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RECOMMENDATIONS AND GUIDELINES

Periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis: Guidance from the SSC of the ISTH

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Abstract

Prolonged prothrombin time and thrombocytopenia are common in patients with cirrhosis. These parameters do not reflect the overall hemostatic rebalance or bleeding risk in the periprocedural setting; however, attempts to correct these parameters remain frequent. We review the literature on periprocedural bleeding risk, bleeding risk factors, and the risk and benefits of hemostatic interventions in patients with cirrhosis. We provide guidance recommendations on evaluating bleeding risk in this patient group and management of hemostatic abnormalities in the periprocedural setting.

KEYWORDS
cirrhosis, hemorrhage, hemostasis, liver diseases, thrombocytopenia

1 | INTRODUCTION

Traditionally, liver disease has been considered an acquired bleeding state but this view is not supported by data and increasing evidence supports rebalanced hemostasis as outlined in detail in the previous SSC working group communication.[1] However, patients with cirrhosis typically present with abnormal routine laboratory measures of coagulation, specifically prolonged prothrombin time (PT) and thrombocytopenia, and therefore transfusion support in the periprocedural setting is commonly considered by clinicians.[2] In addition to recognition of rebalanced hemostasis, awareness of the low bleeding risk associated with common procedures performed in patients with cirrhosis is essential. Contemporary international hepatology/gastroenterology guidance now recommends

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against empirical correction of prolonged coagulation times and/or thrombocytopenia.[3,4] In this guidance document, we summarize the periprocedural bleeding risk for common elective procedures performed in patients with cirrhosis, discuss the risk factors for bleeding, evaluate the benefits and potential risk of attempting to correct thrombocytopenia, prolonged PT, hypofibrinogenemia, and the agents available (summarized in Figure 1).

2 | METHODS

Guidance statements were generated following review of the published literature and are based on consensus opinion of the authors. There is a paucity of high quality randomized clinical trials in this area and thus the strength of guidance statements is based on review of available data and author consensus. The use of "we recommend" reflects a strong guidance statement, and the clinician should adopt the practice in most cases; "we suggest" reflects a weak guidance statement, whereby the evidence to support the statement is not strong and the clinician may adopt the practice in some cases and an alternative practice also may be acceptable.

3 | STAGES OF DISEASE IN PATIENTS WITH CIRRHOSIS

The natural history of liver disease in patients with cirrhosis is characterized by phases of "compensated" or stable disease that may progress to an "acutely decompensated" state associated with ascites, variceal bleeding, jaundice, or encephalopathy.[5] Hospitalization often follows a precipitating event and the majority of patients with cirrhosis admitted to hospital are in an "acutely decompensated" state. Patients may recover from this state or further progress with the development of multi-organ failure to acute-on-chronic liver failure (ACLF); such patients usually require organ support in critical care with high in-hospital mortality.[5] The Child-Turcotte-Pugh score was initially developed to predict surgical mortality (see Table S1 in supporting information) in patients with cirrhosis and has developed to a robust prognostic tool outside the surgical context.[5,6] Routine laboratory markers of hemostasis typically exhibit more marked changes with disease progression; however, global hemostatic assays suggest a hypercoagulable state in both compensated and acute decompensation with wide interindividual variation in those with ACLF (with some patients exhibiting hypocoagulable features).[1] This guidance is relevant to all stages of disease but as discussed further below, bleeding risk appears to increase in parallel with disease severity.

