Risks and predicting factors of bleeding complications in hepatitis B virus-related acute-on-chronic liver failure

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ABSTRACT

Background/Aims: *This study aimed to provide supporting evidence for prevention and prognostic evaluation of bleeding complications in the early stage by exploring the risk and predicting factors in patients with acute-on-chronic liver failure (ACLF).*

Materials and Methods: *A total of 101 hospitalized patients with ACLF were retrospectively included from January 1, 2014 to December 31, 2015. The patients were divided into bleeding (n=38) and nonbleeding groups (n=63). Demographic data and laboratory tests were recorded and compared between the two groups. The incidence, risk factors, and prognosis of bleeding complications among patients with ACLF were investigated.*

Results: *A total of 38 cases (37.62%) had bleeding complications: 26 (25.74%) were spontaneous and 12 (11.88%) were postprocedural. Patients with bleeding complications had lower platelet (p=0.008), fibrinogen (p<0.001), factor V (p=0.001), and factor VII (p=0.026) levels; higher serum creatinine levels (p=0.004); and a higher proportion of cirrhosis (p=0.013). Logistic regression analysis showed that cirrhosis (odds ratio=3.251, p=0.046), fibrinogen level (odds ratio=0.352, p=0.007), and factor VII level (odds ratio=0.951, p=0.011) contributed to the development of bleeding complications. A subgroup analysis of invasive manipulation-induced bleeding complications showed lower levels of factors V (p=0.018) and VII (p=0.021) in the postprocedural bleeding group. Follow-up studies showed that the nonbleeding group had a higher survival rate than the bleeding group at day 90 (73.33% versus 51.85%, p=0.040).*

Conclusion: *Liver cirrhosis, lower levels of fibrinogen, and major coagulation factor activity in patients with ACLF were associated with an elevated risk of bleeding events during hospitalization, which further impaired the 90-day survival rate.*

Keywords: *Acute-on-chronic liver failure, bleeding, risk factors, survival rate*

INTRODUCTION

Acute-on-chronic liver failure (ACLF), a new clinical entity, is defined as acute deterioration of preexisting chronic liver disease, usually related to precipitating events (PEs) and is associated with high short-term mortality rates due to multiorgan failure (1, 2). In Eastern populations with ACLF, hepatitis B virus (HBV) reactivation, bacterial infection, and virus-superimposed infections are the most common PEs (3, 4). There are many complications in ACLF such as hepatic encephalopathy, infection, hepatorenal syndrome, and bleeding. To our knowledge, studies on bleeding complications and its risk factors on patients with ACLF are rare.

Bleeding tendency was thought to be common in liver diseases contributing to coagulopathy, decrease of platelets, and portal hypertension. Gastrointestinal and intraperitoneal hemorrhages are not rare in clinical management (5, 6). Early series studies indicated that bleeding complications increased morbidity and mortality in patients with acute liver failure (ALF) (7-9). However, current clinical data suggest that the incidence of clinically significant bleeding is low in patients with ALF, which leads to death in only 5% of the cases (10). However, as the pathophysiological mechanism of ACLF is totally different compared with ALF, the incidence of bleeding when the condition progresses to ACLF is unknown.

A study determined that higher prothrombin time/international normalized ratio (PT/INR) and lower platelet count (PLT) level increased the risks of postprocedural bleedings such as central vein puncture and catheterization or liver biopsy (11), whereas another study indicated that PT/INR was not a good parameter for predicting bleeding (12). Hence, effective and accurate parameters for predicting bleeding remain unclear.

ACLF occurs in patients with previously diagnosed chronic liver disease or cirrhosis, the coagulopathy of which could be more severe and complicated. However, the

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incidence, site, risk factors, and clinical significance of bleeding complications have not been widely quantified, and the bleeding risk of ACLF remains unclear. The aim of this study was to retrospectively investigate the risk and relevant factors of hemorrhage in a cohort of patients with ACLF.

MATERIALS AND METHODS

Study Population

The complete clinical records of 101 hospitalized patients with ACLF enrolled from January 1, 2014 to December 31, 2015 were collected based on the diagnostic criteria of the Asian Pacific Association for the Study of the Liver: acute hepatic insult manifesting as jaundice (serum bilirubin level >5 mg/dL) and coagulopathy (INR >1.5) and complication occurring within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease (13). ACLF-associated bleeding complication is defined as a decrease in hemoglobin levels below 10 g/L with a clear hemorrhagic site. The exclusion criteria were coinfection with other virus that may lead to liver damage, such as hepatitis A, C, and D; history of hematological diseases or uncontrolled extrahepatic systemic complications with bleeding tendency; patients with primary liver cancer or other cancers; history of hepatotoxic drugs or immunosuppressive drug or anticancer drug usage; and blood component transfusion before data collection.

