

Characteristics of myeloproliferative neoplasm-associated portal hypertension and endoscopic management of variceal bleeding

Xiaoquan Huang*, Ming Zhang*, Yingjie Ai¹, Siyu Jiang, Mei Xiao, Lifan Wang, Yourong Jian, Yuzheng Zhuge, Chunqing Zhang and Shiyao Chen

Abstract

Background: Myeloproliferative neoplasms (MPNs) are a rare yet important clinical cause of portal hypertension, which may cause recurrent gastroesophageal variceal bleeding (GVB). MPN-associated variceal bleeding lacks specific guidelines and clinical consensus and desiderates cohort studies. We performed a multicenter retrospective study to investigate the efficacy of endoscopic management of bleeding in MPNs.

Methods: We included consecutive MPN patients with gastroesophageal varices in eight tertiary university hospitals between January 2007 and March 2020. The clinical characteristics of participants were summarized. MPN patients with a history of GVB were followed up for the rebleeding and death, compared with controls suffering from schistosomiasis-associated portal hypertension who received endoscopic treatment for variceal bleeding at the same period.

Results: A total of 62 MPN patients with gastroesophageal varices were identified, and 37 had a history of GVB. Of these, 24 patients received endoscopic variceal ligation and endoscopic injection of cyanoacrylate for the prophylaxis of variceal rebleeding. Endoscopic treatment significantly reduced the rebleeding rate in MPN patients with a history of GVB (28.2% versus 68.3%, $p=0.0269$). Multivariable Cox regression indicated that endoscopic treatment (HR=0.10, 95% CI: 0.02–0.54, $p=0.008$) was the independent protective factor for decreasing the 3-year rebleeding rate, while the use of non-selective beta-blockers (NSBB) (HR=13.41, 95% CI: 2.15–83.42, $p=0.005$) was the risk factor for increasing the 3-year rebleeding rate. As for the efficacy of endoscopic management, 3-year rebleeding rate was significantly lower in MPN patients in contrast to 46 controls with schistosomiasis-associated variceal bleeding (32.9% versus 59.0%, $p=0.0346$).

Conclusion: Endoscopic treatment might be a feasible and potent approach in the management of gastroesophageal variceal rebleeding in MPNs, while NSBB might be ineffective.

Keywords: chronic hematologic malignancy, endoscopy, gastroesophageal varices, Janus kinase 2, non-cirrhotic portal hypertension, rebleeding prophylaxis

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Introduction

Non-cirrhotic portal hypertension (PHT) includes a group of diseases characterized by splenomegaly, gastric or esophageal varices, ascites,

and preserved liver functions.¹ Myeloproliferative neoplasm (MPN) is an uncommon but important clinical cause of PHT, which might lead to massive splenomegaly, gastroesophageal variceal

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bleeding (GVB), and ascites. MPNs comprise a heterogeneous group of chronic hematologic malignancies, including polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and so on.² Patients with MPN are characterized by erythrocytosis, thrombocytosis, and splenomegaly, which result from the clonal proliferation of myeloid lineages.³ The life quality and prognosis of MPN patients mainly depend on disease-related symptoms, especially thrombotic and bleeding events.⁴

Janus kinase 2 (JAK2) V617 F mutation is most prevalent in MPN⁵ and found in 95% of PV patients while around 50% of ET and PMF cases.⁶ JAK2 V617 F test combined with positive findings in bone marrow is highly predictive of MPN diagnosis.⁷ Previous studies have shown that JAK2 V617 F has a prominent role in vascular risk and MPN-associated PHT.^{8,9} The mechanisms underlying PHT in MPNs remain unclear. Splanchnic vein thrombosis (SVT) is a studied contributing force and extramedullary hematopoiesis within the liver and spleen also plays a pivotal role.^{10,11} Over the past decades, MPN has emerged as the primary systemic cause of non-cirrhotic SVT.¹²

Complications of PHT, such as ascites and GVB, usually appear as the first manifestation in MPN patients.⁹ A previous study demonstrated that 8.2% of all MPN patients suffered from major bleeding events, of which 55.6% were upper gastrointestinal bleeding.¹² Hemorrhage due to underlying diseases, MPN-specific treatment, or both resulted in the recurrence of complications or even death in MPN patients.^{4,13} Meanwhile, considering the lethality of thrombosis or thromboembolism, antithrombotic agents such as acetylsalicylic acid are frequently used in MPN patients for prophylaxis.^{12,14} Yet, these measures lead to the risk of bleeding events and generate difficulties with stopping hemorrhage, thus further complicating the management of MPN.¹⁵ Previous studies indicated that transjugular intrahepatic portosystemic shunt (TIPS) was used to alleviate bleeding, but TIPS-derived thrombosis is a frequent complication in MPN patients.⁸ Endoscopic treatment, including esophageal variceal ligation (EVL) and endoscopic injection of cyanoacrylate (EIC), is the recommended treatment selection for variceal bleeding. In MPN patients with gastroesophageal varices, it might

be necessary to perform monitoring and treatment via endoscopy, considering the possibility of lethal hemorrhage. The clinical presentation of schistosomiasis-associated PHT is similar to non-cirrhotic PHT, and the utilization of endoscopic management for variceal bleeding is accepted.¹⁶ However, only several case reports pinpointed the utilization of endoscopic management of gastroesophageal varices in MPN patients with a recurrent bleeding history. Research on the long-term outcomes of endoscopic management of this patient population is limited.^{17–19} Thus, patients with schistosomiasis-associated PHT were recruited as the control group to compare the efficacy of endoscopic management of gastroesophageal varices in MPN patients.

