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REVIEW

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The use of prothrombin complex concentrate in chronic liver disease: A review of the literature

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Abstract

Patients with chronic liver disease (CLD) and cirrhosis present a rebalanced hemostatic system in the three phases of haemostasis. This balance is however unstable and can easily tip towards bleeding or thrombosis. Management of both spontaneous bleeding and bleeding during invasive procedures remains a challenge in this patient population. Transfusion of blood products can result in circulatory overload and thereby worsen portal hypertension. As an alternative to fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) may have merit in patients with liver disease because of their low volume. The impact of PCC in in-vitro spiking experiments of cirrhotic plasma is promising, but also warrants cautious use in light of thromboembolic risk. The majority of existing studies carried-out in CLD patients are retrospective or do not have an adequate control arm. A prospective study (the PROTON trial) was set up in 2013 to investigate the utility of PCC in patients undergoing liver transplantation. However, the study has never recruited the planned number of patients. Robust data on PCC safety in CLD is also required. The limited existing evidence does not seem to indicate an excessive thromboembolic risk. Currently, the utilisation of PCC in CLD cannot be routinely recommended but can provide an option for carefully selected cases in which other measures were not sufficient to control bleeding and after delicately weighing risks and benefits.

KEYWORDS
bleeding, chronic liver disease, cirrhosis, prothrombin complex concentrate, thromboembolic risk

1 | INTRODUCTION

1.1 | Concept of rebalanced haemostasis

Currently, the concept of rebalanced haemostasis is widely accepted for patients with chronic liver disease (CLD) and cirrhosis. Multiple procoagulant and anticoagulant perturbations give rise to a fragile balance, elevating both hemorrhagic and thrombotic risk. The three phases of haemostasis are affected: primary haemostasis, coagulation cascade and fibrinolysis (Figure 1).[1] Thrombocytopenia is common in CLD patients but seems to be counterbalanced by an increase in von Willebrand factor.[2,3] The study of platelet function is much more complex and conflicting reports exist.[4,5] Some describe decreased platelet function[6,7] while others report enhanced platelet activation.[3,8] Fibrinogen plays a role in both primary haemostasis (platelet aggregation) and coagulation (fibrin formation). Levels of fibrinogen can be elevated in early liver disease but hypofibrinogenemia is often seen in more advanced stages, leading to reduced clot formation potential.[1] Qualitative defects (hypersialated fibrinogen, high carbonyl content) have been described.[9,10] The majority of coagulation factors is synthetized by hepatocytes except for factor VIII which is predominantly produced by liver sinusoidal endothelial cells.[11] A decrease in factor

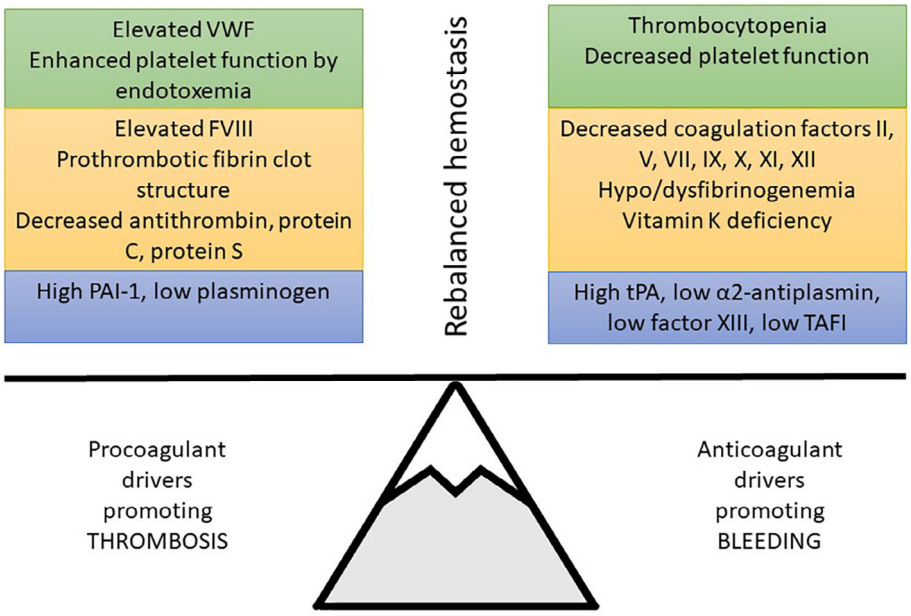

FIGURE 1 Rebalanced hemostatic system in liver disease patients. The three phases of haemostasis are concerned: primary haemostasis (green), coagulation cascade (orange), fibrinolysis (blue). tPA, tissue plasminogen activator; TAFI, thrombin activatable fibrinolysis inhibitor; PAI-1, plasminogen activator inhibitor-1.

