



Risk Factors of Portal Vein Thrombosis in Patients with Different Child – Pugh Classes Liver Cirrhosis

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Aim: to evaluate the frequency of portal vein thrombosis (PVT) and build predictive models of the development of PVT for patients with liver cirrhosis (LC) of A and B/C classes by Child–Pugh.

Materials and methods. Research design is a case-control. The Case group included 130 patients with newly diagnosed PVT not caused by invasive hepatocellular carcinoma (HCC); 29 patients were assigned to class A, 101 patients were assigned to class B/C. From the database of cirrhotic patients without PVT 60 Controls for class A and 205 for B/C were selected using stratified randomization by sex, age and etiology of cirrhosis. The Mann–Whitney *U*-test and Pearson's chi-squared test were used to compare the groups. Odds ratios (OR) and 95 % confidence intervals (95 % CI) were calculated. Logistic regression models are constructed with the separation of the sample into training and test (0.7; 0.3). The operational characteristics of the models were calculated on the test sample; ROC analysis was carried out, the area under the ROC curve (AUC) was calculated.

Results. The overall frequency of PVT was 4.1 % (95 % CI 2.7–5.8 %) in class A and 10.4 % (95 % CI 8.5–12.5 %) class B/C. Patients with class A and B/C PVT differed from the corresponding controls by more severe portal hypertension: the frequency of bleeding / number of interventions on varices compared with the control were 41/45 % vs. 7/8 % ($p < 0.001$) for class A and 25.7/30.7 % vs. 16.1/16.1 % ($p < 0.05$) for class B/C, ascites frequency was 24 % vs. 8 % ($p < 0.05$) for class A and 89.1 % vs. 68.3 % ($p < 0.001$) for class B/C. The cutoff by the portal vein diameter was the same for both classes — 13.4 mm; the spleen length was similar and amounted 17.5 mm for class A, 17.1 mm for class B/C. Patients with PVT differed from the corresponding controls by neutrophil-to-lymphocyte ratio: class A 2.33 (1.82; 3.61) vs. 1.76 (1.37; 2.20), $p < 0.01$, class B/C 2.49 (1.93; 3.34) vs. 2.15 (1.49; 3.26), $p < 0.05$. Patients of class B/C had a higher incidence of newly diagnosed malignant tumors - 23.8% (primarily HCC that does not invade the portal vein), compared with control and cases of class A – 6.3 % and 3 % ($p < 0.05$), respectively. The best model for class A included variceal bleeding, ascites, portal vein diameter, absolute number of neutrophils, for class B — ascites, spleen length, portal vein diameter, malignant tumors / local factors; sensitivity, specificity, accuracy and AUC were 79.3 %, 90 %, 86.5 %, 0.897 and 73.3 %, 68.3 %, 69.9 %, 0.789, respectively.

Conclusion. Independently of the Child–Pugh class of LC, the main risk factor for PVT is severe portal hypertension.

Keywords: portal hypertension, portal vein diameter, spleen length, variceal bleeding, neutrophil-to-lymphocyte ratio, hepatocellular carcinoma, logistic regression, case-control

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Факторы риска тромбоза воротной вены у пациентов с циррозом печени разных классов по Child–Pugh

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Цель исследования: оценить частоту тромбоза воротной вены (ТВВ) и построить предиктивные модели развития ТВВ для пациентов с циррозом печени (ЦП) классов А и В/С по Child–Pugh.

Материалы и методы. Дизайн исследования — «случай-контроль». В группу «случай» включены 130 пациентов с впервые выявленным ТВВ, не обусловленным инвазией гепатоцеллюлярным раком (ГЦР); к классу А отнесены 29, к классу В/С — 101 пациент. Из базы данных пациентов с ЦП без ТВВ с помощью стратифицированной рандомизации по полу, возрасту и этиологии отобраны для класса А — 60, для класса В/С — 205 контролей. Для сравнения групп применялся *U*-критерий Манна — Уитни, критерий хи-квадрат Пирсона. Вычислены отношения шансов (ОШ) и 95 % доверительные интервалы (95 % ДИ). Построены модели логистической регрессии с разделением выборки на обучающую и тестовую (0,7; 0,3). На тестовой выборке рассчитаны операционные характеристики моделей; проведен ROC-анализ, вычислена площадь под ROC-кривой — AUC.

Результаты. Общая частота ТВВ в классе А составила 4,1 % (95 % ДИ 2,7–5,8 %), классе В/С — 10,4 % (95 % ДИ 8,5–12,5 %). Пациенты с ТВВ классов А и В/С отличались от соответствующих контролей более выраженной портальной гипертензией: частота кровотечений / числа вмешательств на варикозно-расширенных венах (ВРВ) по сравнению с контролем для класса А составила 41/45 % vs. 7/8 % ($p < 0,001$), класса В/С — 25,7/30,7 % vs. 16,1/16,1 % ($p < 0,05$), частота асцита: класс А — 24 % vs. 8 % ($p < 0,05$), класс В/С — 89,1 % vs. 68,3 % ($p < 0,001$). Точка разделения по диаметру воротной вены была одинаковой для обоих классов — 13,4 мм; по длине селезенки была сходной и составила для класса А — 17,5 мм, для В/С — 17,1 мм. Пациенты с ТВВ отличались от соответствующих контролей по значению нейтрофильно-лимфоцитарного индекса: класс А — 2,33 (1,82; 3,61) vs. 1,76 (1,37; 2,20), $p < 0,01$, класс В/С — 2,49 (1,93; 3,34) vs. 2,15 (1,49; 3,26), $p < 0,05$. В классе В/С наблюдалась более высокая частота впервые выявленных злокачественных опухолей — 23,8 % (прежде всего ГЦР, не инвазирующего воротную вену), по сравнению с контролем и случаями класса А — 6,3 % и 3 % ($p < 0,05$) соответственно. Лучшая модель для класса А включала кровотечения из ВРВ, асцит, диаметр воротной вены, абсолютное число нейтрофилов, для класса В: асцит, длина селезенки, диаметр воротной вены, злокачественные опухоли / локальные факторы; чувствительность, специфичность, точность и AUC составили: 79,3 %, 90 %, 86,5 %, 0,897 и 73,3 %, 68,3 %, 69,9 %, 0,789 соответственно.

Выводы. Независимо от класса ЦП по Child–Pugh основным фактором риска ТВВ является тяжелая портальная гипертензия.