In this study, we aimed to summarize the characteristics of MPN patients with gastric or esophageal varices. We also aimed to evaluate the efficacy of endoscopic treatment in managing variceal bleeding by comparing the outcomes among patients with MPN who underwent endoscopy, with MPN who did not undergo endoscopy, with schistosomiasis-associated liver cirrhosis, and with alcoholic-associated liver cirrhosis.

Methods

Study design

This retrospective study screened all consecutive patients diagnosed with MPNs at eight China tertiary university hospitals between January 2007 and March 2020. We included consecutive patients with MPN-associated gastric or esophageal varices who were (1) diagnosed as PHT and gastroesophageal varices by contrast-enhanced computed tomography (CT) and upper digestive endoscopy; and (2) diagnosed as MPNs via blood or bone test according to World Health Organization (WHO) 2016 criteria. Patients combined with known etiologies of chronic liver disease, including alcoholic liver disease (ALD), hepatitis B or C, primary biliary cirrhosis, autoimmune liver disease, schistosomiasis, and non-alcoholic fatty liver disease and hepatic carcinoma, were excluded from the MPN group. Inclusion criteria for schistosomiasis-related PHT were (1) patients with a history of schistosomiasis infection confirmed by detection of eggs in stool or positive *Schistosoma* spp. serology in combination with clinical and CT presentation; and (2) endured

GVB and received endoscopic treatment for the secondary prevention of rebleeding. Inclusion criteria for alcoholic-related PHT were (1) ALD diagnosed by excluding other liver diseases and alcohol abuse of >40 g/d in women and >60 g/d in men for >5 years; and (2) endured GVB and received endoscopic treatment for the secondary prevention of rebleeding. We excluded patients who (1) had hepatic carcinoma or other malignant tumor, (2) had other etiology of chronic liver disease, and (3) had a history of abdominal surgery, including splenectomy, liver transplantation, portosystemic shunts, and so on. The medical data of the included patients were recorded in a predesigned case report form. All the patients were followed up via phone calls, outpatient clinic visits, and chart reviews.

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institute's Ethics Committee approval was obtained (B2020-125). Written informed consent was obtained from all individual participants included in the study.

Definitions and study endpoints

The primary outcome of this study was the 3-year rebleeding rate after the first GVB episode. Rebleeding was defined as bleeding from the gastrointestinal tract with a decrease in hemoglobin ≥ 20 g/L, causing hematemesis, hematochezia, or melena according to the guidelines and previous studies.^{20,21} The secondary outcome was the 3-year all-cause mortality rate.

Endoscopic treatment of varices

All gastroscopies were performed using the electronic endoscope GIF-XQ260 (Olympus, Tokyo, Japan) to determine the severity of gastroesophageal varices and treatment selection. EVL is the primary choice for esophageal varices^{20,22} and gastric varices were treated with EIC using the sandwich method as previously described.^{21,23} All endoscopy and treatment procedures were performed by experienced endoscopists (S.C., M.Z., and M.X.), with more than 10 years of endoscopic experience. Follow-up was performed at an interval of 8–12 weeks. Endoscopy was performed, and treatment was repeated until

complete obliteration of varices was achieved. All eight hospitals specialized in endoscopic treatment of gastroesophageal varices. All the patients were routinely followed up by phone every 6 months until death or study termination on 30 June 2020.

Statistical analysis

All categorical variables are reported as *n* (proportion). Continuous variables are reported as mean \pm standard error (SE) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. Normally distributed continuous variables are calculated using Student's unpaired *t* test, and all the other variables are calculated using the Mann–Whitney *U* test. Rebleeding rate and overall mortality rate are compared using Kaplan–Meier analysis. Independent factors were identified using Cox proportional hazards regression model. Covariates with a *p*-value less than 0.100 were included simultaneously in the multivariable Cox proportional hazards regression. Two-tailed test was used for statistical testing significance. A *p*-value of less than 0.05 was considered statistically significant. SPSS 24.0 (SPSS Inc., IL, USA) and STATA 16.0 (StataCorp LP, Texas) were used for calculations.

