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Article

Causes for the absence of thrombocytopenia in patients with liver cirrhosis and portal vein thrombosis: A case-control study

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Background: Complications of liver cirrhosis (LC), such as thrombocytopenia and portal vein thrombosis (PVT), have similar pathophysiology. However, the association between PVT and platelet count in LC patients is contradictory.

Aim: To assess factors affecting the platelet count in patients with LC and PVT.

Materials and methods: This was a retrospective case-control study. The cases were 114 patients with LC of various etiologies and newly diagnosed PVT unrelated to invasive hepatocellular carcinoma. From the database of LC patients without PVT, 228 controls were randomly selected with stratification by gender, age and etiology of cirrhosis. The patients from both groups were divided into subgroups with thrombocytopenia (< 150 × 10^9/L) and without thrombocytopenia (≥ 150 × 10^9/L). We analyzed the LC etiology, portal hypertension severity (ascites, hepatic encephalopathy, gastroesophageal varices and associated bleedings, the spleen length, and portal vein diameter), laboratory parameters (white blood cell counts, neutrophils, lymphocytes, hemoglobin levels, total protein, albumin, total bilirubin, fibrinogen, neutrophil-to-lymphocyte ratio, and prothrombin); also, the rates of newly diagnosed malignant tumors was assessed. The statistical analysis included calculation of odds ratios (OR) and 95% confidence intervals (CI), logistic regression models with assessment of the model accuracy, and the area under the ROC curve (AUC).

Results: There were no differences in the severity of thrombocytopenia between the case and control groups: thrombocytopenia was severe in 15.8% (18 patients) vs 13.6% (31 patients, p = 0.586); moderate, in 41.2% (47 patients) vs 46.1% (105 patients, p = 0.398) and mild, in 31.6% (36 patients) vs 24.5% (56 patients, p = 0.168). The proportion of the patients without thrombocytopenia was 11.4% (13 patients) in the case group and 15.8% (36 patients) in the control group, with the between-group difference being non-significant (p = 0.276). In the subgroups of patients without thrombocytopenia (both in the cases and in the controls), the proportion alcoholic etiology of LC, white blood cells counts, neutrophils, lymphocytes, and fibrinogen concentrations were significantly higher (p < 0.05) than in those with thrombocytopenia. The model based on the outcome "absence of thrombocytopenia" included white blood cells counts, hemoglobin and albumin levels, the presence of newly diagnosed malignant tumors in the case group (model accuracy 90.4%, AUC 0.873), and neutrophil counts and spleen length in the control group (model accuracy 86.4%, AUC 0.855). In the patients with PVT and platelet counts of ≥ 150 × 10^9/L, the OR for all newly diagnosed malignant tumors was 26.3 (95% CI 7.37–93.97, p < 0.0001), for newly diagnosed hepatocellular carcinoma without portal vein invasion 17.42 (95% CI 4.84–62.65, p < 0.0001).

Conclusion: In LC patients, the prevalence and severity of thrombocytopenia are not different depending on the PVT presence or absence. The absence of thrombocytopenia in PVT patients is associated with a higher risk of malignant tumors identification, primarily that of hepatocellular carcinoma.

Key words: portal hypertension, portal vein, platelets, hepatocellular carcinoma, spleen length, model accuracy, logistic regression

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Liver cirrhosis (LC) is complicated by thrombocytopenia in 56-78% of patients and by portal vein thrombosis (PVT) in 25% of patients [1, 2]. In most cases, thrombocytopenia is mild or moderate [1, 3]. An increase in the splenic macrophage phagocytic activity due to portal hypertension is a key factor in the pathophysiology of thrombocytopenia in LC patients [3-5]. It is well known that thrombopoietin (TPO) and interleukins (IL), IL-3, IL-6, IL-11, in particular, are involved in the regulation of platelet formation. TPO is the main thrombopoietic factor synthesized in the liver. With a decrease in the liver synthetic function, TPO deficiency occurs contributing to thrombocytopenia [1, 6]. Myelosuppression due to the use of antiviral agents, direct toxicity of alcohol, and platelet destruction by antiplatelet antibodies also can contribute to thrombocytopenia [7].

PVT is a complication of LC, with its frequency depending on the degree of decrease in the synthetic liver function. Thus, the rates of PVT in cirrhotic patients with Child-Pugh class B/C are 2 to 3-fold higher than in patients with class A [8, 9]. Severe portal hypertension is another risk factor for PVT and is characterized by a reduced blood flow velocity in the portal vein (PV), formation of portosystemic collaterals, including gastroesophageal varices and associated bleedings, as well as ascites [10, 11]. Low-grade inflammation, which has been studied in the recent years, is another risk factor for PVT in LC patients. It is promoted by proinflammatory mediators (C-reactive protein, IL-1β, IL-6, and tumor necrosis factor-α); their high levels are related to increased intestinal permeability and disruption of the gut microbiome due to portal hypertension, as well as to the appearance of malignancies, most often hepatocellular carcinoma (HCC) [10, 12].

