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Clinical Outcome Comparison between Transjugular Intrahepatic Portosystemic Shunt and Endoscopic Treatment in Patients with Cavernous Transformation of the Portal Vein Presenting with Variceal Bleeding: A Retrospective Study

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Keywords:

Cavernous transformation of the portal vein; Portal hypertension; Variceal bleeding; Overt hepatic encephalopathy

1. Abstract

1.1. Background: Cavernous transformation of the portal vein (CTPV) is often associated with portal hypertension and varicose bleeding. Endoscopic treatments (ETs) and transjugular intrahepatic portosystemic shunts (TIPS) can prevent rebleeding in patients with CTPV. This study aimed to compare the clinical outcomes of TIPS and ET in patients with CTPV presenting with variceal bleeding.

1.2. Methods: We reviewed the data of patients with CTPV presenting with variceal bleeding at Nanjing Drum Tower Hospital from February 2014 to August 2022.Ultimately, 22 patients were included in the ET and TIPS groups, respectively.

1.3. Results: During the follow-up period, the upper gastrointestinal rebleeding rate and survival rate were not significantly different between the ET group and TIPS group (40.91% VS 36.36%, 13.63% vs 13.64%, P >0.05). The median hospitalization cost in the TIPS group (92968.00 Chinese Yuan) was significantly higher than that in the ET group (47603.00 Chinese Yuan) (P = 0.001), and the median length of hospital stay in the TIPS group (13.00 days) was much shorter than that in the ET group (22.00 days) (P = 0.004). The incidence of OHE in the TIPS group was higher than that in the ET group (36.36% VS 4.55%, P = 0.027).

1.4. Conclusion: For patients with CTPV presenting with variceal bleeding, TIPS was not better than ET regarding preventing postoperative rebleeding and long-term survival. The prevalence of OHE after TIPS was significantly higher than that of ET. ET, rather than TIPS, may be a better choice for patients with CTPV presenting with variceal bleeding regarding medical expenses and length of stay.

2. Introduction

Cavernous transformation of the portal vein (CTPV), also known as cavernous hemangioma of the portal vein, was first reported by Balfour et al. in 1869[1]. CTPV refers to the spider web-like structure of numerous collateral vessels located in the liver hilum, which is a sequelae of portal vein occlusion [2, 3]. Once CTPV has developed, the human body compensates for the circulation by forming a large number of collateral circulations around the portal vein. This compensatory mechanism, however, is frequently done at the expense of portal hypertension, which leads to varicose vein rupture, hemorrhage, ascites, and other problems [4].

The diagnosis of CTPV is based on portal venography, which is widely recognized as the gold standard, but this examination is invasive. Ultrasound, computed tomography (CT), and MRI have unique characteristics in terms of the diagnosis of CTPV [5]. Esophagogastric varices bleeding is a major complication of portal hypertension and has a high mortality rate [6]. The therapy of variceal hemorrhage in patients with CTPV includes medicine, traditional surgery, endoscopic therapy and transjugular intrahepatic portosystemic shunt (TIPS) [7][8]. Endoscopic treatment (ET) includes obliteration for varices, endoscopic variceal band ligation (EBL), and endoscopic

injection sclerotherapy (EIS)[8]. TIPS is another minimally invasive interventional technique that can effectively reduce portal pressure. The main goal of this research was to compare the effect and safety between the two methods for patients with CTPV presenting with variceal bleeding.

3. Methods

3.1 Study Design

Medical records of study subjects with CTPV who were admitted to the Department of Gastroenterology, Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University School of Medicine due to variceal bleeding between February 2014 and August 2022 were retrospectively investigated. All patients in this study were diagnosed with portal cavernous transformation based on clinical and imaging findings[3] but without serious cardiopulmonary disease, hepatocellular carcinoma or other malignant tumors, or abnormal blood coagulation, and who received TIPS or ET. Furthermore, patients who had already been treated with ET or TIPS who had received another treatment for ruptured esophagogastric variceal rebleeding were defined as a discontinuation event, and the last follow-up time was December 2022. If there was no rebleeding event and they received another treatment measure, this group of patients was excluded. In addition, patients who received other interventional treatments, such as balloon-occluded retrograde transvenous obliteration (BRTO) were excluded.

