Article

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Carvedilol Combined with Endoscopy vs. Endoscopy for Prevention of Esophagogastric Varices Rebleeding in Cirrhotic Patients with Different Severity of Esophagogastric Varices

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Purpose: This study aimed to assess the efficacy of endoscopic treatment alone compared to the combination of carvedilol with endoscopic treatment in preventing rebleeding of esophagogastric varices of varying severity in patients with hepatic cirrhosis.
Methods: The study included 867 patients with hepatic cirrhosis and esophagogastric varices, who were admitted to Nanjing Drum Tower Hospital between July 2018 and December 2022. A 180-day follow-up period was implemented to evaluate the association between the combined use of carvedilol and endoscopy and clinical outcomes, focusing on esophagogastric variceal rebleeding and all-cause mortality. Propensity score matching (PSM) was performed on initially enrolled patients meeting the inclusion criteria (n = 232), resulting in the selection of 105 patients each in the endoscopy group and the combined carvedilol and endoscopy group. Subgroup analyses based on the severity of esophagogastric varices were conducted to compare the efficacy of the two treatment modalities.
Results: After PSM, the endoscopy group and the combined carvedilol and endoscopy group exhibited a significant difference in rebleeding rates (29.52% vs. 14.29%, $p = 0.006$) and no significant difference in all-cause mortality (6.67% vs. 1.90%, $p = 0.085$). Multivariate Cox regression analysis revealed that the severity of esophagogastric varices was an independent risk factor influencing rebleeding ($\chi^2 = 3.993$, $p = 0.046$, hazard ratios (HR) = 2.85, 95% confidence intervals (CI): 1.02–7.95), while carvedilol emerged as an independent protective factor against rebleeding ($\chi^2 = 6.222$, $p = 0.013$, HR = 0.46, 95% CI: 0.25–0.85). Subgroup analysis based on the severity of esophagogastric varices showed that among patients with severe esophagogastric varices, the endoscopy group and the combined carvedilol and endoscopy group exhibited significant differences in rebleeding rates (34.12% vs. 16.25%, $p = 0.009$) and no significant differences in all-cause mortality (7.06% vs. 1.25%, $p = 0.063$). Among patients with non-severe esophagogastric varices, the endoscopy group and the combined carvedilol and endoscopy group showed no significant differences in rebleeding rates (10.00% vs. 8.00%, $p = 0.684$) and all-cause mortality (5.00% vs. 4.00%, $p = 0.860$).
Conclusion: Combining carvedilol with endoscopy is more effective than endoscopy alone in preventing rebleeding from esophagogastric varices, though it does not impact patient survival. In patients with non-severe esophagogastric varices, the incorporation of carvedilol alongside endoscopy does not yield significant benefits in rebleeding or survival compared to endoscopy alone. Conversely, for patients with severe esophagogastric varices, the combined use of carvedilol and endoscopy demonstrates greater efficacy in preventing rebleeding than endoscopy alone, yet it does not influence all-cause mortality.
Clinical Trial Registration: Chinese Clinical Trial Registry: ChiCTR-IPR-17012836.

Keywords: propensity score matching; carvedilol; esophagogastric varices bleeding; secondary prevention; endoscopy

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Introduction

Hepatic cirrhosis, a prevalent chronic disorder of the digestive system, commonly induces portal hypertension, leading to the development of esophagogastric varices. Among the complications observed in the decompensated phase of hepatic cirrhosis, bleeding from esophagogastric varices is one of the most severe, affecting approximately 52% of cirrhotic patients with esophagogastric varices [1]. The annual incidence rate of bleeding from esophagogastric varices ranges between 10% and 15%, accompanied by a mortality rate ranging from 15% to 25% within six weeks after onset of the condition [2,3]. For patients who have experienced bleeding from esophagogastric varices, secondary prevention aims to eradicate or alleviate the severity of esophagogastric varices to mitigate the risk of rebleeding [4]. Strategies for secondary prevention include endoscopic treatment, pharmacotherapy (non-selective beta-blockers (NSBBs), nitrates, etc.), combined endoscopic and drug therapy, and interventional treatments. However, a consensus on the efficacy of these treatment modalities has yet to be established.

The commonly used NSBBs currently included propranolol, nadolol, and carvedilol. Carvedilol, identified as a novel NSBB, can potentially reduce portal vein pressure and inhibit the recurrence of bleeding from esophagogastric varices [5]. Recent investigations [6–8] have revealed that carvedilol exhibits greater potency than propranolol in reducing hepatic venous pressure gradient (HVPG) and mean arterial pressure (MAP) during acute and prolonged administration. While the Baveno VII consensus conference has recognized carvedilol as a promising NSBB for managing portal hypertension in hepatic cirrhosis [9]. In comparison, strategies to address bleeding obstruction involve endoscopic treatments, such as Endoscopic Varices Ligation (EVL), Endoscopic Injection Sclerotherapy (EIS), and tissue adhesive injection. Current guidelines suggest that endoscopic treatment should be combined with NSBBs to strengthen the prevention of rebleeding. A meta-analysis [10] showed that combination treatment significantly reduced the risk of rebleeding and bleeding-related mortality. However, the overall mortality rates were similar in both treatment groups. Another meta-analysis [11] reported similar results, comparing the efficacy of patients treated with NSBBs and isosorbide mononitrate with those treated with the same drug combined with EVL. The results showed that combination treatment slightly reduced the risk of rebleeding and did not affect the mortality rate.

It is observed that numerous Chinese patients continue to receive endoscopic treatment alone as a secondary prevention strategy. According to a practice assessment in the Asia-Pacific region [12], it was observed that only 56.7% of gastroenterologists integrate carvedilol into the treatment approach for compensated hepatic cirrhosis. In cases involving high-risk esophagogastric varices within compensated cirrhosis, 66.8% of gastroenterologists support the simultaneous application of NSBBs and endoscopic band ligation, with 7.6% advocating the use of band ligation in isolation [12]. Research on the utilization of carvedilol in combination with endoscopy for preventing rebleeding from esophagogastric varices in the Chinese population remains insufficient.

