Bleeding risk with invasive procedures in patients with cirrhosis and coagulopathy

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ABSTRACT

Purpose of review

Previous perceptions of cirrhosis as a hypocoagulable state have resulted in empirical blood product transfusions prior to invasive procedures. We evaluate procedure-related bleeding risks in patients with cirrhosis, assess the utility of conventional and newer global coagulation tests, and explore evidence surrounding prophylactic transfusion strategies.

Recent findings

Recent literature supports the concept of a rebalanced, albeit fragile, haemostasis equilibrium in cirrhosis, with a potential hypercoagulable tendency in stable patients. Standard coagulation tests provide a poor reflection of bleeding risks and yet are relied upon for transfusion thresholds. Consequently, a sizeable proportion of patients receive unnecessary blood products. The role of viscoelastic tests to guide transfusions requires further evaluation.

Summary

In stable cirrhotic patients procedure-related bleeding rates appear low. Prophylactic transfusion strategies based on arbitrary thresholds lack evidence of clinical benefit. There is a pressing need for point-of-care coagulation tests that represent the complex coagulopathy of cirrhosis, and well-powered randomised controlled trials to develop evidence-based pre-procedure transfusion guidelines.

Introduction

Cirrhosis has been traditionally perceived as a hypocoagulable state, prompting concern amongst clinicians over increased risks of bleeding when performing invasive procedures in this patient group [1]. As a consequence, it has remained common practice to empirically transfuse patients with impaired coagulation parameters with platelets, plasma or pro-haemostatic agents to reduce bleeding risk. Recent literature has, however, challenged this notion by acknowledging the presence of a re-balanced haemostasis equilibrium in stable patients with cirrhosis [1-3]. This suggests that conventional concerns over augmented bleeding risks in cirrhosis are likely misconceived.

In this review we describe the altered haemostatic profile in patients with cirrhosis, the paradoxical pro-thrombotic tendency, and limitations of interpreting standard coagulation tests. We review recent literature assessing bleeding risks of invasive procedures in such patients, and evaluate whether empirical transfusion strategies and the use of global haemostasis assays may play any beneficial role in reducing procedure-related bleeding complications.

A rebalanced haemostasis equilibrium in cirrhosis

The liver plays a key role in haemostasis, as the primary site of synthesis for the majority of factors involved in coagulation and fibrinolysis. In addition, it produces thrombopoietin, which regulates the production of platelets from megakaryocytes. In cirrhosis, impaired protein synthesis leads to a marked reduction of both procoagulant factors (factors II, V, VII, IX, X, XI, XII) and anti-coagulant factors (anti-thrombin III, protein C and protein S) [2, 3].

An exception is von Willebrand factor (VWF), derived from endothelial cells and megakaryocytes, which has increased expression due to endothelial dysfunction and reduced levels of ADAMTS13, a VWF cleaving protease. VWF promotes platelet adhesion to endothelial surfaces, platelet aggregation under high shear stress, and acts as a carrier for the procoagulant factor VIII, preventing its degradation. Increased VWF expression thereby leads to elevated factor VIII levels [2].

Thrombocytopenia occurs due to splenic sequestration from splenomegaly in portal hypertension, increased platelet destruction mediated by platelet-associated immunoglobulins, a reduced production of thrombopoietin, as well as toxic effects of ethanol on platelet production and function [3]. Unless the platelet count is severely low ($<50x10^9$/L) thrombocytopenia does not confer increased bleeding risk, as it is offset by higher levels of VWF, mediating greater platelet adhesion [2, 4]. In vitro studies have demonstrated normal thrombin generation in cirrhosis in the presence of endothelial-derived thrombomodulin, and adequate platelet counts ($>50x10^9$/L) [5, 6].

Hyper-fibrinolysis has been described in cirrhosis, resulting from elevated levels of tissue plasminogen activator and a deficiency of thrombin-activatable fibrinolysis inhibitor; both changes are proportional to the severity of liver disease [2, 3]. Not all studies agree though, and it is debated whether there may be compensation from a reduction in profibrinolytic factors [2].

