Procedural bleeding risk, rather than conventional coagulation tests, predicts procedure related bleeding in cirrhosis

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Background Standard coagulation parameters are used to guide prophylactic blood product transfusion prior to invasive procedures in cirrhotic patients despite limited high-quality evidence.
Aims We aimed to describe coagulation parameters and prophylactic blood product use in cirrhotic patients having invasive procedures, and the influence of both on periprocedural bleeding.
Methods We conducted a cohort study of cirrhotic patients undergoing invasive procedures at a referral hospital. Procedures were classified into low or moderate-high bleeding risk. Prophylactic blood component was defined as fresh frozen plasma, cryoprecipitate or platelet transfusion prior to procedures. Univariate and multivariate logistic regression was performed to identify factors associated with procedure-related bleeding.
Results We identified 566 procedures in 233 cirrhotic patients. Prophylactic blood product was given before 16% of high-risk and 11% of low-risk procedures ($P=0.18$). Eight (8.3%) high-risk procedures were complicated by postprocedural bleeding, six of which occurred in patients without significant coagulopathy. The bleeding rate for low-risk procedures was 0.4%. For patients with international normalized ratio >1.5, platelet count <50 x 10^9/L, or both, the rate of bleeding was comparable between those given and not given prophylactic blood products (3.1 vs. 1.9%; $P=0.63$). After adjusting for age, sex, platelet count, international normalized ratio, acute kidney injury, sepsis and model of end-stage liver disease, the only factor significantly predicting procedure-related bleeding was the procedural bleeding risk category ($P<0.01$).
Conclusions Procedure-related bleeding in cirrhotic patients cannot be accurately predicted by INR or platelet count, nor prevented by blood component prophylaxis using these parameters. Procedure-related bleeding is best predicted by the bleeding risk status of procedures. Eur J Gastroenterol Hepatol 34: 192–199

Introduction

Liver cirrhosis has been considered a bleeding disorder due to its frequent association with prolonged prothrombin time, prolonged activated partial thromboplastin time (APTT), low fibrinogen levels and low platelet count. The standard of care has been to attempt to correct these parameters through the use of blood products such as fresh frozen plasma (FFP) and platelets before invasive procedures in order to prevent bleeding complications [1]. However, more recent guidelines have placed less emphasis on some of the coagulation parameters as a guide for preprocedural prophylaxis [2,3]. Studies looking at procedure-related bleeding rates in patients with cirrhosis are scarce, but report bleeding rates between 0.2 and 21% depending on the type of procedures included, and the patient and proceduralist characteristics and definition of bleeding used in the study [4].

Despite current transfusion practice, there is little evidence to suggest that abnormal international normalized ratio (INR), prothrombin time and APTT predicts procedure-related bleeding [5]. Although these parameters are frequently abnormal in patients with cirrhosis, thrombin generation is largely preserved [6]. Furthermore, the administration of pooled plasma to correct abnormal prothrombin time and APTT has minimal effect on thrombin generation [7]. In addition, the relationship between procedure-related bleeding and severe thrombocytopenia in cirrhosis is unclear. While some studies suggest the bleeding risk is higher with platelet count less than 50×10^9/L [8], others have shown no association between severe thrombocytopenia and bleeding risk [9,10] arguing that the underlying portal hypertension rather than the severe thrombocytopenia that predisposes to bleeding complications.

It is recognized that the reduction in pro-coagulant proteins and platelet number and function in cirrhosis, is accompanied by a reduction in the level of anticoagulant proteins (protein C, protein S and antithrombin) and activation of other prohemostatic mechanisms such as increased von Willebrand factor and factor VIII [11]. This has led to the concept of 're-balanced hemostasis' in cirrhosis [12]. This hemostatic balance is indeed delicate and patients with cirrhosis are at risk of both bleeding

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and thrombotic events [13]. While certain clinical practice guidelines now acknowledge that INR-based prophylactic FFP transfusion may have limited utility in patients with cirrhosis [2], patients with cirrhosis are still given prophylactic FFP and/or platelet transfusion before invasive procedures on the basis of their INR and platelet counts in an attempt to reduce periprocedural bleeding [14].

There is limited 'real-world' data available on the management of coagulopathy in patients with cirrhosis undergoing invasive procedures. Hence, we conducted a retrospective study of procedures performed on cirrhotic patients at a tertiary teaching hospital over a 1-year period, with the aims of assessing the use of prophylactic blood products and bleeding complications in (1) those with and without significant coagulopathy and (2) those who did and did not receive prophylactic blood products.

