

## ORIGINAL ARTICLE

# Prophylactic fresh frozen plasma versus prothrombin complex concentrate for preprocedural management of the coagulopathy of liver disease: A systematic review

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## Abstract

**Background:** The optimal prophylactic preprocedural management of patients with coagulopathy due to liver disease is not known.

**Objectives:** Our objective was to compare the efficacy and safety of fresh frozen plasma (FFP) with prothrombin complex concentrate (PCC) in the preprocedural management of patients with coagulopathy of liver disease.

**Methods:** We conducted a systematic review to examine published evidence regarding treatment with FFP or PCC in adults with coagulopathy of liver disease undergoing an invasive procedure. Direct comparisons and single-arm studies were eligible. Efficacy outcomes included major bleeding, mortality, and correction of prothrombin time (PT) and/or international normalized ratio (INR). Safety outcomes included thrombosis and transfusion-related complications.

**Results:** A total of 95 articles were identified for full-text review. Nine studies were eligible and included in the review. No randomized trials comparing FFP versus PCC were identified. Only two studies directly compared FFP versus PCC. In these studies, PCC appeared to result in higher rates of correction of PT/INR, but bleeding outcomes were not different. In the single-arm studies, bleeding events appeared low overall. Volume overload was the most common recorded adverse event in patients receiving FFP. Thromboembolic events occurred rarely, but exclusively in the PCC group. Due to heterogeneity in study definitions and bias, meta-analysis was not possible. Our study found no evidence to favor a specific product over another.

**Conclusions:** Insufficient data exist on the effects of FFP versus PCC administration before invasive procedures in patients with coagulopathy of liver disease to make conclusions with respect to relative efficacy or safety.

## KEYWORDS

blood coagulation factors, hemorrhage, international normalized ratio, liver diseases, prothrombin time

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## Essentials

- The best strategy to reduce bleeding with procedures in patients with liver disease is unknown.
- We reviewed preprocedural fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) use.
- There is limited evidence for either preprocedural FFP or PCC in patients with liver disease.
- Clinical trials of preprocedural management in patients with liver disease are needed.

## 1 | INTRODUCTION

Patients with liver disease can develop a wide range of hemostatic abnormalities.<sup>1</sup> The coagulopathy of liver disease can be associated with an increased risk of thrombosis or with an elevated bleeding risk, but the risk is not directly related to prothrombin time (PT) and/or international normalized ratio (INR) elevation.<sup>2-5</sup> How to manage the coagulopathy before invasive procedures is controversial.<sup>6</sup> Patients with elevated PT/INR values often receive fresh frozen plasma (FFP) infusions. However, FFP infusions may cause adverse events, including volume overload and worsening portal hypertension, and may not reduce bleeding outcomes.<sup>7-10</sup> Accordingly, the American Association for the Study of Liver Diseases and American Gastroenterological Association recommend against the routine use of FFP for minor procedures such as paracentesis to correct an elevated PT/INR in a patient with liver disease.<sup>11,12</sup> Prothrombin complex concentrate (PCC) has potential benefits over FFP, including smaller volume and decreased risk of transfusion-related adverse events.<sup>13-17</sup> Furthermore, in patients with trauma-induced coagulopathy, a randomized controlled trial comparing FFP to clotting factor concentrates (four-factor [4F]-PCC or fibrinogen) was stopped early due to lack of safety and efficacy in the FFP arm. More patients in the FFP arm required other “rescue therapies” for hemostasis and massive transfusions than in the clotting factor concentrates arm.<sup>18</sup> This randomized controlled trial raises questions as to the efficacy of FFP in other patient populations. However, particularly in patients with coagulopathies not due to vitamin K antagonist therapy, PCCs may be associated with a risk of thrombosis, presumably due to imbalances in circulating procoagulant and anticoagulant proteins.<sup>19</sup> Data regarding their safety and efficacy in the preprocedural setting for hepatic coagulopathy are limited.

