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Risk stratification for secondary prophylaxis of gastric varices due to portal hypertension

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ABSTRACT

Background: Gastroesophageal variceal hemorrhage is a common complication associated with portal hypertension. Current guidelines provide well-established recommendations for esophageal varices, while that of gastric varices remain scarce and lack evidential strength. The aim of the study is to identify a feasible risk stratification method based on imaging findings to evaluate patient response to cyanoacrylate injection for the treatment of gastric varices.

Methods: A prospective cohort study including patients diagnosed with gastric varices admitted for initial secondary prophylactic treatment for GV was conducted. Routine endoscopic examination and endoscopic ultrasound (EUS) were performed on all subjects to evaluate extraluminal collaterals. All patients with gastric varices were treated uniformly with cyanoacrylate injection. Patients were prospectively followed for at least 12 months and any occurrence of variceal rebleed was recorded.

Results: 102 subjects were enrolled in the study, 66.7% had GOV Type 2, 27.5% had GOV Type 1 and 5.9% had IGV Type 1. During the 12 months follow-up, 33.3% patients experienced variceal rebleed. A risk assessment scoring system was proposed based on endoscopic and EUS findings. A Cox regression analysis demonstrated a significant association between the merited risk score and incidence of variceal rebleed ($P < 0.001$).

Conclusions: Presence of red wales sign, size of varix, and presence of para-gastric vein were all independent risk factors for variceal rebleed after endoscopic therapy for the treatment of gastric varices. Early identification of this subgroup, especially those with higher risk scores, necessitates a change in course of treatment, which can improve prognosis and overall patient outcome.

1. Introduction

Portal hypertension is the main consequence of liver cirrhosis and is often associated with severe complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and gastroesophageal variceal bleeding [1]. Liver cirrhosis remains a global health burden responsible for over one million deaths in 2010 and is even more tangible in developing countries. The major causes of cirrhosis include chronic hepatitis B virus (HBV), hepatitis C virus (HCV) infection, alcohol abuse, and autoimmune hepatitis. Other etiologies, such as nonalcoholic steatohepatitis and drug-induced liver cirrhosis are increasing in prevalence [2–4].

Among the many presentations of decompensated cirrhosis, variceal hemorrhage is associated with a high mortality rate of 10–20% at 6 weeks [5]. Despite adequate resuscitation and survival from an initial bleeding episode, the risk of variceal rebleed remains at an alarming 60% within the first year [6,7]. Currently, the first line recommendation for preventing recurrent variceal hemorrhage from esophageal varices (EV) is a combination of endoscopic band ligation (EBL) and non-selective beta blockers (propranolol or nadolol). However, recommendations regarding gastric varices (GV) are scarce and lack evidential strength [8]. To date, many

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studies have mainly focused on risk stratification or therapeutic response for esophageal varices. Although lower in incidence, the severity of GV hemorrhage and its associated mortality is substantially higher than that of EV. In addition, majority of patients experience GV rebleed even after spontaneous hemostasis, ranging from 35%–90% [9].

Repeated sessions of cyanoacrylate injection is widely accepted as primary and secondary prophylaxis therapy for GV [10,11]. However, a randomized control trial (RCT) had shown that transjugular intrahepatic portosystemic shunt (TIPS) is more effective than cyanoacrylate in preventing variceal rebleed, but has a higher rate of hepatic encephalopathy without difference in overall survival [12]. Therefore, whether repeated cyanoacrylate injection therapy or early TIPS placement is more effective in preventing variceal rebleed from gastric varices (GV) remains controversial [8,13,14]. In accordance with the tenet of Baveno VI, "Stratifying risk and individualizing care for portal hypertension", the present study is aimed at developing a feasible, widely available method to evaluate patient response to cyanoacrylate injection for secondary prophylaxis of gastric variceal bleeding [8].

The current study offers a risk stratification system for patients undergoing cyanoacrylate injection for the treatment of gastric varices based on real-world clinical evidence.

