Rational hemostatic management in cirrhosis: from old paradigms to new clinical challenges

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Abstract. Introduction: Patients with cirrhosis are at risk of both thrombotic and hemorrhagic events. Traditional hemostatic tests are inadequate to assess the complex and fragile balance of hemostasis in this setting, especially in advanced stages of disease such as decompensated cirrhosis or acute on chronic liver failure (ACLF). Furthermore, the indiscriminate use of pro-hemostatic agents for prophylaxis and treatment of bleeding episodes is still debated and often contraindicated. Alongside, splanchnic, and peripheral thrombotic events are frequent in this population and require management that involves a careful balance between risks and benefits of antithrombotic therapy. **Areas covered**: This review aims to address the state of the art on the clinical management of the hemostatic balance of cirrhosis in terms of established knowledge and future challenges. **Expert opinion**: The old paradigm of cirrhosis as a naturally anticoagulated condition has been challenged by more sophisticated global tests of hemostasis. Integrating this information in the clinical decision making is still challenging for physicians and experts in hemostasis.

Key words: bleeding, thrombosis, hemostasis, cirrhosis, portal hypertension

Article highlights

- Traditional hemostatic tests are inadequate to assess hemostatic balance of patients with cirrhosis.
- Disease severity and clinical stability profoundly impact on both thrombotic and bleeding risk.
- The interest on global hemostatic tests, especially viscoelastic assays, is rising but further evidence is required to be definitely translated into clinical practice.
- Prophylactic use of hemostatic products prior to invasive procedures is often useless or even harmful.
- Anticoagulant and antiplatelet therapy should be prescribed if clinically indicated, as benefits generally outweighs risks.
- Direct oral anticoagulants (DOACs) can be used in cirrhosis, but studies in patients with advanced disease are warranted.

1. INTRODUCTION: THE NEW PARADIGMA

Hemostasis alterations in cirrhosis are considered the hallmark of severe prognosis associated with advanced liver dysfunction (cirrhosis).[1] Traditionally, thrombocytopenia, elongation of common coagulation tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) together with the relatively high mortality rate (mainly from acute variceal bleeding), have fostered the concept of cirrhosis as a condition at high hemorrhagic risk.[2] However, presently, it is widely appreciated that the most common laboratory tests are inadequate to assess the complex balance between pro- and anticoagulant factors [1,3] and variceal bleeding is mainly driven by the severity of portal hypertension rather than coagulopathy.[4] As matter of fact, thrombotic events in the splanchnic circulation are frequent and the highest prevalence is observed in candidates to liver transplantation.[5,6] In addition, non-splanchnic thrombosis ranges unexpectedly from 0.5 to 6% in patients with chronic liver disease [5,7,8] and can be influenced by the development of hepatocellular carcinoma [9] demonstrating the existence of a non-negligible thrombotic risk in this setting. The above observations underline a fragile and unstable hemostatic equilibrium due to the alteration of both pro- and anticoagulant factors, which better describes the so-called cirrhotic coagulopathy in terms of a syndrome at a (paradoxical) risk of thrombosis and hemorrhage.[3,10] Therefore, the challenge is no longer limited to cure a "natural anticoagulation", but to address the correct management of the “coagulopathy” in its various and often coexisting clinical phenotypes, in terms of prophylaxis and therapy of both bleeding and thrombosis. The purpose of this review is to discuss evidence, current knowledge, and future challenges on this topic.

2. HEMOSTATIC BALANCE IN CIRRHOSIS: LABORATORY TESTS

2.1 Platelet count: same number, different clinical scenarios

Thrombocytopenia is the hallmark of cirrhosis, it correlates with the hypersplenism due to portal hypertension, and was historically associated with the defect of primary hemostasis (i.e., platelet-vessel wall interaction).[11–13] In 2006, Lisman et al, through an in vitro flowing model, showed that increased levels of von Willebrand factor (VWF) (typical feature of cirrhosis) may compensate for thrombocytopenia by increasing platelet adhesion. It is anticipated that more specific tests are warranted to explore the complex

and multifaceted role of platelets in hemostasis such as adhesion at the site of vessel wall injury, aggregation, interaction with fibrinogen and VWF, and their contribution to the activation of coagulation factors and thrombin generation.[14–16] Moreover, endotoxemia, a condition frequently observed in decompensated cirrhosis, may activate platelets from patients with cirrhosis, [17,18] thus suggesting a potential effect of bacterial derived byproducts on hemostasis in advanced stages of the disease. As matter of fact, a recent study from Zanetto et al. demonstrated that patients with cirrhosis had a platelet aggregation higher than healthy individuals.[19] Importantly, in this study, platelet aggregation in patients with decompensated cirrhosis was even higher than patients with compensated cirrhosis and was a marker of risk of further liver-related complications and death. This observation reinforces the concept of hyperactivation of hemostasis as mediator of liver damage in cirrhosis. [20,21] Because of their crucial role in both primary and secondary hemostasis, platelets have always attracted the interest of scientists and physicians to manage the clinical risks associated with the impairment of hemostasis in cirrhosis. Unfortunately, methods and devices have been developed over the years to assess platelet function, but to date, few of them have proved reliable enough and, most importantly, none have been tested against clinical decisions of transfusion policy before an invasive procedure. Accordingly, perioperative platelets evaluation (and prophylactic correction) is still an unmet need in patients with cirrhosis awaiting surgery or invasive procedures. As a consequence, in daily practice, physicians often consider platelet count below $50x10^9$/L as an indication of platelet transfusion before any invasive procedure. This attitude is in contrast with the most recent guidelines from the European Association for the study of the Liver (EASL) which do not recommend platelet transfusion unless the procedures is considered at high risk of bleeding in which case it is recommend a case by case decision.[22] In our opinion, the divergence of physicians' from the recommendation may be in part explained by the different hemorrhagic risk observed in different stages of cirrhosis. In a prospective study of 280 patients with cirrhosis (PRO-LIVER), Basili et al showed no correlation between platelet count and unprovoked major or minor bleeding.[23] Importantly, this study included a relatively homogeneous and stable cirrhotic outpatient population [53% were Child-Pugh A and the median MELD (model of end stage liver disease) was 11±6]. In contrast, Drolz et al, in a series of 211 critically-ill patients with cirrhosis (median MELD: 26;IQR: 20-26) admitted to intensive care unit, demonstrated that platelet count below $30x10^9$/L, along with an aPTT >100s and fibrinogen <60 mg/dL, were independently associated with major bleeding (gastrointestinal and post interventions such

