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TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT OR A COMBINATION OF NONSELECTIVE BETA-BLOCKERS AND ENDOSCOPIC VARICEAL LIGATION FOR PROPHYLAXIS OF BLEEDING IN WAITLISTED CIRRHOTIC PATIENTS

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Objective: to substantiate the choice of an optimal method of preventing and reducing the risk of variceal bleeding (VB) and cardia in patients with decompensated cirrhosis who have been enlisted for liver transplantation (LT). **Materials and methods.** Patients with diuretic-resistant and diuretic-responsive ascites underwent prophylaxis for recurrent bleeding via transjugular intrahepatic portosystemic shunt (TIPS) or a combination of endoscopic variceal ligation (EVL) and nonselective beta-blockers (NSBB). **Results.** Leukocyte counts, Na levels, and Child–Turcotte–Pugh (CTP) liver disease class in patients with diuretic-resistant ascites had significant differences when comparing individuals who received EVL + NSBB or underwent TIPS. In diuretic-responsive patients, there were significant differences for blood platelet count, albumin and Na levels, and CTP class when comparing EVL + NSBB and TIPS groups. In diuretic-resistant patients, incidence of grade 2 varices in EVL + NSBB group was significantly higher than in TIPS. Incidence of grade 3 varices was significantly higher in TIPS patients than in EVL + NSBB cohort. In diuretic-responsive patients, incidence of grade 2 and 3 varices had no significant differences when comparing these indicators in both groups. The proportion of patients with CTP class B was significantly higher both in diuretic-resistant and diuretic-responsive patients with various methods of rebleeding prophylaxis. The proportions of CTP class C patients with both forms of ascites were significantly higher in EVL + NSBB group than in TIPS. During the LT wait period within 2 years from the start of bleeding prophylaxis in diuretic-resistant patients, 78.4% of patients who underwent TIPS implantation developed recurrent bleeding, 100% of EVL + NSBB group within the same time frame, developed recurrent bleeding. Using the Kaplan–Meier estimate with the Log-Rank test, we were able to establish that there is a significant difference between the proportions of patients with recurrent VB in EVL + NSBB or TIPS groups with both forms of ascites.

Keywords: liver transplant waiting list, ascites, recurrent VB, endoscopic variceal ligation, nonselective beta-blockers, TIPS implantation.

INTRODUCTION

VB is a life-threatening complication of portal hypertension, which is a marker of decompensated cirrhosis [1, 2] and high mortality [3]. The first episode of variceal hemorrhage occurs with a frequency exceeding 85% in patients with decompensated CKD [4]. In patients who recovered from the first bleeding episode, the risk of recurrent bleeding (RB) is 60% in the first year with a mortality of up to 33% [2]. Other publications report 30% of patients with a first episode of VB within the first two years [5]. The authors of the study found that after the first episode of VB, at least 60% of them are predisposed to RB with a mortality risk of 30% if they are not treated with secondary prophylaxis [6, 9]. But even, in case of secondary prophylaxis of bleeding with a combination of NSBB and EVL for VB in accordance with the guidelines of the American Association for the Study of Liver Diseases (AASLD) [2] and the Guidelines for the Management of Patients with portal hypertension – Baveno VI and Baveno VII [7, 8], RB risk within

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2 years after the first episode increases from 29% to 57%, and the risk of death increases from 16% to 26% [10].

Increased hepatic venous pressure gradient (HVPG) of 20 mmHg or more is the main predictor of early RB and high mortality for acute rebleeding in cirrhotic patients awaiting LT [11, 12]. It has been shown that in patients awaiting LT, each 1 mmHg increase in HVPG increases the risk of death by 3% in a 19-month liver transplant waitlist (LTWL) stay [13].

As established by studies, EVL is not a measure to restrain an increase in HVPG during cirrhosis progression [11–13], and NSBB reduces HVPG level to a small extent (propranolol could only lower it by 10.1–23.2%, carvedilol by 18.6–27.7%) [14]. In addition, response to the use of propranolol or carvedilol in high HVPG has resulted in two categories of individuals: responders and non-responders [14–16], which reduces the efficacy of NSBB + EVL, which is well established in the primary prophylaxis of VB [17]. La Mura et al. [16] found that the incidence of primary or recurrent bleeding from esophageal varices within 1 year was 7% in responders of acute hemodynamic response to propranolol use, and 21% in non-responders.

Therefore, for patients with HVPG or portal pressure gradient (PPG) ≥25 mmHg, neither EVL, NSBB therapy, nor EVL + NSBB is effective in preventing VB when waiting for LT for 2 or more years [18].

