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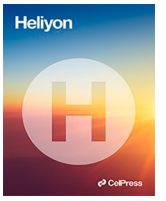

Research article

Prophylactic endotracheal intubation before endoscopic surgery reduces the rebleeding rate in acute esophagogastric variceal bleeding patients

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ABSTRACT

Objectives: Esophagogastric variceal bleeding (EVB) is one of the main causes of cirrhosis-related deaths, and endoscopic therapy is the first-line treatment of choice. However, the efficacy of prophylactic endotracheal intubation (PEI) before endoscopy remains controversial.
Methods: Data were collected from 119 patients who underwent endoscopic confirmation of an EVB. Inverse probability of treatment weighting was applied to reduce bias between the two groups. The primary outcomes included rebleeding rates within 24 h and 6 weeks post-endoscopic surgery and 6-week mortality.
Results: After endoscopic surgery, the rebleeding rate within 24 h in the PEI group was significantly lower than non-PEI group (1.2 % VS 12.6 %, P-value = 0.025). Although PEI did not reduce 6-week mortality, it significantly reduced the risk of rebleeding within 24 h (odds ratio [OR]: 0.89, 95 % confidence interval [CI]: 0.82–0.97, P = 0.008) and within 6 weeks (hazard ratio [HR]: 0.36, 95%CI: 0.14–0.90, P = 0.029). In multivariate regression analyses, maximum varices diameter >1.5 cm (OR: 1.23, 95 % CI: 1.09–1.37, P < 0.001) was independent risk factor for rebleeding within 24 h. Creatinine (HR: 1.01, 95 % CI: 1.01–1.02, P < 0.001) and

Abbreviations: ALT, Alanine aminotransferase; APASL, Asian Pacific Association for Study of the Liver; AST, Aspartate aminotransferase; CI, Confidence interval; CT, Computed Tomography; CTP, Child Turcotte Pugh; ESGE, European Society of Gastrointestinal Endoscopy; EVB, Esophagogastric variceal bleeding; EVO, Endoscopic variceal obturation; EVL, Esophageal variceal ligation; GOV2, Gastroesophageal varices type 2; HE, Hepatic encephalopathy; HR, Hazard ratio; ICU, Intensive Care Unit; IGV, Isolated gastric varices; IPTW, Inverse probability of treatment weighting; IQR, nterquartile range; INR, International normalized ratio; MELD, Model for end-stage liver disease; PEI, Prophylactic endotracheal intubation; PH, Portal hypertension; PPI, proton pump inhibitor; PRBC, Packed red blood cell; PSM, Propensity score matching; SBP, Systolic blood pressure; SD, Standard deviation; TIPS, Transjugular intrahepatic portosystemic shunt; UGIB, Upper gastrointestinal bleeding.

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international normalized ratio (HR: 2.99, 95 % CI: 1.99–4.65, P < 0.001) were independent risk factors for rebleeding within 6 weeks.
Conclusions: PEI before endoscopic surgery reduced the incidence of rebleeding within 24 h and 6 weeks after endoscopic surgery. However, PEI did not reduce the 6-week mortality rate after endoscopic surgery and might increase the length of hospital stay.

1. Introduction

The 2017 Global Burden of Disease Study reported that liver cirrhosis caused over 1.32 million (1.27–1.45 million) deaths, which constituted about 2.4 % (2.3%–2.6 %) of total deaths globally in that year [1]. Portal hypertension (PH) is a group of clinical syndromes associated with decompensated liver cirrhosis. Esophageal and gastric varices are one of the most severe complications of PH in approximately 50 % and 20 % of patients with liver cirrhosis, respectively [2]. Acute esophagogastric variceal bleeding (EVB) is a medical emergency in liver cirrhosis, resulting in approximately 30 % of cirrhosis-related deaths and 70 % of all upper gastrointestinal bleeding events in patients with PH [3]. The 6-week mortality rate of EVB can be as high as 10%–20 % [4]. Endoscopic treatment is the primary choice for EVB and effectively prevents most bleeding episodes [5].

Prophylactic endotracheal intubation (PEI) before gastroscopy can effectively protect the airway and ensure safety throughout the treatment process, making it a promising strategy to reduce the risk of endoscopic surgery. According to the consensus of Baveno VII [6], the Asian Pacific Association for Study of the Liver [3], and the European Society of Gastrointestinal Endoscopy [5], intubation is recommended before endoscopy in patients with altered consciousness and active hematemesis.

However, previous studies have indicated that PEI may lead to an increased incidence of pneumonia, prolonged hospital stays, higher mortality rates, and increased hospital expenses in patients with EVB [7]. Importantly, systematic studies evaluating whether PEI can improve the prognosis of patients with EVB after endoscopic surgery are lacking. Therefore, the purpose of this study was to compare the incidence of rebleeding and short-term mortality in PEI and non-PEI groups, with the aim of evaluating the potential benefits of PEI for patients with acute EVB following endoscopic treatment.