as catheter insertion or paracentesis).[24] Noteworthy, in this experience, the greater the changes of the above parameters, the higher the risk of major bleeding. The comparison of these two studies is paradigmatic to point out how the interpretation of the hemorrhagic risk based on platelet count is complex in cirrhosis. The study from Basili and Droltz included patients with different clinical presentations and different need of invasive procedures at risk of bleeding which can justify the contrasting results on the predictive role of platelet count. Overall, the proportion of patients with stable vs unstable cirrhosis, the clinical setting (e.g. out- vs inpatient clinic), the proportion of patients needing intensive care may account for a large heterogeneity among those studies addressing the impact of low platelet count on the hemorrhagic risk. This could be the case of patients with acute on chronic liver failure (ACLF) whose hemostatic balance can be further compromised by acute clinical events such as infections, hemorrhage, severe liver decompensation, kidney and/or other additional organ failures. [10,25–29] Therefore, the bleeding risk predicted by low platelets count could be different in case of early stages of cirrhosis vs advanced stages but still in stable conditions (e.g. outpatient setting) vs critically-ill patients with ACLF. Accordingly, it is conceivable that an abnormal platelet count before an invasive procedure in the context of a stable disease (e.g outpatient setting) requires just a reactive transfusion policy in case of bleeding. On the contrary, critically-ill patients with thrombocitopenia addressed to invasive procedure should need an individualized approach which could include also a prophylactic strategy.

In conclusion, the interpretation of thrombocytopenia should not disregard the clinical context. On our opinion, the clinical context, rather than the (mere) platelet count, should guide the therapeutic approach and clinical research should be focused on homogeneous cohorts to control the bias of potential confounding factors and bring definitive evidence on the most efficacious transfusion policy of platelets in cirrhosis before an invasive procedure.

2.2 Conventional hemostatic test

The PT, one of the basic tests of coagulation does not predict the risk of bleeding in cirrhosis, and should not be used in this context, although it remains valid as a prognostic index included in the Child-Pugh and the MELD score.[3,10,30] Seminal in vitro studies showed that the time-honored PT test does not take into account the action of anticoagulant factors [i.e., antithrombin, protein C (PC) and protein S] that are reduced in

cirrhosis in parallel with the procoagulants.[31] The *in vitro* evidence is in line with clinical observations that show no role in the prediction of bleeding in cirrhosis and international guidelines and experts opinion clearly advise against the use of PT to estimate the risk of bleeding [10,32,24,33]. The companion coagulation test aPTT shares the same limits as the PT, but may have a role in bleeding risk assessment in critically-ill cirrhotic patients, although its role in the clinical decision making is still doubtful as its values is also influenced by higher levels of factor FVIII alongside cirrhosis severity.[24,34] Lastly, the bleeding time, an old in vivo test, responsive to VWF, thrombocytopenia and platelet dysfunction, though variably prolonged in cirrhosis, has little or no value as a predictor of bleeding during or after surgery or invasive procedures.[11,12,33] In conclusion, conventional hemostatic tests are primarily responsible of the erroneous belief that cirrhotic patients are "naturally anti-coagulated"[1] and should therefore be abandoned.

2.3 Thrombin generation test in defining hemostatic balance and potential hypercoagulability

Thrombin is the ultimate product of the complex biochemical interplay between pro- and anticoagulant factors. Among its functions, thrombin converts fibrinogen into fibrin, activate platelets and PC and has additional properties, which go beyond hemostasis, though closely linked with cirrhosis.[8] In 2003 Hemker established a fluorogenic measurement of thrombin generation in plasma with or without platelets, allowing to estimate the delicate balance of the entire plasmatic phase of hemostasis. [35–37] Moreover, the procedure modified by the addition of thrombomodulin, an endothelial receptor, which acts as the physiologic activator of PC, and downregulates thrombin generation offers a more reliable measure of plasma coagulation activity. In 2005, Tripodi et al firstly used this modified test providing evidence that *in vitro* thrombin generation in cirrhosis is similar to controls.[31] Thrombomodulin-resistance, which is estimated by the ratio between thrombin generation measured in presence vs absence of thrombomodulin, allowed to demonstrate a dysregulation in the PC system alongside with increased factor FVIII activity in patients with liver disease. This hemostatic pattern has been associated with the risk of portal vein thrombosis and worse outcome in cirrhosis. [38,39] The above findings demonstrate a procoagulant tendency in advanced cirrhosis, which can explain (at least in part) the splanchnic and peripheral thrombotic events observed in this clinical setting and reinforce the concept that a procoagulant imbalance may be the target of therapy in cirrhosis. As a