The risk of formation and bleeding from esophagogastric varices is intricately linked to factors such as portal vein pressure, liver functional impairment, and the size and characteristics of the varices [13–15]. The most effective tool for risk stratification in portal hypertension is the HVPG [16,17]. However, the invasive nature of HVPG measurement and strict operational requirements significantly limit its widespread clinical application.

The severity of esophagogastric varices and HVPG are risk factors for variceal rebleeding. The primary risk factor for acute variceal bleeding is the severity of esophagogastric varices. Cirrhotic patients with large esophagogastric varices face a significantly heightened risk of experiencing acute variceal bleeding. The one-year rate of hemorrhagic events is approximately 5% for patients with small esophagogastric varices and increases to 15% for those with large esophagogastric varices [18].

This study aimed to stratify patients' risk based on the extent of esophagogastric varices using electronic gastroscopy to evaluate the correlation between the severity of varices and the likelihood of rebleeding. The objective of the study was to compare the efficacy of endoscopic treatment alone with combined endoscopic treatment and carvedilol in patients with different severity levels of esophagogastric varices.

Patients and Methods

Patients

This study, conducted at the Department of Gastroenterology, Nanjing Drum Tower Hospital, involved a retrospective analysis of 867 inpatients diagnosed with hepatic cirrhosis and esophagogastric variceal bleeding from July 1, 2018, to December 31, 2022. The inclusion criteria comprised: (1) confirmed hepatic cirrhosis diagnosis through radiological imaging and laboratory tests, (2) age between 15 and 90 years, (3) documented esophagogastric variceal bleeding in the most recent endoscopy, (4) receipt of endoscopic treatment in the hospital post-bleeding, and (5) willingness to provide informed consent. The exclusion criteria were: (1) prior transjugular intrahepatic portosystemic shunt (TIPS), (2) concurrent use of medications impacting NSBBs metabolism and absorption, (3) utilization of other drugs reducing portal pressure, (4) coexistence of liver cancer or other malignancies, (5) organ transplant, (6) missing clinical data, (7) lost to follow-up, and (8) unclear consciousness and lack of cooperation in the study.

Study Design

Patients were categorized into two groups based on the treatment received during hospitalization: (1) the endoscopy group and (2) the combined carvedilol and endoscopy group. This study was conducted in adherence to the Declaration of Helsinki, and approval was obtained from the ethics committee at the Drum Tower Hospital, Medical School of Nanjing University (Ethics Number: 2021-134). Additionally, telephone informed consent was obtained from all patients or their guardians.

Of the initially eligible 343 patients, 111 were excluded based on specific criteria. Exclusions included prior TIPS (24 patients), propranolol treatment (11 patients), lost follow-up data (9 patients), concomitant liver cancer or other malignancies (58 patients), organ transplant status (5 patients), Alzheimer's disease (2 patients), and schizophrenia (2 patients). A total of 232 patients were enrolled, with 109 patients (46.98%) in the endoscopy group and 123 patients (53.02%) in the combined carvedilol and endoscopy group, representing the proportion of each treatment group relative to the total study population.

Demographic characteristics, medical and medication histories were documented at enrolment. The Child-Turcotte-Pugh (CTP) [19] classification assessed liver function status at baseline. Baseline laboratory test results (platelets, hemoglobin, alanine transaminase, aspartate transaminase, total bilirubin, creatinine, albumin, prothrombin time) were collected, and the severity of esophagogastric varices was evaluated through endoscopy [4] by senior clinicians.

Methods

Endoscopy Group

The endoscopy group underwent standard endoscopic treatment guided by the judgment from senior clinicians. An optimal endoscopic hemostasis strategy was implemented, including EVL, EIS, and techniques such as clipping or tissue adhesive injection, or a combination of various endoscopic treatments (various endoscopic treatments have demonstrated similar efficacy [20,21]). Endoscopic treatment was administered at intervals of 2–8 weeks until varices eradication was achieved [22].

Main Equipment. Olympus video gastroscope system CV-290 (Olympus Corporation, Tokyo, Japan).

EVL Procedure. Under endoscopic negative pressure, starting 2 cm above the dentate line esophagogastric varices were spirally inhaled into the endoscopic field from top to bottom. The ligating rubber band was released, utilizing its elastic property to ligate the base of the blood vessels in segments, mechanically obstructing blood flow. If the efficacy of a single treatment was unsatisfactory, the procedure was repeated until the esophagogastric varices disappeared.

EIS Procedure. Under endoscopy, a disposable puncture needle was used to inject polydocanol (10 mL/100 mg) into the lumen of esophagogastric varices, focusing on intravenous injection. Each injection was performed at 1–4 points, with an initial injection of approximately 10 mL per point and a total volume generally not exceeding 40 mL per session. The dosage was adjusted based on the severity of esophagogastric varices.

Clipping Procedure. Introduced through the endoscopic channel, a metal clip was deployed. The metal clip was opened and aligned with the bleeding site. Light pressure was applied, and the metal clip was tightened and detached. The metal clip clamped the lesion and adjacent tissue to block the blood flow.

Tissue Adhesive Injection. Commonly used tissue adhesives, such as α-cyanoacrylate butyl ester, were injected intravenously using the sandwich method (polydocanol + α-cyanoacrylate butyl ester + polydocanol). A single injection aimed to completely occlude the esophagogastric varices.