2. Materials and methods

2.1. Patients

This was a single-center retrospective cohort study. The study consecutively enrolled patients diagnosed with acute EVB (defined as hematemesis within last 48 h of presentation, and/or ongoing melena, with last melanic stool within last 48 h in a known or suspected case of PH) who underwent endoscopic treatment between January 1, 2019, and December 31, 2020, at the Second Affiliated Hospital of Chongqing Medical University. The diagnosis of liver cirrhosis was based on established guidelines [8,9]. Inclusion criteria were as follows: (1) patients aged ≥18 years old; (2) patients with EVB who exhibited hemodynamic instability (defined as systolic blood pressure ≤90 mmHg or mean arterial pressure ≤65 mmHg or urine output ≤0.5 ml/kg per hour) after adequate fluid and blood transfusion [10]; Exclusion criteria included: (1) pregnant individuals; (2) patients with contraindications for upper gastrointestinal endoscopy; (3) patients with difficult-to-correct disseminated intravascular coagulation or multiple organ failure; (4) patients with severe liver and kidney function damage or large amounts of ascites; (5) patients who had tracheal intubation due to surgical or other reasons; (6) patients with hepatic encephalopathy (HE) of grade 3 or above; (7) patients who had previously received endoscopic treatment for EVB, where the purpose was endoscopic follow-up; (8) patients who opted for pharmacological treatment following endoscopic confirmation of EVB. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (NO.2021-09-233).

2.2. Definition

Related complications within 48 h after surgery were defined as follows: (1) pneumonia: defined as chest X-ray or chest computed tomography (CT) scan showing new infiltration, accompanied by two of the following symptoms: fever (temperature >38 °C), purulent sputum, leukocytosis (leukocyte count $>9.5 \times 10^9$/L) or leukopenia (leukocyte count $<4 \times 10^9$/L) [11,12]; (2) pulmonary edema: defined as bilateral pulmonary infiltrates on chest X-ray and systolic or diastolic myocardial dysfunction based on echocardiography [13]; (3) malignant arrhythmia: defined as new-onset atrial flutter or fibrillation, supraventricular tachycardia, ventricular tachycardia, or ventricular flutter [14]; (4) cardiac arrest: defined as asystole, pulseless electrical activity, ventricular fibrillation, or pulseless ventricular tachycardia [15]; (5) rebleeding: defined as new-onset hematemesis, coffee-like vomiting, hematochezia, or melena after endoscopic hemostasis when hemoglobin and vital signs were stable [5].

2.3. Data collection

Demographic characteristics (including age, sex, etiology of cirrhosis, comorbidities, history of surgery, grade of HE, shock, use of vasopressors or transfused units of packed red blood cells, and vital signs), laboratory data, imaging examinations, gastroscopic manifestations, and the interval between tracheal intubation and extubation (hereinafter referred to as intubation time) were collected

by querying the electronic medical record system. The Child-Turcotte-Pugh (CTP) score was used to evaluate the liver function reserves [16]. The model for end-stage liver disease (MELD) score was primarily used to predict end-stage liver disease mortality [17]. MELD calculation formula is 3.8 × ln [bilirubin (mg/dl)] + 11.2 × ln (International normalized ratio [INR]) + 9.6 × ln [creatinine (Cr) (mg/dl)] + 6.4 × (1 or 0) (0 is for biliary or alcoholic cirrhosis and 1 for other etiologies).

2.4. Endoscopic treatment procedures

In patients undergoing EVB, early treatment was initiated to ensure hemodynamic stability. This involved rapid rehydration, blood transfusion, and the administration of pharmacological interventions, including vasoactive drugs (such as, terlipressin, octreotide, or somatostatin), proton pump inhibitors (PPIs), and antibiotic prophylaxis. The endoscopic treatment was conducted by senior endoscopists in the Department of Gastroenterology, with a collective experience of 10–25 years and over 500 endoscopic hemostasis treatments. These endoscopists possess the necessary certifications for endoscopic qualifications. Before the treatment, the endoscopists evaluated the risk of aspiration in patients based on factors such as medical history, bleeding time and volume, estimated endoscopic duration, and the quantity of gastric content as shown in CT scans (if available). Patients were assigned to either the experimental or control group after this assessment. In the experimental group, patients were transferred to the intensive care unit (ICU) for hemostasis with PEI; however, in the control group without PEI, hemostasis was performed either at the gastroenterology endoscopy center or the bedside.

The PEI group received tracheal intubation before the endoscopy to protect their airways and prevent aspiration, while the non-PEI group did not. The tracheal intubation was performed by a professional anesthesiologist or a qualified physician in the ICU, typically using 2 % propofol (Sichuan Guorui Pharmaceutical Co., Ltd.) and/or midazolam (Jiangsu Enhua Pharmaceutical Group Pharmaceutical Co., Ltd.) for sedation. Depending on the patient's tolerance, endoscopic treatment in the non-PEI group involved the administration of antiemetics if the patient was conscious.