Ключевые слова: портальная гипертензия, диаметр воротной вены, длина селезенки, кровотечение из варикозно-расширенных вен пищевода, нейтрофильно-лимфоцитарный индекс, гепатоцеллюлярный рак, логистическая регрессия, случай-контроль

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Introduction

Portal vein thrombosis (PVT) is a very rare type of venous thrombosis in the general population. The incidence of PVT is 2.5 per 100,000 people per year, and it accounts for less than 1 % of all thromboembolic complications [1]. However, PVT is a common and predictable disease, as well as an unfavorable prognostic factor for patients with liver cirrhosis (LC) [2].

According to the latest large meta-analysis by J. Pan et al., the prevalence of PVT among cirrhotic patients is 13.92 %, and the incidence is 10.42 %. Overall, the prevalence and incidence of PVT directly correlate with the severity of liver disease by the Child–Pugh score, significantly increasing from class A to classes B/C, moreover, membership to classes is considered a key risk factor of PVT [3].

The Child–Pugh (Child–Pugh–Turcotte) scoring system includes two clinical signs such as ascites, hepatic encephalopathy (HE) and three laboratory parameters such as albumin, total bilirubin, prothrombin) [4]. The combination of these parameters makes it possible to simultaneously assess the liver function (albumin production and detoxification) and portal

hypertension, making this simple scoring system indispensable for predicting complications of LC.

From all parameters in the Child–Pugh system ascites is highlighted as a significant risk factor of PVT, and among other risk factors not included in Child–Pugh, the following are considered: high levels of D-dimer, the use of beta-blockers, thrombocytopenia, reduced blood flow velocity in the portal vein (PV), and the presence of esophageal / gastric varices with the threat of bleeding [3].

The progression of liver disease and a patient's transition from class A to classes B and C result from deterioration in the liver functions and/or an increase in portal hypertension. We couldn't find studies examining which of these factors has more significant impact on the frequency of PVT development in different Child–Pugh classes. The question of additional risk factors that affect the frequency of PVT at different Child–Pugh classes also remains unresolved.

The aim of our study is to evaluate the prevalence of PVT and build predictive models of the development of PVT for cirrhotic patients with A and B/C classes by Child–Pugh.

Materials and methods

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

An electronic database was used for this study from our previous research [5]. The database was corrected, supplemented, and includes information based on primary medical documentation of 1752 patients diagnosed with «liver cirrhosis» who were observed at the Clinic of Propaedeutics of Internal Diseases, Gastroenterology, and Hepatology named after V.Kh. Vasilenko from January 1, 2011 to December 31, 2021. The diagnosis of cirrhosis was established based on clinical, laboratory and instrumental examination, liver elastography, morphological study of the liver.

The inclusion and non-inclusion criteria for the study are presented in Figure 1.

Case and Control Selection

The Case group included patients with newly diagnosed PVT, in the presence of a thrombus of the PV trunk and / or lobar branches or cavernous transformation of the PV according to the ultrasound and contrast-enhanced computed tomography (CT) scans. Tumor invasion of the PV served as the exclusion criterion ($n = 21$). In total, 130 patients were included in the Case group, 65 men and 65 women, median age was 59 (50; 65) years.

At the next stage, patients with PVT were divided into Child–Pugh classes. Class A included 29 patients, 5 men and 24 women, median age was 58 (46; 65). Cirrhosis developed as a result of hepatitis C virus infection in 14 patients, autoimmune hepatitis and / or primary biliary cholangitis in 7 patients, non-alcoholic fatty liver disease in 5 patients, and alcoholic liver disease in 3 patients. Class B/C included 101 patients, 60 men and 41 women, median age 59 (51; 65) years. In this group, alcohol abuse was the most frequent etiological factor of cirrhosis and occurred in 44 (43.5 %) patients, in a third of them in combination with viral hepatitis C or B; LC also developed in the outcome of viral hepatitis C and/or B in 31 (30.7 %), in the outcome of non-alcoholic fatty liver disease in 13 (12.9 %) and in the same number of patients as a result of autoimmune hepatitis and/or primary biliary cholangitis.

Patients without signs of PVT ($n = 1557$) were included in the control database, from which 60 patients with class A and 205 with class B/C were selected using stratified randomization by sex, age, etiology, and a case-to-control ratio was 1:2 (Figure 1).

Assessed risk factors

According to the primary medical documentation, we analyzed the features of the onset, duration and severity of portal hypertension including presence and size of varices, ascites, HE, frequency of variceal bleeding, presence and frequency of interventions

on varices (endoscopic ligation, sclerotherapy, gastric devascularization procedure, surgical shunt), PV diameter, and spleen length by ultrasound.

The study also considered comorbidities such as coronary heart disease (CHD), diabetes mellitus (DM), and gallstone disease (GD).

The grade of ascites was determined according to the international recommendations [6]. All patients with grade 3 ascites had a serum-ascites albumin gradient of ≥ 1.1 g/dL and ascitic fluid protein concentration of < 2.5 g/dL. HE was diagnosed and graded clinically according to West Haven criteria [7].

The following laboratory parameters were evaluated: count of red blood cells, white blood cells, neutrophils, lymphocytes, platelets, concentration of hemoglobin, total bilirubin, total protein, albumin, fibrinogen, international normalized ratio (INR). Inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation index ($SII = \text{platelets} \times \text{neutrophils} / \text{lymphocytes}$) were calculated.

The study also considered local factors associated with PVT, including exacerbation of inflammatory bowel diseases (IBD), *Clostridium difficile* infection, blunt abdominal trauma, abdominal surgeries, splenectomy, acting for 3 months or less until the examination.

Any malignancies newly diagnosed at the time of examination or up to 12 months before the examination were also considered as a risk factor. The newly diagnosed hepatocellular carcinoma (HCC) without PV invasion was diagnosed by contrast-enhanced CT and / or magnetic resonance imaging.

Statistical analysis

Statistical analysis of the data was conducted. Continuous variables were included in the study; variables with less than 5 % missing data were imputed to the mean in subgroups according to age and etiology of liver disease.

The normality of the distribution was tested using the Kolmogorov-Smirnov and Shapiro–Wilk tests. Most of the studied quantitative variables was significantly different from the normal distribution and are presented as the median (Me) and interquartile range (as 25th and 75th percentiles; 25 %; 75 %). Qualitative data were expressed as counts and percentages.

