Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis☆

European Association for the Study of the Liver*

Summary

The prevention and management of bleeding and thrombosis in patients with cirrhosis poses several difficult clinical questions. These Clinical Practice Guidelines have been developed to provide practical guidance on debated topics, including current views on haemostasis in liver disease, controversy regarding the need to correct thrombocytopenia and abnormalities in the coagulation system in patients undergoing invasive procedures, and the need for thromboprophylaxis in hospitalised patients with haemostatic abnormalities. Multiple recommendations in this document are based on interventions that the panel feels are not useful, even though widely applied in clinical practice.

Introduction

Patients with cirrhosis frequently acquire substantial alterations in their haemostatic system that are apparent during screening with basic tests of haemostasis (mainly international normalised ratio [INR], activated partial thromboplastin time [APTT] and platelet count). Historically, these changes were thought to induce a haemostasis-related bleeding tendency.

Nowadays, however, it is well accepted that basic haemostasis tests, such as prothrombin time and APTT, do not truly represent the haemostatic system operating in patients with liver disease who remain in haemostatic balance, as both pro- and anti-haemostatic systems change simultaneously (reviewed in[1]).

Furthermore, it is also acknowledged that although patients with liver disease may experience bleeding complications, many of these bleeds are unrelated to haemostatic failure but are a consequence of portal hypertension or mechanical vessel injury, which could be caused by inadvertent vessel puncture during invasive procedures, for example. It has also been established that patients with cirrhosis are not protected from the occurrence of thrombosis and may require anticoagulant therapy for prevention or treatment of thrombotic episodes. The occurrence of both bleeding and thrombosis may pose difficult clinical questions, which will be addressed in these Clinical Practice Guidelines (CPGs).

The absence of high-quality clinical studies represents an additional challenge in constructing guidance. We have therefore attempted to base our recommendations not only on available clinical literature, but also on biochemical studies, so that our recommendations, when insufficiently supported by clinical data, have a mechanistic basis.

Clinical studies on bleeding and thrombosis in patients with liver disease have been of poor to moderate quality for reasons outlined elsewhere.[2] As an example, the question of how to manage haemostatic abnormalities prior to invasive procedures has not been addressed by adequately powered randomised studies. Ideally, a pragmatic study addressing this issue should include an arm where blood product transfusions are administered on the basis of pre-selected coagulation test cut-offs and a comparison arm where no prophylactic blood product transfusion is mandated, and only rescue treatment is allowed. However, although the results of such a study would provide a definite answer to this long-standing question, it is quite unlikely that it will ever be performed; taking into account the generally low incidence of bleeding (*e.g.*, approximately <1.5%) following the most common procedures, it would require the enrolment of a cohort of 1,531 patients *per* arm in order to detect a statistically significant increase (*i.e.*, from 1.5% to 3.0%, at least 100% of the baseline risk) in peri-procedural bleeding rate. Thus, although the low level of evidence for many of our recommendations should encourage the hepatology community to organise better quality studies, we should accept that many of these studies will not be performed in the foreseeable future. Nevertheless, we are convinced that there is reason to change some widely accepted treatment dogmas as we have outlined in this document.

Multiple recommendations in this document relate to interventions the panel responsible for drafting this document feel are not useful, even though they are currently widely applied in clinical practice. Even though there is no definitive evidence from well-designed clinical studies for many of the statements, the combination of potential harm, cost, and biochemical support for a lack of effect has led to these recommendations that are supported by both the writing panel and the Delphi panel (details provided in the next section). An example of such a recommendation is the advice not to attempt to correct prolonged prothrombin time in a patient with cirrhosis prior to a procedure, as there is evidence that a prolonged prothrombin time does not predict bleeding, likely because patients are in a 'rebalanced' haemostatic state. Furthermore, there is no clinical evidence that fresh frozen

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plasma (FFP) infusion reduces bleeding risk, and there is evidence for a lack of a biochemical response to FFP infusion in this setting. The writing panel proposes that all statements are valid for any patient with cirrhosis, including those who are critically ill. However, there are limited data on bleeding and thrombosis risk in critically ill patients with cirrhosis, and very little is known about the efficacy of pro- and anti-haemostatic interventions in these patients. Therefore, we propose that deviations from our recommendations may be justified in individual cases. For example, it may be justified to provide pro-haemostatic therapy in a patient with extreme changes in the haemostatic system when there is particular concern regarding bleeding among the treating physicians.

Methodology used for the development of the present CPGs

The EASL Governing Board has selected a panel of experts to prepare these CPGs with the purpose of providing the best available evidence on prevention and management of bleeding and thrombosis in patients with cirrhosis. The first task of the panel was to identify the most relevant topics and those for which substantial need for guidance existed. The identified themes were a) prevention of bleeding in patients with liver diseases, including spontaneous and procedure-related bleeding; b) management of bleeding episodes in patients with cirrhosis, including correction of haemostatic alterations c) prevention and management of thrombotic events in patients with liver diseases, including anticoagulant treatments; d) role of new oral anticoagulant drugs in patients with cirrhosis.

The EASL Governing Board has requested that CPGs be based on the PICO format (P Patient, Population, or Problem; I Intervention, Prognostic Factor, or Exposure; C Comparison or Intervention (if appropriate), O Outcome) questions.[3] The panel agreed to use the PICO format, although the panel noted that for some of the topics evidence of good quality was scarce.

An extensive literature search was performed using PubMed, Embase, Google Scholar and Scopus. The initial key words were: “Spontaneous Bleeding” OR “Procedural Bleeding” OR “Haemostasis” OR “Correction of Haemostatic alterations” OR “Invasive procedures” OR “Monitoring” OR “Routine coagulation tests” OR “Viscoelastic tests” OR “Thrombosis” OR “Clinical prediction scores” OR “VKA” OR “LMVH” OR “DOACs” AND “Liver cirrhosis” OR “Chronic liver Disease”. References from papers were searched and identified further.

The selection of references was based on appropriateness of study design, number of patients, and publication in peer review journals. Whenever available, meta-analyses were used; otherwise, original data were used. The quality of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) (adapted from The Oxford 2011 Levels of Evidence).[4] The levels of evidence were classified as follows: 1) systematic reviews (with homogeneity) of randomised controlled trials; 2) randomised controlled trials or observational studies with dramatic effects; systematic reviews of lower quality studies (*i.e.* non-randomised, retrospective); 3) non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study); 4) case series, case-control, or historically controlled studies (systematic review is generally better than an individual study); 5) expert opinion (mechanism-based reasoning).

Each panellist was responsible for a group of questions. After a first in-person meeting, due to the COVID-19 pandemic, all subsequent meetings were held by teleconference. All recommendations were discussed and approved by all panellists. The strength of the recommendations in these guidelines has been graded according to the OCEBM in 2 categories: strong or weak (2). A glossary has also been provided to standardise terminology and definitions. The PICO questions were sent to the Delphi panel made up of 34 international experts in hepatology, gastroenterology, haematology, anaesthesiology, internal medicine, surgery, endoscopy, and radiology with an interest in haemostasis in patients with liver diseases from Europe, Asia and America. After revision of the questions, answers to the questions and recommendations or statements were formulated based on available literature. The panel chose to formulate statements when insufficient evidence for a recommendation was available. The Delphi panel then examined the CPG. Returning scores were graded as follows: less than 50% approval: re-write recommendation and resubmit to the Delphi panel; 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; 75-90% approval: no need to re-write the recommendation but the document will take into account the comments; ≥90% approval: assumed as consensus, no change needed but small corrections possible. To consider a question approved, an agreement from at least 75% of Delphi panel members was required. All but two questions (which had scores of 62% and 69%) received a score above 75%, thus avoiding the need for revision. The final version of the CPG with the marginal corrections mentioned above, was finally sent for approval to the EASL Governing Board. This document is intended to be valid until September 2026 unless the EASL Governing Board indicates the need for an earlier update.

In patients with cirrhosis and abnormal laboratory tests (INR, APTT, platelet count, fibrinogen), is correction of these tests by blood products or factor concentrates indicated to prevent spontaneous bleeding?

Recommendation

- In patients with cirrhosis and abnormal laboratory tests (INR, APTT, platelet count, fibrinogen), attempting to correct these tests by administering blood products or factor concentrates, with the aim of preventing spontaneous bleeding, is not recommended **(LoE 3, strong recommendation).**

Future perspectives

Large observational studies aiming to define the precise incidence of spontaneous bleeding events and their impact on clinical course and survival of patients with cirrhosis are recommended.

Spontaneous haemostasis-related bleeding in cirrhosis is defined as an unprovoked haemorrhagic event of unexplained cause. This definition was recently introduced to distinguish bleeding occurring in patients with cirrhosis as a result of haemostatic abnormalities from bleeding related to portal hypertension, traumatic or iatrogenic vascular lesions, or peptic ulcers.[5] A list of spontaneous bleeding events classified according

to their clinical relevance is reported in Table 1, together with the criteria proposed by the International Society on Thrombosis and Haemostasis to define their severity.[6]

Clinically non-significant bleeding, such as bruises or epistaxis, is common in patients with cirrhosis and contributed to the traditional concept of this disease as exhibiting a bleeding phenotype. Several case reports and case series have been published on this subject. Ragni *et al.*[7] reported a case series of 30 patients with alcohol-related cirrhosis and haemostatic abnormalities: 21 patients (70%) had haemorrhagic complications, 1/3 of these presenting with clinically non-significant bleeding episodes (oozing from venepuncture sites, bruising, and epistaxis), with no difference in prothrombin time or APTT reported between bleeders and non-bleeders.

Gunawan *et al.*[8] reported on a cohort of 60 patients with hyperfibrinolysis, defined by a shortened euglobulin clot lysis time of whom 29 presented with clinically non-significant bleeding episodes (23 subcutaneous/soft tissue bleeding and 6 mucosal bleeding), with no difference in INR, APTT and platelet counts between bleeders and non-bleeders.[8]

Several reports of a wide range of clinically relevant spontaneous bleeding events in patients with cirrhosis are available in the literature. They include intracranial haemorrhage,[9–11] muscular haematomas,[12] orbital haematomas,[12–14] spontaneous haemoperitoneum,[15,16] and spontaneous arterial bleeding.[17,18] Huang *et al.*[10] described a cohort of 36 patients with cirrhosis and spontaneous intracranial haemorrhage; although all patients had thrombocytopenia and increased INR, the occurrence of intracranial haemorrhage and its outcome were not related to these abnormal tests but rather to the presence of alcohol-related liver disease. In a cohort of 61 patients with cirrhosis (23 Child-Pugh class B, 38 class C), Violi *et al.* showed that those with hyperfibrinolysis and comparable platelet counts had a higher risk of bleeding. Many bleeding episodes were, however, related to portal hypertension.[19] Overall, the majority of these studies included patients with a haemostatic defect, and none of them had been designed, or presented data, to prove that the coagulation defect was the exclusive cause of, or even contributed to bleeding.

The administration of vitamin K to correct prolongations in INR has been part of clinical practice for a long time in patients with chronic liver disease. However, this practice is not supported by any evidence, as vitamin K – especially when administered orally or subcutaneously – does not improve the INR.[20] Saja *et al.*[21] demonstrated that 1 subcutaneous dose of vitamin K did not modify coagulation parameters. However, it is well known that intravenous administration of vitamin K can correct the INR in cholestatic liver disease, although its effect is transient.[22] The use of vitamin K to prevent spontaneous bleeding has not been evaluated.

Youssef *et al.*[23] addressed the issue of using FFP transfusions to correct the PT and showed that only a minority (14%) of patients with cirrhosis achieved complete correction. These data were further supported by Abdel-Wahab *et al.*[24] In addition, it is well known that FFP added *in vitro* to plasma of patients with cirrhosis or infused into patients with cirrhosis, despite shortening the INR, does not modify thrombin generation.[25,26] Considering the potential harm from FFP transfusion (mostly consisting of transfusion-associated circulatory overload, but also of rare transfusion reactions including transfusion-related acute lung injury),[27] and the number of units required to meaningfully improve prothrombin time,[23] prophylactic FFP administration should be abandoned, especially in the setting of spontaneous bleeding prevention.

Prevention of spontaneous bleeding by platelet transfusion remains controversial due to the low-grade evidence present in the literature. In patients without underlying liver disease and therapy-induced hypoproliferative thrombocytopenia, platelet transfusions to prevent spontaneous bleeding are only recommended when platelet count is ≤10 × 10^9/L.[28] In a prospective cohort of 280 patients with cirrhosis followed for a median time of about 3 years, neither absolute platelet count (hazard ratio 0.99 95% CI 0.995–1.004) nor platelet count <50 × 10^9/L (hazard ratio 0.65 95% CI 0.31–3.36) were associated with spontaneous bleeding episodes.[29] Currently, there is no clear-cut evidence suggesting that correction of platelet count prevents spontaneous bleeding.

A decreased fibrinogen plasma level is frequently detected in patients with liver disease. Fibrinogen levels have been associated with lower survival in patients with decompensated cirrhosis and gastrointestinal bleeding.[30] This relationship weakens after correction for disease severity. Indeed, in a retrospective cohort of patients with cirrhosis with very low fibrinogen levels (<150 mg/dl), Budnick *et al.*[31] showed that prophylactic cryoprecipitate administration did not modify bleeding or mortality risk.

Table 1. Spontaneous bleeding events related to cirrhosis defined according to severity.[6]

Non-major bleeding
Skin haemorrhages
Bruises
Petechiae purpura
Ecchymosis
Mucosal bleeding
Gum bleeding
Epistaxis
Menometrorrhagia
Dental root bleeding
Major bleeding
Massive spontaneous deep haematomas
Spontaneous intracranial haemorrhage
Spontaneous haemoperitoneum
Orbital haemorrhage

Do traditional haemostasis tests (INR, APTT, platelet count, fibrinogen), or viscoelastic tests, predict bleeding in patients with cirrhosis undergoing invasive procedures at low or high risk of bleeding?

Statement

- INR and APTT do not predict post-procedural bleeding in patients with cirrhosis undergoing invasive procedures **(LoE 3).**
- Studies do not consistently demonstrate a link between thrombocytopenia, hypofibrinogenaemia, or viscoelastic

test results and the risk of post-procedural bleeding, although there may be subgroups in whom thrombocytopenia is related to procedural bleeding risk and there is initial evidence suggesting that viscoelastic tests might help to address this issue **(LoE 4).**

Recommendation

- In patients with cirrhosis, the use of traditional haemostasis tests, or viscoelastic tests, cannot be generally indicated to predict procedural bleeding risk, although they can be used to assess severity of disease or haemostatic status and to provide an initial benchmark to guide management in the case of post-procedural bleeding **(LoE 3, strong recommendation).**

Future perspectives

On the basis of initial evidence provided by the results of viscoelastic tests, their potential to predict post-procedural bleeding should be further explored in prospective, adequately powered studies including different categories of patients with cirrhosis (compensated, decompensated, acute-on-chronic liver failure) undergoing high-risk procedures.

Measures of haemostasis that are commonly used in clinical practice (*e.g.*, INR, platelet count, fibrinogen) are frequently altered in patients with cirrhosis as almost all the coagulation factors are synthesised by the liver. Both hypersplenism and decreased hepatic production of thrombopoietin are the main pathophysiological factors responsible for decreased platelet counts in these patients.[32] However, in patients with cirrhosis, alteration of these parameters should be interpreted with caution as they reflect just one side of the haemostatic balance, and do not take into account compensatory mechanisms that operate in these patients. In fact, the simultaneous changes in pro- and anti-haemostatic pathways in patients with cirrhosis have been proposed to lead to a status of "rebalanced haemostasis".[33,34] Indeed, the INR of the prothrombin time may be prolonged in patients with cirrhosis as it depends on liver-derived procoagulant factors, but this parameter does not take into account the concomitant deficiency in liver-derived anticoagulant factors such as antithrombin, protein C and protein S.[35–37] Likewise, advanced liver disease is often associated with various degrees of thrombocytopenia, although other factors that might compensate for this defect, supporting platelet adhesion despite their reduced count – such as von Willebrand factor, whose levels are consistently elevated in cirrhosis – are not routinely assessed in these patients, and platelet function is seldom evaluated due to the lack of clinically available, reliable tests.[38–40]

The literature regarding the potential association between altered standard coagulation tests and procedure-related bleeding in patients with cirrhosis – besides being limited by the aforementioned issues – is hampered by the lack of prospective, adequately designed, sufficiently powered studies addressing this question, and by the wide array of invasive procedures performed in the various studies, each with a potentially different risk for bleeding. Moreover, based on the traditional tenet that altered coagulation tests should be manipulated to decrease the risk of procedure-associated bleeding, the use of blood product transfusions quite often biased the evaluation of the role of coagulation test alterations in studies addressing this issue. Further, as alterations of coagulation tests and thrombocytopenia are coexistent, in many studies it is also difficult to identify a univocal association between test alteration and outcome of interest. Lastly, compared to patients with stable disease (even if decompensated), patients with acute-on-chronic liver failure portray a different clinical picture, where the presence of renal failure, or sepsis, and the concurrent systemic inflammatory response, may tip the coagulation balance and drive the occurrence of bleeding (or thrombotic) events following invasive procedures independently of coagulation test abnormalities.[41–46]

Bearing all these limitations in mind, and despite the absence of appropriately designed studies with well-defined end-points, there is no evidence that INR alterations are associated with an increased risk of significant bleeding following invasive procedures in stable patients with cirrhosis undergoing paracentesis,[47] thoracentesis,[48] dental extraction[49]), central venous cannulation,[50] percutaneous and transjugular liver biopsy,[51,52] hepatocellular carcinoma percutaneous ablation,[53] prophylactic endoscopic band ligation (EBL) of oesophageal varices,[54,55] and endoscopic polypectomy.[54,56] Further, a recent meta-analytic review of the literature reported that there was no significant difference in mean INR between patients with cirrhosis who bled or did not bleed at, or following, an invasive procedure, and that there was no significant association between peri-procedural bleeding events and pre-procedural INR.[57]

Likewise, the presence of thrombocytopenia, using various cut-offs to define the severity of this alteration, has not been consistently associated with an increased risk of bleeding following paracentesis,[47] thoracentesis,[48] dental extraction,[49] central venous cannulation or hepatic venous pressure gradient measurement,[50,58] EBL of oesophageal varices,[55,56] endoscopic polypectomy,[56] and transjugular or laparoscopic liver biopsy.[51,59] On another note, some retrospective studies have reported an increased risk of bleeding associated with thrombocytopenia following percutaneous ablation of hepatocellular carcinoma, with a post-procedural bleeding rate of 0.6% on a total of 1,843 procedures performed in 1,211 patients.[53] While in 1,267 patients undergoing endoscopic polypectomy, a platelet count <50 × 10^9/L was independently associated with immediate post-procedural bleeding,[54] this finding was not confirmed in a single-centre study of 358 colonoscopies after adjusting for disease severity.[56] Finally, a prospective, multicentre study carried out in 363 patients with cirrhosis undergoing 852 procedures found no evidence of an association between platelet count or INR values and post-procedural bleeding, which in this study was a rare event (*i.e.*, 1 episode every 85 procedures or every 36 patients). In particular, in this study – that included a wide array of invasive procedures categorised on the basis of the estimated risk of bleeding – none of the 89 patients with a platelet count ≤50 × 10^9/L (10.4% of the whole series) had a procedure-related bleeding episode.[60] Lastly, a recent review aimed at examining the association between procedure-related (liver biopsy, paracentesis, invasive endoscopic procedures, thermal ablation, liver surgery) bleeding risk and platelet count in patients with cirrhosis and severe thrombocytopenia (<50 × 10^9/L): the authors concluded that the studies published so far do not support the definition of a target platelet count that can be reliably associated with risk of bleeding.[61]

Finally, fibrinogen levels are usually normal in compensated cirrhosis and are often decreased in end-stage liver disease. Besides quantitative alterations, liver dysfunction may also induce qualitative fibrinogen modifications (*i.e.*, dysfibrinogenaemia) although the exact influence of this latter circumstance on the coagulative balance of patients with cirrhosis is unclear.[62,63] All in all, fibrinogen levels have inconsistently and inconclusively been associated with an increased risk of bleeding following oesophageal varices ligation,[64] and although this parameter has not been routinely evaluated in studies assessing the risk of bleeding following other procedures, low fibrinogen levels were associated with an increased risk of bleeding following paracentesis in patients with acute-on-chronic liver failure.[45] Fibrinogen level <60 mg/dl was the strongest independent predictor of new onset episodes of major bleeding in 1,493 prospectively recorded, critically ill patients with cirrhosis, but a causal relationship was not established, and notably most of the bleeding episodes were related to portal hypertension.[65]

As far as viscoelastic tests of coagulation (thromboelastography [TEG]; rotational thromboelastometry [ROTEM]) are concerned, 3 recent prospective studies carried out in patients with cirrhosis undergoing invasive procedures, randomised to receive TEG-guided or standard test-based blood product transfusions, clearly demonstrated that the use of viscoelastic tests is associated with a decreased requirement for prophylactic blood product transfusions, although they were unable to demonstrate any association between viscoelastic tests alterations and bleeding events, mainly due to the paucity of bleeding events recorded.[66–68] In a study that included 150 patients with cirrhosis (61.3% with an INR ≥1.5, 15.3% with platelet count <50 × 10^9/L, "abnormal" TEG R-time and MA in 39.4% and 24.7% of patients, respectively) undergoing a wide array of invasive procedures without prophylactic administration of blood products, just 1 patient bled (0.7%), thus preventing any meaningful analysis regarding this issue, though indirectly underlying that the absence of correction of common or more sophisticated coagulation tests does not appear to alter post-procedural outcome.[69] Indeed, a recent study did demonstrate that a TEG K-time of 3.05 minutes or more was a weak predictor of bleeding in 90 patients with cirrhosis undergoing central venous cannulation (accuracy 69.4%, p = 0.047), while preliminary results of another study where 41 patients with cirrhosis and an INR ≥1.5 and/or a platelet count ≤50 × 10^9/L undergoing endoscopic procedures were randomised to a ROTEM- or standard coagulation test-based transfusion policy showed that patients in the ROTEM-guided arm received a barely significantly lower volume of transfusions (309 ml *vs.* 461 ml, p = 0.049) with no difference in bleeding events between the study arms.[70,71] Lastly, in a recent report that included patients with decompensated cirrhosis undergoing TEG assessment on admission, 72 patients (30% with platelet count <50 × 10^9/L, median INR 1.6, IQR 1.3-1.8) underwent a total of 153 invasive procedures in the course of the hospitalisation, a median of 5 days after performing TEG assessment, and bleeding occurred in 7 procedures (major bleeding in 3).[72] In this study, where the rate of procedural bleeding was high (*i.e.*, 9.7%) and both bacterial infection (65%) and acute kidney injury (50%) were highly prevalent, common measures of coagulation on admission were not predictive of post-procedural bleeding, while a "hypocoagulable" TEG profile (*i.e.*, longer k-time, wider α-angle, and smaller maximum amplitude) was more frequently observed in patients who experienced a procedure-related bleeding, in particular a maximum amplitude <30 mm was associated with major bleeding episodes.[6,72] All in all, despite routine coagulation tests generally being demonstrated to be a poor guide to identify patients who may experience bleeding complications following invasive procedures, they may serve to provide the clinician with a picture of the severity of liver disease as well as of the patient's baseline haemostatic status in the case of haemorrhagic events, also prompting potential multidisciplinary evaluation in the case of extremely deranged, or unexpected, results; likewise, routine use of viscoelastic tests currently cannot be recommended to predict post-procedural bleeding, although initial evidence suggests that their role should be further explored in prospective and adequately powered studies.

In patients with cirrhosis undergoing invasive procedures with a low risk of clinically relevant bleeding, is laboratory evaluation of haemostasis indicated to predict procedure-related bleeding?