We conducted a systematic review of published evidence on either FFP or PCC given to adults with liver disease before invasive procedures or surgeries. Our objective was to compare the hemostatic efficacy and safety of FFP versus PCC.

## 2 | METHODS

### 2.1 | Search strategy

We performed a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>20</sup> Before conducting the study, we created a protocol specifying inclusion/exclusion criteria and outcome

measures. Institutional review board approval was not necessary for this review of published literature.

We searched PubMed, Embase, and Cochrane from inception to January 31, 2021, for studies in the English language. A librarian trained in literature search assisted in the design of search terms. The search was limited to humans and included the following specific search terms: (((liver dysfunction OR cirrhosis OR liver failure OR coagulopathy)) AND (“Plasma”[Mesh] OR fresh frozen plasma OR fresh-frozen plasma OR Plasmas[tiab] OR Plasma[tiab] OR FFP[tiab])) AND (“Factor IX”[Mesh] OR “Factor IX” OR “Factor Nine” OR “Factor 9” OR “prothrombin complex concentrate” OR PCC). References of included studies and narrative reviews as well as expert reviewer suggestions were evaluated to identify additional studies that met eligibility criteria. An additional reference beyond the end date of the search was added based on expert suggestion.

### 2.2 | Study selection

Two authors (CE, AP) independently reviewed eligible studies based on title and abstract. Articles were further reviewed if they included clinical trials or observational studies of adults with coagulopathy of liver disease who were treated with FFP or PCC before an invasive procedure. Our initial intent was to include only studies that directly compared FFP to PCC. However, due to a paucity of such studies, we included single-arm studies as well. Abstract-only publications were included. Articles that did not report outcomes of bleeding were excluded, as were case reports and studies in which FFP or PCC was given for reversal of anticoagulation or for active bleeding rather than for preoperative management of hepatic coagulopathy. Articles were reviewed by two study authors independently. If there was uncertainty or disagreement between reviewers, a third author (AC) was consulted.

### 2.3 | Outcomes and data collection

The reviewers used a standardized data collection form to collect the following variables from eligible studies: setting, study design, number of participants, intervention (FFP and/or PCC) and dose, demographics, Model for End-Stage Liver Disease and Child-Pugh scores, type of procedure, baseline INR, procedural bleeding, postintervention INR, and adverse events including thrombosis and transfusion-related complications. Disagreements between reviewers were resolved by discussion and consensus.

## 2.4 | Quality appraisal

Quality of eligible studies was assessed through the Risk of Bias in Nonrandomized Studies of Interventions tool that is used by Cochrane Reviews.<sup>21,22</sup>

## 2.5 | Statistical analysis

Our initial plan was to pool data from studies to report on the proportion who experienced major bleeding events and/or INR correction. However, due to heterogeneity in study definitions and bias, we determined that meta-analysis was not appropriate. Study data were reported as mean ( $\pm$ SD) or median (range) when available.

