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TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT WITH GASTRIC VEIN EMBOLIZATION IN LIVER CIRRHOSIS

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Objective: to determine the predictors and risk of recurrent bleeding after implantation of a transjugular intrahepatic portosystemic shunt (TIPS) combined with selective gastric vein embolization in patients with decompensated cirrhosis awaiting liver transplantation (LT). **Materials and methods.** A comparative retrospective study was performed in 54 patients waitlisted for LT between 2017 and 2023, who suffered recurrent variceal hemorrhage after secondary prophylaxis of bleeding prior to inclusion in the study. Demographic, clinical and laboratory parameters, clinical indices, hepatic encephalopathy, severity of ascites, degree of varices, manometric study before and after TIPS implantation with gastric vein embolization, with calculation of portal pressure gradient in patients with (n = 16) and without rebleeding (n = 38), were analyzed. The proportions of patients were compared using the Kaplan–Meier method with determination of the logarithmic test (Log-Rank). Cumulative risks were estimated by means of univariate and multivariate analysis of the Cox proportional hazards model. **Results.** Within 30 weeks from the date of TIPS combined with gastric vein embolization, 16 of 54 patients (29.6%) developed rebleeding. The following risk factors were identified: age, hemoglobin level, white blood cell count, platelet count, creatinine level, severity of ascites, and mean portal pressure gradient after TIPS implantation. It was found that the proportion of patients without bleeding was significantly higher in patients with portal pressure gradient ≤10 mmHg than in patients with this index >10 mmHg (Log Rank = 0.029). The following independent predictors of recurrent hemorrhage were determined: severity of ascites, shunt thrombosis, portal pressure gradient after TIPS implantation, portal pressure gradient after TIPS implantation <30% of the basal level. It has been shown that the risk of recurrent bleeding at portal pressure gradient >10 mmHg progressively increases and reaches maximum values (HR = 1.713) in patients who underwent TIPS combined with gastric vein embolization between 32 and 40 weeks from the time of surgery, while it is absent at portal pressure gradient ≤10 mmHg.

Keywords: liver transplantation, ascites, recurrent variceal bleeding, transjugular intrahepatic portosystemic shunt, portal pressure gradient, risk factors, independent predictors.

INTRODUCTION

The rising number of liver transplants (LT) worldwide, and in Russia in particular, has created a gap between the need for this life-saving operation and the number of donors (donor organs), despite the apparent increase in the activity of donor and transplant coordination centers at a modern stage [1, 2]. Due to the increasing waiting time for LT in patients on the waiting list, progressive decompensation (PD, hereinafter "decompensation") of liver cirrhosis causes a high risk of complications, such as diuretic-resistant ascites, bleeding, and hepatic encephalopathy (HE), increasing to high mortality [3]. Bleeding esophageal varices increases the risk of mortality in patients who are potential candidates for liver transplantation (LT) [4]. After the first bleeding episode, certain patients are at risk of recurrent bleeding (RB) developing early or late, thereby increasing the overall waitlist mortality [5, 6]. The International Committee on the Management of Patients with Portal Hypertension recommend two RB prophylaxis strategies, implemented by first-line therapy, and in case of failure, by second-line therapy [7]. First-line therapy consists of a combination of interventional procedure – endoscopic variceal ligation (EVL) with administration of non-selective beta-blockers (NSBB). The second-line therapy involves implantation of a transjugular intrahepatic portosystemic shunt (TIPS) [7].

Currently, polytetrafluoroethylene (PTFE)-coated TIPS is a well-established intervention for the treatment of complications of portal hypertension (PH) [7, 11–13].

Current guidelines recommend a further development of this procedure for this purpose – a combination of TIPS procedure and extrahepatic collateral vessel chemoembolization (TIPS + GVE) in order to control variceal bleeding and reduce the risk of rebleeding [7, 8, 11, 14]. Implementation of both variants of invasive in-

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terventions (TIPS or TIPS + GVE) has brought attention to the issue of striking a balance between reduction in RB and development of HE, which are linked to hemodynamic changes brought on by these interventional procedures [8, 9]. Portal pressure gradient (PPG) dynamics is the most important characteristic of hemodynamic response after TIPS or TIPS + GVE [8–10].

Decreased PPG due to TIPS procedure raises two big problems that need to be solved: how to effectively prevent rebleeding and how to avoid an increase in the grade of overt HE caused by excessive shunting of portal blood flow [8–10].

