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EDITORIAL

Spontaneous bleeding or thrombosis in cirrhosis: What should be feared the most?

Kryssia Isabel Rodríguez-Castro, Alessandro Antonello, Alberto Ferrarese

Kryssia Isabel Rodríguez-Castro, Alberto Ferrarese, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, 35128 Padua, Italy

Alessandro Antonello, Veneto Oncological Institute (IOV-IRCCS), 35128 Padua, Italy

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Correspondence to: Dr. Kryssia Isabel Rodríguez-Castro, MD, PhD, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Via Giustiniani 2, 35128 Padua, Italy. kryssiarodriguez@yahoo.com
Telephone: +39-33-36167592
Fax: +39-49-8218727

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Abstract

The more modern and accurate concept of a rebalanced hemostatic status in cirrhosis is slowly replacing the traditional belief of patients with cirrhosis being "auto-anticoagulated", prone only to bleeding complications, and protected from thrombotic events. With greater attention to clinical thrombotic events, their impact on the natural history of cirrhosis, and with the emergence and increased use of point-of-care and global assays, it is now understood that cirrhosis results in profound hemostatic alterations that can lead to thrombosis as well as to bleeding complications. Although many clinical decisions are still based on traditional coagulation parameters such as prothrombin (PT), PT, and international normalized ratio, it is increasingly recognized that these tests do not adequately predict the risk of bleeding, nor they should guide pre-emptive interventions. Moreover, altered coagulation tests should not be considered as a contraindication to the use of anticoagulation, although this therapeutic or prophylactic approach is not at present routinely undertaken. Gastroesophageal variceal bleeding continues to be one of the most feared and deadly complications of cirrhosis and portal hypertension, but great progresses have been made in prevention and treatment strategies. Other bleeding sites that are frequently part of end-stage liver disease are similar to clinical manifestations of thrombocytopenia, with gum bleeding and epistaxis being very common but fortunately only rarely a cause of life-threatening bleeding. On the contrary, manifestations of coagulation factor deficiencies like soft tissue bleeding and hemartrosis are rare in patients with cirrhosis. As far as thrombotic complications are concerned, portal vein thrombosis is the most common event in patients with cirrhosis, but venous thromboembolism is not infrequent, and results in important morbidity and mortality in patients with cirrhosis, especially those with decompensated disease. Future studies and the more widespread use of point-of-care tests in evaluating hemostasis will aid the clinician in decision making when facing the patient with bleeding or with thrombotic complications, with both ends of a continuum being potentially fatal.

Key words: Bleeding; Hemorrhage; Thromboembolism; Portal vein thrombosis; Coagulation; Cirrhosis

Core tip: The two-faced, dynamic, and fragile hemostatic and coagulation system of patients with cirrhosis is of increasing interest. Thrombotic complications, and not only the well-known bleeding complications such as gastroesophageal bleeding, are now recognized complications of cirrhosis. Whether confined to the portal vein, due to venous stasis but also to other yet poorly characterized local as well as systemic factors, or in the presence venous thromboembolism, these complications warrant prevention and treatment with anticoagulation. Future clinical studies, as well as the broader implementation of point-of-care instruments and results from studies using global coagulation assays will outline the best strategies, tailored to each patient according to the severity of liver disease and the particular hemostatic alterations present at a given timepoint.

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INTRODUCTION

The traditional concept of an "auto-anticoagulated patient" has given way to the modern, and more accurate notion of a rebalanced hemostatic status in patients with cirrhosis. It is now accepted that classic determinations of the coagulation status such as prothrombin (PT) time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT), although useful in the non-cirrhosis setting, are of much less value in patients with advanced chronic liver disease, firstly because they describe only a fraction of what is actually occurring in the hemostatic system, secondly because this system is fragile and dynamic, and thirdly because they do not predict neither thrombotic nor bleeding events.

Hand in hand with this new bulk of knowledge regarding both the pre-clinical as well as the clinical picture of hemostasis and coagulation in cirrhosis, therapeutic and preventive strategies that were routinely used in the non-cirrhotic population and rigorously avoided in the cirrhotic population, are being used with increasing frequency and confidence.