Comparisons between groups were made by Mann-Whitney U -test; for qualitative variables, Pearson's chi-squared test and Fisher's exact test were used. Odds ratios (OR) and corresponding 95 % confidence intervals (95 % CI) were calculated. Using the ROC curve (receiver operating characteristic), the best cutoff points for quantitative predictors were selected.

Logistic regression models were built to determine the association between PVT and the studied features by step-by-step inclusion and exclusion of predictors and dividing the sample into training and test sets (0.7; 0.3). Sensitivity, specificity, and

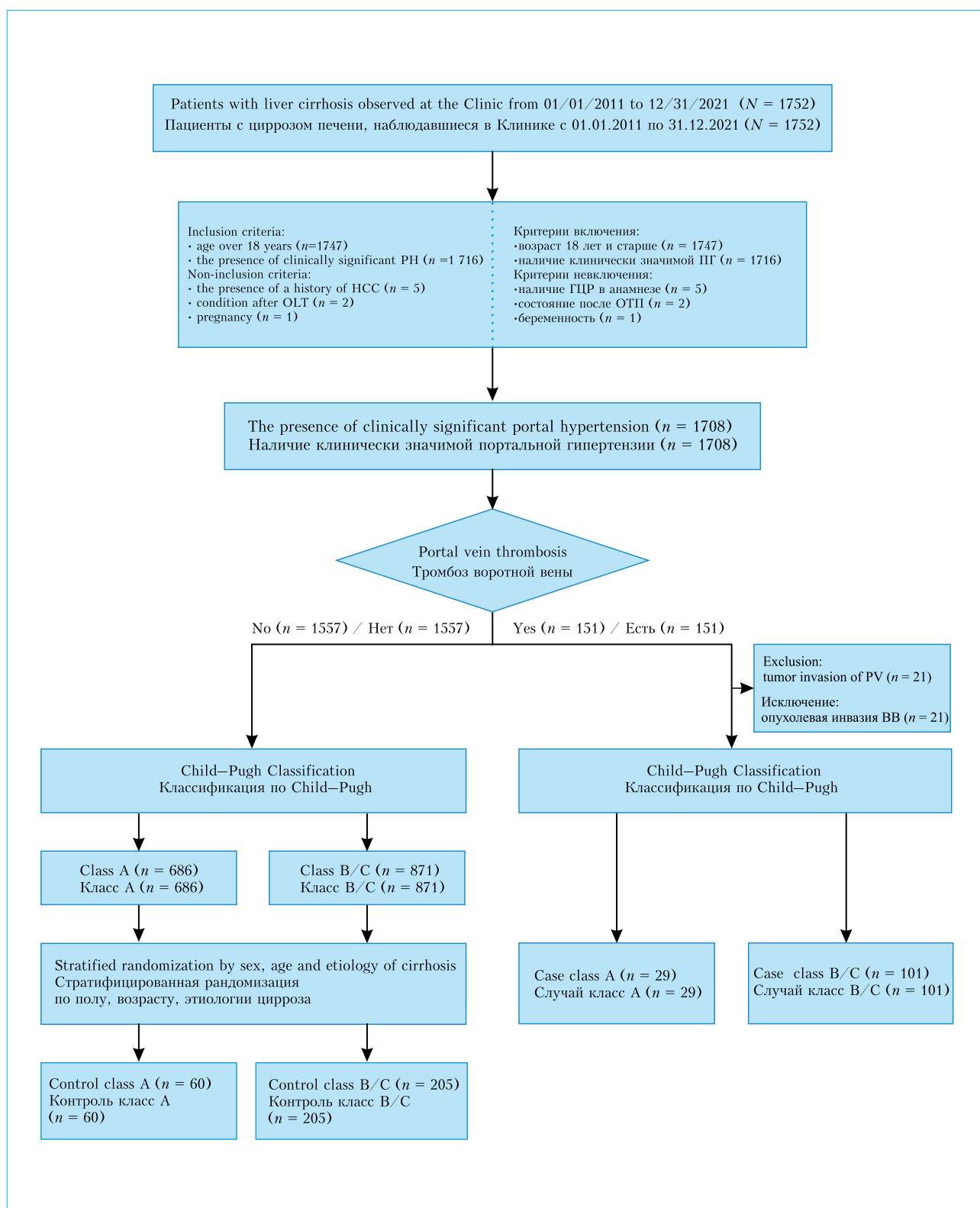


Fig. 1. Flowchart of patient inclusion in the study

Note: PH – portal hypertension, OLT – orthotopic liver transplantation, HCC – hepatocellular carcinoma, PV – portal vein.

Рис. 1. Поточковая диаграмма включения пациентов в исследование

Примечание: ПГ – портальная гипертензия, ОТП – ортотопическая трансплантация печени, ГЦР – гепатоцеллюлярный рак, ВВ – воротная вена.

accuracy were calculated on the test set. The models with the best quality indicators were selected, estimated by the area under the ROC curve – AUC (area under curve). The quality of the model was determined according to the expert scale for AUC values as excellent (0.9–1.0), very good (0.8–0.9), good (0.7–0.8), satisfactory (0.6–0.7), unsatisfactory (0.5–0.6).

The level of significance was set at $p < 0.05$. Statistical analysis of the data was performed using IBM SPSS v.23.0 (SPSS: An IBM Company, USA).

Results

The overall frequency of PVT was 7.7 % (95 % CI 6.5–9.1 %). Among patients with Child–Pugh class A, it was 4.1 % (95 % CI 2.7–5.8 %), and among those with class B/C, it was 10.4 % (95 % CI 8.5–12.5 %).

Child–Pugh class A

Portal hypertension

At the onset of clinically significant portal hypertension, variceal bleeding was observed three times more often in patients with PVT than in controls (21 % vs. 7 %, $p < 0.05$) (Table 1).

Patients with PVT had a statistically significant longer duration of portal hypertension, higher chances of variceal bleeding (OR 9.9; 95 % CI 2.8–34.7, $p < 0.001$) and intervention on varices (OR 11.4; 95 % CI 3.3–39.7, $p < 0.001$) compared to the control group.

At the time of the study, portal hypertension had statistically significant more pronounced manifestations in the PVT group, with a higher proportion of patients with ascites, larger PV diameter and spleen length than in the control group. The cutoff point for PV diameter was 13.4 mm and for spleen length was 17.5 cm; the sensitivity, specificity, and AUC were 66 %, 92 %, 0.788, and 71 %, 79 %, 0.759, respectively. There were no statistically significant differences in the frequency of overt HE between the groups; it was observed in a small proportion of patients in both groups (Table 1).

