DOI: 10.15825/1995-1191-2024-3-32-42

RISK FACTORS AND PREDICTORS OF RECURRENT VARICEAL BLEEDING IN CIRRHOTIC PATIENTS AWAITING TRANSPLANTATION

V.L. Korobka[1, 2], V.D. Pasechnikov[1, 3], Yu.V. Khoronko[2], R.V. Korobka[1, 2], E.S. Pak[1, 2], M.V. Malevanny[1, 2], D.V. Pasechnikov[3]

[1] Rostov Regional Clinical Hospital, Rostov-on-Don, Russian Federation
[2] Rostov State Medical University, Rostov-on-Don, Russian Federation
[3] Stavropol State Medical University, Stavropol, Russian Federation

Objective: to identify the risk factors and predictors of recurrent variceal hemorrhage in cirrhotic patients awaiting liver transplantation (LT). **Materials and methods.** A comparative retrospective study was conducted in 51 patients with decompensated cirrhosis, who were on the waiting list for LT. Demographic, clinical and laboratory parameters, MELD-Na score, Child–Turcotte–Pugh score, hepatic encephalopathy grade, ascites grade, class of varicose veins, number of consecutive variceal ligations, as well as manometric study with calculation of intrahepatic venous pressure gradient index in groups of patients with (n = 39) and without recurrent bleeding (n = 12) were analyzed. The proportions of patients in different groups were compared by the Kaplan–Meier method with determination of the logarithmic test (Log-Rank). The accumulated risks in the compared groups were estimated using the mathematical model of proportional hazards (Cox regression) in univariate and multivariate analysis. **Results.** Within 60 months from the beginning of follow-up and simultaneous prophylaxis by combination of non-selective beta-blockers and endoscopic variceal ligation (EVL), 39 out of 51 patients (75.6%) developed recurrent bleeding. Analysis revealed significant differences (risk factors for recurrent bleeding): creatinine levels, MELD-Na score, hepatic encephalopathy grade, mean hepatic venous pressure gradient (HVPG) and its level >14 mmHg. By the Kaplan–Meier method with the Log-Rank test, it was established that the proportion of patients without recurrent bleeding was significantly higher in the group of patients with HVPG ≤14 mmHg than in the group with HVPG >14 mmHg (p = 0.027). **Conclusion.** The main independent predictor of variceal rebleeding is HVPG >14 mm Hg, which increases the risk by 3.837 times if the gradient value is changed by 1 mm. The second independent predictor is higher hepatic encephalopathy grade: if the grade increases by one, the risk of recurrent hemorrhage increases 1.8 times.

Keywords: liver transplantation, ascites, recurrent variceal bleeding, endoscopic variceal ligation, nonselective beta-blockers, risk factors, independent predictors.

INTRODUCTION

Recurrent variceal bleeding (RVB) is a serious and potentially life-threatening complication of cirrhosis [1]. Garcia-Tsao et al. [2] found that a sizable percentage of patients were still at risk of experiencing recurrent bleeding (RB) even after a period of stabilization following the development of the first variceal bleeding episode. When emergency measures are not taken to stop variceal hemorrhage, early RB develops over the next 2–3 days after the initial episode, and the frequency reaches 60% [3]. Within a period of up to 1 year, the risk of RB is 60% [4] or 29–57% within 2 years following the first bleeding episode, despite prophylactic measures [5].

It is unclear exactly what mechanisms lead to the rupture of esophageal varices. Portal venous pressure (PVP) has been shown to be the primary determinant of the progression of variceal bleeding. It is known that PVP exceeds 10 mmHg and variceal rupture occurs at PVP >12 mmHg in patients with varices without bleeding [3].

Is it possible to predict RB and mortality based on various prognostic models that are built using risk factors and predictors? When analyzing literature sources, we encountered a great deal of discrepancy in both the factual identification of these factors and the identification methodology itself. In our opinion, risk factors and predictors of an event are different epidemiological characteristics. A risk factor is an event, circumstance or characteristic that is present in a subject, that is common in sufferers of a particular disease, or characterizing a certain state (phase or stage) in the development of the disease. A predictor is a circumstance, characteristic or event that occurs while an action is taking place, that favors one particular outcome (positive or negative) [6].

Corresponding author: Victor Pasechnikov. Address: 21, Aviatsionnaya str., Stavropol, 355017, Russian Federation. Phone: (962) 447-75-13. E-mail: passetchnikov@mail.ru

Analysis of scholarly publications show that studies by Moitinho et al. [7] and Abraldes et al. [8] were the first to identify predictors of early RVB and mortality from bleeding. Using multiple logistic regression analysis as a predictive model, the authors of this research found that a hepatic venous pressure gradient (HVPG) ≥20 mmHg was an independent predictor of RB in patients awaiting liver transplantation (LT). A Cox proportional-hazards model was used by Ripoll et al. to establish that each 1-mmHg increase in HVPG predicts a 3% increase in waitlist mortality at 19 months [9].