Endoscopic treatment is performed under the following conditions: apparent variceal rupture, presence of white or red thrombus heads or blood clots on the varices, fresh blood in the esophagus or stomach, or clear red signs [18]. Endoscopic variceal ligation (EVL) is suitable for treating acute EVB. Endoscopic variceal obturation (EVO) is applied to isolated gastric variceal (IGV) bleeding or gastroesophageal varices type 2 (GOV2) that extend beyond the cardia, and a tissue adhesive (e.g., N-butyl cyanoacrylate) is recommended. EVO is usually performed first for gastric varices, followed by EVL for esophageal varices [19]. The treatments utilized FUJIFILM-EG-580RD (FUJIFILM [China] Investment Co., Ltd.) or a Sonoscape gastroscope (Shenzhen Kaili Biomedical Technology Co., Ltd.) with endoscopic six-ring ligating devices (Chongqing Yishitong Supply Chain Management Co., Ltd.), an injection needle (Olympus Trading [Shanghai] Co., Ltd.), and cinnamyl alcohol injection (Shanxi Tianyu Pharmaceutical Co., Ltd.). Both groups of patients underwent a 24-h fasting and water period following endoscopic treatment. They received identical treatments, including PPIs, non-selective beta blockers, antibiotic prophylaxis, rehydration, and nutritional support, provided there were no contraindications.

2.5. Outcomes

The primary outcomes assessed in this study encompassed rebleeding rates within both the 24-h and 6-week postoperative timeframes. The secondary outcomes included a 6-week mortality assessment, the probability of specific complications occurring within 48 h post-endoscopic surgery (including aspiration, pneumonia, pulmonary edema, respiratory failure, HE, sepsis, malignant arrhythmia, and cardiac arrest), and a comparative analysis of hospitalization expenses and the total duration of hospital stay between the two groups.

2.6. Statistical analysis

Inverse probability of treatment weighting (IPTW), using the propensity score (PS), enables the acquisition of unbiased estimates of average causal treatment effects from observational data. Imbalanced variables at baseline were integrated into the logistic regression model to calculate the weights. Subsequently, the resulting weights were applied to each clinical feature, and outcomes were measured for every patient in both groups [20]. Statistical descriptions and regression analyses were performed in the cohorts generated using IPTW.

Continuous data meeting normal distribution criteria were expressed as mean ± standard deviation (Mean ± SD), and the *t*-test was used. The Mann–Whitney *U* test was used for skewed distribution data expressed by the interquartile range (IQR), namely [P25, P75]. Categorical data were tested using Pearson's chi-square or Fisher's exact test and expressed as a percentage (n%). Baseline variables considered clinically relevant or that showed a univariate relationship with the outcome ($P < 0.1$ in univariate regression analysis) were entered into multivariate regression analysis. Subsequently, factors with a P-value ≤ 0.05 in the multivariate logistic regression analysis were identified as statistically significant for rebleeding within 24 h, while factors with a P-value ≤ 0.05 in the multivariate Cox regression analysis were considered statistically significant for rebleeding within 6 weeks and 6-week mortality. The Kaplan–Meier method was used to draw the survival curve, and the log–rank method was used for the test. All data were statistically analyzed using SPSS (version 26.0; SPSS Inc., Chicago, IL, USA) and R (version 4.2.2; R Foundation, Vienna, Austria).

3. Results

3.1. Screening process and baseline characteristics of patients

Fig. 1 shows the flowchart. A total of 1098 patients with suspected EVB were hospitalized, and 119 patients (11 %) ultimately met the inclusion and exclusion criteria. The remaining 979 patients were excluded from the study for various reasons: 469 patients did not undergo endoscopy to diagnose EVB, 452 patients without hemodynamic instability were only sedated using intravenous anesthetics without intubation due to a low risk of aspiration, 44 patients opted for conservative treatment, and 14 patients had severe organ failure. Among the 119 patients, 55 and 64 were included in the PEI and non-PEI groups, respectively.

In total, 273 patients were included in the IPTW analysis. Before IPTW, a higher percentage of patients in the PEI group had a history of hypertension than the non-PEI group (20 % vs. 1.6 %, $P = 0.001$). Additionally, a greater proportion of patients used vasopressors to improve systolic blood pressure (38.2 % vs. 10.9 %, $P < 0.001$) and had preoperative infusion of packed red blood cells ($P = 0.038$) (Table 1). Patients in the two groups had similar results for most laboratory indicators, except for a higher median serum Cr (71 μmol/L vs. 62.2 μmol/L, $P = 0.033$), and a higher INR valuein the PEI group (1.58 vs. 1.46, $P = 0.035$). Furthermore, the PEI group exhibited worse liver function, as indicated by a higher MELD score ($P = 0.002$). After IPTW, there was no statistical difference in the baseline characteristics between the two groups, suggesting that possible confounding factors were approximately evenly distributed between the two groups (Table 1).