A comparative assessment of the effect of a combination of procedures (TIPS + GVE and TIPS) on RB prevention and HE development has very contradictory data and calls for further studies [8–10].

Previous studies have found that the target PPG level after a TIPS procedure is <12 mmHg [15]. Another target is a >50% PPG decrease from baseline before shunt placement [16]. Both indicators ensure effective prevention of RB and other complications of PH [15–17], being a Baveno VII recommendation for the management of patients with PH [7].

The definition of PPG thresholds was derived from careful preliminary studies showing that RB and ascites almost exclusively develop in patients with a PPG of at least 12 mmHg after stent implantation [9, 15–18].

It is important to note that these thresholds of PPG decrease to the target level were achieved prior to coated stents being used in clinical settings [15, 18], which highlights the need to improve them [10]. Specifically, the risk of severe HE is quite high with coated TIPS, even with the current standards, limiting their use in clinical practice [10, 19, 20].

Therefore, it is crucial to determine the threshold of PPG decrease after coated TIPS implantation in order to determine the risks of RB and overt HE [15–17]. Since PPG may, according to Wang et al. [21], increase after GVE, this should be considered when implanting a stent and achieving target gradient values.

Objective: to determine the predictors and risk of RB after PTFE-covered TIPS implantation combined with selective GVE in patients with decompensated cirrhosis awaiting LT.

MATERIALS AND METHODS

A comparative retrospective study was performed in 54 patients with decompensated cirrhosis who were on the LT waitlist between 2017 and 2023. Prior to inclusion in the study, all patients in this group developed recurrent variceal rebleeding after secondary prophylaxis of bleeding through a NSBB + EVL combination.

After approval by the local ethics committee at the Center for Surgery and Donation Coordination (CSDC), Rostov Regional Clinical Hospital, the patients were included in a study of the efficacy and safety of PTFE-covered TIPS procedure combined with GVE.

Inclusion criteria: patients of either sex aged 18 to 75 years, cirrhosis of any etiology: virus-related (HBV- or HCV-), alcohol-related, or cirrhosis of mixed etiology (virus-related and alcohol-related), RB after combination (EVL + NSBB) therapy, complete abstinence in patients with alcohol-related cirrhosis for at least 3 months prior to inclusion in the study (confirmed by narcologists), CTP classes B and C, indications for TIPS procedure [7, 11, 13], availability of a complete electronic database with demographic, clinical, laboratory parameters and instrumental studies, presence of complete hemodynamic parameters before and after PTFE-covered TIPS implantation and GVE.

Exclusion criteria: Hepatocellular carcinoma or any other tumors, severe liver failure, heart failure, severe renal failure, recurrent or persistent overt HE despite adequate therapy, infectious diseases, sepsis; presence of contraindications for TIPS procedure, presence of CTP score >15, MELD-Na score >27, previous surgical shunt or LT, non-cirrhotic (idiopathic) portal hypertension (PH), sinusoidal obstruction syndrome or Budd–Chiari syndrome, portal vein thrombosis or cavernous transformation, pregnancy or lactation.

A regularly updated electronic database of patients with demographic, clinical, and laboratory information, who were on the LT waitlist of the Center for Surgery and Donation Coordination (CSDC), Rostov Regional Clinical Hospital, served as the foundation for the analysis that followed. At CSDC, patients were managed by specialists. When patients were included in the study, they were examined, including undergoing laboratory and instrumental tests (full blood count and biochemical tests, hemostasis indicators, MELD-Na score and CTP class). The frequency of these tests was determined by patient condition. When the patient's condition was stable, repeated examinations were performed once every three months; and abdominal ultrasound once every 6 months. For unstable patients included in the study, the need for laboratory and instrumental studies was determined by the presence of indications.

Esophagogastroduodenoscopy (EGDS) was used to screen all patients for varices with high risk of bleeding (medium and large-sized varices requiring bleeding prophylaxis) in accordance with the guidelines of the Baveno VI Consensus Workshop [22] and the World Gastroenterology Association (WGO) [23].

The International Club of Ascites (ICA) criteria were used to grade the severity of diuretic-responsive and diuretic-resistant ascites [24]. In addition to the ICA criteria [24], the Cirrhotic Ascites Severity (CIRAS) scale [25] was used to characterize diuretic-resistant ascites. When patient CIRAS score was 5–6, diuretic-resistant ascites was deemed to be the definitive diagnosis.