A contemporary study by Ardevol et al. [10] included 369 patients with cirrhosis followed up for 46 months after the first bleeding episode. Forty-five patients (12%) had early rebleeding early (within 6 weeks), 74 patients (20%) had late rebleeding (more than 6 weeks), and 250 (68%) had no rebleeding. Using Cox proportional-hazards model to assess the risks of developing early and late recurrent bleeding, the presence of ascites or hepatic encephalopathy (HE), MELD score >12 and HVPG >20 mmHg were found to be significant predictors of developing early RB. Mortality risk was significantly higher in the early RB group versus late RB (HR = 0.476, 95% CI = 0.318–0.712, p<0.001). Adjustment for baseline risk factors [MELD and Child–Turcotte–Pugh (CTP)], led to the conclusion that early RB is an **independent predictor** of mortality risk (HR = 1.58, 95% CI = 1.02–2.45; p = 0.04). The authors concluded by justifying early implantation of a transjugular intrahepatic portosystemic shunt (pre-emptive TIPS) within 72 hours after the onset of the first bleeding episode in order to prevent early RB and reduce patient mortality.

Objective: to identify the risk factors and predictors of recurrent variceal hemorrhage in cirrhotic patients awaiting LT.

MATERIALS AND METHODS

A comparative retrospective study was conducted in 51 patients with decompensated cirrhosis who were on the LT waitlist (LTWL) between 2018 and 2023. These patients developed RVB following secondary prophylaxis through a combination of non-selective beta-blocker (NSBB) and endoscopic variceal ligation (EVL).

The inclusion criteria were: first episode of variceal hemorrhage during stay in the LTWL in patients with decompensated cirrhosis, cirrhosis of any etiology – virus-related (HBV- or HCV-) cirrhosis, alcohol-related cirrhosis, or cirrhosis of mixed etiology (virus-related and alcohol-related), complete abstinence for at least 3 months (confirmed by narcologists) prior to inclusion in the LTWL, CTP classes B and C.

Exclusion criteria: hepatocellular carcinoma or any other tumors, any infectious diseases, portal vein thrombosis, intolerance or contraindications to NSBB (bradyarrhythmia, bronchial asthma, obstructive pulmonary disease, low mean arterial pressure (mAP)), and diabetes mellitus.

A continuously updated electronic database of patients enrolled in the LTWL at the Center for Surgery and Donation Coordination (CSDC), Rostov Regional Clinical Hospital, was the basis for subsequent analysis of demographic, clinical, and laboratory parameters, after approval of the study by the Local Ethics Committee. Follow-up of patients was conducted by specialists at CSDC. When patients were enrolled in the LTWL, they were examined, and this included laboratory and instrumental tests, the frequency of which depended on the patients' condition. Full blood count and biochemical tests were performed when patients were in a stable condition; hemostasis, MELD-Na score and CTP class were analyzed. Laboratory parameter studies were conducted every three months, and abdominal ultrasounds were conducted every six months. For unstable patients awaiting LT, laboratory and instrumental studies were performed when indicated.

The Baveno VI Consensus Workshop [[11] and the World Gastroenterology Association (WGO) [12] guidelines served as the basis for screening all patients with varices that are at a high risk of hemorrhage (medium-sized and large-sized varices) via esophagogastroduodenoscopy (EGD).

The severity of diuretic-responsive and diuretic-resistant ascites was graded according to the International Club of Ascites (ICA) criteria [13]. In addition to the ICA criteria [13], the Cirrhotic Ascites Severity (CIRAS) scale [14], including clinical and laboratory criteria, was used to characterize diuretic-resistant ascites. When a patient has a CIRAS score of 5–6, the diagnosis of diuretic-resistant ascites was considered quite definite [14].

Hepatic encephalopathy (HE) was graded according to the West Haven criteria [15].

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].

Patients received diuretics; those with diuretic-resistant ascites had 1 to 5 paracentesis. In accordance with recognized expert guidelines, antiviral medication with nucleoside analogs or a combination of direct-acting antivirals was given if HBV- and HCV-associated cirrhosis was identified [17].

In accordance with the Baveno VII guidelines, all patients were treated with first-line therapy with a combination of propranolol or carvedilol and EVL to prevent RB [18].

Propranolol was given to 17 patients at a starting dose of 40 mg/day and the maximum was 240 mg/day. Carvedilol was administered to 34 patients at an initial dose of 6.25 mg/day and the maximum was 25 mg/day. All patients were monitored for heart rate (HR), blood pressure (BP) and mean BP (mAP). A decrease in these indicators served as the basis for dosage modification.

The EVL procedure was performed under EGD sedation using a variceal ligation kit. EVL started at the gastroesophageal junction and continued proximally using multiple rubber ligatures (2 to 4 or more), the number of which was determined by variceal size. Repeated ligations were carried out 1 month after the first procedure, and this manipulation was repeated until all varices satisfying the criteria for emergency therapy were completely obliterated [11, 12]. Repeated EGDs at three-month intervals were used to track variceal obliteration. Repeated ligation procedures were performed for recurrence (appearance of new varices).

The development of re-bleeding during first-line therapy (combination of propranolol or carvedilol + EVL) was considered as a failure of bleeding prophylaxis, which served as a justification for TIPS.

Esophageal manometry (EM) was carried out in all patients in order to clarify the relationship between re-bleeding during prophylaxis with first-line therapy and the magnitude of HVPG.