Thus, PVT and thrombocytopenia in cirrhotic patients have common pathogenetic mechanisms, such as the reduction of synthetic liver function and portal hypertension [8]. However, data on the relationship between PVT and platelet count in these patients is equivocal, since some studies have identified an association of PVT with a low platelet count, while others have not [11, 13-15]. Despite the presence of thrombocytopenia in patients with LC and PVT, the platelet prothrombotic potential may be increased, as evidenced by altered platelet indices [16]. The use of these indices in real-world clinical practice is still limited.

Several studies have shown that one in five cirrhotic patients have no thrombocytopenia [6, 17, 18]. This may be due to both preserved synthetic liver function and minimal portal hypertension, and factors causing a reactive increase in platelets in infectious and inflammatory disorders and malignancies [19]. We were unable to find relevant studies on the factors that affect platelet counts in patients with LC and PVT.

The aim of our study was to assess factors affecting the platelet count in patients with LC and PVT.

Materials and methods

Study design

This was a retrospective case-control study, approved by the Local Ethics Committee of Sechenov University (11.11.2020, ref: 31-20).

An electronic database of pseudonymized medical data of LC patients from our previous research was used for this study [10]. The database was corrected, extended, and included information from source medical documentation of 1752 patients diagnosed with liver cirrhosis who were followed up in the Vasilenko Clinic of Propedeutics of Internal Disease, Gastroenterology and Hepatology from

January 1, 2011 to December 31, 2021. The diagnosis of cirrhosis was based on clinical, laboratory and instrumental assessments, as well as morphological studies of the liver.

All patients included in the database signed an informed consent to the use of their pseudonymized medical health data, the results of examination and treatment, and other results of clinical practice for research purposes, including the creation of electronic databases of pseudonymized medical data and the publication of studies conducted with these databases.

The study inclusion, non-inclusion and exclusion criteria are presented in Fig. 1. The study included patients above 18 years of age with an established diagnosis of liver cirrhosis and clinically significant portal hypertension: gastroesophageal varices and/or ascites [20]. All patients with ascites as the only manifestation of portal hypertension had a serum-ascites albumin gradient of ≥ 1.1 g/dL and ascitic protein concentration of < 2.5 g/dL.

Patients with current and past conditions/diseases that may lead to reactive platelet count abnormalities (history of liver transplantation, pregnancy, acute alcoholic hepatitis, malignancies, hemolytic anemia, splenectomy, recent surgical interventions, blood components transfusion, the use of TPO agents, erythropoietin, corticosteroids, ribavirin, vaccination / history of COVID-19) were not included in the study.

Case and control selection. The case group included patients with newly diagnosed PVT, with a thrombus of the PV trunk and / or lobar branches or PV cavernous transformation verified by Doppler ultrasound and contrast-enhanced computed tomography. Tumor invasion of the PV was an exclusion criterion (n = 16). In total, 114 patients were included into the case group (59 men and 55 women, with their median age of 59 years). From the total pool of patients without PVT (n = 1297), 228 patients were selected into the control group using stratified randomization by sex, age, and cirrhosis etiology; the case-to-control ratio was 1:2 (Figure 1).

Division into subgroups. Depending on the platelet count, the patients in the case and control groups were divided into subgroup with thrombocytopenia (< 150 × 10^9/L) and subgroup without thrombocytopenia (≥ 150 × 10^9/L). The subgroups were compared by the following characteristics: demographic data (sex, age), disease etiology, the presence of ascites, hepatic encephalopathy, gastroesophageal varices and associated bleedings, spleen length and PV diameter by ultrasound, concentration of hemoglobin, counts of white blood cells, neutrophils, lymphocytes,