II, V, VII, IX, X, XI and XII but an increase in factor VIII is observed in patients with liver disease. The natural anticoagulants antithrombin, protein S and C decrease progressively with disease severity.[12] Hyperfibrinolysis is often described in CLD.[13] However, changes in both pro-and anti-fibrinolytic drivers are recognised: increased tissue plasminogen activator, decreased alpha 2-antiplasmin, FXIII and thrombin activatable fibrinolysis inhibitor increase fibrinolytic potential whereas high plasminogen activator inhibitor type 1 and decreased plasminogen levels decrease fibrinolytic capacity. This can lead to a rebalanced system.[1,14]

Routine haemostasis tests, for example prothrombin time (PT) and activated partial thromboplastin time, are only sensitive for procoagulant proteins and only reflect 5% of the total amount of thrombin generated during coagulation.[15] Important information on the anticoagulant pathway is therefore not provided. Viscoelastic tests, like ROTEM and TEG, better reflect this rebalanced hemostatic system than conventional testing but also have their drawbacks. A normal viscoelastic test may be useful to select patients that do not need preprocedural prohemostatic treatment. However, an abnormal viscoelastic test may still not require correction, since existing viscoelastic tests underestimate coagulation capacity (no activation of protein C, insensitivity to von Willebrand factor).[16] The European Association for the Study of the Liver (EASL) recommends that routine use of viscoelastic tests presently cannot be recommended for predicting post-procedural bleeding but that it needs further exploration. Because of rarity of bleeding events documented, studies are often not able to show an association between viscoelastic tests and bleeding events.[17] Plasma-based thrombomodulin-modified thrombin generation, in which exogenous thrombomodulin activates protein C, provide a good appreciation of rebalanced haemostasis.[18] They are however not readily available in clinical laboratories. The predictive value for procedural or spontaneous bleeding of thrombin generation assays (TGA) is unknown.

Whereas hemostatic changes may contribute to bleeding or thrombosis in patients with cirrhosis, other important factors may also play a role in hemorrhagic and thrombotic risk in CLD patients. Variceal haemorrhage is primarily due to portal hypertension.[19] Reduced portal blood flow can lead to portal thrombosis. Recently, Turon et al. demonstrated that hypercoagulability likely plays a minor role in development of portal vein thrombosis.[20] Renal disease, bacterial infection and inflammatory changes in endothelial cells can further impair haemostasis, and thereby contribute to bleeding risk.

1.2 | Prothrombin complex concentrates

Non-activated prothrombin complex concentrates or PCCs are virally inactivated, low-volume prohemostatic products containing non-activated vitamin K-dependent coagulation factors: factor II, (factor VII), factor IX and factor X. Some concentrates also contain anticoagulants protein S, protein C, protein Z, antithrombin or heparin. They were originally designed and intended for use in haemophilia B patients. Nowadays, PCC are primarily used for the rapid reversal of oral vitamin K antagonist-related bleeding.[21] Other indications are congenital or acquired factor deficiencies where purified factor concentrates are not available. The concentration of coagulation factors is on average 25 times higher than in FFP.[22] Multiple 3 (FII, FIX, FX) or 4 factor (FII, FVII, FIX, FX) PCC formulations are available globally: Cofact® (Sanquin, Amsterdam, The Netherlands), Confidex® (CSL Behring, Marburg, Germany) and Octaplex® (Octapharma, Brussels, Belgium), Beriplex® (CSL Behring), Uman Complex® (Kedrion, Barga, Italy), Kcentra® (CSL Behring), Prothrombinex™-VF® (CSL Behring),