Comorbidities, local factors, malignant tumors

Among the concomitant diseases, GD was the most often observed and was diagnosed in 41 % of patients, CHD was diagnosed in approximately 30 % of patients, and DM was observed in one-fifth of patients in both groups. There were no significant differences in the frequency of these comorbidities between the groups (Table 1).

Local factors were identified in two patients in the PVT group (one had splenectomy and the other had a current exacerbation of IBD) and in three patients in the control group (all of them had IBD exacerbation), with no differences between the groups.

Newly diagnosed at the time of the study malignant tumors were identified in one patient in the case (HCC) and in three patients in the control group

(two had HCC and one had stomach cancer), statistically significant differences between the groups were not found (Table 1).

Laboratory parameters

No differences in platelet, red blood cell, and white blood cell counts were found between the groups. There was a trend towards a lower absolute lymphocyte count in the PVT group ($p = 0.078$, close to the level of statistical significance). Of the studied inflammation indices, only NLR showed statistically significant differences between the groups (Table 1).

There were no differences in the studied biochemical parameters and coagulation tests between the groups in terms of total protein, albumin, total bilirubin, INR, and fibrinogen.

Logistic Regression and ROC Analysis

The two logistic regression models had very good quality indicators for class A (Table 2). The first model consisted of a combination of two factors: PV diameter and a history of any intervention on varices. On the test set, the model sensitivity was 75.9 %, specificity was 91.7 %, accuracy was 86.5 %, and AUC was 0.849. The second model included four variables: ascites, variceal bleeding, PV diameter, and absolute neutrophil count. On the test set, this model sensitivity was 79.3 %, specificity was 90 %, accuracy was 86.5 %, and AUC was 0.897 (Fig. 2). The PV diameter, variceal bleeding, and interventions on varices had the highest Wald test and OR.

Child–Pugh Class B/C

Portal hypertension

Ascites and variceal bleeding at the onset of portal hypertension were observed in approximately the same number of patients in the case and control groups, the frequency of ascites was 66 %, bleeding was 11–18 % (Table 1).

The duration of portal hypertension was statistically significantly longer in the case group, and its course was more often complicated by variceal bleeding and interventions on varices (OR 2.3; 95 % CI 1.3–4.1; $p < 0.01$). Among them, as for Class A, the most common procedure was endoscopic ligation (OR 2.4; 95 % CI 1.4–4.4; $p < 0.01$).

At the time of the study, portal hypertension had statistically significant more pronounced manifestations in the PVT group, with a higher proportion of patients with ascites, larger PV diameter and spleen length than in the control group. The cutoff point for the PV diameter was 13.4 mm and for spleen length was 17.1 cm; sensitivity, specificity, and AUC were 64 %, 72 %, 0.711 and 50 %, 81 %, 0.659, respectively.

At the time of the study overt HE was diagnosed more often in patients with PVT, 47.5 % vs. 36.6 % in the control group ($p = 0.066$, close to the level of statistical significance) (Table 1).

Comorbidities, local factors, malignant tumors

In terms of the frequency of concomitant diseases, GD and CHD were statistically significantly more

Table 1. Main characteristics of class A and B/C patients in case and control groups

Таблица 1. Основные характеристики пациентов классов А и В/С в группах «Случай» и «Контроль»

Characteristics Переменная	Child–Pugh class A Класс А по Child–Pugh			Child–Pugh class B/C Классы В/С по Child–Pugh		
	Case «Случай» n = 29	Control «Контроль» n = 60	p-value Значение p	Case «Случай» n = 101	Control «Контроль» n = 205	p-value Значение p
<i>Onset of portal hypertension: Симптомы на момент дебюта портальной гипертензии:</i>						
Variceal bleeding Кровотечение из ВРВ	6 (21 %)	4 (7 %)	<0.05	18 (17.8 %)	23 (11.2 %)	n.s.
Ascites Асцит	7 (24 %)	21 (35 %)	n.s.	67 (66.3 %) ^a	134 (65.4 %)	n.s.
Duration of portal hypertension, months Длительность портальной гипертензии, мес.	33 (13; 49)	8 (1; 31)	<0.05	17 (3; 47)	9 (1; 30)	<0.05
<i>Severity of portal hypertension at the time of the study: Тяжесть портальной гипертензии на момент исследования:</i>						
Variceal bleeding Кровотечение из ВРВ	12 (41 %)	4 (7 %)	<0.001	26 (25.7 %)	33 (16.1 %)	<0.05
EVL ЭЛ ВРВ	13 (45 %)	4 (7 %)	<0.001	29 (28.7 %)	29 (14.1 %)	<0.01
Any interventions on varices Любые вмешательства по поводу ВРВ	13 (45 %)	5 (8 %)	<0.001	31 (30.7 %)	33 (16.1 %)	<0.01
Ascites Асцит	7 (24 %)	5 (8 %)	<0.05	90 (89.1 %) ^a	140 (68.3 %)	<0.001
Hepatic encephalopathy Печеночная энцефалопатия	2 (7 %)	1 (2 %)	n.s.	48 (47.5 %) ^a	75 (36.6 %)	0.066
Portal vein diameter, mm Воротная вена, диаметр по УЗИ, мм	14.5 (12; 15.5)	12 (11; 13)	<0.001	13.8 (13.1; 16.2)	12.5 (11.3; 13.6)	<0.001
Spleen length, cm Селезенка, длинна по УЗИ, см	17.6 (15.7; 20.7)	14.8 (13; 15.9)	<0.001	17.3 (14.7; 18.9)	14.9 (13.6; 16.4)	<0.001
<i>Comorbidities: Сопутствующие заболевания:</i>						
DM СД	6 (21 %)	12 (20 %)	n.s.	31 (30.7 %)	45 (21.9 %)	n.s.
CHD ИБС	8 (28 %)	19 (32 %)	n.s.	42 (41.6 %)	58 (28.3 %)	<0.05
GD ЖКБ	12 (41 %)	25 (42 %)	n.s.	54 (53.5 %)	78 (38 %)	<0.05
Local factors Локальные факторы	2 (7 %)	3 (5 %)	n.s.	12 (11.9 %)	7 (3.4 %)	<0.01
Malignant tumors Злокачественные опухоли	1 (3 %)	3 (5 %)	n.s.	24 (23.8 %) ^a	13 (6.3 %)	<0.001
<i>Laboratory parameters: Лабораторные параметры:</i>						
Red blood cells, $\times 10^{12}/L$ Эритроциты, $\times 10^{12}/л$	4.1 (3.76; 4.38)	4.1 (3.72; 4.43)	n.s.	3.66 (3.3; 4.13) ^a	3.7 (3.21; 4.1)	n.s.
Hemoglobin, g/L Гемоглобин, г/л	121 (104; 129)	127.5 (111.3; 136.4)	n.s.	116 (97; 130)	119 (103.9; 132)	n.s.
Platelets, $\times 10^9/L$ Тромбоциты, $\times 10^9/л$	83 (55; 129)	95 (69; 136)	n.s.	95 (64; 136)	84 (58; 131)	n.s.

