Postprint of a Study on Risk Factors for Gastrointestinal Bleeding in Patients with Liver Cirrhosis Complicated by Portal Vein Thrombosis

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Abstract

Background: Portal vein thrombosis (PVT) and gastrointestinal bleeding are both complications in patients with liver cirrhosis, and PVT can increase the risk of gastrointestinal bleeding; however, the treatments for the two conditions are contradictory, representing another challenge in clinical practice. Objective: To investigate the clinical characteristics and risk factors of gastrointestinal bleeding in patients with liver cirrhosis complicated by PVT. Methods: We retrospectively collected data from 279 hospitalized patients diagnosed with liver cirrhosis and PVT at the First Affiliated Hospital of Kunming Medical University between October 1, 2016, and September 30, 2021. Patients were divided into a bleeding group (n=127) and a non-bleeding group (n=152) based on the presence or absence of gastrointestinal bleeding symptoms (hematemesis and melena) during the current admission. Differences in general data, complications, laboratory and imaging examinations, and surgical history between the two groups were compared. Binary Logistic regression analysis was used to explore the influencing factors of gastrointestinal bleeding in cirrhotic patients with PVT. Results: This study retrospectively surveyed 5,807 patients with liver cirrhosis, among whom 350 had concurrent PVT, yielding a PVT incidence rate of 6.0%. Among the 279 cirrhotic patients with PVT, Child-Pugh class B liver function with concurrent PVT was the most common [146 (52.3%)]. Comparisons between the bleeding and non-bleeding groups revealed statistically significant differences in etiology, vascular involvement, jaundice, main portal vein diameter, esophagogastric varices, white blood cell count (WBC), blood urea nitrogen (BUN), hemoglobin (Hb), hematocrit (HCT), total bilirubin (TBiL), fibrinogen (FIB), and history of abdominal surgery ($P<0.05$). Binary Logistic regression analysis results indicated that elevated WBC [OR=2.555, 95%CI (1.318, 6.542)], decreased HCT [OR=0.511, 95%CI (0.247, 0.925)], decreased FIB [OR=0.085,

95%CI (0.005, 0.661)], and involvement of the superior mesenteric vein thrombosis [OR=27.873, 95%CI (1.452, 1335.715)] were independent risk factors for gastrointestinal bleeding in cirrhotic patients with PVT (P<0.05). Conclusion: Elevated WBC, decreased HCT, decreased FIB, and involvement of the superior mesenteric vein thrombosis are independent risk factors for gastrointestinal bleeding in cirrhotic patients with PVT, and early intervention should be implemented to improve prognosis.

Full Text

Study of Factors Associated with Concomitant Gastrointestinal Bleeding in Patients with Portal Vein Thrombosis in Liver Cirrhosis

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Abstract

Background Both portal vein thrombosis (PVT) and gastrointestinal bleeding are complications in patients with liver cirrhosis, and PVT can aggravate the risk of gastrointestinal bleeding, but the conflicting treatment of both is another challenge in clinical work. **Objective** To investigate the clinical characteristics and risk factors of concomitant gastrointestinal bleeding in patients with PVT in liver cirrhosis. **Methods** A total of 279 patients diagnosed with PVT in liver cirrhosis at the First Affiliated Hospital of Kunming Medical University from 2016-10-01 to 2021-09-30 were retrospectively collected and divided into the bleeding group (n=127) and non-bleeding group (n=152) according to the presence of gastrointestinal bleeding symptoms of hematemesis and melena in this admission. The differences in general information, complications, laboratory and imaging tests, surgical history and other relevant information between the two groups were compared. Binary Logistic regression analysis was used to explore the influencing factors of the complications of gastrointestinal bleeding in cirrhotic patients with PVT. **Results** A total of 5,807 patients were retrospectively investigated in the study, including 350 patients combined with PVT with an incidence of 6.0%. PVT was most common in 279 cirrhotic patients with liver function Child B grade [146 (52.3%)]. There were significant differences in etiology, vascular involvement, jaundice, internal diameter of main portal vein,

gastroesophageal varices, white blood cell (WBC), blood urea nitrogen (BUN), hemoglobin (Hb), hematocrit (HCT), total bilirubin (TBiL), fibrinogen (FIB), and history of laparotomy between the bleeding group and non-bleeding group (P<0.05). Binary Logistic regression analysis showed that elevated WBC level [OR=2.555, 95%CI (1.318, 6.542)], decreased HCT level [OR=0.511, 95%CI (0.247, 0.925)], decreased FIB level [OR=0.085, 95%CI (0.005, 0.661)], and involvement of superior mesenteric vein thrombosis [OR=27.873, 95%CI (1.452, 1,335.715)] were independent risk factors for concomitant gastrointestinal bleeding in cirrhotic patients with PVT (P<0.05). **Conclusion** Elevated WBC level, decreased HCT level, decreased FIB level and involvement of superior mesenteric vein thrombosis are independent risk factors for gastrointestinal bleeding in cirrhotic patients with PVT, and early intervention should be implemented to improve the prognosis.

