Original article / Оригинальная статья
https://doi.org/10.47093/2218-7332.2024.1075.16

Compensated advanced chronic liver disease in patients with metabolic dysfunction-associated steatotic liver disease: association with cardiometabolic factors

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Abstract

Aim. To study cardiometabolic factors and the *PNPLA3* I148M (rs738409 C>G) gene polymorphism in association with the compensated advanced chronic liver disease (cACLD) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).
Materials and methods. A retrospective cross-sectional study was conducted. The total of 108 patients with MASLD (33 men and 75 women aged 28 to 89 years) involved were divided into two groups based on results of transient elastography: group 1 – with the presence of cACLD (liver stiffness ≥ 8.0 kPa) – 18 patients and group 2 – without cACLD (<8.0 kPa) – 90 patients. Cardiometabolic risk factors and the *PNPLA3* I148M (rs738409 C>G) gene polymorphism were studied in both groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and a logistic regression model was constructed for the detection of cACLD.
Results. Compared to group 2, patients with cACLD had statistically significant higher prevalence of: arterial hypertension ($p < 0.05$), type 2 diabetes mellitus ($p < 0.01$), obesity ($p < 0.05$), dyslipidemia ($p < 0.05$), and *PNPLA3* gene polymorphism ($p < 0.05$). The OR for cACLD in individuals with arterial hypertension was 5.58 (95% CI: 1.21–25.71; $p < 0.05$), with type 2 diabetes mellitus – 4.58 (95% CI: 1.59–13.21; $p < 0.01$), with obesity – 3.83 (95% CI: 1.17–12.52; $p < 0.05$), with dyslipidemia – 6.12 (95% CI: 1.33–28.20; $p < 0.05$), in the presence of a polymorphic variant of the *PNPLA3* gene in a hetero or homozygous state – 3.9 (95% CI: 1.28–11.89; $p < 0.05$). The binary logistic regression model for detecting cACLD included type 2 diabetes mellitus, dyslipidemia, and waist circumference. The area under the ROC curve was 0.81 (95% CI: 0.70–0.92), sensitivity was 72.2%, specificity was 74.4%, and accuracy was 84.3%.
Conclusion. Type 2 diabetes mellitus, dyslipidemia, and waist circumference are the determining factors for the development of cACLD in patients with MASLD. The *PNPLA3* I148M gene polymorphism does not play a leading role in the development of progressive MASLD in the study cohort.

Keywords: nonalcoholic fatty liver disease; *PNPLA3*; transient elastography; controlled attenuation parameter; dyslipidemia; type 2 diabetes mellitus; waist circumference
MeSH terms:
FATTY LIVER DISEASE – GENETICS
FATTY LIVER DISEASE – COMPLICATIONS
FATTY LIVER DISEASE – PHYSIOPATHOLOGY
CARDIOMETABOLIC RISK FACTORS
GENOTYPING TECHNIQUES
For citation: Gomonova V.P., Raikhelson K.L., Pazenko E.V., Prashnova M.K., Lapin S.V., Nazarov V.D., Sidorenko D.V. Compensated advanced chronic liver disease in patients with metabolic dysfunction-associated steatotic liver disease: association with cardiometabolic factors. Sechenov Medicine Journal. 2024; 15(3): 15–25. Epub ahead of print 04.09.2024. https://doi.org/10.47093/2218-7332.2024.1075.16

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Ethics statements. This study was not required to be reviewed by the Biomedical Ethics Committee of the N.I. Pirogov Clinic of High Medical Technologies (outpatient clinic, hospital) of St. Petersburg State University due to the retrospective design and the use of patient data in an anonymized form (outgoing No. 11/22 dated November 12, 2022).
Data availability. The data that support the findings of this study are available from the corresponding authors on reasonable request. Data and statistical methods used in the article were examined by a professional biostatistician on the Sechenov Medical Journal editorial staff.
Conflict of interests. The authors declare that there is no conflict of interests.
Financial support. The study was not sponsored (own resources).
Acknowledgments. We would like to express special gratitude to Professor, Doctor of Medical Sciences Lyudmila Konstantinovna Palgova for invaluable contribution to the organization of the study.

