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Non-invasive predictors of the first episode of bleeding from esophageal varices in patients with liver cirrhosis awaiting transplantation

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Abstract

Background. *To date, various non-invasive techniques or tests have been proposed that can identify a high risk of bleeding from esophageal varices. Despite a significant number of studies revealing the presence of venous varices as a likely factor for the development of bleeding due to their rupture, data on predictors of the first episode of bleeding are few and often contradictory.*

Objective. *To determine non-invasive independent predictors of the first episode of bleeding in patients waiting for liver transplantation.*

Material and methods. *A comparative retrospective study was conducted in 729 patients with decompensated cirrhosis who were on the waiting*

list for liver transplantation. We analyzed demographic, clinical and laboratory parameters, MELD-Na, Child-Turcotte-Pugh scores, FIB-4 Index, APRI, AST/ALT ratio; we determined the liver stiffness, spleen diameter, studied the liver stiffness-spleen diameter to platelet ratio risk score (LSPS model), platelet count/spleen diameter ratio in the groups of patients with the first episode of bleeding (n=334) and without ***it*** *(n=395). The accumulated risks in the compared groups were assessed using a model of proportional hazards (Cox regression) in univariate and multivariate analysis.*

Results. *During 48 months of follow-up from the time of patient placement on the liver transplant waiting list, primary bleeding events developed in 45.8%. The risk of developing the first episode of bleeding progressively increased with LSPS ≥3.5 and reached maximum values in patients awaiting liver transplantation within 48 months of inclusion in the waiting list, while with LSPS <3.5, the risk was minimal.*

Conclusion. *Independent non-invasive predictors of the first episode of bleeding are a high level of AST, a high fibrosis index (FIB-4), a decrease in the ratio of platelet count/spleen diameter and a high LSPS value. Their application in clinical practice will improve the results of dispensary and screening examinations of patients with portal hypertension.*

Keywords: liver transplantation, first episode of esophageal varix bleeding, non-invasive predictors

Conflict of interests Authors declare no conflict of interest

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CI, confidence interval
EGDS, esophagogastroduodenoscopy
EV, esophageal varix
HR, hazard ratio
HVPG, hepatic venous pressure gradient
LC, liver cirrhosis
LS, liver stiffness
LTWL, liver transplant waiting list
PH, portal hypertension
RB, recurrent bleeding
SS, spleen stiffness
VVE, varicose vein of the esophagus

Introduction

Portal hypertension (PH) is a consequence of the liver cirrhosis (LC) progression and leads to the development of esophageal varices (EVs), which formation is associated with the development of portosystemic venous collaterals [1, 2]. The EV development is one of PH complications, the PH being caused by increased resistance of the liver vessels in relation to the progression of fibrosis and liver regeneration nodes [3]. Bleeding from esophageal varices (EVs) is one of the most life-threatening PH complications, accelerating the liver decompensation progression to the stage when patients have an extremely high mortality risk [4, 5]. Current guidelines for the management of patients with PH recommend screening by esophagogastroduodenoscopy (EGDS) with subsequent preventive measures in order to identify patients with EVs and a high risk of their rupture and subsequent bleeding [1, 6, 7].

However, since the prevalence of bleeding from varices ranges from 15% to 25%, in most patients, the screening EGDS either does not detect varices or detects varices that do not require prophylactic therapy [8]. Experience shows that routine endoscopic screening is ineffective, since

varices that require prophylactic measures against bleeding are detected in less than 50% of all cirrhotic patients [9].

Therefore, routine endoscopic screening of all LC patients, especially those belonging to the so-called “low-risk group for bleeding,” may unnecessarily increase the financial and medical burden on endoscopy departments. In addition, the use of endoscopy as a screening procedure may be associated with the risk of complications since the patients have to undergo an invasive endoscopic procedure repeatedly.

Therefore, predicting the presence of EVs by using non-endoscopic, non-invasive markers would be appropriate for identifying patients at high risk of developing bleeding from EVs and might significantly reduce the number of unnecessary endoscopies [10].

