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Mini Review

The Mechanisms behind Thrombocytopenia in Patients with Portal Hypertension and Chronic Liver Disease

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Abstract

Persistent liver injury halts the regenerative capacity of hepatocytes and activates mechanisms that result in the replacement of normal hepatic parenchyma with extracellular matrix deposits. As liver fibrosis develops, the liver undergoes architectural changes and alterations in microcirculation that lead to increased intrahepatic vascular resistance and portal hypertension. Thrombocytopenia is a prevalent condition in patients with chronic liver disease and portal hypertension. Multiple mechanisms related to increased platelet destruction or decreased platelet production contribute to thrombocytopenia. Increased platelet destruction occurs due to splenic sequestration caused by hypersplenism or immune-mediated conditions. Decreased platelet production results from a decline in thrombopoietin production, bone marrow suppression by medications, or toxic insults. Therapies aimed at improving thrombocytopenia are controversial, and individual factors must be considered. Although hepatic venous pressure gradient measurement is the gold standard for diagnosing portal hypertension, non-invasive tests show adequate correlation with hepatic venous pressure gradients. Various clinical risk scores consider platelet counts as independent predictors of adverse liver outcomes, such as the development of esophageal varices and the presence of advanced fibrosis. Nonselective beta-blockers are the cornerstone of long-term management for clinically significant portal hypertension. Indications for transjugular intrahepatic portosystemic shunt placement include failure to control portal hypertension-related bleeding, early rebleeding, and refractory or recurrent ascites. Ultimately, liver transplantation is the only definitive cure for portal hypertension and its major complications, including thrombocytopenia. Understanding the mechanisms underlying thrombocytopenia in patients with portal hypertension and chronic liver disease is essential for accurate diagnosis and effective patient management. This review aimed to evidence on the pathophysiological mechanisms linking chronic liver disease, portal hypertension, and thrombocytopenia, and to discuss their diagnostic and therapeutic implications.

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Introduction

Global estimates report that liver disease accounts for over two million deaths annually, while cirrhosis is the 15th leading cause of disability-adjusted life years.[1] Median survival time is more than 12 years in patients with compensated cirrhosis, dropping to two years in those with decompensated cirrhosis.[2] Regardless of etiology, the increased hepatic resistance to portal blood flow in a cirrhotic liver results in portal hypertension, the primary driver and predictor of decompensation in patients with cirrhosis.[3,4] Thrombocytopenia, defined as ≤150,000 platelets per microliter of blood,[5] is a common hematological disturbance associated with disease progression and prognosis in this population.[6]

Non-cirrhotic portal hypertension arises from vascular disorders caused by a primary disease that induces inflammation and obstruction of the portal vein and/or its smaller branches.[7] In this review, we focus on cirrhotic portal hypertension and its relationship with thrombocytopenia. Understanding the close interaction between thrombocytopenia and portal hypertension is essential for accurate diagnosis and effective patient management.

Portal hypertension in cirrhosis

The liver is a highly resilient organ with a distinctive capacity to regenerate after injury.[8] In contrast to other tissues

