Original Article

Association of coagulopathy with the risk of bleeding after invasive procedures in liver cirrhosis

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Abstract

Background/Aim: Bleeding risk among patients with acute or chronic liver disease after invasive procedures is a common concern in clinical practice. This retrospective study aimed to explore whether the presence of coagulopathy increased the risk of major bleeding after invasive procedures in cirrhosis.

Patients and Methods: A total of 874 cirrhotic patients underwent invasive procedures. Coagulopathy was defined as international normalized ratio (INR) ≥1.5 and/or platelets (PLTs) ≤50 × 10^9/L. Severe thrombocytopenia was defined as PLTs ≤ 50 × 10^9/L. Invasive procedures, major bleeding after invasive procedures, and in-hospital deaths were recorded.

Results: In all, 296 patients (33.9%) had coagulopathy. Major bleeding after invasive procedures occurred in 21 patients (2.4%). Major bleeding after invasive procedures was more frequent in patients with coagulopathy than those without coagulopathy (4.1% vs 1.6%, $P = 0.023$). Major bleeding after invasive procedures was more frequent in patients with severe thrombocytopenia than those without severe thrombocytopenia (4.9% vs 1.6%, $P = 0.008$). Incidence of major bleeding after invasive procedures was not significantly different between patients with INR ≥ 1.5 and INR < 1.5 (4.5% vs 2.0%, $P = 0.065$). Patients with INR ≥1.5 had a significantly higher in-hospital mortality than those with INR < 1.5 (6.4% vs 1.3%, $P < 0.001$).

Conclusion: Severe thrombocytopenia significantly increased the risk of major bleeding after invasive procedures in cirrhosis. INR ≥ 1.5 significantly increased in-hospital mortality.

Keywords: In-hospital mortality, international normalized ratio, platelets, prothrombin time, thrombocytopenia

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INTRODUCTION

Prothrombin time (PT), international normalized ratio (INR), and platelet (PLT) counts are conventional coagulation tests. Patients with cirrhosis have higher PT/INR and lower PLT. Thus, cirrhotic patients are traditionally at a high risk of bleeding. However, current evidence regarding the association between conventional coagulation tests and the risk of bleeding in cirrhotic patients remains controversial.[1-9]

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In an Italian study, Napolitano *et al.* found that post-procedural bleeding was rare in cirrhotic patients with abnormal INR and/or low PLT who underwent invasive investigations and could not be predicted by abnormal INR or PLT.[10] In an Indian study, Shah *et al.* also found that abnormal conventional coagulation parameters did not predict clinically significant bleeding in cirrhosis.[11] Tripodi *et al.* indicated no causal relationship between coagulopathy associated with chronic liver diseases and bleeding[5] and further suggested that PT and INR could reflect the severity of liver dysfunction and predict the mortality of acute and chronic liver diseases, but not the risk of bleeding.[6]

In contrast, Cocero *et al.* found that patients with chronic liver disease who had a PLT of $>40 \times 10^3/\mu L$ and an INR of <2.5 had a relatively low risk of bleeding, but an INR of ≥2.5 and a PLT of $\leq 40 \times 10^3/\mu L$ represented significant risk factors of bleeding after extractions.[12] Giannini *et al.* also found that bleeding risk after invasive procedures was associated with the degree of thrombocytopenia in patients with advanced liver diseases, but not PT/INR.[13]

Considering that conventional coagulation tests used to assess the risk of bleeding in cirrhosis has been largely challenged, we explored whether the presence of coagulopathy increased the risk of major bleeding after invasive procedures in liver cirrhosis.