3.2 Study Outcomes and Definitions

The main outcomes observed in this study were the long-term survival rate and all-cause upper gastrointestinal rebleeding rate, and the secondary outcomes were the cost of hospitalization and the occurrence of OHE. Survival in this study did not include survival after liver transplantation. Portal hypertension is the main complication caused by CTPV, which causes rupture and bleeding of esophageal and gastric varices, as described above. Portal hypertension is a clinical syndrome that refers to a pathological increase in the portal pressure gradient between the portal vein and the inferior vena cava [9]. Rebleeding, including recurrent melena or hematemesis, was defined according to Baveno V criteria [10]. The severity and grade of OHE were defined by the West Haven criteria (West Haven grade 2–4) [11, 12]. The clinical diagnosis of OHE is relatively standardized, ranging from asterixis to coma according to the severity of HE.

3.3 Description of Comparing Interventions

3.3.1 Endoscopic Treatments

Endoscopic treatments of varices, including EVL (6 Shooter, COOK, Bloomington, Indiana, USA), sclerotherapy (lauromacrogol Injection, Tian Yu, Shan Xi, China), endoscopic variceal obturation (octyl-α-cyanoacrylate), and combination therapy, were performed by experienced doctors as described previously [13]. In general, endoscopic treatment is required every 2–3 weeks until the varicose vein is eradicated. Then, endoscopy is required every 3–6 months, and if new varicose veins appear, they need to be treated again.[14].

3.3.2 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

All TIPS procedures were performed using X-ray under local anesthesia by the same team of physicians with extensive intervention experience [13, 15]. The portal venous system of each participant was first assessed by indirect portal venography using a contrast agent through the superior mesenteric artery. Then, a catheter was inserted into the jugular vein to locate the portal vein. A stent was placed between the portal vein and the hepatic vein, and the portal pressure was monitored [16]. All patients who received TIPS treatment were given analgesia, anticoagulation, liver protection (hepatoprotective drugs), and prevention of hepatic encephalopathy. Liver function, renal function, coagulation function, blood ammonia level, and TIPS stent patency were monitored at 1, 3, 6, 12, and 24 months after successful surgery to evaluate the treatment effect [17].

3.4 Statistical Analysis

Statistical analysis was performed by using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were expressed as the mean ± standard deviation, and qualitative variables were expressed as numbers and percentages or frequencies. Fisher's exact test and $\chi 2$ test were used to compare the differences between the two groups. Survival data were analyzed using Kaplan–Meier estimates and the log-rank test. The multivariate logistic regression model was used to establish propensity scores for each patient. The clinical indicators included in the propensity score were age and albumin. Then the nearest neighbor propensity score matching method was used, and the caliper value was set to 0.10. A P value of < 0.05 was regarded as statistically significant. SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

4. Results

4.1. Characteristics of the Participants

According to the inclusion and exclusion criteria,22 patients in ET group and 22 patients in TIPS group were finally included after the propensity score matching (PSM) analysis (Figure 1). The demographic and serological data of selected patients in this study are summarized in (Table 1). There was no significant difference between ET group and TIPS group in terms of the median age (57.50 years vs 57.50 years, p=0.751), male proportion (63.60% vs 54.50%, p=0.544), prevalence of cirrhosis (77.30% vs 90.90%, p=0.222), and prevalence of ascites (72.700% vs 81.80%, p=0.477). Child-pugh scores between ET group and TIPS group were not significantly different, which was 7.00 ± 1.25 and 7.50 ± 1.44 scores respectively (p=0.156). White blood cell (WBC) count, hemoglobin(HB) level, platelet(PLT) count, liver function, renal function, and coagulation function did not significantly differ between the two groups (p>0.05).