Received: 06.06.2024
Accepted: 19.07.2024
Date of publication online: 04.09.2024
Date of publication: 25.10.2024

УДК 616.36-003.826-092

Компенсированное продвинутое хроническое заболевание печени у пациентов с метаболически ассоциированной жировой болезнью печени: ассоциация с кардиометаболическими факторами

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Аннотация

Цель: изучить ассоциацию кардиометаболических факторов и полиморфизма гена *PNPLA3* I148M (rs738409 C>G) с развитием компенсированного продвинутого хронического заболевания печени (КПХЗП) у пациентов с метаболически ассоциированной жировой болезнью печени (МАЖБП).
Материалы и методы. Проведено ретроспективное одномоментное исследование с включением 108 пациентов с МАЖБП (33 мужчины и 75 женщин в возрасте от 28 до 89 лет), которые по данным транзиентной эластографии были разделены на две группы: группа 1 – с наличием КПХЗП (жесткость печени ≥ 8,0 кПа) – 18 пациентов и группа 2 – с отсутствием КПХЗП (<8,0 кПа) – 90 пациентов. В обеих группах изучались кардиометаболические факторы риска, полиморфизм гена *PNPLA3* I148M (rs738409 C>G). Рассчитаны отношения шансов (ОШ) и 95% доверительные интервалы (ДИ), построена модель логистической регрессии обнаружения КПХЗП.
Результаты. У пациентов с КПХЗП по сравнению с группой 2 статистически значимо чаще выявлялись: артериальная гипертензия (p < 0,05), сахарный диабет 2-го типа (p < 0,01), ожирение (p < 0,05), дислипидемия (p < 0,05) и полиморфизм гена *PNPLA3* (p < 0,05). ОШ для КПХЗП у лиц с артериальной гипертензией составило 5,58 (95% ДИ: 1,21–25,71; p < 0,05), с сахарным диабетом 2-го типа – 4,58 (95% ДИ: 1,59–13,21; p < 0,01), с ожирением – 3,83 (95% ДИ: 1,17–12,52; p < 0,05), с дислипидемией – 6,12 (95% ДИ: 1,33–28,20; p < 0,05), при наличии полиморфного варианта гена *PNPLA3* в гетеро- или гомозиготном состоянии – 3,9 (95% ДИ: 1,28–11,89; p < 0,05). В модель бинарной логистической регрессии обнаружения КПХЗП вошли сахарный диабет 2-го

типа, дислипидемия и окружность талии. Площадь под ROC-кривой составила 0,81 (95% ДИ: 0,70–0,92), чувствительность – 72,2%, специфичность – 74,4%, точность – 84,3%.
Заключение. Сахарный диабет 2-го типа, дислипидемия и значения окружности талии являются определяющими факторами в развитии КПХЗП у пациентов с МАЖБП. Полиморфизм гена *PNPLA3* I148M не имеет ведущего значения в развитии прогрессирующего течения МАЖБП в исследуемой когорте.

Ключевые слова: неалкогольная жировая болезнь печени; *PNPLA3*; транзиентная эластография; контролируемый параметр затухания ультразвука; дислипидемия; сахарный диабет 2-го типа; окружность талии
Рубрики MeSH:
НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ – ГЕНЕТИКА
НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ – ОСЛОЖНЕНИЯ
НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ – ПАТОФИЗИОЛОГИЯ
КАРДИОМЕТАБОЛИЧЕСКИЕ ФАКТОРЫ РИСКА
ГЕНОТИПИРОВАНИЯ МЕТОДЫ
Для цитирования: Гомонова В.П., Райхельсон К.Л., Пазенко Е.В., Прашнова М.К., Лапин С.В., Назаров В.Д., Сидоренко Д.В. Компенсированное продвинутое хроническое заболевание печени у пациентов с метаболически ассоциированной жировой болезнью печени: ассоциация с кардиометаболическими факторами. Сеченовский вестник. 2024; 15(3): 15–25. Публикация онлайн 04.09.2024. https://doi.org/10.47093/2218-7332.2024.1075.16

