Original Article

A retrospective cohort study of intensive gastric variceal ligation versus endoscopic gastric variceal obturation in the management of gastric variceal bleeding

Xuechen Liu[1#], Na Wang[1#], Shulin Jiang[1], Chuanjie Yang[1], Kunyi Liu[1], Li Liu[1], Hongwei Du[1], Huihui Ma[1], Hui Tian[1], Yonghong Zhou[2], Zhijie Feng[1], Huiqing Jiang[1]

[1]Department of Gastroenterology, Hebei Key Laboratory of Gastroenterology, Hebei Institute of Gastroenterology, The Second Hospital of Hebei Medical University, Shijiazhuang, China; [2]Department of Nutrition, Shijiazhuang Maternity and Child Healthcare Hospital, Shijiazhuang, China

Contributions: (I) Conception and design: H Jiang, Z Feng; (II) Administrative support: H Jiang, N Wang; (III) Provision of study materials or patients: N Wang, S Jiang, C Yang, L Liu, H Du, H Ma, H Tian; (IV) Collection and assembly of data: X Liu, K Liu; (V) Data analysis and interpretation: X Liu, Y Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Huiqing Jiang; Zhijie Feng. Department of Gastroenterology, The Second Hospital of Hebei Medical University, Hebei Key Laboratory of Gastroenterology, Hebei Institute of Gastroenterology, 215 Heping West Road, Shijiazhuang 050000, China.
Email: jianghq@aliyun.com; zhijiefeng2005@163.com.

Background: Gastric variceal bleeding is often more serious and can be fatal. Currently, international consensus recommendations for the treatment of gastric variceal bleeding vary according to endoscopic classification. Few studies have investigated ligation versus gastric variceal obturation (GVO) for the treatment of gastric varices.

Methods: The study included 79 patients with cirrhosis-induced bleeding from esophageal and fundal varices who were treated at the Second Hospital of Hebei Medical University between January 2016 and December 2020 and who met the inclusion criteria. Among them, 42 patients were included in the intensive gastric varices ligation (IGVL) group, and 37 were included in the GVO group. We conducted a retrospective cohort study to analyze the effectiveness and safety of these 2 treatments.

Results: The rebleeding rate after initial treatment was significantly lower in the IGVL group than in the GVO group (23.8% *vs.* 48.6%, P<0.05). No significant between-group difference was observed in overall mortality (14.3% *vs.* 32.4%), 6-week mortality (0.0% *vs.* 2.7%), or 1-year mortality (11.9% *vs.* 13.5%, all P>0.05). The >1-year mortality and bleeding-related mortality rates were significantly higher in the GVO group than in the IGVL group (23.3% *vs.* 2.7%, P<0.05; 27.0% *vs.* 9.5%, P<0.05). The incidence of adverse events was 57.1% in the IGVL group and 48.6% in the GVO group, with no significant difference (P>0.05). Independent predictors for rebleeding after initial treatment were the use of GVO as endoscopic treatment, total bilirubin >17.1 μmol/L, liver cancer, and diabetes. For mortality, the independent predictors were male sex, liver cancer, ascites, and rebleeding after initial treatment.

Conclusions: Rebleeding after initial treatment was lower after IGVL than GVO. Independent predictors for rebleeding after initial treatment were endoscopic treatment method, total bilirubin >17.1 μmol/L, liver cancer, and diabetes. For mortality, the independent predictors were male sex, liver cancer, ascites, and rebleeding after initial treatment.

Keywords: Ligation; tissue adhesive; esophageal and gastric varices; liver cirrhosis

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Introduction

Gastroesophageal variceal bleeding is a significant complication of cirrhosis and has a mortality rate of approximately 10–20% (1). Gastric variceal bleeding is often more serious and can be fatal. Hepatitis C virus (HCV) etiology, hepatic encephalopathy, the model for end-stage liver disease (MELD) score and rebleeding were reported as prognostic factors for mortality (2). Treatments for gastric variceal bleeding include β-blockers, endoscopic variceal ligation, endoscopic variceal obturation, shunt surgery, transjugular intrahepatic portosystemic shunts (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO). Although shunt surgery results in the reduction of variceal bleeding, it is also associated with a significant increase in hepatic encephalopathy and mortality (3).