Table 1 demonstrates the main alterations of haemostasis in cirrhosis. Overall, in stable cirrhosis, the normal generation of thrombin as well as the concomitant acquired deficiency of both procoagulant and anticoagulant factors restores a balance in haemostasis [2, 3]. This

rebalanced equilibrium is fragile, and can easily be tipped towards haemorrhage or thrombosis in the presence of infection, renal dysfunction or variceal haemorrhage [7]. Endogenous heparin-like effects have been demonstrated in cirrhotic patients with bacterial infections [8], explaining the role of sepsis as a contributing factor for bleeding.

Additionally, there is evidence to suggest that stable patients with cirrhosis may in fact exhibit a pro-thrombotic tendency [9], while bleeding risks appear more related to the degree of portal hypertension and collateral vessel formation rather than defective haemostasis [7]. The hypercoagulability in cirrhosis is likely to result from an increased Factor VIII to protein C ratio, as well as thrombomodulin resistance [10, 11].

Standard coagulation tests as a measure of bleeding risk in cirrhosis

Misperceptions of the bleeding risk in cirrhosis largely derive from clinicians' interpretation of standard coagulation tests, including prothrombin time (PT), international normalised ratio (INR), and activated partial thromboplastin time (APTT). However, as these conventional coagulation tests only provide a measure of procoagulant factors and are insensitive to the plasma levels of anticoagulant factors, they do not provide an accurate evaluation of the altered in-vivo haemostatic balance [2, 12].

Although INR is a marker of protein synthetic dysfunction and forms part of the Model for End Stage Liver Disease (MELD) prognostic score, it is a poor indicator for bleeding risk in cirrhosis. Thromboplastin calibration uses plasma obtained from patients taking vitamin K antagonists, and has not been validated or standardised in liver disease [13]. PT and APTT only detect the first 5% of whole thrombin formation, and are performed without adding

thrombomodulin, therefore they do not reflect levels of activated protein C, a principal anticoagulant which relies on thrombomodulin for activation [13]. The lack of reliability of PT or INR to assess coagulation status in cirrhosis has been recognised in the Baveno VI guidelines [14]. Furthermore, a recent meta-analysis comprising 11 guidelines and 64 studies, found only three prospective trials evaluating the use of standard plasma coagulation tests to assess coagulopathy and guide peri-operative bleeding management. The meta-analysis was not confined to patients with cirrhosis, but concluded there was no robust evidence that standard coagulation tests could provide reliable data for assessing coagulopathy, predicting bleeding risks or guiding peri-operative haemostatic therapy [15].

Global haemostasis assays to predict bleeding risk in cirrhosis

There has been considerable recent interest in the role of global haemostasis assays, in particular whole blood viscoelastic tests (VETs), as potential tools to provide more physiologically relevant insights into the coagulopathy of liver disease. Two commercially available VETs currently in clinical use include thromboelastography (TEG®, Haemonetics Corporation, Braintree, MA, United States) and rotational thromboelastometry (ROTEM® Delta, TEM international GmbH, Munich, Germany) [12].

VETs are increasingly being used as point-of-care tests to guide the rapid assessment and management of coagulopathies in trauma, surgery and liver transplantation. VETs provide a dynamic assessment of haemostasis, evaluating the kinetics of the entire coagulation process from initial clot formation to final clot strength, and provide a more comprehensive reflection of the interaction between plasma, blood cells and platelets [12].

Literature evaluating the use of VETs does, however, show discrepancies between results. Cirrhotic patients have demonstrated normal global haemostasis as assessed by TEG, corresponding with the concept of a rebalanced haemostasis equilibrium [16, 17]. In a cohort of 273 stable cirrhotic patients, the median and mean TEG parameters were within normal limits, although the maximum amplitude (MA) decreased proportionally to the degree of thrombocytopenia [16]. An exception to this was patients with cholestatic liver diseases, who demonstrated hypercoagulability and higher clot firmness [18]. On the contrary, other recent studies have identified a hypocoagulable TEG profile in cirrhosis, indicating slower and less stable clot formation compared to healthy controls [12, 19]. In an Italian prospective study of 261 cirrhotic patients undergoing liver transplantation, TEG values were outside the normal reference ranges in 79.3% of patients, with a trend to hypocoagulability [19]. Similarly, in a single-centre prospective study of 40 patients with cirrhosis, ROTEM demonstrated hypocoagulability despite preserved or increased endogenous thrombin potential [20].