Materials and methods

Study design

This was a retrospective cohort study of all patients with cirrhosis undergoing invasive procedures at a large metropolitan tertiary care non-transplant center, between 1 January and 31 December 2017. Patients with cirrhosis were identified through a search of relevant International Classification of Diseases coding (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A617*). The diagnosis of cirrhosis was then verified, and all inpatient and outpatient procedures during this period were captured via a comprehensive search of electronic medical records. The study was approved by the local Human Research Ethics Committee, Melbourne, Australia, who waived the need for informed consent.

Study population

Participants were eligible for inclusion if they were 18 years or older and had a confirmed diagnosis of cirrhosis as defined either by liver biopsy and/or on the basis of the results of clinical, laboratory and imaging studies as described [15]. Emergency procedures performed to control initial active bleeding were excluded from the analysis.

Data collection

Data were extracted from the medical records and health information services from the time of admission or up to three months prior to the procedure to 28 days postprocedure on the following: (1) patient demographics including age and sex; (2) liver disease characteristics at the time of admission including etiology, diagnosis, cirrhosis status, Child-Pugh score, model of end-stage liver disease (MELD) score, presence of ascites, hepatic encephalopathy and hepatocellular carcinoma; (3) admission details including dates of admission and discharge, the reason for admission and presence of complications (e.g. sepsis, acute kidney injury (AKI); (4) procedure details including procedure type, indication, complications (bleeding and other), prophylactic blood product use and transfusion-related side effects and (5) in hospital and 28-day overall survival. The most recent hematology and biochemistry studies prior to the procedure were collected including hemoglobin, platelet count, INR, APTT, prothrombin time, fibrinogen, albumin, bilirubin, sodium and creatinine.

Definitions

Procedures were classified into low-risk and moderate to high-risk for bleeding based on previously published guidelines [1]. Prolonged INR was defined as an INR >1.5. Significant thrombocytopenia was defined as a platelet count $<50\times10^9$/L. Low fibrinogen was defined as fibrinogen <1.2 g/L. Significant coagulopathy was defined as a prolonged INR, significant thrombocytopenia, or both. Prophylactic blood component was defined as one or more units of FFP, cryoprecipitate or platelet transfusion given prior to the procedure. Postprocedural bleeding was defined as per the International Society of Thrombosis and Hemostasis [16] and included clinically significant bleeding with a ≥20 g/L drop in hemoglobin or requiring blood transfusion, readmission or intervention. Sepsis was defined according to sepsis-III criteria [17]. AKI was diagnosed as per the 2015 International Club of Ascites diagnostic criteria [18].

Statistical analysis

All statistical analyses were performed using STATA version 15.1. Continuous variables were assessed for normality and presented as means and standard deviations and analyzed by two-tailed *t*-test, or as medians and interquartile ranges with analysis performed by Mann–Whitney test depending on the distribution of the data. Binomial data were presented as proportions or percentages and compared using Chi-square or Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant in a two-sided test. Multivariate analysis was performed using logistic regression for categorical data.

Results

Study cohort characteristics

A total of 618 procedures were performed on 257 cirrhotic patients during the study period of 1 January–31 December 2017. Fifty-two procedures (8.4%) were excluded because of initial active bleeding leaving 566 procedures performed in 233 patients available for analysis. Of these, 96 (17%) were classified as high-risk and 470 (83%) as low-risk for bleeding. A detailed list of the procedures performed and their classification is available in Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A617*.

Patient characteristics according to bleeding risk

Baseline demographic and clinical characteristics of patients undergoing low- and high-risk procedures are shown in Table 1. The cohort had a mean age of 59 years (range 23–90 years) and was mostly male (73%) with the most common etiologies of the liver disease being alcohol (55%) and hepatitis C (34%). Comparison of clinical characteristics between low-risk and high-risk procedures revealed several notable differences. Low-risk procedures were more likely to be performed in patients with decompensated liver disease and/or renal impairment compared

