viral hepatitis , most of HCV and HBV are chronic patients, and the markers are mildly elevated or near normal level.

In the study of (Huang, 2014) Some finding agreed with current study result, HVC in Huang'S study had statistical lower platelet count in compare to HBV patients, no statistical significant difference in mean level of AST, ALT, albumin snd TSB mean level between HCV and HBV patients, however, the other study finding are inconstant with current finding, in which a statistical significant association between male gender and HBV, HBV patient has a statistical significant higher mean level of WBC, HB and prolonged PT time.

The prevalence of thrombocytopenia in HBV was 39.1% and in HCV 60.9%, a statistical significant association between thrombocytopenia development and being a HCV patient. Despite that no statistical significant association was found between cause of viral hepatitis and development of abnormal liver function test, 22% of patients had prolonged PT, 44% had high ALT level, 58% had high AST, and 22% had low albumin.

The reported prevalence of HCV and HBV (11.86% and 6.35%) in Huang et al., study and by Wang et al., study 10.2% and 1.9%, respectively, is much lower than the reported in current study. The differences are related to study setting, sample size and being the disease is pandemic in some areas.

No study that assess correlation between platelet count with other liver function enzymes in HCV and HBV was found.

Conclusion

In this study, it was found that thrombocytopenia is commonly present in patients with chronic liver disease caused by hepatitis B (HBV) and hepatitis C (HCV) viruses. The research revealed that HCV-infected individuals have a higher prevalence of thrombocytopenia at 60.9%

compared to 39.1% in HBV patients. This emphasizes the importance of closely monitoring and managing platelet counts in HCV patients to prevent potential complications.

The research findings revealed that despite most thrombocytopenic patients being male, there was no substantial gender disparity in the development of thrombocytopenia. This suggests that although males are more commonly affected by HCV and HBV, gender does not have a significant impact on the probability of developing thrombocytopenia.

In addition, the examination of complete blood counts (CBC) and liver function tests (LFTs) demonstrated that patients with Hepatitis C (HCV) have a notably lower average platelet count compared to patients with Hepatitis B (HBV). However, other CBC parameters such as hemoglobin, white blood cell count, and red blood cell count did not display significant variances between the two groups. Similarly, LFTs indicated no substantial differences in average levels of total serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, prothrombin time, partial thromboplastin time, and albumin between HCV and HBV patients.

The results emphasize the intricate nature of low platelet count in chronic liver disease (CLD), which is influenced by various factors such as hypersplenism, decreased thrombopoietin production, and possible bone marrow suppression. The research also underscores the significance of closely monitoring and addressing thrombocytopenia in CLD patients, especially those with hepatitis C virus (HCV), in order to reduce the risk of bleeding-related complications and improve treatment effectiveness.

This study provides important information about the frequency and features of thrombocytopenia in patients with hepatitis B and hepatitis C, highlighting the importance of developing specific clinical approaches to effectively manage this common and complex complication in chronic liver disease.

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