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REVIEW

The coagulopathy of liver disease: a shift in thinking

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Abstract

The coagulopathy of chronic liver disease causes derangement of the results of traditional laboratory tests. As such, there is an expectation that when undergoing invasive procedures patients with cirrhosis are at increased risk of bleeding. Standard practice is to optimise laboratory values with prophylactic transfusions of platelets, plasma and fibrinogen to reduce perceived bleeding risk. There has been a shift in thinking regarding coagulation in patients with chronic liver disease, whereby a rebalancing of haemostasis occurs with reduction in both procoagulants and anticoagulants. Guidelines for the preprocedural management of patients with chronic liver disease are inconsistent and may not account for this new paradigm. The risk of prophylactic transfusion should be measured against the risk of bleeding while considering the rebalancing of haemostasis. Future management may be guided by whole blood viscoelastic tests or use of thrombopoietin receptor agonists to optimise patients in these scenarios.

Key words: Chronic liver disease; Cirrhosis; Coagulation; Invasive procedure; Prophylactic transfusion

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Introduction

Liver disease accounts for nearly 2 million deaths worldwide annually, with approximately 1 million deaths caused by complications of cirrhosis (Asrani et al, 2019). Cirrhosis is the end result of chronic liver disease, resulting in scar formation in the liver parenchyma and subsequent deterioration of the liver's synthetic function. The liver plays a central part in the body's haemostatic function through the synthesis of coagulation factors. The disturbance of coagulation factor synthesis in cirrhosis was traditionally thought to lead to increased bleeding risk (Lisman and Porte, 2010). Standard teaching was that the coagulopathy of chronic liver disease, demonstrated through abnormal results of tests of coagulation (platelet count, activated partial thromboplastin time and prothrombin time), should be prophylactically corrected to prevent procedural complications of bleeding, even in patients with a low risk of blood loss, for example those undergoing ascitic drain insertion or liver biopsy (Malloy et al, 2009).

Recently, there has been a shift in thinking, with evidence favouring the rebalancing of haemostasis in chronic liver disease. The idea of rebalancing of haemostasis may also occur in scenarios of acute liver failure, where both bleeding and thrombotic complication are seen. Alterations in haemostasis in patients with acute liver failure are part of the definition of the syndrome (international normalised ratio >1.5) and the criteria for transplantation. Correction of apparent coagulopathy without bleeding could lead to diagnostic and prognostic dilemmas (Lisman and Stravitz, 2015).

This article reviews the change in thinking around haemostasis in patients with chronic liver disease, as well as approaches to the management of coagulopathy.

The physiology of coagulation

The derangements of standard haematological indices in liver cirrhosis include prolongation of prothrombin time, activated partial thromboplastin time and international normalised ratio, thrombocytopenia and dysfibrinogenaemia – in most cases low fibrinogen on Clauss fibrinogen assessment. The prothrombin time and activated partial thromboplastin time were originally developed to assess and diagnose haemophilic blood disorders and evolved to be used in the measurement of the effectiveness of warfarin and heparin respectively. The international

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normalised ratio is a standardised measure of prothrombin time developed to monitor the effect of warfarin on coagulation, but is used in practice as a screen for coagulopathy.

The classical model of coagulation describes the activation of the intrinsic pathway when blood comes into contact with connective tissue in subendothelial vasculature. A cascade of activation of clotting factors ensues, culminating in thrombin generation. The extrinsic pathway is an alternative pathway of activation of the clotting cascade, which provides a more rapid response to tissue injury than the intrinsic pathway, but it is thought to augment the action of the intrinsic pathway rather than surpass it. The intrinsic and extrinsic systems meet at the activation of factor X to form the final common pathway of coagulation, results in the formation of thrombin (Figure 1).

The classical model of coagulation does not account for the interplay between coagulation factors and cellular components in clot formation and is more representative of in-vitro tests rather than in-vivo actions. The modern concept of clot formation can be described in the cell-based theory of coagulation (Palta et al, 2014). This incorporates humoral and cellular factors, separated into four phases: initiation, amplification, propagation and stabilisation (Figure 2).

