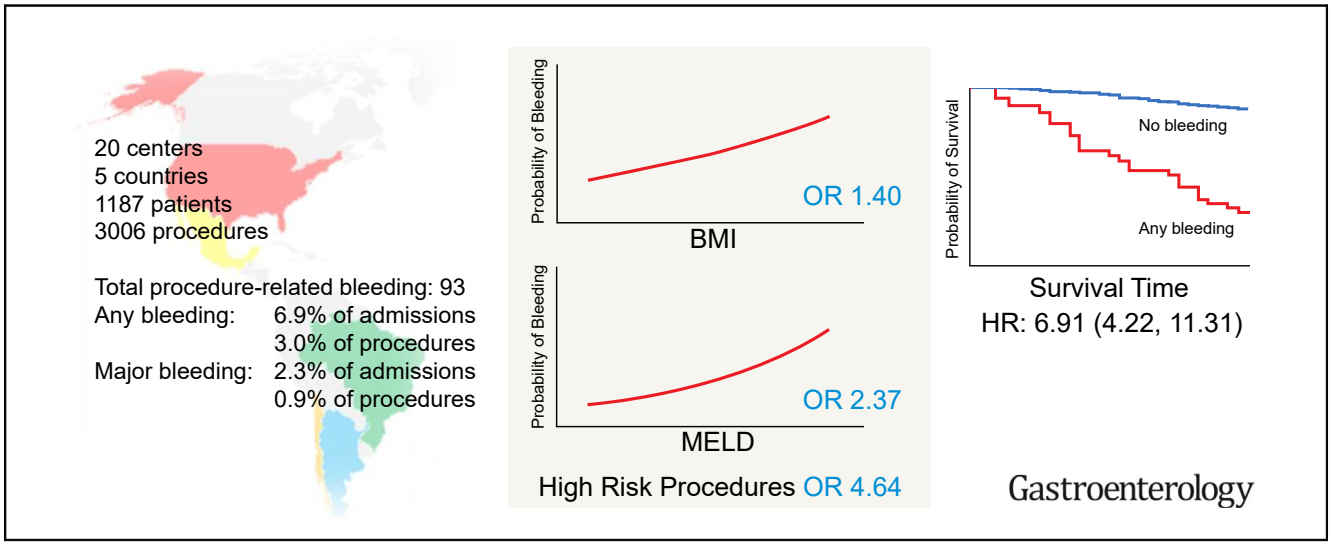
Gastroenterology 2023;165:717–732

Procedural-Related Bleeding in Hospitalized Patients With Liver Disease (PROC-BLeeD): An International, Prospective, Multicenter Observational Study

Nicolas M. Intagliata,[1] Robert S. Rahimi,[2] Fatima Higuera-de-la-Tijera,[3] Douglas A. Simonetto,[4] Alberto Queiroz Farias,[5] Daniel F. Mazo,[6] Justin R. Boike,[7] Jonathan G. Stine,[8] Marina Serper,[9] Gustavo Pereira,[10] Angelo Z. Mattos,[11] Sebastian Marciano,[12] Jessica P. E. Davis,[13] Carlos Benitez,[14] Ryan Chadha,[15] Nahum Méndez-Sánchez,[16] Andrew S. deLemos,[17] Arpan Mohanty,[18] Melisa Dirchwolf,[19] Brett E. Fortune,[20] Patrick G. Northup,[21] James T. Patrie,[22] and Stephen H. Caldwell[1]

[1]University of Virginia Health System, Charlottesville, Virginia; [2]Baylor Scott and White Hospital, Dallas, Texas; [3]Hospital General de México "Dr. Eduardo Liceaga," Saint Luke School of Medicine, Mexico City, Mexico; [4]Mayo Clinic, Rochester, Minnesota; [5]University of São Paulo School of Medicine, São Paulo, Brazil; [6]School of Medical Sciences of University of Campinas (UNICAMP), São Paulo, Brazil; [7]Northwestern University Feinburg School of Medicine, Chicago, Illinois; [8]Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania; [9]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; [10]Bonsucesso Federal Hospital (Ministry of Health), Rio de Janeiro, Brazil, and Estácio de Sá School of Medicine—Instituto de Educação Médica, Rio de Janeiro, Brazil; [11]Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil; [12]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [13]Washington DC Veterans Affairs Medical Center, Washington, DC; [14]Pontificia Universidad Católica de Chile, Santiago, Chile; [15]Mayo Clinic Florida, Jacksonville, Florida; [16]Medica Sur Clinic & Foundation and Faculty of Medicine, National Autonomous University of Mexico, Mexico City, Mexico; [17]Wake Forest University School of Medicine, Atrium Health, Charlotte, North Carolina; [18]Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; [19]Hospital Privado de Rosario, Rosario, Argentina; [20]Montefiore Einstein Center for Transplantation, New York, New York; [21]New York University Langone Health, New York, New York; and [22]University of Virginia School of Medicine, Charlottesville, Virginia



BACKGROUND & AIMS: Hospitalized patients with cirrhosis frequently undergo multiple procedures. The risk of procedural-related bleeding remains unclear, and management is not standardized. We conducted an international, prospective, multicenter study of hospitalized patients with cirrhosis undergoing nonsurgical procedures to establish the incidence of procedural-related bleeding and to identify bleeding risk factors. **METHODS:** Hospitalized patients were prospectively enrolled and monitored until surgery, transplantation, death, or 28 days from admission. The study enrolled 1187 patients undergoing 3006 nonsurgical procedures from 20 centers. **RESULTS:** A total of 93 procedural-related bleeding events were identified. Bleeding was reported in 6.9% of patient admissions and in 3.0% of the procedures. Major bleeding was reported in 2.3% of patient admissions and in 0.9% of the procedures. Patients with bleeding were more likely to have nonalcoholic steatohepatitis (43.9% vs 30%) and higher body mass index (BMI; 31.2 vs 29.5). Patients with bleeding had a

higher Model for End-Stage Liver Disease score at admission (24.5 vs 18.5). A multivariable analysis controlling for center variation found that high-risk procedures (odds ratio [OR], 4.64; 95% confidence interval [CI], 2.44–8.84), Model for End-Stage Liver Disease score (OR, 2.37; 95% CI, 1.46–3.86), and higher BMI (OR, 1.40; 95% CI, 1.10–1.80) independently predicted bleeding. Preprocedure international normalized ratio, platelet level, and antithrombotic use were not predictive of bleeding. Bleeding prophylaxis was used more routinely in patients with bleeding (19.4% vs 7.4%). Patients with bleeding had a significantly higher 28-day risk of death (hazard ratio, 6.91; 95% CI, 4.22–11.31). **CONCLUSIONS:** Procedural-related bleeding occurs rarely in hospitalized patients with cirrhosis. Patients with elevated BMI and decompensated liver disease who undergo high-risk procedures may be at risk to bleed. Bleeding is not associated with conventional hemostasis tests, preprocedure prophylaxis, or recent antithrombotic therapy.

Keywords: Hemostasis; Obesity; Prophylaxis; Risk; Cirrhosis.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Hospitalized patients with cirrhosis can develop bleeding from a wide variety of causes and frequently undergo nonsurgical procedures. Patients with cirrhosis have a complex hemostatic system that is difficult to measure. Bleeding events remain challenging to predict, and consequently, clinicians routinely provide prophylaxis before procedures.

NEW FINDINGS

In patients with cirrhosis undergoing nonsurgical procedures, bleeding is rare and not dependent on the international normalized ratio, thrombocytopenia, or preprocedure bleeding prophylaxis. Factors such as overall degree of hepatic decompensation, obesity, and procedure risk are associated with increased risk of bleeding.

LIMITATIONS

Bleeding events are rare and multivariate models are therefore limited.

CLINICAL RESEARCH RELEVANCE

These findings help to identify which specific patients and procedures may be at highest risk for bleeding and reassures clinicians to avoid strategies unlikely to reduce bleeding risk in all patients.

BASIC RESEARCH RELEVANCE

These findings support past translational studies that indicate conventional measures of hemostasis do not reflect bleeding risk. Future studies of the hemostasis system in models of obesity and decompensated cirrhosis may reveal underlying pathophysiologic mechanisms which explain these clinical findings.

HEPATOBILIARY

Patients with decompensated liver disease are frequently hospitalized and often undergo multiple procedures. Clinicians regularly provide bleeding prophylaxis to patients with cirrhosis before procedures due to concern for bleeding risk.[1] However, studies suggest a lower risk of bleeding secondary to a rebalanced hemostatic system in cirrhosis with preservation of hemostasis, albeit in a more fragile balance.[2] Conventional parameters to assess the hemostatic system do not reliably measure bleeding risk in patients with cirrhosis. As such, current strategies to direct preprocedural prophylaxis may add unnecessary risk.[1,3] Beyond risk of volume overload and lung injury, unnecessary use of blood products may exacerbate resource shortages.[4] Presently, tests cannot predict bleeding associated with procedures in patients with cirrhosis, and clinicians therefore rely on extrapolation and anecdotal approaches.[3,5]

Studies examining bleeding in patients with cirrhosis undergoing procedures differ in many aspects.[3,6] Most studies are retrospective with mixed cohorts undergoing both nonsurgical and surgical procedures, do not control for preprocedure prophylaxis, and lack uniform outcome definitions.[3,7–11] With one exception,[12] studies lack restrictive "control" arms where patients undergo procedures without prophylaxis. Consequently, reported rates of procedural-related bleeding range widely, from 2% to 20%. Small prospective studies have explored alternative measures of hemostasis with viscoelastic testing in patients with cirrhosis undergoing procedures and demonstrated low rates of bleeding.[12-14] Randomized controlled trials investigating the efficacy and safety of thrombopoietin agonists in patients with cirrhosis for low-risk procedures have also found low rates of bleeding events.[15,16]

Hospitalized patients with decompensated cirrhosis may be at higher risk to develop procedural-related bleeding. In particular, patients with acute-on-chronic liver failure (ACLF) may have unique hemostatic profiles placing them at higher risk to develop bleeding or thrombosis.[17,18] Society guidance and consensus statements now recommend against the routine use of preprocedure prophylaxis for prevention of bleeding.[3,5,19-21] However, these recommendations are based on expert opinion from the available limited data.