matter of fact, increased FVIII/PC ratio correlates with thrombomodulin-resistance and increased VWF and FVIII/PC ratio are independent prognostic markers in cirrhosis.[34,40–44] Although valuable to understand the complex pathophysiology of coagulation in cirrhosis, thrombin generation has to date little practical application.[45] First, compared to viscoelastic tests (see below), the measurement of thrombin generation takes much longer time and is therefore not suitable for a context of acute bleeding or for rapid decision making. Second, thrombin generation has not yet been adequately standardized.[46] Finally, there are not yet clinical studies to associate the parameters of thrombin generation with clinical hemorrhagic/thrombotic phenotypes.[47] As a consequence, the procedure still remains confined to research areas. A promising innovation can derive from the new standardized automated procedure (i.e., Genesia [48]) but prospective trials are warranted before recommending its use for decision making.

2.4 Viscoelastic tests to estimate hemostasis

Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) are viscoelastic tests which allow a real time graphical evaluation of different phases of clot formation in whole blood: initiation, propagation, strength, and dissolution of the clot. This permits to evaluate defects of one or more specific components of hemostasis.[49,50] TEG and ROTEM work on slight different principles, however, without clinically relevant differences. In this manuscript we will refer to TEG for both tests. A recent Cochrane review has shown promising TEG results on reduction of blood product infusion during perioperative management of patients undergoing surgery or invasive procedures.[51] However, most of these data are from cardiac surgery or trauma and derived from observational studies rather than randomized controlled trials. This notwithstanding, and despite some variability due to the different clinical context, in cirrhotic patients, TEG may represent a tool to help decision making on the need of transfusion interventions to limit bleeding during or after surgery or any other invasive procedures.[52–56] In 2016, De Pietri et al tested the use of TEG (vs usual care) in a randomized trial in cirrhotic patients who had an indication for prophylactic transfusion of plasma or platelets prior to an invasive procedure. The indication for transfusion was formally based on INR>1.8 and platelet count $<50x10^9$/L but in the TEG arm, plasma or platelets were given only if parameters were altered (r>40min, MA<30mm).[57] There was no difference in bleeding events in the two groups, but the TEG guided policy reduced significantly platelets and plasma transfusion and was

associated with higher post-procedure hemoglobin levels, suggesting lower hemodilution. This study showed that TEG may be useful to safely reduce the use of blood-derived products before invasive procedures. There are, however, aspects that require further consideration. For example, (i) the study did not enroll a control group of patients without prophylaxis whatsoever, (ii) the numbers of bleeding events in the two arms of the study were relatively low and (iii) some events were attributable to trauma during the procedure rather than to the coagulopathy. Similar data were obtained by other authors.[58,59] The above studies provide some value that global tests, when applicable, may be useful to assess the hemostatic balance in cirrhosis better than the conventional tests with the important consequence of reducing the transfusion of platelets and/or plasma. However, the accurate prediction of the bleeding risk in cirrhosis by using TEG or ROTEM is still far reaching, as demonstrated by recent reports, which failed to associate the "hypocoagulable" viscoelastic profile to provoked or unprovoked bleeding events.[27,60]

3. BLEEDING AND THROMBOTIC EVENTS IN CIRRHOSIS: A RATIONAL CLINICAL MANAGEMENT

3.1 The management of bleeding-risk related to invasive procedures

Peri-procedural and spontaneous bleeding in cirrhosis have been the main concern of clinicians and patients and a large amount of blood products have been and are still used as pre-procedural prophylaxis.[61–63] While prophylactic strategies with liberal transfusions of blood products carry significant risk, restrictive use reduced mortality in Child-Pugh A and B patients with upper gastrointestinal bleeding.[64] Most important recommendations issued by international societies of hepato-gastroenterology and interventional radiology are essentially based on minimizing the use of prophylactic strategies, which use is restricted for high risk procedures.[22,65–68] In low risk procedures, no prophylaxis or dedicated hemostasis pre-procedure assessment is recommended. In table 1 we report a comparison of the most important recommendations issued by international societies of hepato-gastroenterology and interventional radiology for high risk procedures.[22,65–68] In this paragraph, we offer an overview of the most important articles these recommendations are based on. Fresh frozen plasma infusion targeting INR below 1.5 may be harmful as it likely increases portal pressure[69,70] and