Combined Carvedilol and Endoscopy Group

Patients in this group received oral carvedilol in addition to standard endoscopic treatment. Initially, 6.25 mg was administered once daily orally. If the baseline heart rate and blood pressure were well tolerated (achieving a reduction in heart rate by 20%–25% or maintaining it between 55 beats/min and 60 beats/min), and ensuring blood pressure remained not lower than 90/60 mmHg, the dosage was gradually increased to 12.5 mg twice daily orally after one week for extended use. Daily monitoring of the heart rate and blood pressure of the patients was conducted for long-term maintenance therapy. If the patient's heart rate and blood pressure were not within the target range, appropriate drug dosage adjustments were made during the study.

Follow-up and Definitions

A 180-day follow-up period post-discharge was conducted using telephone interviews, persisting until the conclusion of the study in July 2023. Each follow-up documented incidences of bleeding and the survival status of the patients. The primary endpoint was esophagogastric variceal rebleeding, encompassing any form of gastrointestinal bleeding, such as hematemesis or melena, and endoscopic bleeding. The secondary endpoint was all-cause mortality.

Statistical Analysis

To mitigate the impact of confounding factors in retrospective research, we employed propensity score matching (PSM) to balance baseline data between groups. IBM SPSS Statistics 26.0 (Version R26.0.0.0, IBM, Chicago, IL, USA) was utilized for data analysis, with continuous variables subjected to normality tests and results presented as mean $\pm$ standard deviation. Group comparisons for continuous variables were executed using a *t*-test, while categorical variables were analyzed using the chi-square test (or Fisher's exact test).

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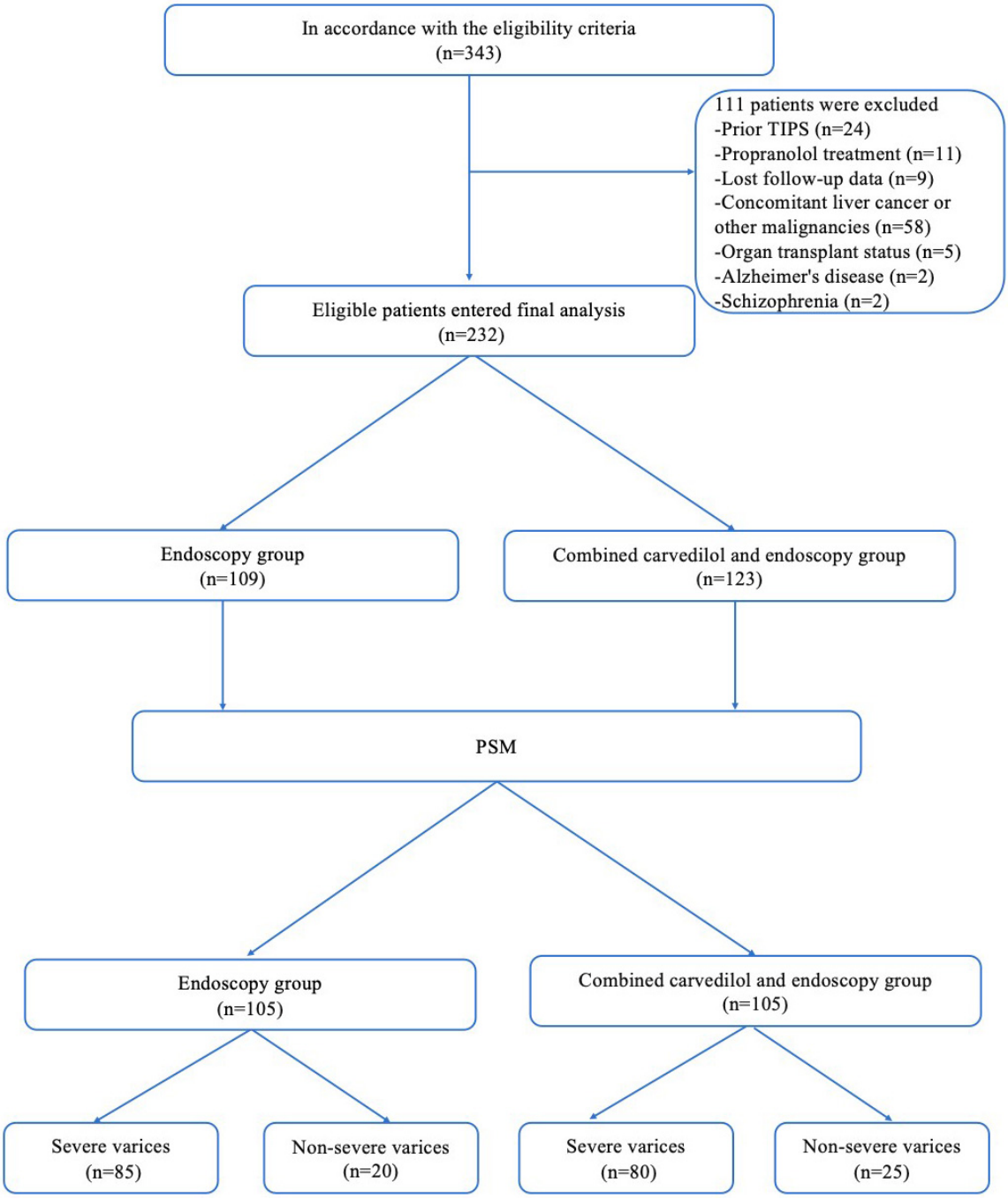

Fig. 1. Flowchart of the study. PSM, propensity score matching; TIPS, transjugular intrahepatic portosystemic shunt.

Survival analysis was conducted through Kaplan-Meier method, assessing the disparity in survival status between the two groups. For statistical comparisons, the Log-rank test was applied. Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model to assess the impact of various factors on prognosis. Candidate variables with $p < 0.25$ in the univariate analysis were subsequently included in the multivariate analysis. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were calculated, with statistical significance set at $p < 0.05$.