# 3 | RESULTS

## 3.1 | Study selection

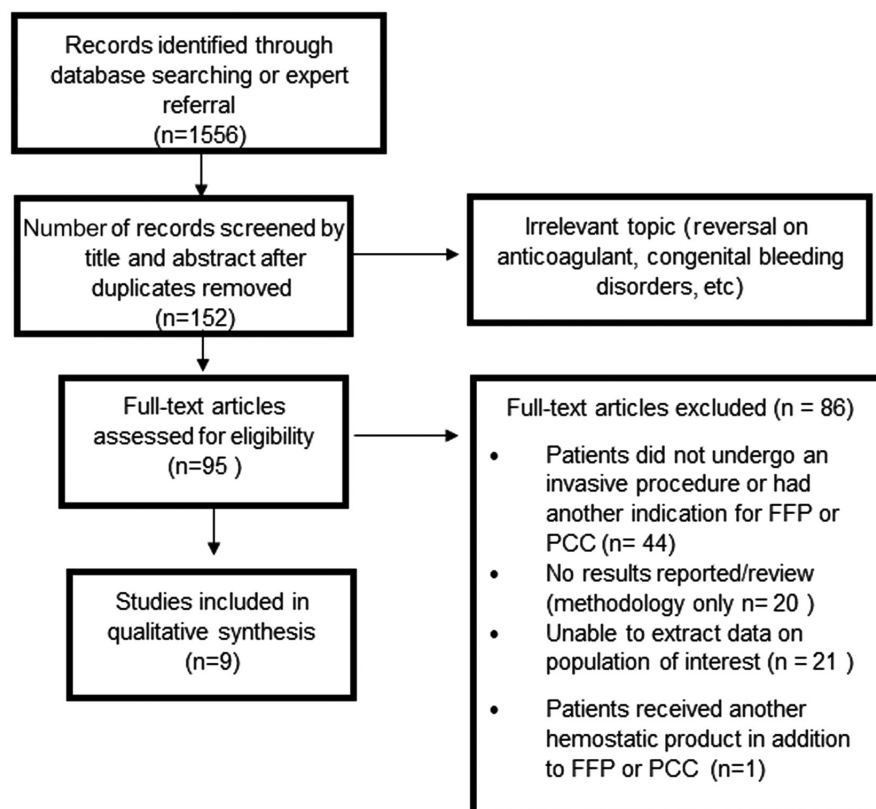
Following removal of duplicates, our search yielded 1514 unique references. After screening title and abstract, the full text of 95 articles was reviewed. Of these, 86 articles were excluded because patients did not undergo an invasive procedure or had another indication for FFP or PCC ( $n = 44$ ), patients received another hemostatic product in addition to FFP or PCC ( $n = 1$ ), bleeding outcomes were not reported ( $n = 21$ ), or the papers were review or methodology articles ( $n = 20$ ), leaving nine eligible studies (Figure 1).

## 3.2 | Study characteristics

Study characteristics are summarized in Table 1. Two of the nine eligible studies included both a PCC and FFP group.<sup>23,24</sup> The others were single-arm studies of FFP ( $n = 4$ )<sup>25-28</sup> or PCC ( $n = 2$ ).<sup>29,30</sup> In one trial, patients could receive prothrombin complex concentrate and/or fibrinogen based on a rotational thromboelastometry (ROTEM) algorithm.<sup>31</sup> Seven studies were observational, one was a nonrandomized interventional trial of PCC versus FFP,<sup>23</sup> and one was a randomized controlled trial comparing solvent-treated versus standard FFP.<sup>25</sup> Studies varied with respect to patient population, dose of PCC or FFP, and type of procedure.

## 3.3 | Study outcomes

Table 2 summarizes the study outcomes. Two studies directly compared FFP versus PCC administration before a procedure in patients with liver disease.<sup>23,24</sup> Gazzard et al<sup>23</sup> performed a nonrandomized trial of 15 patients who received FFP and 15 patients who received 4F-PCC. They found that the PT normalized in a higher percentage of patients in the PCC (46%) versus FFP group (20%). There were no bleeding events in either group. In a more recent study, Kwon et al<sup>24</sup> retrospectively compared outcomes of patients with liver disease receiving FFP versus 4F-PCC for procedures or minor surgical interventions. Mean preprocedure INR was  $2.5 \pm 0.8$  in the FFP group and improved to  $2.2 \pm 0.7$  (4 hours after intervention). In the 4F-PCC group, the mean preprocedure INR was  $2.9 \pm 1.6$  with improvement



**FIGURE 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study inclusion and exclusion. Abbreviations: FFP, fresh frozen plasma; PCC, prothrombin complex concentrate