Attempting to define specific VETs reference ranges for cirrhotic patients, rather than using current reference ranges derived from healthy individuals, may provide a more reliable estimation of coagulation status and bleeding risks [19], however is likely to prove difficult due to expected variability between patients depending on the aetiology and stage of liver disease [17].

Other limitations with the use of VETs need to be taken into consideration; platelet dysfunction is not detected, factor XIII is not adequately displayed, and the assays are insensitive to detect effects of VWF involved in the initiation of clot formation [21]. There are also concerns over standardisation of assays and reproducibility of results given inter-operator variability. A UK quality assurance investigation showed a wide variation of TEG

results between centres [22]. Consequently, while TEG is being used to guide pro-haemostatic product repletion during liver transplantation, there remains insufficient evidence to support the routine use of VETs as a predictor of bleeding risk in cirrhosis, and further evaluation is required.

Paradoxical thrombotic potential and role for anticoagulation in cirrhosis

Contrary to traditional concerns for a predominant haemorrhagic potential, there is growing recognition that cirrhotic patients are at increased risk of venous thromboembolism (VTE) [9, 10, 23]. A recent systematic review and meta-analysis identified an increased risk of deep vein thrombosis (7 studies, OR=2.038, 95%CI=1.817-2.285) and pulmonary embolism (5 studies, OR=1.655, 95%CI=1.042-2.630) in cirrhotic patients compared to controls [23]. A higher 30-day mortality rate following VTE in cirrhotic patients was also observed [24, 25].

The one-year incidence of portal vein thrombosis (PVT) in patients with Child Pugh A or B cirrhosis was demonstrated at 4.6% [26], increasing to 16.6% in a cohort of patients with Child Pugh B or C cirrhosis [27]. The overall prevalence of PVT in cirrhosis is between 10-25%, often leading to portal hypertensive complications [9]. Anticoagulation is indicated in selected cases to prevent extension of the thrombus and in some cases enables splanchnic vein recanalisation [9]. A treatment algorithm using anticoagulation with or without TIPS can improve outcomes in such patients [28] .

Interestingly, additional benefits of anticoagulation in patients with cirrhosis without PVT have been demonstrated. In a single-centre non-blinded randomised controlled trial (RCT) of 70 patients with Child Pugh B or C cirrhosis, a 48-week course of enoxaparin 4000IU daily

resulted in a lower incidence of portal vein thrombosis, with no adverse bleeding events. Secondary outcomes included fewer decompensation events and a higher survival rate compared to the control group. It was hypothesised that a potential protective effect of enoxaparin on decompensation events may be mediated through improved intestinal microcirculation, thereby reducing enterocyte damage and bacterial translocation [27]. A double-blinded multicentre RCT (CIRROXABAN) evaluating the effect of rivaroxaban on the development of portal hypertensive complications and 24-month transplant-free survival in patients with cirrhosis is currently underway (NCT02643212).

Anticoagulation may also have antifibrotic effects. Micro-vascular ischaemia has been implicated as a key factor in the progression of hepatic fibrosis and cirrhosis [29, 30]. Wanless proposed that microthrombi occlusion of branches of the portal and hepatic veins leads to sinusoidal injury, tissue ischaemia and subsequent areas of parenchymal extinction: contiguous hepatocyte apoptosis with replacement by fibrous tissue [30]. Prevention of microthrombi through prophylactic anticoagulation may counteract this. Animal models have demonstrated an improvement in hepatic fibrosis from low molecular weight heparin or warfarin therapy [31, 32]. Interim per-protocol analysis from a UK multicentre open-label RCT (WAFT-C) of warfarin therapy in HCV patients post liver transplantation, has shown a significant reduction in fibrosis progression one-year post transplantation in the warfarin group [33]. Evaluating whether prophylactic anticoagulation could potentially reduce the progression of liver fibrosis, through inhibiting the actions of coagulation factors directly on hepatic stellate cells, represents an exciting area of future research.

