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LETTER TO THE EDITOR

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REVIEW

Hematological abnormalities in liver cirrhosis

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Abstract

Hematological abnormalities are common in cirrhosis and are associated with various pathophysiological mechanisms. Studies have documented a prevalence of thrombocytopenia, leukopenia, and anemia in patients with compensated cirrhosis of 77.9%, 23.5%, and 21.1%, respectively. These abnormalities carry significant clinical implications, including considerations for invasive procedures, infection risk, bleeding risk, and prognosis. Previously, cirrhosis was believed to predispose patients to bleeding due to alterations observed in classical coagulation tests such as prothrombin time, partial thromboplastin time, international normalized ratio, and thrombocytopenia. However, this understanding has evolved, and cirrhosis patients are now also acknowledged as being at a high risk for thrombotic events. Hemostasis in cirrhosis patients presents a complex phenotype, with procoagulant and anticoagulant abnormalities offsetting each other. This multifactorial phenomenon is inadequately reflected by routine laboratory tests. Thrombotic complications are more prevalent in decompensated cirrhosis and may correlate with disease severity. Bleeding is primarily associated with portal hypertension, endothelial dysfunction, mechanical vessel injury, disseminated intravascular coagulation, endotoxemia, and renal injury. This review comprehensively outlines hematologic index abnormalities, mechanisms of hemostasis, coagulation, and fibrinolysis abnormalities, limitations of laboratory testing, and clinical manifestations of bleeding and thrombosis in patients with liver cirrhosis.

Key Words: Cirrhosis; Anemia; Leukopenia; Thrombocytopenia; Coagulopathy; Bleeding; Thrombosis

Core Tip: Cirrhosis, characterized by progressive liver damage due to chronic injury, frequently induces changes in blood cell counts, functions, and coagulation abnormalities. Recognizing and understanding these alterations is pivotal as they often reflect the severity of liver disease. This knowledge enables healthcare providers to anticipate potential complications, initiate timely interventions, and tailor treatment strategies for patients with cirrhosis. This review aims to summarize available data on the prevalence of these abnormalities, delve into their pathophysiology, and elucidate their implications for patient management.

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INTRODUCTION

Cirrhosis is the leading cause of liver-related mortality and ranks among the top ten leading causes of death[1]. Globally, it contributes to over 1.32 million deaths, comprising 2.4% of total mortality[2]. Patients living with cirrhosis develop complications stemming from two different mechanisms: Hepatocyte insufficiency (liver failure) and portal hypertension. These arise predominantly from progressive liver fibrosis, characterized by distorted hepatic architecture, and the loss of normal hepatocytes due to sustained inflammation. Understanding these mechanisms is crucial when addressing hematological abnormalities in patients with cirrhosis.

The hemostatic profile of individuals with cirrhosis typically manifests as thrombocytopenia, reduced levels of coagulation factors and inhibitors, diminished levels of fibrinolytic proteins, and elevated levels of coagulation factor VIII and von Willebrand factor (VWF). Hemostasis in cirrhosis adopts a complex phenotype, where procoagulant and anticoagulant dyscrasias counterbalance each other, resulting in a state of equilibrium[3].

This intricate interplay in cirrhosis is inadequately captured by routine laboratory tests utilized to evaluate coagulopathy. Consequently, emerging techniques such as viscoelastic testing show promise in comprehensively assessing the entire clot-forming process in individuals with liver cirrhosis. Importantly, hemostasis in these patients is precarious and susceptible to disruption by common insults. Hence, seemingly paradoxical occurrences, such as bleeding and thrombosis, can manifest in cirrhosis. In this review, we discuss abnormalities in hematologic indices, mechanisms of hemostasis, coagulation, and fibrinolysis, limitations of laboratory testing, as well as clinical manifestations of bleeding and thrombosis in patients with liver cirrhosis.

Epidemiology of hematological abnormalities in cirrhosis

Hematologic indices are frequently abnormal in patients with cirrhosis. Several studies have reported a prevalence of anemia, thrombocytopenia, and leukopenia between 6%-77%, although the assessment of the true occurrence of abnormal hematologic indices in cirrhosis is limited by the cross-sectional design of these studies[4-10]. A prospective cohort that included 213 patients with compensated cirrhosis followed for 9 years reported a baseline prevalence of thrombocytopenia, leukopenia, and anemia of 77.9%, 23.5%, and 21.1%, respectively[11]. Thrombocytopenia was the most common and earliest hematologic index abnormality to develop, followed by leukopenia and anemia. The occurrence of abnormal hematologic indices in patients with cirrhosis may have significant clinical implications, such as considerations regarding invasive procedures, risk of infections, and risk of bleeding. Therefore, knowing the frequency of these abnormalities helps the clinician to be prepared with the knowledge when facing this type of patients.

Pathophysiology of hematological abnormalities in cirrhosis

The pathophysiological basis of these abnormalities is multifactorial[12], and includes portal hypertension-induced splenic and splanchnic sequestration, alteration in bone marrow stimulating factors [hematopoietic stimulating factor, thrombopoietin (TPO), erythropoietin, granulocyte-colony stimulating factor and granulocyte macrophage-colony stimulating factor], bone marrow suppression mediated by alcohol, hepatitis B and C, alterations in hemostasis (elevated VWF), coagulopathy (increased factor VIII, low levels of all other procoagulation and anticoagulation factors), hyperfibrinolysis (increased tissue plasminogen activator and plasminogen activator inhibitor type 1, low levels of all other profibrinolytic and antifibrinolytic proteins) and increased blood loss[3,11,13-15]. Some of the previously described factors are simultaneously present in patients, contributing to specific hematological abnormalities. Therefore, understanding these factors can assist clinicians in identifying potential modifiable causes, ultimately improving patient outcomes.

