

Bleeding After Elective Interventional Endoscopic Procedures in a Large Cohort of Patients With Cirrhosis

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INTRODUCTION: Elective therapeutic endoscopy is an important component of care of cirrhotic patients, but there are concerns regarding the risk of bleeding. This study examined the incidence, risk factors, and outcomes of bleeding after endoscopic variceal ligation (EVL), colonoscopic polypectomy, and endoscopic retrograde cholangiopancreatography with sphincterotomy in cirrhotic patients.

METHODS: A cohort study of patients with cirrhosis who underwent the above procedures at a single center between 2012 and 2014 was performed. Patients with active bleeding at the time of procedure were excluded. Patients were followed for 30 days to assess for postprocedural bleeding and for 90 days for mortality.

RESULTS: A total of 1,324 procedures were performed in 857 patients (886 upper endoscopies, 358 colonoscopies, and 80 endoscopic retrograde cholangiopancreatographies). After EVL, bleeding occurred in 2.8%; after polypectomy, bleeding occurred in 2.0%; and after sphincterotomy, bleeding occurred in 3.8%. Independent predictors of bleeding after EVL and polypectomy included younger age and lower hemoglobin. For EVL, bleeding was also associated with infection and model for end-stage liver disease-Na. International normalized ratio was associated with bleeding in univariate analysis only, and platelet count was not associated with bleeding in any procedure. Bleeding after EVL was associated with 29% 90-day mortality, and bleeding after polypectomy was associated with 14% mortality. Of the 3 patients with postsphincterotomy bleeding, none were outliers regarding their baseline characteristics.

DISCUSSION: In patients with cirrhosis, bleeding occurs infrequently after elective therapeutic endoscopy and is associated with younger age, lower hemoglobin, and high mortality. Consideration of these risk factors may guide appropriate timing and preprocedural management to optimize outcomes.

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INTRODUCTION

Patients with cirrhosis have an increased risk of bleeding, in part, because of various hemostatic abnormalities (1). Portal hypertension-induced hypersplenism and reduced hepatic synthesis of thrombopoietin can result in thrombocytopenia. In addition, the reduced hepatic synthesis of coagulation factors can lead to impaired coagulation. These defects can increase patients' risk of spontaneous bleeding; they can also predispose patients to bleeding after invasive procedures (2,3). Several invasive endoscopic procedures are frequently required in the routine care of patients with cirrhosis. Upper endoscopy is used to screen patients for gastroesophageal varices, which are highly prevalent in

cirrhosis (4). Colonoscopy is often performed for colorectal cancer screening; most patients with cirrhosis are older than 50 years (the age at which screening is generally recommended), and cirrhosis is an independent risk factor for colonic adenomas (5). Finally, endoscopic retrograde cholangiopancreatography (ERCP) is often needed to assess patients with biliary disease-associated cirrhosis (e.g., primary sclerosing cholangitis), and ERCP may be needed in cases of diagnostic uncertainty when patients with liver disease have cholestasis.

During these procedures, several interventions are considered to have a high associated bleeding risk, including endoscopic variceal ligation (EVL), colonoscopic polypectomy, and biliary

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sphincterotomy (6). The risk of bleeding after these procedures in patients with cirrhosis has been examined in several studies. However, these studies have been limited by small sample sizes (7–11), lack of detailed risk factor assessment for cirrhosis specifically (12), inclusion of noninterventional procedures (e.g., ERCP without sphincterotomy) (13,14), inclusion of emergent procedures performed for active bleeding (15–18), and inclusion of nonendoscopic procedures (19–21). Understanding the bleeding risk in purely elective therapeutic procedures is important because it is in this group that careful decisions can be made regarding procedural timing, preprocedural medication management, and bleeding prophylaxis. These decisions can also be extended to diagnostic procedures with the potential for therapeutic intervention.

To better understand the risk of bleeding after therapeutic endoscopy in this important population, a large cohort of patients with cirrhosis at a tertiary liver center was examined. The primary goals were to examine (i) incidence, (ii) risk factors, and (iii) outcomes of bleeding after therapeutic endoscopy.

METHODS

Patients and study design

This was a retrospective cohort study of all patients with cirrhosis who had any of the following procedures at a large tertiary care teaching hospital between January 1, 2012, and December 31, 2014: EVL, colonoscopy with polypectomy, and ERCP with biliary or pancreatic sphincterotomy. Procedures performed after 2014 were not included because these more recent procedures have been guided, in part, with thromboelastography (TEG), which is not applicable to most clinical practices. For inclusion, patients were initially identified by querying the electronic medical record for the pertinent diagnostic and procedural codes, and eligibility criteria were then confirmed via manual chart review. The diagnosis of cirrhosis was based on clinical, laboratory, imaging, and endoscopic findings, or histology where available. Those patients without a definite diagnosis of cirrhosis, those younger than 18 years of age, pregnant patients, postliver transplant patients, and those with acute gastrointestinal bleeding at the time of the procedure were excluded. Patients' medical records were queried for bleeding events within 30 days from the time of the procedure and for mortality, within 90 days. The study was approved by the Indiana University Institutional Review Board.