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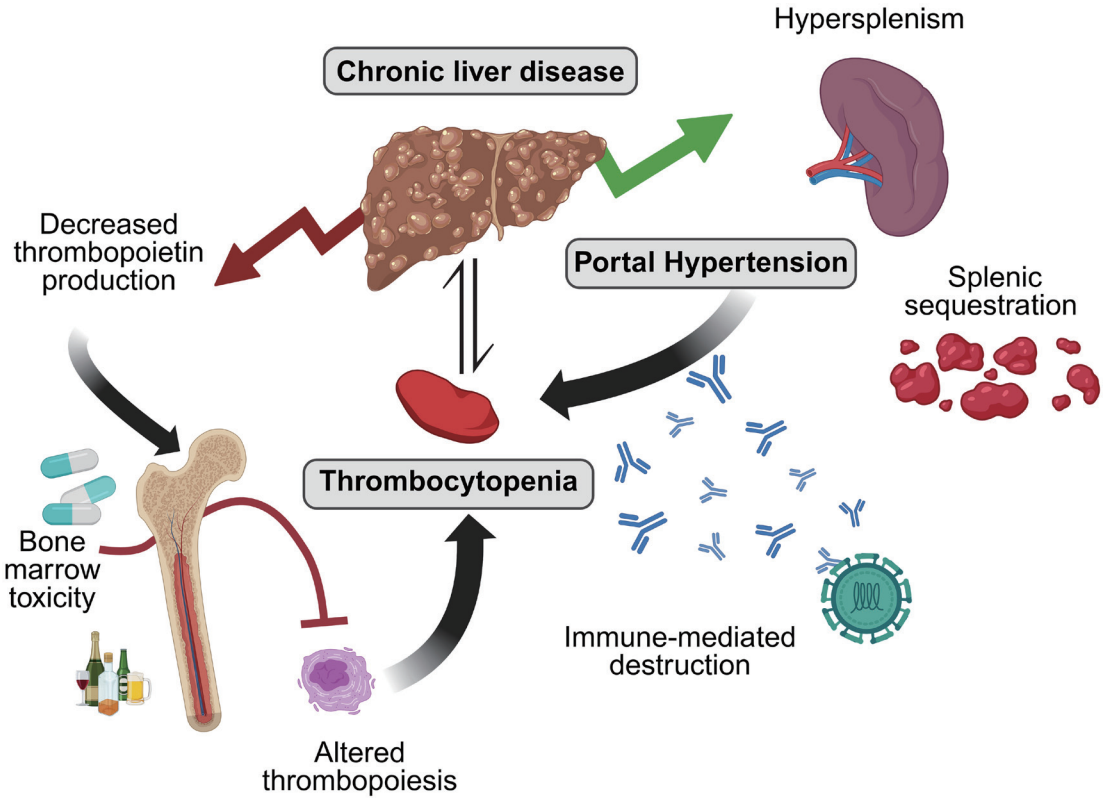

Fig. 1. Pathophysiological mechanisms of thrombocytopenia in patients with portal hypertension and chronic liver disease. Thrombocytopenia in the context of chronic liver disease and portal hypertension is a multifactorial condition. Decreased hepatic production of thrombopoietin results in impaired platelet generation. Bone marrow suppression, whether due to alcohol, medications, or systemic inflammation, contributes to reduced thrombopoiesis. Portal hypertension leads to hypersplenism and splenic sequestration of platelets, further decreasing circulating platelet levels. Furthermore, the potential involvement of immune-mediated platelet destruction should be considered. These interconnected mechanisms underscore the complex etiology of thrombocytopenia in chronic liver disease and its association with portal hypertension. Created with BioRender.

with high cell turnover (e.g., the epidermis, intestinal villi, or blood), where regeneration relies on stem cells, liver regeneration after injury is primarily driven by self-replication of mature hepatocytes and transdifferentiation of cholangiocytes.[9] Unfortunately, in disease states where liver injury causes substantial hepatocyte loss, this regenerative capacity is impaired.[8]

After persistent liver injury, hepatic stellate cells, located in the subendothelial space of Disse, are activated in response to fibrogenic and proliferative cytokines released from damaged hepatocytes.[10] Activation of hepatic stellate cells stimulates their transdifferentiation into myofibroblasts through interactions among multiple cell types and mediators.[11] Newly formed myofibroblasts replace parenchymal cells with the extracellular matrix composed of type I and type III collagen, driving the liver into fibrosis and eventually cirrhosis.[11,12] As fibrosis progresses, the liver undergoes architectural changes and alterations in microcirculation that lead to increased intrahepatic vascular resistance and portal hypertension.[13]

Thrombocytopenia in chronic liver disease

One of the characteristic signs of portal hypertension is thrombocytopenia. In patients with chronic liver disease, its prevalence ranges from 64% to 77%.[14,15] Fortunately, most cases involve mild thrombocytopenia (100,000–150,000 platelets per microliter of blood) and are not generally associated with an increased risk of spontaneous or periprocedural bleeding.[16] A multicenter, international, retrospective study of 1,079 cirrhotic patients with variceal bleeding found that thrombocytopenia was not a predictor of short-term failure of endoscopic therapy.[17] Nevertheless, platelet counts are included in various clinical risk scores and are considered independent predictors of adverse liver outcomes, such as the development of esophageal varices and the presence of advanced fibrosis.[18–20] The etiology of thrombocytopenia is multifactorial and involves mechanisms related to increased platelet destruction or decreased platelet production. Controversy regarding the need for transfusion or treatment persists, and individual factors must be considered (Fig. 1).[21]