Given this uncertainty, we conducted a prospective, international, multicenter, observational cohort study of hospitalized patients with decompensated cirrhosis undergoing nonsurgical procedures. The aim was to define overall incidence of procedural-related bleeding using standard

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; AHR, adjusted hazard ratio; AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; CTP, Child-Turcotte-Pugh; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; VTE, venous thromboembolism.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2023.05.046

Table 1. Baseline Patient Characteristics at Admission[a]

Characteristics	All patients (N = 1187)	All nonbleed patients (n = 1105)	All bleed patients (n = 82)	*P* value[b]
Age, mean (SD), *y*	58.2 (12.2)	58.3 (12.2)	56.3 (12.6)	.197
Male sex	717 (60.4)	672 (60.8)	45 (54.9)	.267
BMI, mean (SD)	29.6 (8.0)	29.5 (8.0)	31.2 (8.4)	**.014**
Etiology of cirrhosis				
Alcohol	526 (44.3)	491 (44.4)	35 (42.7)	.866
NASH	367 (30.9)	331 (30.0)	36 (43.9)	**.005**
Hepatitis C virus	169 (14.2)	159 (14.4)	10 (12.2)	.526
Other	250 (21.1)	237 (21.4)	13 (15.9)	.092
MELD score at admission, mean (SD)	18.9 (8.0)	18.5 (7.8)	24.5 (8.6)	**<.001**
CTP score at admission, mean (SD)	9.9 (1.9)	9.8 (1.9)	10.8 (1.6)	**.004**
CTP score category				
A (5–6)	45 (4.2)	43 (4.4)	2 (2.6)	.768
B (7–9)	409 (38.6)	400 (40.7)	9 (11.8)	**<.001**
C (10–15)	605 (57.1)	540 (54.9)	65 (85.5)	**<.001**
ACLF grade 0 (no ACLF)	827 (78.7)	783 (80.3)	44 (57.9)	**<.001**
ACLF (grades 1, 2, and 3)	224 (21.3)	192 (19.7)	32 (42.1)	**<.001**
ACLF grade 1	112 (10.7)	102 (10.5)	10 (13.2)	.498
ACLF grade 2	84 (8.0)	67 (6.9)	17 (22.4)	**<.001**
ACLF grade 3	28 (2.7)	23 (2.4)	5 (6.6)	**.022**
Organ failures				
0	681 (64.8)	644 (66.1)	37 (48.7)	**.001**
1	258 (24.5)	241 (24.7)	17 (22.4)	.638
2	84 (8.0)	67 (6.9)	17 (22.4)	**<.001**
3	22 (2.1)	17 (1.7)	5 (6.6)	**.006**
≥4	6 (0.6)	6 (0.6)	0 (0.0)	1.000
CLIF-Organ Failure score, mean (SD)	7.8 (1.8)	7.7 (1.8)	8.9 (2.1)	**<.001**
CLIF-C Acute Decompensation score, mean (SD)	54.6 (10.6)	54.4 (10.4)	59.1 (12.4)	**.001**
CLIF-C ACLF score, mean (SD)	50.4 (7.7)	50.3 (7.8)	50.9 (6.7)	.403
Laboratory values at admission, mean (SD)				
Sodium, *mmol/L*	133.8 (6.2)	133.9 (6.2)	132.0 (6.1)	**.003**
Blood urea nitrogen, *mg/dL*	31.2 (23.8)	30.2 (22.7)	44.2 (33.3)	**<.001**
Creatinine, *mg/dL*	1.6 (1.4)	1.5 (1.3)	2.4 (2.0)	**<.001**
Total bilirubin, *mg/dL*	4.9 (7.1)	4.8 (6.9)	6.8 (8.4)	**<.001**
Albumin, *g/dL*	3.0 (0.6)	3.0 (0.6)	2.8 (0.6)	.085
Hemoglobin, *g/dL*	9.9 (2.5)	9.9 (2.6)	9.6 (2.3)	.310
Platelets, *k/μL*	128.0 (85.7)	128.7 (84.7)	118.8 (97.5)	.159
INR	1.7 (0.7)	1.7 (0.7)	2.0 (0.8)	**<.001**
Prothrombin time, *s*	19.5 (7.4)	19.2 (7.1)	23.3 (10.0)	**<.001**
Fibrinogen, *mg/dL*	208.6 (104.9)	214.2 (105.2)	162.9 (92.1)	**.007**
Reason for admission				
Volume overload	335 (28.2)	312 (28.2)	23 (28.0)	.894
Bleeding	279 (23.5)	266 (24.1)	13 (15.9)	**.042**
Hepatic encephalopathy	146 (12.3)	140 (12.7)	6 (7.3)	.101
AKI	66 (5.6)	57 (5.2)	9 (11.0)	**.013**
Other	361 (30.4)	330 (29.9)	31 (37.8)	.070
Infection at admission	300 (25.4)	264 (24.1)	36 (43.9)	**<.001**
AKI at admission	416 (35.1)	371 (33.6)	45 (54.9)	**<.001**
History of CKD	212 (17.9)	191 (17.3)	21 (25.6)	**.011**

Table 1. Continued

Characteristics	All patients (N = 1187)	All nonbleed patients (n = 1105)	All bleed patients (n = 82)	*P* value[b]
Renal replacement therapy at admission	45 (3.8)	38 (3.5)	7 (8.5)	**.012**
History of cardiac disease	204 (17.6)	190 (17.7)	14 (17.1)	.635
History of bleeding disorder	13 (1.1)	13 (1.2)	0 (0.0)	.616
History of thrombophilia disorder	23 (2.0)	20 (1.9)	3 (3.7)	.219
History of current malignancy	179 (15.1)	166 (15.1)	13 (15.9)	.931
History of procedural bleeding	50 (4.2)	43 (3.9)	7 (8.5)	.078
Antiplatelet therapy on admission	121 (10.2)	113 (10.2)	8 (9.8)	.616
Anticoagulation on admission	86 (7.2)	80 (7.2)	6 (7.3)	.889
Medications at admission				
Aspirin	109 (9.2)	102 (9.2)	7 (8.5)	.651
Clopidogrel	21 (1.8)	19 (1.7)	2 (2.4)	.253
Selective serotonin reuptake inhibitor	103 (8.7)	99 (9.0)	4 (4.9)	.306
Direct oral anticoagulant	42 (3.5)	39 (3.5)	3 (3.7)	1.000
Vitamin K antagonist	22 (1.9)	20 (1.8)	2 (2.4)	.660
Medical thromboprophylaxis at admission	300 (25.3)	276 (25.0)	24 (29.3)	.195
Unfractionated heparin	169 (56.3)	153 (55.4)	16 (66.7)	.114
Low-molecular-weight heparin	119 (39.7)	112 (40.6)	7 (29.2)	.130
Other	12 (4.0)	11 (4.0)	1 (4.2)	1.000
Prior admission in 28 days	283 (24.0)	265 (24.1)	18 (22.2)	.976

NOTE. Data are presented as n (%) unless indicated otherwise. Bold *P* values indicate statistical significance ($P < .05$). See Supplementary Table 2 for the percentage of missing data for each variable.
SD, standard deviation.
[a]Baseline characteristics are summarized at the patient level.
[b]For patient-level categorical risk factors in which the risk factor frequencies for both nonbleed patients and bleed patients were ≥ 5, the *P* value was derived via center-adjusted binomial generalized linear model Wald's χ^2 test; otherwise, the *P* value was derived via an unadjusted Fisher's exact test (please see the Supplementary Analytical Methods section for further details).

outcome definitions in a high-risk cohort and to identify factors predicting bleeding.

Materials and Methods

We performed a prospective, multicenter cohort study enrolling adult patients with cirrhosis admitted to the hospital from 20 centers in North and South America (Supplementary Table 1). Patients aged ≥18 years admitted to the hospital for >24 hours and undergoing at least 1 procedure during the hospitalization were included. Exclusion criteria included prisoners, pregnancy, prior liver transplantation, unable to provide consent, or previous enrollment.

Meetings were conducted with each local study team. Local Institutional Review Board and Ethics Committee approvals were obtained at each participating institution. Data were submitted in electronic case format via Research Electronic Data Capture Software (REDCap) and centrally managed at the University of Virginia, Charlottesville, Virginia. Clinical management of each patient was conducted according to the local provider's discretion, and study investigators recorded data from the electronic medical record (Supplementary Methods).

Enrollment was prospective and consecutive, and all patients eligible for inclusion during enrollment periods were evaluated to reduce risk of bias. Patients who met inclusion criteria were consented for enrollment during the index hospitalization. Patients were monitored until 28 days from the admission date, death, liver transplantation, or before 28 days from admission if they underwent a major surgical operation (Supplementary Figure 1).

Data were reviewed contemporaneous to enrollment to rectify any discrepancies. The 28-day observation period from admission was designated to allow for standardized assessment of death and to capture delayed bleeding after procedures. Surgical operations and liver transplantation during hospitalization were chosen as termination end points to the study because surgical-related bleeding (eg, bleeding in the operating room) involves a separate risk profile and subsequent management strategies postoperatively. Individuals were enrolled only once in the study at the time of the hospitalization.