Hepatic encephalopathy (HE) was graded according to the modified West Haven criteria recommended by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [26].

Mean arterial pressure (mAP) was determined by the formula: mAP = (DP) + $^1/_3$(SP – DP), where SP stands for systolic pressure, and DP for diastolic pressure [27].

Patients were given diuretics; 15 patients with diuretic-resistant ascites had paracentesis (7 patients had it once, while 8 had it repeatedly, from 2 to 5). In compliance with recognized expert standards, antiviral medication with nucleoside analogs or a combination of direct-acting antivirals was given if HBV and HCV-associated cirrhosis was diagnosed [26].

Esophageal manometry (EM) was performed on all patients before PTFE-covered TIPS procedure, but after GVE and stent implantation. For this purpose, the J-end of a standard angiographic guidewire was placed in the inferior vena cava (IVC) slightly above the hepatic vein (HV) orifice via transjugular access. EM was performed using a pressure transducer balloon catheter (Edwards Lifesciences, USA) at the end. Immediately after catheter placement into the portal vein (PV), baseline (basal) portal vein pressure (PVP) was measured. After catheter placement in the IVC, baseline basal inferior vena cava pressure (IVCP) was measured. Portal pressure gradient (PPG) was measured by calculating the difference between PVP and IVCP.

TIPS procedure was performed in accordance with the guidelines for the management of patients with decompensated cirrhosis complicated by PH [11]. The shunt was implanted using a Flexor Check-Flo introducer and Rösch curved catheter included in the RUPS-100 instrument set (Cook Medical®, USA) under local anesthesia with additional intravenous sedation with analgesics. After puncture of the right internal jugular vein, under fluoroscopic control a standard angiographic guidewire was advanced through the superior vena cava (SVC) and atrial sinus into the IVC, placing its J-shaped end at a level slightly above the HV orifice. The Flexor Check-Flo introducer with a curved Rösch catheter was guided through the angiographic guidewire, placing them in the right HV closer to its ostium.

The surgical procedure involved creating a tunnel (intrahepatic conduit) running from the right HV to the PV right branch or bifurcation using a Rösch-Uchida needle and a balloon advanced over a guidewire. After balloon retrieval, a PTFE-covered stent graft (Hanarostent® Hepatico (M.I. Tech®) model, 8 or 10 mm in diameter), was implanted through the guidewire. In the next surgical step, the catheter was placed in the splenic vein close to the splenic hilum to perform direct vein portography, which allowed to visualize the mouths of the inflow pathways to the esophageal-gastric varices. Subsequent selective catheterization of the left, posterior and short gastric veins with embolization of each of them was performed. For this purpose, we used MReye® (Cook®) embolization coils, which have high thrombogenicity due to numerous long fibers. The number and size of the coils used were determined by the peculiarities of angioarchitecture, diameter and branches of the inflow pathways and varied from 0 to 14. After vein embolization, PVRembo and IVCPembo were immediately examined and PPGembo was calculated. The surgical intervention was completed by control phlebos shuntography.

The IBM SPSS Statistics software package (version 23) was then used to do a statistical analysis on the collected data. The Kolmogorov–Smirnov test and the Lilliefors significance threshold were used to assess the type of distribution of the obtained variables of the analyzed samples. The arithmetic mean (M) and standard deviation (SD) were computed if it was discovered that the variables had a normal distribution. Using a significance threshold of $p < 0.05$, the Student's t-test was used to assess the significance of differences between the compared values. In the event that it was discovered that the variables did not have a normal distribution, the interquartile range (IQR, the interval between the 25th and 75th percentiles) was used to calculate the median (Me). To determine the significance of differences in pairwise comparisons of dependent variables, the Wilcoxon signed-rank test recommended in nonparametric analysis, was used. Pearson's chi-squared test was used to compare independent variables. For a small sample, the variables were compared using the Mann–Whitney U test. Analysis of variance was carried out through ANOVA test. Conjugacy tables were used to analyze qualitative parameters (frequencies of variables and their percentages); for small samples, Fisher's exact test was used to assess the significance of the relationship between two variables.