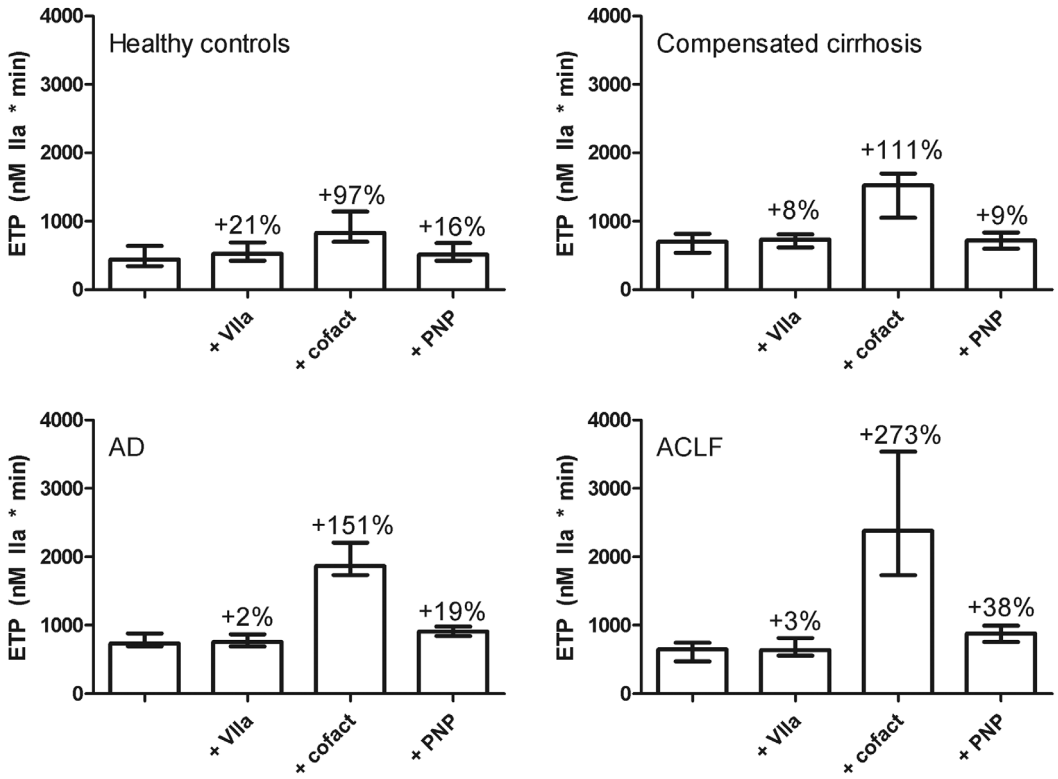

FIGURE 2 Absolute ETP values from thrombomodulin-modified thrombin generation testing in controls and patients with compensated, or acutely decompensated cirrhosis (AD) or acute-on- chronic liver failure (ACLF). VIIa = factor VIIa, Cofact = 4-factor PCC; PNP: pooled normal plasma. Reproduced from Lisman et al. Liver Int. 2018;38(11):1988–1996.

and Profilnine SD® (Grifols Biologicals, Barcelona, Spain). The only activated PCC available is FEIBA (Baxter Healthcare Corporation, Westlake Village, CA). This procoagulant agent has a recognised use as a bypassing agent in haemophilia patients with inhibitors. In this review only non-activated PCCs will be discussed.

In contrast to PCC, FFP has several drawbacks. Large volumes of plasma are needed to significantly improve the PT.[23] This can lead to volume overload and elevation in portal pressure in liver disease patients. Thrombin generation, that is often normal in CLD patients, does not improve considerably after infusion of FFP.[24] Beside volume overload, there are allergic, immunological and infectious transfusion risks associated with plasma transfusions. Thawing FFP takes time, which can be an issue in urgent situations. PCC could be a low volume alternative to FFP as it contains both procoagulant and anticoagulant factors.

In this review we aim to provide an concise overview on existing evidence of PCC use in CLD patients.

2 | MATERIALS AND METHODS

We used the PUBMED database searching for the following key elements: "liver diseases" [MESH] and "PCC" [MESH]. References in articles were also screened. All types of articles including case reports and conference proceedings were considered.