2. Materials and methods

Patients diagnosed with gastroesophageal varices secondary to portal hypertension were admitted to a tertiary medical center for secondary prophylactic endoscopic treatment. Recruitment began on August 2015 through July 2016. Inclusion criteria were as follows: (1) Patients over 18 years of age, naïve to any form of prophylactic treatment for gastroesophageal varices, including endoscopic therapy (endoscopic banding ligation, endoscopic injection sclerotherapy, or cyanoacrylate injection), oral medication (non-selective beta-blockers), interventional radiology (TIPS, transhepatic portosystemic shunt or BRTO, balloon retrograde transvenous obliteration), or surgical therapy (splenectomy and devascularization surgery); (2) Past history of gastroesophageal variceal hemorrhage confirmed via endoscopic examination. Exclusion criteria were: (1) Patients presenting with only esophageal varices, treated with endoscopic banding ligation or endoscopic injection sclerotherapy. (2) Patients who did not receive secondary prophylactic endoscopic treatment due to incompliance, personal or financial reasons. (3) Patients who received non-endoscopic secondary prophylactic treatment including oral medication, TIPS, BRTO, or splenectomy and devascularization surgery. This study was approved by the Ethics Committee at our institution (B2015-135R).

An informed consent was signed by all study subjects, acknowledging the purpose and risks associated with endoscopic examination and treatment. A routine endoscopic examination was performed after an overnight fast to assess the extent and characteristics of gastroesophageal varices. Findings were classified according to Sarin's classification. GOV Type 1 presents as a continuation of esophageal varices extending along the lesser curvature of the stomach, while GOV Type 2 extends beyond the gastroesophageal junction into the fundus. IGV Type 1 is isolated varices of the fundus while IGV Type 2 is ectopic varices located in the gastric body, antrum or pylorus. A subsequent endoscopic ultrasound (EUS) examination with Olympus CV-260, Olympus EUS-MEI (Olympus, Shinjuku, Tokyo, Japan), or Aloka prosound α5 (Hitachi Healthcare, Twinsburg, Ohio, USA) was performed to identify the presence of para-gastric veins (Fig. 1), which is defined as a group of engorged vessels distal to the gastric wall. EUS examination was conducted by placing the probe against the fundic wall to identify the splenic vein, then slowly moved along the fundus towards the cardia, to observe for any extraluminal phenomenon.

After initial evaluation, endoscopic therapy was performed for all patients as secondary prophylaxis. Each patient received appropriate personalized therapy as deemed fit by the operator. Gastric varices were uniformly treated with cyanoacrylate injection abiding by the sandwich technique, which begins with an injection of lauromacrogol (Tianyu Pharmaceutical, Zhejiang, China), followed by *N*-butyl-cyanoacrylate (Beijing Suncon Medical Adhesive Co. Ltd, Beijing, China), then again with a flush of lauromacrogol. The amount of lauromacrogol and cyanoacrylate injected directly correlated with the size of the varix. The volume of lauromacrogol used ranged from 2 to 10 ml, while that of cyanoacrylate ranged from 0.5 to 2 ml per injection site. The operators attempted to obliterate the gastric varices in one session, prompting multiple injection sites when necessary. The needle sheath was held at the puncture site until the varix solidified, turned pale, and became less mobile. Concurrent esophageal varices were treated with endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS) [15]. All endoscopic diagnosis and treatment procedures were performed by one of two experienced endoscopists (LLM and SYC), each with over 20 years of experience. Patients were required to fast for 24–48 h after the endoscopic procedure. Routine intravenous proton-pump inhibitors (PPI) were administered, while somatostatin and antibiotics were given when deemed necessary. Barring complication, patients were hospitalized for 1–2 days before discharge and were followed-up closely at a designated out-patient service clinic.

Patients were prospectively followed for at least 12 months in order to document any incidence of variceal rebleed, evident by melena or hematemesis, confirmed by a subsequent endoscopic examination. Patients were recommended to receive follow-up endoscopic examination within 8 weeks of the initial therapeutic session. Primary endpoints were defined as variceal rebleed or death. Any further therapeutic intervention for gastric varices during the one-year follow-up was also recorded. Repeated therapeutic intervention was deemed necessary if the follow-up endoscopic examination revealed the presence of gastric varices classified as grade 3 (F3) or had obvious red wale marks [16]. While variceal eradication was defined as complete variceal obliteration or small varices (<5 mm) without red wale marks, which did not necessitate further intervention. A thorough review of each subject's patient history was conducted. Any missing information was obtained through a telephone interview or at the designated outpatient service clinic.