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Соответствие принципам этики. Рассмотрение данного исследования на заседании Комитета по биомедицинской этике Клиники высоких медицинских технологий им. Н.И. Пирогова (поликлиники, стационара) ФГБОУ ВО «Санкт-Петербургский государственный университет» не требовалось в связи ретроспективным дизайном и использованием данных пациентов в деперсонифицированном виде (исх. № 11/22 от 12 ноября 2022 г.).
Доступ к данным исследования. Данные, подтверждающие выводы этого исследования, можно получить у авторов по обоснованному запросу.
Данные и статистические методы, представленные в статье, прошли статистическое рецензирование редактором журнала – сертифицированным специалистом по биостатистике.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки.
Благодарности. Выражаем особую благодарность профессору, д-ру мед. наук Пальговой Людмиле Константиновне за неоценимый вклад в организацию проведения исследования.

Поступила: 06.06.2024
Принята: 19.07.2024
Дата публикации онлайн: 04.09.2024
Дата печати: 25.10.2024

Abbreviations:
PNPLA3 – Patatin-Like Phospholipase Domain Containing 3, patatin-like phospholipase domain containing protein-3
AH – arterial hypertension
HCC – hepatocellular carcinoma
CI – confidence interval
CAP – controlled attenuation parameter
cACLD – compensated advanced chronic liver disease
MASLD – metabolic dysfunction-associated steatotic liver disease
NAFLD – non-alcoholic fatty liver disease
T2DM – type 2 diabetes mellitus
TE – transient elastography

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality [1–4]. According to recent meta-analyses, the global prevalence of NAFLD is more than 30% and is on the increase [1, 3]. A similar situation can be observed in the Russian Federation [4].

It is already known that the vast majority of cases of liver steatosis are associated with metabolic dysfunction. An international consensus of 2023 clarified the concept of “metabolic dysfunction-associated steatotic liver disease” (MASLD) and proposed new criteria: the presence of liver steatosis in combination with at least one of the five cardiometabolic risk factors. During the work on establishing the consensus, it was shown that 98% of patients with NAFLD meet the criteria for MASLD [5]. According to Russian experts, despite the continued use of the term NAFLD in our country in official medical documentation, the concept of MASLD and its diagnostic criteria should be actively used in scientific research [6].

In some patients, MASLD can progress with the formation of such unfavorable outcomes as liver cirrhosis, hepatocellular carcinoma (HCC), and increase mortality associated with liver disease [7]. Since the severity of fibrosis is one of the strongest predictors for clinical outcomes of MASLD, special attention is paid to its diagnosis. Liver biopsy remains the reference method for this purpose, but it is not suitable for common clinical practice due to well-known limitations (invasiveness of the procedure and its possible complications) [8]. Therefore, in recent years, emphasis has been placed on the use of non-invasive methods for assessing fibrosis, primarily transient elastography (TE), to identify patients with a likely progressive course of the disease [9–11].

Practical advantages and accessibility of non-invasive methods reduces demand for liver biopsy in determining at what stage the disease is at. The aforementioned and the need for new methods of risk stratification regarding clinically significant portal hypertension led to the emergence of a new term, “compensated advanced chronic liver disease” (cACLD), in 2015 [12]. It represents severe fibrosis and compensated cirrhosis as a continuum, the stages of which are often impossible to distinguish in clinical practice. To identify cACLD, threshold values of liver stiffness based on TE data have been proposed (<10 kPa – excludes cACLD in the absence of other clinical signs, 10-15 kPa – indicate the probability of cACLD, which requires additional studies to confirm, > 15 kPa – highly indicate the presence of cACLD) [11,13].

In recent years, the threshold values of TE have been revised for individual liver diseases. Thus, for NAFLD, it is recommended to use values <8 kPa to exclude cACLD, and a result ⩾ 12 kPa to diagnose cACLD (in the absence of other known clinical/visualizing signs of cACLD) [14]. These liver stiffness threshold criteria are also recommended for use in the Russian Federation [15].