In fact, an EVL plus NSBB, although considered the standard in prophylaxis of recurrent VB, has never been considered the only and indisputable strategy [19].

In recent years, the invasive TIPS procedure has become widespread, and many randomized controlled trials (RCTs) have confirmed that this technique is superior to other RB treatments. Nevertheless, it should be recognized that the use of TIPS has not improved patient survival rates significantly [10, 20].

Implantation of TIPS, while reducing HVPG or PPG, is thus the treatment of choice when first-line therapy (EVL + NSBB) is ineffective [21, 22]. Performing TIPS implantation after the second or third (and/or more) episodes of recurrent VB (especially if they recur at short intervals) is indicated in hemodynamically and clinically stable patients with optimal and manageable risk factors for complications of this procedure [23].

In most RCTs, patients were included in the study within 24 to 96 hours after bleeding occurred [24].

Studies comparing the efficacy of TIPS and EVL + NSBB in preventing recurrent VB are extremely rare [20, 23].

MATERIALS AND METHODS

The comparative retrospective study included 163 cases of patients with established VB awaiting LT between 2016 and 2023.

Inclusion criteria: Patients with diuretic-responsive and diuretic-resistant ascites, presence of one or more episodes of VB while in the liver transplant waiting list (LTWL), complete abstinence for at least 3 months (confirmed by addiction specialists) prior to inclusion in the LTWL for patients with alcohol-related cirrhosis, virus-related cirrhosis (hepatitis B virus (HBV) or hepatitis C virus (HCV)- associated etiology), cirrhosis of mixed etiology (virus-related and alcohol-related), and Child–Turcotte–Pugh (CTP) classes of cirrhosis.

Exclusion criteria: patients with hepatocellular cancer and other tumors accompanied by ascites, hepatic encephalopathy (HE) grade 2 and above, infectious diseases, portal vein thrombosis, contraindications to NSBB (bradyarrhythmia, bronchial asthma, obstructive pulmonary disease), and diabetes mellitus.

The patients included in the study were divided into two groups: group 1 consisted of 130 patients with diuretic-resistant ascites, group 2 included 33 patients with diuretic-responsive ascites. There were subgroups in both groups. In group 1: 1a had patients who received EVL plus NSBB (n = 77), 1b consisted of patients who underwent TIPS implantation (n = 53). Similarly, group 2 had subgroups: 2a was patients who received EVL plus NSBB (n = 9), 2b included patients who were implanted with TIPS (n = 24).

Demographic, clinical, and laboratory parameters were obtained from a permanent, continuously updated electronic database of patients who were under follow-up after their inclusion in the LTWL, after approval of the study by the Local Ethics Committee, Center for Surgery and Donation Coordination, Rostov Regional Clinical Hospital. Where patients' condition was stable, clinical and biochemical blood tests, hemostasis parameters, calculation of MELD-Na scores and CTP liver disease class, were repeated at 3-month intervals.

Where patients' condition were stable, abdominal ultrasound was performed every 6 months after the patients' initial examination.

In all patients, esophagogastroduodenoscopy (EGD) was performed to screen for varices with high risk of VB.

The Baveno VI [7] and World Gastroenterology Association (WGO) [24] guidelines served as a basis for identifying patients with varices requiring urgent therapy (medium and large size varices).

The criteria for diagnosing resistant ascites were as follows: diuretic resistance, decreased plasma Na levels (<125 mmol/L), increased fluid in the abdominal cavity (5–6 points on the CIRAS scale) [25]. The severity of diuretic-responsive ascites was determined according to the International Ascites Club criteria [26]. Mean arterial pressure (mAP) was determined by the formula: $mAP = (DP) + {}^{1}/_{3}(SP - DP)$, where SP is systolic pressure, and DP is diastolic pressure [27].

For the first-line therapy recommended by experts for prevention of recurrent esophageal hemorrhage [2, 7, 8], beta-1 blockers (propranolol, nadolol) and beta-1, beta-2, and alpha-1 adrenergic blocker (carvedilol) were used.

Propranolol was initiated at a starting dose of 40 mg/day, with a maximum dose of 240 mg/day. The starting dose of nadolol was 40 mg/day and the maximum was 80 mg/day. The starting dose of carvedilol was 6.25 mg/day and the maximum was 25 mg/day.

Drug doses were adjusted appropriately whenever there were changes in blood pressure (BP), heart rate (HR) and mAP.