Currently, international consensus recommendations for the treatment of gastric variceal bleeding vary according to endoscopic classification (4-6), usually the Sarin classification (7), categorizes gastric varices as gastroesophageal varices (GOV1 and GOV2) or isolated gastric varices (IGV1 and IGV2). For GOV2/IGV1 gastric varices, recommended treatments include endoscopic injection of N-butyl-2-cyanoacrylate called as gastric variceal obturation (GVO), or BRTO/TIPS. Few studies have investigated ligation versus GVO for the treatment of gastric varices, and the current consensus is based on the results of 2 early prospective randomized controlled trials conducted by Lo *et al.* (8) and Tan *et al.* (9), respectively. Both studies concluded that ligation was associated with higher recurrence and rebleeding rates relative to GVO. However, these studies limited the number of bands for ligation of fundal varices. Therefore, a comprehensive and thorough ligation of fundal varices by intensive ligation without limiting band quantity, which is named as intensive gastric variceal ligation (IGVL), may reduce missed communicating branches of fundal varices. We conducted a retrospective cohort study to analyze the effectiveness and safety of IGVL and GVO for the treatment of fundal varices and to explore the predictors of rebleeding after initial endoscopic treatment as well as mortality. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-138/rc).

Methods

Case description

In total, 374 patients with bleeding from esophageal and fundal varices were treated at the Second Hospital of Hebei Medical University between January 2016 and December 2020. Case data were retrieved from the inpatient medical record system of the hospital, while follow-up data were obtained by phone. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by research ethics committee of the Second Hospital of Hebei Medical University (No. 2017-R201). All patients provided informed consent. The case screening process is shown in *Figure 1*.

The inclusion criteria

Patients with cirrhosis, aged 18 to 78 years; patients with a documented history of bleeding from ruptured gastroesophageal varices; patients with at least 1 endoscopic treatment and 1 follow-up endoscopy; patients with fundal varices, such as GOV2, GOV1 + GOV2, and IGV1; and patients who underwent endoscopic treatment, either IGVL or GVO.

The exclusion criteria

Patients with noncirrhotic portal hypertension such as hypertension due to portal vein spongelike changes; patients with endoscopic contraindications such as perforation of the digestive tract and allergy to sclerosing agents or tissue adhesives; patients with heart failure, renal failure, respiratory failure, or end-stage cancer; patients who underwent liver transplantation; patients who underwent endoscopic treatment in the past year; and patients who did not want to participate.

Materials and treatments

For IGVL, the endoscope (Olympus-260 endoscope, Olympus, Tokyo, Japan) was inverted at the fundus, and the varices were intensively ligated (6 Shooter Multi-Band Ligator, Cook Endoscopy, Inc., Winston-Salem, NC, USA) around the cardiac orifice (U-shaped ligation). The first row of ligation was performed adjacent to the cardiac orifice and usually consisted of 2 to 5 bands; the second row was parallel to the first row, with no gap. In other words, the vascular clusters were in close contact with those of the first row after ligation. Next, ligation continued towards the dome of the fundus until all visible fundal varices were fully and completely ligated. *Figure 2* shows non-IGVL and IGVL treatment.

For GVO of gastric varices, the needle (0910718212, MTW-Endoskopie Manufaktur, Wesel, Germany) was