Following transjugular access, the J-shaped end of a standard angiographic guidewire was placed in the inferior vena cava (IVC) slightly above the hepatic vein orifices. A balloon catheter with a pressure transducer at the end (Edwards Lifesciences, USA) was used for EM. The pressure in the right hepatic vein (RHV) was measured using a catheter, the tip of which was freely placed 1–3 cm from its confluence with the IVC, obtaining a free hepatic venous pressure (FHVP).

When the balloon was inflated and the pressure curve stabilized, we measured the wedged hepatic venous pressure (WHVP). Three measurements were taken in order to get the arithmetic mean of WHVP. Occlusion of the RHV with a catheter was monitored via angiography (sinusoidal graph) after administration of 2–5 mL of contrast agent in the absence of its reflux or washout.

HVPG was calculated using the formula: HVPG = WHVP – FHVP.

The IBM SPSS Statistics software package (version 23) was used to analyze the obtained data for statistical studies. At the first stage, the type of distribution of the obtained variables of the studied samples was determined using the Kolmogorov–Smirnov test and the Lilliefors significance level. For normal distribution of variables, the arithmetic mean (M) was calculated, and the standard deviation (SD) was determined. The significance of differences between the compared values was determined by Student's t test using a significance threshold of $p < 0.05$. For non-normal distribution, the analysis of variables included determination of median (Me) with interquartile range (IQR, the interval between 25th and 75th percentiles). When conducting pairwise comparisons of dependent variables, the Wilcoxon signed-rank test used in nonparametric analysis was used to determine the significance of differences between them. Pearson's chi-squared test was used to compare independent variables For a small sample, the variables were compared by calculating the Mann–Whitney U test. Analysis of variance was performed using ANOVA test. Conjugacy tables were used to analyze qualitative parameters (frequencies of variables and their shares in %); 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 percentage of patients in different groups. The significance of differences between the compared curves (patient proportions) was determined by calculating the logarithmic test [Log-Rank (Mantel-Cox)].

Comparative assessment of accumulated risks in groups was carried out using a 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

The patients, who were enrolled in the study for up to 60 months of being in the LTWL and received secondary prophylaxis through a combination of EVL and NSBB, were divided into two groups. The first group consisted of patients (n = 39) who developed re-bleeding despite prophylaxis, and the second group (n = 12) consisted of patients who had no recurrent bleeding.

Demographic, clinical, laboratory parameters, as well as MELD-Na and CTP scores in the groups of patients with and without RB during their stay in the LTWL are presented in Table 1.

As can be seen from the table presented, hemoglobin level, creatinine content, MELD-Na and CTP scores, HE grade, number of consecutive variceal ligations, mean HVPG and mean HVPG >14 mmHg, which were higher in the RB group than in the non-RB group, reached significant differences between the compared groups.

In the first group of patients with RB before initiation of prophylaxis, 14 patients (27.5%) had a single bleeding episode, and 25 patients (72.5%) had >1 bleeding episode before initiation of prophylactic therapy. As a result of prophylaxis, 2 out of 39 (5.1%) patients developed two RB episodes, and 37 out of 39 patients (94.9%) developed ≥3 RB episodes.

RB developed within 1 week after the first bleeding episode in 3 (7.7%) out of 39 patients, within 4 weeks in 7 (17.9%) out of 39 patients, and within 6 weeks in 10 out of 39 patients (25.6%) awaiting LT.

We compared RB incidence in the two groups of patients differing in HVPG.

The first group consisted of patients with HVPG ≤14 mmHg (n = 8), and the second group with HVPG >14 mmHg (n = 31). In group 1 and 2, 4 (50%) and 26 (83.9%) patients, respectively, experienced re-bleeding, difference between groups (p = 0.046).

Using the Kaplan–Meier method, it was established that the proportion of patients without re-bleeding was significantly greater in the group of patients with HVPG ≤14 mmHg than in the group of patients with HVPG >14 mmHg (Log Rank = 0.027) (Fig. 1).

We used survival analysis to predict the risk of recurrent hemorrhage for patients awaiting LT. This analysis is used in biomedical research to predict mortality, disease recurrence, or recovery, or any other outcomes relative to the time of their occurrence [19]. The influence of independent variables (predictors) on RB risk was assessed 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 development of adverse event (rebleeding) for each predictor. All independent variables (predictors), significantly influencing 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 an adverse outcome (rebleeding) were identified: creatinine level, MELD-Na score, number of consecutive variceal ligations, HE grade, categorical HVPG (HVPG ≤14 mmHg and HVPG >14 mmHg), HVPG ≤14 mmHg, HVPG >14 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 role of all simultaneously acting significant predictors in RB development in multivariate analysis is shown in the second part of Table 2. Here, we used the forced-entry method, in which all variables are simultaneously entered into the model. Statistically significant predictors, determined by univariate analysis (taking into account each predictor separately), as well as known risk factors for RB, regardless of their influence in the univariate analysis, were selected for inclusion in the multivariate

Table 1

Comparative characteristics of patients with and without recurrent bleeding (normal and non-normal distribution)