3.2. The endoscopic features of the patients

The endoscopic features of the patients are shown in Table 2. Before IPTW adjustment, the two groups had no significant differences in the source of hemorrhage, portal hypertensive gastropathy, and maximum varices diameter of up to 1.5 cm. However, in the hemostasis methods, a higher number of patients in the PEI group underwent EVL ($P = 0.050$), EVO ($P < 0.001$), and additional hemostasis procedures, such as the application of vasoconstrictor under endoscopy or the use of peptide clips to clamp blood vessel breaches, among other methods ($P = 0.008$). After IPTW adjustment, there were no significant differences in the sources of bleeding between the two groups. However, a greater proportion of patients in the PEI group underwent EVL ($P = 0.002$) and EVO ($P = 0.041$).

3.3. Outcomes

The rebleeding rates within 24 h was 3.6 % in the PEI group and 10.9 % in the non-PEI group ($P = 0.248$). Within 6 weeks, the rebleeding rates were 30.9 % and 34.3 % for the PEI group and non-PEI group, respectively ($P = 0.185$), with corresponding mortality rates of 18.2 % and 9.4 % ($P = 0.252$). There were no significant differences between the PEI and non-PEI groups in the primary outcomes before IPTW. However, the total hospital stay in the PEI group was longer than that in the non-PEI group (13 vs. 10 days, $P = 0.025$), and the cost of hospitalization in the PEI group was higher (57546 vs. 39499 RMB, $P < 0.001$). Additionally, there was no significant difference in adverse events within 48 h ($P = 0.819$) and in-hospital mortality (non-PEI: 6.3 %, non-PEI: 9.1 %, $P = 0.397$) between the two groups.

After IPTW, the non-PEI group had a higher rate of rebleeding within 24 h (non-PEI: 12.6 %, PEI: 1.2 %, $P = 0.025$) and within 6 weeks (non-PEI: 36.9 %, PEI: 15.9 %, $P = 0.049$) after treatment. The mortality rate within 6 weeks after hemostasis was 7 % in the non-PEI group and 7.8 % in the PEI group ($P = 0.923$). The in-hospital mortality was no significant difference between the two groups (non-PEI: 5.8 %, non-PEI: 4.7 %, $P = 0.267$). The PEI group had a longer hospital stay (non-PEI: 10 days, PEI: 17 days, $P = 0.040$) (Table 3).

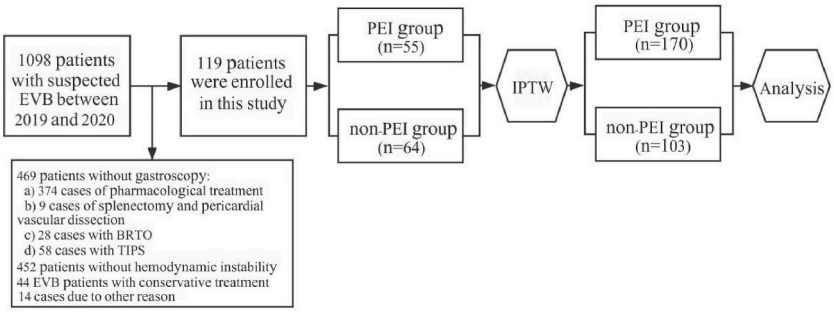

Fig. 1. Patients screening process and study protocol.
Abbreviations: EVB: esophagogastric variceal bleeding; PEI: prophylactic endotracheal intubation; IPTW: inverse probability of treatment weighting; BRTO: balloon-occluded retrograde transvenous obliteration; TIPS: transjugular intrahepatic portosystemic shunt.

Table 1
Patient baseline characteristics.