To date, various noninvasive methods or tests have been proposed to predict the presence or absence of varices; these tools that can identify a high risk of developing bleeding from varices. These include the MELD-Na score, the AST/ALT ratio (AAR), the fibrosis index-4 (FIB-4), determination of liver stiffness (LS) by transient elastography (TE), a combinatorial index (platelet count and LS level), spleen diameter, spleen stiffness (SS), the platelet count/spleen diameter ratio, the AST to platelet count ratio index (APRI), and the liver stiffness-spleen diameter to platelet ratio risk score (LSPS) [11–19].

Despite a significant number of studies identifying the EV presence as a probable factor for the development of bleeding resulting from their rupture, the available data on predictors of the first bleeding episode are few and often contradictory [20, 21]. Thus, according to C. Cifci and N. Ekmen [22], FIB-4 can be considered as a significant predictor of the first episode of bleeding, while B. Kraja et al. [21] found that index as having low significance in predicting bleeding from varices.

Probably, such inconsistency in the conclusions about the suitability of certain non-invasive methods or biochemical parameters for predicting the first bleeding episode is associated with the different number of patients in these studies, as well as the different etiology of LC [11, 13, 14, 23, 24].

Our objective was to identify noninvasive independent predictors of first bleeding episode in patients on the liver transplant waiting list.

Material and methods

A comparative retrospective study was conducted in 729 patients with decompensated LC who were on the liver transplant waiting list (LTWL).

The group I consisted of 334 patients who developed the first episode of bleeding from the varices during their stay in the Rostov Regional Clinical Hospital (45.8%), the group II consisted of 395 patients who did not develop bleeding (54.2%). The study was approved by the local Ethics Committee of the Center for Surgery and Donation Coordination at the Rostov Regional Clinical Hospital (Protocol No. 81 dated 14.05.2024). Subsequent analysis included demographic, clinical and laboratory parameters, as well as using the scoring systems MELD-Na, FIB-4, APRI, AAR, and estimating the liver disease severity up to Child-Turcotte-Pugh (CTP) classification. To calculate the FIB-4 score, the following formula was used: Age (years) x AST (U/L) / [platelet count (10^9/L) x √ALT (U/L)]. The FIB-4 was calculated by using the online calculator available at: https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis
To calculate the APRI, the following formula was used: AST (U/L) / upper limit of normal AST (U/L) × 100/platelet count (10^9/L). The score

by APRI was calculated using the online calculator available at: https://www.mdcalc.com/calc/3094/ast-platelet-ratio-index-apri .

To assess the LS, a FibroScan liver elastography device (Echosens, France) was used; the results were expressed in kPa. Quantitative parameters (liver and spleen size), characteristics of the liver and spleen condition were studied by ultrasound examinations. The spleen diameter was measured in cm, the LSPS index was calculated using the formula: LS (kPa) × spleen diameter (cm) / platelet count (10^9/L). The ratio was calculated as follows: platelet count (10^9/L) / spleen diameter (cm).

Statistical analysis of the obtained data was performed using the SPSS Statistics software package, version 23 (IBM, USA). The Kolmogorov–Smirnov test and the significance level of the Lilliefors test made it possible to determine the distribution type for the obtained variables of the studied samples. The normal distribution type of the variables implied the calculation of arithmetic means (M) and the determination of the standard deviation (SD), and the significance of differences between the compared values was determined by Student's t-test, using the significance threshold ($p<0.05$). For the variables, which distirbution was different from normal, the statistical analysis was performed by determining the median (Me) and interquartile range (interval between the 25^{th} and 75^{th} percentiles). To determine the significance of differences when conducting paired comparisons of dependent variables, the Wilcoxon test recommended in nonparametric analysis was used. When comparing independent variables, the Pearson's χ^2 calculation was used. Variables were compared by the Mann-Whitney test (U-test) calculations.