Statistical analyses were performed via SPSS 22 (IBM Corporation, Armonk, New York, USA). Categorical variables were presented as frequency (%), while continuous variables as mean ± standard deviation. Comparison between categorical variables was achieved through Pearson's correlation, while continuous variables were compared using the independent Student *t* test. Cox regression was used to determine the hazard ratio with a 95% confidence interval. Kaplan-Meier and log rank test were used to assess the difference between strata. All statistical analyses were two-sided, and a *P*-value <0.05 was considered statistically significant.

3. Results

From August 2015 to July 2016, 450 patients were admitted to our hospital for gastroesophageal varices secondary to portal hypertension. 346 subjects were excluded based on the prior established exclusion criteria, including 44 patients with a previous history of splenectomy and devascularization, 62 patients received interventional radiology (TIPS or BRTO), 2 patients were on beta-blockers, 170 patients were admitted for consolidation therapy, 27 patients were incompliant with recommended therapy and 41

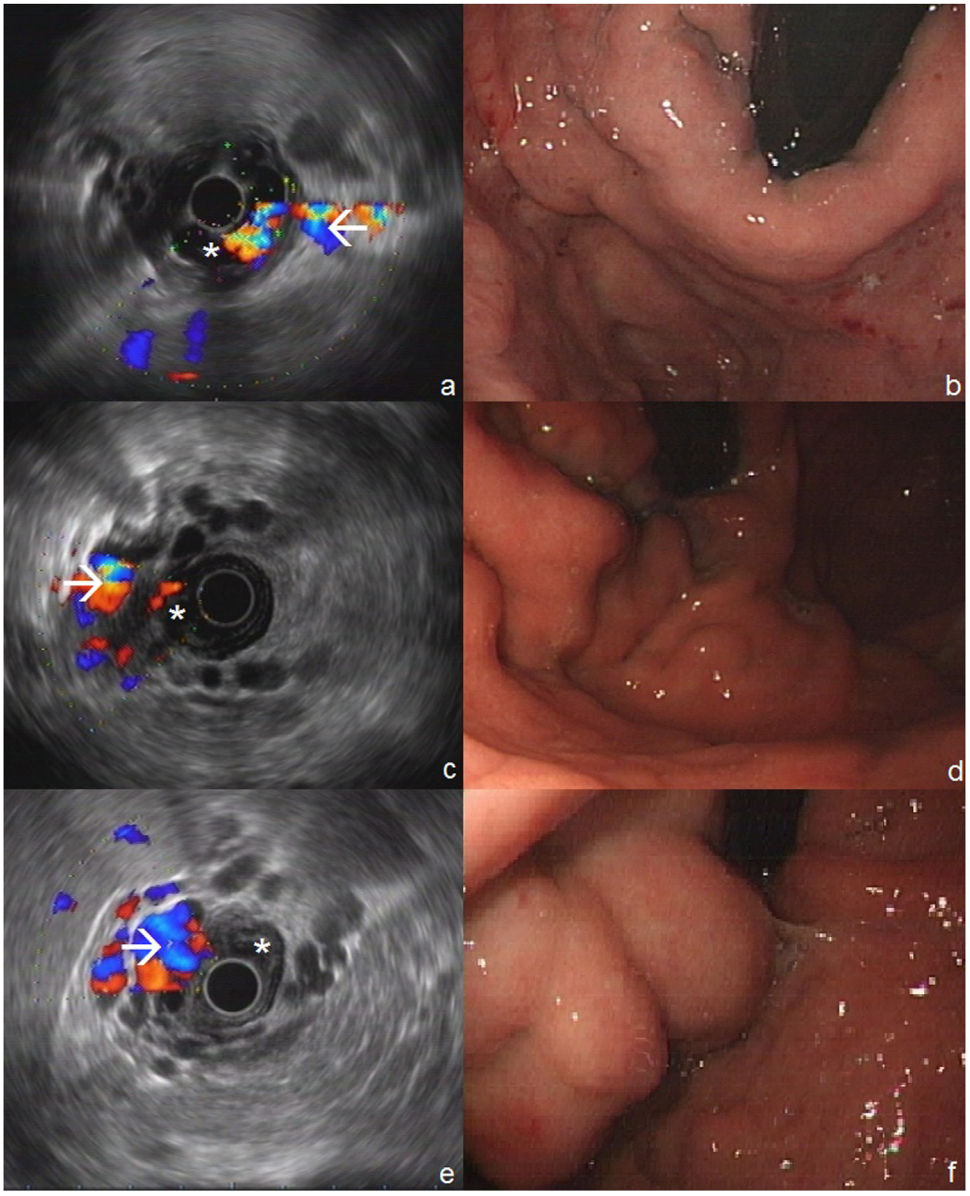

Fig. 1. Presentation of different endoscopic presentation of GOV and extraluminal presentations under EUS observations prior to cyanoacrylate injection. Intraluminal varix is marked by an asterisk (*), while extraluminal para-gastric vein is depicted by the arrow (→). GOV Type 1: Fig. 2a and b; GOV Type 2: Fig. 2c and d; IGV Type 1: Fig. 2e and f.

patients had isolated esophageal varices treated with either EBL or EIS. A total of 104 subjects with gastric varices with or without concurrent esophageal varices fulfilled the inclusion criteria for initial secondary prophylaxis, however, 2 were lost to follow-up. The final inclusion of study subjects was 102 and the baseline characteristics are summarized in Table 1.