This study was performed in accordance with the principles of the Helsinki Declaration II and approved by the hospital ethics committee (201[4]K019). Informed consent was waived owing to the retrospective nature of the study.

Data Collection

The clinical demographic records (sex, age, clinical performance, liver cirrhosis indications, etc.) and laboratory tests (total bilirubin, serum albumin, creatine kinase, lactic acid, INR, activated partial thromboplastin time, fibrinogen, fibrinogen degradation products, D-dimer, factor V, factor VII, serum creatinine [sCr], white blood cells, PLT, etc.) were reviewed. Bleeding condition records were reviewed to determine bleeding severity and sites during hospitalization.

Statistical Analysis

Statistical analysis and plotting were performed using The Statistical Packages for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.0 (GraphPad Software, Inc., La Jolla, CA, USA). All variables were recorded and calculated on the first day of hospitalization or when indicated. Continuous variables have been reported as medians [quartile], analyzed using *t* test for continuous normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables have been expressed as frequencies (proportions), analyzed using the chi-square test or the Fisher's exact test, as appropriate. Binary logistic regression analysis was used to model the relationship between bleeding events and clinical characteristics. The 90-day survival rate for the bleeding and nonbleeding groups were examined by life table analysis. All comparisons were two-tailed, and $P<0.05$ was considered statistically significant.

RESULTS

Etiology and Incidence of Bleeding Complications

Among 101 enrolled patients with HBV-related ACLF, 81 (80.19%) were men and 20 (19.81%) were women. The average age was 52 years [39-60 years]. Of all the bleeding episodes, 38 patients with ACLF (37.62%) had severe bleeding complications, including 26 (25.74%) with spontaneous bleeding and 12 (11.88%) with postprocedural bleeding. For the 26 ACLF cases with spontaneous bleeding, 14 (13.86%) were from a gastrointestinal source (of which 9 (8.91%) were esophageal variceal bleeding caused by portal hypertension), 7 (6.93%) were skin, mucosal, and gingival bleeding, and 5 (4.95%) were intra-abdominal bleeding. For the 12 ACLF cases with postprocedural bleeding, 11 (10.89%) were local bleeding after deep vein catheterization and 1 (0.99%) was postprocedural bleeding due to diagnostic abdominal paracentesis.

Risks and Predicting Factors of Bleeding Complications

The demographic and clinical characteristics were compared between the bleeding and nonbleeding groups. There were no significant differences ($p>0.05$) in age, sex, liver function, and the Model for End-stage Liver Disease

MAIN POINTS

- *The incidence, site, risk factors, and clinical significance of bleeding complications in ACLF patients remains unclear.*
- *Liver cirrhosis, lower levels of fibrinogen, and major coagulation factor activity in patients with ACLF were risk factors of the bleeding complications.*
- *Patients with bleeding complications had lower 90-day survival rate.*

score. Meanwhile, patients with bleeding complications had lower PLT (p=0.008), fibrinogen (p<0.001), and factors V (p=0.001), VII (p=0.026), and VIII (p<0.001); higher sCr (p=0.004) level; and a higher proportion of cirrhosis (p=0.013; Table 1).

Many risk factors, such as sCr, PLT, fibrinogen, incidence of cirrhosis, and factors V, VII, and VIII, were analyzed by multivariate logistic regression. Results revealed the correlations with the predicting factors. Fibrinogen, factor VII, and cirrhosis strongly correlated with bleeding (Table 2).

The area under the curve (AUC) of cirrhosis, fibrinogen, and factor VII were 0.628 (p=0.032), 0.367 (p<0.001), and 0.557 (p=0.026), respectively. Based on the Youden index, the best threshold value of fibrinogen for bleeding prediction was 1.35 g/L (sensitivity, 69.4%; specificity, 71.1%) and the best value of factor VII was 16.7% (sensitivity, 77.4%; specificity, 60.5%). A combination of these three indicators was a great discriminator, and the AUC was 0.871, sensitivity was 81.6%, and specificity was 85.5% (Figure 1). The prediction formula was Y(bleeding)=3.793+1.179×1(cirrhosis)−1.045×2(fibrinogen) −0.050×3(factor VII).

Table 1. Incidence and clinical characteristics of bleeding complications (Continuous variables have been presented as medians [quartile], analyzed using t test, and categorical variables have been presented as n (%)).