Abnormalities in complete blood count in cirrhosis: These abnormalities are influenced by factors associated with the etiology of chronic liver damage (such as alcohol and viral hepatitis), the impact of liver failure (resulting in poor protein synthesis) and portal hypertension, as shown in Figure 1[16]. In addition to these factors, it is worth bearing in mind the

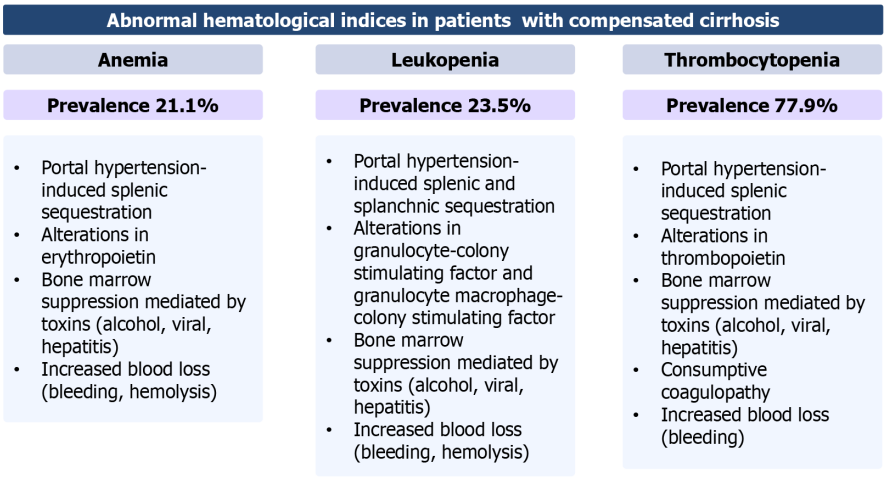

Figure 1 Liver-related causes of abnormal hematological parameters in patients with cirrhosis.

role of extrahepatic factors, leading to hematological abnormalities in cirrhosis, such as hepatitis B or C, autoimmune hepatitis, drugs and nutritional deficiencies (iron, vitamin B12 and folate)[17]. Furthermore, beyond complete blood count, the peripheral blood smear is a cornerstone in evaluating certain hematologic disorders. Its importance is particularly evident in clinical settings where extrahepatic factors are involved and timely diagnosis is crucial for early medical decisions.

Erythrocytes: The main cause of anemia in liver cirrhosis is acute or chronic bleeding in the context of portal hypertension [18]. The prevalence of iron deficiency in these patients approaches 50% compared to 24.3% in the general population[19, 20]. Causes of iron deficiency include bleeding[19], as well as deficiencies in vitamin B12 and folic acid, with some studies indicating a higher prevalence of folate deficiency than vitamin B12 deficiency[21] in patients with cirrhosis.

Macrocytosis (elevated mean corpuscular volume > 100 fL) is present in almost 50% of patients with liver disease, often associated with deficiencies in vitamin B12 and folate, thyroid diseases (more frequent in patients with autoimmune hepatitis-related cirrhosis) and liver disease itself. This abnormality is typically accompanied by a high red cell distribution width[22]. The main alteration in mean corpuscular hemoglobin is hypochromia (< 80 pg), typically linked to iron deficiency[19]. In addition to macrocytosis, another common finding in the peripheral blood smear of patients with cirrhosis is the presence of spur cells (acanthocytes). Proposed mechanisms for these abnormalities include hypersplenism and alterations in lipoprotein metabolism[23], with the reported prevalence of spur cells ranging from 5% to 19% in some series[24].

Leucocytes: Leukopenia is a frequent finding in patients with advanced liver disease. Additionally, up to 26% of patients with cirrhosis exhibit dysplastic changes in leukocytes during bone marrow examination without fulfilling the definition of myelodysplastic neoplasm[25]. These abnormalities have been linked to the proinflammatory state caused by liver cirrhosis and its complications.

Platelets: Thrombocytopenia, defined as a platelet count < 150000/μL, is the most common hematologic abnormality to develop (seen in as high as 64%-80%), and it typically occurs earliest, followed sequentially by leukopenia and anemia. While most patients exhibit mild thrombocytopenia, moderate thrombocytopenia occurs in 13%, and severe thrombocytopenia requiring platelet transfusions in 1%-2% of patients[10,11,26-28]. Thrombocytopenia combined with leukopenia (prevalence 15.5%) is the most common abnormality, followed by thrombocytopenia and anemia (prevalence 9.4%), and anemia with leukopenia (0.5%). Pancytopenia is reported in only 6.6% of these cases. Interestingly, individuals who develop thrombocytopenia and leukopenia have an increased risk of hepatic decompensation, hepatocellular carcinoma, mortality, or requiring transplant, even when controlling for other factors such as Child-Pugh score, hepatic vein pressure gradient, or alcohol use[11].

Prothrombin time/international normalized ratio: Prothrombin time (PT) evaluates the extrinsic and common pathways of coagulation, including the activity of tissue factor, factors II, V, VII, X, and even fibrinogen[29]. International normalized ratio (INR) is calculated as a ratio between the patient's PT to the mean normal PT adjusted with a correction factor called the international sensitivity index[30]. The increase in PT and INR reflects worse liver function in cirrhosis, nevertheless, common tests such as PT/INR oversimplify the adaptations in the balance between procoagulant and anticoagulant factors in liver cirrhosis[31], it is more appropriate to use viscoelastic assays in specific clinical settings, where a more precise estimation of the coagulation status is required (for example, acute bleeding needing a high volume of blood products).

PT and INR are frequently used in patients with cirrhosis as indicators of liver dysfunction severity and are included in severity scores such as Child-Pugh, model for end-stage liver disease, and chronic liver failure. Although these routine laboratory tests have limited value in predicting bleeding or guiding clinical decisions related to the management of bleeding or thrombotic events, they are useful for reflecting the overall severity of liver disease. However, extrahepatic

factors that can modify these results should be considered, including the use of vitamin K antagonists, disseminated intravascular coagulation, prolonged cholestasis and vitamin K deficiency. In these clinical contexts, alterations in PT/INR may falsely suggest more severe liver dysfunction than is present.

Viscoelastic hemostatic assays: Viscoelastic hemostatic assays (VHAs) are tests enabling a rapid and comprehensive assessment of coagulation, from clot formation to clot lysis in whole blood[32]. Currently, the most widely used VHAs include thromboelastography (TEG) and rotational thromboelastometry (ROTEM)[33], which use a variety of activators to examine different aspects of the hemostatic system such as clot formation with activation of the intrinsic and extrinsic pathways, contribution of fibrinogen, fibrinolysis and anticoagulant presence[34].

From a practical standpoint, VHAs allow the detection of specific hemostatic defects, potentially guiding tailored transfusion strategies in certain clinical scenarios such as patients undergoing invasive procedures, experiencing active bleeding and liver transplant surgery[32,35]. While both TEG and ROTEM traces look identical, their values are not interchangeable, necessitating separate interpretation of each test[36]. The main parameters reported in TEG and ROTEM, along with their equivalence, are detailed in Figure 2 and Table 1.