Outcomes

The primary outcome was gastrointestinal bleeding (hematemesis, melena, hematochezia, and acute worsening anemia) within 30 days of the procedure (22) and was further divided into immediate and delayed bleedings. Immediate postpolypectomy bleeding was defined as bleeding occurring immediately after the polypectomy lasting more than 60 seconds, identified at the time of the procedure, and requiring hemostatic intervention (23). Delayed postpolypectomy bleeding was defined as bleeding occurring at the polypectomy site within 30 days of the procedure not meeting the above criteria for immediate bleeding. Secondary outcomes included mortality, blood transfusions, hospital admissions for gastrointestinal bleeding, and a requirement for repeat endoscopy, interventional radiology, or surgery.

Variables

Demographic and clinical information including age, sex, race, body mass index, comorbidities (Charlson comorbidity index) (24), presence of infection, and medication use (antiplatelet

agents, anticoagulants, proton pump inhibitors, nonselective beta blockers, and nonsteroidal anti-inflammatory drugs [NSAIDs]) were collected. Liver disease-specific variables included cirrhosis etiology and liver disease severity (model for end-stage liver disease and Child-Pugh scores) (25,26). Laboratory values of interest included hemoglobin, platelet count, international normalized ratio (INR), and other markers of liver and kidney function (creatinine, sodium, blood urea nitrogen [BUN], albumin, and bilirubin). Fibrinogen was not available for most cases. Procedure-specific variables included patient location (inpatient vs outpatient), procedural indication (including cholangitis for ERCP) (12), and use of prophylactic blood product transfusions. Other procedure-specific variables were examined separately depending on the procedure. For EVL, data included varix size and presence of red wale signs, number of bands placed, and use of postprocedure proton pump inhibitor. For polypectomy, the number of polyps removed, largest polyp size, morphology and histology, polypectomy method, use of prophylactic endoscopic interventions to prevent bleeding (e.g., hemoclip), and the quality of the bowel preparation were recorded. For sphincterotomy, data collected included sphincterotomy length and the presence of periampullary diverticulum.

Statistical analysis

Continuous and categorical index patient characteristic data were summarized using 2 sample *t* tests for means and SDs and χ^2 tests for counts and percentages, respectively, with exact methods in the latter when sample size proved tenuous. Nonparametric tests of medians for continuous variables were used where required. Univariate and multivariable logistic regression models with an added random frailty at the patient level were used to account for patients with multiple procedures, incorporating only those variables significant at $P < 0.05$ in univariate analyses. Unadjusted and adjusted odds ratios and respective 95% confidence intervals (CIs) were reported. All analyses were performed using SAS 9.4.

RESULTS

After applying inclusion and exclusion criteria, the study sample included 1,324 procedures in 857 patients (886 upper endoscopies, 358 colonoscopies, and 80 ERCPs) (Figure 1).

Esophageal variceal ligation

Of 886 upper endoscopy procedures with endoscopic variceal ligation (EVL) in 454 patients, postprocedural bleeding occurred after 25 procedures (2.8%) in 24 patients. Procedural indications were largely variceal screening and surveillance (96%). Active infection was present in 15 procedures—8 were spontaneous bacterial peritonitis and the remainder comprised bacteremia, pneumonia, *Clostridioides difficile*, cellulitis, and urinary tract infection. Patient characteristics at the time of their first procedure ($N = 454$) are shown in Table 1. Only the first procedure for each patient was included in this comparison to avoid double-counting characteristics in those with multiple procedures. A mean of 3.6 ± 1.5 bands were placed per endoscopy session. Five patients were taking NSAIDs, none of whom had bleeding. Among those taking antiplatelet agents, 26 were taking low-dose aspirin, 3 were taking clopidogrel, and 1 was taking both aspirin and clopidogrel. Patients who bled were younger, with lower hemoglobin and greater INR, BUN, bilirubin, MELD-Na score, and Child-Pugh score. Bleeding was also more common in