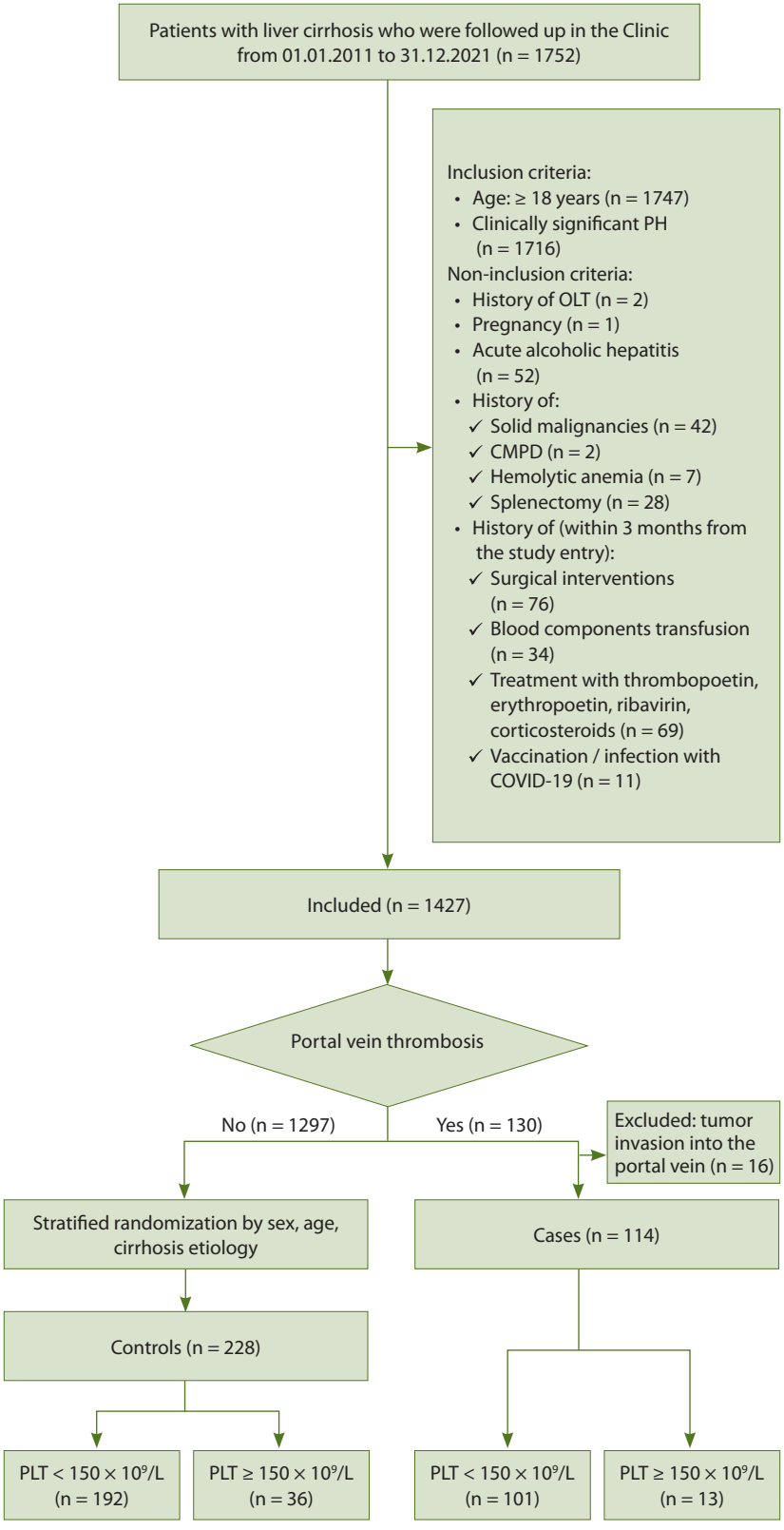

Fig. 1. The flow diagram for the patient recruitment into the study. OLT, orthotopic liver transplantation; PH, portal hypertension; PLT, platelets; CMPD, chronic myeloproliferative disorder

Table 1. Characteristics of the case and control patients with liver cirrhosis

Characteristics	Cases (n = 114)	Controls (n = 228)	*P* value
Male sex, n (%)	59 (51.8)	116 (50.9)	0.879
Age, years	59 (51; 65)	58 (52; 63)	0.698
Causes of liver cirrhosis, n (%)			
Alcohol abuse	28 (24.6)	58 (25.4)	0.861
CVH	42 (36.8)	82 (36)	0.874
CVH and alcohol abuse	16 (14)	29 (12.7)	0.735
NAFLD	16 (14)	35 (15.4)	0.748
Primary biliary cholangitis	9 (7.9)	18 (7.9)	1.000
Autoimmune hepatitis	3 (2.6)	6 (2.6)	1.000
LC Child-Pugh class, n (%)			
A	23 (20.2)	46 (20.2)	1.000
B	62 (54.4)	117 (51.3)	0.593
C	29 (25.4)	65 (28.5)	0.549
Ascites, n (%)	88 (77.2)	129 (56.6)	< 0.001
HE, n (%)	45 (39.5)	69 (30.3)	0.089
GEV, n (%)	105 (92.1)	212 (93)	0.769
History of GEV-associated bleeding, n (%)	36 (31.6)	34 (14.9)	< 0.001
Spleen length (at sonography), cm	16.2 (14.7; 18.2)	14.9 (13.4; 16.1)	< 0.001
PV diameter (at sonography), mm	14 (12.8; 16)	12.5 (11.3; 13.6)	< 0.001
Hemoglobin, g/L	119 (99; 130)	120 (107; 133)	0.244
WBC count, × 10^9/L	4.1 (3.1; 5.3)	4.5 (3.2; 5.9)	0.104
Neutrophils, × 10^9/L	2.35 (1.81; 3.54)	2.6 (1.7; 3.74)	0.293
Lymphocytes, × 10^9/L	0.98 (0.64; 1.37)	1.21 (0.84; 1.75)	< 0.001
NLR	2.48 (1.93; 3.62)	2.07 (1.47; 3.04)	< 0.001
Platelets, n (%)	88 (61; 131)	85 (61; 130)	0.768
< 50 × 10^9/L	18 (15.8)	31 (13.6)	0.586
≥ 50 – < 100 × 10^9/L	47 (41.2)	105 (46.1)	0.398
≥ 100 – < 150 × 10^9/L	36 (31.6)	56 (24.5)	0.168
≥ 150 × 10^9/L	13 (11.4)	36 (15.8)	0.276
Total protein, g/L	69 (64; 75)	70 (65; 76)	0.260
Albumin, g/L	32 (27; 36)	30 (26; 34.7)	0.019
Total bilirubin, mg/dL	1.8 (1.3; 2.9)	2.4 (1.5; 3.8)	0.008
INR	1.29 (1.16; 1.47)	1.24 (1.14; 1.39)	0.032
Fibrinogen, g/L	2.5 (2; 3.1)	2.5 (2; 3.1)	0.745