Sample Size Justification

Study sample size determination was focused on bleeding prevalence estimation precision as well as on multivariate modeling of the risk of procedure bleed. Regarding bleed prevalence estimation precision, we assumed an underlying prevalence for bleeding of 8%. Therefore, it is possible with a total enrollment of 707 patients to estimate bleed prevalence with a precision of ±2%. More recent analyses suggest alternative strategies exist to determine sample size for multivariate regression models that do not rely on events per variable

Table 2. Procedure Characteristics[a]

Characteristic	All procedures (N = 3006)	Nonbleed procedures (n = 2913)	Bleed procedures (n = 93)	*P* value[b]
Trainee performing	2180 (72.7)	2106 (72.4)	74 (79.6)	.390
Any bleeding prophylaxis before	233 (7.8)	215 (7.4)	18 (19.4)	**.001**
Vitamin K	102 (44.9)	96 (45.9)	6 (33.3)	.058
Platelets	73 (32.3)	67 (32.2)	6 (33.3)	.616
Plasma	69 (30.5)	60 (28.8)	9 (50.0)	.297
Cryoprecipitate	51 (22.6)	45 (21.6)	6 (33.3)	.328
Platelet transfusions before procedures	71 (2.4)	65 (2.2)	6 (6.5)	**.024**
Prior platelet transfusions/patient				
0	1137 (95.8)	1065 (96.4)	72 (87.8)	**<.001**
1	36 (3.0)	29 (2.6)	7 (8.5)	**.004**
2	9 (0.8)	7 (0.6)	2 (2.4)	.124
3	3 (0.3)	3 (0.3)	0 (0.0)	1.000
4	2 (0.2)	1 (0.1)	1 (1.2)	.069
Plasma transfusions before procedures	69 (2.3)	60 (2.1)	9 (9.7)	**<.001**
0	1146 (96.5)	1076 (97.4)	70 (85.4)	**<.001**
1	21 (1.8)	13 (1.2)	8 (9.8)	**<.001**
2	16 (1.3)	14 (1.3)	2 (2.4)	.304
3	2 (0.2)	1 (0.1)	1 (1.2)	.133
≥4	2 (0.2)	1 (0.1)	1 (1.2)	.133
Antithrombotic therapy within 24 hours	835 (27.9)	806 (27.8)	29 (31.2)	.198
Aspirin	45 (1.5)	43 (1.5)	2 (2.2)	.648
Clopidogrel	19 (0.6)	16 (0.5)	3 (3.3)	**.019**
Unfractionated heparin prophylaxis	472 (15.7)	455 (15.6)	17 (18.5)	.188
Low-molecular-weight heparin prophylaxis	236 (7.9)	231 (7.9)	5 (5.4)	.412
Unfractionated heparin treatment	26 (0.9)	24 (0.8)	2 (2.2)	.188
Low-molecular-weight heparin treatment	22 (0.7)	21 (0.7)	1 (1.1)	.497
Direct oral anticoagulants	37 (1.2)	34 (1.2)	3 (3.2)	.105
Vitamin K antagonist	13 (0.4)	12 (0.4)	1 (1.1)	.331
Procedure				
Common bedside	1568 (52.2)	1522 (52.2)	46 (49.5)	.757
Vascular	569 (18.9)	544 (18.7)	25 (26.9)	.060
Endoscopic	760 (25.3)	747 (25.6)	13 (14.0)	**.005**
Percutaneous	88 (2.9)	83 (2.8)	5 (5.4)	.211
Dental	11 (0.4)	7 (0.2)	4 (4.3)	**<.001**
Skin	10 (0.3)	10 (0.3)	0 (0.0)	1.000
Overall procedure risk				**.001**
Low risk	2733 (90.9)	2657 (91.2)	76 (81.7)	
High risk	273 (9.1)	256 (8.8)	17 (18.3)	
Preprocedure laboratory values, mean (SD)[c]				
Sodium, *mmol/L*	134.6 (6.1)	134.7 (6.1)	133.8 (6.8)	.117
Blood urea nitrogen, *mg/dL*	34.4 (26.2)	34.0 (25.8)	47.9 (35.2)	**<.001**
Creatinine, *mg/dL*	1.7 (1.4)	1.7 (1.4)	2.5 (2.0)	**<.001**
Total bilirubin, *mg/dL*	5.5 (7.8)	5.4 (7.5)	8.8 (13.4)	**.001**
Albumin, *g/dL*	3.0 (0.7)	3.0 (0.7)	2.9 (0.7)	.342
Hemoglobin, *g/dL*	9.2 (2.1)	9.2 (2.1)	8.8 (2.1)	**.039**
Platelets, k/μL	113.0 (78.4)	113.3 (78.3)	103.7 (81.3)	.114
INR	1.8 (0.7)	1.8 (0.7)	2.0 (0.8)	**<.001**
Prothrombin time, *s*	20.3 (7.0)	20.2 (6.9)	23.3 (8.6)	**<.001**
Fibrinogen, *mg/dL*	194.2 (108.9)	195.9 (109.7)	161.8 (88.9)	.050

NOTE. Data are presented as n (%) unless designated otherwise. Bold *P* values indicate statistical significance ($P < .05$). See Supplementary Table 3 for the percentage of missing data for each variable.
SD, standard deviation.
[a]Procedure characteristics are summarized at the procedure level.
[b]For procedure categorical risk factors in which the risk factor frequencies for both the nonbleed procedures and the bleed procedures were ≥5, the *P* values were derived via center-adjusted binomial generalized estimating equation Wald's χ^2 tests; otherwise, the *P* values were derived via unadjusted Fisher's exact tests (please see the Analytical Methods section of the Supplementary Material for further details).
[c]For preprocedure laboratory data, all laboratory measures were analyzed on the natural logarithmic scale, and the *P* values were derived via center-adjusted linear mixed model *t* tests (please see the Analytical Methods section of the Supplementary Material for further details).

criteria.[22] However, we based the multivariate regression model on the aim for ~10 unique events per predictor variable to have adequate power to detect partial associations without overfitting. As such, we estimated the need for a minimum of 80 to ≥100 bleeding events to identify unique partial associations between predictors of bleed and procedure bleed. Consequently, the patient enrollment goal was liberally set at ~1250 patients (patient enrollment size that conservatively assumes every patient will undergo 1 procedure during hospitalization).

Study Definitions

Cirrhosis was defined according to available clinical, histologic, radiographic, and biochemical data. Definitions for Model for End-Stage Liver Disease (MELD), acute decompensation, and ACLF were defined according to European Foundation for the Study of Chronic Liver Failure and are described in the Supplementary Methods. Ascites grade was defined according to International Club of Ascites and European Association for Study of Liver guidelines.[23,24] Ascites grade was recorded and assessed at the time of admission. Hepatic encephalopathy was defined according to West Haven criteria and was recorded and assessed at the time of admission.

Chronic kidney disease (CKD) was defined as a clinical history or a documented glomerular filtration rate of <60 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} for >3 months.[25] Acute kidney injury (AKI) was defined according to International Club of Ascites definition as an increase in serum creatinine of $\geq$0.3 mg/dL within 48 hours or a 50% increase in 7 days from the baseline serum creatinine.[26]

A nonsurgical procedure was defined as any procedure occurring during the hospitalization as judged by investigators, but could not take place with general anesthesia in an operating room. Procedure-related bleeding was defined as bleeding related in time and location to the procedure, as judged and reported by the local investigator. The severity of bleeding was categorized according to International Society of Thrombosis and Haemostasis definitions for major bleeding[27] and clinically relevant nonmajor bleeding (CRNMB)[28] (Supplementary Methods). Bleeding related to a procedure that was identified by investigators but did not meet the definition of major bleeding or CRNMB was reported as "other bleeding." For each bleeding event submitted, 3 blinded independent adjudicators reviewed a deidentified case report form to verify that the bleeding event met the criteria. A majority agreement was needed to determine whether the bleeding event met criteria and to classify the type of bleeding.

Procedure risk was determined to be low-risk or high-risk based on previously published guidance.[5,29,30] Low-risk procedures include procedures where the expected major bleeding rate is $<1.5\%$ and bleeding can be easily controlled if occurring. High-risk includes procedures where the expected estimated major bleeding rate is $>1.5\%$ or if bleeding would be difficult to control or result in a location causing serious morbidity.

Analytical Methods

The analytical methods are described in detail in the Supplementary Analytical Methods. In 6 subsections we detail the analytical methods used to:

1. summarize the empirical distributions of the baseline and preprocedure and concurrent-procedure patient characteristic data,
2. derive the estimates for the bleeding prevalence and for bleeding incidence rate,
3. compare the baseline characteristics of patients with and without bleeding,
4. compare the preprocedure characteristics of patients with and without bleeding,
5. derive among a set of a priori–selected patient and procedure characteristics those characteristics that are uniquely associated with procedure bleed, and
6. compare 28-day mortality and survival time between patients with and without bleeding.

Missing data were not imputed, and missing data frequencies are summarized in the Supplementary Results (Supplementary Tables 2–4).

Data were contributed by 20 medical centers, and to account for variability between centers, the 20 centers were clustered into 5 center-groups. Cluster criterion was based on geographic location and bleeding events (each center-group had to have at least 10 bleeding events) (Supplementary Tables 5 and 6). All multivariate regression models for bleeding, death, and survival were constructed a priori, and selection of variables was based on prior literature and biologic plausibility.

Results

Cohort Patient Characteristics

The study enrolled 1187 patients undergoing 3006 nonsurgical procedures from 2019 to 2022 from 20 centers throughout North and South America (Table 1 and Supplementary Table 1). The cohort was an average age of 58.2 years, and 60% were men. Volume overload, bleeding, and hepatic encephalopathy were among the most common reasons for admission to the hospital. Overall, the cohort had a mean MELD at admission of 19 and a mean Child-Turcotte-Pugh (CTP) score of 10 (57.1% of patients CTP C). ACLF (grade 1–3) was present in 21.3% of the cohort, with a European Foundation for the Study of Chronic Liver Failure (CLIF)-C ACLF mean score of 50.4. Patients underwent an average of 2.5 procedures during each hospitalization. Medical thromboprophylaxis was started at the time of admission in 25.3% of patients. Infection was present at admission in 25.4% of patients, with the most common type of infection being spontaneous bacterial peritonitis.

The cohort underwent 62 distinct nonsurgical procedures, with 9.1% of procedures classified as high bleeding risk (Supplementary Table 7). The most common procedures included paracentesis, esophagogastroduodenoscopy, and placement of a central venous catheter (Supplementary Table 7). A trainee participated in 72.7% of procedures. Bleeding prophylaxis was provided before 7.8% of procedures (4.2% of patients received at least 1 unit of platelets, and 3.5% of patients received at least 1 unit of plasma).