Of the included study subjects, 65 (63.7%) were male and 37 (36.3%) were female, with an average age of 56.94 ± 11.44 years old. The average time from the initial bleeding episode to endoscopic treatment was 81.51 days. The average Child Pugh score was 6.57 ± 1.28, with 58 patients classified as Child Pugh Class A (56.9%) and 41 as Class B (40.2%). Etiologies for cirrhosis included HBV (57.8%), HCV (5.9%), alcohol (8.8%), primary biliary cirrhosis (4.9%), autoimmune hepatitis (3.9%), schistosomiasis (1.0%), cryptogenic (14.7%), NAFLD (1.0%) and mixed etiologies (2.0%). Based on the routine radiological angiography, presence of para-gastric veins was identified in 71 (69.6%) patients, while portal vein thrombosis (PVT) was observed in 23 (22.5%) patients, hepatocellular carcinoma (HCC) in 13 (12.7%) patients, and mild to severe ascites in 52 (51.0%) patients.

Gastroesophageal varices were classified according to the Sarin's classification. The most common form of gastroesophageal varices is GOV Type 2 (66.7%), followed by GOV Type 1 (27.5%) and IGV Type 1 (5.9%). No IGV Type 2 was observed in the present study cohort. Thirty-eight (37.3%) patients had obvious red wales sign. Para-gastric veins were observed in 33 (32.4%) subjects under endoscopic ultrasound. All patients received appropriate endoscopic therapy as secondary prophylaxis, including 11 (10.8%) cases of cyanoacrylate injection, 88 (86.3%) cases of cyanoacrylate injection + EBL, 3 (2.9%) cases of cyanoacrylate injection + EIS. The average amount of cyanoacrylate used per patient was 2.86 ± 1.24 ml. One patient experienced intra-procedural bradycardia and was treated successfully with atropine. The most common post-procedural complication was infection, presenting as fever and abdominal pain (n = 4), which were generally treated with antibiotics without further complications.

Table 1
Baseline characteristics of the global population (n = 102) and comparison between patients with (n = 34) or without (n = 68) variceal rebleed within 12 months.