CVH, chronic viral hepatitis; GEV, gastroesophageal varices; HE, hepatic encephalopathy; INR, international normalized ratio; LC, liver cirrhosis; NAFLD, non-alcoholic fatty liver disease; NLR, neutrophil/lymphocyte ratio; PV, portal vein; WBC, white blood cell

The values are given as absolute patient numbers and proportions of the total – n (%), or as median and interquartile range (25^{th}; 75^{th} percentiles)

neutrophil-to-lymphocyte ratio, total protein, albumin, total bilirubin, and fibrinogen levels and international normalized ratio. The incidence of newly diagnosed malignant tumors was determined: non-invasive HCC, other solid tumors, and chronic myeloproliferative diseases. Thrombocytopenia was graded as mild (platelet count 100 to 150 × 10^9/L), moderate (50 to 100 × 10^9/L), and severe (less than 50 × 10^9/L). The platelet count of 450 × 10^9/L and more was considered as thrombocytosis [1].

Statistical analysis. The normality of the distribution was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Most of the studied quantitative variables were not normally distributed and are presented as medians (Me) and interquartile ranges (25^{th}; 75^{th} percentiles). Qualitative variables were expressed as numbers of patients with a given characteristic and their proportion (percentage) of the total number of patients in the group. The analyzed variables had less than 5% missing values; missing data was replaced with the median in subgroups based on sex, age, and liver disease etiology. Statistical hypotheses were tested with Mann-Whitney U-test, Pearson's chi-squared test, and Fisher's exact test. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. The association between the presence / absence of thrombocytopenia and the studied variables was assessed by subgroups comparisons and construction of logistic regression models with step-by-step inclusion and exclusion of predictors; the resulting models were tested for accuracy. The models with the best quality parameters estimated by the area under the ROC curve – AUC (area under the curve) were selected. The quality of the model was determined according to the expert scale for AUC values as excellent (0.9 to 1.0), very good (0.8 to 0.9), good (0.7 to 0.8), satisfactory (0.6 to 0.7), and unsatisfactory (0.5 to 0.6). The differences were considered significant at $p < 0.05$. The statistical analysis was performed using IBM SPSS v.23.0 (SPSS: An IBM Company, USA).

Results

Analysis of the case and control patient groups

The initial patient characteristics in the study groups are given in Table 1. The study included equal numbers of men and women, the median age was 58.5 years. In both groups, cirrhosis was caused by chronic viral hepatitis B or C in 36-36.8% of the patients, alcohol abuse in 24.6-25.4%, and chronic viral hepatitis in combination with alcohol abuse in 12.7-14%. Non-alcoholic fatty liver disease (cirrhosis stage) was found in 14-15.4% of the patients, primary biliary cholangitis in 7.9%, autoimmune hepatitis in 2.6%. The distribution of LC severity in the groups

Table 2. Characteristics of the case and control patients with liver cirrhosis with the subgroups based on the presence or absence of thrombocytopenia