While VHAs have utility across various clinical scenarios in patients with end-stage liver disease, their primary application lies in liver transplant surgery[37]. In this regard, a small randomized trial reported lower rates of fresh frozen plasma (FFP) transfusion in the TEG group compared to the control group (12.8 U *vs* 21.5 U, respectively, $P < 0.05$)[38]. Another randomized trial demonstrated a decrease in median intraoperative transfusion requirements in the thromboelastometry group compared to the control group (3 U *vs* 7 U, $P = 0.005$), with FFP and tranexamic acid being administered less frequently in the thromboelastometry group (15% *vs* 46.3% for FFP, $P = 0.002$; 27.5% *vs* 58.5% for tranexamic acid). Conversely, more fibrinogen was infused in the thromboelastometry group (72.5% *vs* 29.3%, $P < 0.001$)[39].

In patients with acute-on-chronic liver failure (ACLF), a syndrome associated with a high risk of short-term mortality in those with decompensated cirrhosis[39], hematologic failure has traditionally been defined solely by INR. However, this approach might oversimplify the complexity of coagulation in end-stage liver disease[40]. Therefore, several studies suggest that VHAs could provide more accurate guidance for the use of blood products in this population[41].

A study comparing TEG parameters with conventional coagulation parameters, including PT, INR, and platelet count, revealed several key findings. Notably, platelet count exhibited a strong correlation with maximum amplitude ($r = 0.712$) and coagulation index ($r = 0.613$), whereas PT and INR showed weak correlations with these parameters. Consequently, the authors concluded that while TEG might not correlate with the severity of liver disease, VHAs could provide better characterization of the type of coagulopathy in this patient population[40]. The main limitation related to VHAs as point-of-care tests is their poor standardization since apart from manufacturers' reported reference ranges, there is no published consensus for normal ranges; thus, hospitals should determine their local reference ranges[34]. However, a significant advantage of VHAs is their application in guiding transfusion therapy in procedural settings. A 2015 Italian retrospective study demonstrated that the use of a VHA reduced platelet infusions by 64%, rendering this intervention cost-effective[41].

Guidelines recommendations and statements of VHAs in liver disease include the International Society on Thrombosis and Hemostasis which states that ROTEM/TEG may be an attractive means to reassure the proceduralist that hemostasis is "normal" as these assays are frequently normal despite prolonged coagulation times[17]. The British Society of Hematology recommends the use of a VHA in bleeding patients to guide fibrinogen replacement[34] and the Society of Critical Care Medicine suggest using viscoelastic testing (TEG/ROTEM) over measuring INR, platelets, and fibrinogen in critically ill patients with acute liver failure or ACLF[42].

DISORDERS OF HEMOSTASIS

Hemostasis is the process that maintains the integrity of a closed circulatory system by sealing breaches in vessel walls after vascular damage occurs[43]. Previously, liver cirrhosis was assumed to predispose individuals to bleeding due to abnormalities observed in traditional coagulation tests such as PT, partial thromboplastin time, and INR. However, this paradigm has gradually become obsolete with the recognition of a relative balance between the procoagulant and anticoagulant pathways in cirrhosis[14]. Moreover, accumulating evidence suggests that patients with cirrhosis are not inherently anticoagulated by the disease itself but, rather surprisingly, are at a higher risk of thrombotic events[44,45].

Primary hemostasis involves platelet and vessel wall interactions, during which platelets adhere to the subendothelium at the site of vessel injury, aggregate with one another, and form a platelet plug[28]. Platelets have two main functions: Adhering to damaged vessel walls by interacting with VWF in the endothelium and supporting thrombin generation on their surface. Primary hemostasis alterations involve thrombocytopenia, impaired platelet function, increased production of nitric oxide, and prostacyclin. However, compensatory effects also occur, including elevated levels of VWF[13] and low levels of the enzyme ADAMTS13[14,46]. Notably, ADAMTS13 concentrations have been observed to decrease with increasing severity of liver disease as assessed by the Child-Pugh score[46].

The pathogenesis of thrombocytopenia involves different mechanisms such as spleen sequestration (hypersplenism), increased turnover[47,48], decreased production due to the diminished TPO[49], bone marrow suppression[28], and increased destruction within the reticuloendothelial system. In addition, circulating antibodies against platelets may play a role, predominantly in chronic hepatitis C virus, although their isolated presence does not appear sufficient to induce thrombocytopenia, and their exact role remains uncertain[50,51]. Other potential mechanisms include alcohol-induced bone marrow suppression, deficiencies in vitamin B12 and folate, and adverse reactions to medications such as acetaminophen, amiodarone, heparin, phenytoin, trimethoprim-sulfamethoxazole, valproic acid and vancomycin[52].

Table 1 Comparison between the definitions of the values reported in thromboelastography and rotational thromboelastometry[34,120]

Section	Parameter	Definition and function
Clot initiation	ROTEM: CT TEG: RT	Measures from test start until fibrin begins to be formed (clot reaches a 2 mm diameter) and reflects time to fibrin formation. Low clotting factors and/or low fibrinogen level, vitamin K antagonists, heparin and DOAC use prolong this measurement. Recommended therapy: Fresh frozen plasma/prothrombin complex concentrate may be considered
Clot kinetics or fibrin polymerization	ROTEM: CFT TEG: KT Both: A angle	Reflects the speed at which fibrin is formed and how well it binds to platelets. It is the time it takes until the clot reaches 20 mm (arbitrary size). α angle is defined as the slope between section 1 and 2 and is a measure of the rapidity of fibrin polymerization. This parameter is dependent on sufficient fibrinogen, fibrin cross-linking and platelet number and function
Clot strength or stiffness	ROTEM: MCF TEG: MA	It is the maximum clot diameter in millimeters and is a combined assessment of fibrinogen and platelet interactions. To differentiate their effects, the standard trace should be compared with the fibrinogen trace. For the clinician, this is the most useful parameter since it represents both primary and secondary hemostasis. Recommended therapy: Platelets (if normal fibrinogen assay), cryoprecipitate or fibrinogen concentrate (if low fibrinogen assay)
Clot breakdown or fibrinolysis	ROTEM: CL-30 TEG: LY30	As platelet retraction is a normal phenomenon, some clot strength diminution is expected. It is usually presented as a percentage reduction in the clot strength measure compared to maximal measurement at a given time (30 minutes after CT). Recommended therapy: Consider anti-fibrinolytic agent or reperfusion (if liver transplantation surgery)

CT: Clotting time; RT: Reaction time; ROTEM: Rotational thromboelastometry; CFT: Clot formation time; TEG: Thromboelastography; KT: Kinetics time; MCF: Maximum clot formation; MA: Maximum amplitude; CL-30: Clot lysis at 30 minutes; LY30: Lysis at 30 minutes; PCC: Prothrombin complex concentrate; DOAC: Direct oral anticoagulant.