Bleeding rates of invasive procedures in patients with cirrhosis

In view of the lack of standardised tests that reliably predict bleeding risk in cirrhosis, invasive procedures in these patients are often met with a degree of unease. However, since liver transplantation can feasibly be performed without requiring blood product replacement, it suggests that the altered haemostatic profile of cirrhosis does not translate to diffuse bleeding risk. Recent studies support this, showing little evidence to suggest a higher prevalence of postprocedural bleeding following invasive procedures (Table 2) [34-39].

A multicentre prospective study assessed the frequency of clinically significant bleeding in 380 cirrhotic patients with or without abnormal coagulation parameters, defined as an INR $\geq$1.5 and/or platelet count $\leq 50 \times 10^9$/L, undergoing both low and high risk invasive procedures [34]. No patients received pre-procedural blood product transfusions. In the low-risk procedure group, mostly entailing abdominal paracentesis, no patients had clinically significant post-procedure bleeding. In the high-risk group, including central venous cannulation or percutaneous liver biopsy, three patients in the abnormal coagulation group had clinically significant bleeding, but this did not reach statistical significance (p=0.061). All three patients with clinically significant bleeding had Child Pugh C cirrhosis, elevated INR and low platelet count, and additional contributing factors of sepsis or acute kidney impairment (AKI) [34]. Similar patients with an elevated INR and low platelet count undergoing high risk procedures, but without additional sepsis or AKI, did not experience clinically significant bleeding. This study implies that invasive procedures can be safely carried out in stable cirrhotic patients without empirical transfusion of pro-haemostatic products; with no pronounced increased bleeding risks in cases of thrombocytopenia and/or prolonged INR.

Additionally, in an Italian case series of 363 cirrhotic patients undergoing a total of 852 invasive procedures, post procedural bleeding was infrequent, occurring in one in every 36 patients, was more common in patients who underwent repeat procedures, and was unrelated to the platelet count, INR, Child Pugh grade, MELD score or risk category of invasive procedures. In fact, none of the ten patients with the most deranged coagulation parameters experienced post-procedural bleeding, including several cases of uncorrected pre-procedure platelet counts of less than $20x10^9$/L or INR values above 2 [37].

Other studies have evaluated bleeding rates in cirrhotic patients according to specific procedure types. In a retrospective USA study of 240 patients undergoing cardiac catheterisation, no procedure-related bleeding events or major vascular complications occurred. INR values ranged from 0.93 to 2.35. 17 patients received fresh frozen plasma (FFP) pre-procedure, in most cases without a significant reduction in INR. No correlation was found between post-procedure changes in haemoglobin and INR values [35].

A small retrospective Korean study of 30 patients with predominantly Child Pugh grade A or B cirrhosis undergoing colonoscopy with polypectomy, found a low rate of immediate post-polypectomy bleeding. The mean prothrombin time of patients was 1.3, and the mean platelet count was $137x10^9$/L. Only 2/66 polyp removals resulted in mild oozing, which was controlled by the application of haemoclips, with no delayed post-polypectomy bleeding [36].

A large retrospective single centre study in USA analysing complications from 3357 percutaneous liver biopsies performed with Klatskin needles across a 36-year period, identified a low total bleeding rate of 0.6% (21/3357 biopsies) [38]. Patients with bleeding complications had higher total bilirubin and alkaline phosphatase levels, and lower albumin

levels. The median pre-biopsy platelet count, PT and APTT did not differ between patients that did or did not experience bleeding complications, however multivariate backward stepwise logistic regression identified a combination of APTT >35s and platelet count ≤100 $x10^9$/L, as predictors of bleeding risk. An elevated PT >13.5s was not significantly associated. Three patients (0.09% of the total cohort) died from massive intraperitoneal haemorrhage; all had been acutely unwell prior to the procedure. Individual coagulation parameters were not described. One patient had decompensated hepatitis C virus (HCV) cirrhosis and a focal liver lesion, the second had decompensated cirrhosis with an underlying glycogen storage disorder, and the third had severe graft-versus-host disease with hepatic involvement following a previous bone marrow transplant. Arterial embolisation and surgical intervention were attempted but unsuccessful [38].