The Kaplan–Meier method was used to compare the proportions of patients in different groups. The significance of differences between the compared curves (patient proportions) was determined by calculating the log-rank [Log-Rank (Mantel-Cox)].

Comparative assessment of cumulative accumulated risks in the groups was performed using the mathematical model of proportional risks (Cox regression) in univariate and multivariate analysis. The risk of occurrence of the tested event (HR) was calculated and the 95% confidence interval (CI) for this indicator was determined. The quality of the model used was determined by estimating the maximum likelihood (log-likelihood, –2LL). The condition of multivariate Cox proportional hazards regression analysis (absence of linear relationship between independent variables, which creates redundancy in the model) was verified by constructing a correlation matrix.

RESULTS

Patients included in the study, from the date of TIPS procedure combined with GVE up to 30 weeks of follow-up (n = 54), were divided into two groups. The first group consisted of those who developed RB after TIPS + GVE (n = 16, 29.6%), and the second group consisted of patients who had no RB after this combined surgical intervention (n = 38, 70.4%).

Demographic, clinical, laboratory parameters, as well as MELD-Na and CTP scores in the RB and non-RB group after the TIPS procedure combined with GVE are presented in Table 1.

Table 1 shows that patient age, hemoglobin, leukocyte level, platelet count, creatinine level, ascites severity, and mean PPG following TIPS surgery were significantly different between the compared groups, with the RB group having higher values than the non-RB group.

We also assessed the reduction in PPG after TIPS procedure as a percentage of its basal value (before shunt placement).In the RB group, PPG decreased by less than 30% of its basal value in 13 out of 16 patients (81.25%), but in the non-RB group, PPG decreased by 55.3% in 21 out of 38 patients (p = 0.04). Shunt dysfunction (shunt thrombosis) occurred in 11 out of 16 patients (68.75%) in the RB group, and in 3 out of 38 patients (7.89%) in the non-RB group (p = 0.02).

We compared the frequency of RB in the two groups of patients differing in PPG value.

The first group consisted of patients whose PPG was ≤10 mmHg (n = 15), and the second group consisted of patients with PPG >10 mmHg (n = 7). Ten of the fifteen patients (66.7%) in the first group and six of the seven patients (85.7%) in the second group both experienced RB, difference between groups (p = 0.047).

Using the Kaplan–Meier method, it was established that the proportion of patients without re-bleeding was significantly higher in the group of patients with PPG ≤10 mmHg than in the group with PPG >10 mmHg (Log Rank = 0.029) (Fig. 1).

We used survival analysis to predict the risk of recurrent hemorrhage for patients who underwent TIPS + GVE, while awaiting LT. Biomedical research uses this approach to predict mortality, disease recurrence, recovery, or any other outcomes relative to the time of their occurrence [29]. The influence of independent variables (predictors) on RB risk was investigated using a mathematical Cox proportional hazards model with calculation of the risk of an adverse event (Hazard Risk; HR) and determination of the 95% CI.

For this purpose, we used univariate and multivariate analysis of the mathematical Cox proportional hazards model (Table 2).

When univariate analysis was applied, a model with one independent variable was created with calculation of the hazard ratio (HR), confidence interval (CI) and assessment of the significance of the effect on the develop-

Table 1

Comparative characteristics of patients with and without rebleeding after TIPS procedure in combination with gastric vein embolization (normal distribution and non-normal distribution)

Indicator	RB (n = 16), M ± SD	No RB (n = 38), M ± SD	p-value
Normal distribution (M ± SD)			
Age	55.31 ± 7.26	50.13 ± 10.8	**0.046**
Hemoglobin (g/L)	83.11 ± 19.21	115.78 ± 17.21	**0.038**
White blood cells ($\times 10^9$/L)	3.53 ± 1.35	4.75 ± 1.83	**0.021**
Plasma albumin (g/L)	29.94 ± 3.28	30.66 ± 3.08	0.46
Creatinine (μmol/L)	117.13 ± 20.04	105.42 ± 11.02	**0.042**
INR	1.91 ± 0.25	1.92 ± 0.46	0.91
MELD-Na (points)	21.59 ± 3.13	20.71 ± 2.67	0.31
mAP (mmHg)	90.13 ± 9.98	88.32 ± 10.41	0.57
PPG basal (mm Hg)	25.94 ± 4.14	24.87 ± 2.97	0.64
PPG after embolization (mmHg)	26.11 ± 3.86	26.07 ± 1.14	0.57
PPG after TIPS (mmHg)	10.93 ± 0.76	8.02 ± 0.69	**0.04**
Non-normal distribution (Me; IQR)			
Platelets ($\times 10^9$/L)	75.0 (54.0–95.0)	105.00 (74.75–141.75)	**0.02**
Bilirubin (μmol/L)	68.0 (56.25–86.0)	76.0 (64.5–79.5)	0.36
Na (mmol/L)	130.5 (130.0–137.0)	131.0 (129.75–132.0)	0.56
CTP (points)	10.5 (7.0–14.0)	10.5 (8.0–13.25)	0.70
Ascites grade	2.0 (1.0–2.75)	3.0 (2.00–4.0)	**0.02**
HE grade (points)	2.0 (1.0–3.0)	2.0 (1.75–2.0)	0.71