Characteristics	Cases (n = 114)		*P* value	Controls (n = 228)		*P* value
	Thrombocytopenia (n = 101)	No thrombocytopenia (n = 13)		Thrombocytopenia (n = 192)	No thrombocytopenia (n = 36)	
Male sex, n (%)	52 (51.5)	7 (54)	0.873	93 (48.4)	23 (63.9)	0.089
Age, years	59 (50; 66)	60 (57; 66)	0.672	59 (52; 63)	57 (46; 63)	0.349
Alcohol etiology, n (%)	35 (34.6)	9 (69)	0.016	65 (33.8)	22 (61)	0.003
Ascites, n (%)	76 (75.2)	12 (92)	0.168	103 (53.6)	26 (72)	0.040
HE, n (%)	38 (37.6)	7 (54)	0.261	58 (30.2)	11 (31)	0.967
GEV, n (%)	94 (93.1)	11 (85)	0.288	178 (92.7)	34 (95)	0.709
History of GEV-associated bleeding, n (%)	34 (33.7)	2 (15)	0.183	31 (16.1)	3 (8.3)	0.228
Spleen length (at sonography), cm	16.2 (14.8; 18.7)	15.3 (13.4; 17.7)*	0.196	14.9 (13.7; 16.4)	13.6 (12.3; 15.5)	0.007
PV diameter (at sonography), mm	14 (12.7; 15.8)	15 (13; 16.1)*	0.273	12.5 (11.2; 13.3)	12.7 (11.4; 14)	0.513
Hemoglobin, g/L	120 (100; 130)	114 (82; 127)	0.102	119 (107; 133)	128 (102; 137)	0.169
WBC count, $\times 10^9$/L	3.9 (2.9; 5.2)	6 (3.8; 9.1)	0.031	4.2 (3; 5.3)	7.6 (6.1; 14.3)	< 0.001
Neutrophils, $\times 10^9$/L	2.3 (1.78; 3.17)	3.61 (2.08; 7.11)	0.016	2.27 (1.62; 3.2)	4.98 (3.5; 9.18)	< 0.001
Lymphocytes, $\times 10^9$/L	0.92 (0.62; 1.25)	1.76 (1.11; 2)	< 0.001	1.15 (0.81; 1.57)	2.1 (1.51; 2.6)	< 0.001
NLR	2.45 (1.96; 3.48)	2.55 (1.73; 3.89)	0.538	2.03 (1.44; 2.99)	2.66 (1.77; 4.49)	0.012
Total protein, g/L	68.5 (63.8; 74.2)	73 (66.6; 80.2)	0.372	70 (65; 75)	68.4 (64.3; 77)	0.285
Albumin, g/L	32 (27; 35.8)	32.1 (26.5; 37)	0.781	30 (26; 34.9)	31 (25.3; 34.8)	0.604
Total bilirubin, mg/dL	1.7 (1.3; 2.9)	2.4 (1.3; 3.5)	0.384	2.3 (1.5; 3.7)	3 (1.6; 6.2)	0.178
INR	1.3 (1.16; 1.49)	1.18 (1.16; 1.29)	0.436	1.24 (1.13; 1.4)	1.26 (1.12; 1.39)	0.790
Fibrinogen, g/L	2.4 (1.9; 3)	3.2 (2.6; 4)	0.029	2.4 (1.9; 3)	3.1 (2.35; 3.88)	0.032
Newly diagnosed malignancies, n (%)	16 (15.8)	8 (62)*	< 0.001	11 (5.7)	5 (13.9)	0.079
HCC	15 (14.8)	6 (46)*	0.007	9 (4.7)	4 (11.1)	0.128
Non-HCC	1 (1)	2 (15)	0.003	2 (1)	1 (2.8)	0.402
CMPD	1 (1)	–		–	–	

CMPD, chronic myeloproliferative disorder; GEV, gastroesophageal varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; NLR, neutrophil/lymphocyte ratio; PV, portal vein; WBC, white blood cell count

The values are given as absolute patient numbers and proportions of the total – n (%), or as median and interquartile range (25^{th}; 75^{th} percentiles)

* $p < 0.05$ for the difference with the patient subgroup without PVT

was similar: 51.3-54.4% of the patients were assigned to Child-Pugh class B, 25.4-28.5% to class C and 20.2% to Class A.

There were no differences between the case and control groups in terms of thrombocytopenia severity and the proportion of patients without thrombocytopenia.

Portal hypertension severity parameters (prevalence of ascites and variceal bleeding, spleen length and PV diameter), the values of neutrophil-to-lymphocyte ratio, serum albumin concentration and international normalized ratio were significantly higher in patients with PVT. The concentration of total bilirubin and the lymphocyte counts were significantly higher in the patients without PVT. There were no differences between the groups for other studied parameters.

Analysis in the subgroups of patients with platelet counts of $< 150 \times 10^9$/L and $\geq 150 \times 10^9$/L

The proportion of alcoholic cirrhosis etiology, white blood cell, neutrophil and lymphocyte counts, and fibrinogen levels were significantly higher in the subgroups of patients with platelet counts of $\geq 150 \times 10^9$/L, both in the group with and without PVT (Table 2).

In the case patients, newly diagnosed malignant tumors were found significantly more often in the subgroup without thrombocytopenia. Among them, HCC was most prevalent, whereas stomach cancer, colorectal cancer, and reproductive system malignancies were less common. A chronic myeloproliferative disorder (masked form) was diagnosed in one patient with PVT and thrombocytopenia.

In the control group, the thrombocytopenic subgroup had higher value of the spleen length, whereas prevalence of ascites and neutrophil-to-lymphocyte ratio were higher in the subgroup without thrombocytopenia.

When comparing the subgroups of patients without thrombocytopenia with each other (the cases vs controls), significant differences were found in the frequency of all newly diagnosed malignant tumors, newly diagnosed HCC, spleen length and PV diameter: these parameters were higher in the patients with PVT.

In the patients without thrombocytopenia, OR was 3.56 for any malignant tumors (95% CI 1.68-7.51; p = 0.0009) and 2.87 for HCC (95% CI 1.28-6.46; p = 0.0107). For two variables combined, such as PVT and the absence of thrombocytopenia, OR was 26.3 for all malignant tumors (95% CI 7.37-93.97; p < 0.0001) and 17.42 for HCC (95% CI 4.84-62.65; p < 0.0001).

In the subgroups of patients without thrombocytopenia, the median platelet count was similar in the case and control group (203×10^9/L and 223×10^9/L, respectively). Thrombocytosis was noted in two patients: one in the case group with Child-Pugh class C alcoholic LC and a newly diagnosed non-invasive HCC, and one patient in the control group with primary biliary cholangitis with Child-Pugh class B, as well as exacerbation of concomitant ulcerative colitis and severe iron deficiency anemia.