White blood cells, $\times 10^9/L$ Лейкоциты, $\times 10^9/L$	4.1 (3.2; 5.2)	3.85 (2.85; 5.43)	n.s.	4.1 (2.9; 6)	4.3 (3.1; 6.3)	n.s.
Neutrophils, $\times 10^9/L$ Нейтрофилы, $\times 10^9/L$	2.57 (1.83; 3.3)	2.14 (1.58; 2.92)	n.s.	2.33 (1.72; 3.65)	2.6 (1.74; 3.86)	n.s.
Lymphocytes, $\times 10^9/L$ Лимфоциты, $\times 10^9/L$	0.99 (0.64; 1.48)	1.25 (0.83; 1.76)	0.078	0.98 (0.64; 1.42)	1.19 (0.84; 1.79)	<0.001
NLR НЛИ	2.33 (1.82; 3.61)	1.76 (1.37; 2.2)	<0.01	2.49 (1.93; 3.34)	2.15 (1.49; 3.26)	<0.05
PLR ТЛИ	93 (70;108)	76 (57; 105)	n.s.	96 (68; 141)	74 (53;101)	<0.001
SII ИСВ	218 (165; 287)	172 (101;267)	n.s.	231 (137; 396)	179 (112; 354)	<0.05
Total protein, g/L Общий белок, г/л	70 (68.2; 74.8)	72.9 (68; 80)	n.s.	68 (62.9; 75)	69 (64; 74.8)	n.s.
Albumin, g/L Альбумин, г/л	37 (34.8; 40.1)	37 (34.3; 40.3)	n.s.	30 (26.2; 34.1) ^a	30.1 (26.1; 35.2)	n.s.
Total bilirubin, mg/dL Билирубин общий, мг/дл	1.2 (0.8; 1.5)	1.1 (0.8; 1.6)	n.s.	2.2 (1.4; 3.5) ^a	2.4 (1.5; 4.1)	n.s.
INR МНО	1.3 (1.17; 1.38)	1.13 (1.06; 1.20)	n.s.	1.28 (1.16; 1.49)	1.26 (1.16; 1.42)	n.s.
Fibrinogen, g/L	2.72 (2.13; 3.21)	2.87 (2.49; 3.28)	n.s.	2.4 (1.93; 3.04)	2.32 (1.89; 3.03)	n.s.

Note: the data is presented as counts and percentages, n (%), or as a median and interquartile range, Me (25th and 75th percentiles; 25 %; 75 %).

^a $p < 0.05$ in comparison of classes B/C and A.

n.s. — not significant, EVL — endoscopic variceal ligation, DM — diabetes mellitus, CHD — coronary heart disease, GD — gallstone disease, INR— international normalized ratio, NLR- neutrophil-to-lymphocyte ratio, PLR — platelet-to-lymphocyte ratio, SII — systemic inflammation index.

Примечание: данные представлены в виде абсолютного числа пациентов и доли от общего числа, n (%) либо в виде медианы и интерквартильного размаха Me (25-й, 75-й процентиля).

^a $p < 0.05$ при сравнении классов В/С и А.

n.s. — not significant, не значимо, ВРВ — варикозное расширение вен (пищевода/желудка), ЭЛ — эндоскопическое лигирование, УЗИ — ультразвуковое исследование, СД — сахарный диабет, ИБС — ишемическая болезнь сердца, ЖКБ — желчнокаменная болезнь, МНО — международное нормализованное отношение, НЛИ — нейтрофильно-лимфоцитарный индекс, ТЛИ — тромбоцитарно-лимфоцитарный индекс, ИСВ — индекс системного воспаления.

Table 2. Variables in the logistic regression equations for Child–Pugh class A

Таблица 2. Переменные в уравнениях логистической регрессии для класса А по Child–Pugh

Variable Переменная	Coefficient B Коэффициент В	Odds ratio Отношение шансов	95 % confidence interval 95 % доверительный интервал	p-value Значение p	Wald test Вальд-тест
Model 1: Модель 1:					
Any interventions on varices Все вмешательства по поводу ВРВ	2.3	9.98	2.57–38.76	<0.001	11.03
Portal vein diameter, mm Воротная вена, диаметр по УЗИ, мм	0.7	2.03	1.43–2.87	<0.001	15.7
Model 2: Модель 2:					
Ascites Асцит	2.5	12.12	1.58–92.93	0.016	5.77
Variceal bleeding Кровотечение из ВРВ	3.4	29.22	3.95–216.04	<0.001	10.9
Portal vein diameter, mm Воротная вена, диаметр по УЗИ, мм	0.89	2.44	1.62–3.66	<0.001	18.46
Neutrophils, $\times 10^9/L$ Нейтрофилы, $\times 10^9/L$	0.9	2.45	1.19–5.04	0.015	5.93

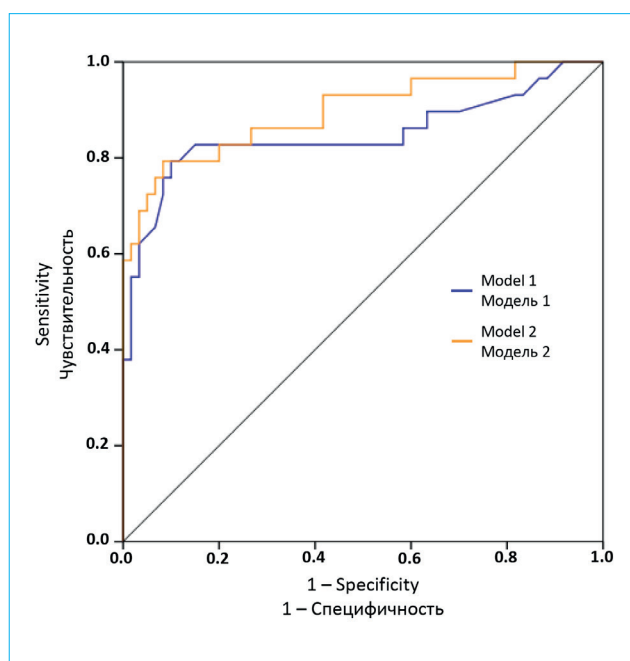


Fig. 2. ROC curves for Child–Pugh Class A

Рис. 2. ROC-кривые для класса А по Child–Pugh

common in the case group than in the control group, and DM also tended to a higher frequency in the case group ($p = 0.097$) (Table 2).