Clot formation is initiated when tissue factor is exposed during vessel wall injury. Tissue factor is a transmembrane protein that acts as a cofactor for factor VII. The interaction between tissue factor and factor VIIa generates a small amount of thrombin. Circulating platelets are attracted to damaged tissue to form an initial platelet plug through their interaction with factor VIII and von Willebrand factor – this is primary haemostasis. The small amount of thrombin generated activates platelets to amplify the reaction (amplification). Activated platelets bind factors Va, VIIIa and IXa at their surface, resulting in a surge of thrombin generation (propagation). This thrombin burst results in conversion of fibrinogen to fibrin and clot development (Sucker and Zotz, 2015). The developing clot is stabilised

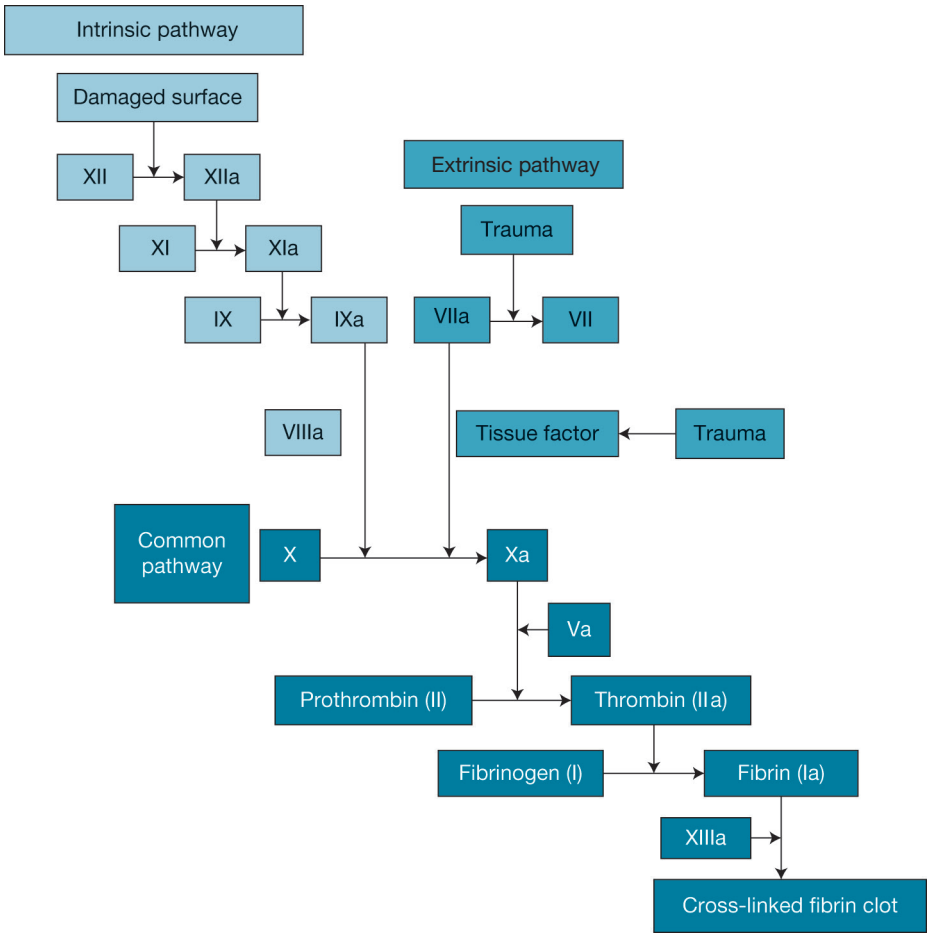

Figure 1. Classical model of coagulation, the intrinsic and extrinsic pathway meet at the activation of factor X to form the common pathway and lead to the formation of thrombin.