Patients received diuretics, and paracentesis was performed in patients with diuretic-resistant ascites.

Patients with virus-related cirrhosis received antiviral therapy with nucleoside alternatives (HBV) and a combination of direct-acting antivirals (HCV) according to the guidelines for the treatment of LTWL patients [28].

EVL was performed using an EGD and a multi-band ligation system, starting at the gastroesophageal junction and continuing this procedure proximally. The number of rubber ligatures (2 to 4) was determined depending on the size of varices. In accordance with guidelines, obliteration of all varices meeting the criteria for emergency therapy [7, 24] was achieved through repeated EVL. Control EGD to monitor the obliteration was performed at 3-month intervals. Where there are recurrences (appearance of new varices), repeat EVL was performed.

TIPS implantation was performed in accordance with the guidelines for the treatment of decompensated cirrhosis [29, 30] under local anesthesia with intravenous sedation with analgesics. For implantation, we used a set of RUPS-100 instruments (Cook Medical®, USA), including Flexor Check-Flo introducer and curved Rösch catheter. After puncture of the right internal jugular vein (RIJV), under fluoroscopic control, a standard angiographic guidewire was advanced through the superior vena cava (SVC) and the atrial sinus into the inferior vena cava (IVC), placing its J-shaped end at a level slightly above the hepatic vein (HV) orifices. Flexor Check-Flo introducer with a curved Rösch catheter was passed through the guidewire and placed in the right hepatic vein (RHV) closer to its mouth. During surgical intervention, an intrahepatic conduit (tunnel) was formed from RHV to the portal vein (PV) right branch or bifurcation using a Rösch-Uchida needle and a balloon guided by a wire. After removal of the balloon, a stent-graft, which is a tubular metal mesh covered inside with a special sealed plastic – polytetrafluoroethylene (PTFE) – was implanted through the guidewire.

The obtained data were analyzed using statistical program IBM SPSS Statistics (version 23). Parameter analysis using the Kolmogorov–Smirnov test with the Lilliefors test for normality allowed us to determine the type of distribution of the obtained variables of the sample indicators (normal or non-normal distribution). In the case of normal distribution, variables were presented as arithmetic mean (M) with determination of standard deviation (SD); significance of differences between compared values was determined by Student's t-test. In the case of non-normal distribution, variables were expressed as median (Me) and interquartile range (IQR, interval between the 75th and 25th percentiles of the data). To determine the significance of differences between variables, the following nonparametric criteria were used: Wilcoxon test for pairwise comparisons of dependent variables, and Pearson's Chi-square for comparison of independent variables. The Mann–Whitney U test was used to compare samples with a small number of variables. Analysis of variance (ANOVA test) was also used. Analysis of frequencies of variables and their shares (%) was used when comparing qualitative parameters. The p value <0.05 was accepted as the criterion of statistical significance between compared parameters. The proportion of patients with RB in the compared groups, as well as the risk of verified event (bleeding) was determined by the Kaplan–Meier method. The significance of differences between compared curves was determined by calculating the logarithmic test [Log-Rank (Mantel-Cox)].

RESULTS

Table 1 and Table 2 present demographic, clinical, and laboratory parameters, as well as MELD-Na scores in the groups of patients with diuretic-resistant and diuretic-responsive ascites, who were treated with EVL + NSBB therapy or underwent TIPS implantation during the LT wait period.

As can be seen from the tables presented, demographic and most of the laboratory and instrumental parameters of patients who received NSBB therapy plus EVL or underwent TIPS implantation in the diuretic-resistant and diuretic-responsive groups had no significant differences.

Exceptions were leukocyte count, Na level and CTP class in the diuretic-resistant group, which had significant differences when comparing subgroups 1a and 1b. Also, when comparing indicators in subgroups 2a and 2b in the non-resistant group, there were significant differences in terms of platelet count, albumin and Na levels, and CTP class.

Table 3 and Table 4 present data on gender composition as well as etiology of cirrhosis, CTP class, and severity of varices in patients treated with NSBB plus EVL or underwent TIPS implantation in the diuretic-resistant and diuretic-responsive groups.

As can be seen from Tables 3 and 4, decompensated virus-related cirrhosis prevailed in the compared subgroups. Table 3 shows that in waitlisted patients with diuretic-resistant ascites, the incidence of grade 2 varices in subgroup 1a (EVL + NSBB) was significantly higher than in subgroup 1b (TIPS implantation). At the same time, the incidence of grade 3 varices was significantly higher in subgroup 1b than in subgroup 1a. In diuretic-responsive ascites patients (Table 4), the incidence of grade 2 and 3 varices was not significantly different when comparing these parameters in subgroups 2a and

2b (who received EVL plus NSBB and underwent TIPS implantation, respectively).