The high prevalence of the disease, the increase in morbidity and the frequency of severe complications determine the importance for studying the various factors of MASLD progression. The progression of the disease depends on a number of characteristics such as genetics, ethnicity, environment, diet and more. These factors differ across populations and regions of the world [16]. In particular, the polymorphism of the *PNPLA3* I148M gene (Patatin-Like Phospholipase Domain Containing 3, patatin-like phospholipase domain containing protein-3) plays a key role in the development of MASLD, but its influence in different ethnic groups is ambiguous which is probably explained by epigenetic components [17]. In the Russian population, the influence of this polymorphism on the course of MASLD has been studied only in certain regions and in isolated studies [18-20].

The aim of the study: to study the association of cardiometabolic factors and the polymorphism of the *PNPLA3* I148M gene (rs738409 C>G) with the development of MASLD.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted. The primary medical records of all patients diagnosed with NAFLD (K76.0 according to the International Classification of Diseases, 10th revision) who underwent liver elastography at the Saint Petersburg State University Hospital in the period from October 14, 2019 to November 4, 2022 were analyzed. Liver stiffness and the severity of steatosis were assessed using a FibroScan® 502 Touch device (Echosens, France) with a controlled attenuation parameter (CAP) function.

Inclusion criteria for the study: age 18 years and older, Caucasian race, presence of steatosis according to TE: CAP > 248 dB/m^2, presence of one or more cardiometabolic risk factors (additional materials on the journal website https://doi.org/10.47093/2218-7332.2024.1075.16-table).

Exclusion criteria were: pregnancy, hereditary lipid metabolism disorders, type 1 diabetes mellitus, HIV infection, another etiology of liver disease: alcoholic (ethanol consumption >30 g/day for men and >20 for women), viral (hepatitis B and C), drug-induced, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, Wilson’s disease, congenital liver fibrosis, diagnosed liver cirrhosis and/or signs of portal hypertension (esophageal varices, portosystemic collaterals, ascites).

Of the 423 patients diagnosed with NAFLD, 108 were included in the study: 33 men and 75 women, aged 28 to 89 years (Fig. 1).

The patients were then divided into two groups based on the threshold liver stiffness value of 8.0 kPa according to TE. Group 1 (presence of NAFLD) included 18 patients with liver stiffness ⩾ 8.0 kPa, and group 2