many solid studies questioned its efficacy in various clinical settings, including critically-ill patients with coagulopathy.[71–76] Platelet transfusions have been associated with an increased risk of hospital-acquired infections[77], with questionable effects on thrombin generation or thromboelastographic parameters.[78] In non-liver setting, widespread thresholds are $10x10^9$/L to avoid spontaneous bleeding and $50x10^9$/L if an invasive procedure is planned, especially when the INR is more than 1.5.[79–81] However, among low risk procedures in patients with liver disease, no relationship between such thresholds and bleeding has been observed for abdominal paracentesis[82–84], endoscopic band ligation, small polypectomy[85], vascular catheterization.[86] Percutaneous liver biopsy and radiofrequency ablation of hepatocellular carcinoma (HCC) are considered moderate/high risk procedures.[10,32] Liver biopsy is in general a safe procedure with low rate of bleeding[33,87,88] and some centers adopt just a reactive strategy in case of bleeding.[86] This notwithstanding, for percutaneous approach a threshold of $50x10^9$/L is still recommended in the absence of clinical trials testing no prophylaxis strategies.[32] Trans-jugular liver biopsy is a valuable and safe alternative in thrombocytopenic patients, with minimal risk of complications if the liver biopsy is aimed to obtain a representative parenchymal liver sample and not to characterize a specific focal lesion.[89] Studies on radiofrequency ablations of HCC commonly excluded patients with INR >1.5-1.8 and platelets $<50x10^9$/L. [90,91] Therefore, such thresholds should be cautiously maintained in the absence of data. High risk procedures (e.g., major surgery, large polypectomy) require careful pre-procedural assessment of the bleeding risk. Interestingly, in 2016 the European Society of Anesthesiology already suggested to evaluate the bleeding history rather than assessing hemorrhagic risk based on standard hemostatic tests (e.g., INR, aPTT and platelet count).[92] This is in line with the concept of a careful evaluation of the clinical context in which hemostatic tests and high risk procedures are going to be performed. Advanced cirrhosis is characterized by great instability and regardless of the risk related procedure, precipitating factors may shift the hemostatic balance toward bleeding. ACLF, acute kidney injury (AKI) and history of previous bleeding have been associated with high hemorrhagic risk associated with invasive procedures.[24,93,94] In particular, AKI has been historically associated in non-cirrhotic patients with an increased risk of bleeding, in particular in patients requiring dialysis, despite an extensive evaluation in cirrhotic patients with AKI described both hyper and hypo-coagulable features.[28,95,96] Alongside, ACLF is characterized by an inflammatory milieu which also leads to mixed hemostatic phenotypes.[27,60,97,98] Due to the aforementioned complex and unstable balance, it

should be considered to treat these patients in conjunction with hemostasis experts and to refer to tertiary centers to plan major surgery or high risk procedures. To warrant equal access to standard therapy, a hub and spoke model of care should be implemented in order to involve experts of hemostasis in the multidisciplinary evaluation of patients with advanced chronic liver disease. Among the instruments available in the vast majority of tertiary centers, viscoelastic tests are the most used to get a global assessment of hemostasis.[99] However, these assays were originally designed to evaluate the hemostatic defect during an acute bleeding episode and not properly to predict it.[100] This notwithstanding, their implementation seems useful to save transfusion products compared to conventional tests, but the need of further confirmatory studies on decisional algorithms based on visco-elastic tests, and the multifactorial nature of both hemostasis and cirrhosis, make the consultation with an expert advisable.[22,57,101–103] As summary, Figure 1 proposes an algorithm of a rational peri-procedure risk management.

3.2 Non transfusion strategies

Several strategies exist to correct deficiency of vitamin K dependent coagulation factors (II; VII, IX, and X; PC and PS). Vitamin K administration is useless in reducing INR or preventing bleeding episodes and it is no longer recommended by experts and guidelines.[32,104–107] The infusion of coagulation factor concentrates would ideally overcome the problem of volume overload associated with plasma infusion, but robust observations on their efficacy to control bleeding are limited and thrombotic complications are of special concern in this population.[108–112] Correction of thrombocytopenia by thrombopoietin receptor agonists is presently of increased interest.[113] The observation that one of such agents (i.e. eltrombopag) increased the frequency of portal vein thrombosis (PVT) [114] prompted studies on alternative thrombopoietin receptor agonists, avatrombopag and lusutrombopag. These agents were reported to increase platelet counts with satisfactory safety profile in two clinical trials.[115,116] However, despite these encouraging results, we believe that extreme caution is still needed in normalizing platelet count in this population, as low risk procedures require no prophylactic strategy.[117] Presently, we recommend to identify patients at high risk with a history of bleeding suggestive of a primary hemostasis defect and to make decision on individual basis .

Antifibrinolytics are often used in cirrhosis, despite lack of high quality supporting evidence and controversies in the tests exploring fibrinolysis.[118,119] Tranexamic acid has

historically been used during dental surgery to reduce bleeding, despite simple compression alone is effective in most cases.[120] Aprotinin, a plasmin inhibitor, showed some efficacy in reducing blood requirement during liver transplantation and liver resection.[121–123] However, high quality clinical trials during cardiac surgery contraindicated aprotinin due to increased mortality.[124] In line with these results and in the presence of conflicting consensus on antifibrinolytics[10,32,125], we believe that their use should be restricted to selected cases under the supervision of hemostasis experts. In this context, a multi-disciplinary approach with synergic effort between experts in bleeding disorders and the hepatologists will be needed, as the number of treatments targeted to control hemostasis is constantly growing.

3.3 Portal hypertension related bleeding and pro-hemostatic drugs

Over the last three decades, the progressive refinement of the treatment and prophylaxis by combining endoscopy, radiology and pharmacology has considerably reduced variceal bleeding related mortality rate from 60-80% to 10-20%.[126] Despite these valuable results, strategies required by resuscitation protocols in the context of active bleeding may cause fluid overload which needs, close monitoring of complications related to the increase of portal pressure.[69,127] To reduce volumes of infused plasma and better control of active variceal, the prohemostatic agents recombinant activated factor VII (rFVIIa) has received major attention after the successful previous experience in patients with congenital or acquired hemophilia.[128] In cirrhotic patients, the in vitro addition or administration of rFVIIa was effective in shortening PT and suggested a potential clinical benefit in isolated reports.[129,130] In 2004, 245 cirrhotic patients with upper gastrointestinal bleeding (UGIB) were randomized to receive rFVIIa or placebo in addition to standard therapy with the primary endpoint to control UGIB and death within 5 days. Overall, no effect of rFVIIa was observed, despite a reduced proportion in bleeding control failures just in the subgroup of patients with a more advanced disease.[131] In line with these results, Bosch et al carried out an additional randomized, controlled trial by including 256 patients with variceal hemorrhage and advanced cirrhosis (Child-Pugh B=26%, C=74%) and with similar end-points.[132] They likewise tested rFVIIa vs placebo in addition to standard therapy. The trial failed to demonstrate any clinical benefit of rFVIIa even in this selected population and, finally, all these results contraindicated the use of rFVIIa in the context of acute variceal bleeding. Similarly, a subgroup analysis from the