Indicator	RB (n = 39), M ± SD	No RB (n = 12), M ± SD	p value
Normal distribution (M ± SD)			
Age	51.26 ± 10.21	46.83 ± 7.48	0.17
Hemoglobin (g/L)	86.32 ± 21.07	116.23 ± 20.35	**0.049**
White blood cells ($\times 10^9$/L)	4.58 ± 1.72	4.30 ± 1.68	0.62
Plasma albumin (g/L)	30.54 ± 2.96	30.75 ± 2.95	0.83
Creatinine (μmol/L)	131.54 ± 10.96	102.33 ± 11.02	**0.042**
INR	1.96 ± 0.45	1.78 ± 0.39	0.19
MELD-Na (points)	25.56 ± 4.57	15.49 ± 5.21	**0.031**
HE grade (points)	1.97 ± 0.99	1.25 ± 1.14	**0.034**
mAP (mmHg)	89.26 ± 11.32	86.08 ± 7.79	0.37
HVPG (mmHg)	16.54 ± 2.86	13.25 ± 1.14	**0.001**
HVPG ≤14 (mmHg)	10.02 ± 1.24	13.65 ± 1.17	0.35
HVPG >14 (mmHg)	18.61 ± 1.12	13.13 ± 1.14	**0.04**
Number of consecutive EVLs	4.46 ± 0.60	1.33 ± 0.35	**0.04**
Non-normal distribution (Me; IQR)			
Platelets ($\times 10^9$/L)	91.0 (67.0–111.0)	117.00 (65.6–168.25)	0.45
Bilirubin (μmol/L)	76.0 (65.0–85.0)	78.0 (74.75–148.00)	0.17
Na (mmol/L)	131.0 (130.0–134.0)	131.5 (129.250–134.25)	0.84
CTP (points)	14.0 (8.0–16.2)	8.0 (8.0–12.5)	**0.04**
Ascites grade	2.0 (1.0–3.0)	2.5 (2.00–4.0)	0.19
Esophageal varices grade	3.0 (3.0–3.0)	3.0 (2.25–3.0)	0.39

Note: RB, recurrent bleeding; EVL, endoscopic variceal ligation; 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; HVPG, hepatic venous pressure gradient.

analysis model, which is allowed in the construction of this regression model [19, 20].

As shown in Table 2, a hazard ratio (HR) >1.0 was significant for HE grade, HVPG (cat.) and HVPG >14 mmHg, which allows us to consider these factors as having an independent effect on RB risk. HR shows how many times the risk of an outcome changes if the predictor value is changed by one. So, applying it to the

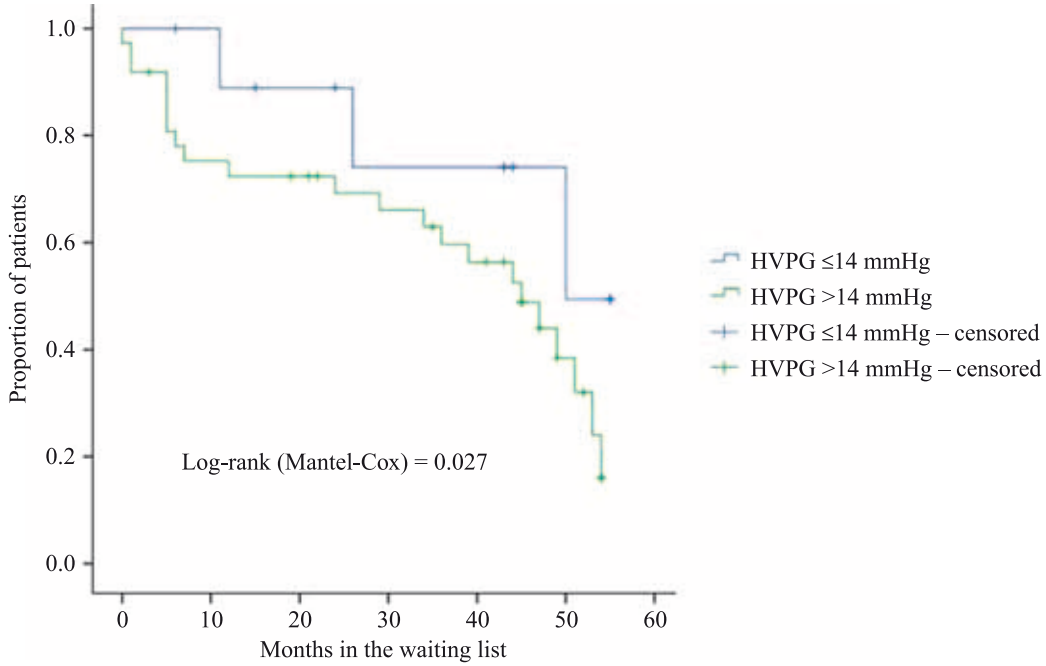

Fig. 1. Proportion of patients without bleeding and with recurrent bleeding after prophylaxis by endoscopic ligation and non-selective beta-blockers, depending on HVPG (Kaplan–Meier method with Log-Rank test)

Table 2

Univariate and multivariate analysis of predictors associated with recurrent bleeding after secondary prophylaxis by a combination of endoscopic variceal ligation and nonselective beta-blockers