Parameter	Nonbleeding group (n=63)	Bleeding group (n=38)	p
Age (years)	47 [37-59]	53 [39-70]	0.071
Sex (male)	48 (76.2)	33 (86.8)	0.302
HBV DNA-positive patients	44 (69.8)	24 (63.2)	0.111
Cirrhosis	20 (34.9)	22 (57.9)	0.013
Total bilirubin (μmol/L)	360.7 [202.7-531.9]	342.1 [93.7-491.2]	0.232
Albumin (g/L)	33.8 [30.1-37.8]	33.6 [32.0-36.9]	0.654
Creatinine (mmol/L)	62.0 [50.8-75.3]	78.4 [67.4-100.0]	0.004
Lactate (mmol/L)	2.08 [1.57-2.75]	2.45 [1.83-3.43]	0.117
CK (U/L)	56.5 [28.0-98.0]	51.0 [39.0-98.0]	0.215
WBC ($\times10^9$/L)	7.15 [4.73-10.5]	5.76 [4.60-10.53]	0.814
PLT ($\times10^9$/L)	101 [54-141]	70 [45-95]	0.008
INR	1.93 [1.47-2.49]	2.00 [1.77-2.82]	0.08
APTT (Second)	54.9 [47.5-65.7]	60.0 [48.4-71.4]	0.274
Fibrinogen (g/L)	1.81 [1.13-2.78]	1.04 [0.75-1.57]	<0.001
FDPs (μg/mL)	7.18 [3.68-12.14]	7.29 [3.41-13.31]	0.782
D-dimer (μg/mL)	3.12 [1.41-5.12]	3.41 [2.03-5.07]	0.619
Factor V (%)	54.0 [43.0-70.0]	32.6 [26.0-57.7]	0.001
Factor VII (%)	24.0 [17.0-37.0]	20.6 [10.2-31.0]	0.026
Factor VIII (%)	290.3 [220.2-300.0]	108.0 [77.5-232.2]	<0.001
MELD score	21.6 [15.0-26.7]	23.7 [15.2-32.4]	0.362

HBV: hepatitis B virus; CK: creatine kinase; WBC: white blood cell; PLT: platelet count; INR: international normalized ratio; APTT: activated partial thromboplastin time; FDPs: fibrin degradation products; MELD: Model for End-stage Liver Disease.

Table 2. Multivariate logistic regression analysis of overall bleeding.

Parameter	B	Wald	Odds ratio	95% Confidence interval	p
Cirrhosis	1.179	3.968	3.251	1.019-10.367	0.046
Fibrinogen	−1.045	7.206	0.352	0.164-0.754	0.007
Factor VII	−0.050	6.537	0.951	0.915-0.988	0.011

B: Binary logistic regression analysis.

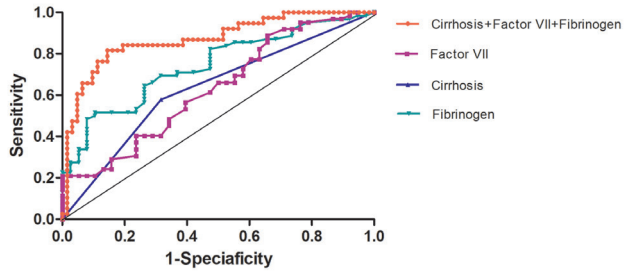

Figure 1. Receiver operating characteristic curves plotting the sensitivity (y-axis) and 1-specificity (x-axis) of various parameters.

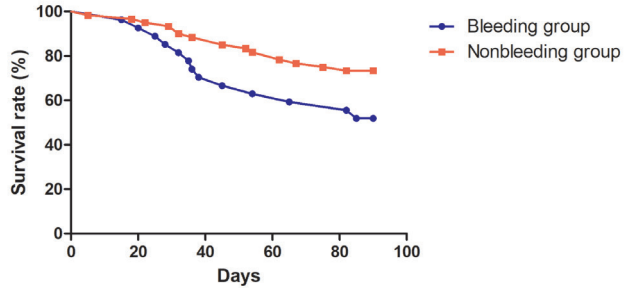

Figure 2. Overall survival for patients with acute-on-chronic liver failure in the bleeding and nonbleeding groups.

Table 3. Comparison of parameters with and without bleeding complications after procedure.

Parameter	Nonbleeding group (n=17)	Bleeding group (n=12)	p
Factor V, median	46.0 [30.8-56.0]	23.53 [17.6-35.5]	0.018
Factor VII, median	32.0 [16.0-86.5]	15.1 [9.0-23.5]	0.021
Cirrhosis, n (%)	3 (17.6)	4 (33.3)	0.403

Continuous variables are presented as medians [quartile]), analyzed using t test, and categorical variables have been presented as n (%), analyzed using the chi-square test or the Fisher's exact test, as appropriate.