Local factors were diagnosed statistically significantly more often in the case group than in the control group (OR 3.8; 95 % CI 1.4–10.0; $p < 0.01$). Among them, abdominal surgeries, performed within 3 months before the diagnosis of PVT, predominated in the PVT group, and current exacerbation of IBD or *Clostridium difficile* infection predominated in the control group.

In 23.8 % of patients in the case group and 6.3 % in the control group, malignant tumors were newly diagnosed simultaneously with PVT (OR 4.6; 95 % CI 2.2–9.5; $p < 0.001$), HCC accounted for most of them (83–85 %) in both groups. Among the other tumors diagnosed simultaneously with PVT, colorectal cancer was diagnosed in one patient in the case group and one in the control group, breast cancer and uterine cancer were diagnosed in two patients in the case group. Prostate cancer was diagnosed two months before inclusion in the study in one patient in the control group.

The *JAK2 (V617F)* mutation was detected in one patient with PVT, splenomegaly, hypersplenism, and minimal degree of varices and very high spleen stiffness according to elastography, and on the basis of bone marrow examination, myeloproliferative disorder (MPD) such as masked polycythemia vera was newly diagnosed.

Laboratory parameters

No differences in red blood cell, platelet and white blood cell counts were found between the

groups. There was a lower level of lymphocytes and higher NLR, PLR and SII in the case group (Table 1).

As in patients with class A, there were no differences in the level of total protein, albumin, total bilirubin, INR, fibrinogen between the case and control groups of patients with class B/C.

Logistic regression and ROC analysis

Two predictive models with good quality indicators were selected for the B/C class (Table 3). Both models included three identical variables: PV diameter, spleen length, and presence of local factors/malignant tumors. The first model was supplemented with the variable "all interventions on varices". The model accuracy was 72.9 %, sensitivity was 74.3 %, specificity was 72.2 %, and AUC was 0.783.

In the second model, ascites was included as the fourth factor, and the sensitivity of the model was 73.3 %, specificity was 68.3 %, accuracy was 69.9 %, and AUC was 0.789 (Fig. 3). The local factors/malignant tumors and the PV diameter had the highest Wald test and OR in both models.

Comparison of Class A and B/C

When comparing the Child–Pugh scale parameters between Class A and B/C cases, statistically significant differences were predictably found in the frequency of ascites and HE, the concentration of albumin and total bilirubin. At the same time, INR did not differ between patients of classes A and B/C.

Among other parameters, significant differences were found in the level of red blood cells (lower in patients with Class B/C) and frequency of malignant tumors (higher in patients with Class B/C).

No differences were established between Class A and B/C in terms of the duration and severity of portal hypertension, frequency of comorbidities and local factors, white blood cells and platelets counts, systemic inflammation indices in patients with PVT.

Discussion

When assessing the prevalence of PVT among all patients in the presented study, it was 7.7 % (2011–2021), which is 1.5 % higher than in our previous study [5] covering 2006–2015 (no other similar studies in Russia could be found). This trend is consistent with the results of international studies demonstrating an increase in the frequency of PVT in recent years [8]. This may be due to several factors, including increased awareness of PVT and improved diagnostics, as well as an increase in the proportion of patients with non-alcoholic fatty liver disease.

The prevalence of non-malignant PVT among patients with Child–Pugh Class A in our study was estimated at 4.1 %, while in patients with Class B/C it was 2.5 times higher and amounted to 10.4 %. These

Table 3. Variables in the logistic regression equation for Child–Pugh class B/C

Таблица 3. Переменные в уравнениях логистической регрессии для класса В/С по Child–Pugh

Variable Переменная	Coefficient B Коэффициент В	Odds ratio Отношение шансов	95 % confidence interval 95 % доверительный интервал	p-value Значение p	Вальд-тест Wald test
<i>Model 1:</i> <i>Модель 1:</i>					
Portal vein diameter, mm Воротная вена, диаметр по УЗИ, мм	0.3	1.35	1.17–1.55	<0.001	16.9
Local factors / malignant tumors Локальные факторы / злокачественные опухоли	1.7	5.37	2.71–10.66	<0.001	23.1
Spleen length, cm Селезенка, длинна по УЗИ, см	0.1	1.15	1.03–1.28	0.012	6.36
Any interventions on varices Все вмешательства по поводу ВРВ	0.7	2.01	1.04–3.89	0.037	4.4
<i>Model 2:</i> <i>Модель 2:</i>					
Portal vein diameter, mm Воротная вена, диаметр по УЗИ, мм	0.3	1.33	1.15–1.54	<0.001	14.78
Local factors / malignant tumors Локальные факторы / злокачественные опухоли	1.5	4.42	2.25–8.70	<0.001	18.57
Spleen length, cm Селезенка, длинна по УЗИ, см	0.2	1.18	1.06–1.31	0.003	9.09
Ascites Асцит	0.9	2.49	1.18–5.24	0.017	5.74

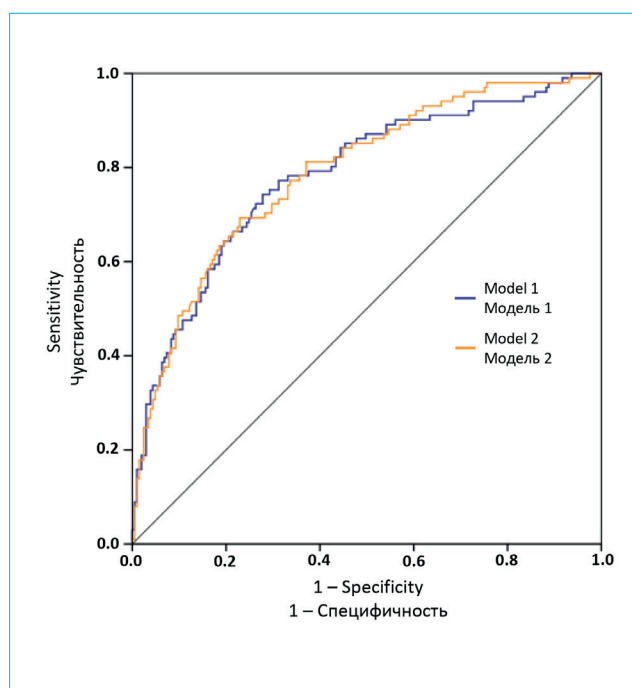


Fig. 3. ROC curves for Child–Pugh class B/C

Рис. 3. ROC-кривые для класса В/С по Child–Pugh

results are consistent with data from other studies, which have shown approximately a twofold increase in the frequency of PVT from Class A to Class B/C [3].