**TABLE 1** Study design, population, and intervention

Study publication (year)	Setting	Study design	Study population, N	Age, y, mean <sup>a</sup>	Sex, % male	Products and dosing	Procedure
Gazzard <sup>23</sup> (1975)	Single-center, UK hospital, inpatients	Nonrandomized controlled trial (first 15 patients received and next 15 patients received PCC)	N = 30 (15 FFP, 15 PCC) Chronic liver disease with prothrombin time prolonged $\geq 4$ s	49.3 FFP group 50 PCC group	NR	FFP (600 mL over 30 min followed by 300 mL 6 h later) 4F-PCC (2000 units)	Liver biopsy
Kwon <sup>24</sup> (2016)	Single-center, US hospital, critical care unit	Retrospective Cohort	N = 30 (15 FFP, 15 PCC) Hepatic impairment, INR $\geq 1.5$	50.1 FFP group 49 PCC group	67 FFP 47 PCC	FFP (Mean 1.1 U $\pm$ 0.5 units) 4F-PCC (mean, 2523 $\pm$ 861 units)	Invasive procedure or minor surgery
Williamson <sup>25</sup> (2002)	Multiple centers, UK hospitals	Randomized controlled trial (not comparing FFP vs PCC)	N = 24 Coagulation deficits due to liver disease (13 undergoing liver transplant)	51 (median)	60	FFP (12–15 mL/kg)	Invasive procedures or liver transplant
von Meijenfeldt <sup>26</sup> (2020)	Single center, UK hospital	Prospective cohort	N = 19 with chronic liver disease and prolonged INR	50 (44–54)	47.3	FFP	Bronchoscopy, endoscopy, transjugular intrahepatic portosystemic shunt
Diaz <sup>27</sup> (abstract only) (2020)	Single-center, US hospital	Retrospective cohort	N = 102	NR	NR	FFP	Vascular access placement/removal, renal biopsy, transjugular liver biopsy
Lorenz <sup>30</sup> (2003)	Multicenter	Prospective	N = 18 underwent intervention/procedure	45 (median) <sup>b</sup>	68.1 <sup>b</sup>	4F-PCC (median, 1500 IU)	Bone marrow, lymph node biopsy, liver biopsy, pancreas biopsy, colon biopsy, operation on fracture of femur, endoscopic retrograde cholangiopancreatography
Parand <sup>29</sup> (2013)	Single-center, Iranian medical center	Case series	N = 9	18 (5.3)	55.6	4F-PCC 25 IU/kg	Surgery or biopsy
Ochi <sup>28</sup> (abstract only) (2021)	8 U.S. hospitals	Retrospective review between 2017 and 2019	N = 119	53.3 FFP	62.2 FFP	FFP (dosing NR)	NR
Kirchner <sup>31</sup> (2014) <sup>c</sup>	Single-center, German medical center	Retrospective review between 2009 and 2010	N = 266 (156 received CFC)	51.2 (10.4) CFC group	64 CFC	PCC 25 IU/kg if EXTEM $> 80$ s	Liver transplant

Abbreviations: UK, United Kingdom; 4F-PCC, four-factor prothrombin complex concentrate; CFC, coagulation factor concentrate; EXTEM, extrinsic thromboelastometry; FFP, fresh frozen plasma; INR, international normalized ratio; NR, not reported; PCC, prothrombin complex concentrate.

<sup>a</sup>Mean age listed unless noted otherwise. Mean (standard deviation) listed if available or median (Interquartile range).

<sup>b</sup>Reflects total study population, which included three patients who received PCC for bleeding.

<sup>c</sup>Study assessed CFC administration based on rotational thromboelastometry results, which could include fibrinogen and/or PCC.

to  $1.6 \pm 0.9$  (4 h after intervention). There was a similar incidence of both major (20% FFP vs 27% PCC) and minor bleeding (80% FFP vs 72% PCC). There was a higher incidence of volume overload in the FFP group (93% vs 40%;  $p = 0.02$ ). There was one (6.6%) thromboembolic event in the PCC group.