When comparing the severity of liver injury according to CTP class A, it was not possible to conduct an analysis due to the absence of such patients in subgroups 1a and 2a (diuretic-resistant and diuretic-responsive ascites). The proportion of patients with CTP class B was significantly higher in both diuretic-resistant and diuretic-responsive patients (subgroups 1a and 1b, respectively). The proportions of patients with CTP grade C for both forms of ascites were significantly higher in subgroups 1a and 2a (EVL + NSBB) compared with subgroups 2a and 2b (TIPS implantation).

During the LT waiting period between 24 and 48 weeks of follow-up in the LTWL (2-year period from the start of bleeding prophylaxis), RB developed in 29 of 37 diuretic-resistant patients (78.4%) who underwent TIPS implantation. In contrast, all patients (100%) who

Table 1

Comparative characteristics of patients with diuretic-resistant ascites (group 1), who received NSBB + EVL or underwent TIPS implantation (normal and non-normal distribution)

Indicator	Subgroup 1a EVL + NSBB (n = 73) M ± SD	Subgroup 1b TIPS (n = 37) M ± SD	Statistical significance
Normal distribution (M ± SD)			
Age	48.82 ± 10.59	51.46 ± 10.67	0.22
Hemoglobin (g/L)	87.91 ± 11.68	87.00 ± 11.39	0.32
Leukocytes ($\times 10^9$/L)	3.38 ± 1.20	4.31 ± 1.68	0.01
Platelets ($\times 10^9$/L)	84.41 ± 44.15	109.73 ± 78.65	0.03
Plasma albumin (g/L)	29.85 ± 3.06	30.38 ± 2.76	0.38
MELD-Na	21.92 ± 3.09	20.76 ± 3.06	0.06
mAP (mmHg)	78.22 ± 20.65	79.35 ± 21.12	0.23
Non-normal distribution (Me; IQR)			
INR	1.90 (1.70–2.05)	1.900 (1.60–2.10)	0.45
Bilirubin (μmol/L)	81.0 (64.50–105.00)	74.0 (64.50–77.50)	0.07
Creatinine (μmol/L)	112.0 (97.0–127.00)	109.0 (101.5–121.00)	0.59
Na (mmol/L)	136.6 (135.0–138.5)	132.0 (129.5–135.5)	0.001
CTP (score)	2.00 (2.00–2.00)	11.00 (8.50–14.00)	0.001

Note: EVL, endoscopic variceal ligation; NSBB, nonselective beta-blockers; TIPS, transjugular intrahepatic portosystemic shunt; mAP, mean arterial pressure; INR, international normalized ratio; Na, sodium; CTP, Child–Turcotte–Pugh.

Table 2

Comparative characteristics of patients with non-resistant ascites (group 2), who received NSBB therapy plus EVL or underwent TIPS implantation (normal and non-normal distribution)

Indicator	Subgroup 2a EVL + NSBB (n = 16) M ± SD	Subgroup 2b TIPS (n = 18) M ± SD	Statistical significance
Normal distribution (M ± SD)			
Age	46.45 ± 7.98	48.50 ± 10.18	0.12
Hemoglobin (g/L)	88.91 ± 10.32	87.38 ± 9.63	0.17
Leukocytes ($\times 10^9$/L)	4.76 ± 1.51	4.96 ± 1.86	0.10
Platelets ($\times 10^9$/L)	80.17 ± 44.05	131.11 ± 52.15	0.04
Plasma albumin (g/L)	26.33 ± 5.20	31.61 ± 2.48	0.03
MELD-Na	21.30 ± 3.49	19.38 ± 2.28	0.13
mAP (mmHg)	79.67 ± 22.43	81.44 ± 23.42	0.19
Non-normal distribution (Me; IQR)			
INR	1.750 (1.475–2.00)	1.700 (1.375–1.950)	0.50
Bilirubin (μmol/L)	107.5 (42.50–652.50)	79.5 (57.0–161.25)	0.55
Creatinine (μmol/L)	99.0 (77.25–104.25)	98.0 (82.25–117.25)	0.64
Na (mmol/L)	136.0 (136.0–137.25)	132.0 (130.0–132.0)	0.001
CTP (score)	2.00 (2.00–2.00)	8.00 (7.00–9.00)	0.003

Note: EVL, endoscopic variceal ligation; NSBB, nonselective beta-blockers; TIPS, transjugular intrahepatic portosystemic shunt; mAP, mean arterial pressure; INR, international normalized ratio; Na, sodium; CTP, Child–Turcotte–Pugh.

received EVL plus NSBB developed RB within the same time frame.