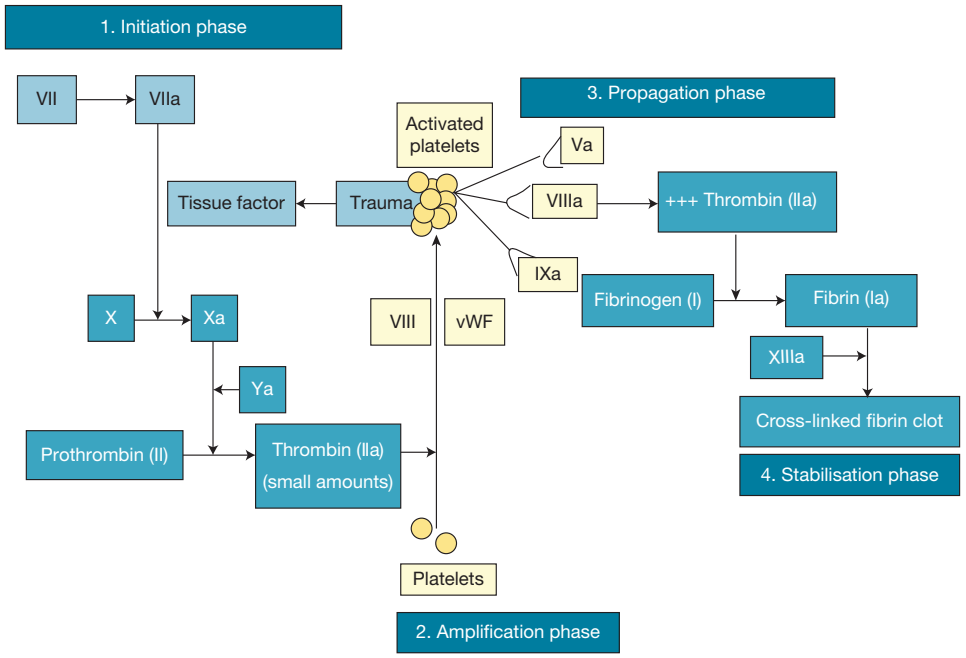

Figure 2. Cell-based theory of coagulation including initiation, amplification, propagation and stabilisation.

by activation of factor XIII, which provides strength and stability through covalent linkage of fibrin polymers. The overall stability of the clot is also dependent on activity of the thrombolytic and fibrinolytic system (Caldwell et al, 2006).

Rebalancing of haemostasis in liver disease

The liver is responsible for synthesis of coagulation factors (apart from von Willebrand factor), proteins required for fibrinolysis and thrombopoietin required for platelet synthesis. Liver disease therefore has an impact on the body's haemostatic function with a decline in levels of procoagulant factors and platelets available for clot formation (Lisman and Porte, 2010). A decrease in levels of procoagulants is accompanied by a decrease in anticoagulants, including antithrombin III and protein C. A reduction in both procoagulant and anticoagulant factors means that haemostasis is rebalanced in patients with liver disease. Thrombin generation is normal or elevated, leading to an increased risk of thrombosis rather than bleeding risk (Gatt et al, 2010) (**Figure 3**).

Basic tests of coagulation are used to assess bleeding risk in patients with and without cirrhosis, but prolonged prothrombin time and activated partial thromboplastin time in patients with cirrhosis correlate poorly with bleeding following invasive procedures (Segal et al, 2005). Standard tests of coagulation fail to accurately reflect in-vivo coagulation status as they do not account for cellular contribution or effects of anticoagulant factors. Reagents used to measure prothrombin time do not contain thrombomodulin, a protein responsible for activation of protein C and deactivation of thrombin. Prothrombin time therefore measures the amount of thrombin generated in the presence of procoagulant factors but not anticoagulant influencers (Tripodi et al, 2009).

Primary haemostasis and the formation of a platelet plug may be adversely affected by chronic liver disease. Moderate thrombocytopenia (platelet count $<50\times10^9$/litre) occurs in approximately 13% of patients with liver disease and can be associated with significant morbidity (Afdhal et al, 2008). Disease factors contributing to this reduction include low thrombopoietin levels and portal hypertension which causes hypersplenism and splenic sequestration. Despite low platelet counts, in-vitro studies have shown compensatory increases in von Willebrand factor (responsible for platelet adhesion) and a decrease in ADAMTS13 (the cleavage enzyme responsible for the breakdown of von Willebrand factor). In patients with cirrhosis, primary haemostasis has not been shown to be defective (Violi et al, 2011).