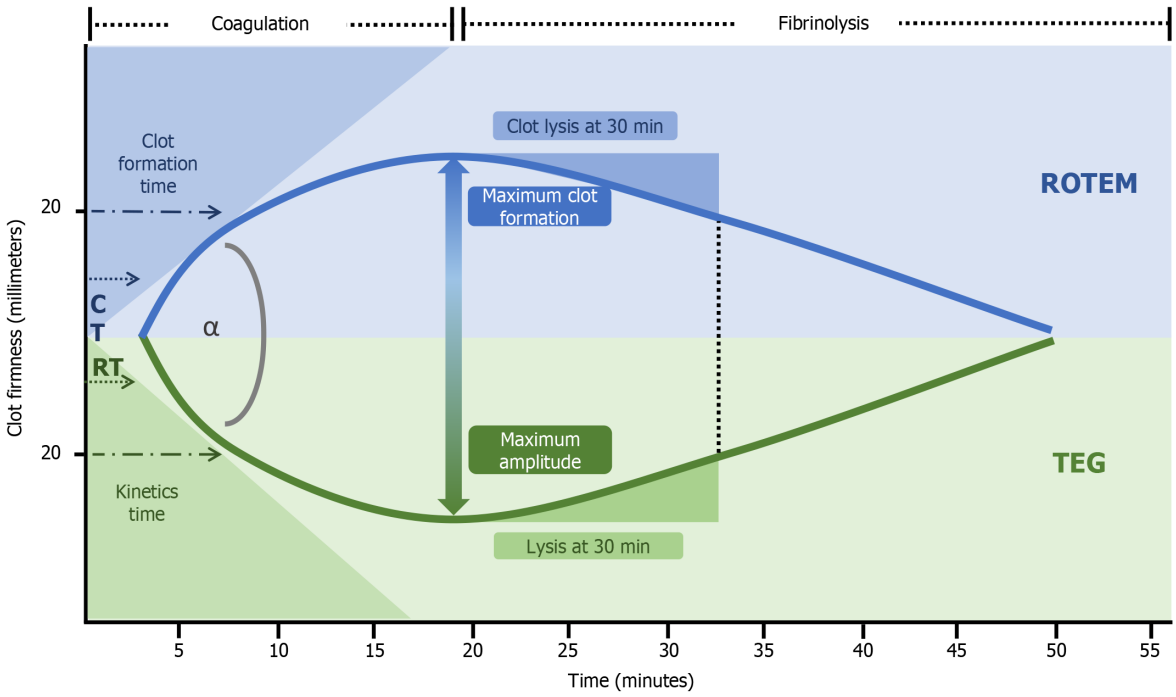

Figure 2 Clot formation and lysis sections in rotational thromboelastometry and thromboelastography tracings. Detailed explanation is in Table 1. CT: Clotting time; RT: Reaction time; ROTEM: Rotational thromboelastometry; TEG: Thromboelastography.

TPO, primarily produced by the liver, serves as the primary regulator for platelet production from megakaryocytes in the bone marrow[28]. Its levels are inversely proportional to platelet count as it is predominantly cleared by platelets. However, it has been observed that patients with cirrhosis often exhibit inadequate TPO levels despite low platelet counts [48,53]. Proposed mechanisms for this discrepancy include decreased liver production, impaired TPO regulation, and increased degradation by pooled platelets in the spleen[52,54].

In addition to lower platelet counts, it remains uncertain whether patients with cirrhosis experience thrombocytopathy, manifested as impaired platelet aggregation. Some studies have demonstrated defective function[55,56], while recent data suggest that platelet function is not impaired under flow conditions and when platelet count and hematocrit are normalized[57,58]. However, patients with decompensated cirrhosis and acute kidney injury (AKI) do exhibit altered platelet function compared to those without AKI[58]. Furthermore, it is proposed that platelet location is crucial, as those in the

portal circulation demonstrate higher activation compared to those in the peripheral blood, likely due to bacterial translocation and oxidative stress[59].

VWF, a multimeric protein produced in the endothelium that acts as an anchor for platelet adhesion at the site of vessel injury, is increased in liver cirrhosis, presumably due to endothelial damage, reduced liver and peripheral clearance. It has been considered to function as a compensatory mechanism[13]. ADAMTS13, produced mainly by hepatic stellate and endothelial cells, cleaves VWF in its antithrombotic role. In liver cirrhosis, ADAMTS13 activity is lowered leading to increased von Willebrand activity as a compensatory effect to thrombocytopenia. However, it is not well established whether these alterations are primary or secondary[52]. Secondary hemostasis comprises thrombin generation to form a clot consisting of fibrin and platelets. Apart from factor VIII (produced by the endothelium) and VWF, hepatocytes produce most procoagulant and anticoagulant mediators[60].

Due to synthetic liver dysfunction, both anticoagulant and procoagulant factors decrease as the disease progresses, leading to a rebalancing of blood coagulation mechanisms between prohemostatic and antihemostatic factors[3,60]. Prohemostatic abnormalities include increased levels of factors VIIa and IXa (due to elevated circulating tissue factor microparticles), high factor VIII, low levels of antithrombin, protein C, protein S, α2-macrogobulin and heparin cofactor II. Antihemostatic factors include decreased levels of fibrinogen, factors II, V, VII, IX, X, and XI, as well as vitamin K deficiency, hypofibrinogenemia, and dysfibrinogenemia[52,61-63]. Additionally, other elements may play a role, such as increased phosphatidylserine in the membranes of erythrocytes, leukocytes, and platelets, cell-free DNA and neutrophil extracellular traps. These elements can accelerate the coagulation cascade, activate the contact phase of coagulation, and increase thrombin generation[64-66]. However, their specific role in cirrhosis is yet to be determined.

Fibrinolysis is the process by which the fibrin produced in the coagulation cascade is degraded[14]. Its pivotal step involves the conversion of plasminogen to plasmin, a proteolytic enzyme responsible for this degradation. Tissue-plasminogen activator mediates the activation of plasmin when bound to fibrin, but its activity is rapidly countered by inhibitors such as plasminogen activator inhibitor 1, α2-antiplasmin and thrombin-activatable fibrinolysis inhibitor, all produced by the liver[67]. In liver cirrhosis, reduced levels of plasminogen and its activity likely stem from decreased synthesis and increased consumption due to coagulation activation[15]. In addition, levels and activity of tissue-plasminogen activator are increased, plasminogen activator inhibitor 1 activity is relatively diminished compared to tissue-plasminogen activator, and both thrombin-activatable fibrinolysis inhibitor and α2-antiplasmin are decreased. These alterations explain both the hyperactive and hypoactive fibrinolytic state reported in patients with chronic liver disease [68]. Consequently, although contradictory findings have been noted, the fibrinolytic imbalance appears to lean toward hyperfibrinolysis[15].