Results

Baseline Characteristics of the Patients

Fig. 1 presents the flowchart for this study, outlining the sequential phases. Table 1 (Ref. [4]) provides a comprehensive overview of the baseline characteristics of patients stratified according to distinct treatment regimens.

Propensity score matching (PSM) process: Prior to matching, notable statistical differences were identified between the two groups in terms of age, albumin levels, prothrombin time, and Child-Turcotte-Pugh (CTP) stage ($p <$

0.05). Age, albumin levels, prothrombin time, severity of esophagogastric varices, and CTP stage were selected as matching covariates, with a caliper value of 0.1. Utilizing a 1:1 nearest-neighbor matching method, 210 patients were selected from both groups, with 105 in the endoscopy group and 105 in the combined carvedilol and endoscopy group.

Post-matching, no statistically significant differences were observed in baseline values for each variable ($p > 0.05$), indicating a high degree of comparability between the two groups.

Rebleeding

31 patients in the endoscopy group experienced rebleeding, whereas 15 patients in the combined carvedilol and endoscopy group experienced rebleeding. The rebleeding rate in the endoscopy group was higher than in the combined carvedilol and endoscopy group, exhibiting a statistically significant difference (29.52% vs. 14.29%, $p = 0.006$) (Fig. 2a).

Survival

In the endoscopy group, there were 7 patients of death, whereas in the combined carvedilol and endoscopy group, there were 2 patients of death. The comparison of all-cause mortality rates revealed no statistically significant difference (6.67% vs. 1.90%, $p = 0.085$) (Fig. 2b). In the endoscopy group, five patients died due to rebleeding, one patient succumbed to a post-discharge surgical infection, and one patient passed away for reasons that remain undetermined. In the combined carvedilol and endoscopy group, one patient succumbed to rebleeding and another to cardiac disease.

Univariate Cox proportional hazards regression analysis was conducted to identify factors significantly influencing rebleeding ($p < 0.25$). Table 2 presents the variables with a p-value < 0.25 before PSM, including mean age, severity of esophagogastric varices, ascites, and carvedilol, which were subsequently incorporated into the multivariate Cox regression model. Following PSM, variables with a p-value less than 0.25, including the severity of esophagogastric varices and carvedilol, were included in the multivariate Cox regression model.

The results of the multivariate Cox regression model are detailed in Table 3. Prior to PSM, the p-value for mean age and ascites exceeded 0.05. The severity of esophagogastric varices and carvedilol were identified as factors influencing rebleeding ($p < 0.05$). The severity of esophagogastric varices was established as an independent risk factor for rebleeding ($\chi^2 = 4.009$, $p = 0.045$, HR = 2.87, 95% CI: 1.02–8.04), while carvedilol emerged as an independent protective factor for rebleeding ($\chi^2 = 6.569$, $p = 0.010$, HR = 0.45, 95% CI: 0.25–0.83). Following PSM, the severity of esophagogastric varices maintained its status as an independent risk factor for rebleeding ($\chi^2 = 3.993$, $p = 0.046$, HR = 2.85, 95% CI: 1.02–7.95), and carvedilol remained an independent protective factor for rebleeding ($\chi^2 = 6.222$, $p = 0.013$, HR = 0.46, 95% CI: 0.25–0.85). The results remained consistent before and after PSM.

Subgroup analysis based on the severity of esophagogastric varices:

Following PSM, 165 patients (78.57%) were categorized into severe esophagogastric varices, with 85 patients in the endoscopy group and 80 in the combined carvedilol and endoscopy group. Additionally, 45 patients (21.43%) were classified as having non-severe esophagogastric varices, comprising 20 patients in the endoscopy group and 25 in the combined carvedilol and endoscopy group.

Within the subset of patients with severe esophagogastric varices, 29 patients in the endoscopy group experienced rebleeding, while 13 experienced rebleeding in the combined carvedilol and endoscopy group. The rebleeding rate in the endoscopy group was higher than in the combined carvedilol and endoscopy group, indicating a statistically significant difference (34.12% vs. 16.25%, $p = 0.009$) illustrated in Fig. 3a.

Further analysis revealed that in the endoscopy group, six patients died, while only one patient succumbed in the combined carvedilol and endoscopy group. However, the comparison of all-cause mortality rates did not demonstrate a statistically significant difference (7.06% vs. 1.25%, $p = 0.063$), as shown in Fig. 3b.

In the subset of patients with non-severe esophagogastric varices, two patients in the endoscopy group and two in the combined carvedilol and endoscopy group experienced rebleeding. The comparison of rebleeding rates revealed no statistically significant difference between the two groups (10.00% vs. 8.00%, $p = 0.684$), as shown in Fig. 4a. Regarding mortality, one patient in the endoscopy group and one patient in the combined carvedilol and endoscopy group succumbed to all-cause mortality. The comparison of all-cause mortality rates showed no statistically significant difference between the two groups (5.00% vs. 4.00%, $p = 0.860$), as illustrated in Fig. 4b.

Discussion

This study aimed to evaluate the efficacy of combining carvedilol with endoscopy in preventing rebleeding of esophagogastric varices compared to using endoscopy alone. Propensity score matching (PSM) was employed to mitigate the impact of baseline data and confounding factors, acting as covariates for the matching process. Following the matching procedure, the two groups exhibited greater comparability in confounding factors, thus enhancing the balance between them compared to the pre-matching phase [23]. This improvement ensured a more robust basis for observing outcomes and enhanced the internal validity of the study.

Table 1. Baseline characteristics.