Results

MPN-associated gastroesophageal varices were identified in a total of 62 patients (mean age 53.0 ± 13.6 ; 30 males: 48.4%) from eight hospitals. Among these 62 patients, 39 (62.9%) suffered from ET, 10 (16.1%) from PV, and 13 (21.0%) from PMF. Among them, 37 MPN patients had a history of GVB (Figure 1). Of these, 24 were diagnosed with MPN before GVB and 13 patients were diagnosed after the bleeding episode. The characteristics of patients grouped by different types of MPN are shown in Table 1. In all, 49 patients underwent JAK2 mutation test, and 46 (93.9%) of them carried JAK2 V617 F mutation, while 1 patient had JAK2 EXON12 mutation. In addition, 42 patients (67.7%) had portal vein thrombosis (PVT) and 31 combined with portal cavernoma (Figure 2(a) and (b)). Among 42 patients with PVT, 29 received antithrombotic treatment. Thereinto, 31 (51.7%) patients had severe esophageal varices, and diffuse

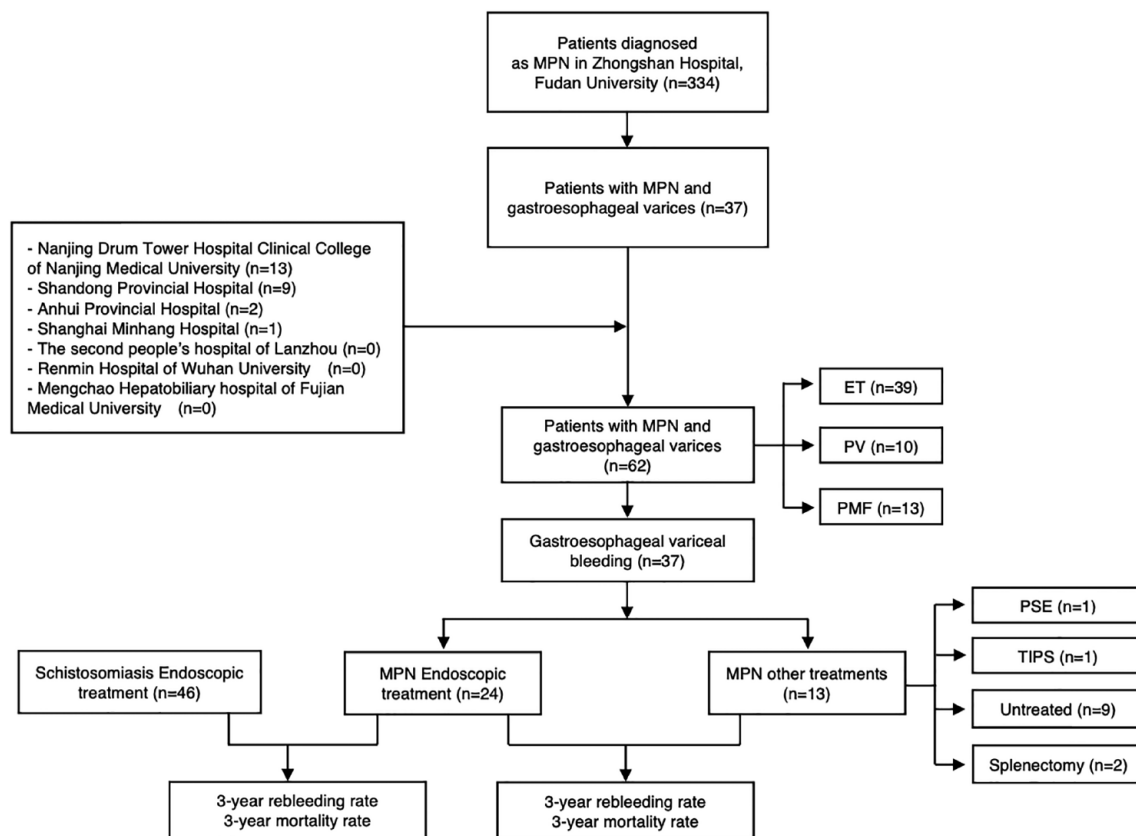


Figure 1. Flowchart of the study.

gastric varices were observed in 29 (61.7%) patients with gastric varices (Figure 2(c)–(h)). Furthermore, there were only two patients combined with Budd Chiari in our cohort, and none of them presented variceal bleeding.

Overall survival

During the 3-year follow-up from the first diagnosis of gastroesophageal varices, seven patients died of variceal bleeding ($n=4$), septic shock ($n=2$), and intestinal necrosis ($n=1$). The 3-year overall survival rate of patients with ET, PV, or PMF was shown in Figure 3(a). MPN patients without a variceal bleeding history seemed to have a better outcome, and MPNs with a variceal bleeding history showed a poor prognosis (Figure 3(b)).

Bleeding episodes in MPN patients

There were 37 MPN patients with a history of GVB, and 14 patients underwent variceal bleeding before the diagnosis of MPN. The

comparison of characteristics of MPN patients with and without bleeding episodes is listed in Table 2. About 86.5% of patients had esophageal varices, and 91.9% of patients had gastric varices in the bleeding group. Patients presenting gastric varices, especially diffuse gastric varices, were more likely to bleed.