Table 1. Baseline characteristics associated with low and high-risk procedures

	Low-risk procedures (*n* = 470)	High-risk procedures (*n* = 96)	All procedures (*n* = 566)	*P* value[c]
Age, years (mean ± SD)	59 ± 11.6	60 ± 13.1	59 ± 11.8	0.60
Female, *n* (%)	134 (29)	19 (20)	153 (27)	0.08
Etiology of liver disease[a], *n* (%)				
Alcohol	276 (59)	37 (39)	313 (55)	
Hepatitis C	160 (34)	33 (35)	193 (34)	
Non-alcoholic steatohepatitis	43 (9)	13 (14)	56 (10)	
Hepatitis B	21 (4)	13 (14)	34 (6)	
Primary biliary cholangitis	17 (4)	1 (1)	18 (3)	
Autoimmune	6 (1	5 (5)	11 (2)	
Primary sclerosing cholangitis	8 (2)	2 (2)	10 (2)	
Other/unknown	30 (17)	10 (11)	40 (7)	
Child-Pugh Score, *n* (%)				
A	66 (15)	55 (62)	130 (22)	0.001
B	218 (50)	23 (26)	241 (46)	
C	150 (35)	11 (12)	161 (31)	
MELD, median (IQR)	13 (11–17)	9 (7–13)	13 (10–16)	0.001
Laboratory parameters, median (IQR)				
Hemoglobin (g/L)	106 (91–123)	133 (113–143)	109 (93–129)	0.001
Platelet count ($\times 10^9$/L)	104 (73–152)	122 (78–158)	107 (74–153)	0.10
APTT (s)	38 (34–44)	32 (30–37)	37 (33–43)	0.001
Prothrombin time (s)	17 (16–19)	15 (1417)	17 (15–19)	0.001
INR	1.4 (1.2–1.6)	1.2 (1.1–1.4)	1.3 (1.2–1.5)	0.001
Fibrinogen (g/L)	3.1 (2.4–3.8)	3.3 (2.5–4.1)	3.1 (2.4–3.9)	0.08
Sodium (mmol/L)	136 (133–138)	138 (137–141)	136 (133–139)	0.001
Creatinine (mcmol/L)	73 (61–128)	69 (59–79)	72 (61–114)	0.004
Albumin (g/L)	30 (26–34)	33 (28–36)	30 (26–35)	0.002
Bilirubin (mcmol/L)	23 (14–40)	16 (11–32)	22 (14–38)	0.002
Significant coagulopathy, *n* (%)[b]				
Prolonged INR >1.5	118 (26)	13 (14)	131 (23)	0.01
Platelets < 50×10^9/L	45 (10)	6 (6)	51 (11)	0.33
INR > 1.5 or platelets < 50 $\times10^9$/L	151 (34)	18 (19)	167 (36)	0.01
Clinical features, *n* (%)				
Hepatic encephalopathy	175 (38)	6 (6)	181 (32)	0.001
Ascites	334 (72)	19 (20)	353 (62)	0.001
Renal impairment	103 (23)	4 (4)	107 (20)	0.001
Acute kidney injury	34 (8)	6 (6)	40 (7)	0.68
Active infection	76 (16)	14 (15)	90 (16)	0.73
Sepsis	29 (6)	8 (8)	3719 (73)	0.50
Hepatocellular carcinoma	47 (10)	49 (51)	96 (17)	0.001

APTT, activated partial thromboplastin time; INR, international normalized ratio; MELD, model of end-stage liver disease.
[a]109 participants had more than one etiology for their liver disease.
[b]Missing platelet count and/or INR values for 20 low-risk and 1 high-risk procedure(s).
[c]Compare low- and high-risk.

to high-risk procedures (Table 1). In addition, aside from the fibrinogen level, derangements in biochemical and coagulation parameters were more pronounced in the low-risk procedure cohort (Table 1). Overall, 169 procedures (31%) were performed in patients with a prolonged INR, significant thrombocytopenia, or both (i.e. significant coagulopathy). Fewer high-risk procedures ($n = 18$, 19%) were performed in patients with significant coagulopathy compared to those having low-risk procedures ($n = 151$, 34%) ($P = 0.005$) (Table 1).

Main study outcomes

Figures 1 and 2 summarize the main outcomes of the study. Prophylactic blood components were given prior to 66 procedures (12%); this included before 16% (15/96) of high-risk and 11% (51/470) of low-risk procedures ($P = 0.18$). Prophylactic blood product administration was guided by local hospital guidelines for procedures where these were available, with over 90% adherence. In patients with abnormal coagulation parameters, the only additional factors significantly predicting an increased likelihood of prophylaxis were low platelet count ($P = 0.01$), presence of AKI ($P < 0.01$), and high procedural bleeding risk category ($P < 0.01$) (see Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/EJGH/A617*).

Overall, clinically significant bleeding occurred in 10 of 566 (1.8%) procedures, including two low-risk (0.4%) and eight high-risk (8.3%) procedures. For patients with significant coagulopathy, the rate of postprocedural bleeding was comparable between those given and not given prophylactic blood products (3.1 vs. 1.9%, respectively; $P = 0.63$).

Factors predicting procedure-related bleeding

When considering both high and low bleeding risk procedures, univariate analysis showed no differences in age, sex, liver disease stage, laboratory parameters or blood component prophylaxis between patients with and without postprocedural bleeding (Table 2). The only characteristics that significantly predicted bleeding were the presence of sepsis ($P = 0.001$), AKI ($P = 0.006$) and high procedural bleeding risk category ($P = 0.001$). On multivariate analysis, adjusting for age, sex, platelet count, INR, renal function, active infection and MELD score, the only factor significantly predicting procedure-related bleeding was the procedural bleeding risk category ($P < 0.01$).