PATIENTS AND METHODS

Patients

This study retrospectively screened all cirrhotic patients who were consecutively admitted to our hospital from 1st January 2011 to 30th June 2014. Patients were diagnosed with cirrhosis on the basis of clinical presentations (decompensated events), liver function tests [i.e., total bilirubin, albumin (ALB), PT, etc.], and abdominal ultrasound and computed tomography (CT) scans (liver contour, spleen size, portal vein diameter, and gastroesophageal varices),[14-17] or histological evidence of cirrhosis, if necessary. All patients with cirrhosis undergoing invasive procedures were included in the study. Exclusion criteria were as follows: (1) patients diagnosed with malignancy, especially hepatocellular carcinoma; (2) incomplete regular coagulation tests, such as PLT, PT, and INR; (3) incomplete medical records; (4) patients receiving anticoagulation and antiplatelet drugs during the past 7 days; (5) patients with a history of hematological diseases; and (6) patients who developed acute hemorrhage 5 days before invasive procedures. The study protocol was approved by the Medical Ethical Committee of our hospital [number k (2016) 39]. The patients' informed consent was waived.

Data collection

The primary data items included sex, age, etiology of liver diseases, ascites, hepatic encephalopathy (HE), laboratory tests, Child–Pugh class/score,[18] and Model for End-Stage Liver Disease (MELD) score.[19] We recorded all invasive procedures carried out during hospitalizations, such as endoscopic band ligation, endoscopic glue injection, endoscopic sclerotherapy, abdominocentesis, pleurocentesis, endoscopic retrograde cholangiopancreatography (ERCP), cholecystectomy, splenectomy, stem-cell therapy, endoscopic polypectomy, central vein cannulation, bone marrow puncture, splenic arterial embolization, and percutaneous liver biopsy. We also recorded the PLTs or plasma transfusion before invasive procedures, the presence of major bleeding secondary to invasive procedures, and in-hospital deaths.

Definitions and classifications

Coagulopathy was defined as INR ≥1.5 and/or PLT $\leq 50 \times 10^9/L$.[11,13,20] Severe thrombocytopenia was defined as PLT $\leq 50 \times 10^9/L$.[11,13,20] Major bleeding after invasive procedures was defined as overt bleeding or decrease in hemoglobin to less than 80 g/L after invasive procedures.[21] They were divided into patients with and without coagulopathy, patients with and without severe thrombocytopenia, and patients with INR ≥1.5 and INR <1.5.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (range) and were compared using independent sample *t*-test. Categorical variables were expressed as frequency (percentage), and were compared using Chi-squared test. A two-tailed *P* value of <0.05 was considered statistically significant. All statistical analyses were used using SPSS Statistics 17.0 (SPSS, Chicago IL).

RESULTS

A total of 874 patients with cirrhosis who underwent invasive procedures were included. The average age was 55.08 years; 65.9% of patients were male; 38.7%, 43.7%, and 14.6% of patients were Child–Pugh class A, B, and C, respectively; 33.9% of patients had coagulopathy; 23.3% of patients had severe thrombocytopenia; and 18.0% of patients had INR ≥1.5. The most common type of invasive procedures was endoscopic band ligation, followed by abdominocentesis.

In all, 21 (2.4%) patients developed major bleeding after endoscopic band ligation (n = 4), endoscopic sclerotherapy (n = 3), large volume abdominocentesis (n = 2), endoscopic sclerotherapy combined with glue injection (n = 2), splenectomy in combination with cholecystectomy (n = 2), endoscopic glue injection (n = 1), endoscopic band ligation combined with glue injection (n = 1), ERCP (n = 1), splenectomy (n = 1), splenectomy in combination with abdominocentesis (n = 1), endoscopic band ligation and sclerotherapy in combination with phlebotomy (n = 1), gastrointestinal polypectomy in combination with abdominocentesis (n = 1), and artificial hip replacement (n = 1). Among them, 16 patients received red blood cell (RBC) transfusions, and 2 patients received PLTs and plasma transfusion.

Nineteen patients died during hospitalization because of multiple organ failure (n = 7), liver failure (n = 5), gastrointestinal bleeding (n = 3), HE with spontaneous bacterial peritonitis (n = 1), HE with renal failure and metabolic acidosis (n = 1), uremia (n = 1), and fungal pneumonia with hyperkalemia (n = 1).