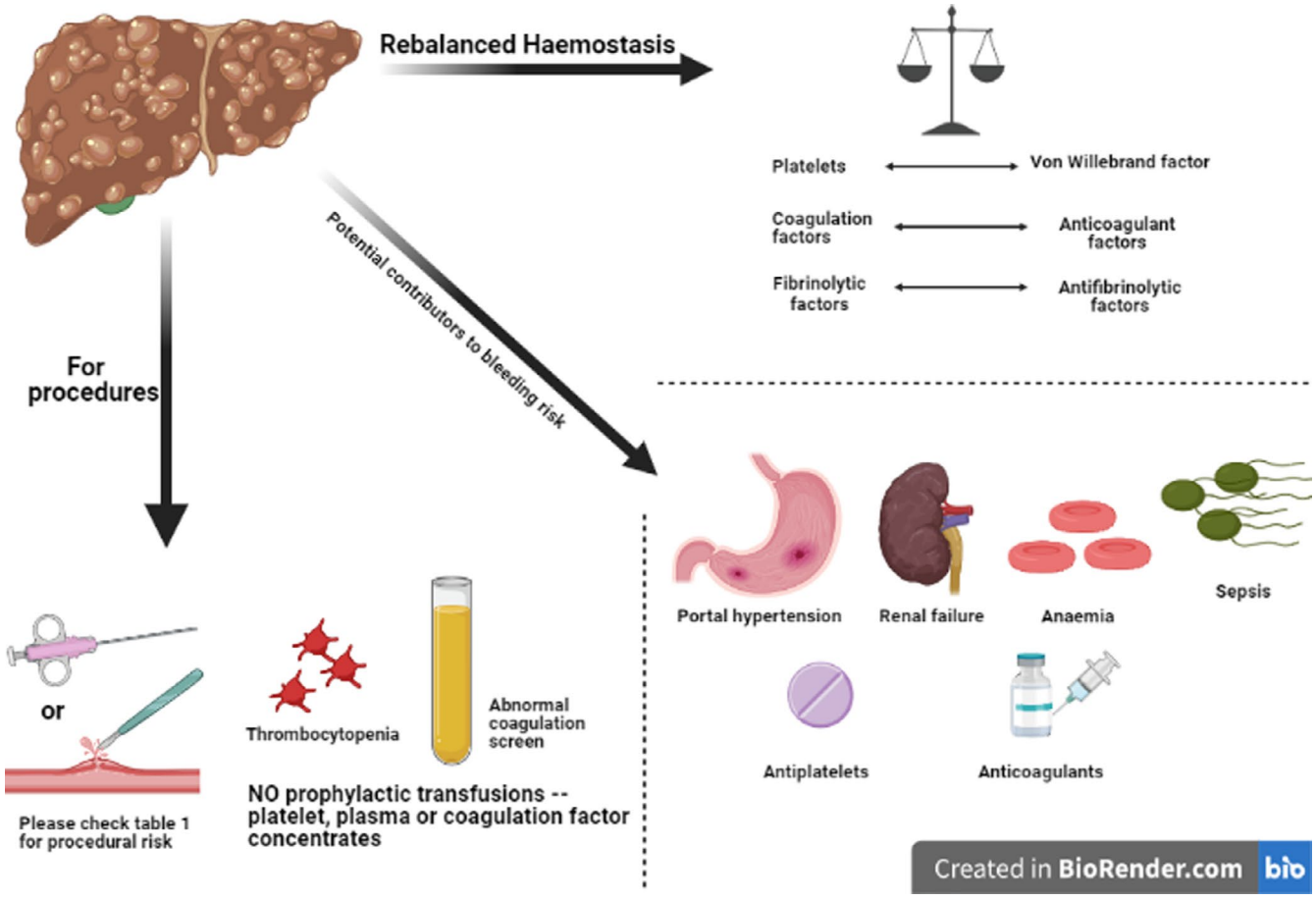

FIGURE 1 Visual summary of bleeding risk factors and approach to periprocedural management of patients with advanced chronic liver disease

4 | PROCEDURAL BLEEDING RISK IN PATIENTS WITH CIRRHOSIS

4.1 | Procedural factors

Evaluation of the inherent procedural risk has been hampered by the empiric correction of underlying prolonged PT/thrombocytopenia and the lack of uniform definition for major bleeding in patients with cirrhosis. While there are established definitions for bleeding and its severity in patients taking anticoagulants,[7,8] these definitions have not been formally validated in non-anticoagulated patients, such as those with cirrhosis. These limitations aside, it is now well recognized that major surgery such as liver transplantation can be safely performed without hemostatic support, with "transfusion-free" procedures the norm at some centers.[9]

Bleeding risk can be defined as low or high based on both the estimated procedural risk, the ease of controlling bleeding (e.g., site compressibility) and its potential consequence (e.g., intracranial bleeding). A procedure with a major bleeding rate of >1.5% is generally considered a high bleeding risk procedure.[10,11] This risk stratification is extrapolated from periprocedural management of anticoagulation[10] but has not been formally evaluated in patients with cirrhosis. Examples of commonly performed procedures and their associated bleeding risk are summarized in Table 1.