Using the Kaplan–Meier method with the Log-Rank test, a significant difference (p = 0.023) was found between the proportions of patients with recurrent VB in the compared groups (Fig. 1).

Fig. 2 shows the diagram of the cumulative risk of RB in the compared groups. The cumulative risk of RB in the EVL + NSBB subgroup was two or more times higher than in the TIPS subgroup (significant difference using Log-Rank test = 0.023).

During the LT wait period between 24 and 48 weeks of follow-up in the LTWL (2 years from the start of bleeding prophylaxis), RB developed in 8 of 18 diuretic-responsive patients (44.4%) who underwent TIPS implantation.

In the EVL + NSBB subgroup, all patients (100%) developed RB within the same time frame.

Using the Kaplan–Meier method with determination of Log-Rank test, a significant difference (p = 0.049) was found between the proportions of patients who developed recurrent VB in the compared groups (Fig. 3).

Fig. 4 shows a diagram of the cumulative risk of RB in the compared groups. The cumulative risk of RB in the EVL + NSBB subgroup was one and a half times higher than in the TIPS subgroup (significant difference using Log-Rank test = 0.023).

DISCUSSION

Our study showed a high rate of RB in diuretic-resistant and diuretic-responsive patients waiting for LT for 24–48 weeks, who received prophylactic therapy with a combination of an invasive procedure – EVL + NSBB (first-line therapy) – or underwent TIPS implantation, considered as second-line therapy in modern guidelines [8]. Note that the first bleeding recurrences occurred in the first 8–10 weeks from the start of secondary prophylaxis for RB in both forms of ascites and both prophylaxis methods. However, as the waiting period for LT increased (>10 weeks from the start of prophylaxis), the proportion of patients with RB became significantly higher, reaching 100% in patients with both forms of ascites when first-line therapy was used, while the use of

Table 3

Comparative characteristics of clinical and gender parameters of patients with diuretic-resistant ascites, who received NSBB plus EVL or underwent TIPS implantation

Indicator	Subgroup 1a NSBB + EVL (n = 73) (%)	Subgroup 1b TIPS (n = 37) (%)	Statistical significance
Male	41 (56.2%)	21 (56.8%)	0.11
Virus-related cirrhosis	35 (48.0%)	19 (32.4%)	0.001
Alcohol-related cirrhosis	19 (26.0%)	9 (24.3%)	0.13
Other CKD etiologies	19 (26.0%)	9 (24.3%)	0.14
Esophageal varices, grade 2	19 (26.0%)	4 (10.8%)	0.001
Esophageal varices, grade 3	54 (74.0%)	33 (89.2%)	0.001
CTP class A	0	1 (2.7%)	–
CTP class B	6 (8.2%)	9 (24.3%)	0.001
CTP class C	67 (91.8%)	27 (73.0%)	0.04

Note: EVL, endoscopic variceal ligation; NSBB, nonselective beta-blockers; TIPS, transjugular intrahepatic portosystemic shunt; CKD, chronic kidney disease; CTP, Child–Turcotte–Pugh.

Table 4

Comparative characteristics of clinical and gender parameters of patients with diuretic-responsive ascites, who received NSBB plus EVL or underwent TIPS implantation

Indicator	Subgroup 2a EVL + NSBB (n = 16) (%)	Subgroup 2b TIPS (n = 18) (%)	Statistical significance
Male	12 (75.01%)	14 (77.7%)	0.16
Virus-related cirrhosis	12 (75.0%)	12 (66.7%)	0.03
Alcohol-related cirrhosis	6 (25.0%)	4 (22.2%)	0.22
Other CKD etiologies	0	2 (11.1%)	–
Esophageal varices, grade 2	2 (12.5%)	2 (11.1%)	0.23
Esophageal varices, grade 3	14 (87.5%)	16 (88.9%)	0.24
CTP class A	0	1 (13.5%)	–
CTP class B	5 (8.2%)	14 (18.9%)	0.001
CTP class C	11 (91.8%)	3 (67.6%)	0.008

second-line therapy gave a significantly lower incidence of RB by the end of follow-up for both forms of ascites.