To predict the risk of the first bleeding episode in patients awaiting liver transplantation (LT), we used the survival analysis or "time-to-event survival" used in biomedical research to predict any other outcomes

relative to the time of their occurrence, including the development of death, the disease relapse, recovery, etc. [25]. A comparative assessment of the accumulated risks in the groups was made using the construction of a mathematical model of proportional risks (Cox regression) with univariate and multivariate analysis. The risk of the occurrence of the event being tested (hazard ratio (HR)) was calculated with the determining the 95% confidence interval (95% CI) for this parameter.

When using a univariate analysis, a model with one independent variable was created with the calculation of the HR, 95% CI with assessing the significance of the impact of each putative predictor on the development of the first bleeding episode. Multivariate analysis involved the creation of a model designed to assess the independent contribution of several predictors simultaneously with the determination of the significance of their impact on the development of the first bleeding episode. This analysis was performed by sequential (stepwise) exclusion of variables. The multivariate analysis model included all statistically significant predictors determined by univariate analysis (taking into account each predictor separately), as well as known risk factors for bleeding, regardless of their impact in the univariate analysis, which is an acceptable approach when constructing this regression model [25, 26].

The quality of the model used was determined by the maximum likelihood index (log-likelihood, -2LL). The condition for conducting multivariate Cox proportional hazards regression analysis (absence of a linear relationship between independent variables that creates redundancy in the model) was checked by constructing a correlation matrix.

Results

Demographic, clinical, laboratory data, scores by the assessment tolls (MELD-Na, CTP, FIB-4, APRI, AAR), as well as LS, the spleen

diameter, platelet count/spleen diameter ratio, and LSPS score in groups of patients with the first episode of bleeding (group I) and without it (group II) are presented in Table 1.

Table 1. Comparative characteristics of patient data between groups I and II (normal distribution and distribution different from normal)

Parameter	Group I (n=334) M±SD	Group II (n=395) M±SD	p
Normal distribution (M±SD)			
Age, years	49.71±10.67	50.71±10.65	0.205
Leukocyte count, $x10^9$ /L	3.93±1.50	3.95±1.68	0.811
Plasma albumin, g/L	29.06±3.75	29.19±3.89	0.643
Serum creatinine, μmol/L	114.06±26.73	112.99±26.57	0.589
International Normalized Ratio	1.93±0.35	1,94 ±0,41	0.778
MELD-Na, score	22.06±3.63	22.01±3.80	0.874
Distribution different from normal Me (IQR)			
Platelet count, $x10^9$ /L	75.0 (52.0;101.0)	87.0 0 (58.0;115.0)	**0.001***
Bilirubin, μmol/L	68.0 (56.25; 86.0)	76, 0 (64.5;79.5)	0.517
Na, mmol/L	135.0 (132.0;138.0)	136.0 (133.00;138.0)	0.083
CTP, score	14.0 (11.0;15.0)	13.0 (11.0;14.0)	0.509
LS, kPa	32.4 (27.6;37.6)	31.5 (26.7;36.2)	0.116
ALT, U/L	64.0 (37.0;88.05)	65.0 (39.0;93.0)	0.154
AST, U/L	88.0 (60.0;122.0)	78.0 (52.0;108.0)	**0.006***
AAR	1.33 (1.10;1.80)	1,275 (1,078;1,653)	0.127
APRI	2.37 (1.58;4.09)	2.11 (1.31;3.67)	**0.034***
FIB-4	6.69 (4.68;10.09)	6.11 (4.08;9.41)	**0.030***
Spleen diameter, cm	15.15 (13.2;17.5)	14.8 (13.0;16.50)	0.256
Platelet count, $x10^9$/L/spleen diameter, cm	494.0 (333.0;754.0)	674.0 (426.25;947.75)	**0.001***
LSPS	18.6 (11.2;29.8)	17.9 (11.2;27.40)	0.493

Note: MELD-Na, Model for End-stage Liver Disease-Na, CTP, Child-Turcotte-Pugh; LS, liver stiffness; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio; APRI, aspartate aminotransferase-to-platelet ratio Index; FIB-4, Fibrosis-4; LSPS, liver stiffness-spleen diameter to platelet ratio score; * Significant differences at $p<0.05$.