HALT-C trial based on patients with liver disease and acute variceal bleeding showed that the addition of tranexamic acid in addition to standard care did not give any advantage on mortality rate.[133] Moreover, in HALT-C study venous thromboembolic events were higher in tranexamic acid group than in placebo group, with an unfavorable benefit-risk ratio of such pharmacological intervention. Two additional studies of patients randomized to rFVIIa failed to show efficacy in patients undergoing liver resection. [134,135] In conclusion, pro-hemostatic approaches are still unsatisfactory during acute variceal bleeding and the management should be based on treating portal pressure. Current guidelines recommend against using pro-hemostatic agents in this setting. [126]

3.4 Portal vein thrombosis (PVT): benefit/risk ratio of anticoagulation

The incidence of PVT ranges from 1% in compensated to 25% in decompensated cirrhosis. [7,5,136] The reduction of portal flow, coexisting with an unstable hemostatic equilibrium worsens with the progression of the disease and are an ideal pabulum for thrombosis development. Whether PVT represents an epiphenomenon linked to the progression of the disease or a complication to be treated as soon as possible to avoid progression of cirrhosis, is still debated.[137] This notwithstanding, PVT has been associated with severe prognosis, due to worsening of liver function, reduced perfusion and increased mortality associated with variceal bleeding.[6,43,138–143] Alongside, prevention of PVT by low molecular weight heparin (LMWH) administration in Child B/C cirrhosis was effective and safe and was associated with an improvement of Child-Pugh score and reduction of the rate of de novo or worsening ascites.[144] Nery et al. prospectively collected data of 1243 cirrhotic patients and described the incidence of PVT and liver-related complications with a mean follow-up of 47 months from inclusion.[145] In this study, PVT was associated with a greater severity of baseline disease, but without further disease progression. Moreover, PVT spontaneously recanalized without the use of anticoagulants in 70% of cases. However, PVT is a condition characterized by a protean presentation, with different involvement of portal branches, crucial in defining the anastomotic availability during orthotopic liver transplantation and can sensibly influence the clinical outcome.[6] For all these reasons, current guidelines recommend anticoagulant treatment to prevent PVT in patients awaiting liver transplantation or symptomatic/progressive PVT.[32,126,146] Presently, LMWH and vitamin K antagonists (VKA) are the most used anticoagulants, although laboratory monitoring of the therapy is

difficult due to the baseline alteration of hemostatic tests. A meta-analysis by Loffredo et al showed that VKA or LMWH are associated with a higher recanalization rate and reduced thrombus extension.[147] Moreover, the therapy has not been associated with an increased risk of minor and major bleeding, in line with previous reports.[148–151] In addition, the risk of upper-gastrointestinal bleeding under VKA in cirrhosis is mainly due to portal hypertension and not to anticoagulation as demonstrated in a retrospective study by our group making multiple comparisons between patients with cirrhosis receiving VKA for PVT, patients with cirrhosis who did not receive VKA and patients without cirrhosis who received VKA for the prevention of venous thromboembolism. [152] Interestingly, in this experience, complete recanalization of the portal vein under VKA was associated with a reduced incidence of liver related complications and better survival rate, particularly in the first 24 months of treatment, confirming a favorable benefit/risk ratio of anticoagulation in cirrhosis. Among the new therapeutic options, direct oral anticoagulants (DOACs) are contraindicated in advanced stages of the disease, where the incidence of PVT is higher, due to the hardly predictable anticoagulant effect and the lack of an antidote, currently available only for dabigatran.[108,153,154] Nevertheless, reports on the use of DOACs in cirrhosis are increasing thanks to observational studies, international registries and metanalysis despite data are not sufficient to draw definitive conclusions on safety and advantages of these drugs.[155,156] In conclusion, anticoagulation in PVT cirrhosis should be evaluated individually, provided that correct prophylaxis and management of the risk of bleeding has been performed. New studies on PVT should be carried out to better define the impact of PVT and anticoagulation on clinical outcomes of cirrhosis, to consider individual benefit/risk ratio posed by anticoagulation.

4. DOAC and aspirin in patients with cirrhosis and cardiovascular diseases

The increasing numbers of metabolic cirrhosis and the better life expectancy after introduction of successful antiviral therapy, drive the considerable increase in the number of cirrhotic patients facing the consequence of short and long term sequelae of hypertension, atherosclerosis, ischemic heart disease and thromboembolic events.[157–159] Therefore, dealing with cirrhotic patients on antiplatelet or anticoagulant therapy due to cardiovascular comorbidities, is a daily clinical conundrum. Aspirin is the universally prescribed antiplatelet medication for secondary prophylaxis of arterial events. In cirrhotic patients, evidence on the aspirin effect on cardiovascular endpoints derives mainly from