We found only five published studies and one meta-analysis (when analyzing the PubMed database up to January 2024) that aimed to compare the efficacy of TIPS implantation or a combination of EVL and NSBB on the rate of RB in patients with decompensated cirrhosis.

The same results as in our study were obtained by Zhou et al. [31], who compared the efficacy and safety of TIPS implantation or a combination of EVL and NSBB (propranolol) for secondary prophylaxis of VB bleeding. The study showed that the proportion of patients without RB was higher in TIPS than in EVL + NSBB (93% and 62%, respectively, $p < 0.001$). The authors concluded that compared to the combination of EVL and

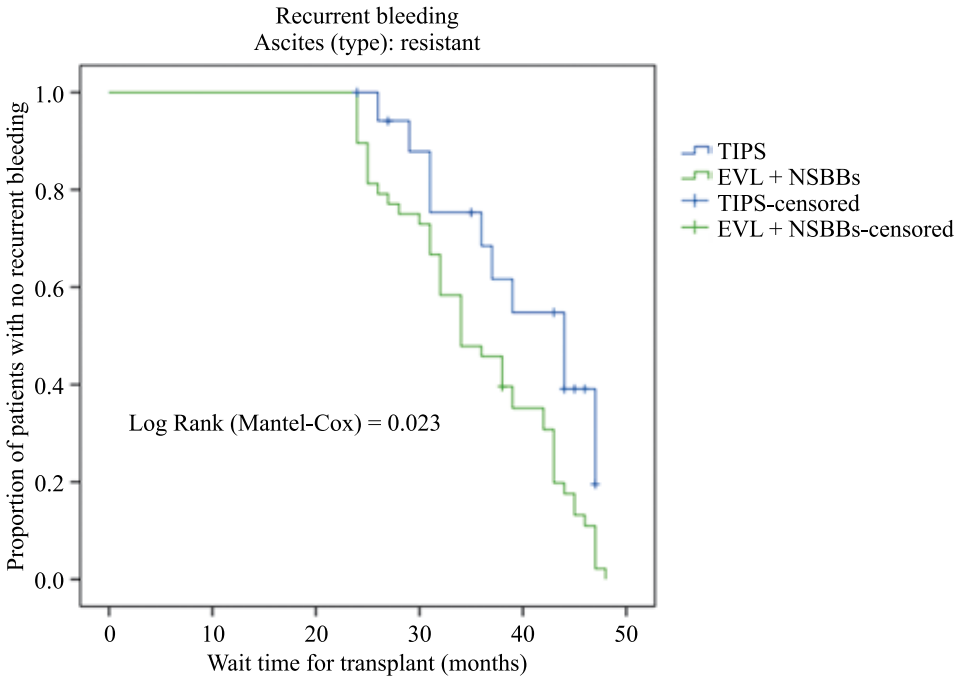

Fig. 1. Proportion of rebleeding patients with diuretic-resistant ascites, who underwent TIPS implantation or received NSBB + EVL (Kaplan–Meier method with Log-Rank test)