Despite this newly established equilibrium, it is evident that it is less stable compared to that in healthy individuals, due to noticeable hypo- and hypercoagulable features that can dynamically predominate over time[69]. Standard tests, such as the INR, primarily reflect variations in procoagulant factors and overlook the concurrent decline of anticoagulant factors[70]. A major limitation of these tests is the absence of thrombomodulin, crucial in *in vivo* coagulation, rendering them inadequate for assessing hemorrhage risk in patients.

Evidence of both procoagulant and anticoagulant alterations lies in thrombin generation tests in cirrhotic patients, which are sensitive to both types of mediators and yield thrombin levels similar to those in healthy patients. These tests incorporate soluble forms of thrombomodulin, the principal activator of protein C, thereby maintaining the balance between factors[71,72]. In addition, when thrombomodulin is added to the plasma of patients with cirrhosis, the thrombin generation ratio exceeds that of healthy controls, indicating partial resistance to thrombomodulin-mediated anticoagulation[14,62,72]. This contrasts with the previously held notion of an auto-anticoagulated state in chronic liver disease patients. This resistance may be attributed to elevated concentrations of factor VIII, a potent thrombin generator [73], and decreased levels of protein C, a potent thrombin generator inhibitor[74].

The concentration of factor VIII increases, likely due to reduced elimination caused by high von Willebrand concentrations, which protect factor VIII from degradation. This reduction in elimination is compounded by low expression of low-density lipoprotein receptor-related protein, a multifunctional endocytic receptor inadequately expressed in cirrhotic patients. This receptor collaborates in the cellular uptake and degradation of factor VIII, resulting in decreased clearance [75]. Moreover, this imbalance correlates proportionally with the severity of cirrhosis, as assessed by the Child-Pugh score [61,62]. Despite decreased fibrinogen concentrations, studies have demonstrated that fibrin clot quality remains unimpaired[76,77].

Many studies have highlighted the limited relevance of routine standard coagulation tests, particularly the INR, in accurately predicting bleeding risks after invasive procedures such as percutaneous[78,79], transjugular[80,81] and laparoscopic liver biopsy[82,83], therapeutic paracentesis[84], colonoscopy with polypectomy[85], percutaneous endoscopic gastrostomy[86], bronchoscopy, kidney biopsy, central venous catheter placement, and arteriography[81], as well as coronary artery catheterization[87].

The European Association for the Study of Liver (EASL) advises against using traditional hemostasis tests to predict procedural bleeding risk before low-risk procedures. They suggest their use solely to assess disease severity and establish an initial benchmark for management in the event of post-procedural bleeding. However, they caution against relying on these tests to predict post-procedural bleeding in high-risk patients, although they may provide a baseline status and aid physicians in managing bleeding events[88]. In contrast, the American Association for the Study of Liver Disease (AASLD) states that there is no data-driven specific INR or platelet cutoff indicating reliably increased procedural bleeding risk. They recommend against using the INR to gauge procedural bleeding risk in cirrhosis patients not taking vitamin K antagonists[89].

Despite this, certain circumstances have been associated with increased bleeding tendencies. AKI, a common complication in decompensated cirrhosis[90], has been linked to increased bleeding tendencies, particularly after invasive procedures[91]. Platelet function is altered in this context, yet coagulation tests show increased thrombin generation,

indicating hypercoagulability[58]. Moreover, both hypofibrinolytic and hyperfibrinolytic changes have been observed to coexist[92], with the former primarily associated with diminished factor XIII concentration and fibrinolysis activation. Importantly, these abnormalities tend to improve upon resolution of AKI[58,93].

Furthermore, patients with cirrhosis and severe infection or sepsis exhibit dynamic coagulation profiles, leading to alterations that may result in hypocoagulable, hypercoagulable, or mixed phenotypes[94]. ACLF, characterized by systemic inflammation and organ system failure, is associated with significant systemic inflammation and an increased risk of death[95]. Such patients are more likely to exhibit hypocoagulable characteristics on TEG than those with acute decompensation, although no difference in bleeding events has been observed[96]. However, evidence also suggests that this "new" equilibrium is maintained in critically ill patients with ACLF[92]. The hemostatic balance in patients with cirrhosis is depicted in Figure 3.

THROMBOSIS

The complex interplay of factors discussed previously contributes to a prothrombotic state in patients with cirrhosis. Venous thromboembolism (VTE), encompassing deep venous thrombosis (DVT) and pulmonary embolism (PE), stands as a common cause of mortality and morbidity. In the general population, the incidence rate ranges from 1 to 2 per 1000 person-years[97]. A Nationwide United States study compared the prevalence of VTE among patients with and without cirrhosis, assessing its impact on in-hospital mortality and length of stay. This study revealed that patients with cirrhosis under the age of 45 years were at higher risk for VTE compared to those without liver disease, warranting consideration for VTE prophylaxis. VTE was equally associated with increased mortality among patients with compensated cirrhosis [odds ratio (OR) = 2.16; 95% confidence interval (CI): 1.96-2.38] or decompensated cirrhosis (OR = 1.66, 95%CI: 1.47-1.87). Moreover, VTE was linked to prolonged hospitalization[98].

Additionally, a large population-based case-control study, including 99444 patients with VTE and a control group, demonstrated a substantially increased risk of VTE among patients with liver disease, approximately twice that of non-liver disease patients. Among cirrhosis cases, the adjusted relative risk was 2.02 (95%CI: 1.78-2.31) for DVT and 1.41 (95%CI: 1.20-1.65) for PE ($P < 0.0001$)[99] (Figure 4). Other retrospective studies have shown that patients with liver disease develop DVT and/or PE with an incidence ranging from 0.5% to 8.2%[100]. Portal vein thrombosis (PVT) is also a fairly common complication of liver cirrhosis; occlusive PVT can be associated with poor prognosis, especially in patients with a prior history of bleeding[101].