retrospective studies, which confirm risk reduction without excess bleeding (Table 2).[160,161] Furthermore, in recent years, the use of aspirin has been associated with a significant reduction in mortality, cirrhosis decompensation and HCC incidence, without a significant impact on bleeding [162–165] Such promising results derives from observational studies and the protective effects seem mainly related to patients with chronic hepatitis rather than to cirrhosis . Interestingly, the effect appears to be aspirin dependent, as the inhibition brought about by NSAIDs is not associated with same liver protective effect.[166] Owing to the lack of detrimental effects due to aspirin, during the last Baveno consensus the final recommendation has been not to preclude or suspend aspirin if rationally prescribed for cardio-vascular reasons in cirrhosis.[126] Studies on modulation of platelet function as a potential non-etiological therapy for cirrhotic patients are expected to expand this indication in the future. Alongside aspirin, double antiplatelet therapy (DAPT) is increasingly considered for the management of cirrhotic patients. In patients awaiting liver transplant, coronary arteries disease is actively sought, with a variable but non-negligible prevalence between the series (3-60%).[157,167–170] Therefore, even in advanced cirrhosis coronary stent placement with DAPT therapy is not uncommon. Again, most of the evidence on the benefit/risk ration of DAPT in cirrhosis derives from retrospective studies and data do not show excess of bleeding (Table 2).[171–173] Nevertheless, the possible greater instability of the hemostatic balance and the frequency of severe thrombocytopenia in this population would mandate (whenever possible) for the evaluation of platelet function and bleeding risk, also considering the prognostic impact of cardiovascular events in the post-transplant period. Finally, studies on non-aspirin antiplatelet agents are scarce and the evidence to assess their effect on platelet function in cirrhosis are insufficient.[174–177] Atrial fibrillation (AF) and deep vein thrombosis (DVT) are the most common non-liver related indication of anticoagulant therapy in cirrhosis .[178–180] We already discussed difficulties in prescribing and monitoring anticoagulant drugs in cirrhosis with splanchnic vein thrombosis above. The advent of DOACs revolutionized anticoagulation therapy for cardiovascular indications, in terms of efficacy, compliance and more favorable risk profile compared to VKA.[181] Despite the exclusion of cirrhotic patients from clinical trials, DOACs have been prescribed also in this population. Table 2 summarizes the main evidence on the indication of DOACs in cirrhotic patients with cardiovascular diseases .[182–188] Most of the patients included in the studies were affected by compensated cirrhosis and DOACs were aimed to treat DVT/pulmonary embolism or to prevent embolic events in AF. DOACs appeared effective,

though with an increased bleeding risk when compared to VKA. However, results in patients with more severe disease, albeit in limited series, showed a significant greater risk of bleeding than in those with compensated disease.[186,187] Therefore, similarly to antiplatelet agents, in patients with cardiovascular indications Baveno VII recommends to prescribe DOACs just in Child-Pugh class A/B cirrhosis since the risk of bleeding in Child-Pugh C could overcome any benefit.[126] However, studies of DOACs, in more advanced stages of cirrhosis and targeted on the efficacy, monitoring and bleeding risk remain an urgent need to ameliorate the management of the thrombotic risk in patients with cirrhosis.

5. CONCLUSIONS

Cirrhosis considerably influences hemostasis shifting to mixed clinical phenotypes, including both bleeding and thrombosis. The management of such situations is extremely complex in line with the fragility of hemostatic equilibrium. Furthermore, in patients with advanced disease, events such as infections or invasive procedures can disrupt this balance. Practical strategies are often not in line with guidelines and probably driven by defensive medicine. [63] We believe that, especially in highly specialized centers, a clinical strategy tailored on individual patients is needed, taking into consideration the phase of illness and the clinical need. To this end, some points are crucial in the research agenda for the cirrhosis coagulopathy. First, new trials in the context of invasive procedures should be carried out to provide a comparison between prophylactic and reactive strategy to bleeding events, without the indiscriminate use of hemostatic agents. In this context, it is needed the development and validation of more appropriate hemostatic tests to evaluate the thrombotic or hemorrhagic risk. Second, the evaluation of the prognostic impact of splanchnic and peripheral thrombotic events in cirrhotic patients should define the most appropriate prophylactic or anticoagulant strategies. Randomized controlled trials on the use of anticoagulants in PVT are still a crucial missing piece in terms of safety and efficacy. In conclusion, despite the revolution shifting the old paradigm of cirrhosis as the epitome of acquired hemorrhagic disease that occurred over the last two decades, much remains to be done to translate our understanding of the pathophysiology to evidence-based clinical recommendations.

6. EXPERT OPINION

The old paradigm of cirrhosis as the epitome of acquired hemorrhagic diseases was challenged upon providing evidence that hemostasis in this condition is rebalanced by the concomitant decrease of pro- and anticoagulants and by increased von Willebrand factor, the latter compensating for thrombocytopenia. These concepts contrast with the occurrence of prolonged PT/aPTT and thrombocytopenia, which supported for decades the common practice of screening cirrhotic patients with PT/aPTT and bleeding time, and correction of the abnormalities by infusion of fresh frozen plasma (FFP), or platelets before surgery/invasive procedures. It is now appreciated that PT/aPTT bear no value in predicting bleeding during surgery/invasive procedures in cirrhosis. The logical consequence is that the old prophylactic strategies lack biological and clinical plausibility. They may also be harmful as it may occur in cirrhotic patients with variceal bleeding, in whom FFP may increases portal pressure, thus (paradoxically) exacerbating bleeding. Platelet transfusion may give rise to allergic reactions and the occurrence of portal vein thrombosis.