	Global population (n = 102)	No variceal rebleed (n = 68)	Variceal rebleed (n = 34)	*p*-Value
General characteristics				
Gender				
Male	65 (63.7%)	42 (61.8%)	23 (67.6%)	0.565
Female	37 (36.3%)	26 (38.2%)	11 (32.4%)	
Age (years)	56.94 ± 11.44	55.93 ± 10.98	58.97 ± 12.21	0.207
Child Pugh score	6.57 ± 1.28	6.68 ± 1.39	6.35 ± 1.01	0.230
Child Pugh classification				
Class A	58 (56.9%)	25 (51.5%)	23 (67.6%)	0.078
Class B	41 (40.2%)	30 (44.1%)	11 (32.4%)	
Class C	3 (2.9%)	3 (4.4%)	0 (0.0%)	
Etiology of portal hypertension				
HBV	59 (57.8%)	40 (58.8%)	19 (55.9%)	0.424
HCV	6 (5.9%)	5 (7.4%)	1 (2.9%)	
Alcohol	9 (8.8%)	7 (10.3%)	2 (5.9%)	
PBC	5 (4.9%)	3 (4.4%)	2 (5.9%)	
AIH	4 (3.9%)	2 (2.9%)	2 (5.9%)	
Schistosomiasis	1 (1.0%)	1 (1.5%)	0 (0.0%)	
Cryptogenic	15 (14.7%)	7 (10.3%)	8 (23.5%)	
NAFLD	1 (1.0%)	1 (1.5%)	0 (0.0%)	
Mixed	2 (2.0%)	2 (2.9%)	0 (0.0%)	
Laboratory parameters				
Total bilirubin (μmol/L)	18.20 ± 9.90	17.51 ± 10.78	19.57 ± 7.82	0.325
Conjugated bilirubin (μmol/L)	8.93 ± 5.27	8.31 ± 5.23	10.15 ± 5.23	0.096
Albumin (g/L)	35.27 ± 5.16	35.24 ± 5.50	35.32 ± 4.46	0.936
ALT (U/L)	29.82 ± 26.78	29.29 ± 29.66	30.88 ± 20.20	0.779
AST (U/L)	37.78 ± 32.66	35.21 ± 32.38	42.94 ± 33.09	0.262
Hemoglobin (g/L)	89.08 ± 25.19	87.13 ± 25.69	92.97 ± 24.04	0.272
Platelet ($\times 10^9$/L)	75.02 ± 38.22	74.35 ± 40.11	76.35 ± 34.65	0.805
Prothrombin time (s)	14.19 ± 1.59	14.33 ± 1.61	13.91 ± 1.55	0.207
Serum creatine (μmol/L)	72.22 ± 28.57	73.04 ± 31.76	70.56 ± 21.14	0.681
Concurrent conditions				
Portal venous thrombosis				
Absent	79 (77.5%)	54 (79.4%)	25 (73.5%)	0.508
Present	23 (22.5%)	14 (20.6%)	9 (26.5%)	
Hepatic cellular carcinoma				
Absent	89 (87.3%)	59 (86.8%)	30 (88.2%)	0.836
Present	13 (12.7%)	9 (13.2%)	4 (11.8%)	
Ascites				
Absent	50 (49%)	35 (51.5%)	15 (44.1%)	0.594
Mild	51 (50%)	32 (47.1%)	19 (55.9%)	
Severe	1 (1.0%)	1 (1.5%)	0 (0.0%)	
Endoscopic and EUS observations				
Gastroesophageal classification				
GOV Type 1	28 (27.5%)	16 (23.5%)	12 (35.3%)	0.153
GOV Type 2	68 (66.7%)	47 (69.1%)	21 (61.8%)	
IGV Type 1	6 (5.9%)	5 (7.4%)	1 (2.9%)	
Para-gastric veins				
Absent	69 (67.6%)	52 (76.5%)	17 (50.0%)	0.007
Present	33 (32.4%)	16 (12.5%)	17 (50.0%)	
Red wale sign				
Absent	64 (62.7%)	50 (73.5%)	14 (41.2%)	0.002
Present	38 (37.3%)	18 (26.5%)	20 (58.8%)	
Treatment received				
Cyanoacrylate	11 (10.8%)	7 (10.3%)	4 (11.8%)	0.444
EBL + cyanoacrylate	88 (86.3%)	58 (85.3%)	30 (88.2%)	
EIS + cyanoacrylate	3 (2.9%)	3 (4.4%)	0 (0.0%)	
Volume of cyanoacrylate	2.86 ± 1.24	2.57 ± 1.04	3.44 ± 1.40	0.001
Follow-up (12 months)				
Repeated therapy for GV				
Absent	50 (49.0%)	38 (55.9%)	12 (35.3%)	0.100
One session	37 (36.3%)	20 (29.4%)	17 (50.0%)	
Two sessions	15 (14.7%)	10 (14.7%)	5 (14.7%)	
Variceal rebleed				
Absent	68 (69.6%)			
Present	34 (33.3%)			
Time to variceal rebleed (days)	170.65 ± 112.87			