An increase in the frequency of PVT with a change in the Child–Pugh class from class A to B/C (or the development of decompensated cirrhosis) may be result from pathological mechanisms underlying the progression of LC and simultaneously constituting the Virchow's triad: portal hypertension and splanchnic vasodilation leading to decreased blood flow velocity in the PV, bacterial translocation causing endothelial damage, as well as an imbalance between physiological pro- and anticoagulants.

For all studied classes, the duration of portal hypertension in patients with PVT was statistically significantly longer than in control groups. This is consistent with prospective studies showing that the incidence of PVT increases with the duration of history of Child–Pugh class A/B LC: the frequency of PVT is 1.6–4.6 % by the end of the first year of follow-up, 6.0–8.2 % by the third year, 8.4–10.7 % by the fifth year [9, 10].

Both in class B/C and in class A, the course of portal hypertension in patients with PVT was more often complicated by variceal bleeding, recurrent bleeding, and interventions. Endoscopic ligation was the most frequent of them. These variables were shown as risk factors of PVT in retrospective studies of cirrhotic patients, who were on the waiting list for liver transplantation [11, 12]. During the multivariate analysis for Child–Pugh class A, one of the best logistic regression models included variceal bleeding (OR 29.22; 95 % CI 3.95–216.04), and another

included interventions on varices (OR 9.98; 95 % CI 2.57–38.76). These results suggest that the severity of portal hypertension is also a key risk factor of PVT for patients with compensated LC.

At the time of the study, portal hypertension had more pronounced manifestations in the PVT group for both class A and B/C, the proportion of patients with ascites, the PV diameter and the severity of splenomegaly were higher in the case group. Other studies have also shown that the PV diameter and large portosystemic collaterals are risk factors of PVT [13, 14]. In one of the studies, a cutoff point with predictive value for PVT of 12.5 mm was proposed for the PV diameter in patients with class A/B (AUC 0.88) [15]. In our study, the cutoff point was 13.4 mm for both class A and B/C (AUC 0.788 and 0.711, respectively).

The increase of PV diameter is an indirect indicator of a decrease in blood flow velocity in cirrhotic patients. In a prospective study by M.A. Zocco et al. [16] observed patients with cirrhosis for one year and proposed a linear velocity of blood flow in the PV of 15 cm/s as a threshold value for the risk of developing PVT. Subsequent studies have yielded conflicting data, with some confirming this value [9, 17] and others not [10]. F. Nery et al. [10] also note limitations of the reproducibility of PV blood flow velocity measurements depending on the equipment and operator. It is likely that the actual decrease in blood flow velocity in a specific patient is a more significant risk factor of PVT than the determination of threshold values. Indirect confirmation of this is the effectiveness of increasing portal blood flow velocity in restoring the patency of thrombosed PV and reducing the number of variceal recurrences after intrahepatic portosystemic shunt procedures [18, 19].

Recent studies have shown that patients with LC have higher concentrations of endotoxins (lipopolysaccharides (LPS)) and endothelial microparticles in the portal circulation compared to the systemic circulation, indicating predominantly endothelial damage in the PV [20]. At the same time, elevated concentrations of von Willebrand factor and factor VIII were detected in the PV, which were directly correlated with LPS levels [21].

Circulation of endotoxins in the blood increases the risk of thrombosis due to several factors. On the one hand, endotoxins activate tissue factor, triggering the extrinsic pathway of blood coagulation, resulting in increased levels of thrombin in the portal and systemic circulation [22]. On the other hand, endotoxins increase the NO production, worsening splanchnic vasodilation and further decreasing PV blood flow velocity [22]. Finally, endotoxins affect the endothelial cells of liver sinusoids, leading to increased synthesis of factor VIII and von Willebrand factor, decreased thrombomodulin activity and contributing to the platelet activation [23, 24].

In our study, no differences were found between the case and control groups in terms of platelet

count, INR, and fibrinogen levels for patients with cirrhosis class A, as well as B/C. Previous studies have also not found a link between these parameters and the development of PVT, which does not allow them to be used in real clinical practice as prognostic markers of PVT [3].

When considering portal hypertension as a key mechanism for the development of PVT in cirrhotic patients, it is important to note that a decrease in its degree and an increase in blood flow velocity, especially after transjugular intrahepatic portosystemic shunt procedure, is not accompanied by PV recanalization in one-third of patients [19]. This may be due to the preservation of prothrombotic factors: an imbalance between pro- and anticoagulants and platelet activation even with reduced numbers. One of the reasons for platelet activation can be inflammation associated with LPS, the concentration of which is increased in PV during portal hypertension and bacterial translocation [25]. Recent data have shown that low-grade systemic inflammation, endotoxemia caused by changes in the gut microbiome and increased intestinal permeability in LC, may be associated with PVT through different mechanisms such as increased NO synthesis and decreased portal blood flow, increased secretion of factor VIII, von Willebrand factor, tissue factor, neutrophil extracellular traps, eicosanoids, and increased activity of the coagulation system [26].

The assessment of inherited and acquired thrombophilias was not performed in our study. According to the results of the meta-analysis by X. Qi et al. [27], the link between the deficiency of natural anticoagulants synthesized in the liver (proteins C and S, antithrombin) and the development of PVT in cirrhotic patients has not been established. The question of the role of inherited thrombophilias (prothrombin *G20210A* gene mutation and factor V Leiden mutations) in the development of PVT in patients with LC remains controversial. Although several meta-analyses have shown an association between these thrombophilias and the risk of PVT in cirrhotic patients, all of these meta-analyses had biased results due to the quality of the included studies [28]. Currently, there are no recommendations on the need to screen all patients with cirrhosis and PVT for inherited thrombophilias [29].