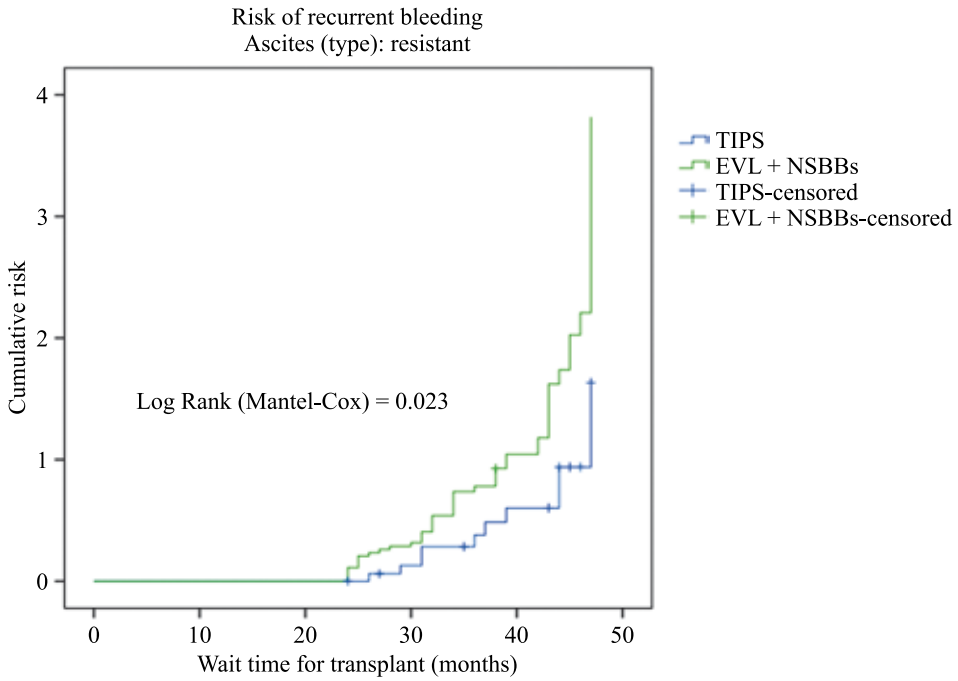

Fig. 2. Cumulative risk of recurrent bleeding in patients with resistant ascites who underwent TIPS implantation or received EVL + NSBB

NSBB, PTFE-covered TIPS could significantly reduce the variceal rebleeding rate in cirrhotic patients with HVPG≥20 mmHg.

Earlier studies comparing the efficacy of implantation of PTFE-covered TIPS and EVL + NSBB combination [10, 20, 32, 33] showed a significant difference between the former method and the latter in terms of RB prophylaxis. Importantly, the use of PTFE-covered TIPS did not increase the risk of patient mortality or the risk of HE.

Miao et al. [19] conducted a meta-analysis of RCTs to comparatively evaluate the efficacy of all proposed methods for prevention of re-therapy in patients with decompensated cirrhosis. Forty-eight trials with 4415 participants with cirrhosis and portal hypertension who had a history of recent variceal bleeding were included in the

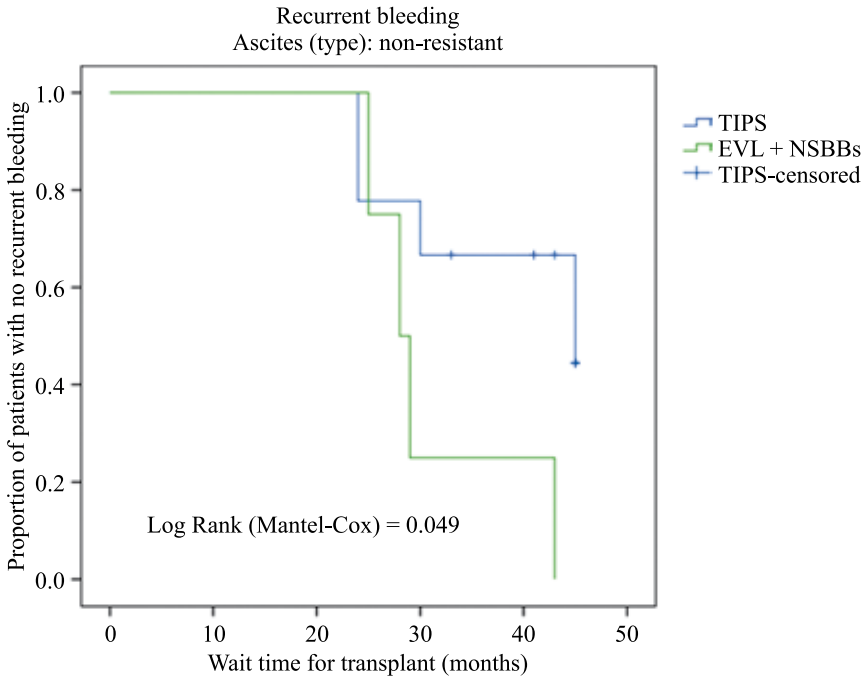

Fig. 3. Proportion of rebleeding patients with diuretic-responsive ascites, who underwent TIPS implantation or received NSBB + EVL (Kaplan–Meier method with Log-Rank test)