Recommendation

- In patients with cirrhosis undergoing invasive procedures with a low risk of bleeding, laboratory evaluation of haemostasis with the aim of predicting post-procedural bleeding is not indicated **(LoE 4, strong recommendation).**

In patients with cirrhosis, the risk of bleeding following an invasive procedure is based on various factors that are not reflected by alterations in haemostatic parameters alone, but that include technical issues, and factors that are inherent to a given procedure where the event can be mitigated in the course of the procedure itself by reactive, non-coagulation related measures (*e.g.*, such as in dental extractions or endoscopic polypectomy). Furthermore, the same procedure may carry different bleeding risks when it is carried out in different clinical situations, as in patients with stable disease or in those with concomitant acute events such as sepsis or acute kidney injury. For example, in patients with stable cirrhosis and deranged coagulation tests (mean platelet count 50.4 × 10^9/L, mean INR 1.7) no bleeding events were reported following paracentesis carried out by trained nurses, whereas a post-paracentesis bleeding rate of 3% was observed in patients with acute-on-chronic liver failure undergoing the same invasive procedure.[45,47] In the study by Lin *et al.*,[45] when patients with acute-on-chronic liver failure were propensity score matched to patients with decompensated cirrhosis based on severity of liver disease, platelet count and INR were not different between those who experienced post-procedural bleeding and those who did not, while hypofibrinogenaemia was the only independent predictor of post-paracentesis bleeding.

Bearing these limitations in mind, according to both data reported in the literature and experts' consensus indications, derived mainly from evidence obtained in patients without liver disease, invasive procedures have generally been subdivided into low-risk – when the expected occurrence of bleeding is ≤1.5% – and high-risk – when the estimated bleeding risk is >1.5%, or

when even minor bleeding may lead to severe consequences, or death, as in the case of intracranial bleeding.[73,74]

Procedures associated with a low risk (*i.e.,* ≤1.5%) and a high risk (>1.5%) of bleeding are reported in Table 2 ([47,48,51,53,54,56,75–81]). Overall, in stable patients with cirrhosis, diagnostic endoscopic procedures (*e.g.*, gastroscopy or colonoscopy with mucosal biopsies), thoracentesis, paracentesis, trans-oesophageal echocardiography, transjugular liver biopsy and hepatic venous pressure gradient measurement, are mainly associated with a low risk of bleeding, and the occurrence of bleeding episodes has not been related to either INR values or degree of thrombocytopenia (reviewed in[61,80]) (Table 3).[45,47–56,58,60,66,68,76–79,81–103] Percutaneous ablation of hepatocellular carcinoma is another procedure where the risk of bleeding is considered low, although in the largest series reporting the occurrence of haemorrhagic complications (0.5% in 1,834 procedures), median platelet count was 140 × 10^9/L and patients with a pre-procedural platelet count <50 × 10^9/L received 10 units of packed platelets as prophylaxis.[53]

Patients with acute complications of cirrhosis, or patients with acute-on-chronic liver failure, may represent a subset where the absence of an association between coagulation tests and bleeding risk may be not as straightforward as in stable patients, although the studies on this subject tend to suggest that management of the complication such as infection or acute kidney injury, rather than the haemostatic abnormality, may improve patient outcome. As a fact, a retrospective study showed that the presence of acute kidney injury was the only independent risk factor for post-paracentesis haemoperitoneum, with both platelet count and INR values not significantly different between patients with or without this complication.[104]

Table 2. Procedural bleeding risk in patients with cirrhosis.

Procedure	Bleeding rate (%)
Low bleeding risk (<1.5%)	
Paracentesis	
1,100 procedures[47]	None
4,729 procedures[76]	0.2
Thoracentesis	
215 procedures[49]	None
Trans-oesophageal echocardiography	
24 procedures[77]	None
Percutaneous liver biopsy	
68,276 procedures[78];	
3,357 procedure[80]	0.06–0.69
Transjugular liver biopsy	
7,493 procedures[51]	0.07
HVPG measurement	
238 procedures[79]	None
Percutaneous ablation of liver cancer	
1,843 procedures[53]	0.5
High bleeding risk (≥1.5%)	
ERCP	
2,620 endoscopic biliary sphincterotomy[74]	3.5
581 endoscopic papillary balloon dilation	1.9
Endoscopic polypectomy	
814 procedures[54]	7.9 immediate, 1.2 delayed
Endoscopic oesophageal varices ligation	
886 procedures[56]	2.8
Dental extraction	
333 extractions[75]	6.3 intraoperative, 6.3 postoperative

ERCP, endoscopic retrograde cholangiopancreatography; HVPG, hepatic venous pressure gradient.

In patients with cirrhosis undergoing invasive procedures with a high risk of clinically relevant bleeding, is laboratory evaluation of haemostasis indicated to predict procedure-related bleeding?

Statements

- There is weak evidence that the measurement of platelet count might be indicated to identify patients at increased procedural bleeding risk. No solid data are available for fibrinogen **(LoE 4).**
- As evidence supporting viscoelastic tests as predictors of procedure-related bleeding in patients with acute decompensation of cirrhosis, with or without organ failure, is weak, it is not possible to advise for or against their use **(LoE 4).**

Recommendation

- In patients with cirrhosis undergoing invasive procedures associated with a high risk of bleeding, laboratory evaluation of haemostasis is generally not indicated to predict post-procedural bleeding, although it may serve to provide a baseline status of the patient and to assist the physician in the case of bleeding events **(LoE 4/5, weak recommendation).**

Procedures with a reported bleeding rate >1.5%, or where the consequences of bleeding may result in severe detrimental *sequelae*, such as those that may occur following intracranial pressure monitoring, or where bleeding cannot be easily managed with local haemostatic manoeuvres are considered as high-risk procedures. Overall, despite some heterogeneity among studies, the procedures associated with a high risk of bleeding are reported in Table 2.

Endoscopic retrograde cholangiopancreatography (ERCP) is associated with a higher risk of bleeding in patients with cirrhosis and clinically significant portal hypertension (20% of them had a platelet count <50 × 10^9/L) compared to patients without cirrhosis (4.0% *vs.* 0%).[105] A study that included 538 procedures (mean platelet count 105 × 10^9/L, INR >1.7 in 8.6% of the patients) found no association between bleeding episodes – that occurred in 1.1% of the procedures – and "coagulopathy" (not clearly defined in the study), even in patients who underwent sphincterotomy, although patients with an INR ≥1.5 received FFP and those with thrombocytopenia (platelet count <50 × 10^9/L) were transfused with platelets.[105,106] However, ERCP is also an example of a procedure where the risk of bleeding can be minimised by means of technical strategies: as a fact, the use of endoscopic papillary balloon dilation is associated with a significantly decreased risk of bleeding requiring endoscopic haemostasis compared to endoscopic biliary sphincterotomy (1.9% *vs.* 3.5%, p = 0.05).[75] Endoscopic polypectomy is another procedure associated with a high risk of bleeding, as the immediate post-polypectomy bleeding rate can be as high as 7.5%, with a delayed bleeding rate of 2.0%.[56,107] In these patients, standard haemostasis tests such as INR and platelet count are often associated with an increased risk of

Table 3. Bleeding risk associated with invasive procedures.

Procedure	Study design	Procedures/patients (n)	PLT count or PLT cut-off	Finding
Paracentesis				
Webster, 1996[101]	Retrospective	179 outpatients	Not specified	4 haemorrhagic complications in patients with PLT >80 × 10^9/L
Grabau, 2004[47]	Retrospective	1,100 in 628 patients	PLT <50 × 10^9/L in 55.64% of procedures	No bleedings in procedures performed with PLT <50 × 10^9/L
Pache, 2005[77]	Retrospective	4,729 patients	Not specified	Severe haemorrhagic complications in 0.2% of procedures without association with PLT count
Lin, 2005[45]	Prospective observational	410 in 163 patients	PLT <50 × 10^9/L in 13% of procedures	Minor bleeding in 0.5% of procedures in patients with PLT = 50-100 × 10^9/L
De Gottardi, 2009[88]	Prospective observational	515 in 171 patients	PLT <50 × 10^9/L in 10% and PLT <100 × 10^9/L in 40% of patients	Association between PLT <50 × 10^9/L and increased risk of overall complications (p = 0.07). Association with bleeding risk not reported
Rowley, 2019[97]	Retrospective	3,116 in 123 patients	PLT <50 × 10^9/L in 12% of patients	Bleeding rate: 0.2%. No bleeding with PLT <50 × 10^9/L
Liver biopsy				
Piccinino, 1986[79]	Retrospective	68,276 percutaneous	PLT >50 × 10^9/L in all biopsies	Bleeding rate: 0.06%. Association between bleeding and PLT not evaluated
Caturelli, 1996[86]	Retrospective	Only abstract available	Not specified	Bleeding rate: 0.13%. Association between bleeding and PLT not evaluated
Actis, 2007[82]	Retrospective	835 patients	Not specified	Bleeding rate: 0.12%. Association between bleeding and PLT not evaluated
West J, 2010[102]	Retrospective	61,187 patients	Not specified	Rate of major bleeding: 0.65%. Association between bleeding and PLT not evaluated
Seeff *et al.*, 2010[52]	Retrospective	2,740 percutaneous biopsies	Patients with PLT <50 × 10^9/L were excluded	Bleeding rate: 0.6%. Patients with PLT = 50-60 × 10^9/L was significantly higher than patients with PLT >60 × 10^9/L (5.3% *vs.* 0.4%)
Kalambokis *et al.*, 2007[51]	Review	7,649 transjugular biopsies in 7,189 patients	Cut-off 60 × 10^9/L	Minor bleeding <2% No association with PLT count
Alessandria, 2008[83]	Retrospective	306 transjugular biopsies	Not specified	No major complications. No association between bleeding rate and PLT count
Mammen *et al.*, 2008[94]	Retrospective	601 transjugular biopsies	PLT >60 × 10^9 in 20% of patients	Bleeding rate: 0.9%. No association with PLT count
Procopet *et al.*, 2012[96]	Prospective	75 transjugular biopsies	Not specified	Bleeding rate: 1.3%. No association with PLT count
Takyar *et al.*, 2017[81]	Retrospective	3,357 percutaneous biopsies	Cut-off 100 × 10^9/L	Bleeding rate: 0.69% (fatal in 0.09%). PLT <100 × 10^9 was an independent risk factors for post-biopsy bleeding, but % patients with PLT <60 × 10^9 were not different between groups
Potretzke *et al.*, 2018[95]	Retrospective	1,876 percutaneous biopsies in 1,732 patients	Cut-off 70 × 10^9/L	Bleeding rate: 0.69%. No association with PLT count
Dentistry				
Ward *et al.*, 2006[100]	Retrospective	35 procedures in 30 patients	Cut-off 35-50 × 10^9/L (depending on the risk group)	No association between PLT count and prolonged post-operative bleeding
Perdigao *et al.*, 2012[49]	Prospective observational	35 procedures in 23 patients	PLT <50 × 10^9/L in 34% of patients	1 postoperative bleeding (2.9%) in patients with PLT = 50 × 10^9/L. No bleeding during procedures (n = 12) with PLT = 30-49 × 10^9/L
Cocero *et al.*, 2017[87]	Retrospective	1,183 extractions in 381 patients	Cut-off PLT ≤40 × 10^9/L	Bleeding rate: 0.4% in patients with PLT >40 × 10^9/L and INR <2.5; 5.88% in patients with PLT ≤40 × 10^9/L
Medina *et al.*, 2018[76]	Retrospective	190 extractions	PLT <150 × 10^9/L in 96.3% of patients	Bleeding rate: 6.3%. Intraoperative bleeding increased proportionally to the decrease in platelet count. However, this platelet level could explain only 16% of the cases of bleeding

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Table 3. (*continued*)

Procedure	Study design	Procedures/patients (n)	PLT count or PLT cut-off	Finding
Endoscopic variceal ligation				
Vieira da Rocha *et al.*, 2009[55]	Prospective observational	150 patients	PLT <50 × 10^9/L in 12% of patients	Severe post-procedural ulcer bleeding in 7.33% of patients. Risk of bleeding was not associated with PLT count
Vanbiervliet *et al.*, 2010[99]	Retrospective	837 ligations in 605 patients	Not specified	Bleeding rate: 2.75%. No association between PLT count and bleeding but high platelet ratio index was an independent predictive factor of bleeding
Endoscopic polypectomy				
Jeon *et al.*, 2012[91]	Retrospective	66 in 30 patients	Not specified	Bleeding rate in 3% of procedures. No association between bleeding and PLT count
Lee *et al.*, 2014[92]	Retrospective	89 patients w/liver cirrhosis + 348 w/o liver disease	Not specified	Bleeding rate in 14.61% of patients. Association between bleeding and PLT not evaluated
Soh *et al.*, 2020[54]	Retrospective	1,267 patients	Cut-off 50 × 10^9/L	Haemorrhagic rate (immediate + delayed): 7.5%. PLT <50 × 10^9/L significantly associated with immediate post-procedural bleeding (rate: 27.5%; OR = 6.6)
Percutaneous ablation				
Cammà *et al.*, 2005[84]	Retrospective	202 patients	≥40 × 10^9/L in all patients	Bleeding rate: 0.50%. Association between bleeding and PLT not evaluated
Livraghi *et al.*, 2008[93]	Retrospective	218 patients	≥40 × 10^9/L in all patients	Bleeding rate: 0.92%. Association between bleeding and PLT not evaluated
Goto *et al.*, 2010[90]	Retrospective	4,133 in 2,154 patients	Mean PLT count = 125 ± 33 × 10^9/L (50-669)	Haemorrhagic complications rate: 1.5%. Low PLT count was a significant risk factor for haemoperitoneum (PLT ≥50 × 10^9/L was an inclusion criteria)
Park *et al.*, 2017[53]	Retrospective	1,843 in 1,211 patients	Mean PLT count = 140 ± 85 × 10^9/L	Post-procedural bleeding rate was 0.6%, and the risk was significantly greater in patients with PLT < 50 × 10^9/L (OR = 8.79)
Vascular catheter insertion				
Fisher *et al.*, 1999[50]	Retrospective	658 cannulations in 283 patients	PLT <50 × 10^9/L in ∼ 25% patients	1 haemothorax in patients with PLT = 68 × 10^9/L. PLT ≤10 × 10^9/L significantly associated with superficial haematoma *vs.* PLT > 50 × 10^9/L (4.8% *vs.* 1.6%, respectively)
Estcourt *et al.*, 2015[89]	Systematic review	—	Not specified	No evidence from RCTs to determine whether PLT transfusions are required prior to central line insertion in patients with thrombocytopenia, and, if a PLT transfusion is required, what is the correct threshold
HVPG measurement				
Bosch *et al.* 2009[58]	Review + single-centre experience	12,000 measurement	Not reported	1 haemothorax in patients with PLT = 68 × 10^9/L. PLT ≤10 × 10^9/L significantly associated with superficial haematoma vs. PLT >50 × 10^9/L (4.8% *vs.* 1.6%, respectively)
Woolfson *et al.*, 2013[103]	Retrospective	52 HVPG measurements in 49 children	PLT <100 × 10^9/L in 28 patients	Variceal bleeding and variceal bleeding + ascites occurred each in 1/7 patients with cirrhosis. Association between bleeding and PLT not evaluated
Thoracentesis				
Castellote *et al.*, 2001[85]	Retrospective	245 thoracentesis in 69 patients with cirrhosis	Not reported	Bleeding rate: 2%. Association between bleeding and PLT not evaluated
Xiol *et al.*, 2001[48]	Retrospective	215 thoracenteses in 60 patients with cirrhosis	Not reported	Association between bleeding and PLT not evaluated

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Table 3. (*continued*)

Procedure	Study design	Procedures/patients (n)	PLT count or PLT cut-off	Finding
Miscellaneous				
Shah *et al.*, 2015[58]	Prospective observational	380 patients	Cut-off 50 × 10^9/L	Clinically relevant bleeding following high-risk procedures occurred in 3 patients with significant coagulopathy and 0 patients without significant coagulopathy (p = 0.061)
De Pietri *et al.*, 2016[66]	RCT open-label ITT	60 patients	Cut-off 50 × 10^9/L	Bleeding occurred in 1.7% of patients (1/60) following paracentesis (PLT = 111 × 10^9/L)
Napolitano *et al.*, 2017[60]	Prospective observational	852 procedures in 363 patients	Cut-off 50 × 10^9/L	Overall bleeding complication rate: 2.75%. No bleeding in 90 procedures with PLT count
Vuyyuru *et al.*, 2020[68]	RCT open- label	60 patients		No bleeding in 58 procedures with PLT count <50 × 10^9/L
Kundumadam *et al.*, 2020[56]	Retrospective (colonoscopy with polypectomy EVL and interventional, ERCP)	1,324 in 857 patients	Not specified	Bleeding rate: 2.0% polypectomy, 2.8% EVL, and 3.8% ERCP Not association between PLT count and bleeding in ERCP and EVL Polypectomy: 29% of those who bled had a PLT count, <50 × 10^9, compared with 6.3% of those who did not bleed (p = 0.08).

ERCP, endoscopic retrograde cholangiopancreatography; EVL, endoscopic variceal ligation; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; ITT, intention-to-treat; OR, odds ratio; PLT, platelet (count); RCT, randomised controlled trial.

bleeding in univariate analysis, although they were not independent predictors on multivariate analysis when other parameters such as technical issues (*e.g.*, use of hot or cold snare), procedure-inherent risks (*e.g.*, performance of endoscopic mucosal resection) and severity of liver disease were identified as independent predictors of bleeding complications. In one of these studies, the presence of lower haemoglobin levels was independently associated with an increased risk of delayed post-polypectomy bleeding, a finding that may potentially be related to the decreased viscosity of blood in anaemic patients.[56] Lastly, a retrospective study carried out in a very large series (n = 814) of patients with cirrhosis undergoing endoscopic polypectomy identified advanced liver disease (Child-Pugh class B or C), technical issues (3 or more polyps removed, endoscopic mucosal resection or submucosal dissection, and polypectomy performed by trainees), and platelet count <50 × 10^9/L as independent risk factors for immediate post-polypectomy bleeding.[54]

Oesophageal varices banding ligation is another procedure associated with a high risk of bleeding (2.7–7.3%), although in this case the bleeding episodes are almost exclusively delayed, between 7 and 14 days following the procedure, when the bands dislodge.[55,56,64,99] In these patients, INR values and platelet counts, or viscoelastic tests results, were not associated with the occurrence of post-banding ulcer bleeding. Nevertheless, in 1 study carried out in patients with thrombocytopenia, low fibrinogen levels (<150 mg/dl) were associated with bleeding and, in another study, the presence of infection and lower haemoglobin values were independently associated with the occurrence of bleeding. Interestingly enough, in the latter, both red blood cell and FFP but not platelet transfusions were associated with an increased risk of bleeding, thus suggesting that the bleeding episodes might also have been related to an increase in portal pressure dictated by volume expansion.[56,64]

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure usually performed in patients with advanced liver disease, who are more likely to have deranged standard coagulation parameters and severe thrombocytopenia. In these patients the risk of complications is mainly related to technical issues, as demonstrated in a study where capsule perforation occurred in 31% of "conventional" TIPS as compared to 9% of cases of ultrasound-guided procedures.[108] The vast majority of bleeding complications, during or following the procedure, are related to technical factors rather than being associated with haemostatic abnormalities.[109]

Lastly, dental extraction, another procedure carried out quite frequently in patients with cirrhosis in preparation for liver transplantation, is often burdened by a high bleeding rate (approximately 6.0%). Although results obtained in a large series of patients identified a platelet count <40 × 10^9/L associated with an INR ≥2.5 as a risk factor for bleeding following dental extraction, this study failed to control for liver disease-related factors, and also technical factors were not systematically addressed.[87] Technical issues (*e.g.*, number of teeth extracted per session) rather than derangement of haemostasis tests seemed to be the main determinant of bleeding following extraction. The only prospective study published on this issue included 23 patients with a mean platelet count of 67 × 10^9/L and a mean INR of 1.5.[49] No prophylactic administration of blood products was allowed and patients underwent a total of 84 extractions;

bleeding occurred in 2.9% of procedures and was stopped by topical haemostasis alone in all patients.[49]

The presence of renal failure and/or sepsis also seems to increase the bleeding risk in patients undergoing high-risk procedures. Indeed, renal function impairment was an independent predictor of bleeding in patients undergoing ERCP,[75] and lower glomerular filtration rate was independently associated with delayed bleeding following endoscopic resection. In both these studies no association with platelet count or INR and bleeding was identified. In patients undergoing EBL, bleeding was associated with infection in models adjusting for model for end-stage liver disease (MELD)-Na or Child-Pugh score but not with platelet count or INR values. These results seem to point towards an increased bleeding risk in patients with cirrhosis and either sepsis or kidney injury. In these patients, there is initial evidence that viscoelastic tests may be able to capture a (relative) hypocoagulable profile, variously defined in the studies as either at least 3 ROTEM parameters out of range (longer k-time, wider α-angle, and smaller maximum amplitude), although this finding needs to be confirmed.[42,110]

All in all, the available evidence seems to suggest that even in patients undergoing procedures associated with a high risk of bleeding, technical factors or complications of liver disease are better predictors of post-procedural bleeding than coagulation test abnormalities.

In patients with cirrhosis undergoing invasive procedures*, does correction of a prolonged INR by infusion of FFP decrease the rate of procedure-related clinical relevant bleeding?

* when the term "invasive procedure" is used, it means both low- and high-risk procedures

Recommendation

- In patients with cirrhosis undergoing invasive procedures, correction of a prolonged INR with FFP is not recommended to decrease the rate of procedure-related clinically relevant bleeding **(LoE 2, strong recommendation).**

As previously stated, INR tests the function of a discrete number of procoagulant proteins (factors VII, X, V, and II and fibrinogen). These tests are insensitive to plasma levels of anticoagulant proteins and do not take into account the role of the endothelium in the haemostatic process.

FFP contains all of the plasmatic pro- and anticoagulant proteins in physiological levels, and therefore, FFP transfusion in patients with cirrhosis and a prolonged INR frequently does not lead to a full normalisation of the prothrombin time.[23,111] *Ex vivo* studies showed that FFP only minimally improves thrombin generating capacity in patients with cirrhosis, which is likely explained by the balanced administration of both pro- and anticoagulant proteins with FFP transfusions.[25,26,112] In patients with compensated and acutely decompensated cirrhosis, acute-on-chronic liver failure, infection or shock, administration of FFP only slightly improved global thrombin generating capacity in a few patients and even worsened them in a third of cases.[26] The absence of a meaningful improvement of haemostatic capacity by FFP is in line with the questionable clinical effect of FFP in patients with cirrhosis. Importantly, as evaluated in a recent Cochrane review, no studies have demonstrated the efficacy of prophylactic FFP in preventing bleeding in patients with cirrhosis undergoing invasive procedures.[113]

Only 2 randomised controlled trials assessed the effect of FFP *vs.* no intervention on post-procedural bleeding in patients without chronic liver disease[114,115] and both studies showed no difference in the occurrence of bleeding events between patients who did or did not receive FFP. In a randomised controlled trial that compared haemostatic management guided by TEG to haemostatic management guided by INR and platelet count in patients with cirrhosis undergoing low- and high-risk invasive procedures, 23 of 60 patients included (inclusion criteria INR >1.8 and/or platelet count $<50 \times 10^9$/L) received FFP, with only 3 of these 23 patients in the TEG arm. Only 1 patient (who received FFP) had a post-interventional bleeding episode.[66] The authors concluded that these findings indicate uncertainty of the utility of prophylactic FFP use in patients with cirrhosis and coagulation test abnormalities prior to invasive procedures.

Plasma transfusion does carry potentially life-threatening risks both in the general population and specifically in patients with cirrhosis. The negative effects commonly associated with FFP transfusions include:

- FFP increases blood volume, and therefore portal pressure, and may thus increase the risk of bleeding by exacerbating portal hypertension.[116]
- Transfusion-related acute lung injury, which is the leading cause of transfusion-related mortality,[117] can be associated with FFP transfusion.[118–120]
- Transfusion-associated circulatory overload (TACO). The reported incidence of TACO ranges from <1% to 8% of transfusions in the general population. Plasma transfusion is a risk factor for TACO since large volumes and increased infusion rates are usually used in adults.[121] A mortality rate of 5–15% has been reported in patients with TACO.[122]
- Allergic/anaphylactic reactions. The rate of allergic or anaphylactic reactions to FFP found in 2 retrospective studies was 1:591 and 1:2,184 plasma units transfused.[123] The estimated incidence of anaphylactic reactions alone ranges from 1:18,000 to 1:172,000 transfusions.[124]
- Other less common risks include transmission of infections, febrile non-haemolytic transfusion reactions, red blood cell allo-immunisation, and haemolytic transfusion reactions.[70,125–127]

In patients with cirrhosis undergoing invasive procedures, does administration of prothrombin complex concentrates (PCCs) decrease the rate of procedure-related clinically relevant bleeding?