All patients were closely followed-up for at least 12 months, during which 34 (33.3%) cases of variceal rebleed and 3 (2.9%) deaths were reported. Amongst which, 5 patients had GV rebleeding, 7 had EV rebleeding, while the site of rebleeding in the remaining 22 cases was difficult to determine. Two deaths were secondary to uncontrolled variceal rebleed, while the remaining case was due to subsequent complications of an orthotropic liver transplantation. The median time to variceal rebleed was 167 days (68.75–241.75 days).

Patients were divided into two groups based on the occurrence of variceal rebleed (Table 1). A univariate analysis identified the presence of red wales sign, para-gastric vein under EUS observation,

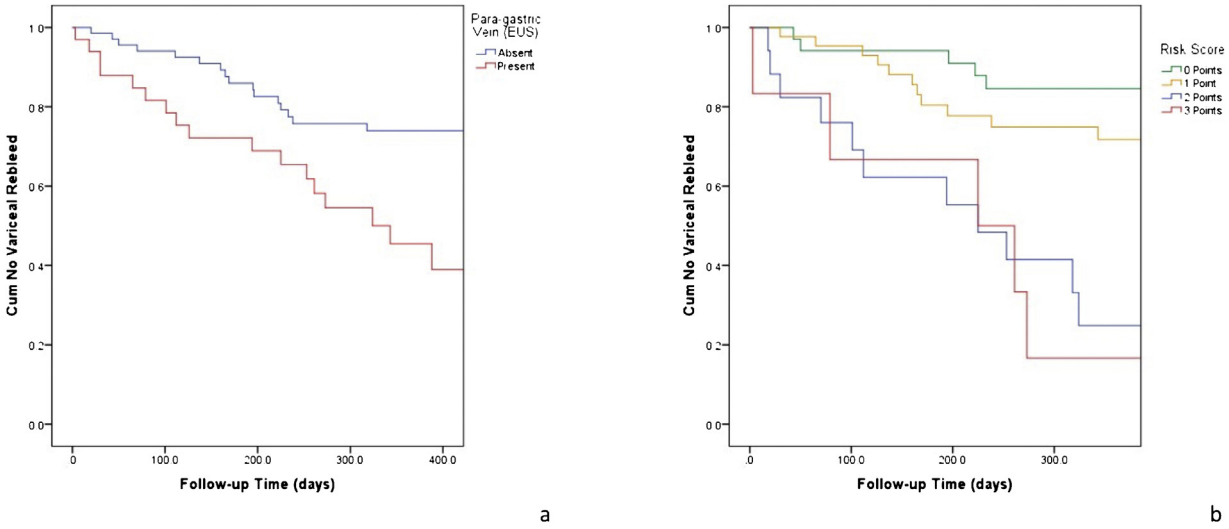

Fig. 2. Kaplan–Meier curve represents the difference in variceal rebleed probability between with or without para-gastric veins under EUS observation (a) and between patients of different risk strata (b).

Table 2
Cox proportional hazard regression analysis for variceal rebleed within 12 months of initial endoscopic therapy and corresponding scoring system for risk stratification.

	Hazard ratio	95% CI	*P* value	Points
Presence of red wale sign	2.645	1.314–5.324	0.006	1
Presence of para-gastric veins (EUS)	2.165	1.073–4.365	0.031	1
Volume of cyanoacrylate ≥ 4.0 mL	2.287	1.117–4.686	0.024	1
Total score	0–3			

and volume of cyanoacrylate injected, as statistically significant parameters associated with variceal rebleed (P < 0.01). Apart from recognized risk factors such as red wales sign and varix size, reflected by the volume of cyanoacrylate injected, the presence of para-gastric vein under EUS observation is significantly associated with an increased incidence of variceal rebleed, log-rank P = 0.005 (Fig. 2a). The three variables were further analyzed with a Cox proportional hazard regression analysis and retained in the final model. The corresponding hazard ratio, with 95% confidence interval (CI) and *P* values are listed in Table 2.