3 | PCC IN CLD

3.1 | Impact of PCC on "in vitro" haemostasis

A thrombomodulin-modified TGA enables us to study the effect of different procoagulant agents on the ability to generate thrombin. Lisman et al. performed TGA on normal patient plasma and plasma from cirrhotic patients with differences in severity: compensated, acutely decompensated and acute-on-chronic liver failure.[25] Plasma was spiked with procoagulant agents: normal pool plasma (to mimic FFP), recombinant factor VIIa (rFVIIa) and PCC (Figure 2).

The effect of rFVIIa was minimal, especially in acutely decompensated and ACLF patients. FFP only marginally increased endogenous thrombin potential (ETP) in compensated and acutely decompensated patients, further corroborating the hesitant approach towards FFP use in liver disease. Tripodi et al already underlined the small effect of FFP on thrombin generation in compensated liver disease patients.[26] The American Gastroenterological Association (AGA) practice guidelines on coagulation in cirrhosis state that the utility of FFP is very limited in cirrhotic patients.[27] In concordance to this, the American Association for the Study of Liver Disease (AASLD) and EASL guidelines advice against preprocedural use of FFP.[16,17]

Interestingly, PCC enhanced thrombin generation to a larger extent in cirrhotic plasma compared to plasma from healthy individuals and this enhanced effect was proportional to disease severity.

TABLE 1 Overview of studies published on PCC use in liver disease.

Author	Study type	Year	# patients	Indication	PCC	TE events	INR outcome	clinical outcome
Huang et al.[31]	Retrospective study	2016	85 (LD = 31/non-LD = 54)	Bleeding	Kcentra	3.2% (LD); 14.8% (non-LD)	Suboptimal correction in LD compared to non-LD	No data
Drebes et al.[35]	Retrospective study	2019	105	Prophylactic/bleeding	Beriplex/Octaplex	3%	Significant reduction	No data
Lesmana et al.[36]	Prospective study, non-randomised	2016	30	Prophylactic	Cofact	No data	Significant reduction	No bleeding events
Kwon et al.[37]	Retrospective study	2016	45 (15 PCC, 15 rFVIIa, 15 FFP)	Prophylactic	Kcentra	7%	Greater reduction in PCC group than in FFP group	Less blood product use in PCC group than FFP group, idem bleeding
Leal-Villalpando et al.[38]	Retrospective study	2016	30 (PCC = 25)	Prophylactic	Confidex/Kcentra	No data	No data	Lower FFP administration
Srivastava et al.[39]	Retrospective study	2018	262 (PCC = 60), propensity score-matched	Prophylactic	No data	0%	No data	Lower RBC/FFP administration in PCC group
Richard-Carpentier and Rioux-Masse[46]	Retrospective study	2013	51	Prophylactic/bleeding	Beriplex/Octaplex	6%	Better INR reduction in CTP A/B compared to CTP C	Poor bleeding control
Small et al.[47]	Retrospective study	2021	58 (PCC = 21)	Bleeding	Kcentra	No data	Significant reduction	No difference
Hartmann et al.[48]	Retrospective study	2019	372 (PCC = 70)	Bleeding	PCC (CSL Behringer)	No data	No data	PCC not independently correlated with mortality
Zamper et al.[51]	Interventional before-after comparative study	2018	237 (54 intervention/183 control; PCC = 6)	Bleeding	No data	Idem TE rate intervention versus control	No data	Reduction allogeneic blood product use
Colavecchia et al.[52]	Retrospective study	2017	212 (PCC: *n* = 39)	Prophylactic	Kcentra	No data	No data	No lower blood product administration
Tischendorf et al.[58]	Retrospective study	2019	347	Prophylactic/bleeding	No data	5.50%	No data	No data
Kirchner et al.[59]	Retrospective study	2014	266 (156CFC group/110 non-CFC group)	Prophylactic (ROTEM guided)	Beriplex	No difference CFC (7.1%)/on-CFC group (4.5%)	No data	No data
Shakowski and MacLaren[60]	Retrospective study	2016	70 (PCC = 27/rFVIIa = 43)	Prophylactic	No data	11.1% (PCC); 14% (rFVIIa)	No data	No difference PCC/rFVIIa in major bleeding
Scott et al.[61]	Retrospective study	2017	41 (LD = 44%)	Prophylactic/bleeding	No data	0%	No difference LD versus non-LD	No data

Abbreviations: CFC, coagulation factor concentrates; CTP, child turcotte pough; FFP, fresh frozen plasma, INR, international normalised ratio; LD, liver disease; PCC, prothrombin complex concentrates; TE, thromboembolic events.