SPECIFIC ALTERATIONS OF THE HEMOSTATIC AND COAGULATION SYSTEM

Although the clinician might be misled to judging the state of a patient with cirrhosis as pro-hemorrhagic due to an alteration of traditional coagulation parameters, in cirrhosis actually both pro- as well as anti-coagulation factors are affected, the latter of which are not adequately reflected in these tests. Typical of cirrhosis are reduced levels of factors Ⅱ, Ⅸ, Ⅺ, and Ⅻ, and the magnitude of the reduction correlates with the severity of liver disease. However, levels of anticoagulant factors including protein S, protein C, and antithrombin, are also decreased in cirrhosis, and procoagulant factor Ⅷ is notably increased. Magnifying the complexity of hemostatic and coagulation abnormalities in cirrhosis, studies have demonstrated that liver damage increases plasminogen activator inhibitor (PAI-1) expression[1,2]. Increased to a greater extent than PAI-1, tissue plasminogen activator is elevated both due to reduced hepatic clearance and to enhanced release[3], which has been interpreted as a hyperfibrinolytic state in cirrhosis[4]. Moreover, levels of plasminogen and anti-plasmin antiplasmin (α 2-antiplasmin) are reduced, as well as levels of thrombin-activatable fibrinolysis inhibitor (TAFI). Whether observed alterations such as elevated fibrin degradation products[5-7], abnormalities in thromboelastography (TEG) tracings[8], and a decrease in TAFI[9] actually correspond to a state of hyperfibrinolysis which would hypothetically be frequent even in compensated cirrhosis is still controversial, however. Other studies have suggested that actually fibrinolysis is not enhanced in cirrhosis, with a balanced reduction of both pro- as well as anti-fibrinolytic agents[10], and a lack of association between TAFI reduction and actual hyperfibrinolysis[11,12]. Moreover, elevated levels of D-dimer may be a consequence of the activation of the coagulation cascade, which might accumulate in the presence of diminished hepatic clearance[13-15].

Responsible for stabilization of the fibrin clot and its resistance to lysis, factor XIII (FXIII) correlates with the liver's biosynthetic capacity, and has been shown to be diminished in nearly half of patients with advanced stages of cirrhosis (Child C); FXIII levels < 50% significantly correlated with an increased risk of severe upper gastrointestinal bleeding and mortality in a 6-year follow-up period[16]. Although this could be a reflection of the severity of liver disease, and despite reduced FXIII activity by itself is probably not sufficient to cause bleeding, the addition of this alteration upon the underlying multiple coagulation and hemostatic defects, might increase the risk of hemorrhage[16,17]. As the only method of detecting FXIII deficiency is at present measuring the factor itself, it is probably reasonable to perform this test in the event of uncontrolled bleeding in the presence of regular rotation thromboelastometry (ROTEM) patterns, and when bleeding cannot be explained by platelet count and serum fibrinogen within the normal ranges[18]. The combination of these events results in the establishment of a new - fragile and dynamic - thrombotic/hemostatic balance[10,11].

Regarding primary hemostasis, chronic liver disease is characterized by a variable degree of thrombocytopenia due to increased platelet destruction, increased splenic and/or hepatic sequestration, and to reduced levels of

thrombopoietin. Moreover, not only platelet number, but also platelet function has been shown to be compromised due to defective thromboxane A2 synthesis, storage pool deficiency and abnormalities of the platelet glycoprotein Ⅰb[19-22]. Different mechanisms compensate for reduced platelet number and function: von Willebrand factor is notably elevated in cirrhosis, probably as a result of its reduced clearance resulting from diminished levels of its cleaver ADAMTS13 and as a reflection of high levels of FⅧ, to which it is bound when circulating in plasma[23].

In addition to these acquired hemostatic and coagulation defects, superimposed (or rather, underlying) genetic thrombophilias may play an important role in tilting the balance towards thrombosis. In a study by Amitrano *et al*[24], the frequencies of factor Ⅴ Leiden and of PT A20210 polymorphism were reportedly 13% and 34.8% in cirrhotic patients with portal vein thrombosis (PVT), whereas frequencies were 7.5% and 2.5% in cirrhotic patients without PVT.

The actual hemostatic and coagulation changes in cirrhosis are not adequately reflected by traditional tests including the INR, aPTT, bleeding time, and platelet count, and are also imprecise in predicting bleeding episodes[25]. These tests are not able to detect natural anticoagulant deficiencies, nor do they reveal other pro-thrombotic alterations such as the elevation of von Willebrand factor. In addition, other aspects related to the risk of bleeding or thrombosis, such as clot formation, firmness, and degradation, are not assessed by conventional tests. Likewise, the determination of the individual factors does not provide a complete picture of hemostatic alterations occurring *in vivo*, either, since the intricate system strongly depends on the balance of pro- and anti-fibrinolytic as well as coagulation factors.