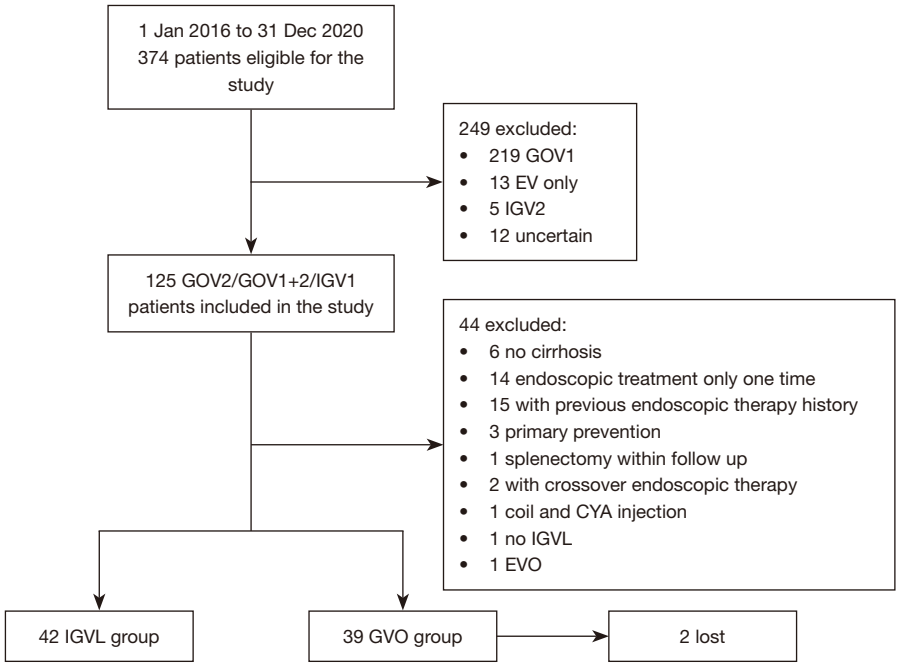

Figure 1 Flowchart of patient selection. GOV, gastroesophageal varices; EV, esophageal varices; IGV, isolated gastric varices; CYA, cyanoacrylate; IGVL, intensive gastroesophageal variceal ligation; EVO, esophageal variceal obturation; GVO, gastric variceal obturation.

prefilled with lauromacrogol (Tianyu Pharmaceutical Co., Ltd., Xi'an, Shanxi Province, China). Once the needle was inserted into the vessel, 3 to 5 mL of lauromacrogol, 0.5 to 2.0 mL of tissue adhesive (α-cyano-n-butyl acrylate, Beijing Compont Medical Devices Co., Ltd., Beijing, China), and 2 to 3 mL of lauromacrogol were quickly injected, after which the needle was promptly withdrawn. The injection sites and the surrounding varices were explored with the needle sheath; if any soft varices were detected, additional injections were performed until all gastric varices were sclerosed.

The esophageal varices were ligated or sclerotherapy was performed after gastric variceal treatment in both groups. Any varicose vein with a diameter ≥5 mm was retreated during endoscopic follow-up.

Related definitions

Cirrhosis was diagnosed based on clinical manifestations of liver damage and portal hypertension.

Esophageal varices were considered "large" if the diameter was ≥5 mm or "small" if the diameter was <5 mm (10-12). Gastric varices were considered "large" if the diameter was >10 mm, "medium" if the diameter was 5–10 mm, and "small" if the diameter was <5 mm (9).

The acute bleeding period (6,13) was defined as bleeding that occurred during the first 120 hours after gastrointestinal bleeding and included vomiting blood and black stool. Any bleeding after 5 days was defined as initial rebleeding.

Outcome measures and follow-up

All patients were followed-up for more than 52 weeks. Gastrointestinal bleeding, time and severity of bleeding, propranolol application, out-of-hospital endoscopic review, complications, death, time of death and cause of death were recorded.

Outcome measures included the success rate of emergency hemostasis, 6-week mortality, 1-year mortality, rebleeding rate, rebleeding rate after initial treatment, and the incidence of adverse events. The predictors of rebleeding after initial treatment and mortality were analyzed.