Recommendation

- In patients with cirrhosis undergoing invasive procedures, routine use of PCCs to decrease the rate of procedure-related clinically relevant bleeding is discouraged **(LoE 3, weak recommendation).**

Future perspectives

Trials – preferably randomised placebo-controlled trials should assess the safety and efficacy of PCCs and their optimal dosage for decreasing procedure-related clinically relevant bleeding episodes.

PCCs are a pooled plasma product, and formulations contain 3 (II, IX, X) or 4 (II, VII, IX, X) vitamin K-dependent procoagulant proteins, proteins C and S, and often heparin; it offers an attractive low-volume therapeutic profile to partly restore a disturbed haemostatic system. PCC factor concentrations are 25 times greater than in FFP. Compared to FFP, PCCs lead to a more rapid and more effective correction of the INR, and infusion is usually completed in 10 minutes. The use of PCCs outside correction of an elevated INR as a result of vitamin K antagonist treatment is considered off-label. Dosage is based on INR and body weight. Decisions on dosing are problematic in patients with cirrhosis as INR is spontaneously altered at baseline in these patients.[128–130]

A recent *in vitro* study showed an exaggerated procoagulant response after addition of PCCs to the plasma of patients with cirrhosis compared to healthy individuals, which differed according to the severity of liver disease. Thrombin generation increased by 150% in plasma from patients with acutely decompensated cirrhosis and by 270% in patients with acute-on-chronic liver failure compared to an increase of 97% in healthy individuals, suggesting a requirement for dose-adjustment in patients with liver disease.[131] This finding was confirmed in patients with cirrhosis in whom an enhanced *in vitro* procoagulant effect of PCCs in blood samples taken during liver transplantation was evident.[132] Data regarding *in vivo* efficacy and safety in patients with liver disease are lacking.[133]

Administration of PCCs to expedite interventions effectively reduced the INR in a retrospective study of 45 critically ill patients with liver disease-associated coagulopathy.[134] Similarly, another study showed that in 105 patients (77% chronic and 33% acute liver disease) PCCs (administered for pre-procedure prophylaxis in 48% and for treatment of bleeding in 52%) produced statistically significant reductions in the INR. Three patients experienced thromboembolic events within 4 weeks of PCC administration.[135]

Although PCCs have been used in the context of liver transplantation in some European centres with positive results in terms of lower red blood cell and FFP requirements, published experience is limited to retrospective observational studies,[136] and thrombotic complications are not reported in all of them.[137,138] The only randomised controlled study planned in this setting was stopped because of low enrolment, so data regarding efficacy and safety in patients with liver disease are scarce.[133]

Use of procoagulant therapeutics in patients with advanced cirrhosis remains challenging and there are concerns over increasing the risk of thrombosis in this population. In 347 patients with cirrhosis receiving PCCs for the prevention or treatment of bleeding, PCC administration was the only factor associated with the occurrence of thromboembolic events (5.5 %) in a short-term follow-up,[139] and isolated cases of disseminated intravascular coagulation-like coagulopathy have been reported in patients with decompensated cirrhosis after administration of PCCs.[140]

On the whole, measures aimed at reducing the pre-procedural INR in patients with cirrhosis who are not taking vitamin K antagonists are very controversial.[134]

In patients with cirrhosis undergoing invasive procedures, does correction of thrombocytopenia by infusion of platelet concentrates or by thrombopoietin receptor (TPO-R) agonists decrease the rate of procedure-related clinically relevant bleeding?

Statement

- In patients with cirrhosis undergoing invasive procedures, no studies have specifically evaluated whether the infusion of platelet concentrates or TPO-R agonists decrease the rate of procedure-related clinically relevant bleeding **(LoE 1).**

Recommendation

- In patients with cirrhosis undergoing invasive procedures, infusion of platelet concentrates or use of TPO-R agonists is not recommended when platelet count is above 50 × 10^9/L or when bleeding can be treated by local haemostasis **(LoE 3/4, strong recommendation).**
- In patients undergoing high-risk procedures in whom local haemostasis is not possible and platelet count is between 20 × 10^9/L and 50 × 10^9/L infusion of platelet concentrates or TPO-R agonists should not be routinely performed but may be considered on a case-by-case basis **(LoE 3/4, strong recommendation).**
- In patients undergoing high-risk procedures in whom local haemostasis is not possible and platelet count is very low (<20 × 10^9/L) infusion of platelet concentrates or TPO-R agonists should be considered on a case-by-case basis **(LoE 3/4, strong recommendation).**

Future perspectives

Large observational cooperative studies are recommended to collect data, in patients with cirrhosis undergoing invasive procedures, on real-life incidence of bleeding and on complications associated with these events and with inherent therapies. Placebo-controlled, randomised trials including a large proportion of patients with cirrhosis and very low platelet counts undergoing high-risk invasive procedures should be performed, with clinically significant bleeding as a primary endpoint, to assess the role of platelet transfusions in extreme situations. Similar trials should be performed to assess the utility of TPO-R agonists.

Thrombocytopenia is common in patients with advanced cirrhosis and its prevalence increases with increasing severity of liver disease. *In vitro* evidence indicates that platelet-dependent thrombin generation is preserved in patients with cirrhosis and platelet counts ≥56 × 10^9/L. This *in vitro* finding has been used to promote a platelet count above 50 × 10^9/L as a target for prophylaxis.[141] However, thrombin generation assays disregard many key aspects of platelet function including adhesion and aggregation, calling into question the aforementioned threshold. In addition, compensatory mechanisms which may alter overall platelet performance, such as elevated von Willebrand factor (VWF),[40] increased circulating activated platelets,[142] and platelet-derived micro-particles[143] as well as the contribution of renal dysfunction to platelet physiology[144] are not evaluated by this test. Anaemia can also increase the risk of bleeding at similar platelet counts.[145]

In an *in vivo* study in patients with cirrhosis and thrombocytopenia, no evidence that prophylactic platelet transfusion improves haemostatic potential was found. In this study, transfusion of 1 standard adult platelet dose slightly increased platelet count (pre-*vs.* post-infusion: 39 × 10^9/L (16-64) *vs.* 52 × 10^9/L (19-91), p <0.001), without significant effects on *ex vivo* haemostatic tests.[146] However, another study showed similar increases in platelet count (from 28 × 10^9/L (21-41) before to 43 × 10^9/L (39-64) after platelet transfusion), with increases in *in vivo* markers of haemostasis activation.[112]

Avatrombopag[147] and lusutrombopag[148] are both oral TPO-R agonists that have completed phase III trials and are now approved in the US and Europe for use in thrombocytopenic patients with liver disease undergoing an invasive procedure. They require completion of a 5- to 7-day treatment course prior to the procedure.[149] Potential advantages of TPO-Rs are: i) improvement of patient clinical management, avoiding the risk of cancellation of procedures due to a platelet count that is perceived as too low by the proceduralist; ii) avoidance of prophylactic use of platelet transfusions (which for these patients is of unpredictable efficacy) and of iii) potential adverse events including refractoriness to further platelet transfusions[150]; and iv) increased availability of platelets for other clinical purposes.[61]

A recent meta-analysis including 6 publications comprising 8 randomised trials showed that TPO-R agonists were significantly more likely to result in a preoperative platelet count >50 × 10^9/L (72.1% *vs.* 15.6%, relative risk (RR): 4.8; 95% CI 3.6–6.4; p <0.00001; number needed to treat: 1.8) and reduced the incidence of platelet transfusions (22.5% *vs.* 67.8%, RR: 0.33; 95% CI 0.3–0.4; p <0.00001), without increasing the risk of thrombosis.[151] Peri-procedural bleeding was likewise reported as decreased, but these bleeding complications included clinically non-significant bleeds and bleeds that occurred prior to the procedure. None of the original studies reported differences in procedure-associated bleeding.[148,152,153]

A secondary, pooled analysis of the lusutrombopag studies showed that the proportion of patients with procedural and post-procedural bleeding events was numerically higher in the placebo with platelet transfusion group compared to the lusutrombopag without platelet transfusion group (11.9% *vs.* 6.5%), although the severity of events was mainly mild in both groups.[154]

In patients with cirrhosis undergoing invasive procedures, does correction of acquired fibrinogen deficiency by administration of fibrinogen concentrate or cryoprecipitate decrease the rate of procedure-related clinically relevant bleeding?

Recommendation

- In patients with cirrhosis undergoing invasive procedures, routine correction of fibrinogen deficiency to decrease the rate of procedure-related clinically relevant bleeding is discouraged **(LoE 4, strong recommendation).**

Future perspectives

Large prospective studies aiming at evaluating the qualitative and quantitative role of fibrinogen deficiency in patients with cirrhosis undergoing invasive procedures are warranted.

Adequate plasma levels of fibrinogen are essential for clot formation, and in severe bleeding, fibrinogen reaches a critically low plasma concentration earlier than other coagulation factors.[155] The critical minimum concentration of fibrinogen required to maintain haemostasis is a matter of debate. Of note, patients with congenital afibrinogenemia may be asymptomatic or even have a thrombotic tendency,[156] which contrasts with the predictable bleeding tendency of patients with congenital haemophilia A or B.

Fibrinogen levels can be effectively increased by administration of cryoprecipitate or fibrinogen concentrate but transfusion thresholds are rather arbitrary. Cryoprecipitate is a plasma-derived product rich in VWF, fibrinogen and fibronectin, while fibrinogen concentrates are derived from pooled plasma following viral exclusion and lyophilisation. The presence of VWF in cryoprecipitate is not apparently necessary in patients with cirrhosis as VWF levels are already elevated, and may pose a thrombotic risk**.** Fibrinogen concentrate has a lower volume (50 *vs.* 250 ml). Standardisation of fibrinogen content and lack of need for cross matching favour its use in cirrhosis, while its cost currently limits wider application.[157,158]

Fibrinogen production and degradation in patients with decompensated cirrhosis remains poorly understood. Some authors propose that low levels of fibrinogen are more indicative of decreased hepatic production and thus reflect advancing hepatic synthetic dysfunction without direct involvement in the pathophysiology of bleeding,[31] whereas others have proposed that low-grade intravascular coagulation contributes to low levels of fibrinogen in cirrhosis.[159]

Plasma fibrinogen levels less than approximately 100 mg/dl are associated with spontaneous and procedure-related bleeding in patients with cirrhosis,[64] but it is unclear whether this association is causal or merely reflects severity of disease. In the setting of trauma surgery in patients without underlying liver disease, fibrinogen replacement to achieve fibrinogen levels >200 mg/dl is associated with more effective haemostasis.[160] In cirrhosis, a fibrinogen threshold from 100 to 200 mg/dl has been recommended to trigger fibrinogen replacement in the setting of bleeding, and in clinical practice the most agreed upon cut-off in the actively bleeding patient with cirrhosis is >120 mg/dl.[32]

In vitro data showed that fibrinogen levels of ≥100 mg/dl resulted in greater mechanical clot stability compared to lower levels of fibrinogen, but no threshold concentrations of fibrinogen were identified for this effect.[161] A reduction in *in vitro* clot permeability (which is an *in vitro* measure of clot quality) was observed when fibrinogen concentrate (1 mg/dl) was added to control samples and a similar reduction was observed in patients with compensated cirrhosis, whereas a slightly more robust effect was observed in patients with acute decompensation and patients with acute-on-chronic liver failure.[131]

A retrospective study including 237 patients with cirrhosis admitted to the intensive care unit with fibrinogen levels <150 mg/dl assessed the association between cryoprecipitate transfusion and bleeding events and mortality. Cryoprecipitate transfusions were routinely given to achieve fibrinogen levels >100 to 120 mg/dl. As expected, patients who received cryoprecipitate transfusions had lower baseline fibrinogen levels (93 mg/dl *vs.* 119 mg/dl; p <0.01). Cryoprecipitate transfusion increased fibrinogen levels by 27.8 mg/dl (standard deviation, 28.2) but had no independent effect on bleeding complications or mortality. These data call into question whether fibrinogen is itself a direct factor in the pathophysiology of bleeding in critically ill patients with cirrhosis.[31]

A randomised controlled trial in the setting of liver transplantation has failed to demonstrate a beneficial effect of pre-emptive fibrinogen administration, although the target fibrinogen levels (>2.9 mg/dl) were not achieved in the experimental

group (1.7 *vs.* 1.5 mg/dl in experimental and placebo groups, respectively).[162]

In patients with cirrhosis undergoing invasive procedures, does correction of anaemia decrease the rate of clinically relevant bleeding?

Recommendations

- In patients with cirrhosis, every effort should be made to optimise haemoglobin levels by treating iron, folic acid, vitamin B6, and vitamin B12 deficiencies, especially in those patients likely to undergo invasive procedures **(LoE 5, weak recommendation).**
- In the setting of invasive procedures, prophylactic red blood cell transfusion with the aim of decreasing the risk of procedure-related bleeding is not recommended **(LoE 5, weak recommendation).**

Future perspectives

Large observational studies are recommended to evaluate whether anaemia (alone or combined with thrombocytopenia) is associated with bleeding events in patients with cirrhosis.

Erythrocytes are involved in primary haemostasis because they flow in the centre of the vessel and push platelets towards the vessel walls in flowing blood; this induces an increased platelet concentration at the site of damaged vessels.[163,164] In addition, erythrocytes may also modulate biochemical reactions and enhance platelet activation. Platelet adhesion to VWF is also regulated by haematocrit level and flow rate.[165] *Ex vivo* studies have shown that correction of haematocrit levels can correct platelet adhesion in blood from patients with cirrhosis,[166] while an *in vitro* study using the PFA-analyser found an inverse correlation between haematocrit and closure time.[167] Very few data are available on anaemia and bleeding risk *in vivo*, although a prolonged bleeding time in patients with anaemia has been described.[168] Furthermore, correction of anaemia has been reported to correct bleeding times in general patients,[169] and a haematocrit <25% has been reported to be associated with a higher bleeding risk in patients with hypoproliferative thrombocytopenia.[170] Treatment of anaemia with erythropoietin in patients with chronic kidney disease improved bleeding times and reduced bleeding complications.[171]

Anaemia is a frequent complication observed in patients with cirrhosis, with a prevalence of about 60%, and its aetiology is usually multifactorial.[172–174] Diverse mechanisms may be implicated: acute or chronic gastrointestinal haemorrhage leading to iron deficiency, hypersplenism secondary to portal hypertension, chronic haemolysis, spur-cell anaemia, aplastic anaemia with hypocellular bone marrow especially secondary to hepatitis, alcohol abuse, and folic acid, vitamin B12 and B6 deficiencies, which could be related to inadequate food intake or intestinal malabsorption.

Despite the high prevalence of anaemia in patients with cirrhosis and its known contribution to bleeding, studies evaluating the incidence of bleeding after invasive procedures have not focused on the possible role of anaemia, or haemoglobin and haematocrit values as risk factors for bleeding.

One retrospective paediatric study concerning 213 children (mostly with cirrhosis) who underwent 328 percutaneous liver biopsies showed that 4.2% experienced a decrease in haemoglobin level >2 g/dl, 3.3% required transfusion and 0.5% died, with younger age and lower pre-procedural haematocrit (29.3% *vs.* 34.3%) being predictive of bleeding complications.[175] Furthermore, a recent study in patients with cirrhosis reported that post-procedural bleeding was independently associated with lower preoperative haemoglobin level in both 327 patients undergoing 358 polypectomies and in 454 patients undergoing 886 EBL procedures.[56] These few data suggest that anaemia in patients with cirrhosis could be associated with an increased risk of bleeding during invasive procedures. However, no data are available on the effect of correcting anaemia on post-procedure bleeding rates. In patients with cirrhosis, transfusion of blood products can increase portal pressure by increasing blood volume, thus increasing the risk of further bleeding. Restrictive packed red blood cell transfusions (transfusion with haemoglobin <7 g/dl with a target haemoglobin of 7-9 g/dl) were associated with lower re-bleeding and mortality in patients with acute upper gastrointestinal bleeding.[176]

In patients with cirrhosis undergoing invasive procedures, does administration of antifibrinolytic drugs such as tranexamic acid decrease the rate of clinically relevant bleeding?

Recommendation

- In patients with cirrhosis undergoing invasive procedures, routine use of tranexamic acid to decrease the rate of procedure-related clinically relevant bleeding is discouraged **(LoE 4, weak recommendation).**

Future perspectives

Prospective studies are needed to evaluate the role of the hyperfibrinolytic state on post-procedural bleeding in patients with cirrhosis undergoing invasive procedures. Large clinical studies are needed to evaluate antifibrinolytic therapy in patients with cirrhosis undergoing invasive procedures, especially in those with an established (or suspected) hyperfibrinolytic state.

Fibrinolysis is a complex process, which is altered in patients with cirrhosis, with decreases in both pro- and anti-fibrinolytic factors resulting in a fragilely rebalanced fibrinolytic system. Both hyperfibrinolysis and hypofibrinolysis may occur in patients with cirrhosis.[43] Tranexamic acid is a synthetic derivative of lysine that exerts antifibrinolytic effects by binding to lysine binding sites on plasminogen molecules, inhibiting the interaction of plasminogen with formed plasmin and fibrin. Tranexamic acid is available in intravenous and oral formulations and it can also be used topically.[177,178] Elimination of the intravenous form of tranexamic acid is exponential with approximately 90% cumulative excretion of the drug in urine in a time span of 24 hours. Renal clearance is the major mechanism of excretion and this correlates with an increased incidence of complications (neurotoxicity, ocular toxicity) in patients with renal dysfunction. Therefore, reduced doses of tranexamic acid are indicated in patients with chronic or acute renal failure, and it should be used with cautious in this setting.

During liver transplantation, hyperfibrinolysis is caused by a high level of tissue plasminogen activator release during the

anhepatic phase, potentially increasing bleeding risk. In randomised controlled trials, antifibrinolytic treatment has been shown to reduce blood loss and transfusion requirements in liver transplantation without increasing thrombotic events.[179–181] Most of these trials used aprotinin, but this drug was withdrawn from the market due to mortality concerns in cardiac surgery. Although aprotinin has been carefully reintroduced into practice for complex cardiac surgery, nowadays tranexamic acid, applied either pre-emptively or therapeutically, is more commonly used during liver transplantation.

Dental extraction in patients with cirrhosis has been shown to be associated with bleeding complications although severe bleeding is rare even in patients with remarkably altered parameters (platelet count <40 × 10^9/L [87] and INR >2.5[76]; platelet count >16 × 10^9/L and INR <3). Data regarding administration of antifibrinolytics to patients with cirrhosis undergoing invasive procedures are scarce. In a prospective observational study in liver transplant candidates, a low risk of bleeding after tooth extractions was found for patients with INR values of ≤2.50 and platelet counts of ≥30 × 10^9/L). Soaking gauze with tranexamic acid did not impact outcomes.[49]

Tranexamic acid has not been studied in patients with cirrhosis undergoing invasive procedures such as liver biopsy, paracentesis, polypectomy, or radiofrequency ablation.

In patients with cirrhosis with abnormal laboratory tests (prothrombin time, APTT, platelet count, fibrinogen) undergoing prophylactic band ligation, is correction of these tests by blood products or factor concentrates indicated to prevent bleeding?

Recommendation

- In patients with stable cirrhosis and abnormal laboratory tests (prothrombin time, APTT, platelet count, fibrinogen) undergoing prophylactic band ligation, administration of blood products or factor concentrates with the aim of avoiding post-ligation bleeding is not recommended **(LoE 5, strong recommendation).**

Prophylactic band ligation is part of the standard of care in the management of varices in patients with cirrhosis.[182] As primary prophylaxis, patients should receive non-selective beta-blockers or band ligation, although the former has further benefits as it treats portal hypertension rather than just the varices. In the prevention of re-bleeding, non-selective beta-blockers and band ligation should be combined to achieve the maximum protection.[182]

Patients who undergo oesophageal varices band ligation can experience several complications including bleeding. Bleeding from patients undergoing EBL can be the consequence of portal hypertension (a variceal bleeding) or can be due to the ulcers that result from the release of the bands. Post-banding ulcer bleeding occurs in 2.7-7.8% of patients, and takes place approximately 10-14 days after the placement of the bands.[55,64,99,183–185] Post-band ligation bleeding is a serious clinical complication as it is associated with a mortality rate of approximately 25-50%.[99,183,185] Several studies have associated post-band ligation ulcer bleeding to coagulation abnormalities such as low fibrinogen[64] or the prothrombin time index.[99] In most studies evaluating the incidence of bleeding after placement of elective band ligation, blood products were transfused at the time of the endoscopy in patients perceived as high risk,[55,64] while other studies do not state whether or not blood products were transfused at the time of the procedure.[99,183–185]

No randomised controlled trials have evaluated the effect of the administration of blood products on the incidence of post-banding ulcer bleeding. In a retrospective study an analysis of post-EBL bleeding was performed according to the presence of baseline increased INR (>1.5) and severe thrombocytopenia (platelets <50 × 10^9/L). In each subgroup, some patients received blood products (INR >1.5 n = 41 (46%), platelets <50 × 10^9/L, n = 39 (57%)) depending on the attending physician's criteria. No differences in the frequency of post-EBL bleeding episodes were observed according to the previous administration of blood products.[186]

A prospective randomised controlled trial evaluating the use of TEG to guide substitution of blood products in patients with cirrhosis undergoing elective procedures included 10 patients who underwent EBL, 6 were randomised to the TEG group while 4 received the standard of care. Although a sub-analysis in this subgroup was not done, in the whole study patients who were assigned to TEG received less blood products without differences in the frequency of bleeding episodes.[66]

Should antiplatelet and/or anticoagulant agents be discontinued in patients with cirrhosis before invasive procedures to decrease the rate of procedure-related clinically relevant bleeding?

Recommendation

- In patients with cirrhosis, antiplatelet and/or anticoagulant agents should be managed following the same guidelines as in patients without cirrhosis before invasive procedures **(LoE 4, strong recommendation).**

Anticoagulant therapy either using low molecular weight heparin (LMWH), vitamin K antagonists and more recently direct-acting oral anticoagulants (DOACs) are gaining acceptance for the treatment of portal vein thrombosis (PVT) in patients with cirrhosis.[32] In addition, antiplatelet agents are widely used in this population given the high incidence of coronary artery disease (around 20-40%).[73,187] Antithrombotic drugs are inherently associated with a bleeding risk, and this bleeding risk may be elevated in patients with cirrhosis due to their fragilely rebalanced haemostatic system. For example, in a nationwide study comparing bleeding events between patients with and without cirrhosis and a previous acute myocardial infarction under double antiplatelet treatment, the risk of gastrointestinal bleeding was significantly higher in patients with cirrhosis.[188] Therefore, the question regarding the management of antiplatelet and anticoagulant treatment before elective invasive procedures is more and more frequently raised in clinical practice. Factors to consider are the procedural bleeding risk, the inherent risk of thrombosis associated with the underlying disease, and whether the procedure is elective or an emergency.

International guidelines use a very practical approach concerning management of anticoagulant and antiplatelet therapy before percutaneous procedures or endoscopic procedures in patients with cirrhosis,[189,190] as they recommend the same rules for patients with and without cirrhosis. Whether to use the same timing for discontinuation of therapy in patients with cirrhosis is unclear as i) clearance of anticoagulants may be delayed as they are often metabolised by the liver and/or kidneys, ii) the efficacy of anticoagulants might be altered in patients with cirrhosis as suggested by *in vitro* studies.[191,192] In a recent study evaluating the risk of variceal band ligation in patients with cirrhosis, only 32 out of 750 patients were under anticoagulation that could not be discontinued. The risk of post-EBL bleeding was 9%, and was associated with secondary prophylaxis (p = 0.05) and previous decompensation of cirrhosis,[193] but not to anticoagulant use during the procedure. These results confirm those obtained in another study that compared 80 patients on LMWH to 185 who were not receiving anticoagulants.[194] In this study, the risk of secondary bleeding was not different between the 2 groups. In this context there are no data regarding TIPS or liver biopsy.