Cautious use may therefore be warranted in light of thrombotic risk in these acutely ill patients. Conservative dosage may have to be applied. This is an important finding: high dosing could be tempting when attempting to correct PT values.

A similar spiking experiment has been done by Werner et al.[28] in plasma from 20 paediatric patients with end stage liver disease before and during LT. Age-matched controls were included. They also demonstrated that FFP had little effect on TGA in controls and patients before LT. Adding FFP to plasma samples during LT significantly increased ETP, although not to physiological levels. PCC remarkably enhanced thrombin generation in both controls and pre-LT patients. During LT an intensified response was seen which inversely correlated with pre-LT factor II.

Taking into account the high in vitro impact of PCC seen in the aforementioned studies, dose adjustments could be necessary when administering PCC in CLD patients to lower thromboembolic risk. However, these in vitro studies do not reflect the patient's characteristics possibly affecting pharmacokinetics.

3.2 | Data on the current PCC use

Table 1 summarises the studies published on PCC use in CLD.

Older papers already demonstrated the ability of PCC to improve the PT, although its effect was suboptimal compared to non-CLD patients.[29–31] However, clear data on improvement of bleeding or blood loss are not available. Because of improved surgical and anesthesiologic techniques, transfusion requirements in LT and other major surgery have greatly diminished over the past two decades. In a study on 500 liver transplantations, 79.6% did not require transfusion of blood products.[32] Several authors demonstrated reduced survival after blood product transfusion.[33,34]

In the following paragraphs, we will review the literature concerning the use of PCC in a prophylactic context (before interventions, surgery) and in an active bleeding context. We will also discuss thromboembolic risk associated with PCC.

3.2.1 | Preoperative/procedural management

In a retrospective, single-center study 194 episodes of PCC administration (105 patients with chronic and acute liver disease) were analysed for improvement of PT.[35] Indications were treatment of bleeding and preprocedural prophylaxis with a variety of different interventions (e.g. TIPS, paracentesis, thoracocentesis, surgery and LT). Improved PT was demonstrated. The design of this study did not allow for information on reduction of administration of blood products. Fibrinogen concentrate or cryoprecipitate were concomitantly used. INR, not representative of rebalanced haemostasis, was used as an outcome measure.

Lesmana et al.[36] evaluated PCC use in various invasive gastrointestinal and hepatobiliary procedures in a small prospective study ($n = 30$) including 14 patients with cirrhosis (46.7%). They concluded improvement of INR and clinical efficacy (control and prevention of bleeding complications). However, no control arm was included. Similarly, Kwon et al.[37] reported improvement of INR and reduction of blood product use in patients receiving PCC ($n = 15$) compared to patients receiving FFP ($n = 15$). Patients underwent an invasive intervention or a minor surgical procedure. Again, no placebo group was included in this study, which makes conclusions regarding clinical efficacy difficult.

In a small cohort of LT recipients ($n = 39$), a retrospective comparison between a group receiving prophylactic PCC ($n = 25$) and a group without prophylactic PCC ($n = 14$) was made. The authors concluded that prophylactic PCC could reduce bleeding and transfusion requirements in LT.[38] Similarly, Srivastava et al.,[39] compared 60 LT patients who received PCC at induction with 60 propensity score-matched LT patients receiving FFP at induction. The administration of PCC and FFP was guided by TEG ($R > 10$). They reported significantly less RBC and FFP administration in the PCC group. Once more, no placebo control arm was included, making it difficult to draw conclusions.

A prospective study (the PROTON trial) was set up in 2013 to investigate the utility of PCC in patients undergoing LT.[40] Adult patients with an INR >1.5, listed for transplantation, and without a history of hemorrhagic or thrombotic disease were included. The study comprised both a PCC and a placebo arm. However, the study never included the planned number of patients.