Statistical analysis

SPSS v25 was used for the data analysis. Measurement

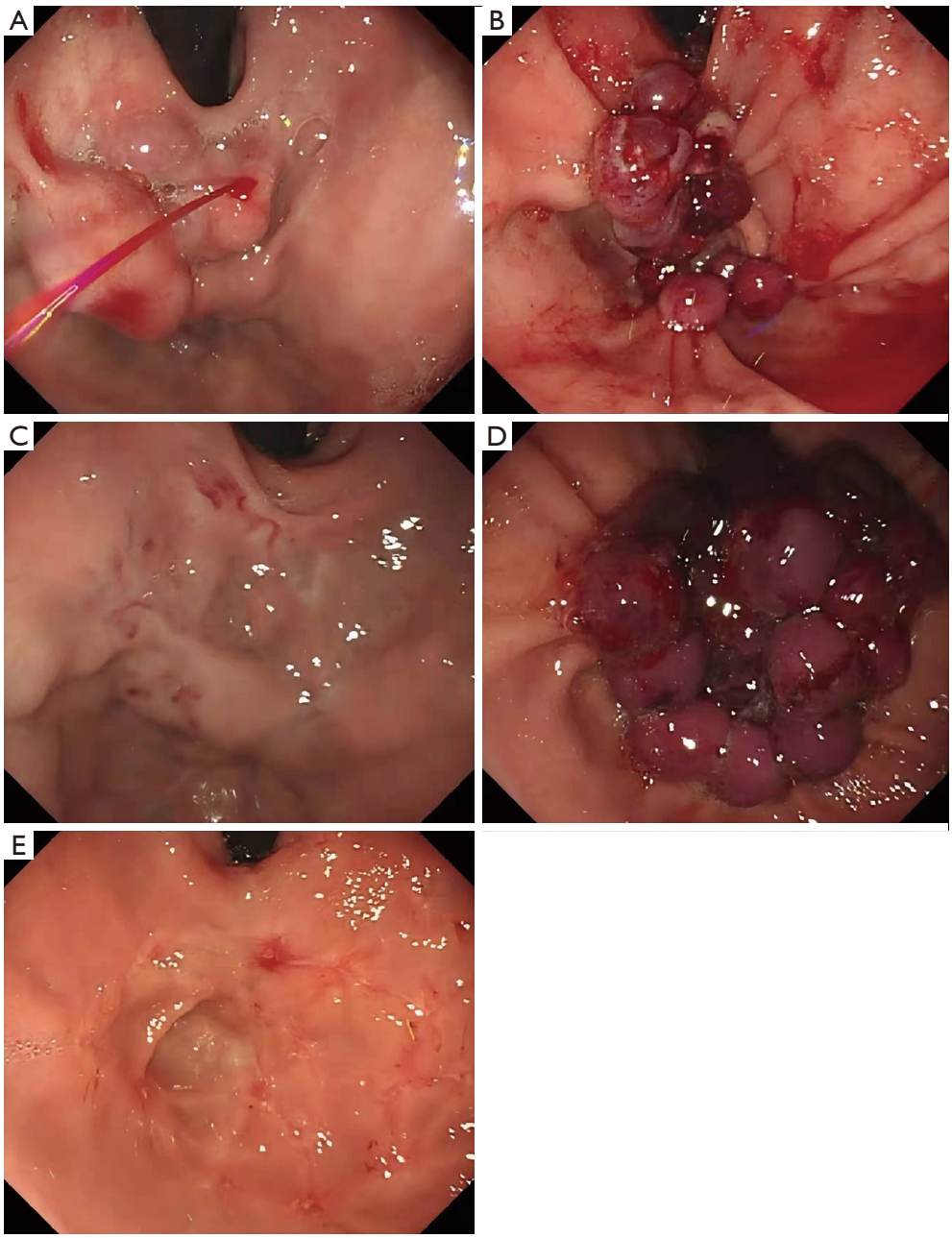

Figure 2 Intensive gastric variceal ligation *vs.* common gastric variceal ligation for gastric varices. (A) IGV1 gastric varices with active bleeding. (B) Band ligation for hemostasis, not intensive. (C) Endoscopic surveillance 6 months later. Gastric varices were not eliminated. (D) IGVL was carried out. (E) Gastric varices were eliminated 2 months later. IGV, isolated gastric varices; IGVL, intensive gastroesophageal variceal ligation.