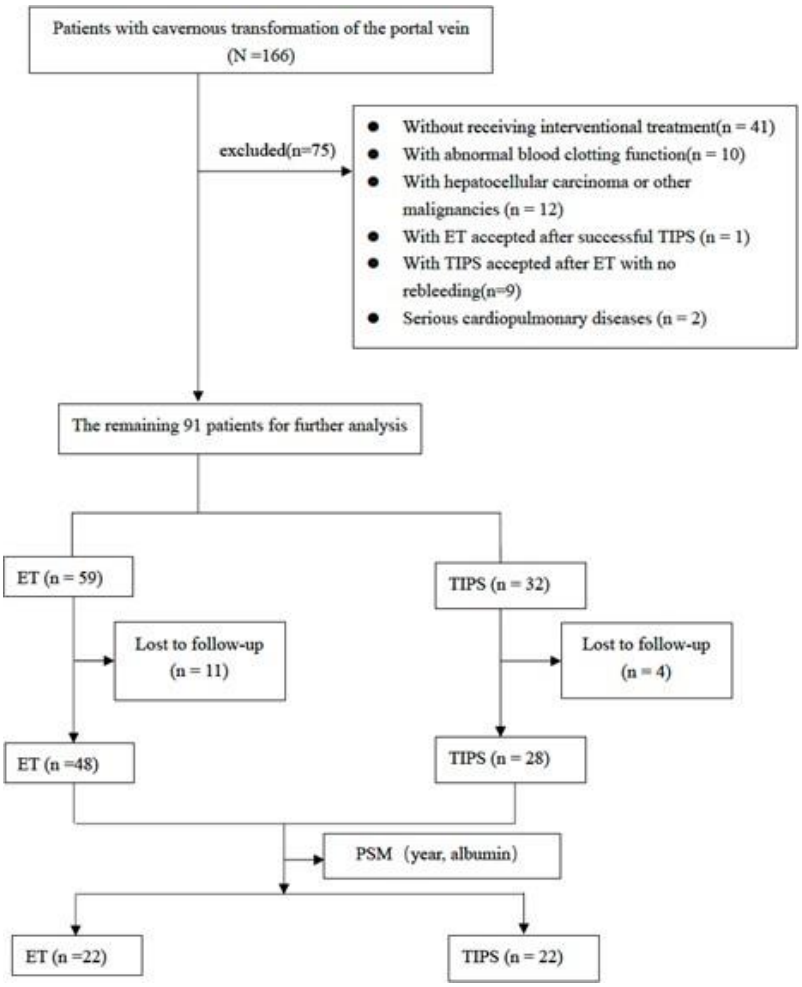

Figure 1: Flowchart of patient enrollment;TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic therapy.

Table 1: Characteristics of patients with CTPV. WBC, white blood cell; HB, hemoglobin; PLT, platelet count; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transpeptidase; Scr, serum creatinine; ALP, alkaline phosphatase; TBil, total bilirubin; PT, prothrombin time; INR, international normalized ratio; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic therapy.