The best logistic regression model for the outcome "platelet count $\geq 150 \times 10^9$/L" in the case group included the following variables: white blood cells count, concentration of hemoglobin and albumin, the

Table 3. Logistic regression models for the outcome "platelet count $\geq 150 \times 10^9$/L" in the case and control patients

Variable	Coefficient B	OR	95% CI	*P* value	Wald test
The case model					
Malignant tumors	3.468	32.061	5.059–203.191	< 0.001	13.548
Hemoglobin, g/L	-0.037	0.964	0.934–0.995	0.024	5.100
Albumin, g/L	0.174	1.190	1.031–1.374	0.017	5.684
WBC, $\times 10^9$/L	0.227	1.254	1.057–1.448	0.009	6.761
The control model					
Neutrophils, $\times 10^9$/л	0.355	1.427	1.238–1.644	< 0.001	24.084
Spleen length (at sonography), cm	-0.204	0.816	0.676–0.984	0.033	4.528

CI, confidence interval; OR, odds ratio; WBC, white blood cell count

presence of malignant tumors (Table 3). The model accuracy was 90.4% (95% CI 83.4-95.1%). The model quality was assessed as very good with AUC of 0.873 (95% CI 0.743-1.0) (Fig. 2).

The best logistic regression model in the control group included such variables as neutrophil count and spleen length (Table 3). The model accuracy was 86.4% (95% CI 81.3-90.6%), the model quality was assessed as very good with AUC of 0.855 (95% CI 0.791-0.918).

Discussion

In our study, thrombocytopenia was identified in the vast majority (85.7%) of LC patients. The study included patients with signs of clinically significant portal hypertension such as gastroesophageal varices and/or ascites. Almost 80% of patients had Child-Pugh class B or C LC, which suggests the involvement of two main mechanisms in the development of thrombocytopenia: portal hypertension and decreased synthesis of TPO.

These results are consistent with data from other studies demonstrating that the prevalence and severity of thrombocytopenia are associated with the severity of liver disease [21, 22]. Thus, in the study by Bashour et al. [23], the prevalence of thrombocytopenia in patients with non-alcoholic fatty liver disease and fibrosis F3-4 was 64% compared with 5.5% in those with fibrosis F1-2. In the study by Qamar et al. [17], 77.9% of patients with compensated LC had thrombocytopenia. Similar values (76%) were obtained by Giannini et al. [18]; severe thrombocytopenia was observed in only 1%, while 61.4% of patients had clinically significant portal hypertension, 65% of patients had Child-Pugh B or C LC. In our study, the overall prevalence of thrombocytopenia and severe thrombocytopenia were higher than in the above-mentioned studies, which may be due to a higher proportion of patients with clinically significant portal hypertension and Child-Pugh class B or C. The spleen length as an indicator of portal hypertension degree was included in the model for the outcome "platelet count ≥ 150 × 10^9/L" for patients without PVT with a negative coefficient B. It means that the higher is splenomegaly, the less is the probability of normal or elevated platelet count.

The prevalence and severity of thrombocytopenia in the case and control patients were not different. Also, no differences in the LC severity by Child-Pugh were found in these groups, but portal hypertension was more severe (prevalence of ascites and variceal bleeding, the spleen length, the PV diameter) in the PVT group, which could have potentially increased the rate and severity of thrombocytopenia in this group. Currently, there are contradictory data on

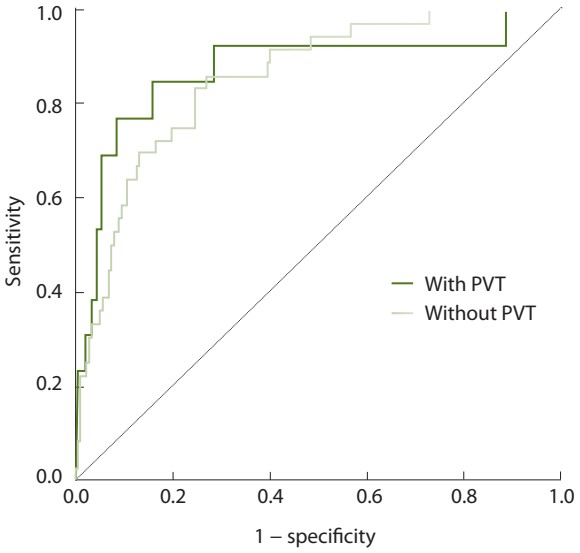

Fig. 2. ROC curves for the models for the outcome "platelet count ≥ 150 × 10^9/L" in the patients with liver cirrhosis with and without portal vein thrombosis (PVT)

specifics of platelet counts in patients with PVT. In a meta-analysis by Pan et al. [8], low platelet count was identified as a risk factor for PVT only in cohort studies, whereas in cross-sectional ones, the association between platelet count and PVT was not established.

It should be noted that the absolute platelet count does not represent the tendency to hemorrhagic complications or PVT in each individual LC patient. Thus, even severe thrombocytopenia in LC patients may be associated with changes in their characteristics towards increased prothrombotic potential due to higher levels of von Willebrand factor, ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin-1-like domains, member 13) and increased Factor VIII / protein C ratio [24, 25].