Variable	Before IPTW(n = 119)		P value	After IPTW(n = 273)		P value
	PEI group(n = 55)	non-PEI group(n = 64)		PEI group(n = 170)	non-PEI group(n = 103)	
Sex (male)	39 (70.9 %)	48(75 %)	0.616	140(82.7 %)	74(71.8 %)	0.317
Age (year)	54 (47–63)	51(48–61)	0.379	47(43–56)	51(48–61)	0.094
Etiology						
Viral	39(70.9 %)	48(75 %)	0.491	145(85.2 %)	75(72.3 %)	0.299
Alcoholic	8(14.5 %)	11(10.2 %)		11(6.5)	16(15.5 %)	
Other[a]	8(14.5 %)	5(7.0 %)		14(8.3 %)	13(12.2 %)	
Comorbidities						
Diabetes	16(29.1 %)	11(17.2 %)	0.122	80(47.0 %)	21(20.4 %)	0.126
Hypertension	11(20.0 %)	1(1.6 %)	**0.001**	12(7.1 %)	7(6.6 %)	0.946
Chronic kidney disease	3(5.5 %)	2(3.1 %)	0.862	3(2.0 %)	3(2.7 %)	0.762
Hepatic carcinoma	14(25.5 %)	15(24.4 %)	0.798	70(41.0 %)	22(20.9 %)	0.251
History of endoscopic surgery (EVL/EVO)	14(25.5 %)	20(31.3 %)	0.485	23(13.8 %)	33(31.8 %)	0.066
History of devascularization [b]	3(5.5 %)	6(9.4 %)	0.646	6(3.5 %)	8(8.0 %)	0.265
History of EVB	32(58.2 %)	32(50.0 %)	0.479	58(33.9 %)	54(52.6 %)	0.213
History of TIPS	3(5.5 %)	1(1.6 %)	0.506	3(2.0 %)	2(1.5 %)	0.810
History of HE	11(20.0 %)	8(12.5 %)	0.265	13(7.9 %)	11(10.6 %)	0.595
Preoperative heart rate (bpm)	89(82–106)	88(76–102)	0.4	85(84–99)	86(71–98)	0.453
Preoperative SBP (mmHg)	97.7 ± 21.9	96.4 ± 15.9	0.715	88.2 ± 21.9	97.1 ± 16.4	0.239
Preoperative shock	27(49.1 %)	24(37.5 %)	0.203	98(57.6 %)	36(34.5 %)	0.149
Preoperative use of vasopressors	21(38.2 %)	7(10.9 %)	**< 0.01**	27(15.7 %)	18(17.0 %)	0.879
Preoperative PRBC transfusion (unit)	2(0–4)	0(0–2)	**0.038**	2(0–3)	0(0–2)	0.130
Hemoglobin (g/L)	66(57–76)	69.5(58.5–92.5)	0.116	76(64–106)	68(56–90)	0.276
Hematocrit	0.21(0.17–0.23)	0.21(0.19–0.27)	0.100	0.23(0.19–0.33)	0.21(0.18–0.26)	0.266
Platelets (× 109/L)	65(48–100)	55(43–84)	0.193	49(49–65)	53(43–80)	0.876
Albumin (g/L)	28.9 ± 5.7	30.1 ± 5.8	0.286	34.0 ± 8	29.7 ± 5.8	0.209
ALT (U/L)	22(16–45)	26.5(19–58)	0.179	37(21–56)	26(16–58)	0.448
AST (U/L)	37(26–89)	41.6(27–74)	0.672	52(27–58)	42(27–74)	0.629
Total bilirubin (μmol/L)	24.2(12.9–41.4)	23.2(16.7–40.3)	0.852	22.8(15.3–31.4)	22.7(15.1–38.1)	0.542
creatinine (μmol/L)	71(58.1–83.6)	62.2(51.6–73.7)	**0.033**	76.8(59.7–79.6)	61(50.4–73.1)	0.075
INR	1.58(1.4–1.98)	1.46(1.31–1.66)	**0.035**	1.38(1.04–1.62)	1.49(1.33–1.69)	0.303
CTP score	9(8–11)	9(7–10)	0.179	8(6–9)	9(7–10)	0.260
MELD score	12(10–16.5)	11(9–12)	**0.002**	10(8–13)	11(9–12)	0.860

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP score: Child-Turcotte-Pugh score; EVB: esophagogastric variceal bleeding; EVL: endoscopic variceal ligation; EVO: endoscopic variceal obturation; HE: hepatic encephalopathy; INR: international normalized ratio; MELD score: model for end-stage liver disease score; PRBC: packed red blood cells (200 ml per unit); SBP: systolic blood pressure; TIPS: transjugular intrahepatic portosystemic shunt.

[a] Represents immunity, metabolism, heredity, and other unknown causes.

[b] Represents splenectomy and cardiac devascularization.

Table 2
Endoscopic features and hemostasis methods between PEI and non-PEI group.

Variable	Before IPTW(n = 119)		P value	After IPTW(n = 273)		P value
	PEI group (n = 55)	non-PEI group(n = 64)		PEI group(n = 170)	non-PEI group(n = 103)	
Source of hemorrhage						
Esophageal variceal bleeding	28(50.9 %)	42(65.5 %)	0.104	77(45.2 %)	75(72.9 %)	0.090
Gastric variceal bleeding	30(54.5 %)	24(37.5 %)	0.063	97(57.4 %)	31(29.9 %)	0.094
Portal hypertensive gastropathy	42(76.4 %)	42(65.6 %)	0.200	88(51.8 %)	73(70.4 %)	0.290
Maximum varices diameter > 1.5 cm	11(20 %)	8(12.5 %)	0.265	25(14.4 %)	15(14.2 %)	0.980
Hemostasis method						
Endoscopic variceal ligation	53(96.4 %)	55(85.9 %)	**0.050**	168(98.8 %)	92(88.9 %)	**0.002**
Endoscopic variceal obturation	44(80 %)	30(46.9 %)	**< 0.001**	125(73.9 %)	43(41.5 %)	**0.041**
other[a]	8(14.5 %)	1(0.8 %)	**0.008**	13(7.9 %)	2(1.5 %)	0.088

Abbreviations: IPTW: inverse probability of treatment weighting; PEI: prophylactic endotracheal intubation

[a] represents spraying vasoconstrictor under endoscopy or peptide clips to clamp blood vessel breach.