Additional procedural factors influencing bleeding risk are operator experience and the use of imaging.[10,11] Ultrasound guidance for procedures such as thoracocentesis is associated with a very low risk of bleeding,[12] with imaging to guide transjugular intrahepatic portosystemic shunt (TIPSS) placement significantly reducing liver capsular perforation (known association with intraperitoneal bleeding) and minimizing the number of attempts needed to reach the portal vein.[13]

4.2 | Patient-specific factors

While coagulation screens are frequently performed in the periprocedural setting, they are insensitive as a screening tool[14] and have limited utility outside monitoring anticoagulation (e.g., ensuring international normalized ratio [INR] is below threshold for patients on vitamin K antagonists). Furthermore, as outlined in the previous SSC communication, the PT/INR does not adequately reflect the rebalanced state of coagulation in cirrhosis.[1] Global assays such as rotational thromboelastometry (ROTEM)/thromboelastography (TEG) may be an attractive means to reassure the proceduralist that hemostasis is "normal" as these assays are frequently normal despite prolonged coagulation times.[15,16] A small prospective study of 82 hospitalized patients with acute decompensation suggests a potential role for TEG maximum amplitude (MA) in predicting post-procedural bleeding.[17] However, further prospective evaluation is required to validate these findings, and to confirm utility in identifying those at higher bleeding risk. Additionally, there are no data on how to intervene in those with hypocoagulable TEG profiles.

A bleeding history is advocated as a more appropriate means of identifying unselected patients (without cirrhosis) who may be at greater periprocedural risk.[18] In the patients with cirrhosis the majority of bleeding events are gastrointestinal and most commonly secondary to portal hypertension.[19] Such a bleeding history is unlikely to influence procedural bleeding risk. Whether procedural bleeding influences future bleeding risk in patients with cirrhosis remains unknown. However, bleeding history predating the onset of cirrhosis may suggest an underlying inherited bleeding disorder, and further investigation should be considered in this small subset of patients.

The lack of association between prolonged coagulation times (PT/INR) in patients with cirrhosis and procedural bleeding risk is well established in the periprocedural setting.[20] This was recognized

TABLE 1 Examples of commonly performed procedures in patients with cirrhosis and their associated bleeding risk

	Low bleeding risk	High bleeding risk[a]
Endoscopic	Diagnostic procedures Endoscopic variceal ligation Transoesopheageal echocardiogram	Bronchoscopy with biopsy Colonoscopy with polypectomy Endoscopic retrograde cholangiopancreatography with sphincterotomy
Percutaneous	Paracentesis Thoracocentesis	Percutaneous liver biopsy Tunnelled ascitic/pleural drain placement Cranial/spinal surgery[b]
Vascular	Peripheral/central venous catheterization Transjugular liver biopsy	Transjugular intrahepatic portosystemic shunt Transcatheter arterial chemoembolization
Other	Dental procedures including extractions Skin biopsy	Intraocular procedures[b]

[a]Classification based on major bleeding >1.5% or where minor bleeding associated with high risk of significant organ damage/death.