Major bleeding after invasive procedures

In univariate analysis, the factors significantly associated with major bleeding after invasive procedures were lower age, higher activated partial thromboplastin time (APTT), and larger proportions of coagulopathy and severe thrombocytopenia [Table 1]. The colinearity between APTT and coagulopathy and that between severe thrombocytopenia and coagulopathy should be acknowledged. We performed logistic multivariate analysis twice. In the first multivariate analysis including age and coagulopathy, we found that coagulopathy was the only independent predictor for major bleeding after invasive procedures [odds ratio (OR) = 2.529; 95% confidence interval (CI) = 1.049–6.098, P = 0.039). In the second multivariate analysis including age, APTT, and severe thrombocytopenia, we found that severe thrombocytopenia was the only independent predictor for major bleeding after invasive procedures (OR = 2.658; 95% CI = 1.097–6.441, P = 0.030) [Table 2].

In univariate analysis after excluding patients who did not receive blood transfusion, the factors significantly associated with major bleeding after invasive procedures were lower age, higher APTT, and larger proportions of coagulopathy and severe thrombocytopenia [Table 3]. Similarly, considering the colinearity among variables, we performed logistic multivariate analysis twice. In the first multivariate analysis including age and coagulopathy, we found that coagulopathy was the only independent predictor for major bleeding after invasive procedures (OR = 2.762; 95% CI = 1.031–7.397, P = 0.043). In the second multivariate analysis including age, APTT, and severe thrombocytopenia, we did not find any independent predictors for major bleeding after invasive procedures [Table 4].

In-hospital death after invasive procedures

In univariate analysis, factors significantly associated with in-hospital mortality were larger proportions of ascites, HE, Child–Pugh class C, post-procedural bleeding, higher white blood cell (WBC), blood urea nitrogen (BUN), creatinine (Cr), PT, APTT, INR, Child–Pugh score, MELD score, lower RBC and ALB, larger proportions of coagulopathy, and INR ≥1.5 [Table 5]. Notably, ascites, HE, PT/INR, and ALB were components of Child–Pugh score. Cr and INR were components of MELD score. The colinearity between PT/INR and APTT and that between BUN and Cr should be acknowledged. We performed logistic multivariate analysis including ascites, HE, WBC, Cr, RBC, ALB, and INR ≥1.5, we found that WBC, Cr, HE, and INR ≥1.5 were the independent predictors for in-hospital mortality (OR = 1.110; 95% CI = 1.024–1.203, P = 0.011; OR = 1.003; 95% CI = 1.000–1.006, P = 0.021; OR = 4.567; 95% CI = 1.352–15.429, P = 0.014; OR = 3.031; 95% CI = 1.074–8.549, P = 0.036, respectively) [Table 6].

Impact of coagulopathy

Major bleeding after invasive procedures was more frequent in patients with coagulopathy than those without coagulopathy (12/296, 4.1% vs 9/578, 1.6%, P = 0.023). In-hospital mortality was significantly higher in patients with coagulopathy than those without coagulopathy (11/296, 3.7% vs 8/568, 1.4%, P = 0.025). In-hospital mortality was significantly higher in patients with coagulopathy who developed major bleeding after invasive procedures than those who did not develop major bleeding after invasive procedures (2/12, 16.7% vs 9/284, 3.2%, P = 0.015).

Impact of severe thrombocytopenia

Ten and 11 patients with and without severe thrombocytopenia developed major bleeding after invasive procedures, respectively. Major bleeding after invasive procedures was more frequent in patients with severe thrombocytopenia than those without severe thrombocytopenia (10/204, 4.9% vs 11/670, 1.6%, P = 0.008), but in-hospital mortality was not significantly different between them (4/204, 2.0% vs 15/670, 2.2%, P = 0.812).