A test that is used ever less frequently, bleeding time correlates with platelet count[26], and is prolonged in nearly half of patients with cirrhosis, without, however a certain relationship with bleeding risk[27].

Whereas traditional coagulation tests measure only the initial 5% of thrombin that is generated and are insensible to detecting deficiencies in the anticoagulation mechanisms, global assays such as the thrombin generation test analyze more components of the hemostatic status and therefore offer a view that is closer to what is actually going on *in vivo*. When performed in the presence of thrombomodulin, which enables the activation of protein C, the amount of thrombin generated in plasma from patients with cirrhosis is at least equal to - even increased with respect to - that of healthy subjects[28,29]. Despite this test yields a more approximate view regarding generation as well as degradation of thrombin, this *in vitro* technique, apart from being impractical and complex, has the drawback of excluding platelets, which serve not only as a scaffold for coagulation, but play an active role in the process.

The "newcomers" in the field of bedside coagulation monitoring, which have actually been around for quite a while in other clinical scenarios, provide a more complete picture of what is going on *in vivo*. Point-of-care coagulation monitoring devices which assessing the viscoelastic properties of whole blood include TEG (Haemonetics Corporation, Braintree, MA, United States), ROTEM™ (Tem International, Munich, Germany), and theSonoclot coagulation and platelet function analyzer or Sonoclot (Sienco Inc., Arvada, CO, United States)[30]. The fact that analyses are performed in whole blood allow for platelets and red cells to be accurately reflected[31] and the interactions between plasmatic and cellular components of hemostasis to be analyzed. The rate of fibrin formation, clot strength, and clot lysis[32,33] can be determined by all three instruments. Moreover, TEG provides a more adequate characterization of hypofibrinogenemia and hyperfibrinolysis[34] than the clot lysis time and global fibrinolysis capacity[35].

At present, ROTEM™ or TEG™ are valuable tools that aid in decision making in the context of direct therapeutic interventions in the actual case of bleeding[18]. TEG is in fact currently employed to guide therapy during liver transplantation in many centers[36-38] and is gaining importance in the assessment of liver-disease associated hemostasis alterations[39,40], with a possible role in predicting variceal rebleeding[41] and guiding pre-procedural transfusions[42]. Intense correction of coagulation abnormalities should be avoided, and rather transfusions and other therapeutic interventions should be tailored to each patient's specific case, hopefully guided by point-of-care testing. This is very important in order to avoid risks associated with transfusions (acute lung injury, increase in portal pressure, *etc.*) and the increased risk of thromboembolism with, for example, the use of recombinant factor ⅦⅡa[43].

GASTROESOPHAGEAL VARICEAL BLEEDING

Gastroesophageal variceal bleeding (GEVB) constitutes a landmark in the natural history of a patient with cirrhosis, represents decompensated disease, and is one of the most feared complications. Mortality reaches 15%-20% during the 6 wk that follow an episode of variceal bleeding and is closely related to the severity of the underlying liver disease, ranging from 0% in patients in Child-Pugh class A to 40% in Child-Pugh class C patients[44,45]. Mortality significantly correlates with the presence of ascites or encephalopathy (OR = 4.18, 95%CI: 1.58-11.06; P = 0.004), the finding of fresh blood in the upper gastrointestinal tract at endoscopy (OR = 2.40, 95%CI: 1.28-4.51; P = 0.01), the presence of INR > 1.5 and/or PT prolonged > 3 s (OR = 3.06, 95%CI: 1.29-7.26; P = 0.01), in-patient status at the time of bleeding (OR = 7.14, 95%CI: 3.45-14.3; P < 0.001), and the presentation with hemodynamic shock (OR = 2.10, 95%CI: 1.07-4.13; P = 0.03), as demonstrated in a large United Kingdom study[46]. The principal determinants of GEVB are the severity of liver disease - as expressed by a Child Pugh class B

or C, the presence of portal hypertension, variceal wall tension, and the characteristics of the varix wall[47-50]. In fact, anticoagulants at a prophylactic dose do not seem to increase the risk of GEVB, even in patients with advanced stages of liver disease, while actually preventing thrombotic events and decompensation[51].