Note: RB, recurrent bleeding; INR, International normalized ratio; MELD-Na, Model for End-Stage Liver Disease-Sodium; CTP, Child–Turcotte–Pugh; Na, sodium; HE, hepatic encephalopathy; mAP, mean arterial pressure; PPG, portal pressure gradient.

ment of an adverse event (rebleeding) for each predictor. All independent variables (predictors) that significantly influence the development of RB in univariate analysis, are presented in the first part of Table 2.

As can be seen from Table 2, in the univariate analysis of the mathematical Cox proportional hazards model, independent variables that significantly influence the development of RB were identified: ascites severity (gra-

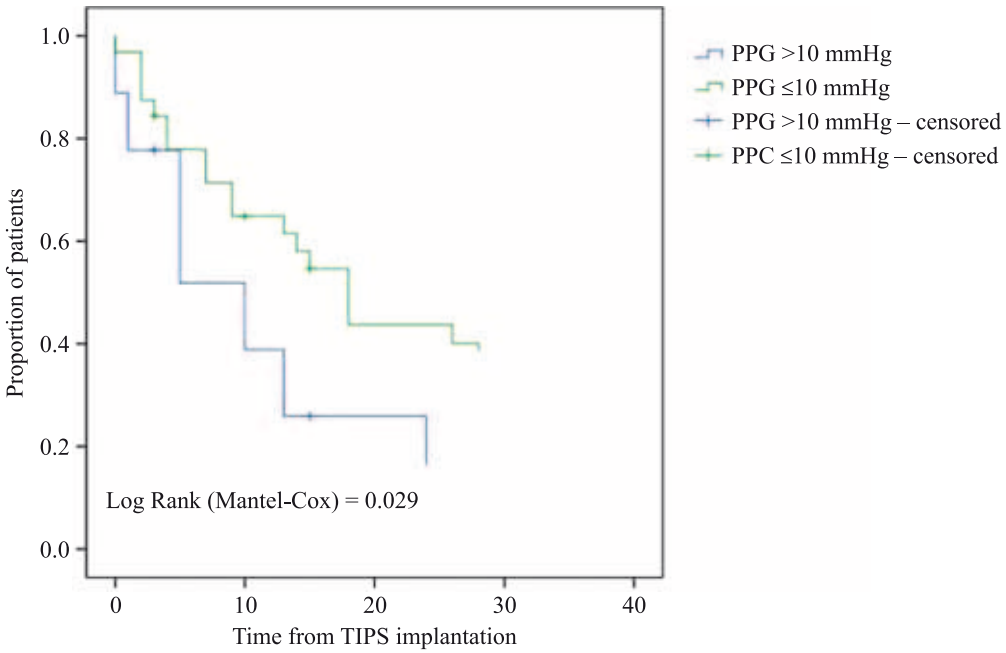

Fig. 1. Proportion of patients without bleeding and with rebleeding after TIPS procedure combined with gastric vein embolization, depending on PPG (Kaplan–Meier method with Log-Rank test)

Table 2

Univariate and multivariate analysis of predictors associated with recurrent bleeding after TIPS procedure combined with gastric vein embolization