Different guidelines exist for periprocedural management of CLD patients. The AASLD guidelines state that efficacy and safety data are lacking for the use of PCC in liver disease.[16] PCC use risks overcorrection to a hypercoagulable state. In accordance, the AGA 2019 guidance document says that 4-factor PCC are an attractive low-volume therapeutic to rebalance a disturbed hemostatic system. However, dosage guidance is based on INR, which is problematic, and published experience in liver disease is limited.[27] They also state that for minor interventions (dental extraction, paracentesis, diagnostic endoscopy, central line placement and cardiac catheterization) no prophylactic prohemostatic treatment is generally needed. In the recent AGA 2021 update,[41] no recommendation is made for PCC use. They recommend against blood product use (e.g. FFP and platelets) for stable cirrhosis patients undergoing common gastrointestinal procedures. In patients with severe coagulatopathy decisions about prophylactic blood product use should include discussions about potential benefits and risks in consultation with a haematologist. The International Society on Thrombosis and Hemostasis Scientific and Standardization Committee (ISTH SSC) guidance document[42] state that PCC should be avoided in the periprocedural setting. The updated EASL guidelines,[17] discourage the use of PCC to lower clinically relevant procedural bleeding. Studies are needed to address safety and efficacy of PCC and to assess their optimal dosage in this indication.

3.2.2 | Spontaneous/procedural bleeding

Variceal bleeding in cirrhotic patients is mainly due to high portal pressure and not directly correlated with hemostatic abnormalities.[43]

Standard approaches to manage portal hypertension, endoscopic treatment and a restrictive transfusion policy are recommended. In decompensated patients non-variceal bleeding also remains a frequent clinical problem.[44] Only a minority of bleeding events are solely due to hemostatic failure.[45] LT still poses a major hemostatic challenge possibly requiring transfusion of blood products.

In the study by Drebes et al,[35] treatment of varied categories of active and recent bleeding was studied. PCC did have an impact on INR but this study did not allow for information on clinical improvement of bleeding.

A small retrospective study included 51 bleeding patients of which 80% had cirrhosis. No data were provided on the nature of bleeding in these patients. PCC dosing was based on the NAC (Canadian national advisory committee) recommendations. The authors concluded a low control of bleeding with PCC and an absence of correlation between INR correction and hemorrhagic control.[46]

The use of a single dose of PCC was also studied in a retrospective study including patients with cirrhosis and intracranial haemorrhage.[47] A stable head CT at 24 h was the outcome measure. Of 59 patients 21 received PCC. No difference was seen in the rate of stable head CT. Mortality was higher in the PCC group. PCC group patients had more severe cirrhosis and higher INR. Results could have been impacted by a treatment bias in this study.

Hartmann et al.[48] did a retrospective data analysis on 372 liver transplantations. The administration of coagulation factor concentrates was guided by a ROTEM based algorithm, published previously.[49] PCC were only used in patients with massive diffuse bleeding and pathologic ROTEM parameters. No FFP was administered. Of the 372 patients undergoing liver transplantation, 50.2% received fibrinogen concentrate, 18.8% PCC, 21.2% platelet concentrates, 4.5% tranexamic acid and 59.4% red blood cell concentrates. The administration of fibrinogen and PCC was not independently correlated with mortality. Infused volume, MELD score and platelet concentrates were independent predictors of mortality. A more recently published ROTEM-based algorithm[50] suggests a dose of 10–15 IU/kg body weight PCC in diffusely bleeding patients. They also consider concomitant administration of antithrombin in patients with a high thromboembolic risk.

Zamper et al.[51] designed a LT before-after study comparing an interventional group with VET based administration of fibrinogen and PCC with a retrospective control group (based on conventional coagulation tests, no fibrinogen/PCC). The intervention group comprised of 54 patients and the control group of 183 patients (46 and 89 after propensity score-matching). Of 54 patients only 6 received PCC based on diffuse bleeding and an EXTEM clotting time > 80s. Overall the authors saw a decrease in allogeneic blood product (RBC and FFP) use in the interventional group. Interestingly, they also saw a decline in upper digestive haemorrhage, possibly reflecting a decrease in volume overload.