data were expressed as the mean ± standard deviation and were analyzed using a *t*-test. Nonnormally distributed measurement data were analyzed using the Mann-Whitney U test. Count data were expressed as n (%) and analyzed using the χ^2 test or Fisher's exact test. A Kaplan-Meier survival curve was used to describe survival and rebleeding, the logrank test was performed for univariate analysis to screen the potential predictors with a significance level of $P<0.05$, and a Cox proportional hazards regression model was used for multivariate analysis. All tests were 2-sided,

Table 1 Characteristics of both study groups

Characteristics	IGVL group (N=42)	GVO group (N=37)	P value
Sex (M/F)	29/13	24/13	0.693
Age (years, mean ± SD)	53.2±11.9	54.3±14.9	0.715
Etiology, n (HBV/HCV/alcohol/others)	23/2/7/9	18/1/6/12	0.758
HCC, n (%)	5 (11.9)	5 (13.5)	1.000
Child-Pugh categorization, n (A/B/C)	18/20/4	15/17/5	0.900
Ascites, n (%)	21 (50.0)	20 (54.1)	0.719
Portal venous thrombosis, n (%)	9 (21.4)	10 (27.0)	0.719
DM, n (%)	7 (16.7)	6 (16.2)	0.957
Propranolol, n (used/non/uncertain)	14/24/4	11/23/3	0.901
Splenectomy, n (%)	5 (11.9)	3 (8.1)	0.717
Hemoglobin (g/L)	82.3±25.2	85.7±20.8	0.513
Platelet count ($\times10^9$/L)	88.5±53.4	93.0±107.5	0.813
TB (μmol/L)	21.5±12.5	21.5±11.7	0.993
Albumin (g/L)	32.9±9.8	31.4±7.0	0.429
Cholinesterase (U/L)	3,672.2±1,537.0	3,625.1±1,217.9	0.882
BUN (mmol/L)	6.5±3.1	6.5±3.0	0.948
PT (s)	14.4±2.4	14.5±2.9	0.515
Follow-up time (months)	27.5±14.3	33.2±18.3	0.124
Classification of gastroesophageal varices, n (GOV2/GOV1+2/IGV1)	14/25/3	15/16/6	0.256
Form of gastric fundal varices, n (F1/F2/F3)	26/11/5	14/17/6	0.096
Grade of esophageal varices, n (non/small/large)	3/8/31	4/12/21	0.290
Grade of gastric varices, n (small/medium/large)	4/30/8	1/26/10	0.467
Other treatment during follow-up time (splenectomy or TIPS), n (%)	4 (9.5)	5 (13.5)	0.727

F, female; M, male; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation; HCC, hepatocellular carcinoma; DM, diabetes mellitus; TB, total bilirubin; BUN, blood urea nitrogen; PT, prothrombin time; IGVL, intensive gastroesophageal variceal ligation; GOV, gastroesophageal varices; IGV, isolated gastric varices; TIPS, transjugular intrahepatic portosystemic shunt.

and P<0.05 was considered statistically significant.

Results

Basic data

A total of 81 patients met the inclusion criteria for the study, including 42 in the IGVL group and 39 in the GVO group (2 patients in the GVO group were lost to follow-up). The mean follow-up time was 27.5±14.3 months (range, 3–59 months) in the IGVL group and 33.2±18.3 months (range, 2–63 months) in the GVO group. Baseline data were comparable between both groups. The basic data are shown in *Table 1*.

Endoscopic treatment

In the IGVL group, the number of bands for fundal varices averaged 14.21±7.4. The average amount of tissue adhesive used was 2.99±1.85 mL, with an average of 1.84±1.28 injection points in the GVO group. During the first year, the IGVL group received a total of 168 endoscopies and 133 endoscopic treatments, with an average of 3.17±3.178 endoscopies per patient. The GVO group received a total