Variables	ET	TIPS	P value
	(n = 22)	(n = 22)	
Age, (years，mean±SD)	57.50(49.00~64.25)	57.50(51.00~62.00)	0.751
Male, n(%)	14 (63.60)	12 (54.50)	0.544
Liver cirrhosis, n(%)	17 (77.30)	20 (90.90)	0.222
Ascites, n(%)	16 (72.70)	18 (81.80)	0.477
Child-pugh sores(mean±SD)	7.00±1.25	7.50±1.44	0.156
A, n(%)	8(36.36)	6(27.27)	
B, n(%)	14(63.64)	15(68.18)	
C, n(%)	0	1(4.50)	
WBC count [×10^9/L，m(Q1~Q3)]	5.05 (3.25~8.75)	4.80 (3.38~7.55)	0.925
D-dimer [mg/L, m(Q1~Q3)]	3.90(2.65~6.58)	2.11(0.59~6.92)	0.251
HB [g/L, m(Q1~Q3)]	79.50(62.00~96.75)	89.00(76.75~106.25)	0.057
PLT count [×10^12/L, m(Q1~Q3)]	163.00(87.75~218.00)	176.00(100.75~231.00)	0.716
Albumin (g/L, mean±SD)	32.38±407	32.19±4.93	0.76
ALT [U/L, m(Q1~Q3)]	19.95 (13.10~28.98)	19.25(14.05~26.73)	0.981
AST [U/L, m(Q1~Q3)]	26.85 (21.90~31.55)	29.85 (23.60~37.80)	0.432
γ-GT [U/L, m(Q1~Q3)]	24.65 (15.73~48.05)	27.15 (17.65~61.32)	0.787
SCr [μmol/L, m(Q1~Q3)]	55.50 (46.75~66.13)	59.50 (42.25~67.25)	0.869
ALP [U/L, m(Q1~Q3)]	72.30 (55.70~103.25)	81.60 (59.30~123.43)	0.241
TBil [μmol/L, m(Q1~Q3)]	19.50 (10.80~23.48)	19.60 (11.70~32.05)	0.63
PT [s, m(Q1~Q3)]	13.55 (12.30~14.73)	13.75 (12.68~14.78)	0.445
INR, m(Q1~Q3)	1.19 (1.10~1.28)	1.23 (1.10~1.39)	0.27

4.2. Upper Gastrointestinal Rebleeding Rate and Survival Rate

The median follow-up time between the ET and TIPS groups (27.33 vs. 36.15 months; P = 0.650) was not significantly different, which is conducive to the accuracy of the results. During the follow-up period, a total of 16 variceal rebleeding episodes occurred: 8(36.36%) patients from the TIPS group and 9 (40.91%) patients from the ET group. Rebleeding events were defined as hematemesis or hematochezia[18]. The outcome of postoperative rebleeding prevention in the TIPS group was not better than that in the endoscopic group (P = 0.601, Figure 2A). In CTPV patients with or without cirrhosis, there was no statistically significant difference between ET group and TIPS group in the cumulative upper gastrointestinal rebleeding rate after operation (p=0.925, p=0.223, Figure 2B, 2C).

Three (13.64%) cases that accepted a TIPS operation and three (13.64%) that accepted ET died. The causes of death included gastrointestinal bleeding, hepatic encephalopathy, progressive liver failure, multiple organ failure, and unknown reasons. Among the patients in the ET group, one died of gastrointestinal rebleeding, and two died of unknown causes. In the TIPS group, one died of gastrointestinal rebleeding, one died of liver failure, and one case died of intestinal perforation. Regarding survival advantages, TIPS did not outperform the endoscopic treatment group, as previously reported by other studies (P = 0.963, Figure 3A). The survival rate of CTPV patients with cirrhosis who received endoscopic therapy was not statistically different from that of CTPV patients with TIPS therapy (P = 0.476, Figure 3B). For patients without cirrhosis, there was no statistically significant difference in the cumulative survival rate between ET and TIPS (P <0.999, Figure 3C). (Table 2) summarizes the upper gastrointestinal rebleeding rate and the survival rate without liver transplantation in the two groups.