Keywords Liver cirrhosis; Portal vein thrombosis; Gastrointestinal bleeding; Risk factors

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Introduction

Portal vein thrombosis (PVT) is a rare but serious complication of decompensated liver cirrhosis, referring to thrombus formation in the portal vein (PV) and its main branches, including the splenic vein (SV) and superior mesenteric vein (SMV). Gastrointestinal bleeding is a critical and dangerous complication of liver cirrhosis with high mortality, with a prevalence of approximately 11.1% [1]. Due to persistent inflammatory responses, continuous hepatocyte damage and repair in cirrhotic patients lead to weakened liver synthetic function, causing physiological disturbances in the coagulation system and increasing the risk of both bleeding and thrombosis [2]. Gastrointestinal bleeding is not only a complication of liver cirrhosis but also a complication of PVT formation. When liver cirrhosis and PVT coexist, the risk of gastrointestinal bleeding increases significantly, resulting in extremely high mortality. In theory, cirrhotic patients with PVT should receive anticoagulation therapy, but the inherent coagulation dysfunction and bleeding risk in cirrhosis create a therapeutic paradox. If anticoagulation is chosen, the risk of gastrointestinal bleeding increases again. Currently, there is still a lack of effective or unified treatment protocols for cirrhotic patients with combined PVT and gastrointestinal bleeding. Therefore, studying the risk factors associated with both conditions and implementing early intervention is particularly important for cirrhotic PVT patients, especially those with gastrointestinal bleeding.

Methods

1.1 Study Subjects We retrospectively collected data from hospitalized patients diagnosed with liver cirrhosis and PVT at the First Affiliated Hospital of Kunming Medical University between October 1, 2016, and September 30, 2021.

According to the presence of gastrointestinal bleeding symptoms (hematemesis and melena) during the current admission, patients were divided into a bleeding group (n=127) and a non-bleeding group (n=152). The diagnostic criteria for liver cirrhosis with PVT complied with the "Guidelines for the Diagnosis and Treatment of Liver Cirrhosis" [3] and imaging manifestations of PVT [4]. Inclusion criteria were: (1) meeting diagnostic criteria for liver cirrhosis; (2) meeting diagnostic criteria for PVT; and (3) having complete clinical data. Exclusion criteria were: (1) incomplete data; (2) concurrent liver transplantation, hematological diseases affecting coagulation function, Budd-Chiari syndrome, or other non-liver disease-related PVT; and (3) concurrent suspected or confirmed abdominal or systemic malignancies. This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University [Approval No.: (2023) Ethics Review L No. 81], and all subjects provided informed consent.

1.2 Data Collection We collected general information and laboratory indicators for all patients, including white blood cell count (WBC), hemoglobin (Hb), hematocrit (HCT), platelet count (PLT), total bilirubin (TBiL), albumin (ALB), serum creatinine (Scr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer (D-D), and fibrinogen (FIB). Imaging findings included thrombus location, portal vein flow velocity (VPV), diameter of the main portal vein (DMPV), splenic vein width, collateral circulation opening, gastroesophageal varices (GOV), splenomegaly, cavernous transformation of the portal vein, and clinical symptoms and complications. Surgical history and other relevant indicators were also recorded, and Child-Pugh liver function classification was calculated for each patient.

1.3 Statistical Methods Statistical analysis was performed using R software version 4.1.2. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using Mann-Whitney U test. Categorical data were analyzed using chi-square test. Multivariate Logistic regression analysis was used to explore influencing factors for gastrointestinal bleeding in cirrhotic patients with PVT. $P<0.05$ was considered statistically significant.

Results

2.1 Clinical Data This study retrospectively investigated 5,807 patients with liver cirrhosis, of whom 350 had concurrent PVT, yielding a PVT incidence of 6.0%. According to inclusion and exclusion criteria, 279 cirrhotic patients with PVT were enrolled, including 190 males (68.1%) and 89 females (31.9%). Viral hepatitis was the most common etiology [156 cases (55.9%)]. PVT was most frequently observed in patients with Child-Pugh grade B [146 cases (52.3%)]. The most commonly affected single vessel was the portal vein [148 cases (53.0%)], while the most common pattern of multiple vessel involvement was PV+SMV

[55 cases (19.7%)]. There were no significant differences between the bleeding and non-bleeding groups in terms of gender, age, smoking history, or Child-Pugh classification (P>0.05). However, significant differences were observed in etiology, vascular involvement site, and history of abdominal surgery (P<0.05, Table 1).