Table 2 Clinical outcomes of rebleeding

Variable	IGVL group (N=42)	GVO group (N=37)	P value
Rebleeding count, n (%)	18 (42.9)	24 (64.9)	0.05
Rebleeding after initial treatment			
Rebleeding count, n (%)	10 (23.8)	18 (48.6)	0.021
Early rebleeding, n (%)	4 (9.5)	6 (16.2)	0.502
Later rebleeding, n (%)	6 (14.3)	12 (32.4)	0.055
Bleeding site, n (stomach/esophagus/uncertain)	6/3/1	13/1/4	0.299
Bleeding associated with gastric varices, n (%)	6 (14.3)	13 (35.1)	0.03
Bleeding associated with gastric variceal therapy, n (%)	6/10 (60.0)	8/18 (44.4)	0.43
Severity of bleeding, n (blood transfusion or death *vs.* no blood transfusion)	9/1	11/7	0.149

IGVL, intensive gastroesophageal variceal ligation; GVO, gastric variceal obturation.

of 128 endoscopies and 82 endoscopic treatments, with an average of 2.22±1.456 endoscopies per patient. The mean number of treatments per patient was significantly higher in the IGVL group than in the GVO group (P<0.05). The success rate of endoscopic hemostasis was 100% (19/19) in the IGVL group and 84.2% (16/19) in the GVO group in the acute bleeding period, with no significant between-group difference.

Rebleeding

The overall rebleeding rate was 42.9% (18/42) in the IGVL group and 64.9% (24/37) in the GVO group (P=0.05). The rebleeding rate after initial treatment was 23.8% (10/42) in the IGVL group, which was significantly lower than that in the GVO group [48.6% (18/37), P=0.021]. After initial treatment, gastric varices were the most common bleeding site, with an incidence of 14.3% (6/42) in the IGVL group, which was lower than that in the GVO group [35.1% (13/37), P<0.05]. In the IGVL group, all bleeding was treatment-related, whereas in the GVO group, 8 of 13 incidences of bleeding were due to tissue adhesive displacement. Nine of 10 cases in the IGVL group and 11 of 18 cases in the GVO group required blood transfusions. The detailed results are shown in *Table 2*.

Survival

In the IGVL group and the GVO group, the overall mortality, 6-week mortality, and 1-year mortality were 14.3% (6/42) versus 32.4% (12/37), 0.0% (0/42) versus 2.7% (1/37), and 11.9% (5/42) versus 13.5% (5/37), respectively, with no significant between-group differences (all P>0.05). The >1-year mortality was significantly higher in the GVO group than in the IGVL group [23.3% (7/30) *vs.* 2.7% (1/37), P<0.05]. Bleeding-related mortality was also significantly higher in the GVO group than in the IGVL group [27.0% (10/37) *vs.* 9.5% (4/42), P<0.05]. The detailed results are shown in *Table 3*. The survival curves of both groups are shown in *Figure 3*.

Adverse events

The incidence of adverse events was 57.1% (24/42) in the IGVL group and 48.6% (18/37) in the GVO group, with no significant difference between the groups (P<0.05). The adverse events included transient fever, infection, chest pain or upper abdominal pain, nausea, and heartburn, but there were no serious life-threatening adverse events. Transient fever, mostly low-grade fever, was the most common and was resolved after 1 to 2 days. The incidence of transient fever was 42.9% (n=18) in the IGVL group and 27% (n=10) in the GVO group, with no significant between-group difference (P>0.05).

Analysis of risk factors

In the analyses of rebleeding after initial treatment, 29 variables, including sex and endoscopic treatment method, were included in the Kaplan-Meier survival curve for the univariate analysis. The results indicated 5 significant clinical risk factors, including endoscopic treatment

Table 3 Mortality of patients in the IGVL and GVO groups

Variable	IGVL group (N=42), n (%)	GVO group (N=37), n (%)	P value
Overall mortality	6 (14.3)	12 (32.4)	0.055
Bleeding	4 (9.5)	10 (27.0)	0.042
Hepatic failure	1 (2.4)	1 (2.7)	1
Liver cancer	1 (2.4)	1 (2.7)	1
6-week mortality	0 (0.0)	1 (2.7)	0.468
1-year mortality	5 (11.9)	5 (13.5)	1
1-year later mortality	1/37 (2.7)	7/30 (23.3)	0.018

IGVL, intensive gastroesophageal variceal ligation; GVO, gastric variceal obturation.