Given similar regression coefficient, a scoring system was proposed to simplify the estimation of associated risk. One point was assigned for the presence of any risk factor at the time of initial endoscopic therapy for the treatment of gastric varices. Each patient was given a score, ranging from 0 to 3 points (Table 2).

Of the 102 patients, 36 (35.3%) had 0 points, 43 (42.2%) had 1 point, and 17 (16.7%) had 2 points, and 6 (5.9%) had 3 points. A Kaplan–Meier curve further demonstrated that the predicted risk was consistent with patient outcome (Fig. 2b). A long-rank (Mantel-cox) test verified the statistical difference between each stratum (P < 0.001).

According to the proposed scoring system, each patient was merited a score to reflect the risk of variceal rebleed within one year. A subsequent cox proportional hazard regression demonstrated that the number of points was significantly associated with the occurrence of variceal rebleed (P < 0.001), with a hazard ratio of 2.348 (95% CI 1.666–3.308). The independent hazard ratio and 95% CI associated with each point increment is depicted in Fig. 3. Overall, during the 12 months follow-up, variceal rebleed was observed in 13.9% of patients with zero points, 27.9% of patients with 1 point, 64.7% of patients with 2 points, and 100% patients with 3 points.

3.1. Consolidation therapy

In order to reflect a real-world clinical data, patients who received consolidation of the treatment of gastric varices during the 12 months follow-up were entered into a subgroup analysis. Due to the lack of active intervention, only 52 (51%) patients received consolidation treatment for gastric varices via endoscopic intervention (cyanoacrylate injection with or without EBL/EIS). Patients were divided into two subgroups based on whether consolidation therapy was performed. A cox proportional hazard regression revealed that even with consolidation therapy, patients with a risk score of 2–3 points still have an alarming hazard ratio of 4.662–4.836 (P < 0.01). Thus, repeat endoscopic therapy may not be adequate to decrease variceal rebleed in patients with higher risk score (Table 3).

4. Discussion

Gastroesophageal varices secondary to portal hypertension and its associated complications remain a clinical adversity faced by both physicians and patients alike. The reported overall prevalence of gastroesophageal varices ranges from 40 to 85% in patients with cirrhosis. Even with aggressive resuscitation and appropriate prophylactic therapy, treatment failure is reported in 10–15% patients necessitating salvage treatment [5,17]. The current consensus of Baveno VI, entitled stratifying risk and individualizing care for portal hypertension recommends a combination of NSBB (propranolol or nadolol) and EBL for preventing recurrence of esophageal varices. However, recommendations for preventing GV recurrence remain divisive, ranging from additional glue injection (after 2–4 weeks), beta-blocker treatment or a combination of both or TIPS, with low