INR ≥1.5 versus INR <1.5

Seven and 14 patients with INR ≥1.5 and INR <1.5 developed major bleeding after invasive procedures,

Table 1: Comparison between patients with and without bleeding after invasive procedures

Variables	Bleeding (*n*=21)		No bleeding (*n*=853)		*P*
	Pts available	Value	Pts available	Value	
Sex (male/female), *n* (%)	21	12 (57.1%)/(42.9%)	853	564 (66.1%)/289 (33.9%)	0.391
Age (years)	21	51.72±6.30	853	55.17±11.94	***0.024***
Etiology of liver diseases, *n* (%)	21		852		0.684
Viral hepatitis		9 (42.8%)		340 (39.9%)	
Alcohol		3 (14.3%)		190 (22.3%)	
Viral hepatitis + alcohol		1 (4.8%)		84 (9.8%)	
Others		2 (9.5%)		80 (9.4%)	
Unknown		6 (28.6%)		158 (18.5%)	
Ascites, *n* (%)	21	11 (52.4%)	853	437 (51.2%)	0.917
Hepatic encephalopathy, *n* (%)	21	1 (4.8%)	853	33 (3.9%)	0.834
Laboratory tests					
RBC (10^{12}/L)	21	2.99±0.79	853	3.19±0.79	0.268
Hb (g/L)	21	83.38±27.80	853	94.89±27.17	0.056
WBC (10^9/L)	21	4.14±3.08	853	4.58±3.34	0.525
PLT (10^9/L)	21	79.86±75.15	853	99.60±73.21	0.223
TBIL (μmol/L)	21	49.43±82.07	840	40.05±67.80	0.533
ALB (g/L)	21	32.36±6.25	832	33.05±6.82	0.645
ALT (U/L)	21	48.81±103.65	840	35.54±52.97	0.565
AST (U/L)	21	72.19±133.75	840	58.60±51.24	0.429
ALP (U/L)	21	135.79±123.34	839	117.09±108.62	0.438
GGT (U/L)	21	91.19±105.70	838	98.33±153.33	0.832
BUN (mmol/L)	21	7.90±5.62	833	7.37±6.94	0.733
Cr (μmol/L)	21	103.43±157.28	833	88.60±116.14	0.567
PT (s)	21	18.32±7.16	853	15.83±3.42	0.127
APTT (s)	21	46.76±7.92	852	42.97±8.09	***0.034***
INR	21	1.58±0.89	853	1.28±0.40	0.137
Child-Pugh class, *n* (%)	21		827		0.877
A		8 (38.1%)		330 (39.9%)	
B		9 (42.9%)		373 (45.1%)	
C		4 (19.0%)		124 (15.0%)	
Child-Pugh score	21	7.71±2.76	827	7.32±1.98	0.371
MELD score	21	9.51±12.14	830	7.00±7.23	0.357
Coagulopathy, *n* (%)	21	12 (57.1%)	853	284 (33.3%)	***0.023***
INR ≥1.5, *n* (%)	21	7 (33.3%)	853	150 (17.6%)	0.063
Severe thrombocytopenia, *n* (%)	21	10 (47.6%)	853	194 (22.7%)	***0.008***
Invasive procedures, *n* (%)	21		853		
Endoscopic band ligation		4 (19.0%)		158 (18.5%)	0.951
Abdominocentesis		2 (9.5%)		129 (15.1%)	0.478
Endoscopic glue injection		1 (4.8%)		125 (14.7%)	0.202
Endoscopic band ligation + glue injection		1 (4.8%)		81 (9.5%)	0.462
ERCP		1 (4.8%)		68 (8.0%)	0.590
Splenectomy		1 (4.8%)		31 (3.6%)	0.786
Stem-cell therapy		0 (0.0%)		28 (3.3%)	0.399
Endoscopic sclerotherapy		3 (14.3%)		15 (1.8%)	***<0.001***
Splenectomy + cholecystectomy		2 (9.5%)		13 (1.5%)	***0.005***
Splenic arterial embolization		0 (0.0%)		13 (1.5%)	0.569
Pleurocentesis		0 (0.0%)		12 (1.4%)	0.584
Central vein cannulation		0 (0.0%)		12 (1.4%)	0.584
Stem-cell therapy + endoscopic treatment		0 (0.0%)		11 (1.3%	0.600
Gastrointestinal polypectomy		0 (0.0%)		10 (1.2%)	0.618
Marrow puncture		0 (0.0%)		10 (1.2%)	0.618
Stem-cell therapy + abdominocentesis		0 (0.0%)		9 (1.1%)	0.636
Abdominocentesis+endoscopic treatment		0 (0.0%)		9 (1.1%)	0.636
Endoscopic glue injection + sclerotherapy		2 (9.5%)		6 (0.7%)	***<0.001***
Liver biopsy		0 (0.0%)		3 (0.4%)	0.785
Others		4 (19.0%)		110 (12.9%)	0.408
Transfusion of fresh frozen plasma and/or platelet within 24 h before invasive procedure, *n* (%)	2		5		
Fresh frozen plasma alone		1 (50.0%)		2 (40.0%)	0.809
Platelet alone		1 (50.0%)		3 (60.0%)	0.809
Transfusion of fresh frozen plasma and/or platelet after invasive procedure, *n* (%)	6		24		
Fresh frozen plasma alone		4 (66.6%)		21 (87.5%)	0.827