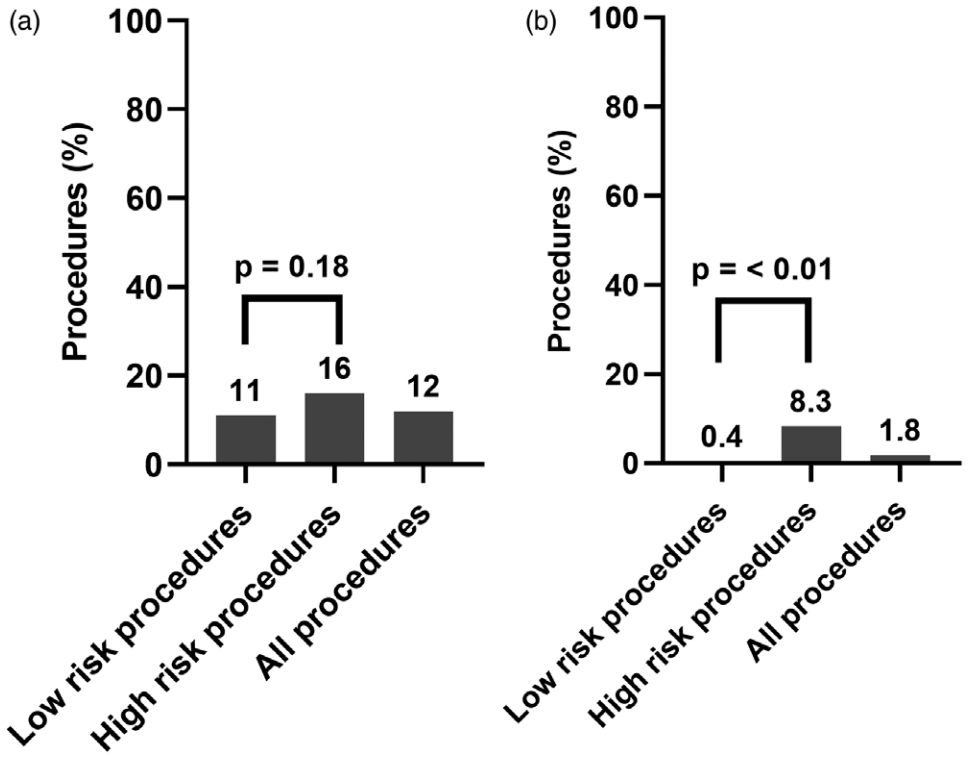

Fig. 1. Prophylactic blood product use (a) and clinically significant bleeding complications (b) in low-risk, high-risk and all procedures.

Table 2. Characteristics of patients with and without postprocedural bleeding

Variable	Postprocedural bleeding		
	Yes ($n=10$)	No ($n=556$)	*P* value
Age, mean ± SD	54 ± 17 years	59 ± 12 years	0.14
Female, *n* (%)	1 (10)	152 (27)	0.22
Liver disease stage, median (IQR))			
Child-Pugh score	7 (6–12)	9 (7–10)	0.42
MELD	14 (10–25)	13 (10–16)	0.55
Laboratory values, median (IQR)			
Platelet count ($\times 10^9$/L)	98 (73–150)	107 (74–153)	0.80
INR	1.5 (1.2–1.9)	1.3 (1.2–1.5)	0.22
APTT (s)	44 (33–54)	37 (33–43)	0.45
Prothrombin time (s)	18 (15–21)	17 (15–19)	0.32
Fibrinogen (g/L)	3.3 (2.1–4.1)	3.1 (2.4–3.9)	0.99
Creatinine (mcmol/L)	70 (63–81)	72 (61–114)	0.88
Coagulation parameters[a], *n* (%)			
Abnormal	4 (40)	165 (31)	0.51
Normal	6 (60)	370 (69)	
Clinical features, *n* (%)			
Sepsis	4 (40)	33 (6)	0.001
Renal impairment	2 (20)	105 (20)	0.99
Acute kidney injury	3 (30)	37 (7)	0.006
Hepatocellular carcinoma	2 (20)	94 (17)	0.80
Bleeding risk category, *n* (%)			
Low	2 (20)	472 (85)	0.001
High	8 (80)	84 (15)	
Blood component prophylaxis, *n* (%)			
Given	2 (20)	64 (12)	0.41
Not given	8 (80)	492 (88)	

APTT, activated partial thromboplastin time; INR, international normalized ratio; MELD, model of end-stage liver disease; IQR, interquartile range.
[a]Missing platelet count and/or INR values for 20 low-risk and 1 high-risk procedure(s)

Low-risk procedures

There were 470 low-risk procedures performed during the study period, the most common being large volume abdominal paracentesis (LVAP, $n=267$, 57%) and routine gastroscopy and colonoscopy ($n=118$, 25%).