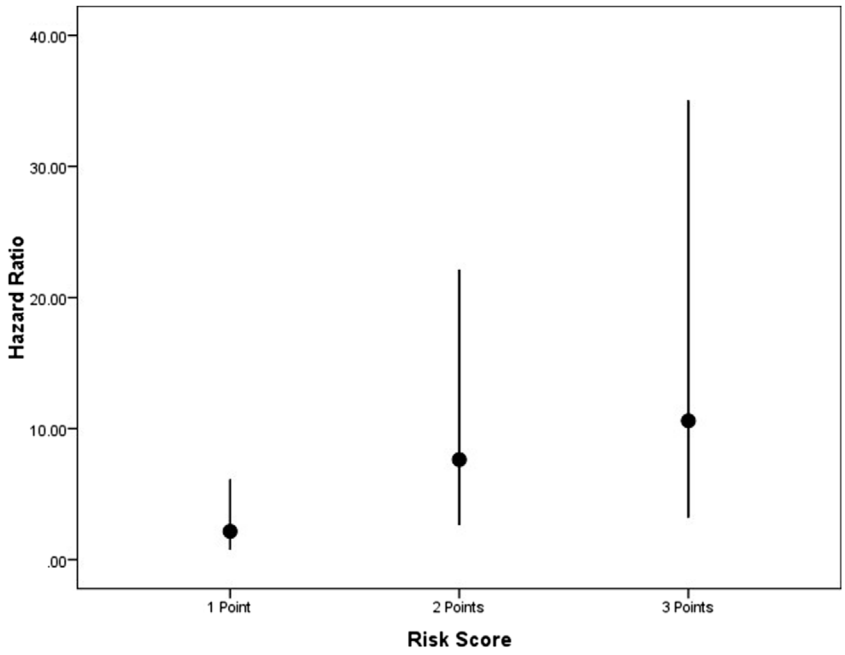

Fig. 3. Individual hazard ratio and 95% confidence interval with every increment in risk score.

Table 3
Cox proportional hazard regression analysis for variceal rebleed within 12 months in patients who received consolidation therapy.

Risk score	Hazard ratio	95% CI	*P* value
1 point	1.788	0.483–6.622	0.384
2 points	4.562	1.162–17.920	0.030
3 points	4.836	0.964–24.254	0.055

evidential strength [8]. Gastric varices (GV) are lower in prevalence compared to EV but are associated with a considerably higher mortality and rebleeding rate. Unfortunately, there is currently no reliable prognostic indicator or instructive data on patient management regarding this subset [18,19].

Multiple clinical studies have investigated clinical value and prognostic abilities of extraluminal collateral phenomena under EUS observations. Carneiro et al. reported the diameter of paraesophageal varices measured under EUS observation as a predictive indicator of EV recurrence within one year [20]. While a different study reported similar findings associated with the presence of severe type peri-esophageal collateral veins for EV [21]. To date, most studies have focused on predicting the recurrence or rebleeding of esophageal varices alone, while gastric varices have often been neglected. To the best of our knowledge, the present study is the first to propose a risk stratification scoring system based on endoscopic and EUS findings for patients with GV treated with cyanoacrylate injection.

Patients included in the present study cohort were admitted for secondary prophylaxis for gastroesophageal varices secondary to portal hypertension, wherein gastric varices were uniformly treated with cyanoacrylate injection. Based on the proposed scoring system, a higher score is significantly associated with risk of variceal rebleed within 12 months of the initial intervention with a hazard ratio of 2.348 (95% CI 1.666–3.308).

Due to the observational nature of the study, and to accurately reflect real-world clinical data, only 52 (51%) patients received consolidation treatment for gastric varices. Among patients who did not receive consolidation therapy, the proposed risk score was significantly associated with variceal rebleed, $P < 0.001$. However, in patients treated with endoscopic consolidation therapy, the hazard ratio did not decrease as expected, especially in patients with a higher risk score (2–3 points). Physicians should encourage frequent follow-ups and surveillance for this subgroup of patients. Repeat endoscopic therapy may not be adequate in preventing variceal rebleed, especially in patients with a higher risk score.

There are several limitations to the present study. Not all patients included in study cohort had available HVPG measurements, which is referred to as the gold-standard for assessing disease severity. Higher HVPG can contribute to the incidence of variceal rebleeding after endoscopic therapy, which should be compared to the proposed scoring system. Post-injection evaluation of the extraluminal collaterals was not conducted to assess the effect of cyanoacrylate on para-gastric veins. The obturation of both gastric varices and para-gastric veins may decrease the risk of variceal rebleed. The size of para-gastric veins was not measured or classified into levels, which may potentially provide a more accurate risk stratification. Another limitation to the study is the composition of enrolled subjects. Majority of the patients were classified as Child A and B, while the main etiology of cirrhosis is viral hepatitis (HBV > HCV). This may hinder the application of study results on patients with advanced chronic liver disease (Child C) or different etiologies of portal hypertension.

EUS is a convenient way to assess the portosystemic collaterals, which can be performed alongside endoscopic therapy. Combined with endoscopic observations for red wales sign and varix size, which is accurately reflected by the amount of cyanoacrylate injected, a feasible risk assessment can be performed for all patients undergoing treatment for gastric varices.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.05.020.

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