Contd...

Table 1: Contd...

Variables	Bleeding (*n*=21)		No bleeding (*n*=853)		*P*
	Pts available	Value	Pts available	Value	
Platelet alone		1 (16.7%)		3 (12.5%)	0.337
Fresh frozen plasma + platelet		1 (16.7%)		0 (0.0%)	0.053

Values are presented as mean±SD or *n* (%). RBC: Red blood cell; Hb: Hemoglobin; WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; BUN: Blood urea nitrogen; Cr: Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MELD: Model for End-Stage Liver Disease; Pts: Patients. Note: The values in bold and Italics mean statistically significant.

Table 2: Multivariate analysis of predictors of major bleeding after invasive procedures

Variables	*P*	OR	95% CI
In the first multivariate analysis			
Age	0.281	0.98	0.944-1.017
Coagulopathy	***0.039***	***2.529***	***1.049-6.098***
In the second multivariate analysis			
Age	0.296	0.98	0.943-1.018
APTT	0.146	1.029	0.99-1.069
Severe thrombocytopenia	***0.030***	***2.658***	***1.097-6.441***

APTT: Activated partial thromboplastin time; OR: Odds ratio; 95% CI, 95% confidence interval. Note: The values in bold and Italics mean statistically significant.

respectively (7/157, 4.5% vs 14/717, 2.0%, $P = 0.063$). However, in-hospital mortality was significantly higher in patients with INR ≥1.5 than those with INR <1.5 (10/157, 6.4% vs 9/717, 1.3%, $P < 0.001$).

DISCUSSION

Cirrhotic patients with coagulopathy need to be carefully assessed for the risk of bleeding before invasive procedures. At present, in addition to PT/INR and PLT, no coagulation tests have been formally recommended for the assessment of coagulation status in clinical practice. However, the relationship between PT/INR and the risk of bleeding in cirrhosis has been frequently questioned. In this study, we collected data of patients with cirrhosis to further explore the value of PT/INR and PLT in predicting the risk of major bleeding after invasive procedures.