Anticoagulation or antiplatelet therapy (prophylaxis or therapeutic) within 24 hours of the procedure was present during 27.9% of procedures. In patients on anticoagulation, therapy was continued uninterrupted during 76% of procedures. The most common anticoagulation used in the

cohort was venous thromboembolism (VTE) prophylaxis, with unfractionated heparin in 15.7% and low-molecular-weight heparin in 7.9% of procedures. At the conclusion of the analysis, 10 patient admissions had procedures included beyond defined study termination points (n = 21 procedures, all without bleeding). Procedures included beyond study end points were uniformly excluded in all time-dependent, death, and survival analyses (Supplementary Methods).

Prevalence and Incidence Rates

We identified 93 procedural-related bleeding events in this cohort (31 major, 37 CRNMB, and 25 other) (Table 2 and Supplementary Table 8). A single bleeding event occurred in 72 patients (87.8%), and >1 bleeding event occurred in 10 patients (12.2%), comprising 9 patients with 2 bleeding events and 1 patient with 3 bleeding events. Procedural-related bleeding occurred in 6.9% (95% confidence interval [CI], 5.6%–8.5%) of patients per admission and 3.0% (95% CI, 2.5%–3.8%) per procedure. Major bleeding occurred in 2.3% (95% CI, 1.6%–3.3%) of patients per admission and 0.9% (95% CI, 0.7%–1.5%) per procedure. The mean incidence rate per hospitalization day for all bleeding was 6 bleeds (95% CI, 5.0–7.6 bleeds) per 1000 patient hospitalization days. The mean incidence rate per hospitalization day for major bleeding was 2.1 (95% CI, 1.4–2.9) per 1000 patient hospitalization days. Among those who had a bleeding event, the median time to the first bleed was 3.5 days (95% CI, 2.5–6.0 days) from admission, and the mean time to first bleed was 6.0 days (95% CI, 4.9–7.3 days) from admission. Bleeding unrelated to procedures occurred in 16.2% (95% CI, 14.2%–18.4%) of patients, with portal hypertension–related gastrointestinal bleeding being the most common type of bleeding. Venous thrombosis was diagnosed in 8.0% (95% CI, 6.6%–9.7%) of patients, with portal vein thrombosis the most common thrombosis identified (5.3%; 95% CI, 4.2%–6.7%).

Comparison of Patients With and Without Bleeding

When patients with bleeding events were compared with patients without bleeding, multiple significant differences were identified in univariable analysis (Table 1). Admission characteristics, including age, sex, etiology of cirrhosis, and reason for admission, were generally similar between the groups. However, patients with bleeding were more likely to have nonalcoholic steatohepatitis (NASH) as an etiology to cirrhosis (43.9% vs 30%; $P = .005$) and had significantly higher mean body mass index (BMI; 31.2 vs 29.5; $P = .014$). Based on univariate analysis, when categorized into BMI classes, patients with BMI ≥40 were at significantly higher risk of experiencing ≥1 procedure bleeds compared with patients with normal BMI patients ($P = .042$) (Supplementary Table 9).

Patients with bleeding had significantly higher MELD scores and CTP scores at admission. A univariate analysis showed patients who had a MELD >25 at admission were at higher risk of experiencing ≥1 procedure bleeds compared with patients who had a MELD ≤25 at admission ($P < .001$) (Supplementary Table 10). In the bleeding group, 42.1% of patients had ACLF compared with 19.7% in the nonbleeding group ($P < .001$). Specifically, higher proportions of advanced ACLF grade 2 and 3 were more common in the bleeding cohort. Procedural-related bleeding was more likely to develop in patients with ACLF (relative risk, 2.05; 95% CI, 1.32–3.19; $P = .001$).

Patients with bleeding underwent more procedures during the hospitalization (mean 4.4 vs 2.4 procedures, $P < .001$). During each hospitalization, patients had an incidence rate of 2.0 procedures (95% CI, 1.9–2.1 procedures) per 10 patient hospital days. The median time to the first bleed among the cohort with bleeding was 3.5 days (95% CI, 2.5–6.0 days) from admission. Patients with bleeding were more likely to have undergone high-risk procedures compared with patients who did not bleed (relative risk, 2.23; 95% CI, 1.35–3.73; $P = .002$).

Admission laboratory values were significantly different, with elevated creatinine, total bilirubin, and international normalized ratio (INR) in the bleeding group (Table 1). Patients with bleeding were more likely to have AKI (54.9% vs 33.6%, $P < .001$), CKD (25.6% vs 17.3%, $P = .011$), and infection (43.9% vs 24.1%, $P < .001$) at admission. There were no significant differences in presence of antiplatelet therapy, anticoagulation, or initiation of medical thromboprophylaxis at admission between groups.

Procedures With Bleeding Compared With Those Without Bleeding

The cohort underwent 3006 procedures, with 93 procedures associated with a bleeding event (Table 2). Bleeding events were encountered in 2.9% (46 of 1568) common bedside procedures, 4.4% (25 of 569) vascular, 1.7% (13 of 760) endoscopic, 5.7% (5 of 88) percutaneous, 36.3% (4 of 11) dental, and 0% (0 of 10) skin procedures (Supplementary Figure 2 and Supplementary Tables 7 and 8). There was no significant difference in trainee involvement in procedures (nonbleed 72.4% vs bleed 79.6%, $P = .382$). Patients with bleeding underwent a higher proportion of high-risk procedures (Supplementary Figure 3).

Laboratory values before procedures with bleeding demonstrated significantly higher blood urea nitrogen, creatinine, total bilirubin, INR, and significantly lower fibrinogen (Table 2). Notably, the mean platelet count before procedures was similar between procedures with bleeding 103.7 k/μL and procedures without bleeding 113.3 k/μL ($P = .11$). When high- and low-risk procedures were stratified, the presence of severe thrombocytopenia (platelets <50,000/μL) was not significantly different between groups (Supplementary Figure 4). Owing to the low prevalence of fibrinogen values checked before procedures, multivariable analysis of fibrinogen could not be performed (data missing in 81.6% of patients).

Procedures in which prophylaxis was administered before the procedure had a higher percentage of bleeds than procedures in which prophylaxis was not administered before the procedure (19.4% of procedures with bleeding vs 7.4% of procedures without bleeding, $P = .001$) (Table 2). Specifically,

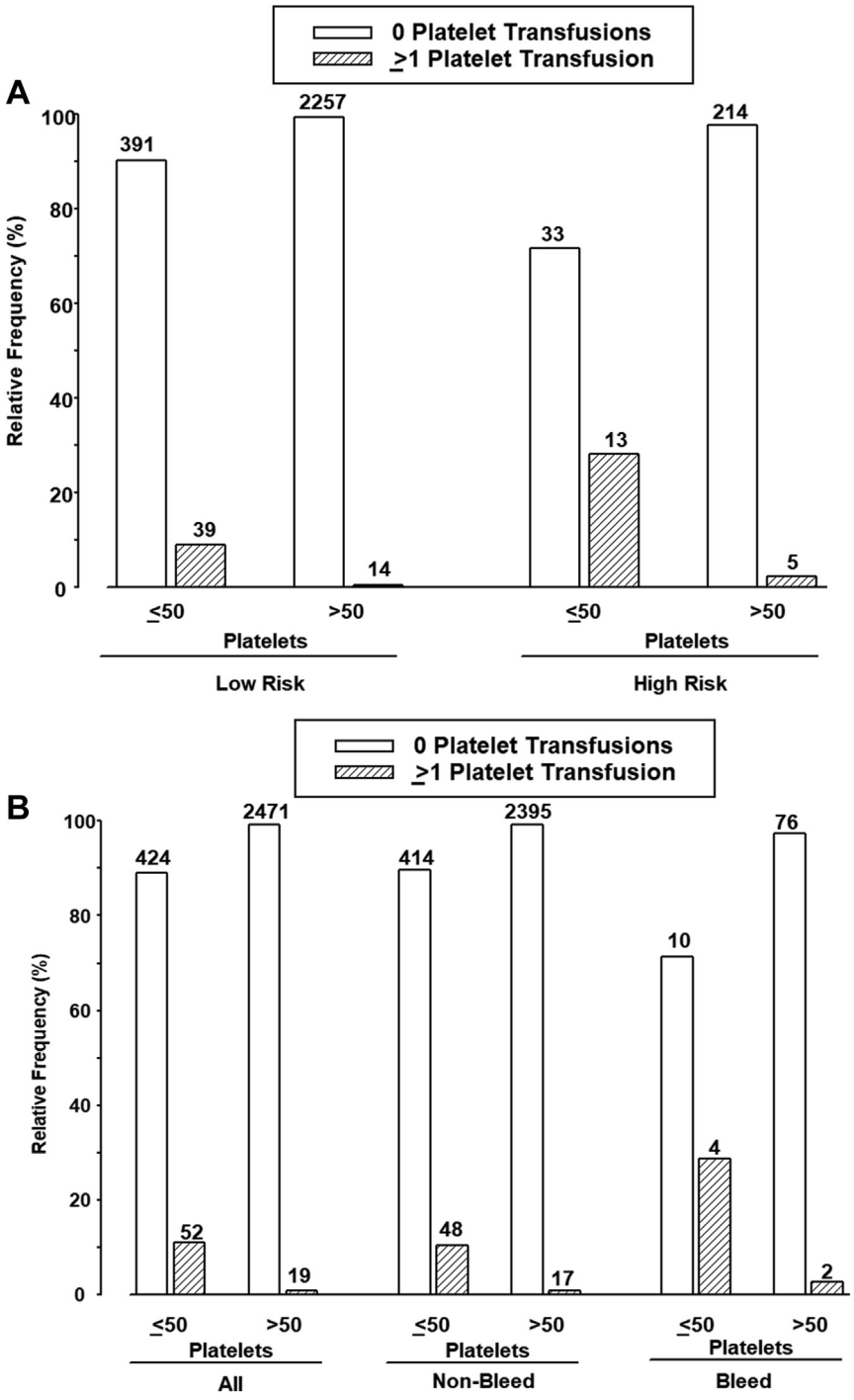


Figure 1. (*A*) The relative frequencies between patients who did or did not receive platelet transfusions before the procedure as stratified by procedure risk are compared. Platelet transfusion was significantly different depending on the preprocedure platelet count for both low- and high-risk procedures. With severe thrombocytopenia (platelet count $\leq$50,000/μL) before the procedure, platelet transfusions were used more often for high-risk procedures ($P = .001$). In severe thrombocytopenia before the procedure, platelet transfusions were used more often for high-risk procedures than for low-risk procedures. ($P = .021$). (*B*) The relative frequencies between patients who did or did not receive platelet transfusions before a procedure as stratified by the degree of thrombocytopenia and bleeding outcome are compared. Platelet transfusion was significantly dependent on platelet count in all patients ($P < .001$). Similarly, among nonbleeding procedures, platelet transfusion was dependent on platelet count ($P < .001$), and likewise among bleeding procedures ($P = .004$). Values above the *bars* identity the number of patients upon which the relative frequency is based.

bleeding from procedures was more likely if a prophylactic platelet transfusion was administered before the procedure (6.5% vs 2.2%, $P = .024$) and if a plasma transfusion was administered before the procedure (9.7% vs 2.1%, $P < .001$).