Mechanisms associated with increased platelet destruction

In cirrhotic portal hypertension, increased splanchnic circulation induces a hyperdynamic state in the spleen, leading to vascular congestion, splenomegaly, and hypersplenism.[22] Hypersplenism is a clinical syndrome caused by overactivity of the spleen, resulting in splenic sequestration and variable reductions in different cell lines, including platelets.[23,24]

Immune-mediated thrombocytopenia can also play an important role, particularly in autoimmune states and hepatitis C virus infection.[23,25] The prevalence of thrombocytopenia in patients with chronic hepatitis C ranges from 9% to 45%.[26] Antiplatelet antibodies are present in these patients,

and their levels inversely correlate with platelet counts.[27] Immune-mediated thrombocytopenia can also occur in patients with autoimmune liver diseases, such as autoimmune hepatitis and primary biliary cirrhosis.[28,29] Reports indicate that thrombocytopenia occurs in up to 40% of patients with primary biliary cholangitis.[30]

Mechanisms associated with decreased platelet production

The main driver of platelet production and peripheral release is thrombopoietin (TPO), a hormone primarily produced by hepatocytes.[31] When TPO binds to its receptor on platelets, it is internalized and destroyed as part of a negative feedback mechanism. TPO levels rise in response to platelet depletion and degrade rapidly with higher platelet counts.[30] However, in chronic liver disease, low platelet counts do not result in increased TPO levels due to reduced hepatic production.[25] Circulating TPO levels in cirrhotic patients with thrombocytopenia are lower than in cirrhotic patients with normal platelet counts.[32,33]

Altered thrombopoiesis can also result from direct bone marrow suppression or toxicity caused by external insults.[30] Unlike newer agents, interferon-based therapies, once considered the standard treatment for viral hepatitis, have a myelosuppressive effect consistently associated with thrombocytopenia in patients with chronic liver disease.[34] Persistent alcohol ingestion, one of the major causes of chronic liver disease, can cause direct toxicity to developing megakaryocytes through unknown mechanisms and is also associated with abnormal platelet size and function.[35]

Other mechanisms associated with thrombocytopenia

In patients with cirrhosis, increased portal pressure leads to splenomegaly, and platelets are redistributed from the circulating pool to the splenic pool, where they become sequestered.[30,36] There is an inverse relationship between spleen size and platelet count.[30] Since the sequestered platelets can still clear TPO from the circulation, they further contribute to the development of thrombocytopenia by reducing TPO levels.[30]

Recent studies have shown that platelets can degrade damaged organelles through autophagy, a mechanism necessary to maintain intracellular homeostasis and preserve platelet function.[37] In cirrhotic patients with thrombocytopenia, platelet autophagy marker levels are significantly reduced, while platelet aggregation increases, leading to enhanced platelet destruction through accelerated apoptosis.[37,38]

Measurement of portal hypertension

Direct portal vein pressure measurement is rarely used in clinical practice due to the complex and invasive technique required to access the portal vein. Therefore, the gold standard for determining portal hypertension is the hepatic venous pressure gradient, a surrogate for portal vein pressure. This procedure requires hepatic venous catheterization and the calculation of the difference between wedged and free hepatic vein pressures. Although it is generally well tolerated, with few major complications (such as local injury, hematoma, hemorrhage, and arteriovenous fistula formation), it is not routinely available due to its invasiveness.[39] A hepatic venous pressure gradient of ≥5 mmHg defines portal hypertension, and a value of ≥10 mmHg defines clinically significant portal hypertension.[40]

Noninvasive tests mitigate the risks associated with hepatic venous pressure gradient measurement. Transient elastography, an ultrasound-based technique that detects liver stiffness, shows adequate correlation with hepatic venous pressure gradient.[41] A transducer probe, placed in an intercostal space at the mid-axillary line, detects shear wave velocity caused by vibrations and determines liver stiffness in kilopascals (kPa).[42] A liver stiffness measurement by elastography of ≤15 kPa combined with platelets ≥ 150 × 10^9/L rules out clinically significant portal hypertension with a negative predictive value >90%.[40] Although it shows reliable interobserver agreement between novice and expert operators,[43] it is not without limitations. Any factor that exerts pressure within or around the liver parenchyma can affect shear wave propagation and confound elastography readings.[44] A body mass index ≥ 28 is associated with unreliable measurements, a limitation that may be mitigated by using an XL probe.[45] Recent meal intake can overestimate liver stiffness, so a fasting state of at least 3 h is recommended.[46] Other potential limitations include ascites, transaminase flares in viral hepatitis, cholestasis, hepatic infiltration, and congestive heart failure. Alanine aminotransferase values greater than 100 U/L increase the probability of overestimating liver stiffness by two or more fibrosis grades.[47] Due to these potential variations, the American Gastroenterological Association established cutoffs for cirrhosis in different liver disease etiologies, including hepatitis C virus infection (≥12.5 kPa), hepatitis B virus infection (≥11 kPa), and alcoholic liver disease (≥12.5 kPa).[48] Recently, spleen stiffness measurement by transient elastography has also shown adequate performance. A spleen stiffness measurement > 50 kPa has a positive predictive value of 98% and a specificity of 98.8% for clinically significant portal hypertension.[49]