[b]Very high risk procedures.

as far back as 30 years ago, with no relationship seen between PT and duration of bleeding post liver biopsy.[20,21] As a more recent example, a prospective study of 150 patients with cirrhosis undergoing endoscopic variceal band ligation (EVL) reported post-EVL ulcer bleeding in 7% (without hemostatic support).[22] Importantly, no hemostatic test results including TEG parameters were associated with bleeding, but severity of liver disease (Child Pugh C status) was a significant predictor of bleeding. The association between severity of liver disease and bleeding may be at least in part explained by increased portal pressures in decompensated disease.[22,23] Also of note, the median time to bleed post EVL was 9 days, highlighting that any blood product replacement pre-procedure is unlikely to impact later bleeding risk following EVL. Severity of liver disease is also reported to mediate post procedural bleeding risk in low risk procedures such as paracentesis with increasing risk paralleling progression from stable cirrhosis to acutely decompensated and ACLF.[24] While an association between fibrinogen levels and bleeding has been reported in an observational cohort of patients undergoing EVL ($n = 150$), fibrinogen levels have been demonstrated to fall with increasing severity of liver disease.[25,26] In this cohort, all bleeds were controlled with endoscopic intervention with no blood product replacement required, with fibrinogen predominantly >1 g/L. Lower fibrinogen levels are more frequent in critically ill patients with cirrhosis and reported in a single study ($n = 211$) as a predictor of bleeding, particularly when <0.6 g/L without adjustment for disease severity.[27] A subsequent retrospective cohort study ($n = 267$), however, found fibrinogen as a marker of disease severity and not an independent predictor of bleeding.[28]

Thrombocytopenia is the commonest hematological abnormality noted in patients with liver disease. Approximately half of the patients with chronic liver disease and nearly 80% of patients with cirrhosis have subnormal platelet counts (less than 150×10^9/L).[29,30] Liver disease can cause a drop in the platelet count due to various factors including decreased platelet production secondary to bone marrow suppression or inadequate thrombopoietin release, splenic sequestration in patients with portal hypertension-related splenomegaly, or increased destruction by an autoimmune process.[30]

Patients with decompensated cirrhosis have more severe thrombocytopenia but the platelet count does not predict major or clinically relevant nonmajor bleeding. Basili et al. followed 280 patients with cirrhosis for approximately 4 years and found bleeding is predominantly gastrointestinal in nature at an annual rate of 5.5%.[31] Platelet counts in these patients progressively decreased with the worsening of liver disease, but there were no differences in bleeding in those with counts ≤50×10^9/L (platelet count <50×10^9/L in 6% with bleeding and 9% without any bleeding).[31] The previous prospective study of factors associated with procedural bleeding risk in acute decompensation also found no association with admission platelet count (platelet count <50×10^9/L in 29% of those with bleeding and 28% of those without).[17] This suggests factors other than platelet count are an important determinant of bleeding risk, as also recognized in patients with bone marrow failure.[32] Rebalanced hemostasis with the lower platelet counts compensated by highly elevated levels of von Willebrand factor means that the degree of thrombocytopenia may not correlate with bleeding.[33]

Platelet count thresholds are often stipulated for invasive procedures in patients with severe thrombocytopenia related to cirrhosis. Although a specific platelet count cut-off, below which platelet-raising treatments is recommended by many international guidelines, there is no firm evidence for this practice.[3,4] From a laboratory perspective, *in vitro* data suggested a platelet count threshold of 55×10^9/L to be necessary for adequate platelet procoagulant function, but the study did not evaluate the platelet function related to primary hemostasis (i.e., adhesiveness and aggregation).[34] In an analysis of the *in vivo* relevance of these *in vitro* findings, it was noted that 26 patients with cirrhosis who required variceal banding, transfusion of one adult dose of platelets, despite increasing the count, did not have a significant effect on thrombin generation while the minor increment in the platelet count reflected only a small improvement in thromboelastometry markers.[35] TEG-guided transfusion strategy was examined in a randomized controlled trial of 60 patients in which the researchers found a significantly lower blood product usage in the "guided" cohort compared to the standard of care, but once again, procedural bleeding was extremely rare in both the arms even among those with significant coagulopathy (defined as INR >1.8 and/or platelet count <50×10^9/L).[15]