Risk factors of rebleeding

Among 37 patients with a history of GVB, 24 patients received endoscopic treatment, including EVL and EIC, for the prophylaxis of rebleeding, while other 13 patients received partial splenic embolization ($n=1$), TIPS ($n=1$), splenectomy ($n=2$), and no treatment ($n=9$). The Kaplan–Meier analysis demonstrated that the rebleeding rate significantly declined in patients who received endoscopic treatment compared to others (28.2% versus 68.3%, $p=0.0269$) (Figure 4). The multi-variable Cox regression analysis for age, MPN type, PVT, endoscopic treatment, MPN treatment, antithrombotic treatment, splenectomy,

Table 1. The baseline characteristics among different types of myeloproliferative neoplasms with gastroesophageal varices.

	ET (N=39)	PV (N=10)	PMF (N=13)	Total (n=62)
Sex (male, %)	18 (46.2)	5 (50.0)	7 (48.4)	30 (48.4)
Age (years)	51.4 ± 2.2	54.1 ± 3.5	56.8 ± 4.2	53.0 ± 1.7
PVT, n (%)	31 (79.5)	6 (60.0)	5 (38.5)	42 (67.7)
Caver cavernoma	23 (59.0)	4 (40.0)	4 (30.8)	31 (73.8)
Portal-systemic shunt	5 (12.8)	1 (10.0)	2 (15.4)	8 (12.9)
Child grade, n (%)				
A	22 (56.4)	4 (40.0)	7 (53.8)	29 (51.8)
B	17 (43.6)	4 (40.0)	5 (38.5)	24 (42.9)
C	0	2 (20.0)	1 (7.7)	3 (5.4)
Child score	6.4 ± 0.2	7.4 ± 0.6	6.6 ± 0.4	6.6 ± 0.2
Ascites, n (%)				
Absent	15 (38.5)	2 (20.0)	3 (23.1)	20 (32.3)
Mild	12 (30.8)	5 (50.0)	6 (46.2)	23 (37.1)
Severe	12 (30.8)	3 (30.0)	6 (46.2)	19 (30.6)
GVB, n (%)	22 (56.4)	6 (60.0)	9 (69.2)	37 (59.7)
Esophageal varices, n (%)				
Absent	6 (15.4)	0	2 (15.4)	8 (12.9)
Mild	3 (7.7)	2 (20.0)	2 (15.4)	7 (11.3)
Moderate	10 (25.6)	2 (20.0)	2 (15.4)	14 (22.6)
Severe	20 (51.3)	6 (60.0)	7 (53.8)	33 (53.2)
Gastric varices, n (%)	32 (82.1)	8 (80.0)	9 (69.2)	49 (79.0)
Diffuse gastric varices	20 (62.5)	7 (77.8)	4 (50.0)	31 (63.3)
RBC (×10 ⁹ /L)	3.8 ± 0.2	5.1 ± 0.7	3.3 ± 0.2	3.9 ± 0.2
Hemoglobin (g/L)	103.9 ± 5.4	131.0 ± 18.7	88.9 ± 9.9	105.1 ± 5.1
Platelet (×10 ⁹ /L)	372 (254–518)	240 (188–291)	280 (105–351)	326 (219–451)
WBC (×10 ⁹ /L)	7.8 (5.7–12.8)	11.8 (9.8–12.7)	7.5 (3.9–9.8)	8.1 (5.8–12.7)
Total bilirubin (U/L)	15.2 (9.8–20.1)	24.4 (17.3–52.2)	23.8 (18.3–31.1)	5.7 (4.1–10.5)
Direct bilirubin (U/L)	15.2 (9.8–20.1)	24.4 (17.3–52.2)	23.8 (18.3–31.1)	17.9 (10.4–26)
ALT (U/L)	23 (17–37)	23 (18–28)	18 (9–28)	22 (17–36)
AST (U/L)	29 (22–35)	29 (24–34.1)	25 (21–31)	29 (22–35)

(Continued)

Table 1. (Continued)

	ET (N=39)	PV (N=10)	PMF (N=13)	Total (n=62)
Albumin (g/L)	38.0 ± 1.0	33.8 ± 2.3	34.8 ± 1.6	36.6 ± 0.8
Creatine (µmol/L)	63.1 ± 2.8	69.0 ± 6.8	77.6 ± 8.9	67.3 ± 2.9
MPN treatment, n (%)	22 (56.4)	8 (80.0)	9 (69.2)	39 (62.9)
JAKi	7 (17.9)	0	4 (30.8)	
Hydroxyurea	13 (33.3)	8 (80.0)	4 (30.8)	25 (40.3)
Antithrombotic treatment, n (%)	30 (76.9)	3 (30.0)	3 (23.1)	36 (58.1)
Splenectomy, n (%)	10 (25.6)	0	1 (7.7)	11 (17.7)
NSBB, n (%)	5 (12.8)	2 (20.0)	4 (30.8)	11 (17.7)
Endoscopic treatment, n (%)	15 (38.5)	5 (50.0)	7 (53.8)	27 (43.5)

ALT, alanine transaminase; AST, aspartate transaminase; ET, essential thrombocythemia; JAKi, JAK inhibitor; NSBB, non-selective beta-blockers; PMF, primary myelofibrosis; PV, polycythemia vera; PVT, portal vein thrombosis; RBC, red blood cell; WBC, white blood cell.