As can be seen from the presented Table 1, significant differences between the compared groups were achieved in the platelet count, CTP, APRI, FIB-4, and platelet count/spleen diameter ratio.

The results of the univariate and multivariate analyses of the mathematical regression model of Cox proportional hazards are presented in Table 2.

All independent variables (predictors) that significantly influenced the development of the first bleeding episode in the univariate analysis are presented in Table 2 (the columns entitled *Univariate analysis)*.

Table 2. Univariate and multivariate analysis of predictors associated with the development of the first episode of bleeding in patients awaiting liver transplantation

Variables	Univariate analysis		Multivariate analysis	
	HR [95%CI]	p	HR [95%CI]	p
Age, years	0.992 [0.981–1.002]	0.115	—	—
Platelet count, x10^9/L	0.994 [0.991–0.997]	**0.0001**	—	—
23.1>LS≥23.1, kPa	1.011 [0.998–1.024]	0.095	1.384 [0.960–1.995]	0.081
ALT, U/L	0.998 [0.996–1.00]	**0.026**	—	—
AST, U/L	0.998 [0.996–1.00]	**0.013**	0.997 [0.995–0.999]	**0.011**
AAR	0.977 [0.851–1.121]	0.740	—	—
APRI	1.014 [0.989–1.039]	0.277	—	—
FIB-4	1.091 [0.996–1.021]	0.175	1.022 [1.001–1.041]	**0.020**
Spleen diameter, cm	0.999 [0.983–1.05]	0.881	—	—
Platelet count, 10^9/L/spleen diameter, cm	0.999 [0.999–1.000]	**0.0001**	0.998 [0.996–1.000]	**0,0001**
3.5>LSPS≥3.5	1.002 [0.996–1.007]	0.590	3.666 [1.065–12.62]	**0.039**

As can be seen from Table 2, a univariate analysis of the mathematical regression model of Cox proportional hazards identified the following independent variables that significantly influenced the development of the first bleeding episode: platelet count, ALT activity, AST activity, and the platelet count/spleen diameter ratio.

The column entitled *Multivariate analysis* in Table 2 shows the impact of all simultaneously significant predictors on the development of the first bleeding episode in a multivariate analysis.

At the last step of the Cox proportional hazards regression model, in multivariate analysis using the stepwise elimination of variables, we identified the independent variables that significantly influenced the development of the first bleeding episode, which turned out to be the AST activity, FIB-4, the platelet count/spleen diameter ration, and the LSPS grade 3.5>LSPS≥3.

As shown in Table 2, the hazard ratio (HR)>1.0 was significant for FIB-4 and 3.5>LSPS≥3.5, which prompted to consider these factors as having an independent effect on the risk of developing a first bleeding episode.

Probable significant independent predictors of the first bleeding episode also include increased AST activity and decreased platelet/spleen diameter ratio. For these parameters, HR values were close to 1 (0.997 CI [0.995–0.999] and 0.999 CI [0.999–1.000], respectively).

The quality of the selected model of the multivariate Cox proportional hazards regression analysis was proven by the assessment of the -2LL parameter. In comparison with the parameter of the basic model (Block 0), the -2LL was 3748.377; at the last step of sequential exclusion of independent variables (predictors), the -2LL decreased (3798.709, Pearson χ^2=36.188) at a significance level of 0.0001. This analysis allows us to reject the null hypothesis, which in fact means an improvement in the predictive ability of the multivariate Cox proportional hazards regression model with independent predictors included in it.

To check the condition (absence of a linear relationship between independent variables, which creates redundancy in the multivariate Cox proportional hazards regression model), we constructed a correlation

matrix. The identified correlations were very weak (from 0.001 to 0.038), weak (from 0.039 to 0.353), and moderate (0.353 to 0.586), which does not negatively affect the model use [25].