Variables	Univariate analysis		Multivariate analysis	
	HR (CI)	p-value	HR (CI)	p-value
Age	1.034 (0.972–1.099)	0.293	–	–
Platelets ($\times 10^9$/L)	0.985 (0.970–1.00)	0.054	–	–
White blood cells ($\times 10^9$/L)	0.696 (0.480–1.010)	0.057	–	–
Plasma albumin (g/L)	0.858 (0.724–1.016)	0.076	–	–
INR	1.214 (0.393–3.749)	0.736	–	–
Bilirubin (μmol/L)	0.999 (0.986–1.011)	0.830	–	–
Creatinine (μmol/L)	1.021 (0.992–1.050)	0.151		
Na (mmol/L)	1.091 (0.988–1.205)	0.363	–	–
Hemoglobin (g/L)	1.011 (0.954–1.151)	0.352	–	–
MELD-Na (points)	1.072 (0.899–1.279)	0.439	–	–
CTP (points)	0.964 (0.812–1.144)	0.673	–	–
Ascites grade	0.479 (0.284–0.807)	**0.006**	0.591 (0.412–0.848)	**0.004**
HE grade (points)	1.137 (0.654–1.974)	0.650	–	–
mAP (mmHg)	1.005 (0.958–1.055)	0.829	–	–
Shunt thrombosis	1.239 (0.945–1.350)	**0.035**	1.003 (0.967–1.367)	**0.041**
PPG basal (mmHg)	1.129 (1.015–1.522)	0.181	1.638 (0.645–4.163)	0.299
PPG after embolization (mmHg)	0.563 (0.312–0.789	0.129	0.811 (0.391–1.684)	0.575
PPG after TIPS (mmHg; cat*)	1.153 (0.997–1.452)	**0.011**	1.168 (0.989–1.435	**0.023**
PPG after TIPS <30% of basal level (mmHg)	1.012 (0.961–1.097)	**0.035**	1.009 (0.834–1.069)	**0.043**

Note: * – variable including two HVPG categories: ≤10 and >10 mmHg. HR, hazard ratio; MELD-Na, Model for End-Stage Liver Disease-Sodium; INR, International normalized ratio; CTP, Child–Turcotte–Pugh; Na, sodium; HE, hepatic encephalopathy; mAP, mean arterial pressure; HVPG, hepatic venous pressure gradient; PPG, portal pressure gradient.

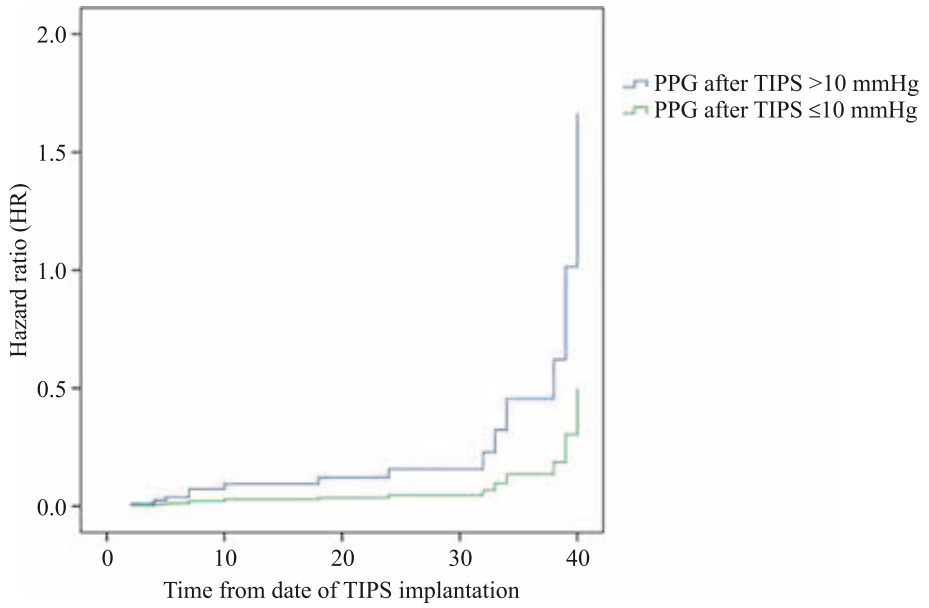

Fig. 2. Hazard ratio (HR) for rebleeding as a function of time and categorical variable PPG after TIPS procedure (≤10 mmHg; >10 mmHg)

de), shunt thrombosis, PPG (cat.) after TIPS, PPG after TIPS <30% of basal level (mmHg).