In the overall analysis, 2.4% of patients developed major bleeding after invasive procedures. Similarly, some prospective studies also showed that cirrhotic patients rarely developed major bleeding after invasive procedures and that the incidence of major bleeding after invasive procedures was 0%–2.3%.[10,11,22]

In addition, 4.1% of patients with coagulopathy developed major bleeding after invasive procedures. Notably, the most common type of invasive procedures in our patients was endoscopic treatment, which carries a relatively high risk of bleeding. In a randomized controlled trial by De Pietri *et al.*,[21] the incidence of bleeding after invasive procedures in 60 patients with severe coagulopathy appeared to be lower (1/60, 1.7%). By comparison, several features of the randomized controlled trial should be noted: (1) large volume paracentesis was the most common type of invasive procedure, which carried a relatively low risk of bleeding (19/60, 31.7%) and (2) 58% (35/60) of patients received fresh frozen plasma or PLT transfusion before invasive procedures.

In this study, 33.9% of cirrhotic patients who underwent invasive procedures had coagulopathy. The incidence of major bleeding after invasive procedures was more frequent in patients with coagulopathy than those without coagulopathy. In contrast, De Pietri *et al.* indicated that post-procedural bleeding risk is not related to coagulopathy itself, but the occurrence of local procedure-related complications.[21] However, the following issues should be noted: (1) the number of patients included in De Pietri's trial was relatively small ($n = 60$); (2) all included patients were diagnosed with coagulopathy, and no control group without coagulopathy was established; (3) only one patient developed major bleeding after an invasive procedure which carried a low risk of bleeding, and therefore, the statistical power of the study is questionable.

Our study demonstrated that the presence of INR ≥1.5 alone was not significantly associated with an increased risk of major bleeding, which might confirm Baveno VI consensus recommendations that PT/INR might not be a reliable indicator of assessing the risk of major bleeding after invasive procedures in patients with cirrhosis.[3,5,8,13]

Our study also found that patients with coagulopathy had a significantly higher in-hospital mortality than those without coagulopathy. In addition, if patients with coagulopathy developed major bleeding after invasive procedures, the in-hospital mortality would be higher. In particular, INR ≥1.5, but not severe thrombocytopenia, was significantly associated with an increased in-hospital mortality. Therefore, INR could have a closer relationship with mortality of cirrhotic patients who carried out invasive procedures.

Our study has some drawbacks. First, this was a retrospective study, the data were not available for some patients, and

Table 3: Subgroup analysis after excluding patients who received blood transfusion: comparison between patients with and without bleeding after invasive procedures

Variables	Bleeding (*n*=17)		No bleeding (*n*=767)		*P*
	Pts available	Value	Pts available	Value	
Sex (male/female), *n* (%)	17	9 (52.9%)/8 (47.1%)	767	499 (65.1%)/268 (34.9%)	0.301
Age (years)	17	51.66±6.68	767	55.60±11.81	***0.030***
Etiology of liver diseases, *n* (%)	17		766		0.748
Viral hepatitis		7 (41.2%)		303 (39.6%)	
Alcohol		2 (11.8%)		167 (21.8%)	
Viral hepatitis + alcohol		1 (5.9%)		72 (9.4%)	
Others		2 (11.8%)		76 (9.9%)	
Unknown		5 (29.4%)		148 (19.3%)	
Ascites, *n* (%)	17	10 (58.8%)	767	387 (50.5%)	0.495
Hepatic encephalopathy, *n* (%)	17	1 (5.9%)	767	32 (4.2%)	0.728
Laboratory tests					
RBC (10^{12}/L)	17	3.14±0.81	767	3.26±0.78	0.547
Hb (g/L)	17	87.18±29.02	767	97.98±26.15	0.093
WBC (10^9/L)	17	4.46±3.33	767	4.64±3.22	0.827
PLT (10^9/L)	17	87.71±81.74	767	100.40±72.32	0.476
TBIL (μmol/L)	17	57.16±89.88	755	41.06±69.13	0.346
ALB (g/L)	17	32.89±6.60	747	33.17±6.79	0.866
ALT (U/L)	17	54.00±114.95	755	37.00±55.47	0.551
AST (U/L)	17	78.47±148.39	755	50.30±53.25	0.446
ALP (U/L)	17	123.98±106.63	754	120.37±112.28	0.896
GGT (U/L)	17	87.29±112.28	754	103.62±158.47	0.673
BUN (mmol/L)	17	7.98±5.94	749	7.44±7.03	0.754
Cr (μmol/L)	17	71.88±51.35	749	89.91±119.26	0.534
PT (s)	17	18.49±7.95	767	15.77±3.43	0.178
APTT (s)	17	47.06±8.71	766	42.91±7.99	***0.035***
INR	17	1.61±0.99	767	1.27±0.41	0.176
Child-Pugh class, *n* (%)	17		743		0.576
A		7 (41.2%)		300 (40.4%)	
B		6 (35.3%)		331 (44.5%)	
C		4 (23.5%)		112 (15.1%)	
Child-Pugh score	17	7.94±2.99	743	7.31±1.98	0.196
MELD score	17	8.88±12.45	746	7.09±7.28	0.563
Coagulopathy, *n* (%)	17	10 (58.8%)	767	249 (32.5%)	***0.022***
Severe thrombocytopenia, *n* (%)	17	8 (47.1%)	767	172 (22.4%)	***0.017***
INR ≥1.5, *n* (%)	17	5 (29.4%)	767	130 (16.9%)	0.178
Severe thrombocytopenia + INR ≥1.5, *n* (%)	17	3 (17.6%)	767	53 (6.9%)	0.089