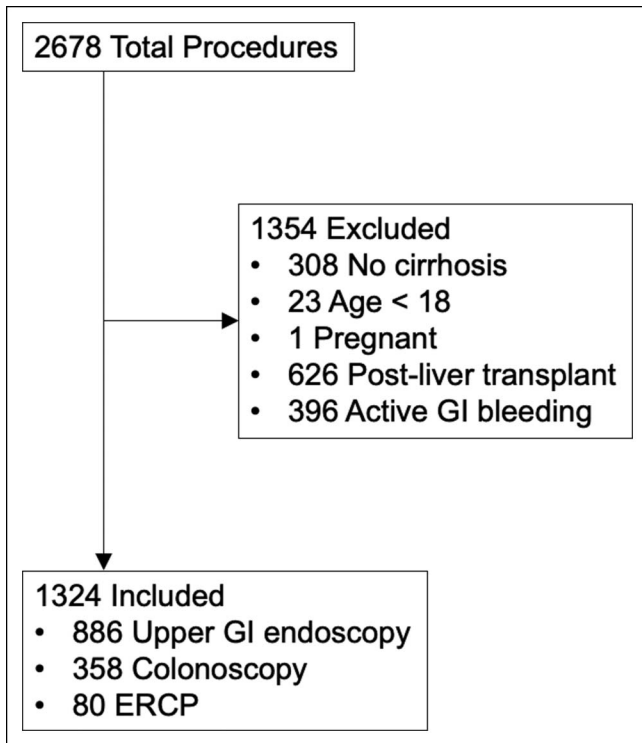


Figure 1. Total procedures included in the study after exclusion criteria. ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal.

hospitalized patients and in those with active infection. Bleeding was not associated with any of the examined medications, platelet count, or variceal characteristics. Preprocedure platelet transfusions were given to 23 patients. Twenty-three patients received prophylactic fresh frozen plasma (FFP), and 9 patients received packed red blood cell (pRBC) transfusions. Those who received pRBC transfusion were more likely to have postprocedure bleeding (odds ratio [OR] 10.61, 95% CI: 2.03–55.35), and FFP transfusion was also associated with postprocedural bleeding (OR 8.01, 95% CI: 2.57–24.94). Prophylactic platelet transfusion was not associated with bleeding.

Table 2 shows factors significantly associated with bleeding on univariate analysis across all 886 procedures. On univariate analysis, factors associated with bleeding included younger age, infection, inpatient location, lower hemoglobin, elevated INR, BUN, and MELD-Na and Child-Pugh scores. As both INR and liver disease severity have interdependent contributions to hemostasis, 3 separate multivariable models were created, separately adjusting for (i) MELD-Na, (ii) Child-Pugh score, and (iii) the individual laboratory components. In all 3 multivariable models, bleeding was associated with younger age and lower hemoglobin. Bleeding was associated with infection in models adjusting for MELD-Na and Child-Pugh score, but not adjusting for individual laboratory values. Bleeding was associated with MELD-Na, but not with Child-Pugh score or with the individual laboratory results (including INR).

Bleeding occurred 12 ± 7 days postprocedure. Fifty percent presented with hematemesis, 27% with melena, 18% with hematochezia, and 5% with worsening anemia. Sixteen of 24 patients received pRBC transfusion (6.4 ± 7.6 units), 10 received platelet

transfusion (1.7 ± 1.1 units), 11 received FFP (5.2 ± 3.7 units), and 4 received cryoprecipitate (2.8 ± 1.0 units). Ten patients required endoscopic intervention to control bleeding, and 1 patient required transjugular intrahepatic portosystemic shunt. Of the 24 patients who had postprocedure bleeding, 7 died in the 90-day follow-up period (29%). Three died from gastrointestinal bleeding with hemorrhagic shock, 2 died from sepsis, 1 from both bleeding and sepsis, and 1 from respiratory failure and cardiac arrhythmia.

Colonoscopy with polypectomy

Of 358 procedures in 327 patients, there were 7 bleeding episodes (2.0%) in 7 patients. Colonoscopy indications were most often colorectal cancer screening (44%) and polyp surveillance (35%), with the remainder comprising liver transplant evaluation, lower gastrointestinal symptoms, and abnormal abdominal imaging. Patient characteristics at the time of their first procedure during the study period ($N = 327$) are shown in Table 3. There were 3.2 ± 2.6 polyps removed per colonoscopy (48% cold snare, 11% cold forceps, and 39% hot snare), with a maximum polyp size of 7.4 ± 6.5 mm, and prophylactic hemoclip was used in 14% of patients. Eight patients were taking NSAIDs, none of whom had bleeding. Patients who bled were younger, with lower hemoglobin and albumin, and greater INR, bilirubin, and MELD-Na and Child-Pugh scores. Platelet counts were not significantly different (mean 85 vs 117; $P = 0.17$), although 29% of those who bled had a platelet count $< 50 \times 10^3/\text{mm}^3$ compared with 6.3% of those who did not bleed ($P = 0.08$). Antiplatelet agents, anticoagulants, and polyp characteristics were not associated with bleeding. In particular, polyp size examined as both a continuous and as a categorical variable (≥ 1 vs < 1 cm) was not associated with bleeding. Three patients received preprocedure prophylactic pRBC transfusion, 5 received prophylactic platelet transfusion, and 12 received FFP.