Four studies evaluated FFP alone.<sup>25-28</sup> Williamson et al<sup>25</sup> randomly assigned 49 patients with liver disease and an elevated INR to treatment with FFP or solvent/detergent-treated plasma before an invasive procedure or liver transplant. Patients in the FFP arm who underwent an invasive procedure (other than liver biopsy such as liver transplantation) had a preintervention median INR of 2.0 (range, 1.3-3.1) with improvement to 1.8 (1.4-2.4) following FFP administration. There were no bleeding events. Patients in the FFP arm undergoing liver transplant had a median INR of 1.5, which did not improve following FFP administration (INR following FFP median, 1.6; range, 1.0-3.5). One patient in the liver transplant group had a bleeding event that required return to the operating room, and one patient had volume overload. Von Meijenfeldt et al<sup>26</sup> performed a prospective cohort study of FFP administration in 19 patients with coagulopathy due to liver disease before undergoing procedures. All patients underwent low or intermediate risk procedures as defined by expert consensus. The dose of FFP was determined by the treating clinician. There were no bleeding events or adverse events. Diaz et al<sup>27</sup> described a retrospective cohort from a single institution of 102 patients with cirrhosis receiving FFP before undergoing vascular access procedures or biopsies. Seven (6.9%) experienced bleeding events, 14 (13.7%) had volume overload, and 1 (1.0%) experienced infection following FFP. Ochi et al<sup>28</sup> described a retrospective multicenter study of 537 patients with coagulopathy secondary to liver disease who were undergoing elective or emergent procedures. A total of 119 patients received FFP before the procedure; 5.0% (6/119) had procedural-related bleeding.

Two studies assessed PCC only.<sup>29,30</sup> Parand et al<sup>29</sup> reported a case series of nine patients with liver disease and an elevated INR, who were scheduled for an unspecified biopsy or other procedure. All were treated with 25 IU/kg of 4F-PCC. Mean pretreatment INR was  $4.3 \pm 0.4$  and improved to a mean INR of  $1.3 \pm 0.1$  following 4F-PCC administration. No bleeding events were reported. Lorenz et al<sup>30</sup> reported a prospective, multicenter study of 4F-PCC in 22 patients with liver disease, 18 of whom received 4F-PCC for a procedure or surgery. The dose and duration of PCC treatment was determined by the clinician. No abnormal bleeding occurred in the 18 patients undergoing procedures. No adverse events were reported.

In one study, patients received coagulation factor concentrate (CFC), consisting of 4F-PCC and/or fibrinogen concentrate based on a ROTEM-based algorithm. Kirchner et al<sup>31</sup> reported on 266 patients undergoing liver transplantation and compared those who received CFC ( $n = 156$ ) to those who did not receive any CFC (non-CFC group,  $n = 110$ ). Additional hemostatic therapy was given on the basis of intraoperative ROTEM results. Patients received 25 IU/kg of PCC if they had an extrinsic thromboelastometry clotting time of more than 80 seconds and were bleeding. If patients continued to bleed

and had a prolonged intrinsic thromboelastometry  $\geq 240$  seconds, they received FFP at a dose between 15 and 20 mL/kg. In this cohort, postoperative bleeding occurred in 28 patients (10.5%), but postoperative bleeding outcomes were not compared between the CFC and non-CFC group. There were no significant differences in adverse events between the groups, with 7.05% (11/156) patients in the CFC group experiencing thrombosis, embolism, or ischemia versus 4.5% (5/110) in the non-CFC group.

### 3.4 | Heterogeneity and evidence synthesis

Due to substantial heterogeneity among eligible studies with respect to study design, patient population, types of procedures, FFP/PCC dosing, and outcomes, we determined that meta-analysis was not appropriate.