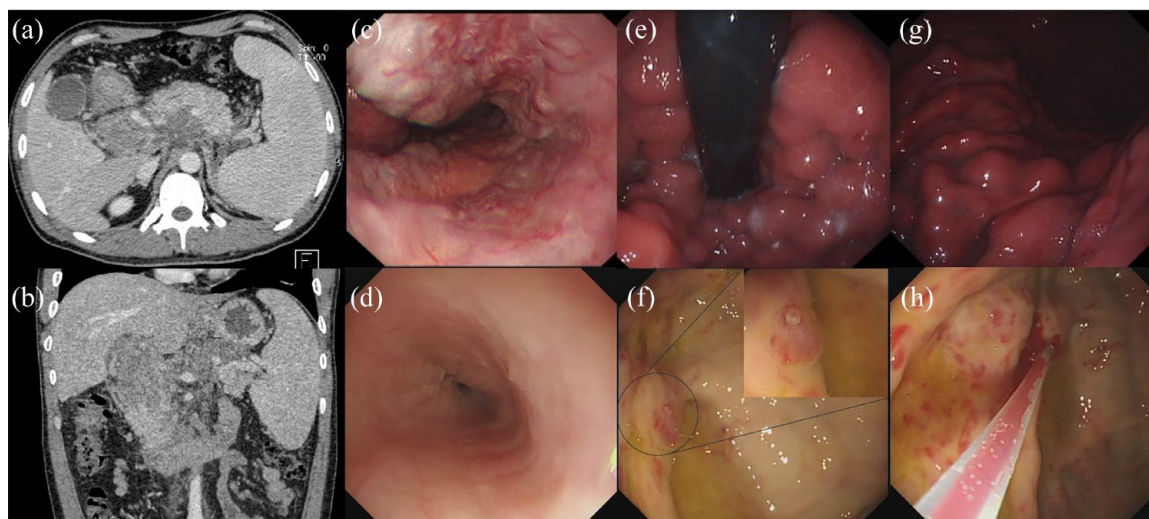


Figure 2. (a) and (b) The portal venous phase of CT shows portal vein thrombosis and portal cavernoma. (c) and (d) Endoscopic image shows diffuse or absence of esophageal varices. (e–g) Diffuse gastric varices and thrombus on the varices and (h) endoscopic injection of cyanoacrylate.

and the use of non-selective beta-blockers (NSBB) indicated that endoscopic treatment [hazard ratio (HR) = 0.10, 95% confidence interval (CI): 0.02–0.54, $p=0.008$] was the independent protective factor while the use of NSBB (HR = 13.41, 95% CI: 2.15–83.42, $p=0.005$) was the risk factor for 3-year rebleeding. Similarly, antithrombotic treatment might be the protective

factor for rebleeding (HR = 0.51, 95% CI: 0.15–1.69, $p=0.270$), yet with no statistical significance (Table 3).

Comparison of endoscopic efficacy

Schistosomiasis-associated PHT exhibits non-cirrhotic pathological manifestations and clinical

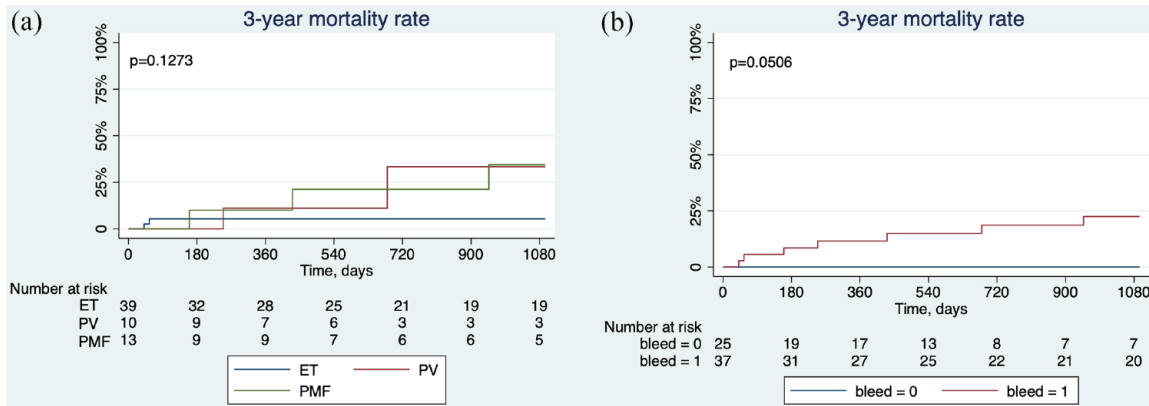


Figure 3. Kaplan–Meier curves showing (a) the 3-year overall survival rate from the first diagnosis of gastroesophageal varices in patients with ET, PV, and PMF. (b) The 3-year overall survival rate in MPN patients with or without a history of variceal bleeding.