Table 4 shows factors significantly associated with bleeding on univariate analysis across all 358 procedures. On univariate analysis, factors associated with bleeding included younger age, inpatient location, lower hemoglobin, lower albumin, elevated INR, elevated bilirubin, and higher MELD-Na and Child-Pugh scores. As with the EVL analysis, 3 separate multivariable models were created, adjusting for MELD-Na, Child-Pugh score, and individual laboratory values. In all 3 models, bleeding was associated with younger age and lower hemoglobin. Bleeding was not significantly associated with the other laboratory values or measures of liver disease severity.

Postpolypectomy bleeding occurred 10 ± 10 days after the procedure, and all were delayed bleeds. Five of 7 presented with hematochezia and 2 patients presented with worsening anemia. All 7 warranted hospital admission; 5 bleeds stopped spontaneously without intervention, and 2 patients underwent successful endoscopic intervention. Five patients required pRBC transfusion (4.2 ± 3 units), 2 required platelet transfusion (6 ± 7 units), 2 required FFP (6 ± 4.2 units), and 1 patient required cryoprecipitate (3 units). One of 7 died during the 90-day follow-up period (unrelated to the bleeding).

ERCP with sphincterotomy

Eighty procedures were performed in 76 patients, with 3 episodes of postsphincterotomy bleeding (3.8%). ERCP was performed for choledocholithiasis in 45% and for biliary stricture in 14%. Cohort characteristics are shown in Table 5. Mean sphincterotomy

Table 1. Patient characteristics according to the bleeding outcome at the index visit for endoscopic variceal ligation

	Overall (N = 454)	No bleeding (N = 430)	Bleeding (N = 24)	P
Age (yr)	57.1 ± 11.1	57.5 ± 10.9	51.1 ± 12.7	0.02
Female sex	176 (38.8)	172 (40)	4 (16.7)	0.11
White race	416 (91.6)	401 (93.3)	15 (62.5)	0.07
Cirrhosis etiology				0.91
Alcohol	81 (17.8)	78 (18.1)	3 (12.5)	
Alcohol/HCV	35 (7.7)	33 (7.7)	2 (8.3)	
Hepatitis C	118 (26.0)	112 (26.0)	6 (25.0)	
NASH	121 (26.7)	116 (27.0)	5 (20.8)	
Other	99 (21.8)	96 (22.3)	3 (12.5)	
Infection	11 (2.4)	7 (1.6)	4 (16.7)	0.001
Charlson comorbidity index				0.83
0–2	125 (27.5)	119 (27.7)	6 (25)	
3–4	113 (24.9)	107 (24.9)	6 (25)	
5–6	146 (32.2)	141 (32.8)	5 (20.8)	
>6	70 (15.4)	68 (15.8)	2 (8.3)	
Antiplatelet agents	30 (6.6)	29 (6.7)	1 (4.2)	1
Anticoagulation	8 (1.8)	7 (1.6)	1 (4.2)	0.29
PPI	293 (64.5)	281 (65.3)	12 (50)	0.90
Beta-blocker	196 (43.2)	188 (43.7)	8 (33.3)	0.92
Hemoglobin (g/dL)	11.7 ± 2.2	11.8 ± 2.2	10.3 ± 1.7	0.004
Platelets (10 ³ /mm ³)	98.6 ± 59.9	98.6 ± 60.2	98.3 ± 56.1	0.98
INR	1.3 ± 0.3	1.3 ± 0.3	1.6 ± 0.6	<0.0001
Creatinine (mg/dL)	1.0 ± 0.7	0.9 ± 0.7	1.2 ± 0.8	0.15
Sodium (mmol/L)	136.3 ± 3.9	136.4 ± 3.9	134.7 ± 3.9	0.08
BUN (mg/dL)	15.2 ± 11.2	14.9 ± 10.7	21.3 ± 18.5	0.02
Albumin (g/dL)	3.3 ± 0.6	3.2 ± 0.6	3.5 ± 0.8	0.14
Bilirubin (mg/dL)	2.0 ± 2.3	1.9 ± 2.1	4.7 ± 4.2	<0.0001
MELD-Na	14.9 ± 5.5	14.6 ± 5.3	20.9 ± 7.7	<0.0001
Child-Pugh score	7.6 ± 1.9	7.5 ± 1.9	8.5 ± 2.3	0.03
Inpatient location	38 (8.4)	33 (7.7)	5 (20.8)	0.01
Large varices	437 (96.3)	418 (97.2)	19 (79.2)	0.37
No. of bands	3.6 ± 1.5	3.6 ± 1.5	3.9 ± 1.6	0.34
Red wale signs	104 (24.7)	100 (23.3)	4 (16.7)	1
Postprocedure PPI	316 (72.3)	303 (70.5)	13 (54.2)	0.69

Values expressed as n (%) or mean ± SD.