### 3.5 | Quality appraisal

Risk of bias among eligible studies is summarized in Table 3. All nine studies were judged to be at overall serious risk of bias. Major sources of bias included observational or nonrandomized design, a lack of standardized outcome definitions (eg, six of nine studies did not provide a definition of bleeding), and a lack of independent adjudication of study outcomes. With respect to the outcome of PT/INR reduction, only one study<sup>24</sup> defined when the postinfusion PT/INR was drawn relative to PCC/FFP administration.

## 4 | DISCUSSION

We conducted a systematic review to compare the effectiveness and safety of prophylactic FFP versus PCC in patients with hepatic coagulopathy who require an invasive procedure. Our findings highlight the paucity and poor quality of evidence available to address this common clinical scenario. Given the significant heterogeneity among studies, meta-analysis was not possible. Our study found no clear evidence to favor one product over another.

In patients who require urgent vitamin K antagonist reversal, PCC results in more rapid PT/INR reduction, less volume overload, and lower all-cause mortality than FFP.<sup>32-34</sup> A systematic review of randomized controlled trials evaluating the efficacy of FFP for a wide range of indications suggested that there was no consistent evidence of benefit for prophylactic or therapeutic use across all indications, including liver disease.<sup>35</sup> The studies in our systematic review that evaluated FFP found only modest reductions in PT/INR in patients with coagulopathy of liver disease. Despite theoretical benefits based on less volume, the use of PCC has not been well defined in patients with coagulopathy of liver disease regardless of indication (bleeding or before surgery/procedure). In our review, PCC appeared to correct the PT/INR to a greater degree than FFP. However, similar rates of major and minor bleeding were observed in

TABLE 2 Study outcomes

Study (publication year)	FFP group: PT/INR Preintervention	PCC group: PT/INR Preintervention	FFP group: PT/INR Postintervention, n (%)	PCC group: PT/INR Postintervention, n (%)	Bleeding definition	FFP group: bleeding events, n (%)	PCC group: bleeding events, n (%)	FFP group: adverse events, <sup>a</sup> n (%)	PCC group: Adverse events, <sup>a</sup> n (%)
Gazzard <sup>23</sup> (1975)	NR	NR	3 (20) corrected PT to normal range	7 (46) corrected PT to normal range	NR	0 (0)	0 (0%)	1 hepatitis B antigen positive	1 hepatitis B antigen positive 2 (13) superficial thrombophlebitis
Kwon <sup>24</sup> (2016)	Mean INR, 2.5 ± 0.8 (4 h before procedure)	Mean INR, 2.9 ± 1.6 (4 h before procedure)	Mean INR, 2.2 ± 0.7 (4 h postintervention) 2.7 ± 1.2 (12 h postintervention) 2.5 ± 0.7 (24 h postintervention)	Mean INR, 1.6 ± 0.9 (4 h postintervention) 2.8 ± 1.4 (12 h postintervention) 3.0 ± 1.7 (24 h postintervention)	<b>Minor</b> —notation of bleeding associated with the procedure in the medical record <b>Major</b> —defined as minor bleeding and the need for a transfusion of packed red blood cells during or after the procedure)	Minor—12 (80) Major—3 (20)	Minor—11 (72) Major—4 (27)	5 (33) Fever 14 (93) Fluid overload 4 (27) TRALI 0 (0) thrombosis	4 (27) Fever 6 (40) Fluid overload 0 (0) 1 (7) Thrombosis
Williamson <sup>25</sup> (2002)	Median INR 2.0 (nontransplant) Median INR, 1.5 (liver transplant)	NA	Median INR, 1.8 (1.4–2.4) (nontransplant) Median INR 1.6 (1.0–3.5) (liver transplant)	NA	NR	0 (0) non-liver transplant 1 (4) liver transplant patient requiring return to OR	NA	1 (4) fluid overload	NA
von Meijenfeldt <sup>26</sup> (2020)	Median INR, 2.0 (1.8–2.4)	NA	Median INR, 1.68 (1.51–1.77)	NA	NR	0 (0)	NA	0	NA
Diaz <sup>27</sup> (abstract only) (2020)	Mean INR, 3.0	NA	Mean INR, 2.4 <sup>b</sup>	NA	Persistent oozing or hematoma requiring transfusions	7 (6.9)	NA	14 (13.7) fluid overload 1 (1) infection	NA
Lorenz <sup>30</sup> (2003)	NA	NR	NA	NR	Assessed by treating physician using a standard scale: “very good” (normal hemostasis); “satisfactory” (mildly delayed but still efficient); “doubtful” (moderately delayed hemostasis, eg, moderate but controllable bleeding); “none” (severely delayed hemostasis uncontrollable bleeding); and “no judgment possible”	NA	0 (no increased or prolonged bleeding noted in procedure group)	NA	3 (13.6) hepatitis A positive <sup>b</sup>
Parand <sup>29</sup> (2013)	NA	INR, 4.3 ± 0.4	NA	INR, 1.3 ± 0.1	NR	NA	0 (0)	NA	0 (0) thrombosis
Ochi <sup>28</sup> (2021)	Mean INR, 2.15	NA	NR	NA	NR	6 (5)	NA	NR	NA