Bleeding complications following percutaneous liver biopsies remains overall though a rare event. A total bleeding rate of 0.6% (16/2740 procedures) was identified in a cohort of patients with HCV and advanced fibrosis or cirrhosis enrolled in the HALT-C trial. Bleeding risk was higher in patients with a platelet count of less than $60x10^9$/L, while none of the eight patients with an INR above 1.5 experienced bleeding complications [39].

In our centre, percutaneous liver biopsies require a platelet count of above $50x10^9$/L and INR less than 1.5; outside these parameters, transjugular liver biopsies are preferred, without necessitating prophylactic transfusions. For radiofrequency ablation of hepatocellular carcinoma, we require a platelet count of above $70x10^9$/L and INR below 1.8. We do not routinely correct deranged coagulation parameters for abdominal paracentesis, banding of oesophageal varices or central venous cannulation in stable cirrhotic patients; experienced operators are recommended to minimise procedural bleeding risks.

Our practice remains the same for patients with compensated and decompensated cirrhosis, provided there is no active bleeding. Invasive procedures in cirrhotic patients with renal failure, sepsis or disseminated intravascular coagulation, however, pose greater uncertainty as the fragile haemostasis equilibrium is disrupted. There is an apparent paucity of literature in this area, thus the best approach to procedure management in these patients has not been established. Acknowledged limitations of standard coagulation tests also provides additional challenges. In cirrhotic patients with renal failure, we opt for more conservative platelet thresholds due to anticipated platelet dysfunction, transfusing a single pool of platelets for a pre-procedure platelet count of less than $80x10^9$/L. In patients with sepsis our standard practice is unchanged, except in cases of disseminated intravascular coagulation, where due to considerably augmented bleeding risks we aim to correct deranged coagulation parameters prior to invasive procedures to achieve a target INR of less than 1.5 and platelet count above $50x10^9$/L.

Empirical transfusion strategies prior to invasive procedures

In a retrospective study of 1595 cirrhotic patients across 11 tertiary-care hospitals in China, 14.8% of patients received one or more plasma transfusions during their hospital admission. The majority of plasma transfusions (73.3%) were administered to patients without signs of bleeding, and in 70.4% of cases there were no planned invasive procedures [40].

There is a recognisable lack of well-powered randomised controlled trials to provide evidence based pre-procedure transfusion guidelines. Recently updated recommendations from the British Committee for Standards in Haematology advise platelet transfusion thresholds

according to procedure type; less than $50x10^9$/L for percutaneous liver biopsy or major surgery, less than $20x10^9$/L for central venous line insertion, and no routine platelet transfusion for bone marrow aspiration or trephine biopsy. No specific recommendations for cirrhotic patients are defined [41].

Traditionally patients with cirrhosis have been empirically transfused with plasma or pro-haemostatic agents prior to invasive procedures in an attempt to reduce bleeding complications. Evidence supporting this practice is however lacking, and a sizeable proportion of inpatients with cirrhosis end up receiving unnecessary transfusions. An INR above 1.5 and a haemoglobin level less than 8g/dL represent arbitrary thresholds used to guide pre-procedure prophylactic FFP and red blood cell (RBC) transfusions respectively, although this practice remains essentially habit driven rather than evidence-based [15]. UK [42] and Baveno VI [14] guidelines for the management of variceal bleeding in cirrhotic patients recommend RBC transfusion to a target haemoglobin between 7g/dL and 8g/dL, with consideration for individual patient factors and haemodynamic stability.