presentation, and the utilization of endoscopic management for variceal bleeding is accepted. Patients with schistosomiasis-associated PHT were chosen as the controls to evaluate the endoscopic efficacy of non-cirrhotic portal hypertensive bleeding. Patients with schistosomiasis-associated PHT who received endoscopic treatment for variceal bleeding at the same period were compared to evaluate the efficacy of endoscopic treatment for variceal bleeding. The characteristics of patients with MPN- and schistosomiasis-associated PHT are manifested in Supplemental Table 1. The Kaplan–Meier analysis delineated that the cumulative incidence of 3-year rebleeding rate significantly dropped in the MPN group compared with the schistosomiasis group (32.9% *versus* 59.0%, $p = 0.0346$), and the all-cause mortality rate was similar in both groups (Figure 5).

We also used a control group of patients with alcoholic cirrhosis to analyze the efficacy difference in endoscopic treatment between non-cirrhotic MPN-associated variceal bleeding and cirrhotic variceal bleeding. Patients who had alcoholic cirrhosis and PHT and received endoscopic treatment for variceal bleeding at the same period were included for the comparison of the efficacy of endoscopic treatment, and their characteristics compared with MPN patients are shown in Supplemental Table 2. The Kaplan–Meier analysis delineated that the cumulative incidence of 3-year rebleeding rate and mortality rate was similar in both groups. (Supplemental Figure 1)

Discussion

Erythrocytosis, thrombocytosis, and platelet dysfunction result in thrombotic events and eventually PHT and varices.²⁴ Due to the slow progression of MPNs and lack of symptoms, some patients may not be aware of the development of varices until occasional gastroscopy or even recurrent attack of variceal bleeding. This study included the largest number of patients with MPNs and PHT who received endoscopy treatment for GVB. In our study, about half of the included patients came to hospitals because of gastric or esophageal varices or suffered from variceal bleeding before being diagnosed with MPNs. Attention is required to patients with gastric or esophageal varices with the unexplained reason for PHT, especially in those with PVT, diffuse gastric varices, or whose red blood cell or platelet count is inconsistent with splenomegaly.

In our cohort, ET was the most common type of MPNs with gastroesophageal varices, followed by PMF and PV. PHT in MPNs may attribute to thrombosis of the portal venous system and infiltration of myeloid cells in the spleen.¹⁷ Massive splenomegaly, portal thrombosis, portal cavernoma, ascites, and relatively normal liver functions were usually found in these patients. MPN patients had different extents of splanchnic thrombosis, and clinically significant PVT was observed in about 67.7% of patients. The JAK2 V617 F mutation rate was about 93.9% in this population. Constitutive phosphorylation of JAK2 was caused by JAK2 V617 F mutation, thus promoting clonal

Table 2. Characteristics of myeloproliferative neoplasms patients had a history of variceal bleeding and no bleeding.

	Bleeding (N=37)	Non-bleeding (N=25)	p
Sex (male, %)	16 (43.2)	14 (56.0)	0.438
Age (years)	51.4 ± 2.2	54.1 ± 3.5	
PVT, n (%)	27 (73.0)	15 (60.0)	0.407
Caver cavernoma	21 (56.8)	10 (40.0)	0.300
Portal-systemic shunt, n (%)	7 (18.9)	1 (4.0)	0.128
Child grade, n (%)			0.633
A	20 (54.1)	13 (52.0)	
B	16 (43.2)	10 (40.0)	
C	3 (4.8)	2 (8.0)	
Child score	6.6 ± 0.2	6.6 ± 0.3	0.962
Ascites, n (%)			0.419
Absent	10 (27.0)	10 (40.0)	
Mild	16 (43.2)	7 (28.0)	
Severe	11 (29.7)	8 (32.0)	
Esophageal varices, n (%)			0.089
Absent	5 (13.5)	3 (12.0)	
Mild	3 (8.1)	4 (16.0)	
Moderate	5 (13.5)	9 (36.0)	
Severe	24 (64.9)	9 (36.0)	
Gastric varices, n (%)	34 (91.9)	15 (60.0)	0.002
Diffuse gastric varices	26 (76.5)	5 (33.3)	0.004
MPN treatment, n (%)	24 (64.9)	15 (60.0)	0.791
JAKi	7 (18.9)	4 (16.0)	0.768
Hydroxyurea	14 (37.8)	11 (44.0)	0.628
Antithrombotic treatment	18 (48.6)	18 (72.0)	0.068
NSBB, n (%)	8 (21.6)	3 (12.0)	0.331
JAKi, JAK inhibitor; NSBB, non-selective beta-blockers; PVT, portal vein thrombosis.			

proliferation through the activation of the JAK/STAT pathway, which in turn augmented the risk for splanchnic circulation thrombosis or extramedullary hematopoiesis.²⁵ About half of the patients

were first diagnosed with varices and were later confirmed with MPNs by bone biopsy. The test of JAK2 V617F mutation in peripheral blood might be the most effective method for rapid screening

of the underlying blood disease in non-cirrhotic PHT with unknown etiologies populations.