Table 3
Outcome events between PEI and non-PEI group.

Variable	Before IPTW (n = 119)		P value	After IPTW (n = 273)		P value
	PEI group(n = 55)	Non-PEI group(n = 64)		PEI group (n = 170)	Non-PEI group (n = 103)	
Rebleeding in hospital (≤24 h)	2 (3.6 %)	7 (10.9 %)	0.248	2 (1.2 %)	13 (12.6 %)	**0.002**
Rebleeding in hospital (> 24 h)	4 (7.3 %)	2 (3.1 %)	0.541	7 (4.1 %)	2 (1.9 %)	0.557
Adverse events (≤48 h)	13 (23.6 %)	14 (21.9 %)	0.819	23 (13.5 %)	23 (22.3 %)	0.303
Pneumonia	7 (12.7 %)	7 (10.9 %)	0.763	13(7.6 %)	13 (12.6 %)	0.413
Pulmonary edema	3 (5.5 %)	0	–	3 (1.8 %)	0	–
Aspiration	1 (1.8 %)	0	–	1 (0.5 %)	0	–
Respiratory failure	2 (3.6 %)	0	–	5 (2.9 %)	0	–
Sepsis	2 (3.6 %)	1 (1.6 %)	0.894	4 (2.4 %)	1 (0.9 %)	0.575
Hepatic encephalopathy	4 (7.3 %)	7 (10.9 %)	0.491	5 (2.9 %)	10 (9.7 %)	0.112
Malignant arrhythmia	2(3.6 %)	1 (1.6 %)	0.894	2 (1.2 %)	2 (1.9 %)	0.927
Cardiac arrest	0	2 (3.1 %)	–	0	6 (5.8 %)	–
Length of stay (days)	13(8–18)	10 (7–14.5)	**0.025**	17 (9–23)	10 (7–15)	**0.040**
Cost of hospitalization (RMB)	46851.06 (32509.40)	72740.18 (41261.02)	**< 0.001**	51008.67 (40377.31)	71686.55 (34389.09)	0.055
Rebleeding within 6-weeks	17 (30.9 %)	22 (34.3 %)	0.185	27 (15.9 %)	38 (36.9 %)	**0.049**
Death within 6-weeks	10 (18.2 %)	6 (9.4 %)	0.252	12 (7 %)	8 (7.8 %)	0.923
In-hospital mortality	5 (9.1 %)	4 (6.3 %)	0.397	8 (4.7 %)	6 (5.8 %)	0.267

Abbreviations: IPTW: inverse probability of treatment weighting; PEI: prophylactic endotracheal intubation.

3.4. Regression analysis

In univariate logistic regression, the factors significantly associated with rebleeding within 24 h were Cr, maximum varices diameter >1.5 cm, and PEI (all variables with $P < 0.1$). In multivariate logistic analysis, the factors significantly associated with rebleeding within 24 h were PEI (Odds ratio [OR]: 0.89, 95 % CI: 0.82–0.97, $P = 0.008$) and maximum varices diameter >1.5 cm (OR: 1.23, 95 % CI: 1.09–1.37, $P < 0.001$). This indicates that PEI can reduce the rebleeding within 24 h rate by 11 %, and maximum varices diameter >1.5 cm is a risk factor for rebleeding within 24 h.

Univariate Cox regression analysis was conducted to identify the variables affecting rebleeding within 6 weeks. The factors significantly associated with rebleeding within 6 weeks were male sex, hepatic carcinoma, Cr, INR, maximum varices diameter >1.5 cm, and HE after treatment (all variables with $P < 0.1$). In multivariate analysis, PEI significantly reduced the risk of rebleeding within 6 weeks (hazard ratio [HR]: 0.36, 95%CI: 0.14–0.90, $P = 0.029$). Meanwhile, Cr (HR: 1.01, 95 % CI: 1.01–1.02, $P < 0.001$) and INR (HR: 2.99, 95 % CI: 1.99–4.65, $P < 0.001$) were identified as independent risk factors for predicting rebleeding within 6 weeks (Table 4). The Kaplan–Meier analysis of rebleeding within 6 weeks following endoscopic surgery revealed no significant difference between the two groups before IPTW (Fig. 2A). However, a greater number of patients in the PEI group did not experience rebleeding within 6 weeks after IPTW (Fig. 2B). The log–rank test was not statistically significant ($P = 0.24$). Regarding the 6-week mortality outcome, PEI did not reduce the 6-week mortality rate (HR: 0.94, 95%CI: 0.27–3.25, $P = 0.918$). Additionally, Cox univariate regression analysis did not identify any risk factors with $P < 0.1$.