Colavecchia et al. studied the impact of factor concentrates on blood product use in patients undergoing LT ($n = 212$; PCC = 39). In the presence of major and/or microvascular bleeding during LT and based on other elements (routine haemostasis, VET) the clinician decided if blood products (RBC, FFP or platelets) and/or coagulation factors (fibrinogen, PCC) were warranted. No standard protocol was followed. They did not demonstrate lower blood product administration in patients treated with PCC and fibrinogen concentrate compared to patients not receiving PCC/fibrinogen concentrate.[52] However, a treatment bias could have been present: PCC/fibrinogen concentrate use in patients with more refractory bleeding.

The Liver Intensive Care Group Europe (LICAGE) guidelines on perioperative coagulation management in LT recommends to consider the use of PCC in bleeding patients once fibrinogen and platelets have been replaced and fibrinolysis is excluded. They also state that more data are needed on safety and efficacy of PCC in LT.[53] As already mentioned, Gorlinger et al designed a ROTEM-guided algorithm for the management of bleeding in patients undergoing LT.[50] In this algorithm, PCC are only administered in diffusely bleeding patients with pathological ROTEM parameters. VET can have a role in guiding PCC administration but currently lack validated target levels.[27]

3.3 | Thromboembolic risk of PCC

A review of the literature evaluating the overall safety of four-factor PCC concludes a fairly low thrombotic risk in patients without underlying risk factors.[54] Thrombogenicity of PCC has greatly diminished in today's PCC formulations compared to historic preparations. The main determinant of thrombogenicity in PCC is thought to be prothrombin which has the longest half-life.[55]

Case reports have been published describing the development of disseminated intravascular coagulation after PCC use in decompensated cirrhotic patients.[56,57] A PCC-product not containing anticoagulant factors, was used in one of those two reports.

Tischendorf et al. retrospectively evaluated 347 patients with cirrhosis that received PCC for the prevention or treatment of bleeding. In a 4-week long period after PCC administration they found 19 patients or 5.5% with a thromboembolic event.[58] Richard-Carpentier and Rioux-Masse[46] showed a similar thromboembolic event rate (6%). Drebes et al did not report an excess of thromboembolic events (3% of patients) for a median dose of 22 IU/kg.[35] A retrospective study including 266 patients who underwent orthotopic LT did not see a significant difference in thromboembolic events between groups receiving PCC or not (ROTEM-guided).[59] In three small retrospective CLD cohorts ($n = 70$; $n = 31$ and $n = 41$), no significant difference between factor VIIa and PCC was demonstrated in thrombotic and bleeding events[60] and no excess thromboembolic event rate (3.2%; 0%) was seen.[31,61] Srivastava et al.[39] did not report any thromboembolic events in a retrospective study including 262 LT patients of which 60 received PCC.

Thromboembolic events could be related to high or repeated doses of PCC. In the previous studies the dose of PCC was predominantly based on vitamin K antagonist dosing taking into account patient weight and INR (information provided with the product used; based on FIX content). No guidelines exist on PCC dosing in CLD patients.

4 | CONCLUSION

Only limited evidence suggests that PCC diminish allogeneic blood product administration in a variety of procedures, LT or other major surgery and are beneficial in bleeding management in CLD patients. The existing evidence relies on retrospective studies lacking power and a control group to prove clinical efficacy. These studies are also very heterogeneous regarding population studied and prophylactic/bleeding protocols used. Despite guidance documents arguing against FFP prophylaxis, there is an on-going urge to correct PT/INR. In carefully selected cases and after weighing risks and benefits, PCC could be an attractive alternative due to the lack of volume overload. In a therapeutic context, where other measures to stop the bleeding were not sufficient, PCC could also be considered. PCC administration is associated with a risk of thromboembolic events. This risk does not seem to be excessive in CLD patients compared to other patient groups (3%–6%). Disseminated intravascular coagulation has been described in decompensated cirrhotic patients.

Randomised controlled trials assessing both prophylactic and bleeding context are needed to evaluate the safety and efficacy of PCC administration in CLD patients. However, patient inclusion will be challenging in these studies.

AUTHOR CONTRIBUTIONS

Véronique Deneys and Marie-Astrid van Dievoet developed the initial idea for this review, which was further refined with Xavier Stephenne, Madeleine Rousseaux, Ton Lisman and Cedric Hermans. Marie-Astrid van Dievoet did the writing of this review with support of all other authors. All authors approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest

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