Thrombotic complications are more prevalent in decompensated cirrhosis and may correlate with disease severity. Patients with compensated cirrhosis have an estimated incidence of PVT of 1%, while those being evaluated for liver transplantation have an incidence ranging from approximately 8% to 25%[100]. Additionally, in post-transplant patients, PVT has been linked to a 30% increase in mortality[97]. In a prospective study conducted in France and Belgium, 1243 adults with cirrhosis without PVT were enrolled. A five-year cumulative incidence of PVT of 10.7% was observed, but the development of PVT was not associated with subsequent disease progression[102]. Furthermore, in a recent meta-analysis encompassing 74 studies, approximately one-seventh of cirrhotic patients were found to have PVT, with one-tenth developing it. The progression of liver cirrhosis and portal hypertension appears to parallel the risk of PVT. Based on cross-sectional data, factors such as Child-Pugh class B/C, higher D-dimer levels, ascites, and the use of non-selective beta-blockers were associated with the presence of PVT in liver cirrhosis[103].

Numerous investigators have explored additional risk factors linked to peripheral and portal thrombosis, identifying age, gender, comorbidities, nutritional status, and the presence of indwelling central lines as potential contributors[100]. One consistent finding across studies has been the association with low albumin levels. A retrospective case-control study conducted in the United States revealed a five-fold increase in the risk of VTE when albumin levels were below 1.9 mg/dL compared to patients with normal albumin levels[104].

MANAGEMENT OF THROMBOSIS

Failure to detect and treat thrombosis can result in mesenteric ischemia, chronic cavernous transformation, and complications of portal hypertension. In patients with cirrhosis, the development of PVT often progresses insidiously and may remain undetected until incidentally discovered[105]. The AASLD recommends that in patients with cirrhosis, it is mandatory to initially rule out malignant venous obstruction attributable to hepatocellular carcinoma with appropriate contrast-enhanced imaging studies[89].

There are no specific guidelines for the treatment of DVT or PE in patients with liver disease, so the safety of anticoagulation in these patients is extrapolated from the treatment of patients with PVT. Early anticoagulation for PVT represents a therapeutic consideration, supported by retrospective studies that found excellent recanalization rates in patients maintained on anticoagulation[100]. However, the possibility of spontaneous resolution of partial PVT raises questions about the necessity of anticoagulation for its treatment. Additionally, a relatively low recanalization rate of complete PVT after anticoagulation therapy suggests its limited usefulness in patients with complete PVT[101]. Due to the lack of well-designed prospective trials, the AASLD does not provide a recommendation for or against anticoagulation in patients with PVT and cirrhosis, emphasizing the need for individualized treatment decisions[89,100,106]. Moreover, there is insufficient data to support pretransplant treatment of PVT to improve post-transplant outcomes[89].

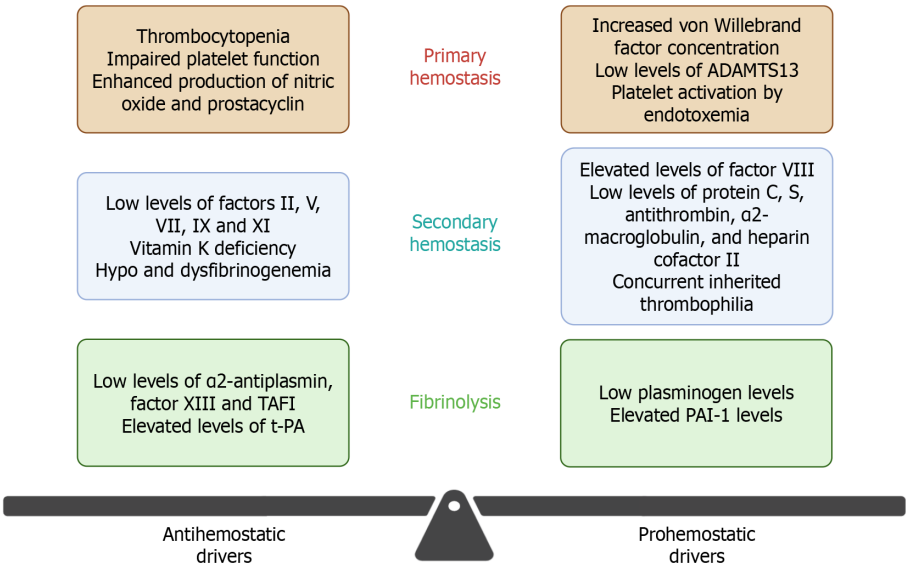

Figure 3 Hemostatic balance in patients with chronic liver disease. Created with BioRender.com. TAFI: Thrombin-activatable fibrinolysis inhibitor; tPA: Tissue-plasminogen activator; PAI: Plasminogen activator inhibitor.

In a study of 55 patients receiving both low-molecular-weight heparin and vitamin K antagonists for PVT, there were 5 clinical bleeding events related to anticoagulation during 19 months of follow-up. An assessment of increased bleeding risk revealed a statistically significant association with platelet counts below 50 and a non-statistically significant association with the use of vitamin K antagonists[107]. Regarding PVT, previous meta-analyses have demonstrated the safety and efficacy of anticoagulation in recanalization in patients with cirrhosis. However, given the uncertainty regarding the role of anticoagulation in improving survival by recanalization of PVT in patients with cirrhosis, a recent meta-analysis (The IMPORTAL study) compared anticoagulation *vs* no treatment in patients with cirrhosis and PVT. Five studies were included, and the results indicated that anticoagulation reduced all-cause mortality in patients with cirrhosis and PVT (hazard ratio = 0.59; 95%CI: 0.49-0.70), independently of thrombosis severity and recanalization, but at the expense of increasing non-portal hypertension-related bleeding, with a significantly higher bleeding rate in the anticoagulation group[108].

Regarding VTE prophylaxis, a systematic review was conducted to analyze bleeding and VTE events in cirrhosis patients and controls receiving VTE prophylaxis. Ten studies were included, revealing bleeding and VTE events in 8.2% and 2.8% of cases, respectively. Surprisingly, the administration of VTE prophylaxis did not appear to reduce the incidence of VTE events. Consequently, the current evidence is deemed insufficient to either recommend or discourage the use of VTE prophylaxis, primarily due to the lack of quality and consistency in available data[109]. In this complex scenario, to date, there remains no clear consensus regarding the primary prevention of thrombosis in cirrhosis[60].

BLEEDING

Bleeding emerges as a multifaceted complication arising from diminished synthesis of clotting factors, platelet dysfunction, and compromised vascular integrity. Thrombocytopenia, a common manifestation, further heightens the risk of bleeding. The convergence of hematology and hepatology is extensive due to the liver's central role in synthesizing pro- and anti-coagulation factors and clearing byproducts of hemostasis and coagulation[110]. Although thrombotic risk may be more severe, numerous hematologic aberrations in cirrhosis contribute to bleeding complications, making them prevalent[60]. In this context, variceal bleeding is the most common and concerning type of bleed, occurring in 25% to 35% of patients with cirrhosis. Nonvariceal bleeding is almost equally prevalent, noted in 20% of patients admitted with decompensated cirrhosis[100]. Other common presentations include bruising, purpura, epistaxis, menorrhagia, and procedural bleeding[60].