Rebleeding occurs in approximately 26% of cases and results in a dramatic increase in mortality of up to 39%. This event correlates with the presence of INR > 1.5 and/or PT prolonged > 3 s (OR = 2.23, 95%CI: 1.22-4.07; P = 0.01), as well as with the presence of high risk endoscopic stigmata (OR = 1.74, 95%CI: 1.02-2.99, P = 0.04)[46]. Moreover, an underlying bacterial infection, followed by the circulatory release of endogenous heparin-like substances with established anti-Xa activity[52] and abnormal thromboelastographic curves, appears to be an important trigger for bleeding, for the persistence of bleeding, and correlates with the impossibility of controlling bleeding[41,53-56]. Supporting this concept, a consistent reduction of both mortality and frequency of early rebleeding has been achieved with the use of antibiotics following GEVB[57].

The risk of bleeding from variceal ulcers following endoscopic band ligation seems to depend exclusively on the severity of liver disease, and not the hemostatic status, as demonstrated by thromboelastographic parameters and traditional coagulation tests[58]. As in the occurrence of a spontaneous event of GEVB, the use of anticoagulants - may it be vitamin k antagonists or heparins - does not seem to increase the risk further[59,60].

NON-VARICEAL SPONTANEOUS BLEEDING

Upper non-variceal gastrointestinal bleeding

Non-variceal upper gastrointestinal bleeding is not an infrequent cause of morbidity and mortality in patients with cirrhosis. In a recently published cross-sectional nationwide study conducted in the United States, of 96887 hospital discharges for peptic ulcer bleeding, 3574 (3.69%) occurred in patients with cirrhosis[61]. Mortality of peptic ulcer bleeding was significantly higher in patients with cirrhosis (5.5%) *vs* in the group without cirrhosis (2%, P = 0.01), and decompensated cirrhosis was associated with a significantly higher mortality than that of patients with compensated cirrhosis (6.6% *vs* 3.9%; P = 0.01). Moreover, multivariate analysis demonstrated that the presence of cirrhosis independently increased mortality (adjusted odds ratio) 3.3; 95%CI: 2.2-4.9)[61]. A prospective, 10-year study analyzing patients admitted for non-variceal upper gastrointestinal bleeding showed that of 2217 patients with upper gastrointestinal bleeding, 1077 patients had non-variceal bleeding (48.7%) patients, and amongst these, 160 (14.8%) were patients with cirrhosis[62]. Of note, within the group of cirrhosis patients with non-variceal upper gastrointestinal bleeding, rebleeding occurred in 3 patients (1.9%), and in-hospital mortality was 13.75% (22 of 160 patients). Although deaths were due to reasons other than hypovolemia in 12 patients, and other causes of death included renal, hepatic, or respiratory failure, amongst others, the initial reason for hospitalization had been the bleeding episode[62].

Portal hypertensive gastropathy, which has been described in as many as 80%-90% of patients with cirrhosis[63,64], has been shown to correlate with severity of liver disease and to hepatic venous portal gradient in patients with cirrhosis[63,65]. Bleeding from portal hypertensive gastropathy most often leads to chronic anemia, but can also cause important blood losses over a short period of time. In a multi-center Italian study published on behalf of the New Italian Endoscopic Club for the Study and Treatment of Esophageal Varices, the prevalence of portal hypertensive gastropathy was 80% and was associated to the duration of liver disease, past medical history of endoscopic variceal slerotherapy, and with the presence and size of esophagogastric varices. During the follow-up period of 18 mo (± 8 mo), acute bleeding from portal hypertensive gastropathy was observed in 2.5% of patients (8 of 315 patients), with bleeding-related mortality rate of 12.5%, and chronic bleeding in 10.8% (34 patients)[64]. Treatment and prevention consist primarily in reducing portal pressure, principally with the use of non-selective beta-blockers[66], although treatment with other vasoactive drugs such as long-acting somatostatin, TIPS placement[67], argon plasma coagulation[68], and newer therapies such as hemospray[69] are increasingly being used.