In patients with cirrhosis, should invasive procedures be performed with specific modalities (*e.g.* experienced operators, imaging guidance) to reduce procedure-related bleeding?

Recommendation

- In patients with cirrhosis, imaging guidance is recommended for liver biopsy, central venous line placement and jugular puncture for TIPS placement **(LoE 3, strong recommendation).**

Future perspectives

Any new specific modality aimed at reducing the risk of procedure-related bleeding should be evaluated in prospective randomised trials.

Invasive procedures are usually stratified as low (*i.e.*, <1.5% bleeding complications) or high (>1.5% bleeding complications) risk.[80,195] This stratification reasonably considers not only the frequency of the bleed but also the potential severity of this complication (Table 2, adapted from[80,195]). In this setting, various measures to reduce the bleeding risk associated with these procedures have been explored, including using imaging guidance, proper training, or even allowing only experienced operators to perform such procedures.

Role of operator's experience

The role of operator's experience on the bleeding risk remains debated in technically simple and low-risk procedure such as paracentesis or percutaneous liver biopsy. For paracentesis, a minimum of 10 procedures performed under supervision was sufficient to achieve low complications after paracentesis when performed by a trained nurse even in patients with low platelet count or altered INR without corrective measures.[47] As far as liver biopsy is concerned, 1 report showed a lower incidence of bleeding following the procedure among physicians who had carried out more than 100 biopsies compared to less experienced physicians who had carried out less than 20 biopsies (1.1% *vs.* 3.2%), although this study did not control for severity of liver disease.[196] However, in another study, the reverse phenomenon was observed as, among 2,229 biopsies, a higher risk of bleeding was observed when liver biopsy was performed by experienced operators (more than 150 procedures, bleeding incidence 2.2%) *vs.* less experienced operators (bleeding incidence, 1.1%), although once again it was not reported whether these findings were independent of several other confounding factors (*e.g.*, stage of liver disease, biopsy technique, number of passes)[197] and this finding may be due to selection bias.

Retrospective studies suggested that patients with cirrhosis had an increased risk of bleeding during more demanding endoscopic procedures such as polypectomy or ERCP compared to patients without cirrhosis.[54,107,198] However, the bleeding episodes were mostly self-limited by using local haemostatic manoeuvres, suggesting the importance of endoscopic skills. One study showed an increased risk of bleeding when polypectomy is done by experienced operators, which again may reflect a selection bias.[54]

In a recent review of TIPS procedures, transcapsular puncture during TIPS has been reported in up to 33% of cases, leading to peritoneal bleeding in 1-2% of cases.[199] Better stent patency and decreased mortality following TIPS have been demonstrated when more experienced operators performed the procedure.[200] When inexperienced operators used intravascular ultrasound for TIPS needle visualisation, it reduced procedure time and frequency of capsular perforation in a small series of 109 TIPS procedures.[108]

Role of imaging guidance

The impact of ultrasound guidance on reducing bleeding complications has been clearly demonstrated for central line placement in patients with coagulopathy[201] and has become standard of care in this setting.[202] For paracentesis,[203] the use of ultrasound guidance did not seem to be associated with a lower rate of haemorrhage or haematoma formation following the procedure (with 2/723 procedures, 0.28% *vs.* without 5/574 procedures, 0.87%, p = 0.25), although this study was retrospective and based on billing codes.[203]

The use of ultrasound guidance significantly reduced the number of complications when used to guide double-pass liver biopsy compared to the traditional Menghini technique in a randomised trial including 200 liver biopsies.[204] These results were confirmed later in a multicentre randomised trial that showed that ultrasound guidance significantly reduces pain and bleeding episodes in percutaneous liver biopsy.[205]

Bleeding complications during TIPS are linked to capsular puncture while attempting to puncture the portal vein. Several methods have been suggested to reduce this risk, such as transparietal ultrasound[206] or using more sophisticated 2D/3D fusion image guidance[207] to reduce the number of passes from the hepatic vein to the portal vein. These imaging techniques reduced TIPS procedure duration and reduced the number of passes required to reach the portal vein and their use is therefore recommended despite a lack of evidence that they reduce bleeding complications.[208]

Should patients with cirrhosis undergoing invasive procedures be monitored differently for bleeding complications than patients without cirrhosis?

Recommendation

- Patients with cirrhosis undergoing invasive procedures should be monitored for bleeding complications in the same way as patients without cirrhosis **(LoE 3, strong recommendation).**

Future perspectives

Any change in standard surveillance after invasive procedures in patients with cirrhosis (e.g. shortened hospital surveillance) should be evaluated prospectively.

In patients with cirrhosis undergoing procedures associated with a low risk of bleeding, there is no medical justification to monitor them differently to patients without cirrhosis. In general, bleeding associated with invasive procedures mainly occurs during the procedure itself and is usually identified and managed immediately by appropriate local treatment. However, an increased risk of delayed bleeding after specific invasive procedures could justify intensified post-procedural monitoring in patients with cirrhosis. For example, decompensated cirrhosis is described as a risk factor for bleeding post-sphincterotomy in a recent meta-analysis with an odds ratio of 2.05 (95% CI 1.62-2.58).[209] An analysis based on the National NIS survey[210] confirmed a statistically significant difference in the incidence of bleeding episodes after ERCP between patients with (n= 1,930) and without cirrhosis (n= 5,790) (2.3 *vs.* 1%; p <0.0001). However, it is unknown whether prolonged surveillance or additional endoscopic examination may decrease the bleeding risk associated with these procedures in patients with cirrhosis.[105,210,211] In procedures typically associated with a risk of delayed bleeding such as colonic polypectomy, delayed bleeding remains a rare event (0.3% of colonoscopies). A recent study involving 307 colonoscopies with 638 polypectomies in patients with cirrhosis reported a similar incidence of delayed bleeding as would be expected in patients without cirrhosis.[107]

Importantly, identification of anaemia after an invasive procedure may lead to an erroneous diagnosis of occult bleeding. Anaemia is frequent in patients with cirrhosis (reported in 51% to 66% of patients), is usually multifactorial, and is associated with severity of liver disease and degree of portal hypertension.[212,213] A pre-procedural haemoglobin level would be helpful to avoid the erroneous diagnosis of occult bleeding based on a post-procedural haemoglobin measurement.

In patients with cirrhosis and active variceal bleeding, besides vasoactive treatment and endoscopic therapy, is correction of haemostatic alterations indicated to stop bleeding?

Recommendations

- In patients with cirrhosis and active variceal bleeding, if haemostasis is achieved with portal hypertension-lowering drugs and endoscopic treatment, correction of haemostatic abnormalities is not indicated **(LoE 3, strong recommendation).**
- In case of failure to control haemorrhage, the decision to correct haemostasis should be considered on a case-by-case basis **(LoE 3, strong recommendation).**
- In patients with cirrhosis and active variceal bleeding, tranexamic acid should not be used **(LoE 2, strong recommendation).**

Variceal bleeding is still associated with a 6-week mortality rate of 15-20%. Standard therapy for variceal bleeding includes prompt initiation (before endoscopy) of vasoactive therapy (terlipressin, somatostatin or octreotide), antibiotics, and EBL.[182]

Few studies have evaluated the effect of correction of haemostasis in the context of variceal bleeding. A recent study evaluated the use of TEG to guide transfusion in the context of acute variceal bleeding. Interestingly, only patients with severe haemostatic abnormalities (platelets <50 × 10^9/L and/or INR >1.8) were included. The standard of care group received platelets and/or FFP when the values were under/above these cut-offs, respectively. The TEG-guided group received platelets and/or FFP according to the TEG results. As TEG results are frequently normal in patients with cirrhosis, even in the presence of thrombocytopenia and/or a prolonged INR, the TEG group required less blood products. No difference in outcomes regarding early re-bleeding and 6-week mortality was observed, although the trial was not powered to evaluate these outcomes.[214]

The use of recombinant factor VIIa has been evaluated in 2 studies[215,216] and their results have been combined in a meta-analysis of individual patient data.[217] The meta-analysis reported a beneficial effect of recombinant factor VIIa in the prevention of early re-bleeding among high-risk patients with active bleeding at endoscopy, particularly in patients with a Child-Pugh score above 8 points. No differences were observed in 6-week re-bleeding rates or mortality. Administration of recombinant factor VIIa was potentially associated with an increased rate or arterial thromboembolic events, and it has been argued that this drug has no net clinical benefit in the setting of variceal bleeding.[218]

Use of intravenous tranexamic acid has been evaluated in a large randomised placebo-controlled trial including 12,009 patients with acute upper gastrointestinal bleeding, of which nearly 50% of cases were suspected variceal bleeding.[219] The primary outcome of the trial was death due to bleeding within the first 5 days. No beneficial effect of tranexamic acid was observed in the whole group nor in the subgroup analysis of patients with suspected variceal bleeding and liver disease comorbidity. Possible reasons why an antifibrinolytic is ineffective in variceal bleeding include the limited role of haemostasis in variceal bleeding and the frequent occurrence of a hypofibrinolytic state in critically ill patients with cirrhosis.[43] In the whole study population, an almost 2-fold increase in the incidence of venous thromboembolic events was observed in the tranexamic acid group compared to the placebo group. A subgroup analysis showed that the risk of venous thromboembolic events was concentrated in patients with comorbid liver disease/suspected variceal bleeding. Thrombotic events could be related to the high doses of tranexamic acid used in this trial but could also be related to the relative hypofibrinolysis observed in acute-on-chronic liver failure.

In both animal models and patients with cirrhosis, evidence suggests that administration of blood products leads to an increase in portal pressure.[116,220–223] Higher portal pressure has been associated with worse outcomes (failure to control bleeding or early

re-bleeding).[224,225] This mechanism likely explains why a restrictive red blood cell transfusion strategy is beneficial and indicates that administration of large volumes of blood products may paradoxically increase bleeding rather than contribute to control of bleeding.

In patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (*e.g.* portal hypertensive gastropathy), is correction of a prolonged prothrombin time, fibrinogen deficiency or thrombocytopenia by transfusion of FFP, fibrinogen concentrate/cryoprecipitate, PCCs, or platelet concentrate indicated to stop bleeding?

Statement

- No studies evaluating correction of haemostasis in patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (*e.g.*, portal hypertensive gastropathy), are available **(LoE 5).**

Recommendations

- In patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (*e.g.*, portal hypertensive gastropathy), bleeding should be managed with portal hypertension-lowering measures **(LoE 5, weak recommendation).**
- In the case of failure to control haemorrhage with portal hypertension-lowering drugs, the decision to correct haemostasis should be considered on a case-by-case basis **(LoE 5, weak recommendation).**

Future perspectives

Large observational cooperative studies are recommended to collect data on the treatment (including correction of haemostatic abnormalities) of patients with overt portal hypertensive gastropathy-related bleeding and/or chronic anaemia due to portal hypertensive gastropathy-related bleeding in whom vasoactive treatment and endoscopic therapy failed to stop bleeding.

Patients with cirrhosis may have other sources of bleeding related to portal hypertension. Portal hypertensive gastropathy is the most common source,[190] although similar lesions may be detected in other parts of the gastrointestinal tract including portal hypertensive enteropathy (small bowel) and portal hypertensive colopathy.[226–228] These entities are mainly a cause of chronic bleeding and chronic anaemia.[229–231] Nevertheless, they may also present as acute gastrointestinal bleeding. Portal hypertensive gastropathy was identified as the source of bleeding in 2-12% of patients with cirrhosis who presented with gastrointestinal bleeding.[229,232,233] Although portal hypertension plays the main role in determining bleeding from portal hypertensive gastropathy, increased fibrinolysis has also been implicated.[190,234]

The mainstay of the treatment of bleeding (both acute and chronic) from portal hypertensive gastropathy is based on portal pressure-lowering strategies.[235–238] Vasoactive therapy is recommended in the acute setting, while beta-blockers are recommended in the chronic setting.[190]

Patients who have refractory bleeding from portal hypertensive gastropathy can be considered for TIPS placement.[182] No studies have evaluated the effectiveness of correcting haemostatic abnormalities in order to stop bleeding related to portal hypertension but not varices. A case report has described the use of tranexamic acid in the context of refractory bleeding due to gastric vascular ectasia in cirrhosis.[239] This bleeding, although common in cirrhosis, is typically not associated with portal hypertension and should be treated with endoscopic procedures.

In patients with cirrhosis that are actively bleeding from a non-portal hypertensive cause, is correction of a prolonged prothrombin time, fibrinogen deficiency, or thrombocytopenia by transfusion of FFP, fibrinogen concentrate/cryoprecipitate, PCCs, or platelet concentrate indicated to stop bleeding?

Recommendations

- In patients with cirrhosis who are actively bleeding from a non-portal hypertensive cause, active bleeding should first be addressed by local measures and/or interventional radiology procedures **(LoE 4, strong recommendation).**
- In those patients in whom local measures fail to stop the bleeding, addressing contributing factors (renal failure, infection or sepsis, and anaemia) may reduce bleeding while correction of haemostatic abnormalities can be considered on a case-by-case basis **(LoE 5, weak recommendation).**

Future perspectives

Preferably randomised, placebo-controlled studies should explore the best strategies to correct haemostasis in patients with non-portal hypertension-related bleeding which is unresponsive to local measures. Depending on the clinical context, low-volume products (fibrinogen concentrates and PCCs) or platelet concentrates are the agents of choice for such studies.

In patients with cirrhosis who are actively bleeding, there may be at least 3 underlying causes for the bleed.[240] First, bleeding may be directly related to portal hypertension, which is the case for variceal bleeding. Portal hypertension-related bleeding requires local measures and pharmacological therapies to reduce portal pressure, but pro-haemostatic therapy is not indicated. The observation that patients on anticoagulants at the time of a variceal bleed do not bleed more or have worse outcomes than patients who are not on anticoagulants confirms that the role of the haemostatic system in variceal bleeding, if present, is minor.[241] Second, bleeding may be caused by inadvertent puncture or laceration of vessels during invasive procedures. If such a bleed is accessible, for example during surgery, repair of the vessel by simple suturing is indicated. Alternatively, the bleed may be addressed endoscopically or by interventional radiology. Whether pro-haemostatic therapy is beneficial in cases of inadvertent vessel puncture, in which the vessel is not readily accessible, for example if the vessel is injured during percutaneous liver biopsy or paracentesis, is uncertain. Third, some bleeds may be related to haemostatic failure. Such bleeds include large spontaneous or procedure-related haematomas, oozing from indwelling catheters, and dental bleeds. Whereas some of these haemostasis-related bleeds are cosmetic or can be stopped with local measures, some may be more severe and may require intervention. For example, continuous oozing from indwelling catheters or expanding haematomas in critically ill patients with cirrhosis may not respond to local measures. These

patients may have multiple factors that may contribute to bleeding including renal failure, infection or sepsis, and anaemia.[46,104,242,243] These factors have direct effects on the haemostatic system and addressing these issues may reduce bleeding risk. Successful treatment of acute kidney injury and infection in patients with cirrhosis has been demonstrated to improve *ex vivo* measures of haemostasis.[46] In addition, adequate management of anaemia reduces bleeding risk in patients with renal failure without underlying liver disease.[144,244] Nevertheless, there are no clinical data showing that addressing these issues reduces bleeding severity in actively bleeding patients with cirrhosis. Whether transfusion of blood components is effective at stopping bleeding in these scenarios is also unclear, but it is evident that profoundly bleeding patients may develop hypovolemic shock, which requires resuscitation using blood component transfusion. *Ex vivo* studies have demonstrated that FFP and platelet concentrates hardly improve haemostasis in non-bleeding patients,[26,112,146] whereas fibrinogen concentrates and PCCs have been shown to effectively improve haemostasis *in vitro*.[131] It is important to note that there is very little evidence on the efficacy of haemostatic products in bleeding patients without underlying liver disease. For example, although FFP is the accepted standard treatment for replacement of clotting factors in bleeding patients undergoing cardiac surgery, in a Cochrane review only 1 study out of 14 identified trials (n = 738 participants) has evaluated the efficacy of FFP in bleeding patients, and this was underpowered to determine differences in mortality.[245] There is evidence that PCCs are beneficial in actively bleeding patients.[246] Similarly, the clinical efficacy of therapeutic platelet transfusions is unclear. In the SPRINT trial, bleeding grades were assessed before and after 186 therapeutic platelet transfusions given for active bleeding. WHO bleeding grades decreased following only 21% of the transfusions; they were unchanged after 69%, and they actually increased after 10%.[247] In addition, a recent large national audit reported the resolution of bleeding after a therapeutic platelet transfusion in 58% of cases with clinically relevant bleeding (WHO grade 2 or above).[248] Nevertheless, despite the lack of firm evidence of efficacy, guidelines do suggest to transfuse FFP or platelets in patients that are actively bleeding.[249,250] Thus, there is little evidence on how to best treat active bleeding in the general population, and randomised trials addressing management of non-portal hypertension-related bleeds in patients with cirrhosis are absent.

In patients with cirrhosis that are actively bleeding from a non-portal hypertensive cause, is administration of antifibrinolytic drugs such as tranexamic acid indicated to stop bleeding?

Recommendation

- In patients with cirrhosis, routine use of antifibrinolytic agents to treat active bleeding from a non-portal hypertensive cause is discouraged **(LoE 5, weak recommendation).**

Future perspectives

Preferably randomised, placebo-controlled trials should assess the safety and efficacy of antifibrinolytic agents in treating active non-portal hypertensive bleeding episodes that are unresponsive to local measures.

Antifibrinolytic drugs such as tranexamic acid, epsilon aminocaproic acid, and aprotinin have been widely used in the general population to prevent or treat bleeding. Large, randomised studies have demonstrated that tranexamic acid reduces bleeding and mortality in trauma and post-partum bleeding.[251,252] However, tranexamic acid was not effective in subarachnoid haemorrhage,[253] and was ineffective and caused harm in patients with gastrointestinal bleeding.[219] In the HALT-IT trial on the use of tranexamic acid in gastrointestinal bleeding, a subgroup of patients had suspected variceal bleeding or liver disease. This trial concluded that tranexamic acid should not be used to treat bleeding in patients with cirrhosis. Since in other settings it has been demonstrated that tranexamic acid is only effective when administered within 3 hours of the onset of bleeding, the delay between onset of bleeding and tranexamic acid administration could explain its inefficacy in this trial. Although antifibrinolytics do not seem to have a role in gastrointestinal bleeding, they may be effective in other settings. Prophylactic use of antifibrinolytic agents has been shown to reduce blood loss and transfusion requirements during liver transplantation in multiple randomised controlled trials without increasing the risk of thrombotic complications.[179,181,254] Such studies align with the beneficial effects of antifibrinolytics in cardiac surgery.[255] Antifibrinolytics have shown benefit in the general population in patients with heavy menstrual bleeding,[256] and may be beneficial for epistaxis.[257] No studies on the efficacy of antifibrinolytics in patients with cirrhosis who are actively bleeding from causes other than liver transplant surgery or from a gastrointestinal sources are available.

In patients with cirrhosis who are actively bleeding, is pro-haemostatic management better guided by viscoelastic tests than by routine coagulation tests?

Statement

- There is initial evidence that the use of viscoelastic tests is associated with decreased blood product use in patients with cirrhosis and active upper gastrointestinal bleeds, without differences in bleeding control and mortality **(LoE 3).**

Recommendation

- Given the benefits of reducing blood transfusion, viscoelastic tests can be used when available **(LoE 1, strong recommendation).**

Future perspectives

Viscoelastic tests' ability to guide pro-haemostatic management in patients with cirrhosis and active bleeding should be prospectively evaluated in randomised controlled trials.

Patients with cirrhosis may experience a bleeding complication due to haemostatic failure or non-haemostatic causes. Notably, a bleed that is not primarily caused by haemostatic failure can become a haemostatic bleed. For example, a surgical bleed that is not promptly addressed may become a haemostatic bleed due to severe blood loss and consumption of haemostatic factors, ultimately resulting in haemostatic failure. When a bleeding complication is likely the result of haemostatic failure, laboratory testing may help in identifying which factors (platelets, coagulation factors, fibrinogen) require repletion.[249,258]

Routine diagnostic tests of haemostasis (platelet count and prothrombin time) may have limited value in patients with liver disease as the platelet count does not indicate the functionality of the circulating platelets[40,142] and the prothrombin time only assesses the activity of pro- and not anticoagulant factors.[259] Viscoelastic tests more accurately demonstrate the functional status of platelets and coagulation factors, although there remain important limitations. Specifically, viscoelastic tests are insensitive to the VWF and the protein C system, both of which are profoundly altered in patients with liver disease.[260] Another advantage of viscoelastic tests relates to the identification of (severe) hyperfibrinolysis,[261] and the fact that viscoelastic tests can be performed as point-of-care tests. One randomised controlled study has shown that the use of viscoelastic tests to determine transfusion requirements in patients with cirrhosis with non-variceal upper gastrointestinal bleeding does not result in superior control of bleeding compared to the use of routine diagnostic tests to guide transfusion, although blood product transfusion was much lower in the viscoelastic test group.[262] It has been shown that the use of viscoelastic tests reduces blood product use in patients with variceal bleeding without differences in outcomes,[214] but it is questionable whether pro-haemostatic therapy contributes at all to stopping a variceal bleed when the standard treatment with vasoactive drugs and endoscopic treatment is administered. There are data showing that the use of viscoelastic tests in the general population, specifically acutely bleeding trauma, surgical, and critically ill patients was associated with a tendency towards fewer blood product transfusions.[214] Transfusions guided by viscoelastic tests were associated with a reduced number of additional invasive haemostatic interventions (angioembolic, endoscopic, or surgical) in surgical patients. Viscoelastic tests appear to be helpful in guiding haemostasis management in patients during liver transplantation,[263] although it is not clear whether viscoelastic tests are useful to guide transfusion in actively bleeding patients in this setting. Since viscoelastic tests are quicker than routine diagnostic tests and provide information on fibrinolysis (which may prompt anti-fibrinolytic therapy), they have a theoretical advantage over routine diagnostic tests in guiding active bleeding, although this has not been formally compared in a (randomised) clinical study.

Are patients with cirrhosis at risk of developing venous thromboembolism (VTE/deep vein thrombosis [DVT]/ pulmonary embolism [PE])?

Statement

- Based on clinical observations and laboratory findings, it can be concluded that the risk of developing DVT/PE is at least as high in patients with cirrhosis as in the general population **(LoE 2).**

Future perspectives

Data from large observational studies will provide the basis for prophylactic treatment of venous thromboembolism in patients with cirrhosis.

Patients with cirrhosis show distinct hypercoagulable changes in their haemostatic system. These hypercoagulable changes include a VWF/ADAMTS13 imbalance,[40] hyperactive platelets,[142] enhanced thrombin generating capacity as assessed by thrombomodulin-modified thrombin generation,[264] and a hypofibrinolytic state in the sickest patients.[43,265] These hypercoagulable changes may increase the risk of thrombotic disease.