Despite the presence of pathogenetic factors for thrombocytopenia in all study patients, the peripheral platelet count was ≥ 150 × 10^9/L in 11.4% (13 patients) in the case group and in 15.8% (36 patients) in the control group.

Among the studied factors, a higher frequency of alcoholic etiology of cirrhosis was found in the patient subgroups without thrombocytopenia compared with those with thrombocytopenia, both in the case and control groups. It is well known that thrombocytopenia is often observed in patients with alcohol abuse (up to 81% among hospitalized patients); it develops due to direct damaging effect of alcohol on platelet production and acceleration of their degradation and apoptosis [26]. After

alcohol withdrawal, the platelet count usually returns to normal or even exceeds it within a week, with the development of the so-called rebound thrombocytosis [26]. Similarly, in patients with alcoholic cirrhosis, at the time of hospitalization the toxic factor ceases to act, and the platelet numbers can increase reactively.

The same factors associated with the absence of thrombocytopenia were identified for both the case and control groups: a higher count of white blood cells, neutrophils, lymphocytes and fibrinogen concentration. The predictive model for the absence of thrombocytopenia included white blood cell count in the case group and the neutrophil count in the control group. The inclusion of these variables in the models may be associated with the development of low-grade inflammation [12]. In response to inflammation, the production of IL-6 increases, which stimulates the production of TPO by hepatocytes both *in vitro* and *in vivo* [27, 28]. To increase the production of TPO, preserved synthetic liver function is necessary, which explains the inclusion of albumin concentration (with a positive coefficient B) in the predictive model for the absence of thrombocytopenia in patients with PVT.

Another factor in the model of the absence of thrombocytopenia in patients with PVT was the hemoglobin concentration with a negative coefficient B. It means that the lower is the hemoglobin concentration, the higher will be the probability of normal or elevated platelet count. In the study, we did not aim at identification of the causes of anemia. Taking into account that iron deficiency anemia is the most frequent anemia among LC patients, and in our study 31.6% patients with PVT had a history of variceal bleeding, iron deficiency anemia can be assumed to be one of the most likely causes of decreased hemoglobin in our patients [29]. It is well known that iron deficiency anemia can be associated with a reactive increase in platelet counts due to the stimulating effect of erythropoietin on TPO receptors or due to TPO-independent factors [30].

The predictive model of the absence of thrombocytopenia in patients with PVT included all newly diagnosed malignant tumors. Non-invasive HCC was the most frequent among newly diagnosed malignancies, and malignant neoplasms of other location were detected in a smaller patient number. Thrombocytosis is often associated with various cancer types as a result of overproduction of thromboplastic factors by tumor cells, in particular TPO and IL-6, activating megakaryocytes and their precursors [31, 32].

The prevalence of thrombocytosis in patients with LC and HCC varies from 2.7 to 9%, which is lower than in patients with other types of solid cancer without concomitant cirrhosis [31, 32]. This may be explained by baseline thrombocytopenia, which is usually observed in LC patients. In the study by Zanetto et al. [33], a higher platelet count (although still thrombocytopenic) in the presence of HCC was found in LC patients compared to those in the control group (117×10^9/L vs 82×10^9/L; $p = 0.046$). In a recent major study by Liu et al. [34] in 4706 patients from Taiwan and the USA, thrombocytosis in HCC patients (defined as platelet count $\geq 300 \times 10^9$/L) was detected in 9.0% of patients in the Taiwan cohort and in 6.9% in the USA cohort. Thrombocytosis in HCC patients is associated with a poor prognosis, a large tumor volume, more frequent vascular invasion and distant metastases [34].

HCC and other tumors are also risk factors for PVT due to the secretion of tissue factor by the tumor, induction of thrombin formation, hypofibrinolysis, increased levels of prothrombotic microvesicles, increased platelet activity and function, which together contribute to hypercoagulation and thrombosis [33].

Currently, complete blood counts including with platelets and Doppler ultrasound of the portal system vasculature are methods available in routine clinical practice when monitoring LC patients. As the results of our study have shown, if a LC patient was diagnosed with PVT and the peripheral platelet count was $\geq 150 \times 10^9$/L, the chances of having any newly detected malignant tumor increased 26.3-fold and the chances of having HCC by 17.42-fold.

Limitations of the study

The study limitations include its retrospective design and inclusion of in-patients only. However, for such rare diseases as PVT, this design makes it possible to study risk factors and potential cause-effect relationships in a short time and using minimal resources [35, 36]. We minimized the risk of systematic errors by carefully analyzing primary medical documentation, conducting stratified randomization based on demographic characteristics and etiology of LC, including variables with less than 5% missing data.

As directions for further research, prospective studies could be considered on detailed evaluation of platelet increments (within the thrombocytopenic range or reference values) in LC patients as a risk factor for malignant tumors and low-grade inflammation.