Coagulation parameters

Of low-risk procedures with complete data, 34% (151/450) were performed in patients with significant coagulopathy. This included significant thrombocytopenia in 45 (10%) and prolonged INR in 118 (25%) cases. Only 12 low-risk procedures (2.5%) were associated with both an INR >1.5 and platelets <50×10^9/L. Preprocedural fibrinogen was low prior to 10 (2%) procedures. INR, platelet count and fibrinogen level were missing prior to 20 (4%), 6 (1%) and 62 (13%) procedures, respectively.

Prophylactic blood product transfusion

Prophylactic blood components were given prior to 51 (11%) low-risk procedures. In the vast majority of cases (92%) only one type of blood product was given, with both platelets and FFP transfused preprocedure on only four occasions (with cryoprecipitate administered as an adjunct in two of these).

Transfusion thresholds for patients administered prophylactic FFP and platelet are shown in Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A617*. Platelets were given prior to 26 (6%) procedures. Of the low-risk procedures conducted in patients with significant thrombocytopenia ($n=45$), in only 23 (51%) cases were preprocedural platelet transfusions given compared to three of 425 (0.7%) cases with platelet count ≥50×10^9/L ($P=0.001$). Prophylactic FFP was given before 29 (6%) low-risk procedures, all with a preprocedural INR of >1.5, with 65% (19/29) of these procedures performed in patients with an INR >2.0. Cryoprecipitate was transfused prior to two (0.4%) low-risk procedures (for fibrinogen of 0.9 and 1.9 g/L).

In patients with abnormal coagulation parameters, blood component prophylaxis varied somewhat according to the sub-type of the procedure. For example, 37%

(34/93) of patients undergoing LVAP receiving prophylaxis compared with only 3% (1/30) of patients undergoing endoscopic procedures.

For procedures performed by more than one department, such as LVAP, we did not find any difference in the amount of prophylactic blood products administered between different departments.

Bleeding complications

Two (0.4%) low-risk procedures were complicated by postprocedural bleeding; one LVAP and one central venous catheter insertion (Table 3). In both cases, the patients had advanced decompensated liver disease with Child-Pugh scores of 13 and 15, respectively. Notably, both patients had preprocedural platelet counts above 50×10^9/L while one patient had low fibrinogen. Both patients had elevated INRs in keeping with their advanced liver disease.

Among patients with significant coagulopathy having low-risk procedures ($n=151$), the rate of bleeding was comparable between those given and not given prophylactic blood products (2 vs. 1%, respectively; $P=1.0$; Fig. 2).

Moderate to high-risk procedures

A total of 96 high-risk procedures were performed on cirrhotic patients during the study period. The most commonly performed were percutaneous liver biopsy ($n=14$) and HCC-related procedures, including radiofrequency ablation (RFA; $n=18$) and trans-arterial chemoembolization (TACE; $n=10$). Thirty major surgeries were performed, including six laparotomies, five orthopedic, three cardiothoracic and two spinal surgeries.

Coagulation parameters

Eighteen (19%) high-risk procedures were performed in patients with significant coagulopathy, of which 13 (14%) were associated with prolonged INR and 6 (6%) with significant thrombocytopenia. Only one high-risk procedure was performed in a patient with both a prolonged INR and significant thrombocytopenia. No patients having high-risk procedures had a low preprocedural fibrinogen level.

Prophylactic blood product transfusion

In four of six (67%) high-risk procedures performed in patients with significant thrombocytopenia, prophylactic platelet transfusions were given. Prophylactic platelet transfusions were also given prior to 3 (30%) of 10 procedures performed in patients with platelet counts between $50–69\times10^9$/L. Of the 80 high-risk procedures conducted in patients with platelet counts $>70\times10^9$/L, preprocedural platelets were only given on 2 (2.5%) occasions. FFP was given before 9 (9%) high-risk procedures. In all of these cases, the preprocedural INR was >1.5. Further detail regarding FFP and platelet transfusion at different INR and platelet cutoffs is given in Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A617*.