Variceal hemorrhage is associated with higher morbidity and mortality than other causes of gastrointestinal bleeding, as well as increased hospital costs[111]. However, variceal bleeding is primarily driven by portal pressure and is not attributable to failure of the hemostatic system[69]. The AASLD has defined 3 causes of bleeding in patients with cirrhosis [89]. First, portal hypertension-related bleeding complications, such as variceal bleeding, which appear to be unrelated to hemostatic failure, as mentioned above. Second, provoked bleeds may occur during procedures due to vessel mechanical injury. Third, spontaneous or unprovoked bleeds that may be related to hemostatic failure include bruising, mucosal bleeding, and oozing from puncture sites[69,89]. The presence of portal hypertension, infection, or renal dysfunction correlates with bleeding events in patients with cirrhosis[100]. The use of medication also plays a significant role. In a recent study, anti-platelet use was associated with increased bleeding and decompensation events among privately insured cirrhosis patients. Non-steroidal anti-inflammatory drugs use was associated with significant early bleeding but not with decompensations. Anticoagulants were not associated with bleeding or decompensation outcomes[112].

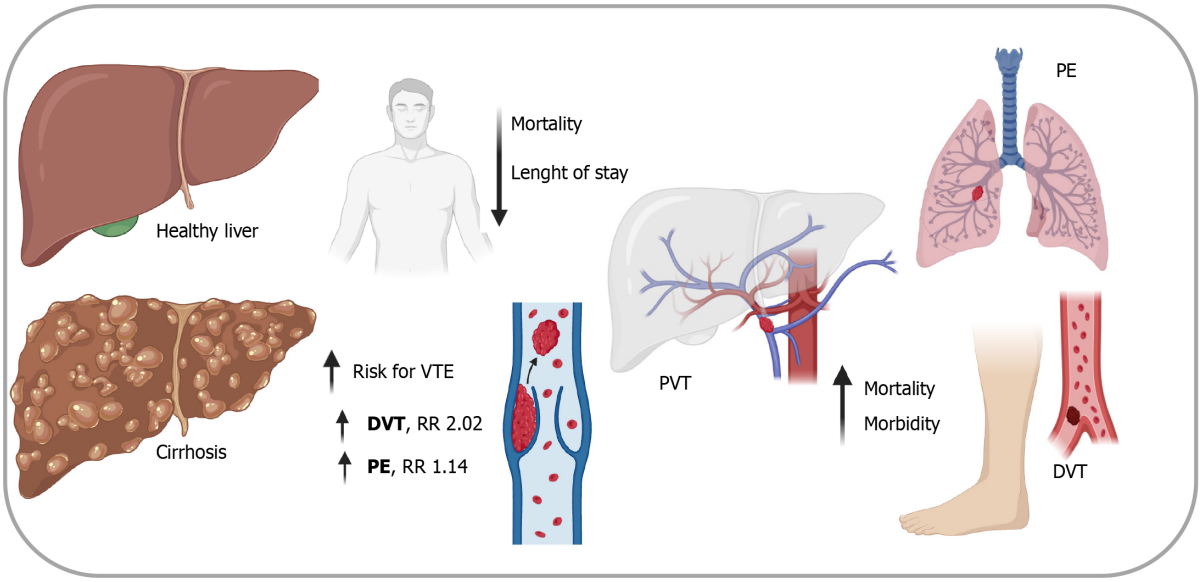

Figure 4 Relative risk of venous thromboembolism in patients with cirrhosis *vs* healthy individuals. Created with BioRender.com. VTE: Venous thromboembolism; PE: Pulmonary embolism; PVT: Portal vein thrombosis; DVT: Deep venous thrombosis; RR: Relative risk.

Procedural bleeding

Multiple factors such as patient-specific bleeding diatheses and the type of anesthesia, may contribute to the overall estimation of bleeding risk in procedural settings[113]. Current EASL and AASLD guidelines emphasize the importance that FFP, prothrombin complex concentrates, and fibrinogen sources should not be used to reduce periprocedural bleeding risk[88,89]. EASL also recommends a case-by-case consideration of platelet transfusion/TPO receptor agonist therapy for patients undergoing high-risk procedures with a platelet count of $< 50 \times 10^3/\mu L$[88,114]. However, this requires time and planning, therefore, these interventions only apply to elective procedures. The risk lies predominantly on inherent procedural risk for which little preemptive action can be taken, mainly in the emergency setting[114]. Many non-surgical invasive procedures, including liver biopsy, paracentesis, thoracentesis, transesophageal echocardiography, central vein catheter insertion, endoscopic esophageal varices ligation, and transarterial chemoembolization, are safe and not associated with increased bleeding risk in cirrhosis[60].

Bleeding rates for paracentesis (0%-3.3%) and thoracentesis (2%) in cirrhosis patients are low and do not require routine preprocedural coagulation assessment, in decompensated cirrhosis or even in ACLF[115]. Common coagulation tests (PT/INR, partial thromboplastin time, platelet count, and fibrinogen) are often inaccurate predictors of bleeding risk as they do not reflect more clinically relevant hemodynamic risk factors[60]. In terms of hemoglobin, packed red blood cell transfusion before high-risk procedures or major surgery is recommended to maintain hematocrit > 25% in cirrhosis, as this is thought to improve platelet margination[116]. If packed red blood cell transfusion is required in the setting of active bleeding, a restrictive transfusion threshold of hemoglobin of 7 g/dL is known to significantly improve outcomes of upper gastrointestinal bleeding, particularly in patients with cirrhosis[117]. We must also take into consideration that blood product transfusions deliver substantial volumes of oncotically active fluid, which can exacerbate portal hypertension through circulatory overload as well as increase the risk of infection and transfusion reactions[60].

As for platelets, in the event of an upcoming high-risk procedure or surgery, targeting a platelet count of 50000-60000 either *via* TPO administration or platelet transfusion is suggested[60,116]. In the specific setting of liver biopsy, due to the conflicting data in the literature, current AASLD guideline recommendations do not specify a particular INR or platelet cutoff at which the risk of bleeding is substantially increased but suggest individualized approaches and assessment of other risk factors that may increase bleeding risk[89].