P value comparisons across outcome categories are based on the χ^2 tests (or Fisher exact test) for categorical variables; P values for continuous variables are based on ANOVA or Wilcoxon (Normal Approximation).

Only the first (index) procedure during the study period was included in this comparison to avoid double counting patients.

BUN, blood urea nitrogen; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PPI, proton pump inhibitor.

length was 8.5 ± 1.6 mm, and 13% had a periampullary diverticulum. Six patients were on antiplatelet agents (all aspirin), and 1 patient who did not bleed was taking NSAIDs. Four patients received preprocedure platelet transfusions, and 10 received preprocedure FFP. None received postprocedural NSAIDs. Characteristics of the 3 patients who had a postsphincterotomy

bleeding event are shown in Table 5. None of the 3 were outliers regarding any of the baseline characteristics, and none received either prophylactic FFP or platelet transfusions. One bleed was immediate, one occurred after 1 day, and the third occurred after 6 days. All 3 were hospitalized and were successfully treated endoscopically. None died within 90 days.

Table 2. Predictors of bleeding in patients after esophageal variceal ligation

Variable	Unadjusted ^a	Adjusted (MELD-Na) ^b	Adjusted (Child-Pugh) ^b	Adjusted (individual labs) ^b
Age	0.96 (0.93–0.99), 0.02	0.96 (0.93–0.99), 0.04	0.96 (0.93–1.00), 0.05	0.96 (0.93–1.00), 0.05
Infection	14.72 (4.42–49.00), <0.001	4.11 (1.05–16.12), 0.04	5.02 (1.01–25.02), 0.05	3.73 (0.74–18.76), 0.11
Hemoglobin	0.66 (0.57–0.77), <0.001	0.78 (0.66–0.93), 0.005	0.75 (0.64–0.88), <0.001	0.76 (0.65–0.91), 0.002
INR	7.84 (3.76–16.34), <0.001			1.46 (0.44–4.82), 0.54
BUN	1.03 (1.01–1.06), 0.02			1.02 (0.99–1.04), 0.27
Bilirubin	1.23 (1.08–1.39), 0.001			1.10 (0.97–1.25), 0.14
MELD-Na	1.16 (1.10–1.23), <0.001	1.10 (1.04–1.17), 0.002		
Child-Pugh	1.44 (1.19–1.75), <0.001		1.16 (0.91–1.47), 0.24	
B vs A ^c	1.18 (0.38–3.65)			
C vs A ^c	5.28 (1.78–15.67)			
Inpatient	1.91 (0.40–4.19), <0.001			

All values displayed as odds ratio (95% confidence interval), *P* value.
 BUN, blood urea nitrogen; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.
^aWithin-subject cluster-adjusted univariate odds ratio.
^bWithin-subject cluster-adjusted multivariable odds ratio using continuous scores to increase degrees of freedom.
^cOdds ratios calculated for Child-Pugh B and C cirrhosis with Child-Pugh A as the referent.

DISCUSSION

This study of 1,324 endoscopic interventions in 857 patients is the largest to date examining postendoscopy bleeding in patients with cirrhosis. Three commonly performed endoscopic interventions associated with a high risk of bleeding (EVL, polypectomy, and sphincterotomy) were examined (6), with a relatively low post-procedural bleeding rate (2%–4%) across procedures despite frequent thrombocytopenia and prolonged INR. For both EVL and polypectomy, postprocedural bleeding was associated with several measures of liver disease severity, notably elevated INR, as well as younger age, lower hemoglobin, active infection, and inpatient location. Importantly, bleeding was not associated with platelet count. In those who experienced bleeding, short-term mortality was high, particularly in those who bled after EVL.

The observed postpolypectomy bleed rate of 2% is similar to other studies of cirrhosis (8–10,27), and greater than rates in the general population (0.2%–0.6%) (22,28), reinforcing the importance of this topic in cirrhosis clinical care. EVL was also associated with bleeding in 2.8%, consistent with previous work showing rates of 2%–8% (7,15–18,29). In both procedures, bleeding was associated with elevated INR in univariate analysis, but not in multivariable analysis, and in neither procedure was bleeding associated with platelet count. The lack of association between standard hemostasis measures and postprocedural bleeding highlights the evolving notion that these measures do not adequately capture the complex nature of hemostasis and coagulopathy in patients with liver disease (1). Although some studies have shown increased bleeding related to elevated INR (often in the context of broader liver disease severity measures such as Child-Pugh score and MELD), this has not been a universal finding, and elevated INR has also been associated with increased thrombosis. The results are also consistent with others showing a lack of association of bleeding with platelet count, a finding that may relate to increased levels of von Willebrand factor in cirrhosis (which promotes and enhances platelet adhesion) and preserved thrombin generation, even in the setting of