Multivariate analysis involved the creation of a model designed to assess the independent contribution of several predictors simultaneously, while determining the significance of their influence on RB. The second part of Table 2 shows the effect of all simultaneously acting significant predictors on RB development in the multivariate analysis. This analysis was performed by forced-entry (Enter) method, in which all variables are simultaneously entered into the model. The multivariate analysis model included all statistically significant predictors identified by the univariate analysis (considering each predictor separately), as well as known risk factors for RB, regardless of their influence in the univariate analysis, which is an acceptable technique for building this regression model [29, 30].

As shown in Table 2, a hazard ratio (HR) >1.0 was significant for the presence of shunt thrombosis, post-TIPS (cat.) PPG, and post-TIPS PPG <30% of basal level (mmHg), which allows us to consider these factors as having an independent influence on RB risk.

HR <1 was significant for the independent variable – ascites severity (grade). For HR <1, the influence of these factors is associated with increased survival time, i.e., a factor reducing the RB risk [29, 30].

The quality of our chosen model of multivariate Cox proportional hazards regression analysis was confirmed by estimation of the maximum likelihood indicator (log-likelihood or –2LL). In comparison with the base model (Block 0), the value of –2LL was 99.924; after introducing independent variables (predictors) into the model, –2LL decreased (76.657, Pearson's Chi-square = 23.454) at a significance level of 0.005. This analysis allows us to reject the null hypothesis, which in fact means that the predictive ability of the multivariate Cox proportional hazards regression analysis model is improved when independent predictors are included.

We constructed a correlation matrix to test the condition (no linear relationship between independent variables, which creates redundancy in the multivariate Cox proportional hazards regression analysis model). The correlations found were very weak (0.002 to 0.197), weak (0.198 to 0.395) and moderate (0.396 to 0.510), which does not negatively affect application of the model [29].

In multivariate analysis, we plotted the hazard ratio (HR) of RB for different values of the categorical variable PPG (≤10 mmHg; >10 mmHg) (Fig. 2).

As can be seen from Fig. 2, RB risk at PPG >10 mmHg progressively increases and reaches maximum values (HR = 1.713) in patients who underwent TIPS + GVE at 32 to 40 weeks from the time of surgery, while it is absent at PPG ≤10 mmHg, reaching HR = 0.517 within the same timeframe from the time of surgery.

DISCUSSION

We have shown that in patients who underwent TIPS procedure combined with gastric vein embolization (second-line therapy), due to the failure of previous first-line therapy (EVL + NSBB), 16 of 54 patients (29.6%) developed RB within up to 30 weeks of follow-up after surgery.

Zhao et al. [8] analyzed the incidence of post-TIPS rebleeding combined with GVE. The authors showed that 17.6% of patients included in the study developed RB during a mean 32.5-month follow-up period. The incidence of RB in the TIPS + GVE group was signifi-

cantly lower than in the TIPS group (17.6% and 23.2%, respectively).

A meta-analysis was conducted by a group of researchers to compare the incidence of RB, shunt dysfunction, and other outcomes between the TIPS and TIPS + GVE patient groups [31]. The TIPS + GVE combination was found to have a significantly lower incidence of RB compared to the TIPS group.

However, several studies have found no significant differences in the incidence of RB after these two types of surgery were obtained [32–34].

The higher incidence of RB after TIPS + GVE surgery in our study when compared with other reports is down to several factors. First, the success of RB prevention after TIPS or TIPS + GVE is linked to the PPG level after shunt placement. Bosch showed that to prevent RB after stent implantation, PPG level should be reduced to <12 mmHg (or 50% or more of the PPG level before stent implantation). Controlled stent dilation is recommended until the PPG level is ≤12 mmHg. At the same time, PPG decrease to <10 mmHg causes a significantly higher incidence of HE and acute liver injury [9].

The experience of foreign studies [9, 15] and our results show that, in practice, achieving the target level of PPG decrease (<12 mmHg) in many cases causes significant difficulties faced by the surgeon that is implanting TIPS. This is particularly the case when it comes to performing the stent implantation procedure with controlled dilation until the level of effective PPG decrease is achieved. The narrow therapeutic window for achieving the target PPG level is evidenced by data from a study by Bosch et al. [9], who showed the existing problems on the following example: when the stent is dilated up to 8 mm, PPG is reduced to 13 mmHg, and when the stent is dilated up to 10 mm, PPG decrease can be 6–7 mmHg. It is known that RB after TIPS or TIPS + GVE procedure develops when the target PPG is not reached after stent placement [9, 32, 33].