A UK nationwide prospective audit of 1313 consecutive patients with cirrhosis across 85 hospitals, found that 30% of patients were transfused at least one blood product during admission. In 61% of cases this was for treatment of bleeding, and in 39% for prophylaxis. There were no planned invasive procedures in 61% of patients that were prophylactically transfused. In the bleeding group, 25% of patients received RBC transfusion for a haemoglobin >8g/dL, 40% received FFP for an INR<1.5, and 46% received platelets for a pre-transfusion platelet count $\geq 50x10^9$/L. In the prophylaxis group, in the absence of bleeding, 29% of patients received FFP, 20% received RBC for a haemoglobin >8g/dl, and 36% received platelets prior to procedures for a platelet count $\geq 50x10^9$/L [43]. The

widespread practice of unnecessary transfusions in this patient population carries a significant financial impact and increases demands on an already scarce resource.

A single-centre observational study evaluating hospital blood product use, showed that patients with liver disease disproportionately received 32.4% of all FFP administered, the majority for pre-procedure prophylaxis [44]. However, no clear benefit to this practice has been demonstrated. In a case series of 363 cirrhotic patients, the transfusion of platelets or FFP prior to invasive procedures led to only a modest improvement in platelet count or INR, without any evidence for clinical benefit, and in the majority of cases not achieving normalisation of coagulation parameters. In fact, no bleeding events occurred in all 89 patients with platelet counts below $50x10^9$/L, challenging the widely-employed platelet transfusion threshold [37].

As well as increased healthcare costs from the unnecessary transfusion of blood products, the risks of inflicting harm need to be considered. Although rare, transfusion related adverse reactions after FFP have been demonstrated, including transfusion-related acute lung injury, bacterial infections and volume overload [45]. Over-transfusion of RBC in the context of variceal bleeding is associated with worse outcomes, likely due to a rise in portal venous pressure. A RCT of 921 patients with severe acute upper gastrointestinal bleeding showed that a restrictive transfusion strategy (transfusion for a haemoglobin below 7g/dL) in cirrhotic patients was associated with reduced rates of re-bleeding and fewer adverse events compared to a liberal transfusion strategy (transfusion for a haemoglobin below 9g/dL). Subgroup analysis further demonstrated a lower mortality rate with restrictive transfusion for patients with Child Pugh A or B cirrhosis [46].

The practice of transfusing platelets pre-procedure remains arbitrary, as neither a threshold value to trigger transfusion nor an effective target platelet count to aim for have been established [2]. In a cohort of 26 thrombocytopenic patients with cirrhosis (platelet count $<50\times10^9$/L) undergoing variceal ligation, the transfusion of a single adult platelet pool was barely able to increase the platelet count. There was no significant effect on thrombin generation, and while a marginal improvement in thromboelastography occurred, no patients reached normal values. Whether more vigorous transfusion strategies aimed at achieving greater increases in platelet levels may normalise global haemostasis results and confer true prognostic benefit remains to be elucidated [5].

Initial studies evaluating the use of thrombopoietin receptor agonists prior to elective invasive procedures in patients with cirrhosis, demonstrate a rise in platelet counts thus reducing platelet transfusion requirements, but with no established reduction in bleeding events (53-57). In a single-centre double-blinded RCT of 292 cirrhotic patients (platelet count $<50x10^9$/L), avoidance of platelet transfusions prior to elective procedures was achieved in 72% of patients who received 14-days of eltrombopag, compared with 19% of patients in the placebo group ($p<0.001$). Higher pre-procedure platelet counts achieved by the treatment group did not improve bleeding outcomes; however, the risk of thrombotic events increased when the platelet count exceeded $200x10^9$/L. Thrombosis of the portal venous system was observed in six patients in the eltrombopag group compared with one patient in the placebo group, resulting in early termination of the study (54). Therefore, eltrombopag is not currently recommended as an alternative to platelet transfusions in cirrhotic patients with thrombocytopenia undergoing invasive procedures. Other thrombopoietin receptor agonists, romiplostim and avatrombopag, show efficacy in improving platelet counts but detailed data regarding adverse events are not provided and larger scale RCTs are required (55-57).