Renal impairment and infection are common in patients with cirrhosis and may be a cause or consequence of acute decompensation; both are reported as risk factors for procedural bleeding. *In vitro* studies demonstrate greater platelet dysfunction and factor XIII deficiency in patients with decompensated cirrhosis and acute kidney injury (AKI), compared to those without AKI.[36] Furthermore, AKI is reported as an independent risk factor for post paracentesis hemoperitoneum, independent of severity of liver disease.[37] Sepsis has been associated with increased circulating endogenous heparinoids potentially leading to increased bleeding risk.[38]

Anticoagulant and/or antiplatelet therapy should be reviewed, and interrupted as per existing guidance based on risk:benefit evaluation of the underlying thrombotic risk and procedural bleeding risk.[10] There is emerging evidence to support continuing anticoagulation for low risk procedures with no excess bleeding following EVL in those on anticoagulants.[39]

5 | BENEFITS/RISKS OF INTERVENTIONS TO ADDRESS COAGULATION IN THE PERIPROCEDURAL SETTING

5.1 | Fresh frozen plasma

Fresh frozen plasma (FFP) has often been utilized in the periprocedural setting in an attempt to correct a prolonged PT/INR.[2] However, as discussed above, the PT/INR is a measure of disease severity and does not reflect the overall hemostatic balance in cirrhosis. There is good evidence that it does not predict procedural

bleeding (see above) and no evidence that correction reduces procedural bleeding risk. Additionally, FFP carries the potential risk of transfusion-related acute lung injury, and the volume required for a "therapeutic" dose may lead to transfusion-associated circulatory overload.[40] Recent studies of the *in vitro* effect of FFP transfusion in patients with cirrhosis highlight pre-existing normal to hypercoagulable coagulation profiles (evaluated with global thrombin generation assays), with FFP leading to enhanced hypercoagulability.[41,42] Furthermore, therapeutic transfusions of FFP have been shown to significantly increase portal pressures and may thereby paradoxically increase bleeding risk (e.g., in EVL).[43] Finally, a retrospective multicenter study evaluating the use of FFP in management of acute variceal bleeding reported increased mortality and 5-day rebleeding risk in those who received FFP after adjustment for confounders.[44]

There are increasing guidance documents from expert societies recommending against the prophylactic use of FFP in the periprocedural setting (Table 2) irrespective of procedural bleeding risk.

5.2 | Cryoprecipitate and fibrinogen concentrates

There are few studies investigating the effects of concentrated sources of fibrinogen (cryoprecipitate or concentrates) on hemostasis in patients with cirrhosis but there are reports of increasing use associated with implementation of TEG in the peritransplantation setting.[45] There is potential for use to further increase in response to recent expert guidance documents.[11,46] Given *in vitro* data suggest an enhanced thrombogenicity of the fibrin clot in patients with cirrhosis and that fibrinogen is rarely <1 g/L in non-critically ill patients,[25,47] we suggest fibrinogen should not be routinely measured in the non-critically ill prior to elective procedures. There is considerable interest in fibrinogen as a predictor of mortality in patients with major bleeding, for example postpartum hemorrhage (PPH) or trauma, with similar analyses in cirrhosis.[27,48] As discussed above, there is conflicting data regarding the association between low fibrinogen and bleeding.[27] In the cohort adjusting for disease severity, there was no independent association between fibrinogen level and mortality. Additionally, the use of cryoprecipitate did not influence bleeding rates or survival.[28] There are no prospective studies evaluating the role of cryoprecipitate/fibrinogen concentrates in patients with cirrhosis in the periprocedural setting. While it may be common practice to do so in the critical care setting, we suggest prophylactic use of cryoprecipitate/fibrinogen concentrates is not indicated. It may have a role as rescue therapy in those with post procedural bleeding and hypofibrinogenemia.

5.3 | Prothrombin complex concentrate and recombinant activated factor VII

Prothrombin complex concentrate (PCC) may be viewed as an attractive alternative for coagulation factor replacement given the considerably smaller volume required. As discussed above there is no evidence to support correcting PT/INR and limited data on PCC in cirrhosis outside liver transplantation, or indeed any clinical setting.[49,50] PCC should therefore be avoided in the periprocedural setting. Recombinant activated factor VII (rFVIIa) has been used in two randomized clinical trials of patients with variceal bleeding[51,52] and in two studies of patients undergoing liver transplantation.[53,54] The above studies showed poor efficacy of rFVIIa to stop bleeding, despite its efficacy in shortening the PT.