Platelet transfusion before both low- and high-risk procedures was more common for procedures performed on patients with severe thrombocytopenia than performed in patients who had a preprocedure count >50,000/μL (Figure 1*A*). In 28.6% of the procedures performed on patients who had bleeding and severe thrombocytopenia, the patient had received at least 1 platelet transfusion before the procedure compared with 10.4% of the procedures performed on patients who had no bleeding but severe thrombocytopenia ($P = .055$) (Figure 1*B*). A higher proportion of low- and high-risk procedures was performed on patients who had received a plasma transfusion when the preprocedure INR was >1.5 (Figure 2*A*). In 14% of the procedures performed on patients with bleeding and an INR >1.5, the patient had received at least 1 unit of plasma before the procedure compared with only 3.5% of the procedures performed on patients without bleeding and an INR >1.5 ($P = .001$) (Figure 2*B*).

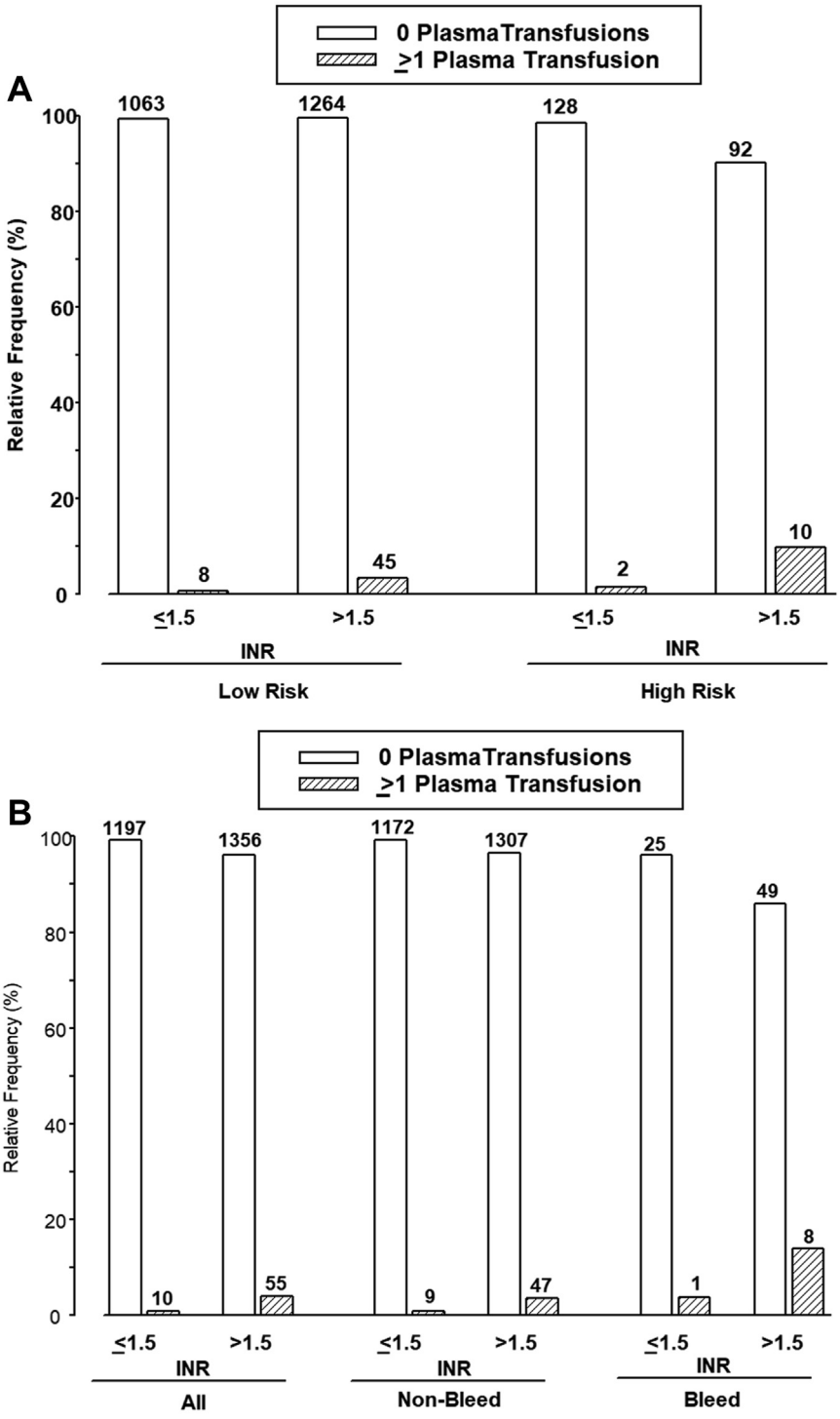


Figure 2. (*A*) The relative frequencies of patients who did or did not receive a plasma transfusion before procedures stratified by procedure risk are compared. Frequency of plasma transfusion was significantly dependent on INR. When the INR was >1.5 before the procedure, a plasma transfusion was given more often for high-risk procedures ($P = .005$). (*B*) The relative frequencies between patients who received a plasma transfusion before the procedure, as stratified by INR and bleeding outcome, are compared. Among all procedures, a plasma transfusion was more frequently provided before procedures with an INR >1.5. ($P < .001$). Among nonbleeding procedures, a plasma transfusion was more frequently provided in procedures with an INR >1.5 ($P < .001$). However, among bleeding procedures, plasma transfusions were not significantly dependent on the INR ($P = .261$). Patients with bleeding more frequently received a plasma transfusion before the procedure when the INR was >1.5 compared with patients without bleeding and an INR >1.5 ($P = .001$). Values above the *bars* identity the number of patients upon which the relative frequency is based.

The presence of anticoagulation or antiplatelet medication at the time of the procedure was similar between the nonbleed (27.8%) and bleed (31.2%) groups ($P = .198$). However, clopidogrel use at the time of the procedure was more common among bleed procedures (3.3% vs 0.5%, $P = .019$).

Predictors of Procedural-Related Bleeding

Multivariate analysis showed that high-risk procedures (adjusted odds ratio [AOR], 4.64; 95% CI, 2.44–8.84; $P < .001$), MELD score (AOR, 2.37; 95% CI 1.46–3.86; $P < .001$), and higher BMI (AOR, 1.40; 95% CI, 1.10–1.80; $P = .007$) were uniquely associated with procedure bleeding (model C statistic, 0.77; 95% CI, 0.75–0.78) after adjusting for all remaining predictor variables and center-group variation (Table 3). The presence of ascites at admission, trainee involvement in the procedure, AKI present at admission, platelet level before the procedure, INR before the procedure, infection at admission, antithrombotic therapy, number of prior procedures, VTE prophylaxis at admission, and

Table 3. Multivariable Binomial Generalized Estimating Equation Model Adjusted Odds Ratios for Comparing the Odds for Procedural-Related Bleeding[a]

Predictor variable	Ratio[b]	AOR (95% CI)	*P* value[c]
Procedure risk	High: Low	4.64 (2.44–8.84)	**<.001**
MELD score at admission	3rd quantile (25.9): 1st quantile (13.6)	2.37 (1.46–3.86)	**<.001**
BMI	3rd quantile (33.3): 1st quantile (24.1)	1.40 (1.10–1.80)	**.007**
Ascites present	Present: Absent	1.31 (0.99–1.75)	.062
Trainee performed	Yes: No	1.56 (0.81–2.99)	.177
AKI present at admission	Present: Absent	0.72 (0.42–1.22)	.223
INR prior to procedure	3rd quantile (2.0): 1st quantile (1.3)	1.22 (0.84–1.79)	.294
Infection at admission	Present: Absent	1.26 (0.76–2.08)	.337
Antithrombotic prior to procedure	Yes: No	1.34 (0.69–2.61)	.394
Platelet level prior to procedure	3rd quantile (137.0): 1st quantile (59.0)	0.93 (0.65–1.27)	.635
Number of prior procedures	$x + 1$: x	1.02 (0.92–1.13)	.657
ACLF present at admission	Yes: No	1.04 (0.80–1.35)	.776
VTE prophylaxis at admission	Yes: No	1.01 (0.52–1.96)	.972

NOTE. Bold *P* values indicate statistical significance ($P < .05$). See Supplementary Table 3 for the percentage of missing data for each variable.
[a]Procedure is the analytical unit, and 2324 of the 3006 total procedures (77.3%) had a complete set of risk factor data and were included in the analysis. Please see Supplementary Table 6 for the center-group related AORs that were omitted from this AOR summary.
[b]Ratio notation: 1st quantile denotes the value of the predictor variable at the 25th percentile of the predictor variable empirical distribution. The 3rd quantile denotes the value of the predictor variable at the 75th percentile of the predictor variable empirical distribution.
[c]*P* values were derived from the multivariate binomial generalized estimating equation multivariate adjusted type III Wald's χ^2 tests (please see the Analytical Methods section of the Supplementary Methods for further details).

presence of ACLF were not significant predictors of procedure bleeding. Center-group was included in the multivariate analysis to adjust for between center-group variability, and the center-group adjusted AORs are presented separately in Supplementary Table 6. Data for individual center-specific enrollment and bleeding incidence are listed in Supplementary Table 5.