Bleeding complications

Eight (8.3%) of the 96 high-risk procedures were complicated by postprocedural bleeding. This included 6/77 (7.8%) procedures without significant coagulopathy (INR ≤ 1.5 and a platelet count $\geq50\times10^9$/L) and 2/18 (11.1%) procedures with significant coagulopathy ($P=0.64$), (associated with an INR of 1.9 and 1.8, respectively, and none with significant thrombocytopenia or low fibrinogen) (Fig. 2). In one of the two cases, prophylactic FFP was given (Table 3). Of the group with significant coagulopathy ($n=18$), bleeding was observed in 1/13 (7.7%) given blood products compared to 1/5 (20%) who were not given such products ($P=0.49$) (Fig. 2).

All procedures

Survival

Overall, 17 (7%) patients died within the 28-day follow-up period. The cause of death in these cases was not related to postprocedural bleeding.

Table 3. Characteristics of the procedures where postprocedural bleeding occurred

Case	Procedure	Bleeding risk	Age (years)	Sex	Child-Pugh score	Platelet count	INR	Fibrinogen	AKI	Sepsis	Prophylactic blood component
1	Bilateral lung transplant	High	24	Male	6	150	1.2	6.4	No	No	No
2	Irreversible electroporation of HCC	High	74	Male	6	191	1.4	4.1	No	No	No
3	Debridement and skin graft for burn	High	59	Male	6	99	1.5	-	No	No	No
4	Mitral valve replacement and closure patent foramen ovale	High	81	Male	7	104	1.9	2.4	No	No	No
5	Debridement for extensive perianal necrosis	High	42	Male	12	62	1.8	1.7	Yes	Yes	2 units FFP
6	Open hepatectomy and cholecystectomy	High	55	Male	5	82	1.0	3.9	No	No	No
7	Proctectomy and abdominoperineal resection	High	65	Male	7	194	1.2	4.6	No	Yes	No
8	Laminectomy	High	43	Male	7	73	1.4	3.3	Yes	Yes	No
9	Large volume abdominal paracentesis	Low	52	Female	15	96	2.3	2.1	No	No	No
10	Central venous catheter insertion	Low	42	Male	13	70	2.4	0.9	Yes	Yes	1 unit platelets 1 unit FFP 1 unit cryoprecipitate

AKI, acute kidney injury; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; INR, international normalized ratio.