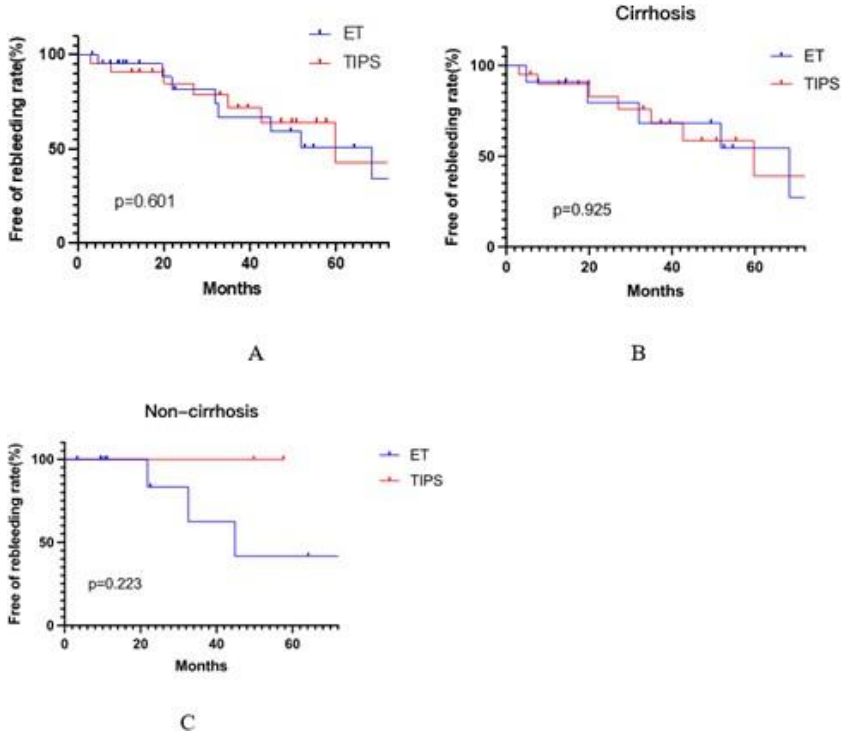

Figure 2: Kaplan–Meier curves of upper gastrointestinal rebleeding rates in the different groups. TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic treatment.A. Kaplan-Meier curve of upper gastrointestinal rebleeding rates in the ET and TIPS groups;B. Kaplan-Meier curve of upper gastrointestinal rebleeding rates in the ET and TIPS groups with cirrhosis;C. Kaplan-Meier curve of upper gastrointestinal rebleeding rates in the ET and TIPS groups without cirrhosis.

Table 2: The date of postoperative outcomes. TIPS, transjugular intrahepatic portosystemic shunt; ET, endoscopic treatment; OHE: overt hepatic encephalopathy.

values	ET	TIPS	P value
	(n=22)	(n=22)	
Rebleeding rate, n(%)	9(40.91)	8(36.36)	0.757
Survival rate, n(%)	3(13.64)	3(13.64)	> 0.999
OHE rate, n(%)	8(36.36)	1(4.55)	0.021
Hospitalization expenses	47603.00 (28816.00~79030.00)	92968.00 (70105.00~106061.25)	0.001
[Chinese yuan, m(Q1~Q3)]			
Length of stay [days, m(Q1~Q3)]	22.00(15.50~28.50)	13.00(9.75~18.00)	0.004
Number of hospitalizations (median)	2	1	< 0.000