The development of PHT in MPNs is progressive, and the occurrence of GVB might be lethal. Although recent guidelines including European Association for the Study of Liver disease (EASL) highlight the importance and prevalence of MPN as an etiological factor in SVT, they only put emphasis on the necessity of examining MPN in SVT patients and MPN's impact on thrombosis management but fail to discuss specific treatment for MPN-related variceal bleeding.^{26,27} Endoscopic treatment, including esophageal ligation, sclerotherapy, and gastric cyanoacrylate obliteration, is recommended in managing variceal bleeding in cirrhotic and non-cirrhotic PHT.^{20,22} Thus, endoscopic treatment might also be useful for MPN-related bleeding but lacks systematic investigation on its efficacy despite several case reports that declared successful application of rubber band ligation, EVL, or TIPS for hemostasis in PMF patients.^{28–30} We provided evidence for the utilization of endoscopic treatment in managing variceal bleeding in MPNs. Our multicenter cohort study investigated the effect of endoscopic treatment on gastroesophageal varices in MPN patients and uncovered that endoscopy had a satisfying efficacy in preventing recurrent bleeding and improving the overall survival in these non-cirrhotic MPN patients. The 3-year rebleeding rate after the first episode of variceal bleeding was significantly lower in patients who underwent endoscopic treatment compared to those who did not. The

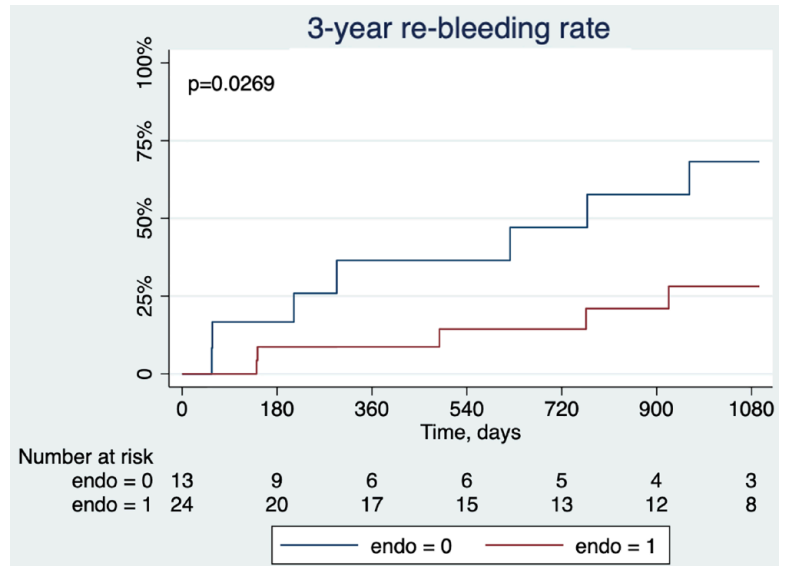


Figure 4. Kaplan–Meier curves showing the cumulative incidence of 3-year rebleeding rate after first bleeding episode in MPNs who underwent endoscopic treatment and those who did not undergo endoscopic treatment ($p=0.0269$).

efficacy of endoscopic treatment in MPNs patients was even better than in patients with schistosomiasis-associated variceal bleeding. Endoscopic therapies should be considered at the diagnosis of gastroesophageal varices in MPN patients for primary or secondary prophylaxis of variceal bleeding.

The combination of NSBB and endoscopic treatment was recommended in cirrhotic patients with recurrent variceal bleeding.^{22,31} However, there is

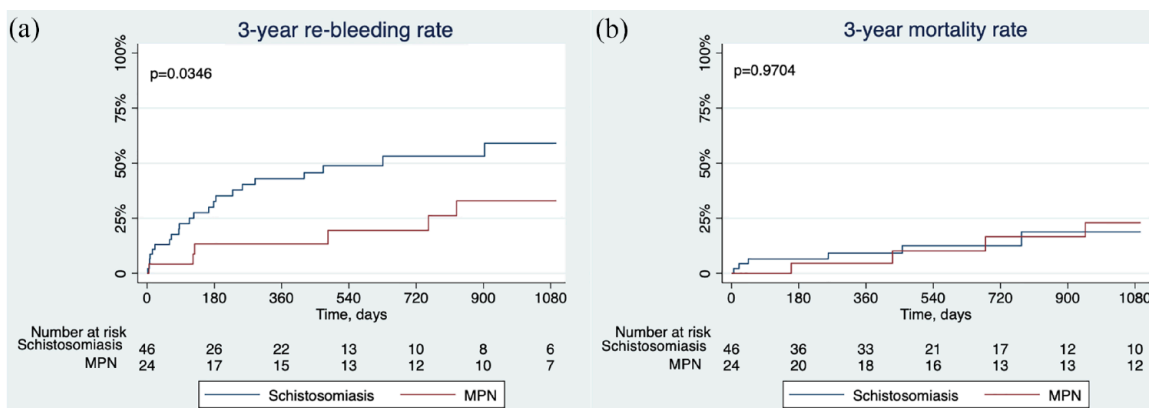


Figure 5. Kaplan–Meier curves showing the cumulative incidence of mortality rate and 3-year rebleeding rate in MPN and schistosomiasis-associated portal hypertension patients who underwent endoscopic treatment for the prevention of variceal rebleeding: (a) 3-year mortality and (b) 3-year rebleeding rate.