In our study, we found that PPG >10 mmHg after TIPS + GVE surgery increases the incidence of RB, and being a significant independent predictor, increases the risk of RB. Studies have shown, using multivariate Cox proportional hazards regression model analysis that PPG after TIPS + GVE is an independent predictor of RB [32, 33]. A 1 mm increase in PPG increases the risk of developing RB by 9% [33]. In our study, in multivariate Cox regression analysis, the risk of RB was even higher than in the cited study if PPG after TIPS + GVE was >10 mmHg. Thus, a 1 mm increase in PPG was associated with a 16.8% increase in RB risk.

Second, the increased incidence of RB after the TIPS + GVE procedure may be due to the development of more frequent shunt dysfunction (thrombosis) in our study. Shunt dysfunction occurred in 14 out of 54 patients in the TIPS + GVE group, accounting for 25.9% of cases. Jahangiri et al. [35] showed that primary TIPS thrombosis occurred in 17 cases (9.8%) within up to 24 months of follow-up after shunt surgery, and after 5 years, shunt dysfunction was determined at 21.8%. The annual calculated incidence of thrombosis was 38.7 per 1,000 person/year (95% CI, 19.3–77.3). The risk of shunt thrombosis was found to be related to post-TIPS PPG value. Thus, PPG <5 mmHg, 5–8 mmHg, and >8 mmHg had a 4.3%, 6.4%, and 17.7% risk of shunt thrombosis, respectively.

In our study, shunt dysfunction (shunt thrombosis) occurred in 11 (68.75%) out of 16 patients with RB developing after TIPS + GVE, and in 3 (7.89%) out of 38 in patients without RB, which was significantly lower than in the compared group ($p = 0.02$). In this regard, it is appropriate to cite the results obtained by Rosenqvist et al. [36], who showed that post-TIPS recurrent bleeding was associated with shunt thrombosis on one hand and with post-TIPS PPG on the other hand. The authors concluded that a PPG ≥5 mmHg after TIPS procedure is associated with increased risk of RB, and risk of shunt dysfunction. Another study showed that a post-TIPS PPG of 8.5 mmHg is significant for the development of shunt thrombosis [37].

In addition, our univariate and multivariate analysis of the Cox proportional hazards regression model established that shunt thrombosis is an independent predictor of RB after TIPS + GVE. Jahangiri et al. [35] came to similar conclusions, demonstrating that a 1 mmHg increase in post-TIPS PPG causes a 14% risk of thrombosis ($HR = 1.14$, $p = 0.023$).

The second independent predictor of RB risk after TIPS + GVE that we identified in both univariate and multivariate studies was the severity of ascites. We believe that ascites progression is a consequence of changes in portal hemodynamics and, therefore, may reduce the likelihood of developing RB, because the hazard ratio (HR) for this independent variable was <1. We reference a study by Liu et al. [38] that indicated that patients with ascites have a lower predictive value of hepatic venous pressure gradient (HVPG), an independent predictor of early rebleeding in the absence of ascites. This finding lends weight to our conclusion.

Insufficient decrease in PPG after shunt implantation relative to its basal level (<30%) is another significant predictor of RB after TIPS + GVE in our multivariate analysis.

Using a multivariate Cox model, Biecker et al [39] showed that post-TIPS PPG is an independent predictor of recurrent bleeding. Patients with a <30% post-TIPS PPG decrease were at the highest risk for rebleeding, and, on the contrary, patients with a >60% PPG decrease rarely suffered from rebleeding.

CONCLUSION

Within up to 30 weeks of follow-up after a TIPS + GVE procedure, RB develops in 29.6% of patients who

have been waiting for LT for a long time due to lack of donor organ.

Ascites severity (grade), presence of shunt thrombosis, post-TIPS (cat.) PPG, and post-TIPS PPG of <30% of baseline level (mmHg) are independent significant predictors of RB.

Patients who underwent TIPS + GVE treatment had a progressive increase in risk of developing RB at PPG >10 mmHg, which peaked 32–40 weeks after surgery. At HVPG ≤10 mmHg, however, there is no risk of developing RB.

The authors declare no conflict of interest.

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