	Before PSM				After PSM			
	Endoscopy group (n = 109)	Combined carvedilol and endoscopy group (n = 123)	t/χ^2	*p*-value	Endoscopy group (n = 105)	Combined carvedilol and endoscopy group (n = 105)	t/χ^2	*p*-value
Sex (male/female)	62/47	71/52	0.017	0.897	58/47	60/45	0.077	0.781
Mean age (years)	60 ± 13.26	56 ± 13.81	–2.267	0.024	60 ± 13.20	57 ± 13.89	–1.543	0.124
Etiology, virus/others	43/66	63/60	3.226	0.072	40/65	53/52	3.262	0.071
Severity of esophagogastric varices, severe/non-severe	89/20	91/32	1.954	0.162	85/20	80/25	0.707	0.400
RC, yes/no	84/25	94/29	0.013	0.908	80/25	82/23	0.108	0.742
OHE, yes/no	6/103	4/119	0.711	0.522	4/101	3/102	0.148	1.000
Ascites, yes/no	82/27	84/39	1.366	0.242	78/27	75/30	0.217	0.642
Endoscopic strategy, Single/Combined	57/52	62/61	0.082	0.774	56/49	56/49	0.000	1.000
Diabetes mellitus, yes/no	32/77	29/94	0.996	0.318	31/74	25/80	0.877	0.349
Hypertension, yes/no	22/87	21/102	0.370	0.543	22/83	20/85	0.119	0.730
Platelets ($\times 10^9$/L)	103.14 ± 99.82	99.85 ± 88.24	–0.267	0.790	104.60 ± 101.29	101.36 ± 92.173	–0.242	0.809
Hemoglobin (g/L)	78.94 ± 22.28	82.55 ± 19.96	1.301	0.195	79.24 ± 22.59	82.97 ± 20.27	1.261	0.209
ALT (U/L)	27.39 ± 22.77	33.51 ± 33.40	1.645	0.101	27.05 ± 22.65	34.66 ± 35.34	1.857	0.065
AST (U/L)	34.62 ± 27.85	40.31 ± 37.18	1.305	0.193	33.99 ± 26.99	41.89 ± 39.37	1.694	0.092
Tbil (μmol/L)	23.50 ± 16.37	20.70 ± 18.67	–1.207	0.229	22.96 ± 16.26	21.55 ± 19.91	–0.561	0.576
Creatinine (μmol/L)	69.74 ± 33.50	65.88 ± 24.01	–1.016	0.311	69.26 ± 33.85	67.34 ± 25.00	–0.468	0.641
Albumin (g/L)	33.24 ± 4.18	34.38 ± 4.50	1.986	0.048	33.35 ± 4.13	34.17 ± 4.67	1.361	0.175
Prothrombin time (s)	14.33 ± 2.03	13.76 ± 1.87	–2.216	0.028	14.14 ± 1.77	13.86 ± 1.97	–1.080	0.282
CTP stage A/B/C	37/61/11	53/67/3	6.877	0.032	37/59/9	41/61/3	3.238	0.198

RC, red signs; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tbil, total bilirubin; OHE, overt hepatic encephalopathy; CTP, Child-Turcotte-Pugh.

Severity of esophagogastric varices [4]: Classified into mild, moderate, and severe (G1, G2, G3) based on morphology and bleeding risk.

Mild (G1): Esophagogastric varices are linear or slightly tortuous, without red signs.

Moderate (G2): Esophagogastric varices are linear or slightly tortuous, with red signs, or serpentine and tortuous but without red signs.

Severe (G3): Esophagogastric varices are serpentine and tortuous with red signs, or they appear beaded, nodular, or tumor-like (regardless of the presence of red signs). In this study, the severity of esophagogastric varices was dichotomized into severe and non-severe.

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Table 2. Univariate Cox analysis of rebleeding in patients.

	Before PSM		After PSM	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex	0.76 (0.43–1.34)	0.343	1.23 (0.69–2.19)	0.492
Mean age	1.01 (0.99–1.04)	0.207	1.01 (0.99–1.03)	0.446
Etiology	0.88 (0.50–1.56)	0.666	0.92 (0.51–1.65)	0.779
Severity of esophagogastric varices	3.31 (1.19–9.20)	0.022	3.03 (1.09–8.46)	0.034
RC	1.16 (0.58–2.32)	0.685	1.05 (0.52–2.12)	0.886
OHE	1.11 (0.27–4.58)	0.884	1.73 (0.42–7.13)	0.450
Ascites	1.52 (0.76–3.06)	0.236	1.36 (0.68–2.74)	0.390
Endoscopic strategy	1.03 (0.59–1.81)	0.919	1.03 (0.58–1.84)	0.912
Diabetes mellitus	0.94 (0.49–1.80)	0.847	0.99 (0.51–1.90)	0.964
Hypertension	0.73 (0.33–1.62)	0.433	0.69 (0.31–1.55)	0.372
Platelets	1.00 (1.00–1.00)	0.591	1.00 (1.00–1.00)	0.597
Hemoglobin	0.99 (0.98–1.01)	0.287	0.99 (0.98–1.01)	0.445
ALT	1.00 (0.99–1.01)	0.927	1.00 (0.99–1.01)	0.946
AST	1.00 (0.99–1.01)	0.773	1.00 (0.99–1.01)	0.734
Tbil	1.01 (0.99–1.02)	0.509	1.00 (0.99–1.02)	0.650
Creatinine	1.00 (1.00–1.01)	0.370	1.00 (1.00–1.01)	0.377
Albumin	1.01 (0.94–1.07)	0.865	1.01 (0.94–1.07)	0.873
Prothrombin time	0.95 (0.81–1.11)	0.489	0.94 (0.80–1.11)	0.453
CTP stage A		0.516		0.710
CTP stage B	1.43 (0.77–2.65)	0.262	1.23 (0.66–2.30)	0.521
CTP stage C	1.48 (0.43–5.10)	0.538	1.56 (0.45–5.40)	0.481
Carvedilol	0.41 (0.22–0.74)	0.003	0.44 (0.24–0.81)	0.008

HR, hazard ratios; CI, confidence intervals.