2.2 Univariate Analysis of Gastrointestinal Bleeding in Cirrhotic Patients with PVT There were no significant differences between the bleeding and non-bleeding groups in abdominal pain, fever, ascites, pulmonary infection, pleural effusion, cholelithiasis, hepatic encephalopathy, splenic infarction, intestinal obstruction, VPV, splenomegaly, collateral circulation opening, cavernous transformation of the portal vein, PLT, Scr, ALT, AST, ALB, or D-D (P>0.05). However, significant differences were found in jaundice, DMPV, GOV, WBC, Hb, HCT, TBiL, BUN, and FIB (P<0.05, Table 2).

2.3 Multivariate Logistic Regression Analysis of Gastrointestinal Bleeding in Cirrhotic Patients with PVT Using the occurrence of gastrointestinal bleeding as the dependent variable (yes=1, no=0) and variables with statistically significant differences in univariate analysis as independent variables [etiology (unknown=1, viral hepatitis=2, alcoholic=3, schistosomiasis=4, drug-induced=5, two or more etiologies=6, autoimmune=7), vascular site (PV=1, SV=2, SMV=3, PV+SV=4, PV+SMV=5, PV+SV+SMV=6), history of abdominal surgery (TIPS=1, endoscopic hemostasis=2, splenic embolization=3), jaundice (yes=1, no=0), DMPV (actual value), GOV (yes=1, no=0), WBC (actual value), Hb (actual value), HCT (actual value), TBiL (actual value), BUN (actual value), FIB (actual value)], multivariate Logistic regression analysis showed that WBC, HCT, FIB, and superior mesenteric vein thrombosis (SMVT) were influencing factors for gastrointestinal bleeding in cirrhotic patients with PVT (P<0.05, Table 3).

Discussion

Currently, there are studies on liver cirrhosis with PVT and liver cirrhosis with gastrointestinal bleeding, but few studies have examined PVT combined with gastrointestinal bleeding. Moreover, almost all previous studies have not analyzed the cause of bleeding—whether it is due to portal hypertension, mucosal or wound bleeding, or other unknown reasons [5]. Therefore, this study grouped patients based on the presence of gastrointestinal bleeding symptoms (hematemesis and melena) to explore the risk factors for gastrointestinal bleeding in cirrhotic patients with PVT and provide clinical reference. Early intervention on these influencing factors may improve patient prognosis and survival.

The incidence of PVT in healthy populations is approximately 1%, while in cirrhotic populations it ranges from 5% to 20% [6], increasing with the severity of cirrhosis. The pathogenesis remains unclear. This study retrospectively investigated 5,807 cirrhotic patients, including 350 with concurrent PVT, yielding an

incidence of 6.0%. PVT formation may be caused by one or more factors. In 2020, the Hepatobiliary Disease Group of the Chinese Society of Gastroenterology proposed that Virchow's triad for venous thrombosis can also explain the formation mechanism of PVT in cirrhosis, including slow blood flow (reduced VPV), local vascular injury (most commonly splenectomy), and hypercoagulable state (thrombophilia, inflammation) [4]. PVT primarily affects the prognosis of cirrhotic patients with poor liver function. NERY et al. [7] demonstrated that PVT formation and progression correlate with liver disease severity. In this study, cirrhotic patients with PVT were predominantly Child-Pugh grade B [146 cases (52.3%)] and grade C [80 cases (28.7%)], consistent with previous findings that PVT occurs more frequently in patients with worse liver function, and higher Child-Pugh grades are associated with increased rebleeding and mortality risk [8]. The predominance of Child-Pugh grade B in our cohort may be related to significantly reduced platelet counts in advanced cirrhosis leading to higher bleeding risk than thrombosis risk, as well as baseline characteristics during data collection.