Another potential noninvasive test involves the Von Willebrand factor, a protein released by endothelial cells in response to injury. Increased levels of this protein are present in patients with chronic liver disease and correlate with the degree of portal hypertension.[50] Several diagnostic models for clinically significant portal hypertension that incorporate biochemical and imaging parameters have also shown promise as indirect markers of advanced fibrosis and portal hypertension.[51]

Portal hypertension management

Nonselective beta-blockers, the cornerstone of long-term management for clinically significant portal hypertension, decrease cardiac output and induce vasoconstriction of splanchnic vessels by inhibiting β_1 and β_2 receptors, respectively.[52] A hepatic venous pressure gradient reduction of at least 10% from baseline or to <12 mmHg is associated with a significant decrease in variceal bleeding risk.[40] Carvedilol is the preferred nonselective beta-blocker, as it has intrinsic anti-alpha-1 receptor activity and causes a greater reduction in portal pressure than traditional beta-blockers.[52] Additionally, treatment with carvedilol improves decompensation-free survival in patients with clinically significant portal hypertension.[53,54] However, carvedilol must be used with caution due to its potent systemic effects. Approximately 15% of patients discontinue the drug because of intolerable side effects, so dose titration should be guided by patient tolerance. Current evidence does not support therapy with nonselective beta-blockers prior to the development of clinically significant portal hypertension.[40]

Statins, known for their lipid-lowering effects through inhibition of HMG-CoA reductase, also exhibit multiple antiproliferative, antiangiogenic, proapoptotic, and immunomodulato-

ry properties.[55] Their hepatoprotective effects are associated with reduced inflammation, oxidative stress, endothelial dysfunction, and vasoconstriction.[55] Simvastatin, in particular, has shown a significant reduction in portal pressure versus placebo in several randomized controlled trials and is a promising agent for long-term management of portal hypertension.[56]

A transjugular intrahepatic portosystemic shunt (TIPS) involves placement of a stent between the portal and hepatic veins, bypassing hepatic circulation and reducing portal hypertension.[57] A portal venous pressure gradient reduction to <12 mmHg within 24 h of placement is considered an optimal target.[58] Indications for TIPS include failure to control portal hypertension-related bleeding, early rebleeding, and refractory or recurrent ascites.[59] An individual patient data meta-analysis reported a two-year cumulative incidence of further decompensation (new or worsening ascites, variceal bleeding, hepatic encephalopathy, jaundice, hepatorenal syndrome–acute kidney injury, and spontaneous bacterial peritonitis) of 0.48 in patients with TIPS versus 0.63 in the standard-of-care group. Two-year cumulative survival probability with TIPS was also superior (0.71 vs. 0.63).[60] In patients awaiting liver transplantation, TIPS decreased mortality risk compared with those without TIPS.[61] Contraindications to TIPS include sepsis, severe cardiac dysfunction, untreated severe valvular heart disease, pulmonary arterial hypertension, unrelieved biliary obstruction, anatomic barriers to shunt creation, and recurrent or refractory hepatic encephalopathy.[62]

Ultimately, liver transplantation is the only definitive cure for portal hypertension and its major complications, including thrombocytopenia.[63] Although some patients may experience transient post-transplant thrombocytopenia, with a nadir around day 5, platelet counts usually increase gradually in the following weeks. This phenomenon results from immunosuppressive medications, splenic and liver graft sequestration, delayed TPO response, and hemodilution.[64] Several studies suggest that severe postoperative thrombocytopenia predicts complications such as the need for invasive procedures, organ failure, and early allograft dysfunction, although robust evidence is lacking.[65,66] Platelet transfusion is controversial and should be reserved for cases where the theoretical benefits outweigh transfusion-related risks.[67,68] Early identification of potential transplant candidates is crucial to prevent disease progression and improve survival outcomes.[69]