Univariate analysis revealed that the risk for procedural bleeding was higher among procedures performed on patients with a BMI ≥40 than among procedures performed on patients with a BMI within the normal reference range ($P = .016$) (Supplementary Table 9). Univariate analysis also revealed that the risk for procedural bleeding was higher among the procedures performed on patients who had an admission MELD >25 than among the procedures performed on patients who had an admission MELD ≤25 ($P < .001$) (Supplementary Table 10)

Patient Mortality and Survival Analysis

Death during hospitalization and the 28-day follow-up period was more common in patients who experienced procedural-related bleeding. Patients in the bleeding cohort had higher rates of mortality during hospitalization (28.8% vs 6.5%, $P < .001$) and during the 28-day follow-up period (23.8% vs 7.0%, $P < .001$). A total of 94 patients died during hospitalization, and 2 additional patients died after hospitalization during the 28-day follow-up period. Five patients undergoing 8 separate procedures with bleeding died as an indirect or direct result of bleeding. Two patients had multiple procedural-related bleeding events indirectly or directly associated with death. Procedural-related bleeding associated with death was encountered related to the following procedure types: transjugular intrahepatic portosystemic shunt, paracentesis, esophagogastroduodenoscopy with band ligation, and arterial and venous catheter procedures.

When patients with and without bleeding were compared, patients with procedural-related bleeding had a significantly higher risk of death (HR, 6.91; 95% CI, 4.22–11.31; $P < .001$) (Figure 3*A*). Patients with major procedural bleeding had a significantly higher risk of death than patients without bleeding (HR, 12.97; 95% CI, 6.42–26.19; $P < .001$) (Figure 3*B*). When death was examined in multivariate logistic regression, patients with procedural-related bleeding had a significantly higher risk of death (AOR, 3.14; 95% CI, 1.66–5.97; $P < .001$) (Supplementary Table 11).

An increased number of procedures performed was also significantly predictive of risk of death (AOR, 1.14; 95% CI, 1.04–1.27; $P = .008$). A Cox multivariate regression

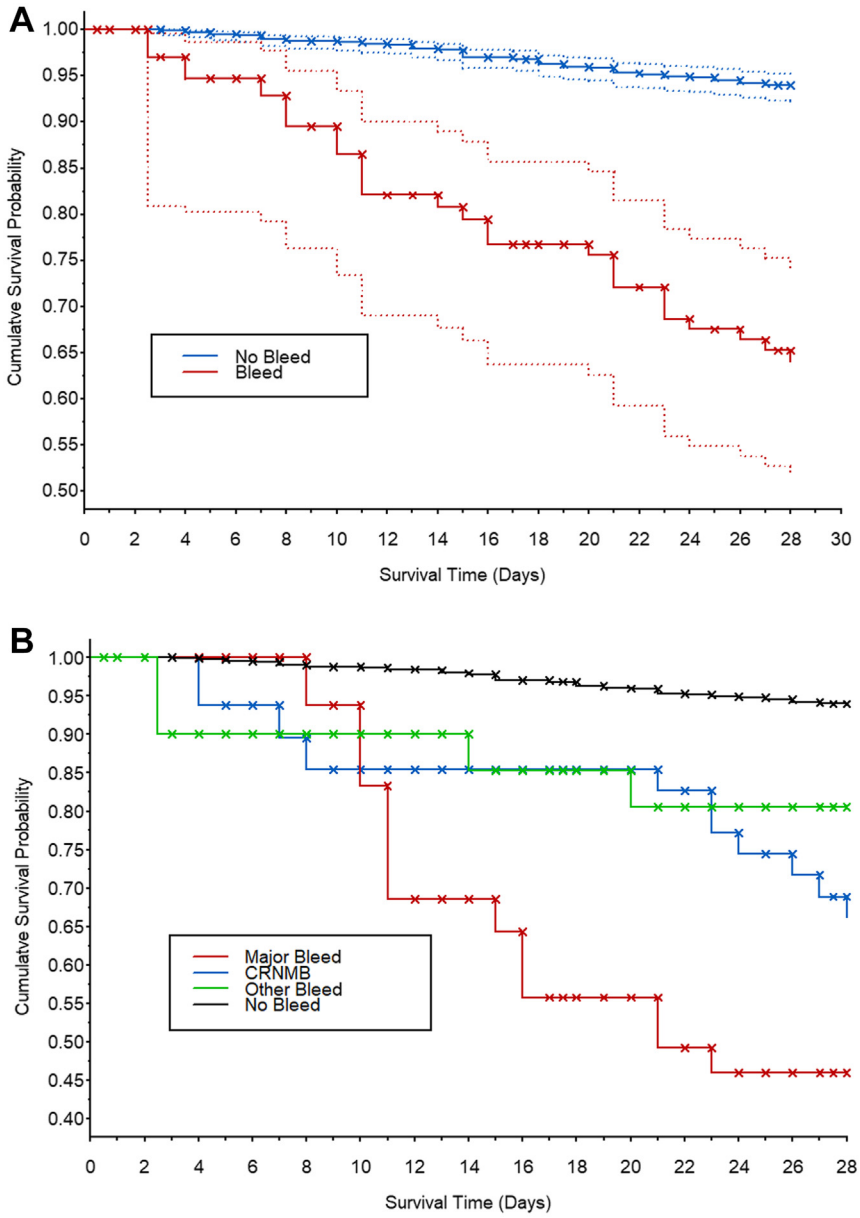


Figure 3. (*A*) Kaplan-Meier survival curves for 28-day survival for non-bleeding and bleeding patients where bleed type is a time-dependent variable. The *solid line* identifies the Kaplan-Meier cumulative probability survival curve, the *hatch lines* identify the point-wise 95% CI, and the *x*-symbols identify right-censored survival times. The HR for those with prior bleeding compared with patients without prior bleeding is 6.91 (95% CI, 4.22–11.31; $P < .001$). (*B*) Kaplan-Meier survival curves for 28-day survival for patients without bleeding, major bleeding, CRNMB, and other bleeding where bleed type is a time-dependent variable. The HR for comparing survival between patients with and without prior major bleeding is 12.97 (95% CI, 6.42–26.19; $P < .001$), the HR for comparing survival between patients with and without prior CRNMB bleeding is 6.20 (95% CI, 3.23–11.91; $P < .001$), and the HR for comparing survival between patients with and without prior other bleeding is 2.27 (95% CI, 0.84–9.15; $P = .095$).

survival analysis also demonstrated a significantly lower likelihood of 28-day survival in patients with procedural-related bleeding compared with patients without a bleeding event (adjusted HR [AHR], 1.71; 95% CI, 1.08–2.73; $P = .023$) (Table 4). Similarly, an increased number of procedures performed was also significantly predictive of lower likelihood of 28-day survival (AHR, 1.25; 95% CI, 1.10–1.41; $P < .001$) in the multivariate regression survival analysis.

When death was examined in respect to the most severe type of bleeding event experienced in a multivariate logistic regression model, patients with major bleeding had a significantly higher risk of death compared with patients without bleeding (AOR, 5.77; 95% CI, 2.20–15.12; $P < .001$) (Supplementary Table 12). Patients with CRNMB compared with patients without bleeding also had a significantly higher risk of death (AOR, 2.89; 95% CI, 1.15–6.28; $P = .024$) (Supplementary Table 10). A Cox multivariate regression survival analysis also demonstrated a significantly lower likelihood of 28-day survival in patients with procedural-related major bleeding compared with patients without bleeding (AHR, 3.49; 95% CI, 1.56–7.80; $P = .002$) (Supplementary Table 13).

Discussion

This is the largest prospective study to date examining procedural-related bleeding in hospitalized patients with decompensated cirrhosis. The dynamic spectrum of decompensated liver disease coupled with the rarity of bleeding presents significant investigational challenges.[31] Our results show that procedural-related bleeding in

Table 4. Multivariate Extended Cox's Regression Adjusted Hazard Ratios for Comparing the Instantaneous Risk of Death at the Patient Level[a]

Predictor variable	Ratio[b]	AHR (95% CI)	*P* value[c]
Procedures during hospitalization, n	$x + 1$: x	1.25 (1.10–1.41)	**<.001**
MELD score at admission	3rd quantile (24.3): 1st quantile (12.5)	2.52 (1.47–4.33)	**.001**
Procedure bleeding event	Yes: No	1.71 (1.08–2.73)	**.023**
History of CKD	Yes: No	0.48 (0.25–0.92)	**.028**
Age	3rd quantile (66.0): 1st quantile (51.0)	1.33 (0.97–1.83)	.076
Infection at admission	Yes: No	1.47 (0.92–2.34)	.111
CTP class at admission	Class C: Class A or B	1.60 (0.67–3.85)	.290
Ascites present	Yes: No	1.66 (0.64–3.29)	.298
AKI at admission	Yes: No	1.26 (0.74–2.12)	.395
Sex	Male: Female	0.84 (0.52–1.35)	.471
ACLF present at admission	Yes: No	0.90 (0.66–1.23)	.503

NOTE. Bold *P* values indicate statistical significance ($P < .05$). Note the Gambsch and Therneau null hypothesis test, in which it is assumed under the null hypothesis that the HR is time independent (ie, the HR remains constant though time), failed to be reject at the predictor variable level for all 11 predictor variables ($P > .150$ for all), and also failed to be rejected at the model level ($P = .817$).

[a]Patient is the analytical unit, and 1021 of the total 1187 patients (86.0%) had a complete set of risk factor data and were included in the analysis.