When cirrhotic patients develop PVT, portal pressure near the thrombus site increases further, reducing hepatic blood flow and causing liver ischemia while increasing the risk of GOV and rupture bleeding. Compared with patients without PVT, those with PVT are more likely to be hospitalized for esophagogastric variceal rupture bleeding [9]. In this study, 127 (45.5%) cirrhotic patients with PVT experienced gastrointestinal bleeding, and the proportion of patients with GOV was higher in the bleeding group than in the non-bleeding group (71.7% vs. 54.6%). However, the number of cirrhotic patients with PVT and gastrointestinal bleeding was smaller than the non-bleeding group, possibly related to previous surgical treatment history in the non-bleeding group, such as endoscopic hemostasis and TIPS. The risk of rebleeding after endoscopic therapy significantly increases in cirrhotic patients with PVT, with higher endoscopic rebleeding risk in the PVT group than in the non-PVT group [10]. TIPS is more effective than endoscopic ligation combined with propranolol and anticoagulants in preventing rebleeding in cirrhotic patients with PVT, though it does not significantly improve survival [11-12]. In this study, the proportion of patients with previous endoscopic hemostasis was lower in the non-bleeding group than in the bleeding group (27.5% vs. 60.0%), while the proportion of TIPS procedures was higher (57.5% vs. 25.7%), providing relevant data support. Bilirubin mainly originates from the breakdown of senescent red blood cells; hemoglobin decomposition releases free bilirubin, which reversibly binds to albumin, Y protein, and Z protein before hepatic metabolism. Cirrhotic patients have impaired synthetic function, affecting bilirubin metabolism. In this study, patients with cirrhotic PVT and gastrointestinal bleeding had lower levels of jaundice and TBiL than the non-bleeding group, possibly related to reduced bilirubin source due to hemoglobin loss.

Univariate analysis in this study showed significant differences between the bleeding and non-bleeding groups in etiology, vascular involvement, jaundice, DMPV, GOV, WBC, BUN, Hb, HCT, TBiL, FIB, and other abdominal surgery

history. Further multivariate Logistic regression analysis revealed that WBC, HCT, FIB, and SMVT were independent risk factors for bleeding in cirrhotic patients with PVT, partially consistent with the findings of LIU Bin et al. [13]. These results demonstrate that multiple factors influence gastrointestinal bleeding in cirrhotic patients with PVT, easily increasing mortality risk and leading to poor prognosis.

Leukocytes play important roles in phagocytosis, immunity, and defense against infection. In cirrhotic patients with portal hypertension, endotoxemia may promote local hypercoagulability in the portal vein, as endotoxins entering the portal venous system cause leukocytosis, activating the coagulation process and leading to thrombosis [14-15]. When cirrhosis is complicated by gastrointestinal bleeding, the patient's stress response can also cause elevated leukocytes. In this study, WBC values were higher in the bleeding group than in the non-bleeding group, and WBC was not only a risk factor but also independently associated with gastrointestinal bleeding in cirrhotic patients with PVT, indicating that markedly elevated WBC in these patients should raise suspicion for gastrointestinal bleeding.

FIB is a coagulation factor synthesized by the liver. In advanced cirrhosis, impaired liver function leads to reduced synthesis of coagulation factors and FIB, causing anticoagulation system disorders. The reduction in anticoagulant synthesis is greater than that of the coagulation system, disrupting the coagulation-anticoagulation balance and promoting thrombosis [16]. Studies suggest that decreased FIB levels are not only closely related to the degree of liver function deterioration in cirrhotic patients and have monitoring value for PVT formation, but also increase bleeding risk in critically ill cirrhotic patients [17-18]. This study also found significantly decreased FIB levels in the bleeding group, which was independently associated with gastrointestinal bleeding in cirrhotic patients with PVT. HCT is a routine blood test indicator, and its abnormal expression is related to bleeding, blood cell destruction, and tissue injury [19]. This study found that HCT can predict the risk of gastrointestinal bleeding in cirrhotic patients with PVT, possibly related to red blood cell loss from bleeding, and dynamic monitoring of its changes can help predict bleeding risk.

SMVT is a rare and insidious disease with high mortality, and liver cirrhosis is one of the predisposing factors for mesenteric thrombosis. In this study, SMVT formation occurred in 10.4% of cirrhotic patients and was independently associated with gastrointestinal bleeding in cirrhotic patients with PVT. SMVT formation affects blood return, and if collateral circulation cannot compensate, oxygen consumption in intestinal capillaries further aggravates intestinal ischemia, leading to intestinal barrier damage, intolerance to enteral nutrition, bacterial and endotoxin translocation into the bloodstream, and complications of sepsis, septic shock, and multiple organ failure [20].

In summary, WBC, HCT, FIB, and SMVT are independent risk factors for gastrointestinal bleeding in cirrhotic patients with PVT. Effective interventions

based on these risk factors can prevent and delay disease occurrence and progression, providing auxiliary reference for clinical diagnosis and treatment. However, this study is limited by its single-center design, and more prospective trials are needed to investigate the clinical application of these indicators.

Author Contributions: DONG Wendi was responsible for conceptual design, data analysis, and manuscript writing. YANG Jiani and ZHU Jie provided manuscript revision suggestions. QUAN Yujie, ZHANG Jinjing, and LIU Yan performed data collection. ZHANG Hairong was responsible for quality control and review of the article, overall responsibility, and supervision.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.