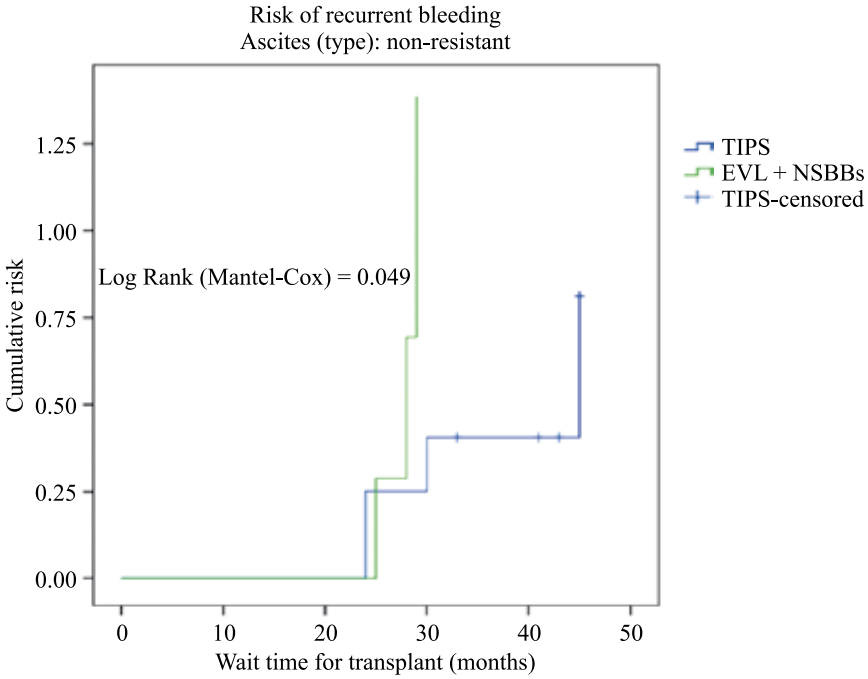

Fig. 4. Cumulative risk of recurrent bleeding in patients with diuretic-responsive ascites who underwent TIPS implantation or EVL + NSBB

meta-analysis. International databases, including EMBASE, PubMed, and Cochrane Database of Controlled Trials, were checked to identify relevant randomized controlled trials up to December 2019.

The authors of the meta-analysis concluded that NSBB + isosorbide mononitrate ranked significantly higher than NSBB + EVL (63.9% vs 49.6%, respectively) in reducing patient mortality. TIPS (98.8%) ranked higher than other treatments in reducing rebleeding but did not confer any survival benefit.

The risk of RB in our study was significantly higher in the EVL + NSBB subgroup than in the TIPS subgroup. Note that in our study, rebleeding occurred in diuretic-resistant and diuretic-responsive ascites patients, with high MELD-Na scores, as well as in a significant proportion of patients with grade 2 and 3 varices.

It is known that the main risk factor for recurrent variceal hemorrhage is elevated HVPG (≥20 mmHg) [11, 12, 33]. The increased proportion of patients with RB in both forms of ascites in those who received EVL plus NSBB in our study, compared with those who underwent TIPS implantation, is associated with higher HVPG while waiting for LT for 2 or more years. As found by Liu et al. [18], when HVPG or PPG ≥25 mmHg, neither EVL, NSBB therapy, nor EVL + NSBB provide reliable prophylaxis of recurrent variceal hemorrhage. A similar conclusion was reached by Zhang et al. [33] who showed that TIPS are more effective than NSBB (propranolol) + EVL in cirrhosis patients with high HVPG (≥20 mmHg).

In addition to HVPG ≥20 mmHg, other risk factors for RB in patients receiving NSBB plus EVL include ascites, HE, MELD score >12 [34], which is consistent with our study. Undoubtedly, the risk factors of re-bleeding should include medium- and high-grade esophageal varices that we identified in both forms of ascites. A study conducted by Irisawa et al. [35] showed that the size (diameter) of paraesophageal varices is a risk factor for RB.

How to reduce the risk of RB? Early use of TIPS implantation is the optimal strategy for rebleeding prophylaxis. The concept of "pre-emptive TIPS" was first introduced by Monescillo et al. [36], who showed that in patients with HVPG ≥20 mmHg, stent implantation in the first 24 hours after stabilization of the patient's condition against the background of the first bleeding provides better survival and lower rate of recurrent variceal hemorrhage than standard prophylactic therapy.

Ardevol et al. [34] confirmed this concept by showing that early use of TIPS after the first bleeding significantly reduces the risk of rebleeding.

Limitations of this approach include the need to measure HVPG to decide on the choice of prophylaxis for recurrent VB. This technique is not available in all medical centers, and its introduction may be considered as a prospect towards improving the diagnosis of portal hypertension and the choice of the method of prophylaxis of recurrent variceal hemorrhage with a long LT waiting period.

CONCLUSION

We found a high rate of rebleeding in both forms of ascites in patients awaiting LT within 24–48 weeks after inclusion in the LTWL.

Probable risk indicators for rebleeding in the patients are ascites, high MELD-Na score (≥19), and large (diameter) varices.

Prophylaxis of recurrent bleeding during the specified length of LTWL stay, while waiting for LT, is more effective with TIPS than with EVL + NSBB.

The authors declare no conflict of interest.

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