The prevalence of venous thrombosis in patients with cirrhosis is highly variable. In patients with cirrhosis admitted to hospital, the incidence of VTE has been reported to be between 1.2% to 7%.[187,266,267] During hospital stay, the occurrence of VTE fluctuates widely, occurring in 0.5% to 7% of patients with chronic advanced liver disease.[267–271] In the setting of hospitalised patients, data from a meta-analysis indicate that about 1% of patients with liver diseases develop or are diagnosed with VTE during their hospitalisation.[272] However, there are apparently contrasting data showing that the overall incidence of VTE in patients with no liver disease, mild liver disease and moderate-severe liver disease was 2.7, 2.4 and 0.9 per 100 patient discharges, respectively.[273] A recent systematic review and meta-analysis showed a 1.7-fold increased risk of VTE in patients with cirrhosis compared to individuals without cirrhosis.[274] A nationwide study from Taiwan indicated that the adjusted hazard ratio of VTE was 1.7 in patients with cirrhosis compared to the general population.[275] In a study from a medical claim database, in patients with cirrhosis and in comparators, the crude rates of any thromboembolic event were 561.1 and 249.7 per 10,000 person-years, respectively.[276] In a population-based case-control study, patients with cirrhosis had a 1.74-fold increased RR of VTE.[277] In a recent study exploiting nationwide Danish healthcare registries, patients with cirrhosis, mostly of alcoholic aetiology, were matched with comparators from the general population and were prospectively followed up until development of VTE, or other vascular events, or death. The 10-year risk of VTE was 2.5% for patients with cirrhosis *vs.* 1.7% for controls.[278]

Caution is needed in interpreting these data, because the apparently increased risk of VTE in patients with cirrhosis may be related to the fact that they did not receive prophylactic anticoagulation when hospitalised. The prevalence of VTE prophylaxis, when indicated, in the population with cirrhosis was low and reported to be 24-56%.[268,270,279] However, in patients with cirrhosis and VTE, the proportion of patients treated with anticoagulants was similar to the population without cirrhosis (*i.e.* 98.4%)[280] and the incidence of mortality, PE, and fatal bleeding episodes was higher.[280]

Can clinical prediction scores be used to decide which patients with cirrhosis are at risk of VTE (DVT/PE)?

Recommendation

- Clinical prediction scores, such as the Padua prediction score (>3[281] or ≥4[282] or IMPROVE score (≥4[283]) can be used to predict which patients with cirrhosis are at high risk of developing lower limb DVT and/or PE **(LoE 3, strong recommendation).**

Future perspectives

Large observational cooperative studies are recommended to collect data on the real-life ability of clinical prediction scores to assess the risk for VTE in patients with cirrhosis.

Lower albumin, alone or in combination with other biochemical parameters (*e.g.*, APTT[266]) has been indicated as a relevant risk factor for VTE development by several studies,[63,266,271,284] although another study failed to confirm this association.[268] VTE incidence was not related to the severity of liver disease according to the Child-Pugh or the MELD score (Child-Pugh A *vs.* Child-Pugh B/C cirrhosis; continuous MELD score).[266,285] Additional risk factors are Black race, malnutrition and the presence of a central venous line.[286] It is not well known whether the concomitant presence of cancer, chronic renal failure or congestive heart disease increases VTE risk in cirrhosis as it does in the general population.

Several risk-assessment models have been set up in general surgical or medical patients to identify those at increased thrombotic risk (Caprini score, Geneva risk score, Padua prediction score). The latter is a risk-assessment model based on clinical features of hospitalised patients. The Padua prediction score was shown to be able to discriminate between patients at high and low VTE risk.[287] This study did not include patients with cirrhosis. The Padua prediction score, however, is the only one, among the above-cited risk-assessment models, which was later validated as a risk-stratification tool for VTE in the setting of cirrhosis. In a retrospective cohort of 163 patients in a single academic medical centre in the United States,[282] the Padua prediction score was identified as an effective risk-assessment tool for VTE in patients hospitalised with cirrhosis. The ability of the Padua prediction score to predict VTE in patients with chronic liver disease was also assessed by Moorehead *et al.*[281] They showed that patients with a Padua prediction score >3 were significantly more likely to develop VTE than those with a score <3.

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score is another risk-assessment model that was more recently developed in a large cohort of patients, which also included patients with chronic liver disease.[283] Davis *et al.*[288] used the IMPROVE risk score to identify patients with cirrhosis at higher risk of developing VTE. Thrombotic events were significantly more common in patients with an IMPROVE score ≥4.

Can viscoelastic tests or other laboratory tests be used to decide which patient with cirrhosis is at risk of VTE (DVT/PE)?

Recommendation

- The use of viscoelastic tests or other laboratory tests to identify which patients with cirrhosis are at risk of VTE (DVT/PE) is not recommended **(LoE 5, strong recommendation).**

Future perspectives

Prospective studies should explore the predictive value of laboratory tests alone or in combination with clinical scores to predict the risk of VTE during hospitalisation.

Viscoelastic tests provide more accurate information on haemostatic status in patients with cirrhosis compared to routine diagnostic tests. However, there are at least 2 important limitations of viscoelastic tests that deserve attention.[260] First, viscoelastic tests are insensitive to the platelet adhesive protein VWF. As VWF plasma levels are highly elevated in patients with cirrhosis and appear to compensate in part for cirrhotic thrombocytopenia,[40] this leads to an underestimation of true haemostatic capacity by viscoelastic tests. Similarly, viscoelastic tests are insensitive to the anticoagulant action of the protein C system, and as decreased levels of protein C contribute to the hypercoagulability of patients with cirrhosis,[289] this again leads to an underestimation of haemostatic capacity. There are several validated clinical prediction models for venous thrombosis risk in the general population.[290] These risk-assessment models generally rely on clinical factors and known heritable thrombophilia (factor V Leiden, prothrombin 20210A variant, protein C, S and antithrombin deficiency), but not on global laboratory tests of coagulation. In theory, hypercoagulability as assessed with global tests, such as viscoelastic tests or thrombin generation tests, could be associated with an increased risk of venous thrombosis, but little data in support of this hypothesis are available. A meta-analysis has shown viscoelastic tests to have a moderate ability to predict venous thromboembolic events,[291] but whether the performance of these tests is sufficient for clinical use is questionable.

Routine coagulation tests are not able to correctly identify patients at risk of thrombotic events in patients with cirrhosis.[292] A retrospective study by Dabbagh *et al.*[270] was among the first to show that an elevated INR is not associated with a sufficient anticoagulant effect to prevent VTE in patients at risk. A recent prospective study by Zermatten *et al.*[285] showed that a prolonged INR and APTT were related more with an increased risk of thrombosis rather than bleeding. On the whole, no single laboratory assay is able to identify all known thrombophilic disorders.[284,293] Rogers *et al.*[293] set up a comprehensive diagnostic algorithm including more than 20 different parameters to identify patients with suspected thrombophilia. However, the complexity of the algorithm means that a specialised laboratory and coagulation specialists are required for its application and interpretation, respectively.

Heritable thrombophilia, plasma levels of individual coagulation factors, and plasma hypofibrinolysis have been identified as risk factors for VTE.[259,294] In addition, other widely available laboratory tests, such as the shortened APTT[295] and mean platelet volume,[296] are associated with an increased risk of venous thrombosis. None of these studies, however, have been applied in the general population, as knowledge of the thrombophilic status of a given individual does not alter treatment decisions.[297] No studies on laboratory tests in relation to venous thrombosis risk in patients with cirrhosis are available in the literature.

Is administration of thromboprophylaxis with LMWH or DOACs indicated to decrease the incidence of lower limb DVT (DVT/PE) in high-risk patients with cirrhosis?

Recommendations

- In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with LMWH can be recommended as it has a reasonable safety profile, but efficacy is unclear based on available data **(LoE 3, weak recommendation).**
- In patients with Child-Pugh class A and B cirrhosis at risk of DVT/PE, thromboprophylaxis with DOACs can be recommended as DOACs have a reasonable safety profile in these patients, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis, DOACs are not

recommended **(Safety: LoE 2; Efficacy: LoE 4; weak recommendations).**

Future perspectives

Large observational cooperative studies, or ideally randomised controlled trials, are recommended to determine the safety and efficacy of LMWH or DOACs in hospitalised patients with cirrhosis at high risk of VTE.

The occurrence of DVT/PE in patients with cirrhosis is associated with prolonged hospital stay and has a clear-cut impact on prognosis, with several studies – including systematic reviews, literature reviews and data from registries and large cohorts – reporting, with few isolated exceptions,[286] significantly increased mortality.[187,270,273,274,280,298] According to these data, thromboprophylaxis would appear a sensible option to offer to patients with cirrhosis and risk factors for DVT/PE (such as prolonged hospitalisation and immobilisation, surgery, male sex).[299] However, to date, thromboprophylaxis for VTE has not been extensively used in patients with cirrhosis because of the perceived increased risk of bleeding associated with the coagulopathy of cirrhosis. Most available studies on prophylaxis for DVT/PE are retrospective and uncontrolled, and data have often been extracted from heterogeneous cohorts, which also fortuitously included patients with chronic liver disease.

LMWH

Most studies in the setting of cirrhosis have evaluated thromboprophylaxis using LMWH or unfractionated heparin (UFH). Shatzel *et al.*[300] retrospectively reviewed 600 hospital admissions accounting for 402 patients. About half of the patients received VTE thromboprophylaxis (LMWH in 134 (45%) and UFH in 141 (48%) at a prophylactic dose). Prophylaxis did not reduce the risk of VTE (odds ratio 0.94, 95% CI 0.23–3.71). Yerke *et al.*[301] retrospectively evaluated 2 groups of 903 patients propensity score matched according to whether they had or had not received anticoagulation; on multivariate analysis they found that anticoagulation did not reduce the incidence of VTE. In a small retrospective cohort study, Bogari *et al.*[282] evaluated VTE incidence in a group of patients defined as at high-risk of VTE according to the Padua prediction score. The incidence of VTE in those who received pharmacological prophylaxis was halved (13% *vs.* 27% without prophylaxis), although the difference was not statistically significant ($p = 0.239$).

In most studies, bleeding events were similar in patients who did or did not receive thromboprophylaxis, with a trend towards an increased risk for in-hospital bleeding in patients receiving UFH.[300] Administration of thromboprophylaxis in hospitalised patients with cirrhosis was not associated with increased rates of gastrointestinal bleeding or death (overall rate of 2.5% of patients with documented gastrointestinal bleeding events). Moreover, Intagliata *et al.*[302] showed that patients with cirrhosis receiving thromboprophylaxis during hospitalisation did not have an increased risk of gastrointestinal bleeding or death. In contrast, Reichert *et al.*,[303] in a cohort of 256 patients, identified pharmacological VTE prophylaxis use as an independent risk factor for bleeding.

DOACs

Several studies have evaluated the use of DOACs in patients with cirrhosis, exploiting large series of patients with atrial fibrillation. However, most if not all studies reported on DOACs safety rather than efficacy in preventing VTE. Data on the latter are scarce and indirect. Kunk *et al.*[304] reported on a small group of 22 patients with cirrhosis and atrial fibrillation who received DOACs for stroke prevention. On follow-up assessment for DVT onset, DOACs maintained a good safety profile and none of these patients developed VTE while on treatment.

Experience with DOACs in patients with chronic liver disease is still not extensive, although preliminary results do not seem to indicate an increased risk of bleeding events.[305,306] A single-centre retrospective study of 138 patients with mostly advanced cirrhosis (93 Child-Pugh class B or C) on DOAC therapy suggested that long term DOAC treatment was associated with fairly high treatment discontinuation rate and frequency of bleeding events.[307] Fu *et al.*,[308] in a meta-analysis on 41,954 patients with atrial fibrillation and liver disease, found that DOACs were associated with reduced risks of all-cause death (RR 0.78; 95% CI 0.66–0.93), major bleeding (RR 0.68; 95% CI 0.53–0.88), and intracranial haemorrhage (RR 0.49; 95% CI 0.41–0.59), but comparable risks of stroke or systemic embolism (RR 0.80; 95% CI 0.57–1.12) and gastrointestinal bleeding (RR 0.90; 95% CI 0.61–1.34), compared to patients receiving traditional anticoagulant drugs. In the subgroup with cirrhosis (n = 3,111), the risks of major bleeding (RR 0.53; 95% CI 0.37–0.76), gastrointestinal bleeding (RR 0.57; 95% CI 0.38–0.84), and intracranial haemorrhage (RR 0.55; 95% CI 0.31–0.97) were significantly reduced when compared with warfarin. Similar results in terms of bleeding and occurrence of ischaemic stroke were obtained by Menichelli *et al.*[309] while a decreased occurrence of ischaemic stroke was reported by Huang *et al.*[310]

Can vitamin K agonists or LMWH be used in the treatment of DVT/PE in patients with cirrhosis?

Recommendation

- For treatment of DVT/PE, vitamin K antagonists should be used with caution in patients with cirrhosis, as these patients can have baseline altered INR and thus target INR remains unknown. In patients with Child-Pugh A, LMWH, and vitamin K antagonists are reasonable options. Until more data become available, LMWH is recommended for treatment of DVT/PE in patients with Child-Pugh B and Child-Pugh C cirrhosis, whereas UFH is the treatment of choice in case of renal failure **(LoE 4, weak recommendation).**

Future perspectives

Large observational cooperative studies are needed to assess safety and efficacy of vitamin K antagonists and LMWH in the treatment of DVT/PE in patients with cirrhosis. Tools able to monitor their effects on haemostasis should be refined.

In recent guidelines, UFH, LMWH and vitamin K antagonists are included in the standard of treatment for DVT/PE in patients without cirrhosis, while there is no mention about patients with advanced cirrhosis.[311] The use of LMWH in patients with cirrhosis is complicated by 2 factors. First, the anticoagulant effect of LMWH may be different in patients with cirrhosis compared to patients with adequate liver function, because of the haemostatic changes in patients with cirrhosis. Indeed, the *in vitro* anticoagulant effect of LMWH was reported to be increased in plasma from patients with cirrhosis.[312] Second, monitoring of LMWH by the anti-Xa assay may be unreliable. Specifically, LMWH levels are underestimated in patients with cirrhosis when anti-Xa reagents do not contain exogenously added antithrombin.[192] Caution is needed when treating patients who develop acute kidney injury during treatment. In this case, LMWH should be stopped and replacement with UFH considered until normalisation of kidney function. Monitoring issues also complicate the use of vitamin K antagonists. Due to their narrow therapeutic range and significant drug-drug interactions, close monitoring is required to avoid side effects and to maintain the patient in a therapeutic range. However, defining a therapeutic range may be challenging in patients with cirrhosis as the baseline INR may be elevated in many patients[5] so that a target INR value cannot be defined. In addition, the inter-laboratory variation in the INR in patients with cirrhosis is very high.[37]

While clinical studies assessing the effects of UFH or LMWH for the treatment of VTE/PE in patients with cirrhosis are lacking, some data are available concerning the safety of anticoagulation in patients with cirrhosis with PVT; these data suggest that anticoagulation is a relatively safe treatment that may lead to partial or complete recanalisation of the portal vein in patients with cirrhosis and PVT.[313–315] In a retrospective Spanish study including 17 patients with cirrhosis with non-splanchnic VTE (11 patients with DVT, 7 with PE and 1 with both), 11 patients were treated with LMWH, while 6 were switched to vitamin K antagonists within a week after initiating LMWH treatment. The majority of these patients (83%) suffered from bleeding complications with 6 (35%) of them requiring blood transfusions.[316]

In a recent meta-analysis, data have been collected from patients with cirrhosis treated with vitamin K antagonists and LMWH for splanchnic vein thrombosis.[317] In spite of the aforementioned drawbacks, these findings suggest that anticoagulation can also be used for the treatment of venous thrombosis in patients with cirrhosis, even though more data on efficacy and safety are needed.

Can DOACs be used in the treatment of DVT/PE in patients with cirrhosis?

Recommendations

- For the treatment of DVT/PE in patients with cirrhosis, currently available data suggest that there are no major concerns regarding the safety of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in Child-Pugh class C patients is not recommended **(LoE 4, strong recommendation).**

Future perspectives

Large observational cooperative studies are needed to assess the safety and efficacy of DOAC therapy in patients with Child-Pugh B or C cirrhosis.

DOACs were found to be non-inferior or slightly superior to the existing standard of care, warfarin or LMWH, in patients without underlying liver disease.[318,319] DOACs are the recommended first-line treatment for DVT/PE in patients without cirrhosis, whereas patients with liver disease have been systematically excluded from these clinical trials.[311] Some observational studies have suggested that DOACs are effective and safe for the treatment of VTE in patients with cirrhosis,[320] although these are limited by their small sample size, their retrospective and observational design and the lack of adequate control groups and sufficient follow-up.

DOACs have not been extensively studied in patients with cirrhosis. While there are no formal contraindications in patients with Child-Pugh class A or B cirrhosis, DOACs should not be administered in Child-Pugh C patients and their dose should be adapted in case of renal insufficiency (a creatinine clearance <30 ml/min) (Table 4).[321,322] A small study revealed an increased drug exposure of rivaroxaban in patients with Child-Pugh class B cirrhosis relative to those with class A and healthy controls.[323] Data on the safety and efficacy of DOACs in patients with cirrhosis, with indications for anticoagulant therapy, including

Table 4. Adapting dose of DOACs in liver or kidney failure.

	DOACs			
	Dabigatran	**Apixaban**	**Edoxaban**	**Rivaroxaban**
Renal function				
Cr Cl >50 ml/min	No action needed	No action needed	No action needed	No action needed
Cr Cl 30–50 ml/min	Consider therapy modification (reduce)	No action needed	Consider therapy modification (reduce)	Consider therapy modification (reduce)
Cr Cl 15–30 ml/min	Do not prescribe	Consider therapy modification (reduce)	Consider therapy modification (reduce)	Consider therapy modification (reduce)
Cr Cl <15 ml/min	Do not prescribe	Do not prescribe	Do not prescribe	Do not prescribe
Liver function				
Child-Pugh A	No action needed	No action needed	No action needed	No action needed
Child-Pugh B	Consider therapy modification (reduce)	Consider therapy modification (reduce)	Consider therapy modification (reduce)	Do not prescribe
Child-Pugh C	Do not prescribe	Do not prescribe	Do not prescribe	Do not prescribe

Cr Cl, creatinine clearance; DOACs, direct oral anticoagulants.
Adapted from Steffel J, Eur Hear J, 2016[321]; Prisco *et al.* Inter Emerg Med 2017.[322]

atrial fibrillation, VTE, and PVT, have been reported in several retrospective studies. DOACs showed similar safety profiles as traditional anticoagulants, including vitamin K antagonists, UFH and LMWH, and the rates of bleeding complications were similar in patients receiving DOACs and those receiving traditional anticoagulants. In a study that included a historical control group of patients treated with warfarin, a significantly larger percentage of patients receiving edoxaban achieved complete resolution of PVT (70% *vs.* 20%) and a significantly smaller proportion of patients (5% *vs.* 47%) had thrombosis progression.[324] The results of a study comparing rivaroxaban to warfarin for the treatment of acute PVT demonstrated that treatment with rivaroxaban was associated with recanalisation of the portal vein at much higher rates (34/40) compared with warfarin (18/40).[325] In both studies the incidence of bleeding complications was similar or lower in patients who were treated with DOACs. However, caution is needed, in particular when using rivaroxaban and dabigatran, because their use has been associated with a higher incidence of major gastrointestinal bleeding[326,327] and their dose should be adapted in patients with renal failure (creatinine clearance <30 ml/min).[321] Attention should also be paid to potential drug-drug interactions (Table 5).[321,328,329]

Clinical case reports and *in vitro* studies suggest that the efficacy of DOACs targeting factor Xa in patients with cirrhosis can be attenuated.[192,330] In addition, a recent study has shown a reduced *in vivo* anticoagulant effect of the anti-Xa DOAC edoxaban.[132] Whether dose-adjustments of anti-Xa-targeting DOACs are indicated in patients with cirrhosis requires clinical study.

Table 5. Significant drug interactions with DOACs.

Frequently used drugs in hepatology	Mechanism of interaction	DOACs			
		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Carvedilol/ (propranolol)	P-gp inhibition	Consider therapy modification (reduce)	No action needed	Consider therapy modification (reduce)	No action needed
Simvastatin/ atorvastatin	P-gp inhibition	Consider therapy modification (reduce)	No data	No data	No data
Proton pump inhibitors	Decreased GI absorption	-30%	No relevant effect	No relevant effect	No relevant effect
Cyclosporine/ tacrolimus	P-gp + CYP3A4 inhibition	Consider therapy modification (reduce)	No action needed	Consider therapy modification (reduce)	No action needed
Sirolimus/ everolimus	No relevant interaction anticipated	No action needed	No action needed	No action needed	No action needed
Sorafenib/ nivolumab/ ramucirumab/ atezolizumab/ bevacizumab	No relevant interaction anticipated	No action needed	No action needed	No action needed	No action needed

Comment: All DOACs are substrates of P-gp, an efflux transporter located in the gut mucosa and regulates absorption of drugs. P-gp inducers may reduce plasma DOAC concentrations (increasing risk of thrombosis) and P-gp Inhibitors may increase plasma DOAC concentrations (increasing risk of bleeding). Adapted from Steffel J, Eur Hear J, 2016[321]; Burnett J. J Thromb Thrombolysis, 2016[328]; Wessler JD JACC, 2013.[329]
DOACs, direct oral anticoagulants; GI, gastrointestinal; P-gp, P-glycoprotein.