TABLE 2 (Continued)

Study (publication year)	FFP group: PT/INR Preintervention	PCC group: PT/INR Preintervention	FFP group: PT/INR Postintervention, n (%)	PCC group: PT/INR Postintervention, n (%)	Bleeding definition	FFP group: bleeding events, n (%)	PCC group: bleeding events, n (%)	FFP group: adverse events, <sup>a</sup> n (%)	PCC group: Adverse events, <sup>a</sup> n (%)
Kirchner <sup>31</sup> (2014) <sup>c</sup>	NA	NR	NA	POD 1: INR, 2.02 ± 0.5 POD 7: INR, 1.09 ± 0.19 POD, 14 1.07 ± 0.13	NR	NA	NR	NA	7 (4.5) thrombotic, thromboembolic, and ischemic

Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; NA, not applicable; NR, not reported; OR, operating room; PCC, prothrombin complex concentrate; POD, postoperative day; PT, prothrombin time; TRALI, transfusion-related acute lung injury.

<sup>a</sup>Adverse events extracted included transfusion reactions, fluid overload, TRALI, fever, viral infections, and thrombosis. If adverse event not listed, it was not reported in the study.

<sup>b</sup>Adverse events were not reported separately for patients who received PCC for bleeding or for procedure. Adverse events include full cohort of 22 patients.

<sup>c</sup>Study assessed coagulation factor concentrate administration based on rotational thromboelastometry results, which could include fibrinogen and/or PCC.

the FFP and PCC groups (when these outcomes were reported), and there are concerns that PCC may be associated with an increased risk of avoidable thromboembolism in these patients.<sup>23,24</sup>

With respect to adverse events, as expected, fewer volume overload and transfusion reactions were reported in the PCC group compared to the FFP group.<sup>24</sup> The coagulopathy of liver disease is a prothrombotic state, and therefore monitoring for thrombotic complications when attempting to correct the coagulopathy is imperative.<sup>11</sup> Fortunately, in the included studies, thrombosis was uncommon, but all events occurred in patients who received PCC. The reported thromboembolic events in the majority of included studies were relatively minor (superficial thromboses or catheter-related thromboses). Kirchner et al reported rare pulmonary embolism and portal vein thrombosis in patients undergoing liver transplants receiving CFC based on ROTEM-results, but thrombotic events were similar to the non-CFC group.<sup>31</sup> No fatal adverse events were reported. Most of the studies included in our systematic review had a small sample size (<30 patients); thus, adverse event rates should be interpreted with caution. Larger studies are needed to better define the safety of these interventions. Our study was limited by a lack of high-quality published studies evaluating the use of preprocedural FFP or PCC in patients with liver coagulopathy. Eligible studies differed widely in their definition of bleeding events, with six of nine studies not stating how bleeding was defined. Randomized trials are needed to determine the optimal approach for preprocedural management of patients with hepatic coagulopathy with a focus on patient-important outcomes (eg, major bleeding) rather than on surrogate outcomes (eg, correction of PT/INR). Furthermore, the coagulopathy of liver disease is complex, and PT/INR, although commonly used to guide the administration of hemostatic agents, has been previously shown not to correlate with bleeding events.<sup>36</sup> Use of other laboratory techniques (eg, ROTEM or TEG) have been studied in the coagulopathy of liver disease and may be preferred for guiding hemostatic factor management rather than traditional PT/INR.<sup>37</sup> Multiple meta-analyses suggest a TEG or ROTEM-guided transfusion protocol decreased the use of blood products without a change in safety outcomes in patients with chronic liver disease.<sup>37,38</sup> A multicenter, randomized controlled trial (<http://www.trialregister.nl> NTR3174) to address the use of PCC versus placebo before liver transplantation began enrollment in 2012, but its status is currently unclear.<sup>39</sup> Additional questions remain on the optimal dosing of PCC as in vitro studies suggest that the coagulopathy of liver disease may require lower doses than that required for warfarin reversal.<sup>40</sup>