Values are presented as mean±SD or *n* (%). RBC: Red blood cell; Hb: Hemoglobin; WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; BUN: Blood urea nitrogen; Cr: Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MELD: Model for End-Stage Liver Disease; Pts: Patients. Note: The values in bold and Italics mean statistically significant.

Table 4: Subgroup analysis after excluding patients who received blood transfusion: multivariate analysis of predictors of major bleeding after invasive procedures

Variables	*P*	OR	95% CI
In the first multivariate analysis			
Age	0.274	1.024	0.981-1.068
Coagulopathy	0.043	2.762	1.031-7.397
In the second multivariate analysis			
Age	0.289	1.024	0.980-1.069
APTT	0.145	0.970	0.932-1.010
Severe thrombocytopenia	0.058	2.590	0.970-6.913

APTT: Activated partial thromboplastin time; OR: Odds ratio; 95% CI: 95% confidence interval. Note: The values in bold and Italics mean statistically significant.

selection bias was inevitable. Second, the cutoff values to define coagulopathy and severe thrombocytopenia were derived from a previous study carried out in a similar setting. However, there is no consensus regarding this definition.[7,13] Third, we did not assess other coagulation and fibrinolytic parameters. Fourth, international guidelines did not recommend the correction of INR and PLT by blood product transfusion.[23] The data regarding patients with cirrhosis who received the transfusion of blood products before invasive procedures were heterogeneous and not collected in our study. Unlike De Pietri's trial, we did not explore the significance of blood product transfusion before invasive procedures.

CONCLUSION

Assessment of bleeding risk is one of the most important challenges in clinical management of patients with liver diseases. Severe thrombocytopenia significantly increased the risk of major bleeding after invasive procedures in cirrhosis. INR ≥1.5 significantly increased in-hospital mortality.

Table 5: Comparison between patients with and without in-hospital death after invasive procedures