Appendix: Delphi round agreement on the statements and recommendations of the present CPGs

Question number	Statement/recommendation	Delphi panel agreement*
1.	• In patients with cirrhosis and abnormal laboratory tests (INR, APTT, platelet count, fibrinogen), attempting to correct these tests by administering blood products or factor concentrates, with the aim of preventing spontaneous bleeding, is not recommended (LoE 3, strong recommendation).	100%
2.	• INR and APTT do not predict post-procedural bleeding in patients with cirrhosis undergoing invasive procedures (LoE 3). • Studies do not consistently demonstrate a link between thrombocytopenia, hypofibrinogenaemia, or viscoelastic test results and the risk of post-procedural bleeding, although there may be subgroups in whom thrombocytopenia is related to procedural bleeding risk and there is initial evidence suggesting that viscoelastic tests might help to address this issue (LoE 4). • In patients with cirrhosis, the use of traditional haemostasis tests, or viscoelastic tests, cannot be generally indicated to predict procedural bleeding risk, although they can be used to assess severity of disease or haemostatic status and to provide an initial benchmark to guide management in the case of post-procedural bleeding (LoE 3, strong recommendation).	62%
3.	• In patients with cirrhosis undergoing invasive procedures with a low risk of bleeding, laboratory evaluation of haemostasis with the aim of predicting post-procedural bleeding is not indicated (LoE 4, strong recommendation).	96%
4.	• There is weak evidence that the measurement of platelet count might be indicated to identify patients at increased procedural bleeding risk. No solid data are available for fibrinogen (LoE 4). • As evidence supporting viscoelastic tests as predictors of procedure-related bleeding in patients with acute decompensation of cirrhosis, with or without organ failure, is weak, it is not possible to advise for or against their use (LoE 4). • In patients with cirrhosis undergoing invasive procedures associated with a high risk of bleeding, laboratory evaluation of haemostasis is generally not indicated to predict post-procedural bleeding, although it may serve to provide a baseline status of the patient and to assist the physician in the case of bleeding events (LoE 4/5, weak recommendation).	80%

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Question number	Statement/recommendation	Delphi panel agreement*
5.	• In patients with cirrhosis undergoing invasive procedures, correction of a prolonged INR with FFP is not recommended to decrease the rate of procedure-related clinically relevant bleeding (LoE 1, strong recommendation).	93%
6.	• In patients with cirrhosis undergoing invasive procedures, routine use of PCCs to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 3, weak recommendation).	96%
7.	• In patients with cirrhosis undergoing invasive procedures, no studies have specifically evaluated whether the infusion of platelet concentrates or TPO-R agonists decrease the rate of procedure-related clinically relevant bleeding (LoE 1). • In patients with cirrhosis undergoing invasive procedures, infusion of platelet concentrates or use of TPO-R agonists is not recommended when platelet count is above 50 × 109/L or when bleeding can be treated by local haemostasis (LoE 3/4, strong recommendation). • In patients undergoing high-risk procedures in whom local haemostasis is not possible and platelet count is between 20 × 10^9/L and 50 × 10^9/L infusion of platelet concentrates or TPO-R agonists should not be routinely performed but may be considered on a case-by-case basis (LoE 3/4, strong recommendation). • In patients undergoing high-risk procedures in whom local haemostasis is not possible and platelet count is very low (<20 × 10^9/L) infusion of platelet concentrates or TPO-R agonists should be considered on a case-by-case basis (LoE 3/4, strong recommendation).	69%
8.	• In patients with cirrhosis undergoing invasive procedures, routine correction of fibrinogen deficiency to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 5, strong recommendation).	97%
9.	• In patients with cirrhosis, every effort should be made to optimise haemoglobin levels by treating iron, folic acid, vitamin B6, and vitamin B12 deficiencies, especially in those patients likely to undergo invasive procedures (LoE 5, weak recommendation). • In the setting of invasive procedures, prophylactic red blood cell transfusion with the aim of decreasing the risk of procedure-related bleeding is not recommended (LoE 5, weak recommendation).	93%
10.	• In patients with cirrhosis undergoing invasive procedures, routine use of tranexamic acid to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 4, weak recommendation).	90%
11.	• In patients with stable cirrhosis and abnormal laboratory tests (prothrombin time, APTT, platelet count, fibrinogen) undergoing prophylactic band ligation, administration of blood products or factor concentrates with the aim of avoiding post-ligation bleeding is not recommended (LoE 5, strong recommendation).	97%
12.	• In patients with cirrhosis, antiplatelet and/or anticoagulant agents should be managed following the same guidelines as in patients without cirrhosis before invasive procedures (LoE 4, strong recommendation).	97%
13.	• In patients with cirrhosis, imaging guidance is recommended for liver biopsy, central venous line placement and jugular puncture for TIPS placement (LoE 3, strong recommendation).	93%
14.	• Patients with cirrhosis undergoing invasive procedures should be monitored for bleeding complications in the same way as patients without cirrhosis (LoE 3, strong recommendation).	97%
15.	• In patients with cirrhosis and active variceal bleeding, if haemostasis is achieved with portal hypertension-lowering drugs and endoscopic treatment, correction of haemostatic abnormalities is not indicated (LoE 3, strong recommendation). • In case of failure to control haemorrhage, the decision to correct haemostasis should be considered on a case-by-case basis (LoE 3, strong recommendation). • In patients with cirrhosis and active variceal bleeding, tranexamic acid should not be used (LoE 2, strong recommendation).	83%
16.	• No studies evaluating correction of haemostasis in patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (e.g., portal hypertensive gastropathy), are available (LoE 5). • In patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (*e.g.*, portal hypertensive gastropathy), bleeding should be managed with portal hypertension-lowering measures (LoE 5, weak recommendation). • In the case of failure to control haemorrhage with portal hypertension-lowering drugs, the decision to correct haemostasis should be considered on a case-by-case basis (LoE 5, weak recommendation).	93%
17.	• In patients with cirrhosis who are actively bleeding from a non-portal hypertensive cause, active bleeding should first be addressed by local measures and/or interventional radiology procedures (LoE 4, strong recommendation). • In those patients in whom local measures fail to stop the bleeding, addressing contributing factors (renal failure, infection or sepsis, and anaemia) may reduce bleeding while correction of haemostatic abnormalities can be considered on a case-by-case basis (LoE 5, weak recommendation).	97%
18.	• In patients with cirrhosis, routine use of antifibrinolytic agents to treat active bleeding from a non-portal hypertension-related cause is discouraged (LoE 5, weak recommendation).	90%
19.	• There is initial evidence that the use of viscoelastic tests is associated with decreased blood product use in patients with cirrhosis and active upper gastrointestinal bleeds, without differences in bleeding control and mortality (LoE 3). • Given the benefits of reducing blood transfusion, viscoelastic tests can be used when available (LoE 1, strong recommendation).	90%
20.	• Based on clinical observations and laboratory findings, it can be concluded that the risk of developing DVT/PE is at least as high in patients with cirrhosis as in the general population (LoE 2).	93%
21.	• Clinical prediction scores, such as the Padua prediction score (>3[281] or ≥4[282] or IMPROVE score (≥4[283]) can be used to predict which patients with cirrhosis are at high risk of developing lower limb DVT and/or PE (LoE 3, strong recommendation).	93%
22.	• The use of viscoelastic tests or other laboratory tests to identify which patients with cirrhosis are at risk of VTE (DVT/PE) is not recommended (LoE 5, strong recommendation).	93%
23.	• In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with LMWH can be recommended as it has a reasonable safety profile, but efficacy is unclear based on available data (LoE 3, weak recommendation). • In patients with Child-Pugh class A and B cirrhosis at risk of DVT/PE, thromboprophylaxis with DOACs can be recommended as DOACs have a reasonable safety profile in these patients, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis, DOACs are not recommended (Safety: LoE 2; Efficacy: LoE 4; weak recommendations).	89%

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Question number	Statement/recommendation	Delphi panel agreement*
24.	• For treatment of DVT/PE, vitamin K antagonists should be used with caution in patients with cirrhosis, as these patients can have baseline altered INR and thus target INR remains unknown. In patients with Child-Pugh A, LMWH, and vitamin K antagonists are reasonable options. Until more data become available, we recommend LMWH for treatment of DVT/PE in patients with Child-Pugh B and Child-Pugh C cirrhosis, whereas UFH is the treatment of choice in case of renal failure (LoE 4, weak recommendation).	87%
25.	• For the treatment of DVT/PE in patients with cirrhosis, currently available data suggest that there are no major concerns regarding the safety of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in Child-Pugh class C patients is not recommended (LoE 4, strong recommendation).	90%

*Levels of agreement are rounded to the nearest whole number.

Abbreviations

APTT, activated partial thromboplastin time; CPG, Clinical Practice Guidelines; DOACs, direct-acting oral anticoagulants; DVT, deep vein thrombosis; EASL, European Association for the Study of the Liver; EBL, endoscopic band ligation; ERCP, endoscopic retrograde cholangiopancreatography; FFP, fresh frozen plasma; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; INR, international normalised ratio; LMWH, low molecular weight heparin; MELD, model for end-stage liver disease; OCEBM, Oxford Centre for Evidence-based Medicine; PCCs, prothrombin complex concentrates; PE, pulmonary embolism; PVT, portal vein thrombosis; ROTEM, rotational thromboelastometry; RR, relative risk; TACO, transfusion-associated circulatory overload; TEG, thromboelastography; TIPS, transjugular intrahepatic portosystemic shunt; UFH, unfractionated heparin; VTE, venous thromboembolism; VWF, von Willebrand factor.

Conflict of interest

Please refer to the accompanying EASL disclosure forms for details.

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Glossary

Cirrhosis

Compensated cirrhosis: a clinical condition of histologic, imaging proven cirrhosis and/or clinically significant sinusoidal portal hypertension and Child-Pugh class A, in a patient who has never experienced an episode of acute decompensation (*i.e.* ascites, hepatic encephalopathy, gastrointestinal haemorrhage or bacterial infection or any combination of them). Compensated cirrhosis is by definition a state of clinical stability.[182,331]

Decompensated cirrhosis and unstable decompensated cirrhosis: acute decompensation is defined as an acute development of clinically significant ascites, hepatic encephalopathy, portal hypertensive-related gastrointestinal bleeding or bacterial infection or any combination thereof. Decompensated cirrhosis can be characterised by recurrent episodes of acute decompensation and in this case is defined as unstable decompensated cirrhosis.[332–334]

Stable decompensated cirrhosis: the clinical state achieved after the first episode of acute decompensation, characterised by the persistence of a given clinical condition without worsening of ascites, bacterial infection, hepatic encephalopathy or portal hypertensive bleeding or new onset of one of these conditions.[332,334]

Stable cirrhosis: refers to the condition of clinical stability within an otherwise compensated OR decompensated cirrhosis.

Bleeding

Spontaneous bleeding (not associated with portal hypertension)**:** any unprovoked bleeding, at gastrointestinal level or at any other organ level.

Procedure-related bleeding: a haemorrhagic event (overt or obscure) following or happening within 24 hours of an interventional procedure[335]

Failure to control bleeding: death or need to change therapy after a bleeding episode defined by:

- new development of overt haemorrhage (*i.e.* fresh haematemesis or nasogastric aspiration of ≥100 ml of fresh blood), ≥2 hours attempting to control bleeding (with a specific drug treatment or procedure);
- development of hypovolemic shock;
- 3 g drop in Hb (9% drop in haematocrit) within any 24 hours if no transfusion is administered (adapted from[182,336]).

Clinically relevant bleeding: any bleeding causing

- haemodynamic instability ((blood pressure less than 100 mmHg or pulse more than 100 beats per min);
- requiring additional and non-expected haemostatic measures;
- requiring transfusions of more than 2 units of blood in 24 hours;
- requiring hospitalisation for patients in whom the procedure was carried out as outpatients;
- requiring bleeding-related extension of hospital stay in patients who received the procedure as inpatients.

Major bleeding: according to the International Society on Thrombosis and Haemostasis criteria, major bleeding is defined as

- fatal bleeding, and/or
- bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, peri-cardial, intramuscular with compartment syndrome), and/or
- bleeding causing a fall in haemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units of whole blood or red cells.

Note that a non-major bleeding episode can also be clinically relevant if: (a) required medical intervention by a healthcare professional or (b) led to hospitalisation or increased level of care or (c) prompted a face-to-face evaluation.

Hyperfibrinolysis
Fibrinolysis is the physiologic counterbalance of coagulation, functioning to maintain vasculature patency. Hyperfibrinolysis defines a situation with markedly enhanced fibrinolytic activity, resulting in increased bleeding. *The diagnosis of hyperfibrinolysis is made indirectly with immunochemical methods which detect the elevation of* biomarkers *such as D-Dimer (cross-linked fibrin degradation products), fibrinogen split products, complexes of plasmin and alpha-2-antiplasmin, by the* euglobulin lysis time *test, or by* viscoelastic *methods in whole blood.*

Transfusion
Transfusion-associated cardiac overload (TACO): condition of overload that manifests as respiratory system-related signs and symptoms such as tachypnoea, dyspnoea, and decreased oxygen saturations, typically occurring during or within 12 hours of transfusion.[337,338]
Transfusion-related acute lung injury (TRALI): a clinical syndrome that presents as acute hypoxemia and non-cardiogenic pulmonary oedema during or after blood transfusion.[339,340]

Case-by-case basis
Decisions that are made separately, each adapted to the facts of the particular situation.

Invasive procedure
A procedure in which the body is penetrated or entered, *e.g.* by a tube, needle, or ionizing radiation.

Standard coagulation tests
Standard coagulation tests include prothrombin time, partial thromboplastin time, and fibrinogen levels.

Supplementary data
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References
Author names in bold designate shared co-first authorship

[1] Lisman T, Hernandez-Gea V, Magnusson M, Roberts L, Stanworth S, Thachil J, et al. The concept of rebalanced hemostasis in patients with liver disease: communication from the ISTH SSC working group on hemostatic management of patients with liver disease. J Thromb Haemost 2021;19(4):1116–1122.
[2] Northup P, Davis J. Shortcomings in design and analysis of clinical studies on bleeding and thrombosis in patients with cirrhosis. Semin Thromb Hemost 2020;46(6):665–672.
[3] Cornberg M, Tacke F, Karlsen TH, European association for the study of the L. Clinical practice guidelines of the European association for the study of the liver - advancing methodology but preserving practicability. J Hepatol 2019;70(1):5–7.
[4] Group CLoEW. "The Oxford 2011 Levels Oxford Centre for Evidence-Based Medicine https://wwwcebmnet/wp-content/uploads/2014/06/CEBM.
[5] Rodriguez-Castro KI, Simioni P, Burra P, Senzolo M. Anticoagulation for the treatment of thrombotic complications in patients with cirrhosis. Liver Int 2012;32(10):1465–1476.
[6] Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692–694.
[7] Ragni MV, Lewis JH, Spero JA, Hasiba U. Bleeding and coagulation abnormalities in alcoholic cirrhotic liver disease. Alcohol Clin Exp Res 1982;6(2):267–274.
[8] Gunawan B, Runyon B. The efficacy and safety of epsilon-aminocaproic acid treatment in patients with cirrhosis and hyperfibrinolysis. Aliment Pharmacol Ther 2006;23(1):115–120.
[9] Boudouresques G, Hauw JJ, Meininger V, Escourolle R, Pertuiset B, Buge A, et al. Hepatic cirrhosis and intracranial hemorrhage: significance of the association in 53 pathological cases. Ann Neurol 1980;8(2):204–205.
[10] Huang HH, Lin HH, Shih YL, Chen PJ, Chang WK, Chu HC, et al. Spontaneous intracranial hemorrhage in cirrhotic patients. Clin Neurol Neurosurg 2008;110(3):253–258.
[11] Niizuma H, Suzuki J, Yonemitsu T, Otsuki T. Spontaneous intracerebral hemorrhage and liver dysfunction. Stroke 1988;19(7):852–856.
[12] Mangla A, Hamad H, Yadav U, Telfer M. Alcohol abuse and alcoholic liver cirrhosis leading to spontaneous muscle hematoma: an event fraught with danger. Case Rep Gastroenterol 2015;9(1):93–100.
[13] Nemiroff J, Baharestani S, Juthani VV, Klein KS, Zoumalan C. Cirrhosis-related coagulopathy resulting in disseminated intravascular coagulation and spontaneous orbital hemorrhages. Orbit 2014;33(5):372–374.
[14] Ness C, Sakpal SV. Cirrhosis induced spontaneous orbital hemorrhage. Dig Liver Dis 2020;52(8):922–923.
[15] Akriviadis EA. Hemoperitoneum in patients with ascites. Am J Gastroenterol 1997;92(4):567–575.
[16] Urrunaga NH, Singal AG, Cuthbert JA, Rockey DC. Hemorrhagic ascites. Clinical presentation and outcomes in patients with cirrhosis. J Hepatol 2013;58(6):1113–1118.
[17] Best JA, Smith MW. Spontaneous retroperitoneal hematoma originating at lumbar arteries in context of cirrhosis. J Hosp Med 2010;5(5):E4–E5.
[18] Lee TH, Park YS, Chung DJ, Kim JH, Kim SM, Im EH, et al. Spontaneous rupture of the lateral thoracic artery in patients with liver cirrhosis. Korean J Intern Med 2008;23(3):152–155.
[19] Violi F, Ferro D, Basili S, Quintarelli C, Saliola M, Alessandri C, et al. Hyperfibrinolysis increases the risk of gastrointestinal hemorrhage in patients with advanced cirrhosis. Hepatology 1992;15(4):672–676.
[20] Aldrich SM, Regal RE. Routine use of vitamin K in the treatment of cirrhosis-related coagulopathy: is it A-O-K? Maybe not, we say. P T 2019;44(3):131–136.
[21] Saja MF, Abdo AA, Sanai FM, Shaikh SA, Gader AG. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrinol 2013;24(1):10–17.
[22] Douvres PA. Effect of high parenteral doses of vitamin-K analogs and serum albumin on the prothrombin level and liver function in alcoholic cirrhosis. Am J Dig Dis 1965;10:635–642.
[23] Youssef WI, Salazar F, Dasarathy S, Beddow T, Mullen KD. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. Am J Gastroenterol 2003;98(6):1391–1394.
[24] Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion 2006;46(8):1279–1285.
[25] Tripodi A, Chantarangkul V, Primignani M, Clerici M, Dell'era A, Aghemo A, et al. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. Intern Emerg Med 2012;7(2):139–144.
[26] Rassi AB, d'Amico EA, Tripodi A, da Rocha TRF, Migita BY, Ferreira CM, et al. Fresh frozen plasma transfusion in patients with cirrhosis and coagulopathy: effect on conventional coagulation tests and thrombomodulin-modified thrombin generation. J Hepatol 2020;72(1):85–94.

[27] Roubinian NH, Hendrickson JE, Triulzi DJ, Gottschall JL, Michalkiewicz M, Chowdhury D, et al. Contemporary risk factors and outcomes of transfusion-associated circulatory overload. Crit Care Med 2018;46(4):577–585.
[28] Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162(3):205–213.
[29] Basili S, Raparelli V, Napoleone L, Talerico G, Corazza GR, Perticone F, et al. Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER study. Am J Gastroenterol 2018;113(3):368–375.
[30] Desborough MJ, Kahan BC, Stanworth SJ, Jairath V. Fibrinogen as an independent predictor of mortality in decompensated cirrhosis and bleeding. Hepatology 2017;65(3):1079–1080.
[31] Budnick IM, Davis JPE, Sundararaghavan A, Konkol SB, Lau CE, Alsobrooks JP, et al. Transfusion with cryoprecipitate for very low fibrinogen levels does not affect bleeding or survival in critically ill cirrhosis patients. Thromb Haemost 2021.
[32] Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F, et al. Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th international coagulation in liver disease conference. Thromb Haemost 2018;118(8):1491–1506.
[33] Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116(6):878–885.
[34] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365(2):147–156.
[35] Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. J Hepatol 2002;37(2):280–287.
[36] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137(6):2105–2111.
[37] Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. Am J Transpl 2007;7(6):1624–1628.
[38] Adinolfi LE, Giordano MG, Andreana A, Tripodi MF, Utili R, Cesaro G, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001;113(3):590–595.
[39] Giannini E, Borro P, Botta F, Fumagalli A, Malfatti F, Podesta E, et al. Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. J Hepatol 2002;37(5):572–577.
[40] Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology 2006;44(1):53–61.
[41] Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63(5):1272–1284.
[42] Blasi A, Calvo A, Prado V, Reverter E, Reverter JC, Hernandez-Tejero M, et al. Coagulation failure in patients with acute-on-chronic liver failure and decompensated cirrhosis: beyond the international normalized ratio. Hepatology 2018;68(6):2325–2337.
[43] **Blasi A**, **Patel VC**, Adelmeijer J, Azarian S, Hernandez Tejero M, Calvo A, et al. Mixed fibrinolytic phenotypes in decompensated cirrhosis and acute-on-chronic liver failure with hypofibrinolysis in those with complications and poor survival. Hepatology 2020;71(4):1381–1390.
[44] **Fisher C**, **Patel VC**, Stoy SH, Singanayagam A, Adelmeijer J, Wendon J, et al. Balanced haemostasis with both hypo- and hyper-coagulable features in critically ill patients with acute-on-chronic-liver failure. J Crit Care 2018;43:54–60.
[45] Lin S, Wang M, Zhu Y, Dong J, Weng Z, Shao L, et al. Hemorrhagic complications following abdominal paracentesis in acute on chronic liver failure: a propensity score analysis. Medicine (Baltimore) 2015;94(49):e2225.
[46] Zanetto A, Rinder HM, Campello E, Saggiorato G, Deng Y, Ciarleglio M, et al. Acute kidney injury in decompensated cirrhosis is associated with both hypo-coagulable and hyper-coagulable features. Hepatology 2020;72(4):1327–1340.
[47] Grabau CM, Crago SF, Hoff LK, Simon JA, Melton CA, Ott BJ, et al. Performance standards for therapeutic abdominal paracentesis. Hepatology 2004;40(2):484–488.
[48] Xiol X, Castellote J, Cortes-Beut R, Delgado M, Guardiola J, Sese E. Usefulness and complications of thoracentesis in cirrhotic patients. Am J Med 2001;111(1):67–69.
[49] Perdigao JP, de Almeida PC, Rocha TD, Mota MR, Soares EC, Alves AP, et al. Postoperative bleeding after dental extraction in liver pretransplant patients. J Oral Maxillofac Surg 2012;70(3):e177–e184.
[50] Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy–a prospective audit. Intensive Care Med 1999;25(5):481–485.
[51] Kalambokis G, Manousou P, Vibhakorn S, Marelli L, Cholongitas E, Senzolo M, et al. Transjugular liver biopsy–indications, adequacy, quality of specimens, and complications–a systematic review. J Hepatol 2007;47(2):284–294.
[52] Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8(10):877–883.
[53] Park JG, Park SY, Tak WY, Kweon YO, Jang SY, Lee YR, et al. Early complications after percutaneous radiofrequency ablation for hepatocellular carcinoma: an analysis of 1,843 ablations in 1,211 patients in a single centre: experience over 10 years. Clin Radiol 2017;72(8). 692 e9- e15.
[54] Soh H, Chun J, Hong SW, Park S, Lee YB, Lee HJ, et al. Child-pugh B or C cirrhosis increases the risk for bleeding following colonoscopic polypectomy. Gut Liver 2020;14(6):755–764.
[55] Vieira da Rocha EC, D'Amico EA, Caldwell SH, Flores da Rocha TR, Soares ESCS, Dos Santos Bomfim V, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol 2009;7(9):988–993.
[56] Kundumadam S, Phatharacharukul P, Reinhart K, Yousef A, Shamseddeen H, Pike F, et al. Bleeding after elective interventional endoscopic procedures in a large cohort of patients with cirrhosis. Clin Transl Gastroenterol 2020;11(12):e00288.
[57] Kovalic AJ, Majeed CN, Samji NS, Thuluvath PJ, Satapathy SK. Systematic review with meta-analysis: abnormalities in the international normalised ratio do not correlate with periprocedural bleeding events among patients with cirrhosis. Aliment Pharmacol Ther 2020;52(8):1298–1310.
[58] Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6(10):573–582.
[59] Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. Dig Dis Sci 1981;26(5):388–393.
[60] Napolitano G, Iacobellis A, Merla A, Niro G, Valvano MR, Terracciano F, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med 2017;38:79–82.
[61] Alvaro D, Caporaso N, Giannini EG, Iacobellis A, Morelli M, Toniutto P, et al. Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia. Eur J Clin Invest 2021;51(6):e13508.
[62] de Maat MP, Nieuwenhuizen W, Knot EA, van Buuren HR, Swart GR. Measuring plasma fibrinogen levels in patients with liver cirrhosis. The occurrence of proteolytic fibrin(ogen) degradation products and their influence on several fibrinogen assays. Thromb Res 1995;78(4):353–362.
[63] Hugenholtz GC, Macrae F, Adelmeijer J, Dulfer S, Porte RJ, Lisman T, et al. Procoagulant changes in fibrin clot structure in patients with cirrhosis are associated with oxidative modifications of fibrinogen. J Thromb Haemost 2016;14(5):1054–1066.
[64] Giannini EG, Giambruno E, Brunacci M, Plaz Torres MC, Furnari M, Bodini G, et al. Low fibrinogen levels are associated with bleeding after varices ligation in thrombocytopenic cirrhotic patients. Ann Hepatol 2018;17(5):830–835.
[65] Drolz A, Horvatits T, Roedl K, Rutter K, Staufer K, Kneidinger N, et al. Coagulation parameters and major bleeding in critically ill patients with cirrhosis. Hepatology 2016;64(2):556–568.
[66] **De Pietri L**, **Bianchini M**, Montalti R, De Maria N, Di Maira T, Begliomini B, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. Hepatology 2016;63(2):566–573.
[67] Kovalic AJ, Khan MA, Malaver D, Whitson MJ, Teperman LW, Bernstein DE, et al. Thromboelastography *vs.* standard coagulation testing in the assessment and reversal of coagulopathy among cirrhotics: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2020;32(3):291–302.
[68] Vuyyuru SK, Singh AD, Gamanagatti SR, Rout G, Gunjan D, Shalimar. A randomized control trial of thromboelastography-guided transfusion