Management of thrombocytopenia

In general, the treatment of thrombocytopenia should be individualized, carefully considering the severity of thrombocytopenia, the bleeding risk associated with the surgery or procedure, and whether it is an emergency or elective procedure. According to current studies, procedures with a mild bleeding risk include abdominal paracentesis, thoracic paracentesis, central venous catheterization, and endoscopic examination. Procedures with a high bleeding risk include endoscopic variceal ligation, liver biopsy, biliary drainage, hepatectomy, and abdominal surgery.[70,71] Mild thrombocytopenia with low-risk procedures usually does not require additional intervention.[70] For patients with severe thrombocytopenia or those undergoing elective high-bleeding-risk surgeries, TPO receptor agonists should be considered.[72,73] For patients requiring emergency surgery or procedures, platelet transfusion therapy should be administered.[72,73] These treatment protocols should be verified by large-scale, high-quality clinical studies.

The use of direct-acting antiviral agents to achieve sustained virologic response is the first-line treatment for hepatitis C virus–associated thrombocytopenia.[74] Consistent with previous reports, Kholy *et al*. reported that although there was an initial decrease in platelet counts at four weeks after starting treatment, therapy with sofosbuvir and daclatasvir normalized platelet counts in 32% of patients, while 69% achieved values above 100,000 platelets per microliter of blood at 24 weeks.[75] For patients with alcoholic liver disease without significant liver fibrosis, platelet counts can return to normal after abstaining from alcohol.[30]

TPO stimulants, which act as TPO receptor agonists, were initially developed for patients with immune thrombocytopenia but are now approved for use in thrombocytopenia related to chronic liver disease. Eltrombopag has demonstrated adequate efficacy and safety in phase III trials in patients with hepatitis C-associated thrombocytopenia and in those with advanced liver disease undergoing invasive procedures.[34] Avatrombopag and lusutrombopag are also approved for managing perioperative thrombocytopenia in patients with chronic liver disease. The ADAPT-1 and ADAPT-2 studies reported Avatrombopag's superiority over placebo in reducing the need for rescue procedures or platelet transfusions and in increasing the proportion of patients achieving platelet counts $\geq 50\times10^9$/L on the day of the procedure.[76]

Splenectomy is a therapeutic option for hypersplenism in cirrhosis, as it helps correct cytopenias, but it carries considerable risks.[77,78] A recent meta-analysis of 23 studies concluded that partial splenic embolization may be an alternative to splenectomy due to its less invasive nature and fewer complications, with similar efficacy in hematological parameters.[79] However, these approaches are not considered first-line therapies since they are associated with significant periprocedural complications and have not shown benefit in relevant clinical outcomes.[78,80] As discussed further below, hypersplenism is not the sole cause of thrombocytopenia but rather one component in a complex array of contributing factors.

Increasing evidence highlights portal hypertension–related thrombocytopenia in children. Pediatric portal hypertension often includes cases of non-cirrhotic portal hypertension, with portal vein obstruction and congenital diseases being common etiologies, such as biliary atresia, history of umbilical vein catheterization, Alagille syndrome, and α-1 antitrypsin deficiency.[81] Studies have shown that children with portal hypertension have high success rates and mid-term stent patency after TIPS treatment; splenomegaly improves after TIPS, but hypersplenism does not.[82] An Expert Pediatric Opinion proposed that children with extrahepatic portal hypertension accompanied by thrombocytopenia (Platelets <50,000) have a strong indication for meso-Rex bypass.[83] The mechanisms of thrombocytopenia caused by portal hypertension in children require further exploration and research.

Conclusions

Thrombocytopenia in chronic liver disease arises from a variety of factors related to liver disease etiology, progression, and treatment. It is common in patients with cirrhosis and is a distinctive sign of portal hypertension. The appropriate management of thrombocytopenia and portal hypertension is an area of ongoing research with major implications for patient care.

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Conflict of interest

XQ has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023, NMS has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication.

Author contributions

Concept and design (NMS, VMFG), drafting of the manuscript (VMFG, MMRM, GPR, RW), critical revision of the manuscript for important intellectual content (NMS, XQ), and supervision (NMS). All authors have made significant contributions to this study and have approved the final manuscript.

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