Risk Factors of Bleeding Complications in Postprocedural Patients With ACLF

The predicting factors for bleeding were analyzed in postprocedural patients with ACLF. The activity of factors V (p=0.018) and VII (p=0.021) showed significant difference between two groups (bleeding group versus nonbleeding group); in contrast, liver cirrhosis had no contribution to the incidence of bleeding in this subgroup (p=0.403; Table 3).

As bleeding complications have been proven to influence the prognosis of patients with ACLF, we analyzed the three-month overall survival (OS) in the bleeding and nonbleeding groups. The cumulative survival rates of patients in the bleeding and nonbleeding groups were 85.19% and 93.33%, respectively, at day 30 and 51.85% and 73.33%, respectively, at day 90. Patients with bleeding complications had worse OS, whereas the three-month OS rate in the nonbleeding group was much higher (p=0.040; Figure 2).

DISCUSSION

The results of this study showed that bleeding was a common complication in patients with ACLF, with an incidence rate of 37.62%, including spontaneous and postprocedural bleeding, both of which increased the mortality rate of patients with ACLF. The incidence of bleeding events in patients with ACLF was much higher than that of patients with ALF (11%) (10). The most common bleeding sites are in the gastrointestinal tract, intra-abdominal, deep vein, and artery. Patients with ACLF have relatively lower PLT levels and coagulation factor activities and higher incidence of complications such as portal hypertension, severe infection, and disseminated intravascular coagulation than the ALF population, which possibly explain the high incidence of bleeding. The follow-up time of the patients was three months, which was much longer than that of patients with ALF (21 days). Some patients with ACLF died after 21 days. In recent years, few studies of bleeding complications in patients with ACLF have been reported.

In our study, there was no statistical difference in the PT/INR between the bleeding and nonbleeding groups, consistent with the results of past studies in patients with liver cirrhosis (5). Routine PT/INR testing cannot accurately predict the risk of bleeding complications in chronic liver disease. A recent study showed that patients with severe liver cirrhosis who had bleeding episodes had much lower PLT levels than the control group; moreover, a low level of fibrinogen in liver disease indicates high risk of bleeding incidence (14). We found many risk factors in this study. Compared with the control group, the bleeding group had a higher proportion of liver cirrhosis, higher sCr level, and lower level of the PLT, fibrinogen, and factors V, VII, and VIII. Aside from a decrease in coagulation factor synthesis, secondary hyperfibrinolysis (i.e., the early stage of disseminated intravascular coagulation) may

occur in some patients with ACLF, leading to utilization of large amounts of coagulation factors and, subsequently, bleeding. In line with another study on ALF, sCr level was higher in the bleeding group (10). Bleeding leads to a decrease in effective circulating blood volume, which will reduce the glomerular filtration rate. It may be one of the reasons for the higher levels of sCr in the bleeding group. Clinicians should practice considerable caution if patients with ACLF have low levels of these factors.

The multivariate logistic regression analysis showed that liver cirrhosis, fibrinogen, and factor VII had good correlation with bleeding. A combination of these three indicators is a great discriminator with high specificity and sensitivity. The results of a study showed that a combination of PLT, INR, and estimated glomerular filtration rate, rather than any single independent risk factor, was a better predictor of postbiopsy bleeding (15). Considering the correlation between the level of factors V and VII and the risk of postprocedural bleeding, the benefits and risks should be cautiously evaluated for patients with liver cirrhosis who have low levels of these two factors.

The three-month follow up of hospitalized patients revealed that patients with ACLF who had bleeding complication had lower OS rate. A recent study on ICU patients with liver cirrhosis has shown that bleeding is the most life-threatening complication and largely contributes to mortality rate during hospitalization (16). This may indicate that certain patients with liver cirrhosis require correction of their coagulopathy before certain invasive procedures, especially when they have low levels of PLT, fibrinogen, and coagulation factors (17).

Our study had some limitations. This was a single-center retrospective study with a small sample size. Increasing the sample size and verifying the predicting factors should be done in a further study. Further prospective clinical study should be designed to observe whether the incidence of bleeding decreases after supplementation with fibrinogen, coagulation factors, or fresh-frozen plasma. Thromboelastography should be introduced to assess the bleeding risk in ACLF patients for an accurate prediction.

The results of our study indicate that clinicians should carefully evaluate for risk factors in patients with ACLF, especially when accompanied by liver cirrhosis. This work has practical benefits because these factors are evaluated routinely.

Ethics Committee Approval: The study was approved by the Ethics Committee of Shanghai Public Health Clinical Center, Fudan University (Decision date 01.25.2015. Decision number 201[4] K019).

Informed Consent: N/A.

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