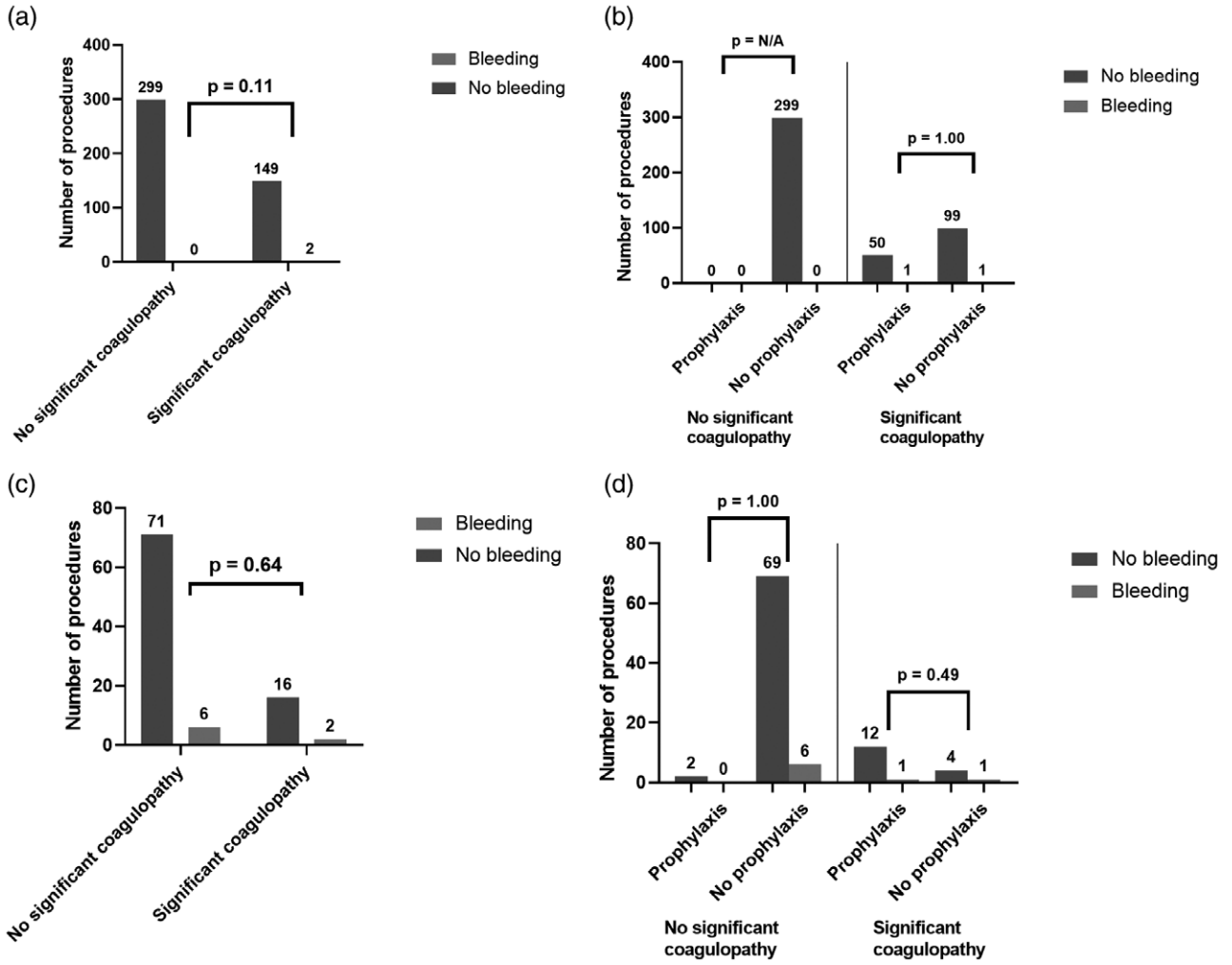

Fig. 2. Effect of significant coagulopathy on bleeding complications for low-risk (a) and high-risk (c) procedures. Effect of prophylactic transfusions on bleeding complications for low-risk (b) and high-risk (d) procedures. *Missing platelet count, INR or both for 20 low-risk and 1 high-risk procedure(s). INR, international normalized ratio.

Transfusion-related complications

A single transfusion-related side effect was reported namely a mild allergic reaction to FFP. In another case, a fever during a platelet transfusion was deemed most likely nontransfusion related after review by the transfusion safety committee.

Discussion

In our study, over 550 procedures were performed in patients with cirrhosis over a 1-year period confirming the high frequency of procedures performed in these patients and the need for guidelines regarding their periprocedural management, particularly with regards to coagulation status. Overall, we found the periprocedural bleeding risk was low (1.8%), particularly for low-risk procedures (0.4%). We included a large number of low-risk procedures performed in patients with significant coagulopathy ($n=151$), and despite this, no association between prolonged INR >1.5 or significant thrombocytopenia and bleeding risk was observed. Moreover, giving prophylactic blood components prior to these procedures did not affect bleeding outcomes.

These findings are in keeping with a prospective study of cirrhotic patients undergoing invasive procedures conducted across five centers in India [19]. Shah *et al.* stratified patients into groups according to the presence or absence of coagulopathy (defined similarly to our study as INR ≥1.5, and platelets $\leq 50\times10^9$/L). None of the 60 low-risk procedures carried out in patients with coagulopathy were complicated by clinically significant bleeding, despite no prophylactic blood components being administered. Our study included a larger number of low-risk procedures and supported the above findings. Despite this pre-existing evidence suggesting low-risk procedures carry a low bleeding risk, prophylactic blood product was administered in 11% of low-risk procedures in our study. This is comparable to the proportion of moderate to high-risk procedures receiving preprocedural blood components (16%, $P=0.18$), even though the observed bleeding rate was ~20 times higher in the moderate to high-risk procedure group.

A recently published randomized controlled trial comparing three prophylactic transfusion protocols in patients with cirrhosis and coagulopathy undergoing central venous catheterization found that use of a restrictive blood

component strategy (FFP if INR >5, platelets if platelet count <25×10^9/L) significantly reduced blood component use and associated costs, without an increase in bleeding complications [20], further supporting the notion that in most patients with cirrhosis low-risk procedures can be safely carried out without prophylactic blood products.

For patients with cirrhosis undergoing low-risk procedures, our data supports the assertion that prophylactic blood components should not be routinely given on the basis of standard coagulation tests. Although the risk of transfusion reactions may be rare, there is substantial cost and time associated with the administration of prophylactic blood products, as well as the potential to paradoxically increase the patient's bleeding risk by raising their portal-pressure through volume overload [21]. We suggest an approach where patients are managed expectantly for any bleeding that may occur.