Variables	Univariate analysis		Multivariate analysis	
	HR (CI)	p-value	HR (CI)	p value
Age	1.005 (0.966–1.044)	0.82	–	–
Platelets (×10^9/L)	1.002 (0.998–1.007)	0.34	–	–
White blood cells (×10^9/L)	1.086 (0.970–1.300)	0.37	–	–
Plasma albumin (g/L)	1.012 (0.900–1.138)	0.85	–	–
INR	2.045 (0.957–4.369)	0.06	–	–
Bilirubin (μmol/L)	1.002 (0.996–1.007)	0.53	–	–
Creatinine (μmol/L)	1.002 (0.996–1.007)	**0.03**	0.924 (0.929–1.063)	0.85
Na (mmol/L)	1.091 (0.988–1.205)	0.08	–	–
Hemoglobin (g/L)	1.014 (0.921–1.143)	0.79	–	–
MELD-Na (points)	1.236 (1.096–1.394)	**0.01**	1.172 (0.597–2.301)	0.64
CTP (points)	1.312 (1.070–1.234)	**0.003**	1.027 (0.852–1.238)	0.78
Ascites grade	0.651 (0.462–0.919)	0.23	0.591 (0.412–0.848)	**0.004**
Esophageal varices grade	0.780 (0.373–1.631)	0.51	1.362 (0.317–5.847)	0.68
Number of consecutive EVLs	0.881 (0.526–1.473)	**0.04**	0.512 (0.224–1.173)	0.11
HE grade (points)	1.698 (1.192–2.420)	**0.003**	1.800 (1.141–2.841)	**0.012**
mAP (mmHg)	0.989 (0.860–1.019)	0.46	–	–
HVPG (mmHg; cat.)*	1.237 (1.015–1.522)	**0.012**	1.324 (1.050–1.675)	**0.007**
HVPG ≤14 (mmHg)	0.563 (0.312–0.789	**0.007**	0.613 (0.436–0.863)	**0.005**
HVPG >14 (mmHg)	3.563 (3.131–4.075)	**0.009**	3.837 (2.995–4.235	**0.002**

Note: * – variable including two HVPG categories: ≤14 and >14 mmHg. HR, hazard ratio; EVL, endoscopic variceal ligation; 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.

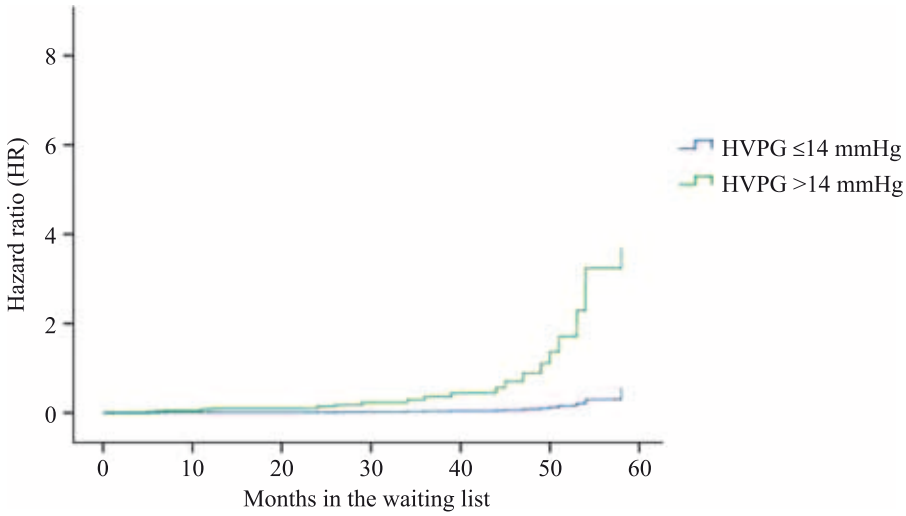

Fig. 2. Hazard ratio (HR) for recurrent bleeding as a function of time and magnitude of the categorical variable (≤14 mmHg; >14 mmHg)

results obtained, we can say that if HE grade increases by one, RB risk increases by 1.8 times, if HVPG increases by 1 mm, RB risk increases by 1.324 times, and if HVPG >14 mmHg, RB risk increases by 3.837 times.

HR <1 was significant for the independent variables: ascites grade and HVPG ≤14 mmHg (0.591 and 0.613, respectively). When HR <1, the effect of these factors was associated with increased survival time, i.e. a factor that reduces RB risk.

The quality of our chosen model of multivariate Cox proportional hazards regression is confirmed by estimating the maximum likelihood (log-likelihood or –2LL). In the SPSS program, this indicator of the model with predictors is compared with the indicator of the base model (without predictors) – Block 0. In our study in the base model (Block 0), the value of –2LL was 283.940, after introducing independent variables (predictors) into the model, –2LL decreased (237.457, Pearson's Chi-square = 57.385) at a significance level of 0.0001. This prevented the acceptance of the null hypothesis, which in fact means that the predictive ability of the multivariate Cox proportional hazards regression analysis model improved when independent predictors were included.

We constructed a correlation matrix to test the condition for multivariate Cox proportional hazards regression analysis (no linear relationship between independent variables, which creates redundancy in the model). The correlations found were very weak (–0.024 to 0.196), or weak (0.196 to 0.435) and of medium strength of expression (0.435 to 0.548), which does not negatively affect application of the model [20].

In multivariate analysis, we plotted the hazard ratio (HR) for different values of the categorical variable HVPG (≤14 mmHg; >14 mmHg) at LT waiting times of up to 60 weeks (Fig. 2).

As shown in Fig. 2, RB risk with HVPG >14 mmHg progressively increases in patients with LT waiting periods after 25 weeks of LT, while it is absent with HVPG ≤14 mmHg, reaching HR = 0.613 at 55 to 60 weeks of LT waiting time.