Coagulation factor concentrates, such as recombinant factor VIIa and prothrombin complex concentrate, have also been suggested as potential alternatives to reduce bleeding risk [47, 48]. Case reports for the prophylactic use of factor VIIa prior to invasive procedures in stable cirrhotic patients with a prolonged INR have been described [48], however strong evidence for its efficacy is lacking, and concerns remain over its cost effectiveness and pro-thrombotic potential. A multicentre RCT found no significant effect of recombinant factor VIIa therapy on controlling 24-hour bleeding, preventing clinically significant re-bleeding or improving day five mortality following variceal bleeding in patients with advanced cirrhosis. No overall difference in adverse events was demonstrated compared to placebo, though arterial thromboembolic events were only observed in the factor VIIa treatment group [49]. RCTs are underway to assess the impact of pre-operative administration of prothrombin complex concentrate on perioperative blood loss and transfusion requirements during liver transplantation [47].

VETs guided pre-procedure transfusions

The first clinical use of TEG in patients with liver disease was to guide the administration of pro-haemostatic products in patients undergoing liver transplantation [18]. However, the efficacy of TEG guided transfusion strategies in reducing bleeding risks from other invasive procedures remains under evaluation. Moreover, the proposed TEG cut-off values for transfusion are subject to great variability.

In a prospective trial of 28 patients undergoing liver transplantation, patients monitored intra-operatively by TEG received significantly less FFP compared to patients monitored by

standard coagulation tests (mean 12.8 units vs. 21.5 units), with no difference in three-year survival [50]. Similarly, a significant reduction in RBC, FFP and platelet transfusions with ROTEM-guided haemostasis management was observed in a prospective study of 200 patients undergoing liver transplantation. The incidence of blood product free transplantations increased from 5% to 24% [51].

A single-centre open label RCT compared a TEG-guided pre-procedure transfusion protocol against standard of care in 60 cirrhotic patients (60% Child Pugh C) with significant coagulopathy, defined as an INR>1.8 and/or a platelet count<$50x10^9$/L. Abdominal paracentesis was the most commonly performed procedure, and endoscopic variceal banding was the most common high-risk procedure. All patients in the control group received blood products, compared to five patients in the TEG group (100% vs. 16.7%, p<0.0001). In both groups transfusion occurred more commonly in low-risk rather than high-risk procedures. Post-procedure bleeding was experienced by only one patient in the control group, with a pre-transfusion INR of 2.03 and platelet count of $111x10^9$/L, who underwent large volume paracentesis and had received prior FFP. No difference in 90-day survival was observed between the two groups [52]. A very low procedure bleeding risk (1.7%) was thus demonstrated, even in predominantly Child Pugh C patients. The bleeding risk was not related to coagulopathy or the use of transfusion products. A TEG-guided transfusion protocol resulted in 83.3% fewer blood products being used; moreover, the TEG thresholds used for transfusion (FFP if reaction time was >40min and/or platelets if maximum amplitude was <30mm) may be conservative and could be re-evaluated to further reduce unnecessary blood product use [52]. Additional RCTs are needed to validate these findings.

Conclusions

Cirrhosis is no longer considered to be a hypocoagulable state; in-vitro studies demonstrate the existence of a re-balanced haemostasis equilibrium, but this can easily be disturbed. In fact, patients with cirrhosis paradoxically often exhibit more of a pro-thrombotic tendency.

The risks of bleeding from invasive procedures in stable cirrhotic patients appears to be low, even in the presence of abnormal coagulation parameters. Empirical pre-procedure transfusion of blood products remains unnecessarily high due to arbitrary transfusion thresholds being relied upon, despite insufficient evidence for any clinical benefit. Conventional coagulation tests are limited in their ability to predict bleeding risk in cirrhosis and a growing body of evidence now questions their efficacy in guiding transfusion decisions.

There is a pressing need for more reliable and comprehensive coagulation tests that accurately represent the complex coagulopathy of cirrhosis and help guide the management of thrombotic or haemorrhagic complications. The use of VETs at present lacks sufficient evidence for routine clinical use but warrants further evaluation. In the meantime, given limitations in accurately predicting bleeding risks, decisions to proceed with invasive procedures in patients with cirrhosis should be made after careful consideration of risks and benefits.