4. Discussion

The most critical phase of decompensated liver cirrhosis is acute EVB, characterized by rapid onset and progression, and associated with an exceptionally high mortality rate [21]. In cases of severe esophageal varices, the annual incidence of initial bleeding episodes ranges from approximately 5–15 %. Without intervention, the rebleeding rate within 1 year can reach approximately 60 %. Therefore, effective treatment and proactive prevention are of utmost importance after an initial bleeding episode [22]. With advancements in medical standards and endoscopic technology, EVL and EVO are recommended worldwide for treating EVB [23]. The results of this

Table 4
Univariate and multivariate Cox regression models predict risk factors for rebleeding within 6 weeks after IPTW.

Predictors	univariate Hazard odds(95%CI)	P value	Multivariate Hazard odds(95%CI)	P value
PEI	0.29 (0.37–0.98)	0.046	0.36 (0.14–0.90)	**0.029**
Sex (male)	2.90 (1.14–7.44)	0.026	1.87 (0.55–6.38)	0.319
Hepatic carcinoma	2.20 (1.14–4.23)	0.019	2.08 (0.82–5.25)	0.121
Cr	1.01 (0.99–1.01)	0.097	1.01 (1.01–1.02)	**<** 0.001
INR	2.10 (1.31–3.34)	0.002	2.99 (1.92–4.65)	**<** 0.001
Maximum varices diameter > 1.5 cm	1.90 (0.89–3.96)	0.097	2.83 (0.94–8.51)	0.063
HE after treatment	2.30 (0.95–5.46)	0.063	2.08 (0.45–9.68)	0.347

Abbreviations: Cr: Creatinine; HE: hepatic encephalopathy; INR: international normalized ratio; IPTW: inverse probability of treatment weighting; PEI: prophylactic endotracheal intubation.

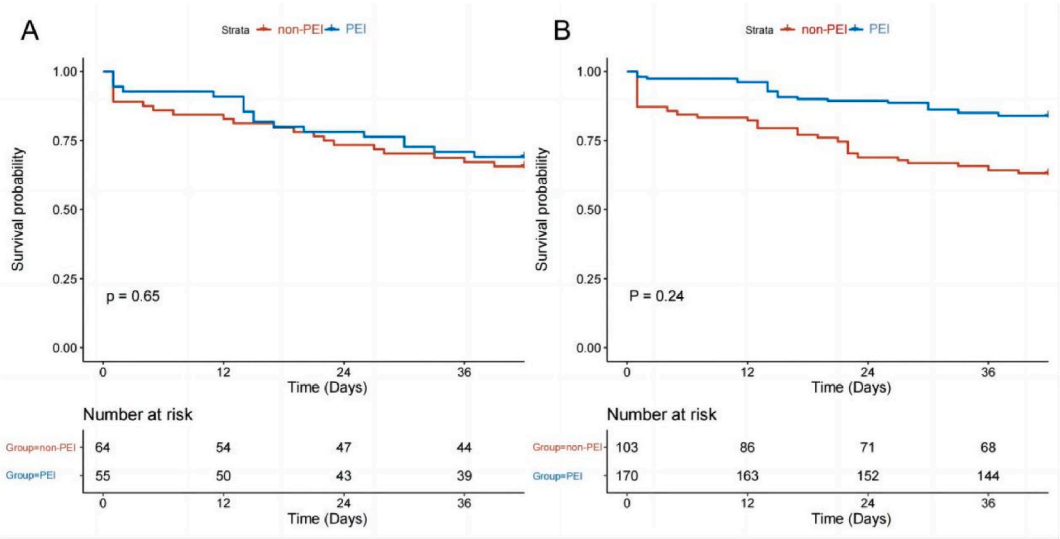

Fig. 2. A: Survival curve for rebleeding within 6 weeks before IPTW. B: Survival curve for rebleeding within 6 weeks after IPTW.
Abbreviations: IPTW: inverse probability of treatment weighting; PEI: prophylactic endotracheal intubation.

study suggest that PEI protects against short-term rebleeding after endoscopic surgery.

Before IPTW, the PEI group had a higher INR value and MELD score, indicating that the coagulation and liver functions of the PEI group were worse. The guidelines suggest that CTP and MELD scores affect the success rate of endoscopic hemostasis in patients with progressive chronic liver disease suspected of having EVB [24]. Therefore, it is important to adjust for differences in MELD scores between the two groups. The baseline characteristics, laboratory indicators, and MELD scores of the matched groups were not significantly different after IPTW adjustment for confounding bias, thus eliminating the influence of selection bias on the outcome.