With regard to high-risk procedures in cirrhosis, we observed a periprocedural bleeding risk of 8.3%. Among this group, there was no association between abnormal coagulation tests and bleeding complications. While the INR was elevated in two patients who experienced a postprocedural bleed, all eight patients had a platelet count above 50×10^9/L. In fact, none of the 51 procedures conducted in patients with significant thrombocytopenia were complicated by bleeding. This is despite only 53% of these patients (27/51) receiving prophylactic platelet transfusions. This is similar to observations reported in the Italian study by Napolitano *et al.,* who found no postprocedural bleeds in 89 procedures performed on patients with platelets ≤50×10^9/L [9]; however, it is unclear how many of these patients were transfused with platelets prior to their procedure.

In their study, Shah *et al*. reported a bleeding rate of 17% (3/18) in patients with coagulopathy undergoing high-risk procedures compared to 0% (0/26) bleeding rate in patients without coagulopathy having high-risk procedures ($P = 0.06$) [19]. The three patients who bled had advanced liver disease (Child-Pugh class C) and AKI or sepsis. Patients with similar INR and platelet derangements without these additional factors did not experience bleeding complications. The authors attributed the increased bleeding risk to the presence of AKI and sepsis. In our study, we observed comparable bleeding rates between patients with and without significant coagulopathy having moderate to high-risk procedures (11 vs. 8%, $P = 0.64$). Sepsis and AKI were both associated with postprocedural bleeding on univariate analysis, but these differences were not statistically significant after adjustments for other relevant variables.

Importantly, we identified the procedural bleeding risk as to the only significant predictor of bleeding in our cohort on multivariate analysis. Among patients with significant coagulopathy in the high-risk group, we observed comparable bleeding rates between those given and not given preprocedural blood product (7.7 vs. 20%, respectively, $P = 0.49$). However, considering the relatively small number of procedures in this group ($n = 18$), it is difficult to draw firm conclusions about the value of prophylactic blood product use in this setting. Hence, it remains unclear whether there is a subgroup of patients with coagulopathy undergoing high-risk procedures that may benefit from prophylactic transfusion. Global hemostatic assays, such as ThromboElastoGraphy (TEG) and ROtational ThromboElastoMetry (ROTEM), that measure the coagulation system as a whole rather than individual components, offer considerable potential to fill this void [22]. Notably, two recent randomized controlled trials found that using TEG to guide prophylactic FFP and platelets in patients with cirrhosis undergoing invasive procedures resulted in decreased blood product use without affecting bleeding outcomes [23,24].

Recently, there has been increasing interest in fibrinogen levels as a predictor of bleeding risk in cirrhosis, with the recently released American Gastroenterology Association clinical practice update suggesting a preprocedural fibrinogen level >1.2 g/L (on the basis of trauma literature) as a potential target prior to high-risk procedures [2]. In support of this, Drolz *et al.*. found that in critically ill patients with cirrhosis, fibrinogen <0.6 g/L was associated with major spontaneous bleeding [25]. Although we did not see any difference in fibrinogen levels between those with and without postprocedural bleeding, in our cohort, there were no high-risk procedures performed in patients with fibrinogen levels <1.2 g/L, so it is difficult to comment about those with severe hypofibrinogenemia.

Although this study was both retrospective and single-center, it has several strengths, including the identification of all eligible cirrhotic patients and all inpatient and outpatient procedures through a comprehensive search of medical records, across all units within the hospital. Due to detailed electronic medical records, we were able to collect detailed information and complete follow-up until 28 days and are confident that we have been able to capture all prophylactic blood component transfusions. Moreover, we collected data on a large number of low-risk procedures, with a significant number performed on patients with significant coagulopathy. Additionally, we used well-defined classifications of procedure risk, bleeding events, AKI and sepsis. However, an important limitation of our study was the small number of high-risk procedures performed in patients with significantly significant coagulopathy. Additionally, both allocation of blood component prophylaxis, and eligibility for procedures, were physician-directed rather than randomized, potentially giving rise to selection bias, which needs to be taken into account when drawing any conclusions. Local procedural guidelines incorporating prophylactic transfusion triggers were only available for few specific procedures and were not fully adhered to. It should also be noted that it is also possible that individual proceduralists may have made modifications to procedures in certain cases due to a perceived increased bleeding risk, although we found no evidence of this from a close review of the electronic medical records.

In conclusion, our study indicates that although procedure-related bleeding is uncommon in patients with cirrhosis having low-risk procedures, the risk of bleeding is higher for those having high-risk procedures, even in the absence of significant coagulopathy. Procedure-related bleeding cannot be accurately predicted by INR or platelet count, nor prevented by blood component prophylaxis using these parameters especially in low-risk procedures; the bleeding risk is best predicted by the type of procedure being performed. Further studies are needed to identify alternative methods for assessing bleeding risk and

guiding prophylactic blood products as a priori particularly for patients having moderate to high bleeding risk procedures.

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Conflicts of interest

There are no conflicts of interest.

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