in cirrhosis for high-risk invasive liver-related procedures. Dig Dis Sci 2020;65(7):2104–2111.
[69] Somani V, Amarapurkar D, Shah A. Thromboelastography for assessing the risk of bleeding in patients with cirrhosis-moving closer. J Clin Exp Hepatol 2017;7(4):284–289.
[70] Pandey CK, Saluja V, Gaurav K, Tandon M, Pandey VK, Bhadoria AS. K time & maximum amplitude of thromboelastogram predict post-central venous cannulation bleeding in patients with cirrhosis: a pilot study. Indian J Med Res 2017;145(1):84–89.
[71] Smart L, Wellner M, Gray NA, Michaels A, Kirkpatrick RB, Conteh L, et al. A prospective, randomized clinical trial comparing blood product use, bleeding events, and cost during and after endoscopic procedures in patients with cirrhosis and coagulopathy: rotational thromboelastometry (ROTEM) *vs.* conventional therapy. Hepatology 2017;66:243A–244A.
[72] Zanetto A, Rinder HM, Senzolo M, Simioni P, Garcia-Tsao G. Reduced clot stability by thromboelastography as a potential indicator of procedure-related bleeding in decompensated cirrhosis. Hepatol Commun 2021;5(2):272–282.
[73] Patel IJ, Rahim S, Davidson JC, Hanks SE, Tam AL, Walker TG, et al. Society of interventional radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-Part II: recommendations: endorsed by the Canadian association for interventional radiology and the cardiovascular and interventional radiological society of Europe. J Vasc Interv Radiol 2019;30(8):1168–11684 e1.
[74] Spyropoulos AC, Brohi K, Caprini J, Samama CM, Siegal D, Tafur A, et al. Scientific and Standardization Committee Communication: guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. J Thromb Haemost 2019;17(11):1966–1972.
[75] Hung TH, Tseng CW, Chen YC, Tseng KC, Hsieh YH, Tsai CC. Endoscopic papillary balloon dilation decreases the risk of bleeding in cirrhotic patients compared with endoscopic biliary sphincterotomy: a national population-based study. Medicine (Baltimore) 2019;98(30):e16529.
[76] Medina JB, Andrade NS, de Paula Eduardo F, Bezinelli L, Franco JB, Gallottini M, et al. Bleeding during and after dental extractions in patients with liver cirrhosis. Int J Oral Maxillofac Surg 2018;47(12):1543–1549.
[77] Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. Aliment Pharmacol Ther 2005;21(5):525–529.
[78] Pantham G, Waghray N, Einstadter D, Finkelhor RS, Mullen KD. Bleeding risk in patients with esophageal varices undergoing transesophageal echocardiography. Echocardiography 2013;30(10):1152–1155.
[79] Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. J Hepatol 1986;2(2):165–173.
[80] Schepis F, Turco L, Bianchini M, Villa E. Prevention and management of bleeding risk related to invasive procedures in cirrhosis. Semin Liver Dis 2018;38(3):215–229.
[81] Takyar V, Etzion O, Heller T, Kleiner DE, Rotman Y, Ghany MG, et al. Complications of percutaneous liver biopsy with Klatskin needles: a 36-year single-centre experience. Aliment Pharmacol Ther 2017;45(5):744–753.
[82] Actis GC, Olivero A, Lagget M, Pellicano R, Smedile A, Rizzetto M. The practice of percutaneous liver biopsy in a gastrohepatology day hospital: a retrospective study on 835 biopsies. Dig Dis Sci 2007;52(10):2576–2579.
[83] Alessandria C, Debernardi-Venon W, Rizzetto M, Marzano A. Transjugular liver biopsy: a relatively simple procedure with an indefinite past and an expected brilliant future. J Hepatol 2008;48(1):171–172. author reply 2-3.
[84] Camma C, Di Marco V, Orlando A, Sandonato L, Casaril A, Parisi P, et al. Treatment of hepatocellular carcinoma in compensated cirrhosis with radio-frequency thermal ablation (RFTA): a prospective study. J Hepatol 2005;42(4):535–540.
[85] Castellote J, Xiol X, Cortes-Beut R, Tremosa G, Rodriguez E, Vazquez S. Complications of thoracentesis in cirrhotic patients with pleural effusion. Rev Esp Enferm Dig 2001;93(9):566–575.
[86] Caturelli E, Giacobbe A, Facciorusso D, Bisceglia M, Villani MR, Siena DA, et al. Percutaneous biopsy in diffuse liver disease: increasing diagnostic yield and decreasing complication rate by routine ultrasound assessment of puncture site. Am J Gastroenterol 1996;91(7):1318–1321.
[87] Cocero N, Bezzi M, Martini S, Carossa S. Oral surgical treatment of patients with chronic liver disease: assessments of bleeding and its relationship with thrombocytopenia and blood coagulation parameters. J Oral Maxillofac Surg 2017;75(1):28–34.
[88] De Gottardi A, Thevenot T, Spahr L, Morard I, Bresson-Hadni S, Torres F, et al. Risk of complications after abdominal paracentesis in cirrhotic patients: a prospective study. Clin Gastroenterol Hepatol 2009;7(8):906–909.
[89] Estcourt LJ, Desborough M, Hopewell S, Doree C, Stanworth SJ. Comparison of different platelet transfusion thresholds prior to insertion of central lines in patients with thrombocytopenia. Cochrane Database Syst Rev 2015;(12):CD011771.
[90] Goto E, Tateishi R, Shiina S, Masuzaki R, Enooku K, Sato T, et al. Hemorrhagic complications of percutaneous radiofrequency ablation for liver tumors. J Clin Gastroenterol 2010;44(5):374–380.
[91] Jeon JW, Shin HP, Lee JI, Joo KR, Pack KM, Cha JM, et al. The risk of postpolypectomy bleeding during colonoscopy in patients with early liver cirrhosis. Surg Endosc 2012;26(11):3258–3263.
[92] Lee S, Park SJ, Cheon JH, Kim TI, Kim WH, Kang DR, et al. Child-Pugh score is an independent risk factor for immediate bleeding after colonoscopic polypectomy in liver cirrhosis. Yonsei Med J 2014;55(5):1281–1288.
[93] Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008;47(1):82–89.
[94] Mammen T, Keshava SN, Eapen CE, Raghuram L, Moses V, Gopi K, et al. Transjugular liver biopsy: a retrospective analysis of 601 cases. J Vasc Interv Radiol 2008;19(3):351–358.
[95] Potretzke TA, Harvey JA, Gunderson TM, Jensen NM, Schmit GD, McBane RD, et al. Frequency of bleeding complications after percutaneous core needle biopsy and the association with aspirin usage and length of aspirin discontinuation. AJR Am J Roentgenol 2019;213(1):211–215.
[96] Procopet B, Bureau C, Metivier S, Selves J, Robic MA, Christol C, et al. Tolerance of liver biopsy in a tertiary care center: comparison of the percutaneous and the transvenous route in 143 prospectively followed patients. Eur J Gastroenterol Hepatol 2012;24(10):1209–1213.
[97] Rowley MW, Agarwal S, Seetharam AB, Hirsch KS. Real-Time ultrasound-guided paracentesis by radiologists: near zero risk of hemorrhage without correction of coagulopathy. J Vasc Interv Radiol 2019;30(2):259–264.
[98] Shah A, Amarapurkar D, Dharod M, Chandnani M, Baijal R, Kumar P, et al. Coagulopathy in cirrhosis: a prospective study to correlate conventional tests of coagulation and bleeding following invasive procedures in cirrhotics. Indian J Gastroenterol 2015;34(5):359–364.
[99] Vanbiervliet G, Giudicelli-Bornard S, Piche T, Berthier F, Gelsi E, Filippi J, et al. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case-control study. Aliment Pharmacol Ther 2010;32(2):225–232.
[100] Ward BB, Weideman EM. Long-term postoperative bleeding after dentoalveolar surgery in the pretransplant liver failure patient. J Oral Maxillofac Surg 2006;64(10):1469–1474.
[101] Webster ST, Brown KL, Lucey MR, Nostrant TT. Hemorrhagic complications of large volume abdominal paracentesis. Am J Gastroenterol 1996;91(2):366–368.
[102] West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology 2010;139(4):1230–1237.
[103] Woolfson J, John P, Kamath B, Ng VL, Ling SC. Measurement of hepatic venous pressure gradient is feasible and safe in children. J Pediatr Gastroenterol Nutr 2013;57(5):634–637.
[104] Hung A, Garcia-Tsao G. Acute kidney injury, but not sepsis, is associated with higher procedure-related bleeding in patients with decompensated cirrhosis. Liver Int 2018;38(8):1437–1441.
[105] Hong J, Zuo W, Wang A, Zhu L, Zhou X, Zhou X, et al. Efficacy and safety of ERCP in patients with gastroesophageal varices. Medicine (Baltimore) 2020;99(37):e22051.
[106] Adler DG, Haseeb A, Francis G, Kistler CA, Kaplan J, Ghumman SS, et al. Efficacy and safety of therapeutic ERCP in patients with cirrhosis: a large multicenter study. Gastrointest Endosc 2016;83(2):353–359.
[107] Huang RJ, Perumpail RB, Thosani N, Cheung R, Friedland S. Colonoscopy with polypectomy is associated with a low rate of complications in patients with cirrhosis. Endosc Int Open 2016;4(9):E947–E952.

[108] Pillai AK, Andring B, Faulconer N, Reis SP, Xi Y, Iyamu I, et al. Utility of intravascular US-guided portal vein access during transjugular intrahepatic portosystemic shunt creation: retrospective comparison with conventional technique in 109 patients. J Vasc Interv Radiol 2016;27(8):1154–1159.
[109] Ripamonti R, Ferral H, Alonzo M, Patel NH. Transjugular intrahepatic portosystemic shunt-related complications and practical solutions. Semin Intervent Radiol 2006;23(2):165–176.
[110] **Campello E**, **Zanetto A**, Bulato C, Maggiolo S, Spiezia L, Russo FP, et al. Coagulopathy is not predictive of bleeding in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. Liver Int 2021;41:2455–2466. https://doi.org/10.1111/liv.15001.
[111] Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004;126(1):139–152.
[112] **von Meijenfeldt FA**, **van den Boom BP**, Adelmeijer J, Roberts LN, Lisman T, Bernal W. Prophylactic fresh frozen plasma and platelet transfusion have a prothrombotic effect in patients with liver disease. J Thromb Haemost 2021;19(3):664–676.
[113] Huber J, Stanworth SJ, Doree C, Fortin PM, Trivella M, Brunskill SJ, et al. Prophylactic plasma transfusion for patients without inherited bleeding disorders or anticoagulant use undergoing non-cardiac surgery or invasive procedures. Cochrane Database Syst Rev 2019;11:CD012745.
[114] Muller MC, Arbous MS, Spoelstra-de Man AM, Vink R, Karakus A, Straat M, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial (CME). Transfusion 2015;55(1):26–35; quiz 25. https://doi.org/10.1111/trf.12750.
[115] Veelo DP, Vlaar AP, Dongelmans DA, Binnekade JM, Levi M, Paulus F, et al. Correction of subclinical coagulation disorders before percutaneous dilatational tracheotomy. Blood Transfus 2012;10(2):213–220.
[116] Giannini EG, Stravitz RT, Caldwell SH. Correction of hemostatic abnormalities and portal pressure variations in patients with cirrhosis. Hepatology 2014;60(4):1442.
[117] Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA, et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19(1):2–31.
[118] Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang 2005;89(1):1–10.
[119] Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion 2009;49(3):440–452.
[120] Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. Transfus Med Rev 2004;18(3):184–188.
[121] Li G, Rachmale S, Kojicic M, Shahjehan K, Malinchoc M, Kor DJ, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion 2011;51(2):338–343.
[122] Popovsky MA. Transfusion and the lung: circulatory overload and acute lung injury. Vox Sang 2004;87(Suppl 2):62–65.
[123] Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. Transfusion 2012;52(1):160–165.
[124] Gilstad CW. Anaphylactic transfusion reactions. Curr Opin Hematol 2003;10(6):419–423.
[125] Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44(12):1774–1789.
[126] Liu F, Zhou FY, Hu LH. RBC alloimmunization is an important complication of FFP transfusion: a case report of immune anti-D induced by apheresis fresh frozen plasma. Transfus Clin Biol 2009;16(4):400–403.
[127] O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004;126(1):11–28.
[128] Franchini M, Lippi G. Prothrombin complex concentrates: an update. Blood Transfus 2010;8(3):149–154.
[129] Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol 2008;83(2):137–143.
[130] Verbeek TA, Stine JG, Saner FH, Bezinover D. Hypercoagulability in end-stage liver disease: review of epidemiology, etiology, and management. Transpl Direct 2018;4(11):e403.
[131] Lisman T, Kleiss S, Patel VC, Fisher C, Adelmeijer J, Bos S, et al. In vitro efficacy of pro- and anticoagulant strategies in compensated and acutely ill patients with cirrhosis. Liver Int 2018;38(11):1988–1996.
[132] Bos S, Schreuder T, Blokzijl H, Adelmeijer J, Lisman T, Kamphuisen PW. Anticoagulant activity of edoxaban in patients with cirrhosis. Blood 2020;136(13):1561–1564.
[133] Arshad F, Ickx B, van Beem RT, Polak W, Grune F, Nevens F, et al. Prothrombin complex concentrate in the reduction of blood loss during orthotopic liver transplantation: PROTON-trial. BMC Surg 2013;13:22.
[134] Kwon JO, MacLaren R. Comparison of fresh-frozen plasma, four-factor prothrombin complex concentrates, and recombinant factor VIIa to facilitate procedures in critically ill patients with coagulopathy from liver disease: a retrospective cohort study. Pharmacotherapy 2016;36(10):1047–1054.
[135] Drebes A, de Vos M, Gill S, Fosbury E, Mallett S, Burroughs A, et al. Prothrombin complex concentrates for coagulopathy in liver disease: single-center, clinical experience in 105 patients. Hepatol Commun 2019;3(4):513–524.
[136] Srivastava P, Agarwal A, Jha A, Rodricks S, Malik T, Makki K, et al. Utility of prothrombin complex concentrate as first-line treatment modality of coagulopathy in patients undergoing liver transplantation: a propensity score-matched study. Clin Transpl 2018;32(12):e13435.
[137] Hartmann M, Walde C, Dirkmann D, Saner FH. Safety of coagulation factor concentrates guided by ROTEM-analyses in liver transplantation: results from 372 procedures. BMC Anesthesiol 2019;19(1):97.
[138] Leal-Villalpando RP, Zamudio-Bautista J, Cardenas-Rodriguez R, Victor AM. Administration of 4 factor prothrombin complex concentrate (4f- PCC) in liver transplant recipients reduces the blood transfusion requirements. The ANESTHESIOLOGY Annu Meet - Am Soc Anesthesiologists 2016.
[139] Tischendorf M, Fuchs A, Zeuzem S, Lange CM. Use of prothrombin complex concentrates in patients with decompensated liver cirrhosis is associated with thromboembolic events. J Hepatol 2019;70(4):800–801.
[140] Harwood M, Robinson C, Wood P. Too much of a good thing: two cases of disseminated intravascular coagulation-like coagulopathy in patients with decompensated cirrhosis after administration of Prothrombinex-VF. Intern Med J 2019;49(5):679–680.
[141] Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, et al. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology 2006;44(2):440–445.
[142] **Raparelli V**, **Basili S**, Carnevale R, Napoleone L, Del Ben M, Nocella C, et al. Low-grade endotoxemia and platelet activation in cirrhosis. Hepatology 2017;65(2):571–581.
[143] Rautou PE, Vion AC, Valla D, Boulanger CM. Circulating platelet derived microparticles are not increased in patients with cirrhosis. J Hepatol 2013;59(4):912.
[144] Mannucci PM, Tripodi A. Hemostatic defects in liver and renal dysfunction. Hematol Am Soc Hematol Educ Program 2012;2012:168–173.
[145] Baimas-George M, Watson M, Salibi P, Murphy KJ, Vrochides D, Martinie JB, et al. A pre-operative platelet transfusion algorithm for patients with cirrhosis and hepatocellular carcinoma undergoing laparoscopic microwave ablation. Surg Endosc 2021;35(7):3811–3817.
[146] Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int 2013;33(3):362–367.
[147] Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 2018;155(3):705–718.
[148] Peck-Radosavljevic M, Simon K, Iacobellis A, Hassanein T, Kayali Z, Tran A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology 2019;70(4):1336–1348.
[149] Qureshi K, Patel S, Meillier A. The use of thrombopoietin receptor agonists for correction of thrombocytopenia prior to elective procedures in chronic liver diseases: review of current evidence. Int J Hepatol 2016;2016:1802932.
[150] https://www.shotuk.org/shot-reports/. 2021.
[151] Lindquist I, Olson SR, Li A, Al-Samkari H, Jou JH, McCarty OJT, et al. The efficacy and safety of thrombopoietin receptor agonists in patients with chronic liver disease undergoing elective procedures: a systematic review and meta-analysis. Platelets 2021:1–7.
[152] Hidaka H, Kurosaki M, Tanaka H, Kudo M, Abiru S, Igura T, et al. Lusutrombopag reduces need for platelet transfusion in patients with

thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol 2019;17(6):1192–1200.
[153] Tateishi R, Seike M, Kudo M, Tamai H, Kawazoe S, Katsube T, et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol 2019;54(2):171–181.
[154] Giannini EG, Kano T, Ochiai T, Bentley R, Shrestha P, Afdhal N. Bleeding events in lusutrombopag-treated thrombocytopenic patients. Eur J Clin Invest 2021;51(6):e13503. https://doi.org/10.1111/eci.13503.
[155] Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81(2):360–365.
[156] Casini A, Neerman-Arbez M, de Moerloose P. Heterogeneity of congenital afibrinogenemia, from epidemiology to clinical consequences and management. Blood Rev 2021;48:100793.
[157] Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus 2012;10(1):23–27.
[158] Pereira A, Beltran J, Blasi A. Who advocates for cryoprecipitate? Transfusion 2014;54(5):1442–1443.
[159] Tytgat GN, Collen D, Verstraete M. Metabolism of fibrinogen in cirrhosis of the liver. J Clin Invest 1971;50(8):1690–1701.
[160] Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth 2009;102(6):793–799.
[161] Dempfle CE, Kalsch T, Elmas E, Suvajac N, Lucke T, Munch E, et al. Impact of fibrinogen concentration in severely ill patients on mechanical properties of whole blood clots. Blood Coagul Fibrinol 2008;19(8):765–770.
[162] Sabate A, Gutierrez R, Beltran J, Mellado P, Blasi A, Acosta F, et al. Impact of preemptive fibrinogen concentrate on transfusion requirements in liver transplantation: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Transpl 2016;16(8):2421–2429.
[163] Aarts PA, van den Broek SA, Prins GW, Kuiken GD, Sixma JJ, Heethaar RM. Blood platelets are concentrated near the wall and red blood cells, in the center in flowing blood. Arteriosclerosis 1988;8(6):819–824.
[164] Turitto VT, Weiss HJ. Red blood cells: their dual role in thrombus formation. Science 1980;207(4430):541–543.
[165] Ruggeri ZM. Mechanisms initiating platelet thrombus formation. Thromb Haemost 1997;78(1):611–616.
[166] Balduini CL, Noris P, Belletti S, Spedini P, Gamba G. In vitro and in vivo effects of desmopressin on platelet function. Haematologica 1999;84(10):891–896.
[167] Eugster M, Reinhart WH. The influence of the haematocrit on primary haemostasis in vitro. Thromb Haemost 2005;94(6):1213–1218.
[168] Valeri CR, Cassidy G, Pivacek LE, Ragno G, Lieberthal W, Crowley JP, et al. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. Transfusion 2001;41(8):977–983.
[169] Ho CH. The hemostatic effect of packed red cell transfusion in patients with anemia. Transfusion 1998;38(11–12):1011–1014.
[170] Uhl L, Assmann SF, Hamza TH, Harrison RW, Gernsheimer T, Slichter SJ. Laboratory predictors of bleeding and the effect of platelet and RBC transfusions on bleeding outcomes in the PLADO trial. Blood 2017;130(10):1247–1258.
[171] Moia M, Mannucci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. Lancet 1987;2(8570):1227–1229.
[172] Gkamprela E, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. Ann Gastroenterol 2017;30(4):405–413.
[173] Gonzalez-Casas R, Jones EA, Moreno-Otero R. Spectrum of anemia associated with chronic liver disease. World J Gastroenterol 2009;15(37):4653–4658.
[174] Qamar AA, Grace ND. Abnormal hematological indices in cirrhosis. Can J Gastroenterol 2009;23(6):441–445.
[175] Short SS, Papillon S, Hunter CJ, Stanley P, Kerkar N, Wang L, et al. Percutaneous liver biopsy: pathologic diagnosis and complications in children. J Pediatr Gastroenterol Nutr 2013;57(5):644–648.
[176] Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368(1):11–21.
[177] Queiroz S, Silvestre VD, Soares RM, Campos GBP, Germano AR, da Silva JSP. Tranexamic acid as a local hemostasis method after dental extraction in patients on warfarin: a randomized controlled clinical study. Clin Oral Investig 2018;22(6):2281–2289.
[178] Whitworth K, Johnson J, Wisniewski S, Schrader M. Comparative effectiveness of topically administered tranexamic acid *vs.* Topical oxymetazoline spray for achieving hemostasis in epistaxis. J Emerg Med 2020;58(2):211–216.
[179] Boylan JF, Klinck JR, Sandler AN, Arellano R, Greig PD, Nierenberg H, et al. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. Anesthesiology 1996;85(5):1043–1048. discussion 30A-31A.
[180] Dalmau A, Sabate A, Acosta F, Garcia-Huete L, Koo M, Sansano T, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. Anesth Analg 2000;91(1):29–34.
[181] Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. Am J Transpl 2007;7(1):185–194.
[182] de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–752.
[183] Duenas E, Cachero A, Amador A, Rota R, Salord S, Gornals J, et al. Ulcer bleeding after band ligation of esophageal varices: risk factors and prognosis. Dig Liver Dis 2020;52(1):79–83.
[184] Schmitz RJ, Sharma P, Badr AS, Qamar MT, Weston AP. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy *vs.* band ligation. Am J Gastroenterol 2001;96(2):437–441.
[185] Sinclair M, Vaughan R, Angus PW, Gow PJ, Parker F, Hey P, et al. Risk factors for band-induced ulcer bleeding after prophylactic and therapeutic endoscopic variceal band ligation. Eur J Gastroenterol Hepatol 2015;27(8):928–932.
[186] **Blasi A**, **Machlab S**, Risco R, Costa-Freixas JP, Hernandez Cely G, Horta D, et al. A multicenter analysis of the role of prophylactic transfusion of blood products in patients with cirrhosis and esophageal varices undergoing endoscopic band ligation. JHEP Rep 2021;3. https://doi.org/10.1016/j.jhepr.2021.100363.
[187] Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. Clin Gastroenterol Hepatol 2010;8(9):800–805.
[188] Wu VC, Chen SW, Chou AH, Ting PC, Chang CH, Wu M, et al. Dual antiplatelet therapy in patients with cirrhosis and acute myocardial infarction - a 13-year nationwide cohort study. PLoS One 2019;14(10):e0223380.
[189] O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. Gastroenterology 2019;157(1):34–43 e1.
[190] Rockey DC. An update: portal hypertensive gastropathy and colopathy. Clin Liver Dis 2019;23(4):643–658.
[191] Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JC, et al. Decreased tissue factor pathway inhibitor (TFPI)-dependent anticoagulant capacity in patients with cirrhosis who have decreased protein S but normal TFPI plasma levels. Br J Haematol 2013;162(6):819–826.
[192] Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Porte RJ, et al. Routine coagulation assays underestimate levels of antithrombin-dependent drugs but not of direct anticoagulant drugs in plasma from patients with cirrhosis. Br J Haematol 2013;163(5):666–673.
[193] Ponthus S, Spahr L, Casini A, Berney T, Frossard JL, Majno P, et al. Safety of variceal band ligation in patients with cirrhosis and portal vein thrombosis treated with anticoagulant therapy: a retrospective study. Eur J Gastroenterol Hepatol 2020;32(3):395–400.
[194] Bianchini M, Cavani G, Bonaccorso A, Turco L, Vizzutti F, Sartini A, et al. Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients. Liver Int 2018;38(7):1253–1262.
[195] Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009;20(7 Suppl):S240–S249.
[196] Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in england and wales: an audit by the British society of