5.4 | Tranexamic acid

Antifibrinolytics have an established role in reducing bleeding in other clinical settings, for example, trauma and PPH.[55,56] However, there was no benefit seen in reducing gastrointestinal bleeding with evidence of increased thrombosis in those with cirrhosis in the HALT-IT trial.[57] There are no studies evaluating its role in patients with cirrhosis in the periprocedural setting but it is recommended as a potential rescue intervention in the management of periprocedural bleeding.[58]

TABLE 2 Thresholds for coagulation parameters prior to high risk procedures in patients with cirrhosis

	ISTH 2021	AASLD 2021[3]	AGA 2021[4]	ACG 2020[46]	SIR 2019[11]
PT/INR	Do not evaluate routinely	Do not correct	Do not evaluate routinely	Do not correct	INR>2.5[a]
Platelet count	Do not correct[b]	Do not correct	Do not evaluate routinely	$>50 \times 10^9$/L	$>30 \times 10^9$/L
Fibrinogen	Do not evaluate routinely	Do not correct	Do not evaluate routinely	No specific recommendation	>1 g/L
VHA	Do not use routinely	Do not use routinely	No recommendation	May be useful	No specific recommendation

Note: Table adapted from Northup et al. with permission from Wiley.[3]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; FFP, fresh frozen plasma; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PCC, prothrombin complex concentrate; PT, prothrombin time; SIR, Society of Interventional Radiology; VHA, viscoelastic hemostatic assay.

[a]Give vitamin K if INR>2.5, do not use FFP/PCC.

[b]Consider correction prior to planned elective very high risk procedures.

5.5 | Vitamin K

Vitamin K deficiency can predispose to bleeding but is rare in ambulatory patients with stable cirrhosis. Replacement of vitamin K may (partially) correct a prolonged PT/INR in patients with cirrhosis admitted to hospital with acute illness in the context of prolonged antibiotic use, malnutrition, or cholestasis.[58] A single dose of 10 mg may be considered; if there is no change in PT/INR at 12–24 h, repeated dosing is not recommended. The effect of vitamin K replacement in this setting has not been formally evaluated to our knowledge.

6 | BENEFITS/RISKS OF INTERVENTIONS TO ADDRESS THROMBOCYTOPENIA IN THE PERIPROCEDURAL SETTING

6.1 | Platelet transfusion

From a clinical standpoint, platelet transfusions are standard of care and often considered routinely pre-procedure for patients with cirrhosis to improve platelet counts with no strong evidence basis in this setting. Recent randomized controlled trials in patients with intracerebral hemorrhage reported more deaths, bleeding, and poor neurological recovery with liberal platelet transfusion.[59]

In one prospective study of 852 procedures in 363 patients with cirrhosis with varying disease severity, platelet infusions did not improve the platelet counts while the rare post-procedural bleeding events were not predicted by the lower counts.[60] One of the commonest procedures which patients with cirrhosis undergo is dental extractions. A retrospective analysis of more than 1100 extractions in 318 patients, a platelet count $>40 \times 10^9$/L (and INR<2.5) was associated with no cases of severe bleeding.[61] Another clinical context in which hemostatic support may be required in patients with cirrhosis is for critically ill patients. Drolz et al. identified platelet count $<30 \times 10^9$/L (and fibrinogen level <60 mg/dL and activated partial thromboplastin time [APTT] > 100 s) to be the strongest predictors for major bleeding in 211 patients with cirrhosis among nearly 1500 patients in a critical care unit in 1 year.[27] Of note, bleeding was predominantly gastrointestinal and related to portal hypertension. In this context, a useful clinical pointer is that platelet counts less than 30×10^9/L is rare in the setting of cirrhosis and should persuade clinicians to look for causes other than liver dysfunction for the thrombocytopenia. It may be considered good practice to regularly revisit and exclude treatable causes of thrombocytopenia in cirrhosis including:

- Treat immune thrombocytopenia that may be related to hepatitis B or C and autoimmune hepatitis.
- Discontinue drugs which may cause thrombocytopenia.
- Consider measures aimed at improving portal hypertension (e.g., splenic artery embolization and TIPSS placement)[62] as these interventions may improve platelet count.
- Correct hematinic deficiencies that can cause cytopenias.