In a multivariate analysis, a graph of the risks for developing a first bleeding episode was constructed for different values of the categorical variable 3.5>LSPS≥3.5 (Fig.).

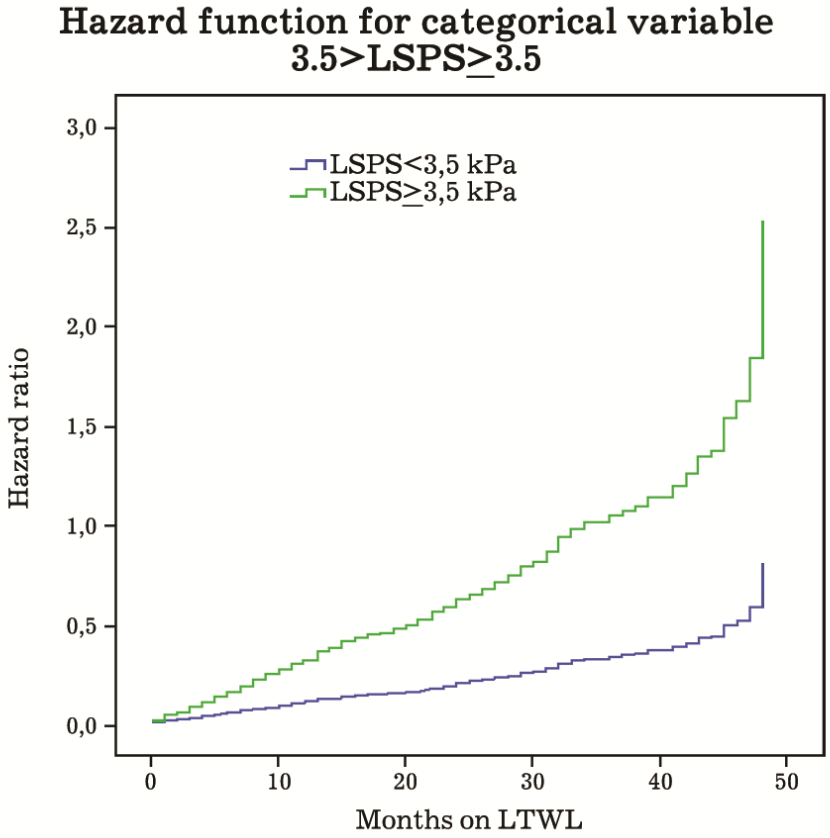

Figure. Hazard ratio for the development of recurrent bleeding with regard to time, and the value of the categorical variable 3.5>LSPS≥3.5

As can be seen from the figure, the risk of developing the first episode with LSPS≥3.5 progressively increases and reaches maximum values (HR=2.521) in patients awaiting LT within 48 months, while with LSPS<3.5 it is minimal, reaching HR=0.774 within the same time frame.

Discussion

Liver cirrhosis is the cause of increased patient mortality worldwide [27]. The increase in the number of patients requiring liver transplantation on the one hand, and the relative shortage of donor organs on the other, increase the waiting time for this surgery [28, 29].

An increase in the waiting time for LT determines the risk of developing PH complications, the variceal bleeding being among the most common of them [4, 5]. PH is a progression of LC, causing the development of complications, including bleeding from esophageal varices, which increases patient mortality [30–33]. The annual prevalence of first bleeding episodes in patients with EVs is 5–15%, and in more than 15% of cases they result in patient death [33, 34]. Despite advances in the diagnosis and treatment of bleeding from varices, mortality related to the first episode of bleeding remains very high [35] even if bleeding is controlled, since the patients remain at a high risk of repeated bleeding (RB). Mortality associated with RB is as high as that due to the first episode of bleeding [36].