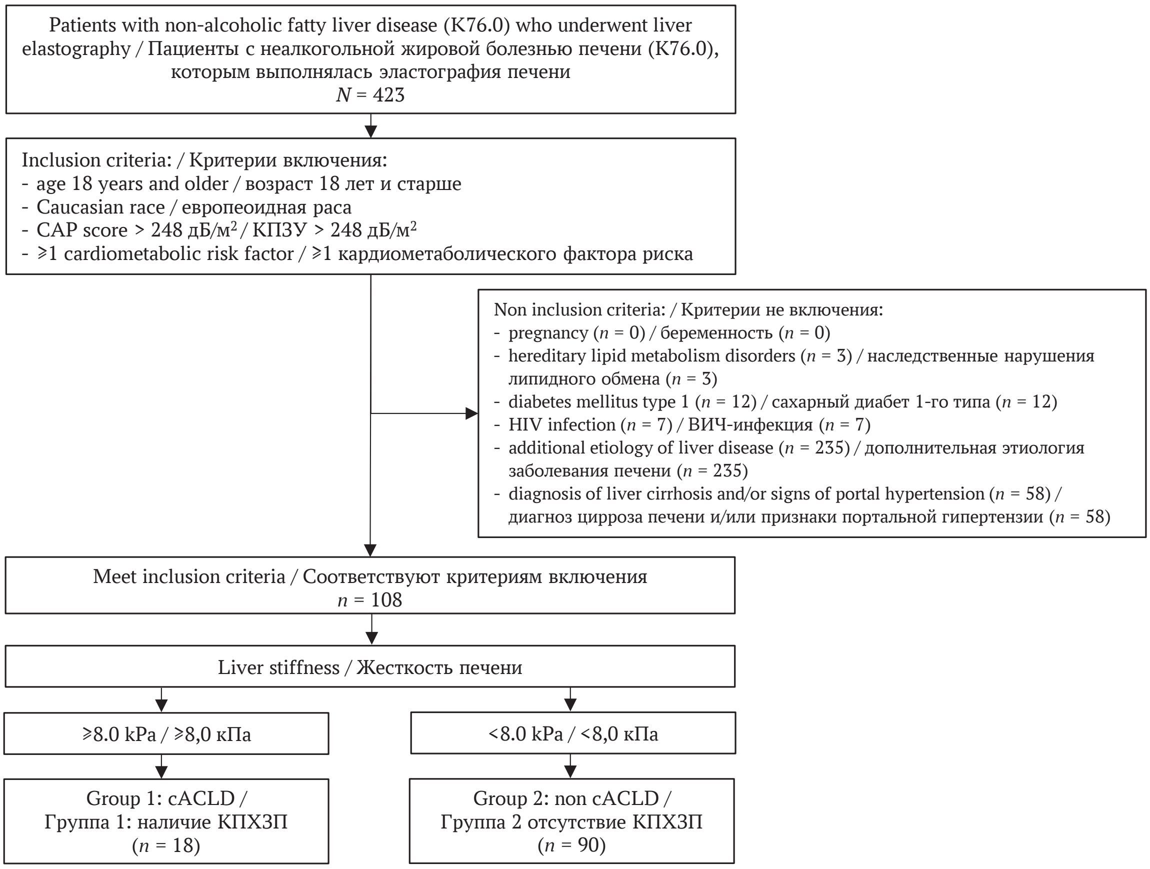

FIG. 1. Study enrollment flowchart.

Note: CAP score – The Controlled Attenuation Parameter; cACLD – compensated advanced chronic liver disease.

РИС. 1. Потоковая диаграмма включения пациентов в исследование.

Примечание: КПЗУ – контролируемый параметр затухания ультразвука; КПХЗП – компенсированное продвинутое хроническое заболевание печени.

(absence of NAFLD) included 90 patients with liver stiffness < 8.0 kPa.

In both groups, cardiometabolic risk factors were studied (https://doi.org/10.47093/2218-7332.2024.1075.16-table): body mass index (the criteria of the World Health Organization were used for classification, where index values ⩾30 kg/m² were regarded as obesity[1]), waist circumference, the presence of arterial hypertension (AH), type 2 diabetes mellitus (T2DM), dyslipidemia. Dyslipidemia was defined based on presence of one or more of the following criteria: triglyceride concentration ⩾1.7 mmol/l, high-density lipoprotein concentration ⩽1.0 mmol/l (in men) and ⩽1.3 mmol/l (in women), or taking lipid-lowering therapy.

All patients had their platelet levels, serum alanine and aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, glucose levels, and lipid spectrum determined.

The *PNPLA3* I148M gene polymorphism (rs738409 C>G) was studied using the polymerase chain reaction in saliva samples (TestGen kit, Russia) in the laboratory for diagnostics of autoimmune diseases (Pavlov First Saint Petersburg State Medical University).

Statistical data processing

The study used parametric and nonparametric analysis methods. Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro–Wilk test (for a sample of less than 50) or the Kolmogorov–Smirnov test (for a sample of more than 50), as well as asymmetry and excess indicators. When comparing average values in normally distributed sets of quantitative data, the Student *t*-test was calculated; in cases with no signs of normal data distribution, the Mann–Whitney *U*-test was used. Comparison of nominal data was carried out using the Pearson χ^2 test; in cases where the number of expected observations in any cell of the four-field table was less than 5, Fisher's exact test was used to assess the significance level of differences. To quantitatively assess the effect, the odds ratio was calculated with the boundaries defined at the 95% confidence interval (CI). The strength of the relationship

[1] World Health Organization. https://www.who.int/health-topics/obesity/#tab=tab_1 (accessed: 10.05.2024).

between categorical data was assessed using the Cramer *V* coefficient.

The construction of a prognostic model for the risk of developing cACLD was performed using the binary logistic regression method. The logistic regression model included the following data: the presence of AH, T2DM, obesity, dyslipidemia, WC values, CAP, and the presence of *PNPLA3* gene polymorphism.

To assess the diagnostic significance of quantitative features in predicting cACLD, the ROC curve analysis method was used. With its help, the optimal cut-off value was determined which allows classifying patients by the risk of cACLD, with the best combination of sensitivity and specificity. The quality of the prognostic model obtained by this method was assessed using the Nigelkirk determination coefficient and the area under the ROC curve with a standard error and 95% CI.