gastroenterology and the royal college of physicians of London. Gut 1995;36(3):437–441.
[197] **Mueller M**, **Kratzer W**, Oeztuerk S, Wilhelm M, Mason RA, Mao R, et al. Percutaneous ultrasonographically guided liver punctures: an analysis of 1961 patients over a period of ten years. BMC Gastroenterol 2012;12:173.
[198] **Kim JY**, **Lee HS**, Chung MJ, Park JY, Park SW, Song SY, et al. Bleeding complications and clinical safety of endoscopic retrograde cholangiopancreatography in patients with liver cirrhosis. Yonsei Med J 2019;60(5):440–445.
[199] Fidelman N, Kwan SW, LaBerge JM, Gordon RL, Ring EJ, Kerlan Jr RK. The transjugular intrahepatic portosystemic shunt: an update. AJR Am J Roentgenol 2012;199(4):746–755.
[200] Buechter M, Manka P, Gerken G, Canbay A, Blomeyer S, Wetter A, et al. Transjugular intrahepatic portosystemic shunt in patients with portal hypertension: patency depends on coverage and interventionalist's experience. Dig Dis 2018;36(3):218–227.
[201] Tercan F, Ozkan U, Oguzkurt L. US-guided placement of central vein catheters in patients with disorders of hemostasis. Eur J Radiol 2008;65(2):253–256.
[202] Rocha LL, Pessoa CM, Neto AS, do Prado RR, Silva E, de Almeida MD, et al. Thromboelastometry *vs.* standard coagulation tests *vs.* restrictive protocol to guide blood transfusion prior to central venous catheterization in cirrhosis: study protocol for a randomized controlled trial. Trials 2017;18(1):85.
[203] Patel PA, Ernst FR, Gunnarsson CL. Evaluation of hospital complications and costs associated with using ultrasound guidance during abdominal paracentesis procedures. J Med Econ 2012;15(1):1–7.
[204] Papini E, Pacella CM, Rossi Z, Bizzarri G, Fabbrini R, Nardi F, et al. A randomized trial of ultrasound-guided anterior subcostal liver biopsy *vs.* the conventional Menghini technique. J Hepatol 1991;13(3):291–297.
[205] Lindor KD, Bru C, Jorgensen RA, Rakela J, Bordas JM, Gross JB, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. Hepatology 1996;23(5):1079–1083.
[206] Farsad K, Fuss C, Kolbeck KJ, Barton RE, Lakin PC, Keller FS, et al. Transjugular intrahepatic portosystemic shunt creation using intravascular ultrasound guidance. J Vasc Interv Radiol 2012;23(12):1594–1602.
[207] Meine TC, Dewald CLA, Becker LS, Mahringer-Kunz A, Massoumy B, Maschke SK, et al. Transjugular intrahepatic portosystemic shunt placement: portal vein puncture guided by 3D/2D image registration of contrast-enhanced multi-detector computed tomography and fluoroscopy. Abdom Radiol (Ny) 2020;45(11):3934–3943.
[208] RiChard J, Thornburg B. New techniques and devices in transjugular intrahepatic portosystemic shunt placement. Semin Intervent Radiol 2018;35(3):206–214.
[209] Mashiana HS, Dhaliwal AS, Sayles H, Dhindsa B, Yoo JW, Wu Q, et al. Endoscopic retrograde cholangiopancreatography in cirrhosis - a systematic review and meta-analysis focused on adverse events. World J Gastrointest Endosc 2018;10(11):354–366.
[210] Inamdar S, Berzin TM, Berkowitz J, Sejpal DV, Sawhney MS, Chutanni R, et al. Decompensated cirrhosis may be a risk factor for adverse events in endoscopic retrograde cholangiopancreatography. Liver Int 2016;36(10):1457–1463.
[211] Chukmaitov A, Bradley CJ, Dahman B, Siangphoe U, BouHaidar D, Warren JL. Polypectomy techniques, endoscopist characteristics, and serious gastrointestinal adverse events. J Surg Oncol 2014;110(2):207–213.
[212] Scheiner B, Semmler G, Maurer F, Schwabl P, Bucsics TA, Paternostro R, et al. Prevalence of and risk factors for anaemia in patients with advanced chronic liver disease. Liver Int 2020;40(1):194–204.
[213] Singh S, Manrai M, Parvathi VS, Kumar D, Srivastava S, Pathak B. Association of liver cirrhosis severity with anemia: does it matter? Ann Gastroenterol 2020;33(3):272–276.
[214] **Rout G**, **Shalimar**, Gunjan D, Mahapatra SJ, Kedia S, Garg PK, et al. Thromboelastography-guided blood product transfusion in cirrhosis patients with variceal bleeding: a randomized controlled trial. J Clin Gastroenterol 2020;54(3):255–262.
[215] Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. Hepatology 2008;47(5):1604–1614.
[216] Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez Abraldes J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology 2004;127(4):1123–1130.
[217] Bendtsen F, D'Amico G, Rusch E, de Franchis R, Andersen PK, Lebrec D, et al. Effect of recombinant Factor VIIa on outcome of acute variceal bleeding: an individual patient based meta-analysis of two controlled trials. J Hepatol 2014;61(2):252–259.
[218] Sozio MS, Chalasani N. Activated recombinant factor VIIa should not be used in patients with refractory variceal bleeding: it is mostly ineffective, is expensive, and may rarely cause serious adverse events. Hepatology 2014;60(5):1786–1788.
[219] HALT-IT Trial collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet 2020;395 (10241):1927–1936.
[220] Castaneda B, Morales J, Lionetti R, Moitinho E, Andreu V, Perez-Del-Pulgar S, et al. Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats. Hepatology 2001;33(4):821–825.
[221] Kravetz D, Sikuler E, Groszmann RJ. Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution. Gastroenterology 1986;90(5 Pt 1):1232–1240.
[222] Villanueva C, Ortiz J, Minana J, Soriano G, Sabat M, Boadas J, et al. Somatostatin treatment and risk stratification by continuous portal pressure monitoring during acute variceal bleeding. Gastroenterology 2001;121(1):110–117.
[223] Zimmon DS, Kessler RE. The portal pressure-blood volume relationship in cirrhosis. Gut 1974;15(2):99–101.
[224] Abraldes JG, Villanueva C, Banares R, Aracil C, Catalina MV, Garci APJC, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48(2):229–236.
[225] Moitinho E, Escorsell A, Bandi JC, Salmeron JM, Garcia-Pagan JC, Rodes J, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology 1999;117(3):626–631.
[226] Higaki N, Matsui H, Imaoka H, Ikeda Y, Murakami H, Hiasa Y, et al. Characteristic endoscopic features of portal hypertensive enteropathy. J Gastroenterol 2008;43(5):327–331.
[227] Ito K, Shiraki K, Sakai T, Yoshimura H, Nakano T. Portal hypertensive colopathy in patients with liver cirrhosis. World J Gastroenterol 2005;11(20):3127–3130.
[228] Menchen L, Ripoll C, Marin-Jimenez I, Colon A, Gomez-Camarero J, Gonzalez-Asanza C, et al. Prevalence of portal hypertensive duodenopathy in cirrhosis: clinical and haemodynamic features. Eur J Gastroenterol Hepatol 2006;18(6):649–653.
[229] Merli M, Nicolini G, Angeloni S, Gentili F, Attili AF, Riggio O. The natural history of portal hypertensive gastropathy in patients with liver cirrhosis and mild portal hypertension. Am J Gastroenterol 2004;99 (10):1959–1965.
[230] Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, et al. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). Gastroenterology 2000;119(1):181–187.
[231] Simbrunner B, Beer A, Woran K, Schmitz F, Primas C, Wewalka M, et al. Portal hypertensive gastropathy is associated with iron deficiency anemia. Wien Klin Wochenschr 2020;132(1–2):1–11.
[232] Gostout CJ, Viggiano TR, Balm RK. Acute gastrointestinal bleeding from portal hypertensive gastropathy: prevalence and clinical features. Am J Gastroenterol 1993;88(12):2030–2033.
[233] Lyles T, Elliott A, Rockey DC. A risk scoring system to predict in-hospital mortality in patients with cirrhosis presenting with upper gastrointestinal bleeding. J Clin Gastroenterol 2014;48(8):712–720.
[234] Minami T. Bleeding in portal hypertensive gastropathy evaluated in terms of gastric mucosal microcirculation and coagulation-fibrinolysis system. Kurume Med J 1997;44(4):241–251.
[235] Bruha R, Marecek Z, Spicak J, Hulek P, Lata J, Petrtyl J, et al. Double-blind randomized, comparative multicenter study of the effect of terlipressin in the treatment of acute esophageal variceal and/or hypertensive gastropathy bleeding. Hepatogastroenterology 2002;49(46):1161–1166.
[236] Hosking SW. Congestive gastropathy in portal hypertension: variations in prevalence. Hepatology 1989;10(2):257–258.
[237] Kouroumalis EA, Koutroubakis IE, Manousos ON. Somatostatin for acute severe bleeding from portal hypertensive gastropathy. Eur J Gastroenterol Hepatol 1998;10(6):509–512.

[238] Zhou Y, Qiao L, Wu J, Hu H, Xu C. Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: a controlled study. J Gastroenterol Hepatol 2002;17(9):973–979.
[239] McCormick PA, Ooi H, Crosbie O. Tranexamic acid for severe bleeding gastric antral vascular ectasia in cirrhosis. Gut 1998;42(5):750–752.
[240] Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. Hepatology 2021;73(1):366–413.
[241] Cerini F, Gonzalez JM, Torres F, Puente A, Casas M, Vinaixa C, et al. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology 2015;62(2):575–583.
[242] Thachil J. Anemia–the overlooked factor in bleeding related to liver disease. J Hepatol 2011;54(3):593–594. author reply 4-5.
[243] Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. Gut 2005;54(4):556–563.
[244] Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. Semin Dial 2009;22(3):279–286.
[245] Desborough M, Sandu R, Brunskill SJ, Doree C, Trivella M, Montedori A, et al. Fresh frozen plasma for cardiovascular surgery. Cochrane Database Syst Rev 2015;(7):CD007614.
[246] Roman M, Biancari F, Ahmed AB, Agarwal S, Hadjinikolaou L, Al-Sarraf A, et al. Prothrombin complex concentrate in cardiac surgery: a systematic review and meta-analysis. Ann Thorac Surg 2019;107(4):1275–1283.
[247] Slichter SJ. Evidence-based platelet transfusion guidelines. Hematol Am Soc Hematol Educ Program 2007:172–178.
[248] Estcourt LJ, Birchall J, Lowe D, Grant-Casey J, Rowley M, Murphy MF. Platelet transfusions in haematology patients: are we using them appropriately? Vox Sang 2012;103(4):284–293.
[249] Hunt BJ, Allard S, Keeling D, Norfolk D, Stanworth SJ, Pendry K, et al. A practical guideline for the haematological management of major haemorrhage. Br J Haematol 2015;170(6):788–803.
[250] Klein AA, Arnold P, Bingham RM, Brohi K, Clark R, Collis R, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 2016;71(7):829–842.
[251] CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23–32.
[252] WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389(10084):2105–2116.
[253] Post R, Germans MR, Tjerkstra MA, Vergouwen MDI, Jellema K, Koot RW, et al. Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. Lancet 2021;397(10269):112–118.
[254] Porte RJ, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, Lindgren L, et al. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. Lancet 2000;355(9212):1303–1309.
[255] Koster A, Faraoni D, Levy JH. Antifibrinolytic therapy for cardiac surgery: an update. Anesthesiology 2015;123(1):214–221.
[256] Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2018;4:CD000249.
[257] Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ. Tranexamic acid for patients with nasal haemorrhage (epistaxis). Cochrane Database Syst Rev 2018;12:CD004328.
[258] Curry NS, Davenport R, Pavord S, Mallett SV, Kitchen D, Klein AA, et al. The use of viscoelastic haemostatic assays in the management of major bleeding: a British Society for Haematology Guideline. Br J Haematol 2018;182(6):789–806.
[259] Lisman T, Porte RJ. Value of preoperative hemostasis testing in patients with liver disease for perioperative hemostatic management. Anesthesiology 2017;126(2):338–344.
[260] Lisman T. Interpreting hemostatic profiles assessed with viscoelastic tests in patients with cirrhosis. J Clin Gastroenterol 2020;54(4):389–391.
[261] Longstaff C. Measuring fibrinolysis: from research to routine diagnostic assays. J Thromb Haemost 2018;16(4):652–662.
[262] **Kumar M**, **Ahmad J**, Maiwall R, Choudhury A, Bajpai M, Mitra LG, et al. Thromboelastography-guided blood component use in patients with cirrhosis with nonvariceal bleeding: a randomized controlled trial. Hepatology 2020;71(1):235–246.
[263] Bonnet A, Gilquin N, Steer N, Gazon M, Quattrone D, Pradat P, et al. The use of a thromboelastometry-based algorithm reduces the need for blood product transfusion during orthotopic liver transplantation: a randomised controlled study. Eur J Anaesthesiol 2019;36(11):825–833.
[264] Lebreton A, Sinegre T, Lecompte T, Talon L, Abergel A, Lisman T. Thrombin generation and cirrhosis: state of the art and perspectives. Semin Thromb Hemost 2020;46(6):693–703.
[265] Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, et al. Detection of the imbalance of procoagulant *vs.* anticoagulant factors in cirrhosis by a simple laboratory method. Hepatology 2010;52(1):249–255.
[266] Gulley D, Teal E, Suvannasankha A, Chalasani N, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhosis patients. Dig Dis Sci 2008;53(11):3012–3017.
[267] Omer Sultan M, Farooque U, Inam Khan M, Karimi S, Cheema O, Jaan A, et al. Frequency of venous thromboembolism in patients with liver cirrhosis. Cureus 2020;12(8):e9594.
[268] Aldawood A, Arabi Y, Aljumah A, Alsaadi A, Rishu A, Aldorzi H, et al. The incidence of venous thromboembolism and practice of deep venous thrombosis prophylaxis in hospitalized cirrhotic patients. Thromb J 2011;9(1):1.
[269] Anthony Lizarraga W, Dalia S, Reinert SE, Schiffman FJ. Venous thrombosis in patients with chronic liver disease. Blood Coagul Fibrinol 2010;21(5):431–435.
[270] Dabbagh O, Oza A, Prakash S, Sunna R, Saettele TM. Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease. Chest 2010;137(5):1145–1149.
[271] Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol 2006;101(7):1524–1528. quiz 680.
[272] Qi X, Ren W, Guo X, Fan D. Epidemiology of venous thromboembolism in patients with liver diseases: a systematic review and meta-analysis. Intern Emerg Med 2015;10(2):205–217.
[273] Barba R, Gonzalvez-Gasch A, Joya Seijo D, Marco J, Canora J, Plaza S, et al. Venous thromboembolism in patients with liver diseases. J Thromb Haemost 2018;16(10):2003–2007.
[274] Ambrosino P, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost 2017;117(1):139–148.
[275] Ng KJ, Lee YK, Huang MY, Hsu CY, Su YC. Risks of venous thromboembolism in patients with liver cirrhosis: a nationwide cohort study in Taiwan. J Thromb Haemost 2015;13(2):206–213.
[276] Enger C, Forssen UM, Bennett D, Theodore D, Shantakumar S, McAfee A. Thromboembolic events among patients with hepatitis C virus infection and cirrhosis: a matched-cohort study. Adv Ther 2014;31(8):891–903.
[277] Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol 2009;104(1):96–101.
[278] Jepsen P, Tapper EB, Deleuran T, Kazankov K, Askgaard G, Sorensen HT, et al. Risk and outcome of venous and arterial thrombosis in patients with cirrhosis: a Danish nationwide cohort study. Hepatology 2021.
[279] Yang LS, Alukaidey S, Croucher K, Dowling D. Suboptimal use of pharmacological venous thromboembolism prophylaxis in cirrhotic patients. Intern Med J 2018;48(9):1056–1063.
[280] Bikdeli B, Jimenez D, Garcia-Tsao G, Barba R, Font C, Diaz-Pedroche MDC, et al. Venous thromboembolism in patients with liver cirrhosis: findings from the RIETE (registro informatizado de la Enfermedad TromboEmbolica) Registry. Semin Thromb Hemost 2019;45(8):793–801.
[281] Moorehead KJ, Jeffres MN, Mueller SW. A retrospective cohort analysis of pharmacologic VTE prophylaxis and Padua prediction score in hospitalized patients with chronic liver disease. J Pharm Pract 2017;30(1):58–63.
[282] Bogari H, Patanwala AE, Cosgrove R, Katz M. Risk-assessment and pharmacological prophylaxis of venous thromboembolism in hospitalized patients with chronic liver disease. Thromb Res 2014;134(6):1220–1223.

[283] Spyropoulos AC, Anderson Jr FA, FitzGerald G, Decousus H, Pini M, Chong BH, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140(3):706–714.
[284] Koliscak L, Maynor L. Pharmacologic prophylaxis against venous thromboembolism in hospitalized patients with cirrhosis and associated coagulopathies. Am J Health Syst Pharm 2012;69(8):658–663.
[285] **Zermatten MG**, **Fraga M**, Calderara DB, Aliotta A, Moradpour D, Alberio L. Biomarkers of liver dysfunction correlate with a prothrombotic and not with a prohaemorrhagic profile in patients with cirrhosis. JHEP Rep 2020;2(4):100120.
[286] Ali M, Ananthakrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: a nationwide analysis. Dig Dis Sci 2011;56(7):2152–2159.
[287] Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8(11):2450–2457.
[288] Davis JPE, O'Leary KE, Intagliata NM. Overuse of venous thromboembolism prophylaxis among hospitalized patients with liver disease. Eur J Haematol 2020;104(3):223–229.
[289] Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. J Hepatol 2013;59(2):265–270.
[290] **Darzi AJ**, **Repp AB**, Spencer FA, Morsi RZ, Charide R, Etxeandia-Ikobaltzeta I, et al. Risk-assessment models for VTE and bleeding in hospitalized medical patients: an overview of systematic reviews. Blood Adv 2020;4(19):4929–4944.
[291] Harahsheh Y, Ho KM. Use of viscoelastic tests to predict clinical thromboembolic events: a systematic review and meta-analysis. Eur J Haematol 2018;100(2):113–123.
[292] Lisman T, Porte RJ. Understanding and managing the coagulopathy of liver disease. In: Kitchens Craig S, Kessler Craig M, Konkle Barbara A, Streiff Michael B, Garcia David A, editors. Consultative hemostasis and thrombosis. 4th ed 2019. p. 734–746.
[293] Rogers HJ, Nakashima MO, Kottke-Marchant K. Hemostasis and thrombosis. In: Hsi Eric D, editor. Foundations in diagnostic pathology, hematopathology. 3rd ed 2018. 57–105.e4.
[294] Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost 1999;82(2):610–619.
[295] Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41(3):553–558.
[296] Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromso Study, Tromso, Norway. J Thromb Haemost 2010;8(1):157–162.
[297] Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematol Am Soc Hematol Educ Program 2016;2016(1):1–9.
[298] Aggarwal A, Puri K, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhotic patients: systematic review. World J Gastroenterol 2014;20(19):5737–5745.
[299] Caldwell S, Carlini LE. Coagulation homeostasis in liver disease. Clin Liver Dis (Hoboken) 2020;16(4):137–141.
[300] Shatzel J, Dulai PS, Harbin D, Cheung H, Reid TN, Kim J, et al. Safety and efficacy of pharmacological thromboprophylaxis for hospitalized patients with cirrhosis: a single-center retrospective cohort study. J Thromb Haemost 2015;13(7):1245–1253.
[301] Yerke J, Bauer SR, Bass S, Torbic H, Militello M, Roach E, et al. Effectiveness of venous thromboembolism prophylaxis in patients with liver disease. World J Hepatol 2019;11(4):379–390.
[302] Intagliata NM, Henry ZH, Shah N, Lisman T, Caldwell SH, Northup PG. Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. Liver Int 2014;34(1):26–32.
[303] Reichert JA, Hlavinka PF, Stolzfus JC. Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. Pharmacotherapy 2014;34(10):1043–1049.
[304] Kunk PR, Collins H, Palkimas S, Intagliata NM, Maitland H. Direct oral anticoagulants in patients with cirrhosis appear safe and effective. Blood 2016;128(22).
[305] Hoolwerf EW, Kraaijpoel N, Buller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: a systematic review. Thromb Res 2018;170:102–108.
[306] Elhosseiny S, Al Moussawi H, Chalhoub JM, Lafferty J, Deeb L. Direct oral anticoagulants in cirrhotic patients: current evidence and clinical observations. Can J Gastroenterol Hepatol 2019;2019:4383269.
[307] Mort JF, Davis JPE, Mahoro G, Stotts MJ, Intagliata NM, Northup PG. Rates of bleeding and discontinuation of direct oral anticoagulants in patients with decompensated cirrhosis. Clin Gastroenterol Hepatol 2021;19(7):1436–1442.
[308] Fu Y, Zhu W, Zhou Y, Chen H, Yan L, He W. Non-vitamin K antagonist oral anticoagulants *vs.* Warfarin in patients with atrial fibrillation and liver disease: a meta-analysis and systematic review. Am J Cardiovasc Drugs 2020;20(2):139–147.
[309] **Menichelli D**, **Ronca V**, Di Rocco A, Pignatelli P, Marco Podda G, Car. Direct oral anticoagulants and advanced liver disease: a systematic review and meta-analysis. Eur J Clin Invest 2021;51(3):e13397.
[310] Huang ZC, Li CQ, Liu XY, Cao ZC, Jia HY, Dong Y, et al. Efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and liver disease: a meta-analysis and systematic review. Cardiovasc Drugs Ther 2020.
[311] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543–603.
[312] **Senzolo M**, **Rodriguez-Castro KI**, Rossetto V, Radu C, Gavasso S, Carraro P, et al. Increased anticoagulant response to low-molecular-weight heparin in plasma from patients with advanced cirrhosis. J Thromb Haemost 2012;10(9):1823–1829.
[313] Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol 2010;44(6):448–451.
[314] Delgado MG, Seijo S, Yepes I, Achecar L, Catalina MV, Garcia-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012;10(7):776–783.
[315] Senzolo M, Sartori TM, Rossetto V, Burra P, Cillo U, Boccagni P, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int 2012;32(6):919–927.
[316] Garcia-Fuster MJ, Abdilla N, Fabia MJ, Fernandez C, Oliver V, Forner MJ. [Venous thromboembolism and liver cirrhosis]. Rev Esp Enferm Dig 2008;100(5):259–262.
[317] Valeriani E, Di Nisio M, Riva N, Cohen O, Porreca E, Senzolo M, et al. Anticoagulant treatment for splanchnic vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. Thromb Haemost 2021;121(7):867–876.
[318] Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. Cochrane Database Syst Rev 2015;(6):CD010956.
[319] Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev 2015;(12):CD010957.
[320] Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol 2017;98(4):393–397.
[321] Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330–1393.
[322] Prisco D, Ageno W, Becattini C, D'Angelo A, Davi G, De Cristofaro R, et al. Italian intersociety consensus on DOAC use in internal medicine. Intern Emerg Med 2017;12(3):387–406.
[323] Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2013;76(1):89–98.
[324] Nagaoki Y, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res 2018;48(1):51–58.
[325] Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban *vs.* warfarin in the management of acute non-neoplastic portal vein thrombosis. Vascul Pharmacol 2019;113:86–91.
[326] Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. Gastroenterology 2017;152(5):1014–10122 e1.

[327] Mazurek M, Lip GYH. Gastrointestinal bleeding and direct oral anticoagulants amongst patients with atrial fibrillation in the "real world. Gastroenterology 2017;152(5):932–934.
[328] Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis 2016;41(1):206–232.
[329] Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol 2013;61(25):2495–2502.
[330] Ponziani FR, De Candia E, De Cristofaro R, Pompili M. Portal vein thrombosis occurrence in a cirrhotic patient during treatment with rivaroxaban. Liver Int 2017;37(8):1251.
[331] Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010;51(4):1445–1449.
[332] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–460.
[333] Jalan R, Pavesi M, Saliba F, Amoros A, Fernandez J, Holland-Fischer P, et al. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. J Hepatol 2015;62(4):831–840.
[334] Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol 2020;73(4):842–854.
[335] Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8(1):202–204.
[336] de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53(4):762–768.
[337] Popovsky MA. Pulmonary consequences of transfusion: TRALI and TACO. Transfus Apher Sci 2006;34(3):243–244.
[338] Popovsky MA, Audet AM, Andrzejewski Jr C. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. Immunohematology 1996;12(2):87–89.
[339] Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest 2004;126(1):249–258.
[340] Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med 2005;33(4):721–726.