thrombocytopenia (1). This lack of association with platelet count also has particular clinical relevance because providers are often reluctant to perform procedures in patients with thrombocytopenia, and several new thrombopoietin agonists have been developed for this purpose. Notably, despite the improvement in platelet counts seen with these agents, more robust outcomes data are needed to establish their efficacy in reducing bleeding (30). These findings suggest that provider perceptions of bleeding risk due to thrombocytopenia may be disproportionate to the actual risk. The limitations of standard measures of hemostasis have prompted several studies of viscoelastic testing, such as TEG, as a more global, functional approach to assessing bleeding risk. Indeed, promising studies have suggested the potential for TEG to reduce blood product use in this population without sacrificing bleeding risk (31,32).

Bleeding after both EVL and polypectomy was independently associated with both younger age and lower hemoglobin. Younger age, although not a traditional risk factor for postendoscopy bleeding, has been noted to be numerically lower in those with bleeding in some studies (8,16–19). Interestingly, several studies have documented increased procoagulant profiles with advancing age (33,34), explaining in part the increased incidence of thrombotic disorders in older individuals. Whether the relative lack of procoagulant factors in liver disease is amplified in younger patients remains to be seen and deserves further study. The relationship between bleeding and low hemoglobin is also novel. Although low hemoglobin has not been associated with postendoscopy bleeding in previous studies, it is associated with an increased risk of major bleeding in patients with acute coronary syndrome (35). Purported mechanisms for this finding include reduced blood viscosity, shear stress, and platelet activation (36). Whether careful correction of anemia with pRBC transfusion might reduce bleeding risk is unclear; there was increased post-EVL bleeding in those who received pRBC transfusion, a finding that may reflect the increased bleeding risk associated with the underlying anemia. Furthermore, in univariate analysis,

Table 3. Patient characteristics according to the bleeding outcome at the index visit for polypectomy

	Overall (N = 327)	No bleeding (N = 320)	Bleeding (N = 7)	P
Age (yr)	59.6 ± 8.6	59.8 ± 8.5	52.0 ± 11.4	0.01
Female sex	138 (42.2)	134 (41.9)	4 (57.1)	0.46
White race	292 (89.3)	285 (89.1)	7 (100.0)	0.35
Cirrhosis etiology				0.06
Alcohol	76 (23.2)	74 (23.1)	2 (28.6)	
Alcohol/HCV	31 (9.5)	28 (8.8)	3 (42.9)	
Hepatitis C	78 (23.9)	77 (24.1)	1 (14.3)	
NASH	73 (22.3)	72 (22.5)	1 (14.3)	
Other	69 (21.1)	69 (21.6)	0	
Infection	10 (3.1)	9 (2.8)	1 (14.3)	0.19
Charlson comorbidity index				0.77
0–2	85 (26.0)	83 (25.9)	2 (28.6)	
3–4	85 (26.0)	84 (26.3)	1 (14.3)	
5–6	106 (32.4)	104 (32.5)	2 (28.6)	
>6	51 (15.6)	49 (15.3)	2 (28.6)	
Antiplatelet agents	43 (13.1)	42 (13.1)	1 (14.3)	1
Anticoagulation	15 (4.6)	14 (4.4)	1 (14.3)	0.28
Hemoglobin (g/dL)	12.4 ± 2.2	12.5 ± 2.2	9.5 ± 2.3	<0.001
Platelets (10 ³ /mm ³)	116.1 ± 61.0	116.8 ± 61.2	85.1 ± 43.6	0.17
INR	1.3 ± 0.3	1.3 ± 0.2	1.7 ± 0.5	0.001
Creatinine (mg/dL)	1.1 ± 1.1	1.1 ± 1.1	1.1 ± 0.8	0.93
Sodium (mmol/L)	136.6 ± 3.6	136.5 ± 3.6	137.7 ± 3.2	0.42
BUN (mg/dL)	15.5 ± 12.6	15.7 ± 12.7	9.7 ± 5.9	0.21
Albumin (g/dL)	3.4 ± 0.6	3.4 ± 0.6	2.8 ± 0.5	0.01
Bilirubin (mg/dL)	1.9 ± 2.6	1.8 ± 1.8	7.5 ± 12.7	<0.0001
MELD-Na	15 ± 5.8	14.9 ± 5.7	19.5 ± 7.4	0.03
Child-Pugh score	7.6 ± 2.1	7.5 ± 2.1	9.8 ± 3.0	0.005
Inpatient location	29 (8.9)	24 (7.5)	5 (71.4)	<0.0001
No. of polyps	3.2 ± 2.6	3.2 ± 2.6	2.8 ± 1.7	0.67
Largest polyp size (mm)	7.4 ± 6.5	7.4 ± 6.5	9.4 ± 7.3	0.41
Morphology (largest)				0.63
Flat	13 (4.4)	13 (4.5)	0	
Pedunculated	26 (8.8)	25 (8.6)	1 (14.3)	
Sessile	258 (86.9)	252 (86.9)	6 (85.7)	
Technique (largest)				1
Cold forceps	34 (10.5)	34 (10.7)	0	
Cold snare	156 (48.0)	152 (47.8)	4 (57.1)	
Hot snare	126 (38.8)	123 (38.7)	3 (42.9)	
Other	9 (2.8)	9 (2.8)	0	
Prophylactic hemoclip	46 (14.1)	45 (14.1)	1 (14.3)	1