DISCUSSION

We showed that rebleeding occurred in 39 out of 51 patients (76.5%) who received first-line prophylactic therapy (EVL + NSBB) and were waiting for LT for up to 60 months. Rebleeding occurred early, before 6 weeks, in almost 25% of patients, and earliest, before 1 week, in 7.7% of cases.

We believe that the high frequency of RB in our study is down to several factors. First, as cirrhosis decompensation progresses, EVL has been shown to have no effect on HVPG [7–9]. Secondly, NSBB (propranolol + carvedilol) reduces HVPG in those patients who received prophylactic therapy (propranolol by 10.1% in 23.2% of cases, carvedilol by 18.6% in 27.7% of cases) [10]. Thirdly, administering NSBB without first determining the hemodynamic response to it at high HVPG levels, implies that nonresponders taking these medications may not respond to treatment [21, 22] and that EVL and NSBB combination therapy may be less effective [23].

Our research supported the findings of Ardevol et al. [10], who demonstrated that certain individuals develop early (up to 6-week) RB even while first-line therapy (EVL + NSBB) for up to 46 months provides satisfactory efficacy for secondary rebleeding prophylaxis. However, the incidence of RB within these periods in our study was nearly twice as high as the cited study. Perhaps this difference in the incidence of early recurrent hemorrhage between our study and the study by Ardevol et al. [10] is due to the larger sample of patients included (51 and 369 patients, respectively). This team of researchers

showed a high mortality in EVL + NSBB patients during RB prophylaxis, which is consistent with the study we have published earlier [23].

The high incidence of rebleeding in secondary prophylaxis is due to progression of cirrhosis with increasing disease duration (increasing MELD score, increasing HE and ascites grades, appearance of resistant ascites, bleeding) and increasing severity of clinically significant portal hypertension (CSPH) [18, 24–28].

Indicators such as hemoglobin, creatinine, MELD-Na and CTP scores, the number of consecutive variceal ligations, mean HVPG, and mean HVPG >14 mmHg differed between patients with and without RB. We listed these as likely risk factors for this adverse clinical outcome since the group of RB patients exhibited a substantial change in these parameters when compared to those without RB. According to foreign reports, variceal diameter [29], patient age, duration of the disease (cirrhosis), high CTP score and variceal size are risk factors for RB [3, 30].

When comparing patients with HVPG ≤14 mmHg and HVPG >14 mmHg, we showed that higher HVPG significantly increased the percentage of patients with RB who received first-line therapy prophylaxis. This is consistent with the results of many studies, showing that progressive increase in HVPG and lack of hemodynamic response to propranolol [33] are the most important factors in variceal hemorrhage [7–9, 28, 31] and their recurrences [32, 33].

We found that in both univariate and multivariate analyses, HE severity (grade), HVPG (cat.) and HVPG >14 mmHg were significant independent predictors of RB. Significant independent predictors (MELD-Na, CTP and creatinine level) in univariate analysis showed no significant effect on RB risk in multivariate analysis. It is known that CSPH signs start to appear at HVPG ≥10 mmHg, and that the progressive course of these symptoms correlates with progressive development of decompensation (larger variceal size with the risk of rupture, bleeding, ascites, HE) [28]. HVPG is a prognostic indicator for patients with cirrhosis [4, 7, 28] and is a commonly used predictor of ascites, HE, first bleeding episode and RB [11, 28].

Our findings somewhat agree with those of Yaru et al. [25], who found that HVPG size, HE, ascites, and CTP score are predictive of RB.

We found that RB risk increases 1.324 times when HVPG increases by 1 mm, and that RB risk increases 3.837 times when HVPG >14 mmHg, which is consistent with other reports. Through multivariate analyses using Cox logistic regression analysis, Zhao et al. [34] showed that for every 1 mm increase in HVPG, there is a 1.534-fold increase in the risk of early rebleeding within 6 weeks of the first bleeding episode with HVPG ≥20 mmHg [OR (odds ratio) = 1.534, 95% CI (CI): 1.062–2.216, p = 0.022)].

We have demonstrated that HVPG ≤14 mmHg and ascites severity have no prognostic value in predicting the risk of rebleeding because their respective hazard ratios in multivariate analysis using the Cox regression model is HR <1 (0.591 and 0.613, respectively). It is known that in survival analysis using Cox proportional hazards regression model, HR <1 indicates the impact of these factors, resulting in a decrease in the risk of an adverse event (RB in our instance). In support of these findings, we cite the study by Liu et al. [1] that showed that HVPG <15 mmHg is not a predictor of early RB occurring after the first bleeding episode in patients with ascites. Wu et al. [35] discovered that in patients with HVPG of 14 mmHg, rebleeding did not occur within a year following the initial bleeding episode, while in those with HVPG of 18 mmHg, rebleeding occurred in 23.6% of cases. Moreover, most rebleeding patients had HVPG exceeding 18 mmHg (51.3% vs. 31.0%, p = 0.021 compared to the group without bleeding.

CONCLUSION

Despite prophylaxis with first-line medication (EVL + NSBB) given after the first bleeding episode, RB occurs in up to 60 months of follow-up in 76.5% of patients who have been waiting for LT for several years due to lack of a donor organ. Of the patients, approximately 25% developed early RB within 6 weeks of the initial bleeding episode.