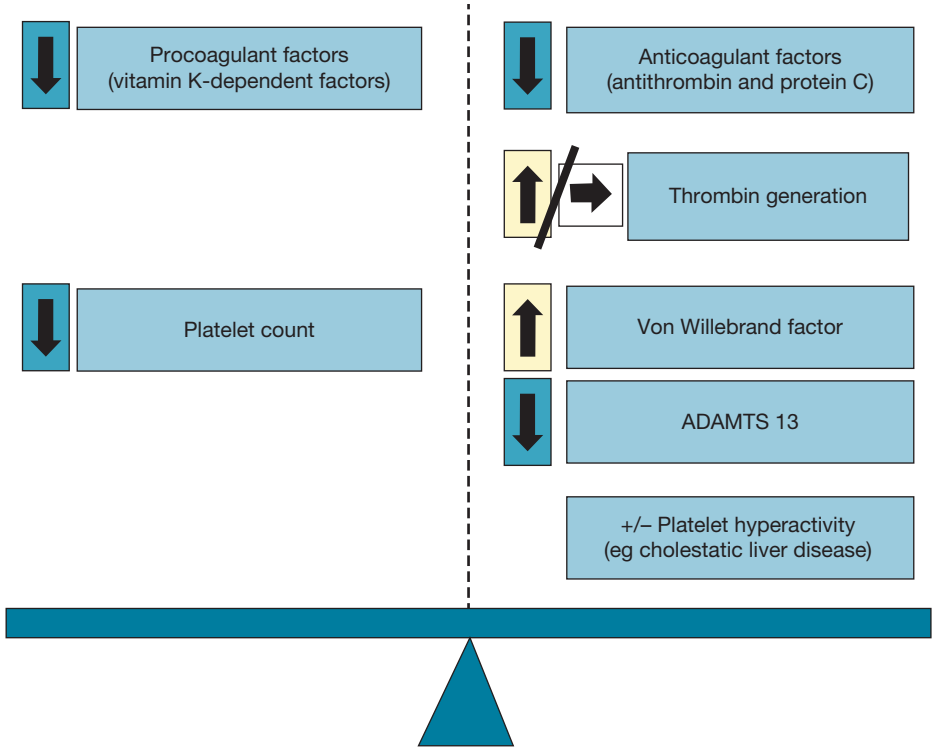

Figure 3. Rebalancing of haemostasis in patients with chronic liver disease. ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

Invasive procedures are frequently required in the management of chronic liver disease. Traditionally, a defined international normalised ratio and platelet count threshold is met when performing invasive procedures, supposedly reducing bleeding complications. To overcome this, platelet transfusion and fresh frozen plasma are used to meet pre-determined thresholds. Given the theory of rebalanced haemostasis in patients with chronic liver disease, it is important to consider the appropriateness of international normalised ratio and/or platelet count thresholds and review prophylactic transfusion guidelines.

Bleeding risk of invasive procedures in patients with cirrhotic coagulopathy

The bleeding risk in those with cirrhotic coagulopathy should be balanced against the intended benefits of the intervention and the risk of transfusion, before performing invasive procedures. Multiple studies report that bleeding complications secondary to invasive procedures in cirrhotic patients are uncommon, including a retrospective study reviewing bleeding risk following paracentesis in 3116 participants (95% of whom were diagnosed with cirrhosis) which reported significant bleeding in only six participants (Rowley et al, 2019). Similarly, bleeding complications were rare in a study of 852 invasive procedures in cirrhotic patients, with only ten bleeding episodes reported (Napolitano et al, 2017). Both studies reported that international normalised ratio and platelet count did not predict bleeding. In contrast, increasing severity of thrombocytopenia has been associated with increased bleeding risk and may be a significant factor in the assessment of bleeding risk (Giannini et al, 2010; Cocero et al, 2017; Li et al, 2018). The low risk of bleeding in cirrhotic coagulopathy can be explained by rebalancing of haemostasis.

The risks of blood product transfusion

Transfusion complications include allergic reactions, haemolytic reactions, transfusion-related acute lung injury, circulatory overload and septic transfusion reactions (Kiefel, 2008). Between 2010 and 2019 over 50% of all transfusion-associated deaths have been

the result of pulmonary complications (Narayan, 2020). The risk of transfusion-associated hepatitis B, C or HIV infection in the UK is low – in 2017 it was estimated as less than one in 2 million donations (Reynolds et al, 2019). Transfusion-associated sepsis, secondary to bacterial contamination of blood products, is a potentially life-threatening complication and platelet concentrates are more susceptible to bacterial contamination because of storage conditions (Prax et al, 2019). Bacterial screening of platelet concentrates has reduced the number of clinically adverse transfusion transmissions by 90%, increasing the safety of blood supply (McDonald et al, 2017). Transfusion-related immunomodulation also poses significant risk, caused by build-up of immune mediators in stored blood, foreign antigens in blood products and the interaction between donor and recipient cells (Waanders et al, 2008).

The cost of collection, testing, storage and distribution of blood products is significant. Additional costs, including management of adverse reactions and those secondary to postponed procedures, should be considered (Barnett et al, 2018). Hepatobiliary disease is reported as a leading indication for blood transfusion, yet availability is limited so appropriate use of resources is paramount (Wells et al, 2009).