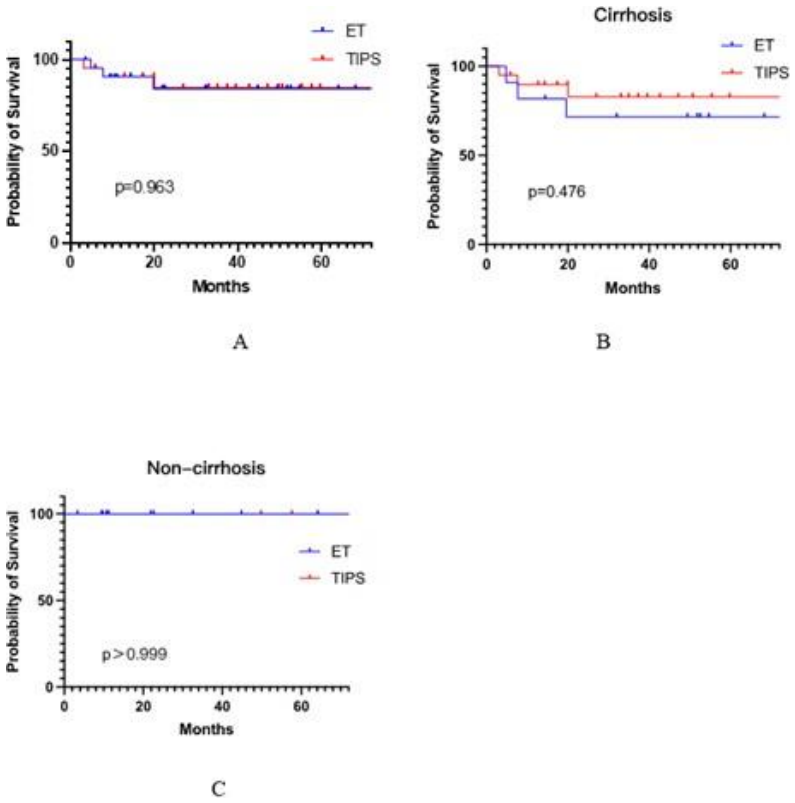

Figure 3: Kaplan–Meier curves of survival rate in each group. ET: endoscopic therapy; TIPS: transjugular intrahepatic portosystemic shunt. A. Kaplan-Meier curve of survival rate in the ET and TIPS groups;B. Kaplan-Meier curve of survival rate in the ET and TIPS groups with cirrhosis;C. Kaplan-Meier curve of survival rate in the ET and TIPS groups without cirrhosis.

4.3. Overt Hpatic Encephalopathy and Hospitalization Cost

Eight (36.36%) persons with TIPS therapy and one (4.55%) with ET developed at least one episode of OHE during the follow-up time. Hepatic encephalopathy was successfully controlled medically in all patients, and the most severe hepatic encephalopathy in all patients was stage II. The probability of OHE in the TIPS group was significantly higher than that in the endoscopic treatment groups (P = 0.027). The Kaplan–Meier curve of OHE incidence is shown in (Figure 4).

In regard to the hospitalization cost of the ET and the TIPS groups, there was a significant difference between the two groups. In terms of treatment expense, the TIPS group (92968.00 Chinese Yuan) was higher than that of the ET group (47603.00 Chinese Yuan) (P = 0.001). It is worth mentioning that the expense of endoscopic treatment involved multiple consolidation and sequential treatments. However, with respect to hospitalization time, the median hospital stay for patients in the TIPS group (13.00 days) was much lower than that of patients in the ET group (22.00 days) (P = 0.004), particularly because endoscopic treatment requires multiple consolidations. It is worth mentioning that the hospitalization time and cost of ET include multiple endoscopic sequential treatment. The treatment cost or hospital stay of postoperative complications are not included.The median number of hospitalizations in the ET group was two, while the median number of hospitalizations in the TIPS group was one (P = 0.000). Data for the OHE rate and hospitalization information is shown in (Table 2).

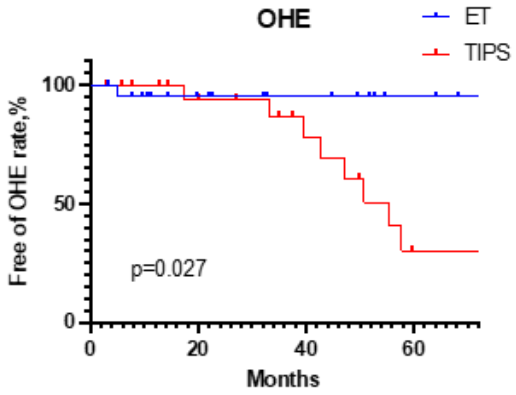

Figure 4: Kaplan–Meier curves of the incidence of overt hepatic encephalopathy. ET: endoscopic therapy; TIPS: transjugular intrahepatic portosystemic shunt; OHE: overt hepatic encephalopathy.

5. Discussion

CTPV is most often caused by chronic portal vein thrombosis. Obstruction of the portal vein can bring about a series of serious complications, including bleeding from gastroesophageal varices, hypersplenism, and ascites [19, 20]. Therefore, clinical treatment for CTPV is mainly to relieve portal hypertension. With the improvement of surgical skills and awareness of diseases in recent years, from solving

complications by the disease to treating the disease itself, CTPV is no longer a strange and incurable disease [21, 22]. Several RCTs have shown that compared with traditional treatment strategies (for example, a combination of endoscopy and drug therapy), TIPS can lower the upper gastrointestinal rebleeding rate of patients with cirrhosis. Many multicenter studies have demonstrated that TIPS can prevent the recurrence of varicose veins in people with PVT [17, 23, 24]. In our study, we were unable to observe a reduction in the rate of postoperative upper gastrointestinal rebleeding rate in patients with TIPS as compared to endoscopic treatment ($P > 0.05$), possibly because the patient population we included was not singularly cirrhotic. Therefore, we further compared the efficacy of ET and TIPS in the treatment of CTPV patients with cirrhosis. The results showed that there was no significant difference between the two treatments in the prevention of upper gastrointestinal rebleeding and overall survival rate.