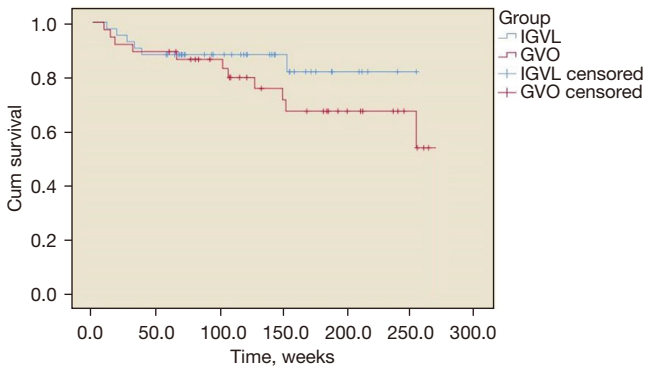

Figure 3 Survival analysis of the patients in the IGVL and GVO groups. IGVL, intensive gastroesophageal variceal ligation; GVO, gastric variceal obturation.

method, total bilirubin, liver cancer, diabetes, and Child-Pugh score. These 5 variables were incorporated into the Cox proportional hazards regression model for multivariate analysis. The results showed that endoscopic treatment method (GVO), increased total bilirubin, liver cancer, and diabetes were independent risk factors.

In all, 32 variables were included in the Kaplan-Meier survival curve for the univariate analysis. The results showed that sex, total bilirubin, albumin, liver cancer, ascites, Child-Pugh score, rebleeding after initial treatment, and overall rebleeding rate were significant variables. Given that total bilirubin and albumin were related to the Child-Pugh score as well as to the sample size, 5 variables including sex, liver cancer, ascites, Child-Pugh score, and rebleeding after initial treatment were incorporated into the Cox proportional hazards regression model for multivariate analysis. The results showed that male sex, liver cancer, ascites, and rebleeding after initial treatment were the 4 independent risk factors for mortality.

Discussion

In 1988, Van Stiegmann *et al.* (14) reported that endoscopic ligation was safe and effective for the treatment of esophageal varices. However, conventional ligation may be associated with reoccurrence due to missed small or invisible varices. In 1995, Umehara *et al.* (15) proposed the concept of "intensive ligation". In 1998, Nagamine *et al.* (16) treated esophageal varices with intensive ligation with better-than-expected outcomes, and the median nonrecurrence period reached 18 months. It remains to be seen whether this approach can be used for endoscopic treatment of gastric varices. The gastric cavity differs from the esophagus in its anatomical structure and acidic environment. Two main causes of rebleeding after ligation for gastric varices have been defined: post-ligation ulcer, which may be why several known related studies restricted the number of bands (8,9,17), and incomplete ligation of gastric varices with missed communicating branches. With the development of acid-suppressing drugs, the perioperative use of proton pump inhibitors effectively reduces the gastric acid level, which helps reduce the risk of postoperative ulcers and bleeding. Intensive ligation of fundal varices involves ligation of all visible fundal varices during a single procedure, with no communicating branches missed. Moreover, multiple bands are applied on the same varicose vein, which reduces the chance of bleeding in the event of detachment of any band. Thus, the use of intensive ligation for fundal varices is worthy of further investigation. In addition, for gastric varices, GVO has certain limitations, such as high risk of ectopic embolism for patients with a gastrorenal shunt (18,19). Intensive ligation may become a

new treatment option for these patients. To the best of our knowledge, no studies have been conducted investigating intensive ligation versus GVO for fundal varices.