Management of cirrhotic coagulopathy before an invasive procedure: current guideline and evidence

The 2019 Society of Interventional Radiology Consensus Guideline, endorsed by the Cardiovascular and Interventional Radiological Society of Europe, makes recommendations for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions (Patel et al, 2019). Procedural bleeding risk is divided into low risk (catheter exchanges, venous access, thoracentesis and transjugular liver biopsy) or high risk (solid organ ablation, gastrostomy placement and transjugular intrahepatic portosystemic shunt). Recommendations for patients with chronic liver disease when performing low-risk procedures are:

- International normalised ratio is not applicable
- Transfusing platelets to threshold of 20×10^9/litre
- Fibrinogen level >1 g/litre using cryoprecipitate.

In high-risk procedures, international normalised ratio should be corrected with vitamin K to <2.5 with platelet count $>30\times10^9$/litre and fibrinogen >1 g/litre (Patel et al, 2019).

The evidence base for this guideline is weak, including a poll of 95 attendees of the Coagulation in Liver Disease symposium. Of the participants 58% did not believe that international normalised ratio was a reliable indicator of procedural bleeding risk; nevertheless, 50% reported that they would transfuse before liver biopsy or dialysis catheter placement to aim for an international normalised ratio of <1.5, and 81% said they would aim for platelets $>30\times10^9$/litre (Caldwell et al, 2006).

An international survey reviewed transfusion practice in non-bleeding critically ill intensive care patients (not specific to patients with chronic liver disease). Participants reported transfusing to a higher platelet threshold for patients planned to undergo an invasive procedure, compared to patients with no upcoming procedures. There was variability in practice, with most transfusing to a platelet count of 40×10^9/litre pre-central venous catheter insertion and 50×10^9/litre for tracheostomy insertion. International normalised ratio was corrected by 31% of participants, most commonly using vitamin K followed by prothrombin complex and plasma (de Bruin et al, 2019).

The American College of Gastroenterology recommends that prophylactic transfusion of plasma to reduce bleeding risk in patients with cirrhosis is ineffective. It carries associated risk as large volumes of plasma are required to significantly reduce international normalised ratio, increasing portal pressure and the risk of variceal haemorrhage (Simonetto et al, 2020). They do not recommend prophylactic platelet transfusion before common invasive procedures and consideration should be made in patients with renal dysfunction and sepsis (Simonetto et al, 2020).

The British Society of Gastroenterology published guidelines for the management of ascites in cirrhosis, reporting no evidence for the use of prophylactic fresh frozen plasma for paracentesis, while platelet transfusion should be considered when platelet count is $<40\times10^9$/litre. This statement is based on how 'most clinicians' practice (Moore and Aithal,

2006). This guideline has recently been updated, recommending that routine measurement of platelet count before therapeutic paracentesis is not required, nor the infusion of blood products (Aithal et al, 2021).

A Cochrane review of transfusion of fresh frozen plasma pre-central venous catheter insertion in coagulopathic patients (not specific to cirrhosis) concluded that there was insubstantial evidence to guide the use of fresh frozen plasma transfusions before insertion of central lines in patients with abnormal coagulation. Only one randomised controlled study met the inclusion criteria for this review (Hall et al, 2016). This open-label trial included 81 critically ill patients with an international normalised ratio of 1.5–3. Patients were randomised to receive fresh frozen plasma or not, before undergoing an invasive procedure including central venous catheter placement, percutaneous tracheostomy, chest tube or abscess drainage. No significant difference in bleeding incidence was reported. The international normalised ratio reduced to <1.5 in just over half of the patients transfused with fresh frozen plasma. Fresh frozen plasma did not reduce the bleeding risk in coagulopathic patients (Müller et al, 2015).

Further evidence is required to come to a consensus regarding a platelet transfusion threshold when performing invasive procedures in cirrhotic patients. Across the guidelines reviewed, the recommendation for the use of fresh frozen plasma was consistent and transfusing with fresh frozen plasma before an invasive procedure to optimise the international normalised ratio was not recommended.

Management of cirrhotic coagulopathy before an invasive procedure: the future

Thromboelastography

Thromboelastography can be used to assess coagulopathy in cirrhotic patients (Hartert, 1948). This point-of-care test is a viscoelastic haemostatic assay measuring the properties of dynamic clot formation by placing whole blood in a cup with a rotating pin attached to a wire. Rotation of the pin is directly affected by the developing clot, allowing measurement of the elasticity and strength of the clot via a mechanical-electrical transducer. This produces measures which reflect clot formation and could more closely represent the balance of haemostasis (da Luz et al, 2013).