Bleeding from esophagogastric varices is a common complication of portal hypertension and a significant contributor to mortality in individuals with hepatic cirrhosis [6]. Non-selective beta-blockers (NSBBs) are typically administered to patients with hepatic cirrhosis and esophagogastric varices [24]. This therapeutic approach aims to reduce pressure within the portal vein system, effectively minimizing the potential for rebleeding [9].

In this study, 232 patients with bleeding esophagogastric varices were included. Among them, 123 received a combination of carvedilol and endoscopy, while 109 received endoscopy alone. Through PSM, 105 patients were selected for each group, resulting in 210 patients in the study. Following PSM, rebleeding occurred in 31 patients in the endoscopy group and 15 in the combined carvedilol and endoscopy group, indicating a statistically significant difference (29.52% vs. 14.29%, $p = 0.006$). Endoscopy alone can impede part of the collateral circulation from the portal vein to the esophageal veins, resulting in an elevated risk of postoperative esophagogastric varices recurrence and rebleeding due to increased portal vein pressure [6]. As a novel NSBB [24], carvedilol possesses additional intrinsic anti-α_1 adrenergic effects compared to conventional NSBBs. Carvedilol induces vasodilation by inhibiting α_1 receptors in the hepatic artery, reducing resistance in the portal venous system and alleviating portal hypertension. As a non-selective β-blocker [24], carvedilol decreases blood supply to the liver by blocking β_1 receptors, reducing the cardiac output directed to the liver. This, in turn, diminishes blood flow to the portal venous system and lowers portal venous pressure. Carvedilol also activates β_2 receptors, causing dilation of the portal venous system and reducing resistance, consequently lowering portal venous pressure.

Additionally, carvedilol demonstrates a blocking effect on post-synaptic α_1 receptors, reducing hepatic vascular resistance and tension and consequently leading to a further decrease in portal vein pressure. The findings of this study align with the majority of domestic and international research [25], indicating that the combination of carvedilol and endoscopy is more effective in reducing the recurrence rate of esophagogastric variceal rebleeding compared to endoscopy alone.

Beyond the mechanism by which carvedilol lowers HVPG to prevent rebleeding, multiple additional potential mechanisms may contribute to its efficacy. The potential of carvedilol to promote hepatic stellate cell (HSC) apoptosis [26] and the modulation of inflammatory factor expression through its antioxidative properties [27] significantly contribute to its efficacy in reducing liver fibrosis. Additionally, carvedilol exhibits anti-angiogenic effects, further facilitating the reduction of liver fibrosis [28].

Following PSM, there were seven deaths in the endoscopy group and two deaths in the carvedilol combined

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Table 3. Multivariate Cox analysis of rebleeding in patients.

	Before PSM		After PSM	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Mean age	1.01 (0.99–1.03)	0.560		
Severity of esophagogastric varices	2.87 (1.02–8.04)	0.045	2.85 (1.02–7.95)	0.046
Ascites	1.24 (0.61–2.52)	0.550		
Carvedilol	0.45 (0.25–0.83)	0.010	0.46 (0.25–0.85)	0.013

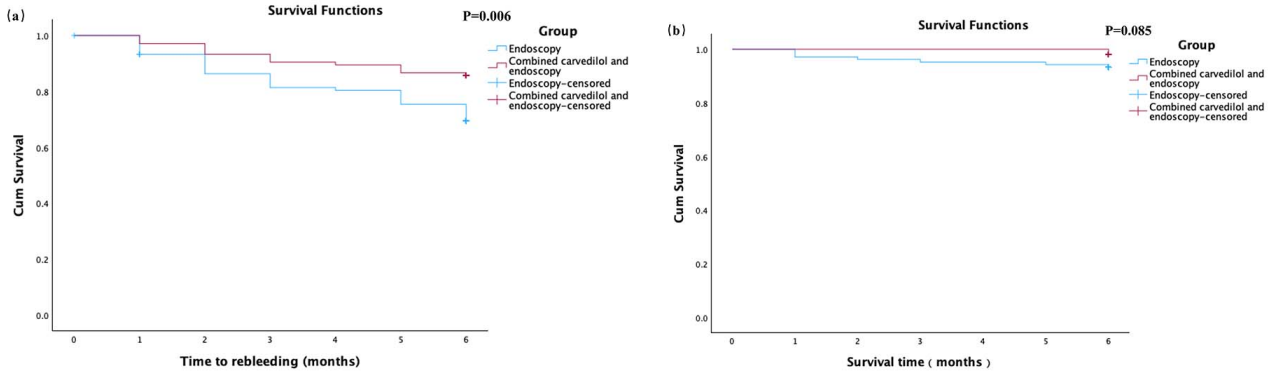

Fig. 2. Kaplan-Meier curves estimating the efficacy post propensity score matching (PSM). (a) Rebleeding. (b) All-cause mortality.