Lower gastrointestinal bleeding

According to the study design, including the population analyzed, portal hypertensive colopathy has been reported to occur in 50%-80% of patients with cirrhosis, and is apparently more frequent in patients with ascites[70-72]. In a study analyzing 60 cirrhosis patients who underwent colonoscopy before undergoing upper endoscopic variceal band ligation, hemorrhoids, anorectal varices, and portal hypertensive colopathy were found in 37%, 40%, and 57% of patients, respectively[73]. A higher prevalence (66%) of portal hypertensive colopathy was found in a Japanese study analyzing endoscopic findings in 47 patients with cirrhosis who underwent colonoscopy for positive fecal occult blood (34%), melena (23%), iron deficiency anemia (10%), diarrhea (4%), abdominal pain (4%), and screening (10%), amongst other causes[74]. Although large, prospective studies are lacking, the presence of portal hypertensive colopathy appears to correlate with severity of liver disease, and an increase in portal hypertension, as that induced by endoscopic esophageal variceal band ligation, does not seem to worsen preexisting colopathy or induce the appearance of new lesions[73]. Whether portal hypertensive colopathy is associated with the degree of portal hypertension as determined by hepatic vein pressure gradient, is yet controversial, however[74,75].

Regarding the ano-rectal tract, rectal varices

have been reported in 8% to 56% of patients with cirrhosis and portal hypertension[72,76,77]. Although hemorrhoids and polyps do not seem to occur more frequently in cirrhotics with respect to non-cirrhotic subjects undergoing colonoscopic evaluation[76], others hypothesize that the degree of portal hypertension and/or disease severity seems to be associated with hemorrhoids but not with rectal varices[78,79]. However, the improvement of bleeding rectal varices seems to point out a role for portal hypertension[80]. Moreover, although hematochezia has been reported[79], and a few cases of massive, fatal bleeding[81], life-endangering hemorrhage from the lower gastrointestinal tract due to complications of cirrhosis is relatively infrequent. Large, prospective studies are warranted in order to accurately determine the incidence and prevalence of these clinical entities, as well as their associated morbidity. Although studies which evaluate the best treatment options are lacking, reduction of portal hypertension with the use of non-selective beta-blockers and the employment of vasoactive agents such as somatostatin, octreotide and terlipressin, have demonstrated some benefit[82,83]. More recently, the use of argon plasma coagulation and hemospray have also been advocated[69,84].

Other bleeding sites

Minor but frequent bleeding in patients with cirrhosis seems to be more akin to that observed in patients with platelet defects than that observed in patients with hemophilia or other disorders that affect coagulation. Thus, aside from variceal bleeding, in which local factors, portal pressure and severity of liver disease play preponderant roles, manifestations of primary hemostasis defects are most frequently encountered in patients with cirrhosis: recurrent and prolonged epistaxis, gingivorrhagia, purpuric skin lesions, menometrorrhagia, and excessive bleeding after dental extractions or other surgical procedures. On the contrary, coagulation-related clinical manifestations such as intracerebral bleeding, deep muscle bleeding, and hemartrosis, are no more frequent in cirrhosis that they are in the general population. Although only very rarely epistaxis[85] and oral cavity bleeding[86] (gum bleeding and dental root bleeding) have been reported to be the cause of bleeding that endangers life, minor but repeated episodes are commonly encountered in cirrhosis.

PVT

PVT is the most common thrombotic event in patients with cirrhosis, and although its frequency is higher in patients with hepatic malignancy (approximately 35%[87], with reportedly 40% of these cases having histological confirmation of neoplastic thrombosis[88]), it is also common in patients with cirrhosis and without malignancy, with a prevalence of reportedly 0.6% to 26%. Moreover, a systematic review analyzing PVT in patients with cirrhosis who underwent liver transplantation found that of 25753 liver transplants, 2004 were performed in patients with PVT, for a prevalence of 9.7% ± 4.5%[89].

The most important risk factor for the development of PVT seems to be the severity of liver disease[90,91], with "paradoxically" a greater frequency of PVT when coagulation factors are lowest, as shown by traditional coagulation tests. Locally, venous stasis favors the development of thrombosis, and a prospective study revealed that reduced portal flow velocity was the only independent variable that correlated with the risk of developing PVT at 1 year follow-up[92], but this finding has not been univocally confirmed[93]. Elevated levels of FVIII have been correlated with PVT both in the presence and in the absence of concomitant cirrhosis[94,95], finding which was confirmed in a larger cohort study demonstrating that the odds ratio for PVT was 6.0 for patients with cirrhosis in whom FVIII levels were above 129 UI/dL[96]. Moreover, genetic thrombophilias have been found in up to 34% of patients with cirrhosis and PVT[24], which is why every patient who present this complication warrants complete thrombophilic screening.