According to the latest European guidelines (2023), early variceal rebleeding is defined as variceal bleeding between 5 days and 6 weeks from the initial presentation to a medical facility, provided initial hemostasis is achieved [5]. As this definition was not available during the design of our study, we focused on assessing rebleeding rates within 24 h and 6 weeks. We found that the incidence of rebleeding within 24 h was lower in the PEI group. We hypothesized that PEI reduced the patient's vomiting reflex, resulting in a clearer endoscopic view to identify the "criminal varices" more easily, leading to more effective hemostasis procedures. Varices diameter >1.5 cm was an independent risk factor, which is consistent with the findings of Salman et al. [25]. Regarding rebleeding within 6 weeks, both multivariate COX regression analysis and survival curves suggested a preventive effect of PEI. However, the log–rank test showed $P > 0.05$ before and after IPTW. This may be related to the small sample size of our study. By increasing the effective sample size using IPTW, we observed a gradual decrease in the P-value (from 0.65 to 0.24). Further enlargement of the sample size may have made the P-value significant. From a statistical perspective, the log–rank test is a non-parametric test, whereas COX regression is a parametric test. When the results of these two tests are inconsistent, the results from COX regression are generally considered more accurate [26].

The mortality rate within 6 weeks is an essential indicator for evaluating the short-term prognosis of patients after EVB. In our study, patients with PEI had a higher 6-week mortality rate than patients without PEI, although the difference was not statistically significant. Previous meta-analysis also showed that PEI can increase the mortality rate of patients with variceal bleeding (OR: 4.45, 95 % CI: 1.46–13.56) [7]. However, it is essential to interpret this result cautiously. The meta-analysis was based on only two small-sample studies involving patients with EVB, while other studies lacked clear definitions of the etiology of gastrointestinal bleeding. Furthermore, the included studies did not explicitly define the monitored time for mortality as 6 weeks. Therefore, further large-scale or prospective studies are needed to identify the cause of death and assess whether PEI increases the mortality rate within 6 weeks in patients with EVB after endoscopic treatment.

The primary concern regarding PEI in endoscopic surgery for EVB is its potential association with cardiopulmonary events, of which pulmonary aspiration and arrhythmia are [27]. However, some studies suggest that PEI may increase the incidence of pulmonary aspiration [18,28]. Contrary to these studies, our study indicated that PEI did not increase the occurrence of pulmonary aspiration. Furthermore, PEI did not contribute to an elevated risk of other cardiopulmonary events, including pulmonary edema, pneumonia, respiratory failure, malignant arrhythmia, and cardiac arrest. This outcome can be attributed to advancements in airway management and endoscopic techniques. There is also controversy in previous studies regarding whether PEI leads to an extension of hospital stay [7,29]. In our study, the hospitalization time of the PEI group was significantly increased because patients in the PEI group were transferred to the ICU for tracheal intubation and intubation-related risk assessment before surgery, and their condition was observed in the ICU after treatment.

This study has several advantages. First, only a few studies have reported the application of PEI to both EVB and ulcer-related bleeding. However, there are distinct differences between these two diseases. Our research specifically focused on the EVB. Second,

IPWT was used to adjust for confounding factors owing to incompatible baseline characteristics; it avoided the loss of sample size, such as propensity score matching. Third, unlike previous studies, this study analyzed the risk factors for rebleeding and identified several independent risk factors through regression analysis.

It is important to acknowledge the limitations of this study. First, this was a single-center, retrospective cohort study with a small sample size. Using IPTW in a study with a limited sample size may lead to underestimating the variance of effect estimates, potentially biasing the results. Second, some confounding biases, such as the operating experience of endoscopists, the accuracy of electronic medical records, and the completeness of postoperative imaging examinations, could not be controlled. Third, due to our adoption of the telephonic follow-up, we were unable to further identify the causes of death among deceased patients. Fourth, hemodynamic instability is a comprehensive assessment that involves physical signs, vital parameters, and laboratory tests. Hemodynamics assessment in this study was limited to non-invasive methods, potentially including patients who might have demonstrated hemodynamic instability through other indicators.

In conclusion, our findings indicate that although PEI does not reduce mortality within 6 weeks and might prolong hospitalization time, it effectively reduces the rebleeding rate within 24 h and 6 weeks after endoscopic surgery without increasing the occurrence of cardiopulmonary events. Multicenter, large-sample clinical studies are needed to validate our findings. Additionally, a cost-benefit analysis is warranted to assess the potential for broader clinical adoption of PEI.

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Data availability statement

Data will be made available on request. Please contact the corresponding author, Zhihang Zhou, Email: zhouzhihang@cqmu.edu.cn.

CRediT authorship contribution statement

Yongqi Dong: Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology. **Haiyan Cao:** Software, Data curation. **Hongyan Xu:** Visualization, Validation, Supervision, Data curation. **Zhihuan Zhang:** Writing – review & editing, Methodology, Data curation. **Zhihang Zhou:** Writing – review & editing, Validation, Supervision. **Song He:** Writing – review & editing, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Zhihang Zhou reports financial support was provided by The National Science Foundation of China.

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