As is known, the hepatic venous pressure gradient (HVPG) is the most reliable of all existing predictors of variceal bleeding [37]. In case of reaching the value of HVPG ≥12 mm Hg in patients with PH, there is a risk of bleeding, and, conversely, if the value of HVPG is <12 mm Hg, or it decreases by more than 20% from the baseline level as a result of the therapy effect, the risk of bleeding is significantly reduced [37, 38]. However, since HVPG measurement is an invasive procedure, its determination is not quite suitable in routine clinical examination in most patients. The second important predictor of possible variceal bleeding is the size of varix as measured during endoscopic screening, which is included in current guidelines for patients with cirrhosis [1]. It is known that the varix size more than 5 mm, and red stripes on the varices

visualized at EGDS are considered as predictors of a high risk of variceal bleeding, although they are seen in only 30% of patients with developed bleeding and the above mentioned EGDS signs [39]. When comparing the results of endoscopic screening and HVPG measurement in the same patients with PH, a highly significant correlation between these parameters was seen [40]. The disadvantages of EGDS screening include a low detection frequency of patients with a risk of variceal rupture (30-50%), invasiveness, and discomfort that develops in patients who have undergone this procedure [9]. Thus, endoscopic screening as an independent method does not allow for the full identification of patients with a high risk of developing the first episode of bleeding from varices.

To date, several non-endoscopic and non-invasive methods and markers have been proposed for the purpose of screening EVs with a high risk of bleeding and identifying predictors of the first bleeding episode [12–21, 41].

We identified noninvasive predictors of the first bleeding episode: high AST level, high fibrosis index (FIB-4), decreased platelet/spleen diameter ratio, and high LSPS grade.

We should note that the significance of a particular predictor or their combination is most likely associated with the time spent in the LTWL, i.e. the time of ongoing LC decompensation and PH progression. In our study, the identification of the above-mentioned predictors of the first bleeding episode was determined by a fairly long waiting period for LT – up to 48 months. In terms of its results (the use of a non-invasive predictor for the purpose of predicting the risk of bleeding), the close to ours is the study by G.L. Wong et al. [41] who showed that during the observation period of 41.3±12.6 months, the SS parameter measured by the transient elastography turned out to be a significant predictor of the first episode of bleeding. The parameters interrelated with SS are the

platelet count/spleen diameter ratio and the LSPS score, since their calculation uses the spleen diameter, which correlates with the SS. A significant correlation was established between the SS and LSPS, SS and the platelet count/spleen diameter ratio in patients with large EVs and the first episode of bleeding [42]. Interestingly, in the same study, a high correlation was established between the HVPG and the SS in predicting large EVs and the likelihood of bleeding.

Another predictor of large EV with the likelihood of developing the first episode of bleeding may be the viral etiology of LC. The viral LC rate in the above-cited study by G.L. Wong et al. [41] was about 85%.

Another study showed significant predictors of the large-sized EV formation, they were a high LS, decreased platelet count/spleen diameter ratio, increased spleen diameter, high fibrosis index FIB-4 score in patients with HCV-associated LC [42].

In patients with HBV-associated cirrhosis, the LSPS exceeding or equal to 6.5 was a significant predictor of the first bleeding episode [43]. These data are very close in their conclusion to our study results, which showed a significant increase in the risk of the first bleeding development if LSPS≥3.5.

Conclusions

1. The development of the first episode of bleeding from esophageal varices was noted in 45.8% of patients during the first 48 months after patients had been placed on the liver transplant waiting list.

2. Independent significant predictors of the first episode of bleeding development are: high aspartic transaminase level, high fibrosis (FIB-4) score, decreased platelet count/spleen diameter ratio and high LSPS (Liver stiffness-spleen diameter to platelet ratio score).

3. The risk of developing the first bleeding episode progressively increases with LSPS≥3.5 and reaches its maximum in patients awaiting liver transplantation within 48 months from the time of inclusion on the waiting list, while with LSPS<3.5 mmHg it is minimal over the same observation period.

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