[b]Ratio notation: 1st quantile denotes the value of the predictor variable at the 25th percentile of the predictor variable empirical distribution, and the 3rd quantile denotes the value of the predictor variable at the 75th percentile of the predictor variable empirical distribution.

[c]*P* value is the *P* value from the multivariate adjusted type III Wald's χ^2 test (please see the Analytical Methods section of the Supplementary Material for further details).

hospitalized patients with cirrhosis is rare. The risk of bleeding is strongly associated with more decompensated disease, higher-risk procedures, and higher BMI. Specifically, patients undergoing high-risk procedures with MELD scores >25 and BMI ≥40 may represent a higher-risk population more prone to develop bleeding from procedures. However, contrary to common perception, bleeding is not associated with conventional coagulation tests, antithrombotic therapy use, or preprocedure prophylaxis. Development of procedural-related bleeding in hospitalized patients with cirrhosis is independently associated with increased mortality and a lower likelihood of 28-day survival.

Many clinicians perceive bleeding risk to be increased in patients with decompensated cirrhosis and therefore may avoid procedures or alter approaches with transfusions for prophylaxis. Our results demonstrate that procedural-related bleeding is very uncommon, irrespective of prophylaxis use. Studies examining bleeding in patients with cirrhosis report varying rates of bleeding and do not always account for prophylaxis. Three retrospective studies conducted in patients with cirrhosis undergoing various procedures reported a wide range of bleeding events from 2% to 20%.[8-10] Our results agree with a previous study of bleeding in hospitalized patients with decompensated cirrhosis where investigators reported bleeding unrelated to portal hypertension developed in 6.7% of patients, with most of the bleeding related to procedures.[7]

Retrospective cohort studies in patients with decompensated cirrhosis indicate conventional tests of hemostasis do not predict bleeding.[32,33] Societal guidance now recommends against the use of platelet count and INR to risk stratify patients before procedures.[5,20,21] Our study supports these recommendations, because neither preprocedure platelet count nor INR predicted bleeding, and correction of these laboratory values did not reduce bleeding risk. Although the use of preprocedure prophylaxis was not randomized in this study, its use was overall low, indicating further evidence of the low likelihood of efficacy to prevent bleeding.

Nonetheless, the INR is inextricably linked to cirrhosis through the MELD score and may remain conflated with bleeding risk. However, we found no evidence that use of plasma to correct the INR prevents bleeding events. Together this suggests that the predictive value of the INR rests only in that it exemplifies disease severity rather than reflecting a risky acquired coagulopathy.

Procedure risk category was the most significant predictor of bleeding in this cohort. This finding corroborates a recent retrospective study examining the risk of bleeding with procedures and surgery.[10] Determining procedure bleeding risk is complex and based on inherent technical factors, organ system involvement, and highly dynamic patient-specific risk factors. Society guidelines advocate for a dichotomous procedure risk categorization (low or high),

where low-risk procedures are unlikely to result in major bleeding (<1.5%). Procedures that involve locations in the body with potential catastrophic consequences or difficulty in controlling bleeding are also considered high risk. These classifications are from expert opinion in the context of managing antithrombotic therapy in patients undergoing procedures.[5,29,30] This finding highlights the importance of future studies to focus on specific high-risk procedures to better clarify future recommendations for periprocedural risk stratification and management strategies.

Obesity is known to have an independent and procoagulant effect on the hemostatic system.[34] In this cohort, however, NASH and higher BMI were more common in patients with bleeding. In multivariate analysis, higher BMI was a significant predictor of bleeding. Previous studies suggest NASH may increase the risk for hypercoagulability with higher risk of thrombosis.[35,36] Obese patients without cirrhosis undergoing procedures, such as percutaneous coronary intervention or surgery, have lower rates of bleeding complications compared with low BMI patients.[37,38] However, a recent large cohort study examined this "obesity paradox" and found that obesity may not actually protect against bleeding.[39] Adipose tissue can obscure anatomic landmarks, suggesting that obesity may increase the risk of procedural-related bleeding.[40]

The relationship with BMI and procedural-related bleeding in this study may possibly be explained by technical challenges during procedures. The use of BMI may have some important limitations in the setting of cirrhosis given the presence of ascites, sarcopenia, and edema. In this study, we controlled for the contribution of ascites in the model and therefore demonstrated BMI, independent of ascites, predicts bleeding. Nevertheless, edema and other features of body habitus, such as sarcopenia, were not assessed in this study and may confound this finding. Further studies are needed to expand and confirm the role of BMI as an easily quantifiable measure to aid in predicting bleeding risk in this population.

Patients admitted to the hospital with cirrhosis are at risk to develop acutely decompensated disease or multiorgan failure consistent with ACLF, often driven by infection and AKI. Previous studies have found associations between acute and chronic kidney disease and risk of bleeding in patients with cirrhosis.[41-43] Our study demonstrated that AKI and CKD were both more common in patients with bleeding. Levels of both blood urea nitrogen and creatinine were significantly higher in patients with bleeding compared with patients without bleeding at admission and before procedures. However, the presence of AKI was not predictive of bleeding in multivariable modeling.

The significant influence of creatinine in the MELD score may partly explain this due to a fundamental confounding relationship between these variables. Patients with acutely decompensated cirrhosis and ACLF have unique hemostatic profiles compared with patients with stable cirrhosis.[17] Patients with ACLF typically have significant kidney disease, and consequently, this confounding relationship could obscure the role that specific organ failures have on bleeding risk.

The presence of medical VTE prophylaxis at admission and other anticoagulation preprocedure did not enhance bleeding risk. This finding supports society guideline recommendations to consider anticoagulation for VTE prophylaxis in high-risk patients with cirrhosis admitted to the hospital. Interestingly, VTE prophylaxis was started at admission in only 25% of patients. Although no difference was observed in bleeding outcomes, future studies should clarify the rationale for providing or withholding VTE prophylaxis in hospitalized patients.[44]

Patients who developed procedural-related bleeding had a significantly lower likelihood of 28-day survival in this cohort, even when controlling for common confounding factors associated with death, such as MELD, ACLF, and CTP grade. This significant and independent risk for death emphasizes the urgent necessity for future studies to develop strategies to prevent bleeding by accurately identifying the highest-risk procedures and patients. It is important, however, to consider the complex relationship between procedural bleeding and death because patients with decompensated liver disease and multiorgan failure more often require procedures, and the consequences of bleeding may contribute to, but not completely explain, the ultimate cause of death. In some cases, bleeding may be a marker of increased mortality risk rather than a contributing factor per se. The small number of deaths in this cohort overall places constraints on statistical modeling, and this finding should be interpreted with caution until future studies can elaborate on these findings.

These results provide clinicians with several direct practical applications. First, procedural-related bleeding is very rare but is associated with higher-risk procedures and a higher risk of death in hospitalized patients with cirrhosis. Therefore, preventive strategies and planning for rescue therapies for potential bleeding in the periprocedural period in high-risk procedures is imperative. Notably, preprocedural prophylaxis in this cohort was not associated with decreased bleeding. This finding is consistent with recent guidance recommending against routine use or preprocedure prophylaxis based on platelet count or INR.[5,20,21] Clinicians can be reassured by the findings that platelet count and the INR do not predict bleeding events and that correction of these values is therefore unlikely to reduce bleeding risk.

Second, patients with elevated BMI may be higher risk for bleeding, and caution in these patients is advised, particularly when they are undergoing high-risk procedures.

Third, the degree of hepatic decompensation is a very important predictor of bleeding, and caution is advised in patients with a higher MELD score.

Our study has several strengths, including the prospective study design with standard clear outcome definitions. Given patients were sampled from multiple centers throughout North and South America, the strong external validity allows for broader application.

We minimized misclassification bias through use of standard bleeding definitions, prospective enrollment, and blinded adjudicators. Nevertheless, classifying bleeding related to procedures is challenging in this population given

the underlying severity of illness, which can contribute to all types of bleeding. We relied on previously published literature and biologic plausibility to construct our multivariable model a priori, which allows for increased validity and generalizability.

As with most observational studies, there are important limitations to recognize. There is potential for selection bias because patients admitted to the hospital who did not undergo procedures were not enrolled, and this population may have included higher-risk individuals who were too unstable to undergo procedures.

The rarity of bleeding events limited construction of a multivariable model, which could lead to inaccurate or overlooked associations. As such, we included the most important variables in the model based on prior studies and plausible biologic relationships, and therefore, many unknown factors that which may affect bleeding risk were not included.

Given the rarity of use of antiplatelet agents and therapeutic anticoagulant agents in this cohort, we combined all agents into one category for multivariate analyses and found no association with bleeding. The bleeding risk with these medications likely depends on many factors, including medications class, timing of administration, dose, and dynamic patient factors that were unable to be measured in the limitations of this study design.

This was an observational study; therefore, the use of preprocedure prophylaxis was not randomized. Because patients who received prophylaxis were more likely to be perceived by local providers to be at higher risk of bleeding, prophylaxis was intentionally excluded from the multivariate model predicting bleeding to reduce introduction of bias.

Although local cohorts were combined into one large cohort in this study, there is a possibility that center-specific factors, including patient characteristics and enrollment approaches, differed between centers. To counter this potential bias, we used extensive instructive guidance and preparation with centers, scrutinized database entries during enrollment, and used independent adjudicators to review bleeding events.

Furthermore, to account for any center-specific effect, we adjusted for center-specific influence in univariate and multivariate modeling, as described above. Center-group designation was intended to distribute bleeding events evenly, and the groups were artificial constructs, and therefore, this study is not powered to compare specific variables unique to local centers that may affect bleeding risk. A limitation of this strategy is the possibility that heterogeneity between center bleeding rates is unaccounted for and may be an unrecognized bias introduced into the analyses.

A 28-day follow-up period was chosen for standardization and logistics for follow-up during enrollment, and therefore, bleeding events, particularly delayed bleeding, may have been missed in extended hospitalizations.