Not only is this complication frequent, but its clinical presentation can be deadly in some cases; in a study analyzing newly diagnosed PVT in 79 patients with cirrhosis, in 39% the initial presentation was gastrointestinal bleeding (from esophagogastric varices or portal hypertensive gastropathy), and abdominal pain was the cardinal symptom in 18% of cases, amongst which 70% had intestinal infarction due to the extension of the thrombosis into the superior mesenteric vein[97]. Although recently it has been reported that PVT, when diagnosed during routine imaging screening in patients with cirrhosis, may not cause clinical deterioration and may even resolve spontaneously[98,99], a recently published systematic review revealed that the presence of non-neoplastic PVT at liver transplant entails a greater 30-d mortality after surgery when compared to patients without PVT (10.5% *vs* 7.7%, respectively (P = 0.01)[89]. Moreover, the presence of PVT at liver transplantation also increases the one-year mortality with respect to that of patients with patent portal vein (18.8% *vs* 15.3%, respectively (P < 0.001), and this is especially true for cases in which PVT is complete and extends into the superior mesenteric vein and the splenic vein.

DEEP VEIN THROMBOSIS AND VENOUS THROMBOEMBOLISM

It has been some time now since the publication of Northup and collaborators' important study demonstrating that not only "coagulopathy" does not protect cirrhosis patients from life-threatening venous thromboembolic events, but that these patients are actually at a greater risk for these events[100]. Low albumin, surrogate of a greater severity of liver disease, was associated with the greatest risk. Although large,

prospective population studies considering out-patient subjects with cirrhosis are needed, it seems that compared to the general population, the incidence of unprovoked deep vein thrombosis and pulmonary embolism (DVT/PE) is increased. In a large, prospective cohort study with case-control analysis of 6550 patients with venous thromboembolism, the presence of chronic liver disease was associated with PE (OR = 1.75, 95%CI: 0.91-3.36) and with DVT/PE combined (OR = 1.65, 95%CI: 0.97-2.82)[101]. Moreover, a large Danish population-based study showed that cirrhosis and liver disease were associated with a greater risk of venous thromboembolism (OR = 2.10) amongst 99000 patients with thromboembolism[102]. Thus, the incidence of DVT/PE in patients with cirrhosis has been reported to be between 0.5% to 8.1%[101-105].

Already deadly in the non-cirrhotic population, venous thromboembolism is associated with increased mortality in patients with compensated cirrhosis (OR = 2.16, 95%CI: 1.96-2.38) and those with decompensated cirrhosis (OR = 1.66, 95%CI: 1.47-1.87), with an in-hospital mortality for patients with venous thromboembolism of 16.8% and 18.6% for patients with compensated and decompensated cirrhosis, respectively[106]. Moreover, although the risk of venous thromboembolism is reduced with prophylactic anticoagulation, it is not annulled, as demonstrated in a recent study in which a higher than expected rate of venous thromboembolism occurred while on prophylaxis with unfractioned heparin or low molecular weight heparin[107].

Although guidelines do not yet provide recommendations regarding anticoagulation neither as prophylaxis nor as therapy, evidence has been accumulating supporting the efficacy and safety of such interventions[108]. Future studies, including the use of new anticoagulants such as direct thrombin inhibitors are warranted to establish which patients will benefit most from treatment, the time after which the risk-benefit ratio becomes inclined towards a greater risk, the most adequate dose, the choice of anticoagulant, and the means of monitoring of anticoagulation[109].

In conclusion, the pro-hemorrhagic and pro-thrombotic alterations of patients with cirrhosis correlate principally with the severity of liver disease, that determine a reduction in both pro- and anti-coagulant factors and an increased derangement of physiological blood flow causing portal hypertension and localized venous stasis. Routine laboratory tests do not reliably predict the risk of bleeding and there is yet no optimal management strategy to foretell potential bleeding complications. Although point-of-care testing is slowly being introduced to avoid intensive correction of coagulation parameters and better guide therapeutic decisions tailored to each patient's clinical and hemostatic status, more studies are clearly needed to determine the actual role of these new tools. A myriad of both thrombotic and bleeding complications can aggravate the clinical course of cirrhosis, but as for frequency and gravity, GEVB remains probably the most feared event. However, thrombotic complications should also be considered, especially in more advanced stages of disease, when anticoagulation prophylaxis and therapy might represent the less traveled, but proper, road to follow.

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