It is well known that compared to EBL, TIPS although have certain advantages in managing variceal rebleeding, is a second-line treatment for patients with cirrhosis because TIPS do not provide a survival benefit [25, 26]. The TIPS treatment in this research did not outperform the endoscopic treatment group in terms of survival rates ($P > 0.05$). In addition, six patients in this study were switched to endoscopic treatment due to failed TIPS procedures. It is evident that TIPS interventions are technically difficult and require more surgeons, which may limit their widespread use. Compared with TIPS, endoscopic interventional therapy is less difficult to perform and requires fewer professional qualifications for the surgeon. Endoscopic interventional therapy can also be carried out in some lower-level hospitals, which is conducive to its wide application. Importantly, the presence of CTPV further increases the difficulty of TIPS surgery due to cavernous changes in blood vessels.

Both ET and TIPS can cause many complications. In this study, the prevalence of OHE in patients after TIPS was significantly higher than that in the ET group (36.36% vs 4.55%, $P < 0.05$). In terms of hospitalization cost, although ET required multiple hospitalizations for sequential treatment, the overall hospitalization cost was still lower than that in the TIPS group ($P < 0.05$). Our study is a hospital-based retrospective study with a longer follow-up period. The results showed that for CTPV patients, TIPS may not be the preferred option because it does not reduce the rate of postoperative rebleeding or improve the survival benefit of patients. In contrast, in terms of hospitalization costs and the risk of OHE, ET is better than TIPS treatment, which is a finding that is different from the results of other studies. In addition, the advantages of our research should be attributed to (1) comparing the advantages and disadvantages of various endoscopic treatment methods and TIPS treatment and (2) a relatively long follow-up time. However, some limitations should be mentioned. Our research was conducted in a single center with relatively small sample size, which may cause selection bias and affect the results. Therefore, further study will be required. To further support the findings of this study, a prospective study that compares the effectiveness of endoscopic therapy and TIPS in the treatment of CTPV has been undergoing in our center.

6. Conclusion

There was no significant difference between TIPS and endoscopic therapy in reducing postoperative rebleeding rate and long-term mortality in patients with CTPV and variceal bleeding. TIPS is more likely to cause postoperative OHE than ET. TIPS is costly and technically difficult.

7. Declarations

7.1. Ethics approval and consent to participate

This study was approved by the ethics committees of Nanjing Drum Tower Hospital and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. This study was a retrospective study, so the authors requested and received permission to waive informed consent from ethics committees of Nanjing Drum Tower Hospital.

7.2. Consent for publication

Not applicable.

7.3. Availability of Data and Material

Data sets used and/or analyzed in the current study may be obtained from the corresponding author upon reasonable request.

7.4. Competing Interests

The authors declare that they have no competing interests.

7.5. Funding

This study was funded by the Special Fund of Nanjing health and Technology Development (JQX18002) ,the Natural Science Foundation of Jiangsu Science and Technology Department (BK20191119) and the Natural Science Foundation of Jiangsu Province, China (BK20191119).

7.6. Authors' Contributions

Bin Zhang and Yuzheng Zhuge designed the study; Yaru Tong collected data; Ming Zhang and Feng Zhang reviewed the literature; Jiangqiang Xiao and Yi Wang reviewed CT imaging; Yaru Tong, Shuling Huang and Bin Zhang analyzed the data, reviewed the chart, and interpreted the data; Yaru Tong and Bin Zhang wrote the paper. All authors have read and approved the manuscript.

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