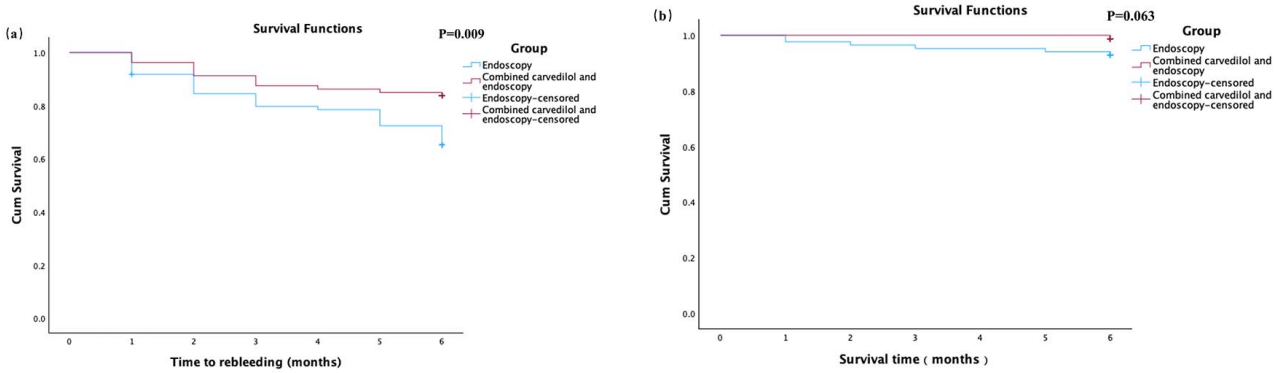

Fig. 3. Kaplan-Meier curves estimating efficacy in the severe esophagogastric varices subgroup. (a) Rebleeding. (b) All-cause mortality.

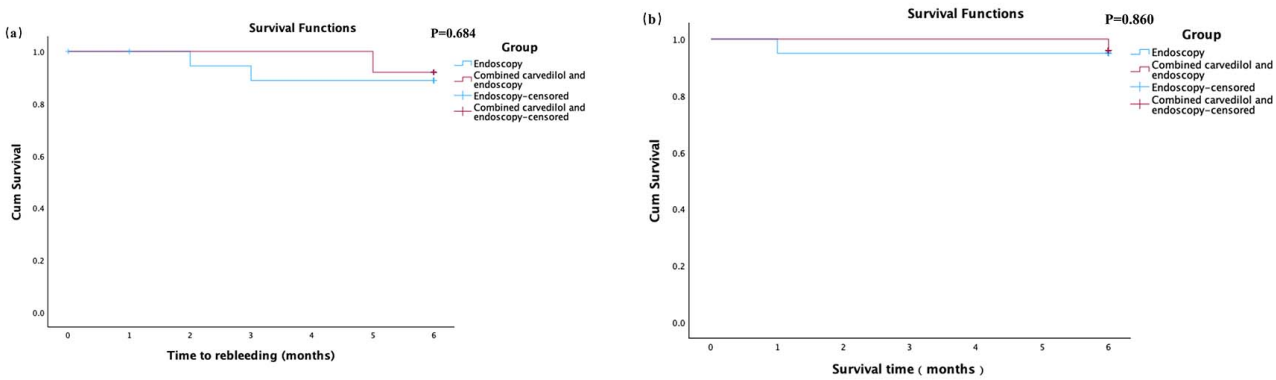

Fig. 4. Kaplan-Meier curves estimating the efficacy in the non-severe esophagogastric varices subgroup. (a) Rebleeding. (b) All-cause mortality.

with the endoscopy group. However, the all-cause mortality rates did not show a statistically significant difference (6.67% vs. 1.90%, p = 0.085). Previous studies [25,29,30] have suggested that carvedilol may reduce liver-related mortality during long-term follow-up. It is crucial to note that our study primarily focused on short-term follow-up, limiting our ability to observe the enduring effects of carvedilol on survival rates. In the short term, carvedilol did not significantly influence survival rates.

Several studies [31,32] have assessed the benefits of carvedilol compared to endoscopy for patients with different HVPG levels. Evidence suggests [33] that NSBBs show no statistically significant differences in mild esophagogastric varices, first bleeding rates, and mortality in primary prevention. Satisfactory efficacy has been achieved in patients with moderate to severe esophagogastric varices [34,35]. Kumar *et al*. [36] conducted a secondary prevention study where baseline HVPG was associated with rebleeding risk. The risk stratification for rebleeding can also be accomplished by assessing the severity of esophagogastric varices through endoscopy.

In our study focusing on the secondary prevention of esophagogastric variceal bleeding, we aimed to observe whether phenomena similar to those observed in previous primary prevention studies could manifest. Therefore, we conducted a subgroup analysis by classifying the severity of esophagogastric varices. According to relevant guidelines [4], patients were categorized into severe esophagogastric varices and non-severe (mild + moderate) esophagogastric varices groups based on the severity of esophagogastric varices assessed through endoscopy. During PSM, the inclusion of the severity of esophagogastric varices served as a covariate to account for confounding variables. The outcomes from the multivariate Cox regression analysis revealed that the severity of esophagogastric varices is an autonomous risk factor influencing rebleeding (χ^2 = 3.993, p = 0.046, HR = 2.85, 95% CI: 1.02–7.95).

In subgroup analysis, the rebleeding rate in patients with severe esophagogastric varices treated with carvedilol combined with endoscopy was significantly lower than with endoscopy alone (16.25% vs. 34.12%, p = 0.009), with no statistically significant difference in all-cause mortality (1.25% vs. 7.06%, p = 0.063). For patients with non-severe esophagogastric varices, there was no statistically significant difference in rebleeding rates between those treated with carvedilol combined with endoscopy and endoscopy alone (8.00% vs. 10.00%, p = 0.684) and no statistically significant difference in all-cause mortality (4.00% vs. 5.00%, p = 0.860).

Since the severity of esophagogastric varices reflects portal vein pressure to some extent, the study by Wadhawan *et al*. [37] observed that the average HVPG in patients with severe esophagogastric varices is higher than in those with mild esophagogastric varices. Therefore, patients with mild to moderate esophagogastric varices have lower HVPG. The prevailing belief is that maintaining an HVPG $\leq$12 mmHg or achieving a reduction of $\geq$10% from the baseline lowers the risk of rebleeding and mortality [8]. However, there is a shortage of convincing evidence on the efficacy of carvedilol in preventing non-severe esophagogastric varices in secondary interventions [24]. In a randomized controlled trial by Bhardwaj A *et al*. [38] for primary prevention, the interventions involved the administration of carvedilol to patients with mild esophagogastric varices over one year. However, the HVPG decreased by 8.64% compared to the baseline (14.49 $\pm$ 4.31 mmHg). No statistically significant differences were observed in reducing HVPG, variceal bleeding, or survival rates compared to the placebo group. Therefore, carvedilol moderately reduces HVPG in patients with mild esophagogastric varices.