Another concept, widely accepted for decades, is the dogma that cirrhotic patients are naturally anticoagulated because of prolonged PT/aPTT and the presence of thrombocytopenia. Until recently, the common practice was that cirrhotic patients do not require pharmacological anticoagulation to cure/prevent thrombosis. The concept of rebalanced hemostasis concurs with many epidemiological observations to conclude that cirrhotic patients are not protected from thrombosis as previously believed. Indeed, the risk of venous thromboembolism in cirrhotic patients, established by nationwide case-control studies is almost doubled when compared with non-cirrhotic patients. These findings point out that whenever indicated and in the absence of strong contraindications, anticoagulants should be given to cirrhotic patients even though they are perceived at bleeding risk. Unfortunately, the new concepts underlining the pathophysiology of hemostasis in cirrhosis are hardly put in practice, despite the effort of scientific societies that issued guidelines on the management of hemorrhage and thrombosis in this setting. The reasons why the application of guidelines is difficult are complex. They are probably driven by medico-legal issues and lack of prospective studies. For example, in the field of hemorrhage, the effect of thrombocytopenia still waits to be addressed in clinical trials aimed to establish/validate threshold platelet counts needed for surgery/invasive procedures. There is also lack of laboratory tests informing clinicians on the efficacy of platelet transfusion. In the field of thrombosis there is an urgent need to address the value of anticoagulation with DOACs.

Cirrhotic patients were not included in clinical trials for DOACs. Studies in cirrhotic patients are warranted as DOACs would have practical advantages over traditional anticoagulants. Unlike VKA, DOACs do not require dose-adjustment by laboratory testing. This would be a distinct advantage as the baseline INRs, a scale used for VKA monitoring, may be relatively high in cirrhosis and would not represent the true level of anticoagulation achieved by VKA. Furthermore, VKA, at variance with DOAC, in addition to procoagulants, diminish the naturally occurring vitamin-K dependent anticoagulants (namely PC and PS), giving rise to a potential (paradoxical) increase of procoagulant imbalance.

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Low risk *(<1.5%)* → **Moderate/High risk** *(≥1.5%)*

Paracentesis (any volume)	Major surgery
Thoracentesis	ERCP
Transjugular liver biopsy	Large Polypectomy
Trans-osesophageal echocardiography	Oesophageal varices ligation
Percutaneous liver biopsy	Dental extraction
HVPG mesaurement	
Percutaneous ablation of HCC	