Local factors (primarily abdominal surgeries) were more frequently detected in patients with Class B/C and PVT than in controls (OR 3.8; 95 % CI 1.4–10.0; $p < 0.01$). Major studies separately evaluating these factors in PVT patients could not be found in the literature. In a large retrospective cohort study, abdominal surgeries and invasive procedures including endoscopic ligation and sclerotherapy were found to be independent predictors of PVT in hospitalized patients with LC (OR 2.03; 95 % CI 1.56–2.64, $p < 0.0001$) [30].

Besides cirrhosis, malignant tumors, mainly HCC, as well as other gastrointestinal cancer, are

considered significant risk factors for splanchnic vein thrombosis [31]. In the study by S. Handa et al. [32], the prevalence of gastrointestinal cancer among patients hospitalized for splanchnic vein thrombosis was 10 %, of which HCC was 5 %, pancreatic cancer was 2.9 %, and colorectal cancer was 1.6 %. The risk of developing new tumors in these locations is estimated to be twice as high in patients with LC as in the general population [33, 34].

In our study, malignant tumors diagnosed simultaneously with PVT were one of the significant risk factors for developing PVT in patients of class B/C (OR 4.6; 95 % CI 2.2–9.5; $p < 0.001$). Among all tumors, non-invasive HCC accounted for 83 %. In the study by A. Zanetto et al. [35], the frequency of PVT associated with HCC was 24.4 %, with half of these patients having Child–Pugh class A, allowing the authors to consider these patients similarly to class B/C, as a risk group for PVT. In our study, only one patient with HCC was diagnosed simultaneously with PVT in class A patients, and no differences were observed between cases and controls. In addition to PVT, three patients of class B/C were diagnosed with other malignant tumors such as colorectal cancer, breast cancer, and uterine cancer. The mechanism of cancer-associated thrombosis in HCC and other malignant tumors is associated with tissue factor production, thrombocytosis, systemic inflammation, increased extracellular microvesicles, and neutrophil extracellular traps [36].

It is well known that one of the most common risk factors for PVT in patients without cirrhosis is MPDs, which can be combined with cirrhosis. In our study, among all groups, only one patient with class B/C was diagnosed with MPD (masked polycythemia vera) simultaneously with PVT, thus, the frequency of MPDs was 0.7 %. Comparable data were obtained by J.I. Fortea et al. [37] when studying thrombophilic factors in patients with cirrhosis and PVT, the frequency of MPD was low and amounted to 1.3 % (1 out of 77 patients). It should be noted that hypersplenism and hemodilution, which occur in LC, make standard MPDs criteria inapplicable, mask the disease, and hinder diagnosis. Molecular diagnostic methods, such as *JAK2* (Janus kinase 2), *CALR* (calreticulin), and *MPL* (myeloproliferative leukemia virus oncogene) gene mutation analysis, can help in diagnosing MPDs. Despite the absence of erythrocytosis and/or thrombocytosis in patients with portal hypertension and hypersplenism, the development of MPD contributes to PVT through the prothrombotic phenotype of tumor blood cells, their secretion of procoagulant cytokines, chronic inflammation, and endothelial damage and dysfunction [31].

When comparing laboratory parameters among patients with class A and those with class B/C, the level of NLR was higher in the group with PVT, and the concentration of neutrophils was included in the predictive model of PVT for LC class A in

our study. Given that patients differed statistically significant in the degree of portal hypertension in the case and control groups, it can be assumed that NLR are also associated with the degree of portal hypertension. An increase in the level of NLR may reflect the presence of a low-grade systemic inflammatory phenotype in patients with PVT [38], which is realized, including through the concentration of bacterial endotoxins (LPS) in the PV, which contributes to thrombosis [39].

Considering the association of PVT with increased levels of systemic inflammatory markers, NLR, PLR, SII, and monocyte-to-lymphocyte ratio have been proposed as available clinical indices. Several studies have shown a positive correlation between the NLR level and the development of LC decompensation [40, 41], and in some studies, the association of all indices with the development of PVT [42] was established. In our study, compared to the control the association with PVT was demonstrated in class A and B/C for NLR and in classes B/C for PLR and SII.

Among cirrhotic patients with class B/C, CHD and GD were more common in case group than in the control. Studies assessing the frequency of these diseases in cirrhotic patients and PVT were not found. In the meta-analysis by J. Li et al. [43], an increased risk of PVT by 3.6 times was shown in the presence of hypercholesterolemia in patients with LC, which can be cautiously assumed as a potential risk factor for CHD and GD in our study (we did not include the cholesterol level in the analysis due to the large number of missing values).

At the same time, it is well known that the frequency of GD in cirrhotic patients is 2–4 times higher than in the population, and in our study, its frequency was 43 %, which is consistent with the data of other studies [44]. The increase in the incidence of GD in cirrhosis is associated with several mechanisms, one of which is portal hypertension [45], which was most pronounced in patients with PVT. Therefore, we consider the high frequency of GD in the group of patients with class B/C and PVT compared to the control group as a consequence of the severity of LC and portal hypertension, rather than as an independent risk factor for PVT.

Two studies published in 2022 (a meta-analysis and one of the largest retrospective cohorts) showed an increased risk of developing PVT in patients with DM by 1.7–1.8 times, which is associated with chronic inflammation, contributing to systemic endothelial dysfunction and hypercoagulability [30, 43]. In our study, there were no significant differences in the frequency of DM between cases and controls, although there was a tendency towards a higher frequency in patients with PVT and class B/C.

The limitations of the study include a relatively small number of observations, a retrospective design, and the inclusion of only hospitalized patients. 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, replacing missing data with the mean in subgroups based on age and etiology of liver disease, and dividing the samples into training and test sets to evaluate the quality of the model.

As directions for further research, prospective studies could be considered to study the phenotype of low-grade systemic inflammation as a risk factor for PVT, its association with bacterial translocation, and other complications of LC.

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Conclusion

The prevalence of PVT increases 2.5 times from Child–Pugh class A to B/C. Regardless of the LC class by Child–Pugh, in the presence of severe portal hypertension (history of variceal bleeding/interventions on varices, presence of ascites, large PV diameter and spleen length), it is necessary to exclude the PVT. The detection of PVT in a patient with LC requires primarily the exclusion of HCC, as well as, if indicated, other malignancies and MPD. Routine parameters for evaluating the hemostatic system are not applicable for assessing the risk of PVT in patients with cirrhosis.

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