Table 3. Univariable and multivariable cox proportional hazards regression analysis of 3-year rebleeding.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age	1.03	0.99–1.07	0.208			
MPN type	1.51	0.81–2.81	0.193			
PVT	0.53	0.17–1.68	0.280			
Endoscopic treatment	0.30	0.09–0.93	0.037	0.10	0.02–0.54	0.008
MPN treatment	1.33	0.36–4.95	0.671			
Antithrombotic treatment	0.51	0.15–1.69	0.270			
Splenectomy	0.23	0.03–1.80	0.161			
NSBB	3.54	1.00–12.56	0.050	13.41	2.15–83.42	0.005

CI, confidence interval; HR, hazard ratio; MPN, myeloproliferative neoplasms; NSBB, non-selective beta-blockers; PVT, portal vein thrombosis.

insufficient data on the effect of NSBB in non-cirrhotic patients with MPNs.³¹ Our results showed that the use of NSBB was a risk factor for rebleeding. NSBB is commonly used to prevent variceal bleeding attributed to its function in reducing cardiac output and splanchnic vasoconstriction, but its contribution to decreased portal vein inflow velocity is a pivotal risk factor for PVT. A prospective longitudinal study reported that NSBB (HR = 10.56, 95% CI: 1.35–82.73, *p* = 0.025) was associated with PVT development.³² A retrospective study also proved that NSBB was significantly associated with PVT progression (OR = 4.400, 95% CI: 1.107–17.482, *p* = 0.035).³³ Besides, a meta-analysis demonstrated that use of NSBB progressed PVT (OR = 4.62, 95% CI: 2.50–8.53, *p* < 0.00001) and subgroup meta-analyses also manifested a consistent association between NSBB and PVT in both cohort studies (RR = 2.57, 95% CI: 1.46–4.51, *p* = 0.001) and case-control studies (OR = 8.17, 95% CI: 2.46–27.06, *p* = 0.0006).³⁴ Therefore, increased risk of PVT development brought by NSBB application might put management of variceal bleeding complicated with PVT into jeopardy.

For MPN-specific therapy, hydroxycarbamide is frequently used as a cytoreductive method, and JAK1/2 inhibitor ruxolitinib is increasingly administered,³⁵ even though the clinical use of ruxolitinib has only been approved for PMF. A case

report showed that the intake of ruxolitinib immediately decreased the hepatic venous pressure gradient (HVPG) from 11 to 6 mmHg and increased the portal venous flow in 30 min, indicating the decline of hepatic resistance.¹⁰ In our study, ruxolitinib was applied to 11 patients; however, no effect on rebleeding reduction was observed.

Prothrombotic disorders that possibly account for PVT and gastroesophageal varices are problematic in these patients. The progression and extension of PVT could amplify the portal venous pressure.³⁶ Due to the hypercoagulable states, antithrombotic treatment might be necessary to prevent PHT complications in MPNs. About 60% of the involved MPN patients received antithrombotic treatment and had a relatively lower rate of variceal bleeding (HR = 0.51, 95% CI: 0.15–1.69). The antithrombotic treatment helped to stop the progression of SVT and reduced gastroesophageal variceal pressure, contributing to the improvement in rebleeding.³⁷

Our study has several limitations. First, some patients with underlying hematological diseases might be misdiagnosed and undiagnosed in clinical practice due to the rareness of this disease. Second, the sample size of this study is still relatively small. Third, as the retrospective nature of this study, the severity and changes of PVT and the use of NSBB might affect the efficacy of endoscopic treatment. Further prospective studies are

needed to confirm the risk factor in the endoscopic management of bleeding in MPNs.

Conclusion

In conclusion, this study uncovered that MPN patients might have PHT and recurrent variceal bleeding. Endoscopic treatment might be applied as the treatment of choice to prevent rebleeding in MPN patients, while NSBB might be ineffective.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institute's Ethics Committee approval was obtained (B2020-125). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Author contributions

Xiaoquan Huang: Conceptualization; Data curation; Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing.

Ming Zhang: Data curation; Formal analysis; Investigation; Methodology.

Yingjie Ai: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Siyu Jiang: Data curation; Formal analysis; Investigation; Visualization.

Mei Xiao: Data curation; Formal analysis; Investigation; Methodology.

Lifen Wang: Data curation; Formal analysis; Investigation.

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Yuzheng Zhuge: Data curation; Formal analysis; Investigation.

Chunqing Zhang: Conceptualization; Data curation; Writing – review & editing.

Shiyao Chen: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The article has been read and approved by all the authors.

Availability of data and material

Raw data and derived data supporting the findings of this study are available from the corresponding author Shiyao Chen on request.

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