When a patient with cirrhosis and thrombocytopenia needs to undergo an invasive procedure, an assessment of the individual's and procedural bleeding risk should be assessed (see Table 1). A detailed discussion with the patient should follow to include the:

- absence of strong evidence for platelet transfusions in this setting;
- standard risks associated with such blood product transfusions;
- experimental evidence for increased thrombin generation with platelet transfusions in patients with liver disease, indicating a prothrombotic effect; and[41]
- ability to treat the rare bleeding episodes that may develop post procedure.

6.2 | Thrombopoietin receptor agonists

As an alternative to platelet transfusions, three thrombopoeitin receptor agonists (TPO-RA) have been trialled in patients with liver disease who had thrombocytopenia: eltrombopag, avatrombopag, and lusutrombopag. Of these, the last two have obtained approval for use in patients with chronic liver disease (CLD) undergoing invasive procedures.[63] In patients with platelet counts $<50 \times 10^9$/L, avatrombopag and lusutrombopag increased the platelet counts adequately and reduced the frequency of platelet transfusions.[63-65] Maximum platelet counts were achieved at around 12 days from the first dose with the counts returning to patients' baseline levels by day 35.[64,65]

A recent meta-analysis from Italy that included almost 2000 patients concluded a 1.6% risk of portal vein thrombosis with TPO-RA versus 0.6% in the placebo group with a significant association observed only with eltrombopag.[66] Two further systematic review and meta-analyses of trials which used TPO-RAs for procedures in patients with CLD demonstrated these drugs to be significantly more successful in raising the platelet count greater than 50×10^9/L thus reducing the need for platelet transfusions. The impact on the clinically important endpoint of periprocedural bleeding was not consistent across the two analyses (of note the majority of bleeding events were mild to moderate), with both studies confirming no increase in the rate of thrombosis.[67,68]

7 | COMPARISON WITH OTHER SOCIETAL GUIDANCE DOCUMENTS

A number of other professional bodies have recently issued updated guidance on management of patients with cirrhosis undergoing procedures. These are summarized and contrasted with this document in Table 2.

8 | RECOMMENDATIONS

1. We suggest PT/INR, APTT, platelet count, and fibrinogen should not be routinely evaluated *to predict bleeding risk* prior

to procedural intervention in patients with cirrhosis, even in those who are critically ill.
2. We recommend potentially modifiable risk factors for bleeding should be addressed in the periprocedural setting (particularly prior to high-risk procedures) including renal impairment, sepsis, and anticoagulant/antiplatelet agents.
3. We recommend investigating causes of thrombocytopenia other than liver disease in those with platelet counts less than 30×10^9/L.
4. We recommend against prophylactic correction of abnormal coagulation parameters in the periprocedural setting in the absence of vitamin K antagonist use.
5. We recommend no treatment to increase the platelet count prior to most procedures for patients with cirrhosis.
6. We suggest strategies to increase the platelet count prior to *very high-risk* surgery (e.g., neurosurgery and intraocular surgery, see Table 1).
7. These strategies may include platelet transfusions (administered an hour before) in non-elective cases or elective cases when thrombopoietin receptor agonists are unavailable or unsuitable. Thrombopoietin receptor agonists to raise platelet count prior to *very high risk* elective surgery may be offered if:
   - platelet counts are $30–50 \times 10^9$/L
   - there is no history of or risk factors for arterial or venous thrombosis.

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CONFLICTS OF INTEREST

We have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

LNR and JT drafted the manuscript; all other authors provided intellectual input for revisions of the draft. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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