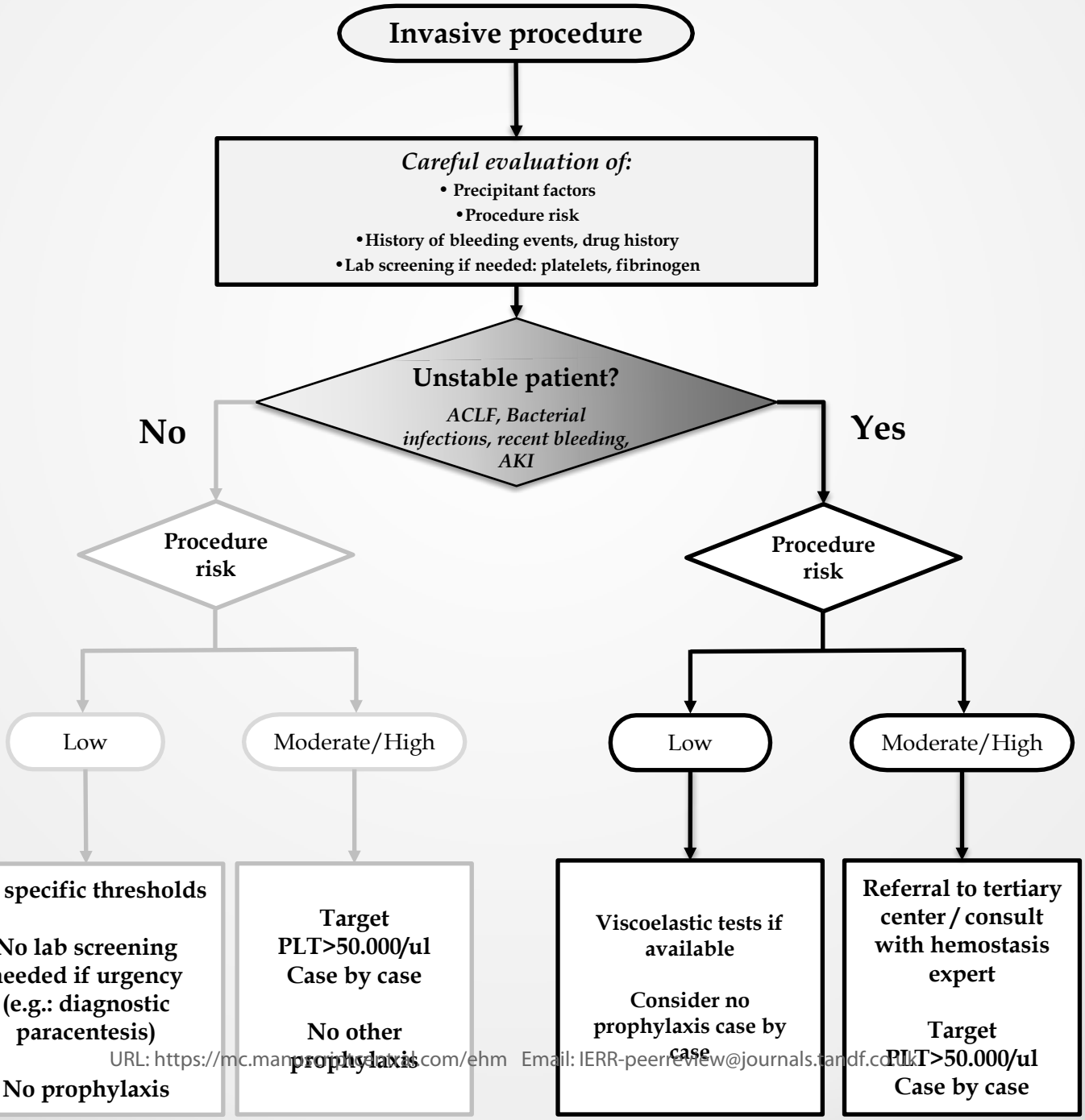

Table 1

	Recommendations issued by scientific societies for hemostatic thresholds guided interventions prior to high risk procedures				
	Society of Interventional Radiology (SIR) [65]	**American College of Gastroenterology (ACG) [66]**	**American Gastroenterological Association (AGA) [68]**	**American Association for the Study of Liver Diseases (AASLD) [67]**	**European Association for the Study of the Liver (EASL) [22]**
Year of publication	2019	2020	2021	2021	2022
Platelet count (10^9/L)	>30	>50	Discussion with hematologist	No routinely correction	20-50: no routinely correction, case by case decision <20: case by case decision
INR	<2.5, no correction	No correction	No correction	No routinely correction	No correction
Fibrinogen (mg/dL)	>100	>120-150	No correction	No routinely correction	No routinely correction

Table 2

Antiplatelets and direct oral anticoagulants (DOACs) in cirrhotic patients with cardiovascular disease

	Year	Author, Journal	Type of study	Population	Main outcomes	Safety
Antiplatelet agents						
SAPT	2012	Chen, Pharmacoep. Drug Saf.[160]	Retrospective	1118 pts with stroke, 2 years SAPT	↓ Risk of stroke	No ↑ risk of bleeding
	2018	Patel, Liver Transpl.[161]	Retrospective	Pts under evaluation for LT, screened for CAD if risk factors or positive stress test 84/228 pts-> CAD	Only 30/84 (36%) pts with CAD on aspirin	No association with AVB, GIB, worsening anemia
DAPT	2012	Russo, J Clin. Gastroenterol.[171]	Retrospective	Coronary stenting in 12/423 pts undergoing LT evaluation vs age and sex matched cirrhotic controls not on aspirin	No difference	No difference
	2017	Krill Aliment Pharmacol Ther.[172]	Retrospective	148 pts with CAD, 68 with stents, 80 medical therapy alone (controls) 99% DAPT in stent group vs 5% controls	Similar mortality between groups	↑ non-fatal bleeding in DAPT group (22% vs 5%)
	2019	Wu, PLoS One[173]	Retrospective	914 cirrhotic vs 3656 non cirrhotic pts with AMI on DAPT	↑ Mortality cirrhosis ↓ AMI recurrence	Not significant ↑ Major bleeding (3.7 vs 2.9%); ↑ GIB
Direct oral anticoagulants						

DOACs	2022	Oldham, Ann. Pharmacother.[186]	Retrospective	101 pts, 69 on DOACs, 32 on LMWH or VKA Indication: 35% VTE, 65% AF	No difference in thromboembolic events	No significant trend of ↑ bleeding in DOACs
	2022	Lee, Am J Cardiovasc Drugs[188]	Meta-Analysis	4011 pts with AF 3 retrospective studies (only 1 reports CP: 70% A vs 30% B)	↓ Thromboembolic events vs VKA	↓ major bleeding vs VKA
	2021	Semmler, Liver Int.[186]	Retrospective	104 pts on DOAC (39% Child-Pugh B/C) vs 58 pts on LMWH or VKA Indication: 74% PVT or BCS; 12% AF, 6% DVT/PE	No-significant ↑ spontaneous bleeding Same procedure related bleeding	Worse CP associated with major bleeding
	2021	Mort, Clin. Gastroenterol. Hepat.[184]	Retrospective	138 pts, 93 with CP B/C Indication: 34% DVT/PE, 44% AF, 28% PVT	21% stopped DOAC due to bleeding	33% bleeding events (8% major) HCC associated to bleeding
	2020	Huang, Cardiovasc Drugs Ther.[185]	Meta Analysis	41859 pts with liver disease from 6 studies. Variable definition of liver disease (1 study with defined cirrhosis)	↓ Ischemic stroke	↓ICH ↓Major bleeding Same GIB risk
	2018	Chokesuwattanaskul, Digestive and Liver Disease[183]	Meta-analysis	19.798 pts with AF and cirrhosis anticoagulant prescription range: 8 to 54%	↓ Risk of stroke	No higher risk of bleeding vs no anticoagulation DOACs ↓ risk of bleeding
	2017	Kuo, J Am. Heart Assoc.[182]	Retrospective	9056 pts with AF and CHADVASC≥2 No treatment vs VKA vs antiplatelet	↓ only in VKA group	No differences in intracranial hemorrhage

Abbreviations: pts,patients; SAPT, single antiplatelet agent; DAPT,double antiplatelet agent; LT,liver transplant; CAD,coronary artery disease; AVB,acute variceal bleeding; GIB,gastro-intestinal bleeding; AMI,acute myocardial infarction; AF,atrial fibrillation; VKA,vitamin k antagonist; LMWH, low molecular weight heparin; DOAC,direct oral anticoagulant; CP,Child Pugh class; PVT,portal vein thrombosis; BCS,Budd Chiari Syndrome; DVT,deep vein thrombosis; PE,pulmonary embolism; ; ICH,intracranial hemorrhage;