Progressive decompensated cirrhosis, development of CSPH manifested by ascites, HE, progressive increase in variceal size and variceal rupture, and variceal hemorrhage are the causes of RB with a prolonged wait for LT (about 60 months).

Changes in hemoglobin and creatinine levels, MELD-Na and CTP scores, the number of variceal ligations in a row, mean HVPG, and mean HVPG >14 mmHg are risk factors for RB. HVPG >14 mmHg is the primary predictor of RB, increasing the risk for a 1-mm change in gradient value by a factor of 3.837. Higher HE severity is the second independent predictor. RB risk increases with a 1.8-fold increase in HE severity.

Early TIPS procedure (preemptive TIPS) is required for a considerable number of patients with early RB before 6 weeks in order to lower the risk of recurrent bleeding and associated mortality.

The authors declare no conflict of interest.

REFERENCES

1. *Liu L, Nie Y, Liu Q, Zhu X.* A Practical Model for Predicting Esophageal Variceal Rebleeding in Patients with Hepatitis B-Associated Cirrhosis. *Int J Clin Pract*. 2023 Aug 3; 2023: 9701841. doi: 10.1155/2023/9701841.
2. *Garcia-Tsao G, Bosch J.* Varices and Variceal Hemorrhage in Cirrhosis: A New View of an Old Problem.

Clin Gastroenterol Hepatol. 2015; 13: 2109–2117. doi: 10.1016/j.cgh.2015.07.012.

3. *Asghar S, Mustafa J, Rehman HU, Farooq MK, Waheed MU, Shahid S.* Predictors Of Re-Bleeding After Oesophageal Variceal Banding In Cirrhotic Patients At 4 Weeks. *J Ayub Med Coll Abbottabad*. 2023 Feb-Mar; 35 (1): 99–103. PMID: 36849386.
4. *Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J.* Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology.* 2017; 65: 310–335. doi: 10.1002/hep.28906.
5. *Lv Y, Qi X, He C, Wang Z, Yin Z, Niu J et al*. PVT-TIPS Study Group. Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial. *Gut.* 2018 Dec; 67 (12): 2156–2168. doi: 10.1136/gutjnl-2017-314634.
6. *Islam M.* What is the difference between predictor and risk factor in Epidemiological Study? Retrieved from: https://www.researchgate.net/post/What-is-the-difference-between-predictor-and-risk-factor-in-Epidemiological-Study/582199ab96b7e45bff5c4489/citation/download.
7. *Moitinho E, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J.* Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology.* 1999 Sep; 117 (3): 626–631. doi: 10.1016/s0016-5085(99)70455-5.
8. *Abraldes JG, Villanueva C, Bañares R, Aracil C, Catalina MV, Garci A-Pagán JC, Bosch J.* Spanish Cooperative Group for Portal Hypertension and Variceal Bleeding. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. *J Hepatol.* 2008 Feb; 48 (2): 229–236. doi: 10.1016/j.jhep.2007.10.008.
9. *Ripoll C, Bañares R, Rincón D, Catalina MV, Lo Iacono O, Salcedo M et al*. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. *Hepatology*. 2005 Oct; 42 (4): 793–801. doi: 10.1002/hep.20871.
10. *Ardevol A, Alvarado-Tapias E, Garcia-Guix M, Brujats A, Gonzalez L, Hernández-Gea V et al*. Early rebleeding increases mortality of variceal bleeders on secondary prophylaxis with β-blockers and ligation. *Dig Liver Dis.* 2020 Sep; 52 (9): 1017–1025. doi: 10.1016/j.dld.2020.06.005.
11. *De Franchis R.* Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015; 63: 743–752. doi: 10.1016/j.jhep.2015.05.022.
12. Esophageal Varices. Practice Guideline of World Gastroenterology Organisation. Available from: https://www.worldgastroenterology.org/UserFiles/file/guidelines/esophageal-varices-russian-2014.pdf.
13. *Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F et al.* The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology*. 2003; 38 (1): 258–266. doi: 10.1053/jhep.2003.50315.
14. *Gantzel RH, Aagaard NK, Vilstrup H, Watson H, Grønbaek H, Jepsen P.* Development and validation of the Cirrhotic Ascites Severity model-A patient-reported outcome-based model to predict 1-year mortality. *Hepatol Commun.* 2022 Nov; 6 (11): 3175–3185. doi: 10.1002/hep4.2065.
15. *Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD et al.* Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology.* 2014; 60 (2): 715–735. doi: 10.1002/hep.27210.
16. *DeMers D, Wachs D.* Physiology, Mean Arterial Pressure. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538226.
17. *Khubutiya MSh, Voskanyan SE, Syutkin VE, Chulanov VP, Novruzbekov MS, Pasechnikov VD et al.* Recommendations for the prevention and treatment of hepatitis B and C infection in patients on the waiting list for liver transplantation and in liver transplant recipients. *Transplantologiya. The Russian Journal of Transplantation*. 2020; 12 (3): 231–244. [In Russ, English abstract]. doi: 10.23873/2074-0506-2020-12-3-231-244.
18. *De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C.* Baveno VII Faculty. Baveno VII – Renewing consensus in portal hypertension. *J Hepatol.* 2022; 76 (4): 959–974. doi: 10.1016/j.jhep.2021.12.022.
19. *Hosmer DW Jr, Lemeshow S, May S.* Applied Survival Analysis: Regression Modeling of Time-to-Event Data, Second Edition. New York: *John Wiley & Sons*, 2008; 416. doi: 10.1002/9780470258019.fmatter.
20. *Sharashova EE, Kholmatova KK, Gorbatova MA, Grjibovski AM.* Cox regression in health sciences using SPSS software. *Nauka i zdravookhranenie* [Science & Healthcare]. 2017; (6): 5–27.
21. *Sinagra E, Perricone G, D'Amico M, Tinè F, D'Amico G.* Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther.* 2014 Mar; 39 (6): 557–568. doi: 10.1111/apt.12634.
22. *Hofer BS, Simbrunner B, Bauer DJM, Paternostro R, Schwabl P, Scheiner B et al.* Acute hemodynamic response to propranolol predicts bleeding and nonbleeding decompensation in patients with cirrhosis. *Hepatol Commun.* 2022 Sep; 6 (9): 2569–2580. doi: 10.1002/hep4.2021.
23. *Korobka VL, Pasetchnikov VD, Korobka RV, Pak ES, Shapovalov AM.* Use of endoscopic band ligation alone and in combination with nonselective beta blockers for prevention of variceal bleeding in ascites patients on the liver transplant waiting list. *Russian Journal of Transplantology and Artificial Organs.* 2022; 24 (3): 42–50. doi: 10.15825/1995-1191-2022-3-42-50.
24. *Hunter SS, Hamdy S.* Predictors of early re-bleeding and mortality after acute variceal haemorrhage. *Arab J*