The critical significance level of the null statistical hypothesis was taken to be 0.05. Statistical data processing was performed using the IBM SPSS v.26.0 program (SPSS: An IBM Company, USA).

RESULTS

The main results of anthropometric, laboratory and instrumental studies are presented in Table 1.

In the group with cACLD, compared to group 2, a statistically significant increase in laboratory markers of cytolysis (alanine and aspartate aminotransferases), as well as gamma-glutamyl transferase was observed while the concentration of platelets, bilirubin, glucose and alkaline phosphatase activity did not differ. A higher average liver steatosis index – CAP was observed in group 1 than in group 2 ($p < 0.01$), as well as higher values of individual cardiometabolic risk indicators: waist circumference and triglyceride content (Table 1).

The vast majority of patients had abdominal obesity without significant differences between the groups, while the waist circumference indicators were higher in the cACLD group.

Analysis of anamnestic data showed that patients with cACLD were more likely to have AH, T2DM, obesity, dyslipidemia, and *PNPLA3* gene polymorphism, than those in group 2. The odds of detecting cACLD in individuals with AH increased by 5.58 times (95% CI: 1.21-25.71, $p < 0.05$), with T2DM − by 4.58 times (95% CI: 1.59-13.21, $p < 0.01$), in the presence of obesity − by 3.83 times (95% CI: 1.17-12.52, $p < 0.05$), dyslipidemia − by 6.12 times (95% CI: 1.33-28.20, $p < 0.05$), polymorphic variant of the *PNPLA3* gene in hetero- or homozygous state – 3.9 times (95% CI: 1.28–11.89, $p < 0.05$). There was a moderate strength of association between all these signs and the presence of cACLD (Cramer's V range = 0.2–0.3).

Using the binary logistic regression method, a prognostic model was developed to determine the probability of developing cACLD depending on the presence of cardiometabolic factors, the *PNPLA3* I148M gene polymorphism, and the CAP value.

The observed dependence is described by equation (1):

$$p = \frac{1}{1 + e^{-z}}, \quad (1)$$

$$z = -9.14 + 1.13 \times X_{T2DM} + 1.77 \times X_{D} + 0.05 \times X_{WC},$$

where p is the probability of having cACLD, T2DM is the presence of type 2 diabetes mellitus (0 – absence, 1 – presence), D is the presence of dyslipidemia (0 – absence, 1 – presence), WC is waist circumference (cm).

The resulting regression model is statistically significant ($p < 0.001$). According to the value of the Nigelkirk determination coefficient, model (1) takes into account 30.3% of the factors determining the dispersion of the probability of detecting cACLD. Based on the values of the regression coefficients, the value of waist circumference, the presence of dyslipidemia and T2DM had a direct relationship with the probability of detecting cACLD. The characteristics of each factor are presented in Table 2.

The threshold value of the logistic function p was determined using the ROC curve analysis method. The resulting curve is shown in Fig. 2.

The area under the ROC curve was 0.81 (95% CI: 0.70–0.92). The value of the logistic function (1) at the cut-off point was 0.192. The sensitivity and specificity of the model (1) at this cut-off value were 72.2% and 74.4%, respectively, and the accuracy was 84.3%.

DISCUSSION

In the cohort of patients studied, an association between detection of cACLD and obesity, waist circumference, T2DM, AH, dyslipidemia, *PNPLA3* gene polymorphism, and the CAP index was shown. Moreover, in patients with dyslipidemia, an increase in the level of triglycerides became the determining factor for identifying cACLD, while other lipidogram indices (total cholesterol, high-density lipoprotein and low-density lipoprotein levels) did not differ significantly in the study groups.

Thrombocytopenia in peripheral blood is considered one of the early markers of liver cirrhosis [21]. No significant difference was found in our study: the platelet count was within the reference values in most of the patients.