Strengths of this study include the use of current guidelines for conducting systemic reviews. Additionally, this study reveals an important gap in the literature.

## 5 | CONCLUSIONS

There is limited evidence regarding the best approach to manage hepatic coagulopathy in patients undergoing invasive procedures. Our systematic review synthesizes and highlights the limitations of

**TABLE 3** Risk of bias using Risk of Bias in Nonrandomized Studies of Interventions tool

Study	Bias due to confounding	Bias in selection of participants into the study	Bias due to missing data	Bias in measurement of outcomes	Bias due to deviations from intended interventions	Bias in selection of the reported result	Overall risk of bias
Gazzard <sup>23</sup>	Serious	Serious	Serious	Serious	Unclear	Serious	Serious
Kwon <sup>24</sup>	Serious	Serious	Serious	Unclear	Serious	Serious	Serious
Parand <sup>29</sup>	Serious	Serious	Unclear	Serious	Serious	Serious	Serious
Williamson <sup>25</sup>	Serious	Serious	Serious	Unclear	Serious	Serious	Serious
Lorenz <sup>30</sup>	Serious	Serious	Serious	Serious	Serious	Serious	Serious
von Meijenfeldt <sup>26</sup>	Serious	Low	Unclear	Serious	Low	Serious	Serious
Diaz <sup>27</sup>	Serious	Serious	Unclear	Serious	Serious	Serious	Serious
Ochi <sup>28</sup>	Serious	Serious	Unclear	Serious	Serious	Serious	Serious
Kirchner <sup>31</sup>	Serious	Serious	Unclear	Serious	Low	Serious	Serious

published evidence and underscores the need for trials on this commonly encountered clinical scenario.

## AUTHOR CONTRIBUTIONS

CRE contributed to the concept and design, data collection, analysis and/or interpretation of the data, critical writing or revising the intellectual content, and final approval of the version to be published. AMP contributed to data collection, analysis and/or interpretation of the data, critical writing or revising the intellectual content, and final approval of the version to be published. AC contributed to concept and design, analysis and/or interpretation of the data, critical writing or revising the intellectual content; and final approval of the version to be published. MC contributed to the concept and design, critical revision of manuscript, and final approval of the version to be published.

## RELATIONSHIP DISCLOSURE

AC has served as a consultant for Synergy; has received royalties from UpToDate; and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, and Spark. AMP receives research funding from Novo Nordisk and Sanofi Genzyme. In the past 24 months, MC has served as a consultant for Precision Biologicals, Hemostasis Reference Laboratory, and Syneos Health; and has prepared educational materials and/or participated in educational sessions for Pfizer, CSL Behring, and Diagnostica Stago. MC receives royalties from UpToDate and has relationships with various not-for-profit entities, including the American Society of Hematology.

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