Variables	In-hospital death (*n*=19)		Alive (*n*=855)		*P*
	Pts available	Value	Pts available	Value	
Sex (male/female), *n* (%)	19	14 (73.7%)/5 (26.3%)	855	562 (65.7%)/293 (34.3%)	0.469
Age (years)	19	55.06±8.20	855	55.08±11.92	0.992
Etiology of liver diseases, *n* (%)	19		854		0.732
Viral hepatitis		6 (31.6%)		343 (40.2%)	
Alcohol		4 (21.0%)		189 (22.1%)	
Viral hepatitis + alcohol		3 (15.8%)		82 (9.6%)	
Others		3 (15.8%)		79 (9.3%)	
Unknown		3 (15.8%)		161 (18.8%)	
Ascites, *n* (%)	19	16 (84.2%)	855	432 (50.5%)	***0.004***
Hepatic encephalopathy, *n* (%)	19	5 (26.3%)	855	29 (3.4%)	***<0.001***
Laboratory tests					
RBC (10^{12}/L)	19	2.81±0.80	855	3.19±0.79	***0.038***
Hb (g/L)	19	88.84±27.45	855	94.74±27.23	0.351
WBC (10^9/L)	19	8.28±5.96	855	4.49±3.21	***0.013***
PLT (10^9/L)	19	86.84±49.06	855	99.40±73.72	0.460
TBIL (μmol/L)	19	90.17±39.15	842	39.15±66.33	0.073
ALB (g/L)	19	28.13±6.37	834	33.15±6.78	***0.001***
ALT (U/L)	19	40.95±36.09	842	35.75±55.05	0.682
AST (U/L)	19	63.11±53.11	842	48.86±54.71	0.262
ALP (U/L)	19	129.72±110.34	841	117.27±108.98	0.623
GGT (U/L)	19	84.05±104.22	840	98.48±153.24	0.683
BUN (mmol/L)	19	17.86±17.42	835	7.15±6.30	***0.015***
Cr (μmol/L)	19	172.35±176.09	835	87.07±114.99	***0.050***
PT (s)	19	19.67±4.87	855	15.80±3.49	***0.003***
APTT (s)	19	48.92±9.08	854	42.93±8.04	***0.001***
INR	19	1.70±0.56	855	1.28±0.42	***0.004***
Child-Pugh class, *n* (%)	19		829		***<0.001***
A		3 (15.8%)		335 (40.4%)	
B		6 (31.6%)		376 (45.4%)	
C		10 (52.6%)		118 (14.2%)	
Child-Pugh score	19	9.68±2.67	829	7.28±1.95	***0.001***
MELD score	19	17.99±11.61	832	6.81±7.08	***0.001***
Coagulopathy, *n* (%)	19	11 (57.9%)	855	285 (33.3%)	***0.025***
Severe thrombocytopenia, *n* (%)	19	4 (21.1%)	855	200 (23.4%)	0.812
INR ≥1.5, *n* (%)	19	10 (52.6%)	855	147 (17.2%)	***<0.001***
Post-procedural bleeding, *n* (%)	19	4 (21.1%)	855	17 (2.0%)	***<0.001***

Values are presented as mean±SD or *n* (%). RBC: Red blood cell; Hb: Hemoglobin; WBC: White blood cell; PLT: Platelet; TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; BUN: Blood urea nitrogen; Cr: Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MELD: Model for End-Stage Liver Disease; Pts: Patients. Note: The values in bold and Italics mean statistically significant.

Table 6: Multivariate analysis of predictors of in-hospital mortality

Variables	*P*	OR	95% CI
RBC	0.786	1.105	0.538-2.272
WBC	***0.011***	***1.110***	***1.024-1.203***
ALB	0.488	0.967	0.879-1.063
Cr	***0.021***	***1.003***	***1.000-1.006***
Ascites	0.278	2.130	0.543-8.354
Hepatic encephalopathy	***0.014***	***4.567***	***1.352-15.429***
INR ≥1.5	***0.036***	***3.031***	***1.074-8.549***

RBC: Red blood cell; WBC: White blood cell; ALB: Albumin; Cr: Creatinine; INR: International normalized ratio; OR: Odds ratio; 95% CI: 95% Confidence interval. Notes: Because ascites: hepatic encephalopathy: PT/INR, and ALB were components of Child-Pugh score, and Cr and INR were components of the MELD score, so we did not include Child-Pugh and MELD scores. Note: The values in bold and Italics mean statistically significant.

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Conflicts of interest

There are no conflicts of interest.

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