Conclusion

In LC patients, the prevalence of thrombocytopenia and its severity do not differ depending on the presence or absence of PVT. Portal hypertension and decreased synthetic liver function are the main causes of thrombocytopenia. Absence of thrombocytopenia is associated with alcoholic etiology of cirrhosis and detection of malignant tumors. When PVT is combined with the absence of thrombocytopenia in LC patients, the chances for detection of malignant tumors, primarily HCC, increase significantly.

Additional information

Conflict of interests

The authors declare no conflict of interests regarding the publication of this article.

Authors' contributions

M.Yu. Nadinskaia, the study concept and design, database management and validation, statistical analysis, text editing; Kh.B. Kodzoeva, database management, statistical analysis, text writing; K.A. Gulyaeva, database management, text writing and editing; M.-D.E. Khen and D.I. Koroleva, database management, literature analysis, text writing; V.T. Ivashkin, project management, text editing. All the authors have read and approved the final version of the manuscript before submission, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Причины отсутствия тромбоцитопении у пациентов с циррозом печени и тромбозом воротной вены: исследование «случай – контроль»

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Обоснование. Осложнения цирроза печени (ЦП) – тромбоцитопения и тромбоз воротной вены (ТВВ) – имеют сходные патогенетические механизмы. Однако данные о взаимосвязи между ТВВ и содержанием тромбоцитов у пациентов с ЦП неоднозначны.

Цель – изучить у пациентов с ЦП и ТВВ факторы, влияющие на содержание тромбоцитов.

Материал и методы. Проведено ретроспективное исследование «случай – контроль». В группу «Случай» включены 114 пациентов с ЦП различной этиологии и впервые выявленным ТВВ, не обусловленным инвазией гепатоцеллюлярным раком. Из базы данных пациентов с ЦП без ТВВ в группу «Контроль» методом стратифицированной рандомизации по полу, возрасту и этиологии ЦП отобрано 228 пациентов. Пациенты в обеих группах разделены на подгруппы в зависимости от наличия/отсутствия тромбоцитопении ($< 150 \times 10^9$/л / $\geq 150 \times 10^9$/л). Проанализирована этиология ЦП, выраженность портальной гипертензии (асцит, печеночная энцефалопатия, варикозное расширение вен пищевода/желудка и кровотечения из них, длинник селезенки, диаметр воротной вены), лабораторные параметры (содержание лейкоцитов, нейтрофилов, лимфоцитов, концентрация гемоглобина, общего белка, альбумина, общего билирубина, фибриногена, нейтрофильно-лимфоцитарный индекс, протромбин); определена частота впервые выявленных злокачественных опухолей. Вычислены отношения шансов (ОШ) и 95% доверительные интервалы (ДИ), построены модели логистической регрессии; рассчитана точность модели, вычислена площадь под ROC-кривой – AUC.

Результаты. Различий по степени выраженности тромбоцитопении между группами «Случай» и «Контроль» не установлено: тяжелую степень имели 15,8% (18 пациентов) vs 13,6% (31 пациент), $p = 0,586$; среднюю – 41,2% (47 пациентов) vs 46,1% (105 пациентов), $p = 0,398$; легкую – 31,6% (36 пациентов) vs 24,5% (56 пациентов), $p = 0,168$. Доля пациентов без тромбоцитопении в группе «Случай» составила 11,4% (13 пациентов), в группе «Контроль» – 15,8% (36 пациентов), разница между группами незначима ($p = 0,276$). В подгруппах пациентов без тромбоцитопении, как в группе «Случай», так и в группе «Контроль», частота алкогольной этиологии ЦП, содержание лейкоцитов, нейтрофилов, лимфоцитов и концентрация фибриногена были статистически значимо выше ($p < 0,05$), чем в подгруппах пациентов с тромбоцитопенией. В модель, построенную на исход «отсутствие тромбоцитопении», в группе «Случай» включены содержание лейкоцитов, концентрация гемоглобина и альбумина, наличие впервые выявленных злокачественных опухолей (точность модели 90,4%, AUC 0,873), в группе «Контроль» – содержание нейтрофилов и длинник селезенки (точность модели 86,4%, AUC 0,855). При одновременном обнаружении ТВВ и содержании тромбоцитов $\geq 150 \times 10^9$/л ОШ для всех впервые выявленных злокачественных опухолей составило 26,3 (95% ДИ 7,37–93,97; $p < 0,0001$), для впервые выявленного гепатоцеллюлярного рака, не инвазирующего воротную вену, – 17,42 (95% ДИ 4,84–62,65; $p < 0,0001$).

Заключение. У пациентов с ЦП частота тромбоцитопении и степень ее выраженности не различаются в зависимости от наличия или отсутствия ТВВ. Отсутствие тромбоцитопении у пациентов с ТВВ ассоциировано с высоким риском выявления злокачественных опухолей, прежде всего гепатоцеллюлярного рака.

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Ключевые слова: портальная гипертензия, воротная вена, тромбоциты, гепатоцеллюлярный рак, длинник селезенки, точность модели, логистическая регрессия

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Финансирование

Работа проведена без привлечения дополнительного финансирования со стороны третьих лиц.

Конфликт интересов

Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Участие авторов

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