Gastroenterol. 2013 Jun; 14 (2): 63–67. doi: 10.1016/j.ajg.2013.05.001.

25. *Yaru H, Mei Z, Kaixin L, Ruyue C, Mingshu L.* Predictive factors for re-bleeding of esophageal varices in hospitalized patients. *Cell Mol Biol* (Noisy-le-grand). 2022 Feb 28; 68 (2): 183–188. doi: 10.14715/cmb/2022.68.2.26.
26. *Pfisterer N, Dexheimer C, Fuchs EM, Bucsics T, Schwabl P, Mandorfer M et al.* Betablockers do not increase efficacy of band ligation in primary prophylaxis but they improve survival in secondary prophylaxis of variceal bleeding. *Aliment Pharmacol Ther.* 2018 Apr; 47 (7): 966–979. doi: 10.1111/apt.14485.
27. *Teng D, Zuo H, Liu L, Dong J, Ding L.* Long-term clinical outcomes in patients with viral hepatitis related liver cirrhosis after transjugular intrahepatic portosystemic shunt treatment. *Virol J.* 2018 Oct 1; 15 (1): 151. doi: 10.1186/s12985-018-1067-7.
28. *Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R et al.* Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology.* 2007 Aug; 133 (2): 481–488. doi: 10.1053/j.gastro.2007.05.024.
29. *Irisawa A, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H et al.* Endoscopic recurrence of esophageal varices is associated with the specific EUS abnormalities: severe periesophageal collateral veins and large perforating veins. *Gastrointest Endosc.* 2001 Jan; 53 (1): 77–84. doi: 10.1067/mge.2001.108479.
30. *Zhang YH, Hu B.* Future directions of noninvasive prediction of esophageal variceal bleeding: No worry about the present computed tomography inefficiency. *World J Gastrointest Endosc.* 2024 Mar 16; 16 (3): 108–111. doi: 10.4253/wjge.v16.i3.108.
31. *Martino A, Amitrano L, Guardascione M, Di Serafino M, Bennato R, Martino R et al.* The role of computed tomography for the prediction of esophageal variceal bleeding: Current status and future perspectives. *World J Gastrointest Endosc.* 2023 Dec 16; 15 (12): 681–689. doi: 10.4253/wjge.v15.i12.681.
32. *Merkel C, Montagnese S.* Should we routinely measure portal pressure in patients with cirrhosis, using hepatic venous pressure gradient (HVPG) as guidance for prophylaxis and treatment of bleeding and re-bleeding? Yes! *Eur J Intern Med.* 2011 Feb; 22 (1): 1–4. doi: 10.1016/j.ejim.2010.08.009.
33. *La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, García-Pagán JC, Bosch J.* Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol.* 2009 Aug; 51 (2): 279–287. Epub 2009 May 24. doi: 10.1016/j.jhep.2009.04.015.
34. *Zhao JR, Wang GC, Hu JH, Zhang CQ.* Risk factors for early rebleeding and mortality in acute variceal hemorrhage. *World J Gastroenterol.* 2014 Dec 21; 20 (47): 17941–17948. doi: 10.3748/wjg.v20.i47.17941.
35. *Wu L, Fang QQ, Huang XQ, Xue CY, Rao CY, Luo JJ et al.* Risk factors associated with failure of endoscopic combined treatment to prevent varices rebleeding in patients with liver cirrhosis. *Expert Rev Gastroenterol Hepatol.* 2023 Mar; 17 (3): 301–308. doi: 10.1080/17474124.2023.2181787.

The article was submitted to the journal on 18.04.2024