Moreover, in a recent randomized controlled trial [39], it was observed that the reduction in HVPG by NSBBs is less pronounced in patients with HVPG $\leq$10 mmHg compared to those with HVPG $>$10 mmHg. This phenomenon is similar in primary and secondary prevention. NSBBs are suitable for preventing decompensation due to portal hypertension in hepatic cirrhosis. However, their potential benefits in the initial phases of hepatic cirrhosis, where the progression of portal hypertension is less pronounced, may be limited [39]. This constrained efficacy of NSBBs in reducing HVPG may be due to their reduced impact on portal vein inflow following high dynamic circulation [39,40]. In patients with cirrhosis and exhibiting HVPG $\leq$10 mmHg, the high dynamic syndrome remains incomplete, and the influence of NSBBs on portal pressure is significantly lower than when HVPG $>$10 mmHg [39]. Simultaneously, the rebleeding rate in non-severe esophagogastric varices is lower, and in patients with non-severe esophagogastric varices, carvedilol seems to be more specifically directed towards preventing the progression of esophagogastric varices to a severe stage [22,38]. The preventive impact on rebleeding necessitates long-term follow-up for observation. For patients with severe esophagogastric varices, due to their elevated HVPG, carvedilol can significantly reduce HVPG [41], thus assuming a pivotal role in preventing rebleeding. Consequently, our investigation has not identified a discernible advantage of carvedilol in the secondary prevention of non-severe esophagogastric varices. However, for patients with severe esophagogastric varices, a combined regimen of carvedilol and endoscopy can effectively prevent rebleeding.

Our study is constrained by various limitations, predominantly from its single-center, retrospective design, limited sample size, and a short-term follow-up period. Given the retrospective nature of our study, potential information bias and uncontrolled confounding factors may have, to some extent, influenced the accuracy of our research findings. We advocate for future research to embrace more extensive prospective study designs to enhance scientific rigor and reliability.

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We acknowledge the inherent limitation of conducting a single-center study, which may constrain the generalizability of our results. To attain a more comprehensive understanding and validate the observed trends, we recommend future endeavors to undertake multicenter research, thereby expanding the sample size and enhancing the reliability of study outcomes.

The 180-day short-term follow-up yields crucial insights into the patient's disease course. However, we must candidly acknowledge that this time limit might not fully explore long-term outcomes, particularly in terms of survival. While short-term prognosis focuses on initial treatment effects and complication development, observing longer-term outcomes is imperative for a comprehensive evaluation of patient prognosis. Future research should incorporate longer-term follow-up to obtain a more comprehensive understanding of the extended prognosis of patients.

In this study, the evaluation of the efficacy of carvedilol in patients with hepatic cirrhosis and esophagogastric varices was confined to short-term observations of rebleeding rates and all-cause mortality. Endoscopic follow-up tracking of the progression and improvement of esophagogastric varices in patients was not conducted. Therefore, the potential for carvedilol to improve the progression of esophagogastric varices severity and achieve long-term benefits cannot be ruled out.

Despite the implementation of PSM to eliminate numerous confounding factors, certain foreseeable confounding factors remain unaddressed. Firstly, the preventive efficacy of carvedilol against esophagogastric variceal rebleeding is based on reducing HVPG. While it is speculated that a potentially lower HVPG may not induce a significant hemodynamic response, previous studies [7,42,43] suggested that even patients with elevated HVPG may not consistently achieve a hemodynamic response. The comparability of hemodynamic responses in patients undergoing carvedilol treatment, as measured by HVPG, was not ensured in our study.

Secondly, the gradual escalation of carvedilol dosage for patients was contingent on their heart rate and blood pressure tolerance levels. Lower doses of carvedilol were exclusively administered to patients manifesting intolerance to heart rate and blood pressure. The impact of varying doses of carvedilol on esophagogastric variceal rebleeding in patients [44,45] was not investigated. Moreover, varying doses of carvedilol may exert divergent effects on the prognosis of rebleeding from esophagogastric varices of varying severities. This represents a potential avenue for future research.

Conclusion

In this study, we observed that among patients with non-severe esophagogastric varices, the combined use of carvedilol and endoscopy did not result in a reduction in both rebleeding and all-cause mortality compared to endoscopy alone. Conversely, among patients with severe esophagogastric varices, the combined use of carvedilol and endoscopy demonstrated greater efficacy in preventing rebleeding compared to endoscopy alone. However, it did not significantly impact patient survival.

Availability of Data and Materials

Upon reasonable request, the corresponding authors can provide the data used to support the study findings.

Author Contributions

Conceptualization, WJJ and WHG; methodology, WJJ, MMP and FZ; software, WJJ and JBQ; validation, WJJ and JBQ; formal analysis, WJJ; investigation, WJJ; resources, QY; data curation, WJJ, QY and JBQ; writing—original draft preparation, WJJ; writing—review and editing, WJJ; visualization, WJJ; supervision, WHG and MMP; project administration, WJJ and MMP; funding acquisition, WHG. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in adherence to the Declaration of Helsinki, and approval was obtained from the ethics committee at the Drum Tower Hospital, Medical School of Nanjing University (Ethics Number: 2021-134). Additionally, telephone informed consent was obtained from all patients or their guardians.

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Conflict of Interest

The authors declare no conflict of interest.

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