Values expressed as n (%) or mean ± SD.

Pvalue comparisons across outcome categories are based on χ^2 tests (or Fisher exact tests) for categorical variables; Pvalues for continuous variables are based on ANOVA or Wilcoxon (Normal Approximation).

Only the first (index) procedure during the study period was included in this comparison to avoid double counting patients.

BUN, blood urea nitrogen; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PPI, proton pump inhibitor.

Table 4. Predictors of bleeding in patients after polypectomy

Variable	Unadjusted ^a	Adjusted (MELD-Na) ^b	Adjusted (Child-Pugh) ^b	Adjusted (individual labs) ^b
Age	0.90 (0.83–0.99), 0.02	0.92 (0.86–0.98), 0.001	0.92 (0.85–0.99), 0.03	0.92 (0.85–0.99), 0.04
Hemoglobin	0.56 (0.37–0.83), 0.004	0.59 (0.41–0.84), 0.04	0.63 (0.47–0.84), 0.002	0.66 (0.45–0.98), 0.04
INR	8.45 (2.31–30.87), 0.001			1.66 (0.31–8.90), 0.55
Albumin	0.26 (0.11–0.61), 0.002	0.39 (0.13–1.16), 0.09		0.36 (0.11–1.20), 0.10
Bilirubin	1.11 (1.03–1.19), 0.006			1.05 (0.96–1.16), 0.28
MELD-Na	1.09 (1.01–1.18), 0.04	0.99 (0.91–1.08), 0.82		
Child-Pugh	1.52 (1.05–2.19), 0.03		1.16 (0.83–1.64), 0.39	
Inpatient	30.00 (5.52–163.15), <0.001			

All values displayed as odds ratio (95% confidence interval), *P* value.
 INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.
^aWithin-subject cluster-adjusted univariate odds ratio.
^bWithin-subject cluster-adjusted multivariable odds ratio using continuous scores to increase degrees of freedom.

elevated INR was also associated with bleeding, potentially accounting for the increased bleeding in those who received pre-procedure FFP transfusions. For both pRBC and FFP transfusions, previous studies have demonstrated transfusion-induced increased portal pressure that could also result in increased bleeding (37,38).

In univariate analysis, inpatient location was associated with bleeding after EVL and polypectomy, and in multivariable analysis, active infection (despite appropriate treatment) was associated with post-EVL bleeding. Hospitalized patients with cirrhosis frequently have coexisting acute medical issues such as acute-on-chronic liver failure or infection, which can increase the risk of bleeding. These findings suggest that elective endoscopic interventions (particularly polypectomy) in this population may not be appropriate for hospitalized patients and may best be deferred to the outpatient setting. These data confirming the increased risk in the setting of infection are consistent with other work showing impaired hemostasis in liver disease resulting from increased circulating endogenous heparinoids (39–41). This increased risk remains substantial despite appropriate antibiotic therapy and suggests that elective endoscopic procedures should wait until infection has been eradicated whenever possible.

This study is the largest detailed examination of bleeding after commonly performed interventional endoscopic procedures in patients with cirrhosis. In contrast to previous work, this study excluded patients with active bleeding and included patients, regardless of the severity of their liver disease or their use of antiplatelet agents and anticoagulants. Thus, this sample best reflects the population in which evidence-based decisions can be made regarding procedural timing and medication continuation or discontinuation. The novel findings of increased bleeding risk in younger patients and in those with lower hemoglobin need further validation and investigation to determine whether prophylactic interventions might be able to further lower the risk for bleeding. In contrast to these strengths, this study has some weaknesses, including its retrospective design and the low number of bleeding events, which limited the ability to examine risk factors, particularly for those undergoing ERCP with sphincterotomy. The low number of bleeding events also prevents the development of a prediction model from these data that could more accurately stratify bleeding risk in this population.