The rebleeding rate after initial treatment was significantly lower in the IGVL group than in the GVO group (23.8% *vs.* 48.6%, P<0.05), which differs from previous results. These differences may be due to several factors. (I) Intensive ligation has the advantage of allowing multiple bands on the same varicose vein, which in theory reduces the risk of rebleeding. (II) Few previous studies have been conducted in GOV2 patients. Lo *et al.* (8) included a total of 13 GOV2 patients, Tan *et al.* (9) included a total of 25, and Robles-Medranda *et al.* (17) included a total of 60 patients without detailed classification of gastroesophageal varices. In this study, the inclusion of 70 GOV2 patients was more than the total number of GOV2 cases in the above 3 studies. (III) The previous 3 studies showed that the rebleeding rate was higher for ligation than for GVO. However, subgroup analysis of the different types of gastroesophageal varices in these studies showed that for GOV2 patients, the rebleeding rate was comparable in the ligation and GVO groups. Thus, IGV1 and GOV1 patients were mainly responsible for the higher overall rebleeding rate in the ligation group. Qiao *et al.* (20) conducted a meta-analysis and reached the same conclusion. (IV) Subgroup analysis of a single gastric varix versus multiple gastric varices revealed that for patients with multiple gastric varices, the rebleeding rate after initial treatment was significantly lower in the IGVL group than in the GVO group [5/19 (26.3%) *vs.* 9/15 (60%), P<0.05]. This suggests that IGVL may be more advantageous than GVO for the treatment of multiple gastric varices, which was not mentioned in previous studies.

The >1-year mortality was significantly lower in the IGVL group than in the GVO group (1/37, 2.7% *vs.* 7/30, 23.3%), whereas in most cases, the cause of death was related to rebleeding (IGVL: 4/6, GVO: 10/12). This may be related to the difference in the number of 1-year endoscopic treatments between both groups. In the IGVL group, the average number of 1-year endoscopic treatments was 3.17±3.178 per patient, which was significantly higher than that in the GVO group (2.22±1.456 per patient; P<0.05). With more endoscopic treatments, it is easier to achieve good control and elimination of gastroesophageal varices. Due to the limitations of a retrospective analysis, we were unable to identify the elimination status of varices in some patients.

Multivariate analysis using the Cox proportional hazards regression model showed that male sex, ascites, liver cancer, and rebleeding after initial treatment were independent risk factors for mortality. Therefore, patients with these risk factors should receive more active interventions, such as TIPS, BRTO, and surgery (21,22).

In this study, it should be noted that the incidence of transient fever was 42.9% in the IGVL group, which may have been due to long operating time, pharyngeal injury due to repeated endoscopic maneuvers, or aspiration. All complications were resolved after conservative medical treatment or monitoring. No serious adverse events, such as ectopic embolism, were observed; however, several studies (18,23) showed that the incidence of ectopic embolism was approximately 3.1% after GVO for gastric varices, which was primarily related to the amount of tissue adhesive used and the presence of a gastrorenal shunt. Therefore, intensive ligation may be beneficial to patients with a gastrorenal shunt.

Due to the limitations of retrospective cohort analysis, some patients were excluded based on the exclusion criteria. The patients finally included in this study were comparable between the groups, but sample bias cannot be excluded. In this study, the rebleeding rate was 100% (3/3) in the IGVL group and 50% (3/6) in the GVO group for IGV1 patients. Further studies are needed to investigate whether IGVL is applicable to IGV1 patients. It should be noted that even when endoscopic findings showed elimination of varices after intensive ligation, 1 patient died of rebleeding within 6 months. The gastric mucosa is thick and becomes thicker in the presence of inflammatory edema, which makes it difficult to determine whether varices have been eliminated. This in turn may lead to a false-negative result. This is a possible reason for rebleeding after elimination of varices. Well-designed multicenter prospective studies are needed to further evaluate the recurrence of gastric varices after IGVL.

In summary, this study showed that for patients with variceal bleeding from fundal varices, intensive ligation and GVO of gastric varices were both effective in controlling acute bleeding, whereas the rebleeding rate after initial treatment was lower for intensive ligation, especially for patients with multiple fundal varices. The independent risk factors for rebleeding after initial treatment were liver cancer, diabetes, total bilirubin >17.1 μmol/L, and GVO. No significant between-group difference was observed in the 6-week mortality or 1-year mortality. For mortality, the independent predictors were male sex, ascites, liver cancer, and rebleeding after initial treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-138/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-138/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-138/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by research ethics committee of the Second Hospital of Hebei Medical University (No. 2017-R201). All patients provided informed consent.

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