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Table 1

Alterations of haemostasis in cirrhosis

	Pro-haemostatic mechanisms	**Anti-haemostatic mechanisms**
Primary haemostasis	Increased VWF Reduced ADAMTS-13	Thrombocytopenia
Coagulation	Increased Factor VIII Reduced production of anticoagulants: anti-thrombin III, protein C, protein S	Reduced production of procoagulant factors II, V, VII, IX, X, XI, XII
Fibrinolysis	Low levels of plasminogen Increased PAI-1	Increased tPA Reduced TAFI Reduced α2-antiplasmin

VWF, von Willebrand factor; *ADAMTS-13*, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (VWF cleaving protease); *PAI-1*, plasminogen activator inhibitor-1; *tPA*, tissue plasminogen activator; *TAFI*, thrombin-activatable fibrinolysis inhibitor.

Table 2

Bleeding rates of invasive procedures in patients with cirrhosis

Authors	**Study design**	**Number of cirrhotic patients (% of Child Pugh grade A/B/C)**	**Procedure types**	**Clinically significant bleeding complications (%)**	**Associations with bleeding complications**
Napolitano *et al.* (2017) [37]	Prospective single centre	363 (34%/43%/23%)	*Low risk:* endoscopic procedures, large volume paracentesis, dental extraction *Intermediate risk:* Percutaneous needle biopsy/HCC ablation, laparoscopic procedures	10/363 patients (2.75%)	Child Pugh A/B/C: 1/5/4 PLT/INR unrelated to bleeding risk PLT > 50: n=10, PLT ≤ 50: n=0 4 transfused PLT INR ≤1.3, n=5, INR >1.3, n=5 INR range 1.10 – 1.85 3 transfused FFP

			High risk: Vascular catheterisation, open incision in body cavity/tissue space		3 low risk/3 intermediate risk/4 high risk procedures
Takyar *et al.* (2017) [38]	Retrospective single centre, 36-year period	341/3357 confirmed cirrhotic (Child Pugh grade not specified)	Percutaneous liver biopsy with Klatskin needle	21/3357 procedures (0.63%)	Bleeding associated with: higher ALP, higher bilirubin, lower albumin, increased biopsy size APTT >35s and platelet count ≤100 K/μL predictors of bleeding risk (multivariate backward stepwise logistic regression) 3 died: intraperitoneal haemorrhage
Shah *et al.* (2015) [34]	Prospective multicentre	380 (39%/40%/21%) 128 with coagulopathy:	*Low risk:* abdominal paracentesis, endoscopic band ligation, glue	3/380 patients (0.79%)	Child Pugh A/B/C: 0/0/3 All 3 had INR ≥1.5 and platelet ≤50,000/cum, and contributing factors

		(INR ≥1.5 +/- platelet ≤50,000/cum) 252: No coagulopathy	injection, sclerotherapy *High risk:* major surgery, central vein cannulation, percutaneous liver biopsy, chemoembolization, endoscopic polypectomy		of sepsis or AKI 3 high risk/0 low risk procedures (p=0.061)
Townsend *et al*. (2012) [35]	Retrospective single centre	240 (Child Pugh grade not specified)	Cardiac catheterisation	0/240 patients (0%)	No major bleeding events INR range 0.93 - 2.35 (17 patients received FFP, 6 received PLT, 6 received RBC transfusion)
Jeon *et al.* (2012) [36]	Retrospective single centre	30 (70%/27%/3%)	Colonoscopy with polypectomy	0/66 procedures major bleeding 2/66 mild bleeding (3%)	Polyp size and morphology associated with immediate post-polypectomy bleeding No association with platelet count, INR,

					Child Pugh grade
Seeff *et al.* (2010) [39]	Retrospective multicentre	Biopsy total: 2740 in HCV advanced fibrosis or Child Pugh A cirrhosis	Percutaneous liver biopsy	16/2740 procedures (0.58%)	Bleeding rate associated with platelet count <60,000/mm^3, INR ≥1.3. But no patients with INR>1.5 had bleeding complications

PLT, Platelets; *INR,* International Normalised Ratio; *ALP,* Alkaline Phosphatase; *AKI,* Acute Kidney Injury; *FFP*, fresh frozen plasma; *RBC,* red blood cell; *APTT,* activated partial thromboplastin time.