Although the procedures occurred several years ago, this time frame was necessary to avoid the confounding impact of TEG, which has been used at this center in the past several years to help stratify bleeding risk. TEG is not readily available for this purpose in most hospitals in the United States and thus including procedures where TEG was considered would not be widely applicable.

Although uncommon, bleeding after therapeutic endoscopy in patients with cirrhosis is associated with significant morbidity and mortality. Knowledge of underlying risk factors, including younger age, lower hemoglobin, greater liver disease severity, and infection may help providers best determine the appropriate timing and preprocedural management of patients to optimize outcomes. Careful collection of these relevant factors can be used to optimize the environment and mitigate potential risks to the greatest extent possible with a goal of preventing postprocedural bleeding. Caution in interpreting standard measures of hemostasis (INR and platelet count) is warranted as well to avoid unnecessary prophylactic blood product transfusions. Future prospective research focused on correcting modifiable risk factors is needed to understand whether bleeding can be further reduced in this population.

CONFLICTS OF INTEREST

Guarantor of the article: Eric S. Orman, MD, MSCR.

Specific author contributions: Shanker Kundumadam, MBBS, and Parkpoom Phatharacharukul, MD, shared first authorship. S.K.: data collection, analysis and interpretation, drafting, and article revision. P.P.: conception and design, data collection, and data analysis. K.R. and A.Y.: data collection and data analysis. H.S.: data collection and data analysis and interpretation. F.P.: data analysis and interpretation and drafting the article. N.C.: conception and design, article revision, and article approval. K.R.P. and M.G.: article revision and article approval. E.S.O.: conception and design, data analysis and interpretation, drafting, revision, and article approval. All authors have approved the final draft.

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Table 5. Characteristics of patients undergoing ERCP with sphincterotomy

	Overall (N = 80)	Patient 1	Patient 2	Patient 3
Age (yr)	56.3 ± 13.8	59	62	71
Female sex	35 (43.8)	F	F	M
White race	75 (93.8)	Black	White	White
Cirrhosis etiology		HCV	Alcohol	Alcohol
Alcohol	20 (25.0)			
Alcohol/HCV	11 (13.8)			
Hepatitis C	10 (12.5)			
NASH	15 (18.8)			
Other	24 (30.0)			
Infection	4 (5.0)	No	No	Yes
Charlson comorbidity index		5	3	10
0–2	21 (26.3)			
3–4	27 (33.8)			
5–6	20 (25.0)			
>6	12 (15.0)			
Antiplatelet agents	6 (7.5)	None	None	Aspirin
Anticoagulation	6 (7.5)	None	None	Warfarin
PPI	43 (53.8)	Yes	Yes	Yes
Beta-blocker	24 (30.0)	No	Yes	Yes
Hemoglobin (g/dL)	11.8 ± 1.9	11.8	14.7	10.6
Platelet count (10 ³ /mm ³)	143.1 ± 109.6	166	89	290
INR	1.3 ± 0.3	1.1	1.3	1.6
Creatinine (mg/dL)	0.9 ± 0.4	1.0	0.6	0.6
Sodium (mmol/L)	136.7 ± 4.2	137	134	131
BUN (mg/dL)	14.0 ± 10.2	12	5	7
Albumin (g/dL)	3.2 ± 0.8	3.2	3.6	1.8
Bilirubin (mg/dL)	4.1 ± 5.3	0.8	1.3	0.5
MELD-Na	16.2 ± 6.3	10	15	18
Child-Pugh score	7.9 ± 2.3	6 (A)	8 (B)	7 (B)
Inpatient location	38 (47.5)	Out	In	Out
Sphincterotomy length (mm)	8.5 ± 1.9	10	10	8
Periampullary diverticulum	10 (12.7)	No	Yes	No
Timing of bleed (d)		1	Immediate	6

BUN, blood urea nitrogen; ERCP, endoscopic retrograde cholangiopancreatography; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PPI, proton pump inhibitor.

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Study Highlights

WHAT IS KNOWN

- ✓ Hemostatic and coagulation abnormalities in cirrhotic patients could potentially increase the risk of bleeding after invasive procedures.

WHAT IS NEW HERE

- ✓ Risk factors of bleeding in cirrhotic patients after endoscopic procedures were studied.
- ✓ This study is the largest detailed examination of bleeding after commonly interventional endoscopic procedures.
- ✓ Low preprocedure hemoglobin and younger age were consistently associated with postprocedural bleeding.
- ✓ Platelet count and International normalized ratio (INR) did not have a significant association with postprocedural bleeding.

TRANSLATIONAL IMPACT

- ✓ These characteristics may be used to help stratify bleeding risk in future practice.

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