Thromboelastography is used to guide blood transfusion during liver transplant and complex cardiac surgery and may be appropriate to guide transfusion for invasive procedures in an intensive care setting. In patients receiving a liver transplant, thromboelastography significantly reduces fresh frozen plasma transfusion with no effect on 3-year survival (Wang et al, 2010). There is also evidence to support thromboelastography-guided intraoperative transfusion in patients undergoing complex cardiac surgery. Thromboelastography-guided transfusion significantly reduces the use of fresh frozen plasma and platelet transfusions, with no difference in mediastinal tube drainage 24 hours post-procedure (Shore-Lesserson et al, 1999).

Specific to invasive procedures, a randomised controlled trial used thromboelastography to guide product transfusion before invasive procedure in patients with cirrhosis, deranged international normalised ratio (>1.8) and platelets (<50×10^9/litre). Sixty patients were randomised to receive either thromboelastography-guided transfusion or standard care (to transfuse fresh frozen plasma, achieving international normalised ratio less than 1.8 and platelets >50×10^9/litre). It reported significantly fewer blood products transfused in the thromboelastography group (total thromboelastography group: 4000 ml fresh frozen plasma and 28 units of platelets) vs the standard care group (total standard group: 17 750 ml fresh frozen plasma and 106 units of platelets), with only one reported episode of post-procedure bleeding in the standard arm. Thromboelastography reduced the use of blood products with no increased risk of bleeding (De Pietri et al, 2016).

Thrombopoietin receptor agonists

Thrombopoietin receptor agonists are used to treat thrombocytopenia in patients with chronic liver disease for whom invasive procedures are planned. The ELEVATE trial compared eltrombopag, a first generation thrombopoietin agonist, to placebo in patients with chronic liver disease and thrombocytopenia when undergoing invasive procedures. In the treatment arm, 72% of patients avoided platelet transfusion compared to 19% in

the placebo arm and the risk of bleeding did not differ between the two groups. However, there was a correlation between the incidence of portal vein thrombosis and platelet count >200×10^9/litre in the eltrombopag arm. The study therefore ended early and its use is not recommended (Afdhal et al, 2012).

The evidence for generation two thrombopoietin agonists in the management of thrombocytopenia in chronic liver disease pre-procedure is more promising. The ADAPT-1 and ADAPT-2 trial were phase III, randomised, double-blinded, placebo-controlled, multicentre international trials. Patients with chronic liver disease and thrombocytopenia were randomised to receive either five daily doses of avatrombopag or placebo before scheduled invasive procedures. In the avatrombopag arm the number of participants not requiring platelet transfusions or intervention for bleeding was reduced compared to placebo. During the study period only three patients from the avatrombopag arm had a platelet count >200×10^9/litre, limiting the risk of portal vein thrombosis reported (Terrault et al, 2018).

Evidence for the use of thrombopoietin receptor agonists requires planned invasive procedures with scheduled administration of treatment to optimise the peak in platelet count (Hidaka et al, 2019).

Conclusions

The guidelines for the management of cirrhotic coagulopathy when performing invasive procedures are inconsistent. The understanding of coagulopathy secondary to cirrhosis, including the rebalancing of haemostasis, has evolved and guidelines should reflect this. The risk associated with transfusion of blood products for the correction of coagulopathy should be balanced against procedural complications and bleeding rates. Randomised controlled trials are needed to evaluate the risk and benefit of prophylactic strategies. Further work could evaluate the use of thromboelastography and thrombopoietin receptor agonists as alternative methods, to ensure patients with coagulopathy of cirrhosis can safely undergo invasive procedures.

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Key points

- Chronic liver disease results in the derangement of traditional measures of coagulation including platelet count, activated partial thromboplastin time and prothrombin time.
- The liver synthesises both procoagulants and anticoagulants, hence in chronic liver disease a reduction in both results in rebalancing of haemostasis. Traditional tests of coagulation do not reflect rebalancing, so should not be used to accurately predict bleeding risk.
- Preprocedure prophylactic fresh frozen plasma and platelet transfusions are used to reduce procedural bleeding risks, but the risk of product transfusion should be balanced against bleeding risk.
- There is no shared consensus for the preprocedural management of patients with cirrhotic coagulopathy. The use of prophylactic fresh frozen plasma to correct international normalised ratio is rarely recommended. The use of platelet transfusion is recommended but target thresholds remain variable.
- The preprocedural management of cirrhotic coagulopathy may be guided by the use of whole blood viscoelastic tests such as thromboelastography.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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