Lastly, we suspect that bleeding risk is unique and inherent to specific procedures, and the rarity of outcome events precluded us from performing extensive subcohort analyses to assess procedures separately. We attempted to mitigate this by using a formal definition of risk stratification; however, future studies may consider focusing on single procedures or groups of procedures with similar features.

Conclusion

In conclusion, procedural-related bleeding is rare in a large and diverse population of hospitalized patients with decompensated cirrhosis. Conventional parameters previously associated with bleeding risk, including thrombocytopenia and coagulopathy measured by INR, do not predict bleeding, and the use of measures to "correct" these values should be avoided. Rather, clinicians should focus individual management strategies on higher-risk populations that appear to include patients undergoing high-risk procedures with higher MELD scores and higher BMI. Although bleeding from procedures is rare, its independent association with death in this study highlights the need for future studies to improve our understanding of bleeding risk in this population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2023.05.046.

References

1. Desborough MJ, Hockley B, Sekhar M, et al. Patterns of blood component use in cirrhosis: a nationwide study. Liver Int 2016;36:522–529.
2. Lisman T, Caldwell SH, Intagliata NM. Haemostatic alterations and management of haemostasis in patients with cirrhosis. J Hepatol 2022;76:1291–1305.
3. Intagliata NM, Davitkov P, Allen AM, et al. AGA technical review on coagulation in cirrhosis. Gastroenterology 2021;161:1630–1656.
4. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood 2019;133:1840–1853.
5. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, 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;73:366–413.
6. Schepis F, Turco L, Bianchini M, et al. Prevention and management of bleeding risk related to invasive procedures in cirrhosis. Semin Liver Dis 2018;38:215–229.
7. Drolz A, Ferlitsch A, Fuhrmann V. Management of coagulopathy during bleeding and invasive procedures in patients with liver failure. Visc Med 2018;34:254–258.
8. Giannini EG, Greco A, Marenco S, et al. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol 2010;8:899–902; [quiz: e109].
9. Napolitano G, Iacobellis A, Merla A, 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.
10. Janko N, Majeed A, Commins I, et al. Procedural bleeding risk, rather than conventional coagulation tests, predicts procedure related bleeding in cirrhosis. Eur J Gastroenterol Hepatol 2022;34:192–199.
11. Alvaro D, Caporaso N, Giannini EG, et al. Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia. Eur J Clin Invest 2021;51:e13508.
12. Rocha LL, Neto AS, Pessoa CMS, et al. Comparison of three transfusion protocols prior to central venous catheterization in patients with cirrhosis: a randomized controlled trial. J Thromb Haemost 2020;18:560–570.
13. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. Hepatology 2016; 63:566–573.
14. Vuyyuru SK, Singh AD, Gamanagatti SR, et al. A randomized control trial of thromboelastography-guided transfusion in cirrhosis for high-risk invasive liver-related procedures. Dig Dis Sci 2020;65:2104–2111.
15. Peck-Radosavljevic M, Simon K, Iacobellis A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology 2019;70: 1336–1348.
16. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 2018;155:705–718.
17. Premkumar M, Saxena P, Rangegowda D, et al. Coagulation failure is associated with bleeding events and clinical outcome during systemic inflammatory response and sepsis in acute-on-chronic liver failure: an observational cohort study. Liver Int 2019;39:694–704.
18. Blasi A, Calvo A, Prado V, et al. Coagulation failure in patients with acute-on-chronic liver failure and decompensated cirrhosis: beyond the international normalized ratio. Hepatology 2018;68:2325–2337.
19. Pillai AA, Kriss M, Al-Adra DP, et al. Coagulopathy and hemostasis management in patients undergoing liver transplantation: defining a dynamic spectrum across phases of care. Liver Transpl 2022;28:1651–1663.
20. O'Shea RS, Davitkov P, Ko CW, et al. AGA Clinical Practice Guideline on the Management of Coagulation Disorders in Patients With Cirrhosis. Gastroenterology 2021;161:1615–1627.e1.
21. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022;76:1151–1184.
22. van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: beyond events per variable criteria. Stat Methods Med Res 2019; 28:2455–2474.
23. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38:258–266.
24. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417.
25. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut 2011; 60:702–709.
26. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64:531–537.
27. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202–204.
28. Kaatz S, Ahmad D, Spyropoulos AC, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13:2119–2126.
29. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. N Engl J Med 2013;368:2113–2124.
30. Patel IJ, Rahim S, Davidson JC, 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;30:1168–1184.e1.
31. Stotts MJ, Lisman T, Intagliata NM. The spectrum of disease severity in cirrhosis and its implications for hemostasis. Semin Thromb Hemost 2020;46:716–723.
32. Vieira da Rocha EC, D'Amico EA, Caldwell SH, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol 2009; 7:988–993.
33. Soh H, Chun J, Hong SW, et al. Child-Pugh B or C cirrhosis increases the risk for bleeding following colonoscopic polypectomy. Gut Liver 2020;14:755–764.
34. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. Curr Opin Hematol 2013;20:437–444.
35. Stine JG, Niccum BA, Zimmet AN, et al. Increased risk of venous thromboembolism in hospitalized patients with cirrhosis due to non-alcoholic steatohepatitis. Clin Transl Gastroenterol 2018;9:140.
36. Stine JG, Shah NL, Argo CK, et al. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. Liver Transpl 2015; 21:1016–1121.
37. Numasawa Y, Kohsaka S, Miyata H, et al. Impact of body mass index on in-hospital complications in patients undergoing percutaneous coronary intervention in a Japanese real-world multicenter registry. PLoS One 2015;10: e0124399.

38. Kindo M, Minh TH, Gerelli S, et al. The prothrombotic paradox of severe obesity after cardiac surgery under cardiopulmonary bypass. Thromb Res 2014;134:346–353.
39. Braekkan SK, van der Graaf Y, Visseren FL, et al. Obesity and risk of bleeding: the SMART study. J Thromb Haemost 2016;14:65–72.
40. Alvarez NH, O'Malley TJ, Abai B, et al. Complications of peripheral cannulation site in obese patients on adult extracorporeal membrane oxygenation. ASAIO J 2021; 67:1294–1300.
41. Zanetto A, Rinder HM, Campello E, et al. Acute Kidney Injury In Decompensated Cirrhosis Is Associated With Both Hypo-Coagulable And Hyper-Coagulable Features. Hepatology 2020;72:1327–1340.
42. Intagliata NM, Davis JPE, Lafond J, et al. Acute kidney injury is associated with low factor XIII in decompensated cirrhosis. Dig Liver Dis 2019;51:1409–1415.
43. 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;38:1437–1441.
44. Davis JPE, O'Leary KE, Intagliata NM. Overuse of venous thromboembolism prophylaxis among hospitalized patients with liver disease. Eur J Haematol 2020;104:223–229.

Received February 13, 2023. Accepted May 11, 2023.

Correspondence
Address correspondence to: Nicolas Intagliata, MD, MS, University of Virginia Medical Center, Division of Gastroenterology and Hepatology, PO Box 800708, Charlottesville, Virginia 22908. e-mail: nmi4d@uvahealth.org.

Acknowledgments
Gabrielle Laskey from University of Virginia, Charlottesville, Virginia; Jorge Martinez Morales, MD, from Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; J. Westley Heinle, MPH, and Breianna Hummer, MS, from Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania; Alex Burdzy, BS, from University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Maria Julia Gabriela Colossi from Division of Gastroenterology (Gastrocentro), Department of Internal Medicine, School of Medical Sciences of University of Campinas (UNICAMP), São Paulo, Brazil; Marina Sycheva from Wake Forest University School of Medicine, Atrium Health, Charlotte, North Carolina; Caroline Marcondes Ferreira, MSc, from University of São Paulo School of Medicine, São Paulo, Brazil; Hannah Amundson and Rehma Shabbir, MBBS, ACRP-CP, BS, from Baylor Scott and White Hospital, Dallas, Texas; Alfredo Servin-Caamaño, MD, from Hospital General de México "Dr. Eduardo Liceaga," La Salle Faculty of Medicine, Mexico City, Mexico; and Kamalpreet S. Hara, MBBS, from Mayo Clinic, Rochester, Minnesota.

CRediT Authorship Contributions
Nicolas M. Intagliata, MD, MS (Conceptualization: Lead; Investigation: Lead; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).
Robert S. Rahimi, MD, MSCR (Investigation: Supporting).
Fatima Higuera-de-la-Tijera, MD, PhD (Investigation: Supporting).
Douglas A. Simonetto, MD (Investigation: Supporting).
Alberto Queiroz Farias, MD (Investigation: Supporting).
Daniel F. Mazo, MD, PhD (Investigation: Supporting).
Justin R. Boike, MD, MPH (Investigation: Supporting).
Jonathan G. Stine, MD (Investigation: Supporting).
Marina Serper, MD, MS (Investigation: Supporting).
Gustavo Pereira, MD, PhD (Investigation: Supporting).
Angelo Z. Mattos, MD, MSc, PhD (Investigation: Supporting).
Sebastian Marciano, MD, MSc (Investigation: Supporting).
Jessica P.E. Davis, MD, MSCR (Investigation: Supporting).
Carlos Benitez, MD (Investigation: Supporting).
Ryan Chadha, MD (Investigation: Supporting).
Nahum Méndez-Sánchez, MD, MS, PhD (Investigation: Supporting).
Andrew S. deLemos, MD (Investigation: Supporting).
Arpan Mohanty, MBBS, MD (Investigation: Supporting).
Melisa Dirchwolf, MD (Investigation: Supporting).
Brett E. Fortune, MD (Investigation: Supporting).
Patrick G. Northup, MD (Investigation: Supporting).
James T. Patrie, MS (Data curation: Supporting; Formal analysis: Supporting).
Stephen H. Caldwell, MD (Investigation: Supporting).

Conflicts of interest
This author discloses the following: Stephen H. Caldwell: royalties from Avanos and research support from Durect. The remaining authors disclose no conflicts.

Funding
None.

Data Availability
Data and study materials will not be made available.