Esophageal variceal bleeding is a severe complication of portal hypertension in cirrhosis patients, with a high bleeding-related mortality rate of up to 20%. Treatment of patients with gastroesophageal varices includes prevention of the initial bleeding episode (primary prophylaxis), either with non-selective beta-blockers or/and endoscopic band ligation (EBL), the control of active hemorrhage, and the prevention of recurrent bleeding after a first episode (secondary prophylaxis) [111,118]. Bleeding from banding ulcers represents the main severe complication of EBL, occurring in 2.3% to 10% of patients. A retrospective multicenter study analyzing data from 1178 prophylactic EBL procedures across two large Vietnamese centers demonstrated that EBL is safe, with procedure-related bleeding rates being rare (2.6%), even in patients with thrombocytopenia $< 50 \times 10^3/\mu L$ or high INR ≥ 1.5. Only high model for end-stage liver disease scores, particularly high bilirubin levels, seemed to be associated with an increased risk of EBL-related bleeding[118]. However, further analysis of these data is needed, along with the development of prospective studies. Table 2 outlines the key interventions for managing bleeding in cirrhosis and includes the evidence supporting each treatment.

Specific interventions in ACLF

Despite intensive care, critically ill patients with cirrhosis are at a high risk of mortality within 1-3 months[115]. In the

Table 2 Summary of blood products and/or drugs recommendations in bleeding in cirrhosis

Choice of agent	Recommendations			Guidelines/evidence
Platelet transfusion	**Prophylaxis**	**Common gastrointestinal procedures1**	AGA suggests against the routine use of blood products for bleeding prophylaxis	AGA[116,121]
		High risk procedures	Decisions about prophylactic blood transfusions should include discussions about potential benefits and risks in consultation with a hematologist. Threshold: > 50 × 10^9/L	
	Acute bleeding	Platelet transfusions should not be administered based on platelet count targets because there is no evidence of benefit of such transfusions in AVH		AASLD[122]
		In patients with cirrhosis and active bleeding (out of the setting of AVH), thrombocytopenia (if platelet count < 50 × 10^9/L)		Clinical Gastroenterology and Hepatology[123], 2023
TPO-RA	**Prophylaxis**	**Common gastrointestinal procedures1**	AGA suggests against the routine use of TPO-RAs for bleeding prophylaxis	AGA[121]
		High risk procedures	Patients who place a high value on the uncertain reduction of procedural bleeding events and a low value on the increased risk for PVT can reasonably select a TPO-RA	
	Acute bleeding	Not appropriate for acute setting		Clinical Gastroenterology and Hepatology[123], 2023
FFP	**Prophylaxis**	**Common gastrointestinal procedures1**	AGA suggests against the routine use of blood products for bleeding prophylaxis	AGA[121]
		High risk procedures	Decisions about prophylactic blood transfusions should include discussions about potential benefits and risks in consultation with a hematologist	
	Acute bleeding	Fresh frozen plasma should not be administered based on INR because there is no evidence of benefit of such transfusions in AVH		AASLD[122]
		Restricted to hemorrhagic shock to compensate blood loss		Clinical Gastroenterology and Hepatology[123], 2023
Fibrinogen	**Prophylaxis**	No routine preprocedure correction		AASLD[89]
	Acute bleeding	The following transfusion thresholds for management of active bleeding or high-risk procedures may optimize clot formation in advanced liver disease: Fibrinogen > 120 mg/dL		AGA[116]
rFVIIa	Not recommended for bleeding episodes in patients with Child-Pugh A cirrhosis. Efficacy of rFVIIa was considered uncertain in bleeding episodes in patients with Child-Pugh B and C cirrhosis			European Consensus Critical Care[124], 2006
PCC	The role of PCC is not yet defined. Limited data based on retrospective studies			AGA[116]
Desmopressin	The agent lacks a sound evidence-based foundation but may be useful in patients with concomitant renal failure			AGA[116]
Antifibrinolytic agents	Anti-fibrinolytic therapy may be considered in patients with persistent bleeding from mucosal oozing or puncture wound bleeding consistent with impaired clot integrity			AGA[125]
	RCT shows tranexamic acid reduces failure to control bleeding and rebleeding in advanced cirrhosis with UGIB. However, further studies and robust evidence are needed to make a definitive recommendation			Hepatology[125], 2024

[1]Paracentesis, thoracentesis, variceal banding.

FFP: Fresh frozen plasma; TPO-RA: Thrombopoietin receptor agonists; INR: International normalized ratio; AVH: Acute variceal hemorrhage; PCC: Prothrombin complex concentrates; rFVIIa: Recombinant activated factor VII; RCT: Randomized controlled trial; UGIB: Upper gastrointestinal bleeding; AGA: American Gastroenterological Association; AASLD: American Association for the Study of Liver Disease; PVT: Portal vein thrombosis.

CANONIC study, kidneys were the most commonly affected organs (55.8%), followed by the liver (43.6%), coagulation (27.7%), the brain (24.1%), circulation (16.8%), and the lungs (9.2%)[119]. ACLF is characterized by systemic inflammation, and the acute phase reaction induced by this process alters blood concentrations of many of the components of hemostasis, including fibrinogen, platelets, and endothelial factors[114]. INR is dependent on procoagulant factors I, II, V, VII, and X and does not account for the rebalanced coagulation in patients with ACLF and decompensated cirrhosis due to anticoagulant deficiencies. In contrast, a VHA provides a functional evaluation of altered pro- and anti-coagulant pathways, measuring platelet function, hyperfibrinolysis, and premature clot dissolution in real-time. However, optimal

cutoffs to guide platelet, cryoprecipitate, or four-factor prothrombin complex concentrate in ACLF have not been studied [115].

Navigating a delicate equilibrium involves addressing bleeding risks with cautious use of blood products and considering prophylaxis against thrombosis. Striking this balance is pivotal in optimizing outcomes for cirrhotic patients. Deeper comprehension of ACLF physiopathology is also necessary in the near future. Advances in understanding these complexities are crucial for refining therapeutic strategies in cirrhotic patients with hematologic challenges. Further research is crucial to refine therapeutic strategies for this intricate hematological landscape in liver cirrhosis.

CONCLUSION

Patients with cirrhosis show numerous hematological abnormalities with a multifactorial origin. Thrombocytopenia is the most frequent cytopenia, but these patients are not particularly prone to bleeding and when it occurs other critical factors such as portal hypertension, endothelial dysfunction, mechanical injury to vessels, disseminated intravascular coagulation, endotoxemia and renal injury should be considered. VTE also poses significant consequences. Finally, these disturbances become more critical with increasing cirrhosis severity, further narrowing the fragile new balance.

FOOTNOTES

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