When compiling a prognostic model that took into account the total contribution of the studied factors, it was found that only T2DM, waist circumference, and the presence of dyslipidemia had a significant impact on the development of cACLD. An analysis of literature from around the world showed an ambiguous influence of metabolic factors on MASLD outcomes in different countries. In the study by F. Kanwal et al., 2020 [22], the independent and combined

Table 1. **Characteristics of the study groups**
Таблица 1. **Характеристики исследуемых групп**

Variable / Параметр	Group 1 (cACLD) / Группа 1 (наличие КПХЗП), *n*=18	Group 2 (non cACLD) / Группа 2 (отсутствие КПХЗП), *n*=90	*p*-value / Значение *p*
Age, years / Возраст, полных лет	61.17 ± 3.06	61.26 ± 1.51	n.s.
Sex, men, *n* (%) / Пол, мужчины, *n* (%)	7 (39)	25 (28)	n.s.
Sex, women, *n* (%) / Пол, женщины, *n* (%)	11 (61)	65 (72)	n.s.
Body mass index, kg/m^2 / Индекс массы тела, кг/м^2	33.92 ± 6.09	31.02 ± 6.63	n.s.
Obesity, *n* (%) / Ожирение, *n* (%)	14 (78)	43 (48)	<0.05
Waist circumference, cm / Окружность талии, см	109.71 ± 16.25	98.41 ± 11.69	<0.01
Abdominal obesity, *n* (%) / Абдоминальное ожирение, *n* (%)	18 (100)	80 (89)	n.s.
Arterial hypertension, *n* (%) / Артериальная гипертензия, *n* (%)	16 (89)	53 (59)	<0.05
Type 2 diabetes mellitus, *n* (%) / Сахарный диабет 2-го типа, *n* (%)	11 (61)	23 (26)	<0.01
Antihypertensive therapy, *n* (%) / Антигипертензивная терапия, *n* (%)	16 (89)	53 (59)	<0.05
Lipid-lowering therapy, *n* (%) / Липидснижающая терапия, *n* (%)	11 (61)	43 (48)	n.s.
Platelets, ×10^9/l / Тромбоциты, ×10^9/л	225.91 ± 83.72	262.5 ± 61.5	n.s.
Fasting blood glucose, mmol/l / Глюкоза крови натощак, ммоль/л	6.59 (5.15; 8.05)	5.73 (5.33; 6.12)	n.s.
Total cholesterol, mmol/l / Общий холестерин, ммоль/л	6.11 ± 1.25	5.45 ± 1.27	n.s.
High-density lipoprotein, mmol/l / Липопротеиды высокой плотности, ммоль/л	1.41 ± 0.46	1.37 ± 0.39	n.s.
Low-density lipoprotein, mmol/l / Липопротеиды низкой плотности, ммоль/л	4.05 ± 1.09	3.36 ± 1.17	n.s.
Triglycerides, mmol/l / Триглицериды, ммоль/л	2.08 (1.61; 2.56)	1.83 (1.16; 2.49)	<0.01
Dyslipidemia, *n* (%) / Дислипидемия, *n* (%)	16 (89)	51 (57)	<0.05
ALT, U/L / АЛТ, Ед/л	73.02 (44.11; 101.93)	46.14 (39.11; 53.18)	<0.05
AST, U/L / АСТ, Ед/л	54.94 (38.55; 71.34)	32.17 (27.23; 37.12)	<0.01
Alkaline phosphatase, U/L / Щелочная фосфатаза, Ед/л	103.62 ± 38.61	110.52 ± 65.11	n.s.
Gamma-glutamyl transferase, U/L / Гамма-глутамилтрансфераза, Ед/л	114.22 (46.71; 181.72)	71.42 (42.13; 100.74)	<0.05
Total bilirubin, µmol/l / Билирубин общий, мкмоль/л /	17.28 (4.26; 30.31)	15.44 (11.74; 19.14)	n.s.
Liver stiffness, kPa / Жесткость печени, кПа	10.92 ± 3.69	5.53 ± 1.08	<0.0001
CAP, dB/m^2 / КПЗУ, дБ/м^2	321.42 ± 25.33	295.81 ± 42.62	<0.01
PNPLA3 I148M (IM+MM)	13 (72)	36 (40)	<0.05

Note: cACLD – compensated advanced chronic liver disease; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CAP – controlled attenuation parameter; *PNPLA3* I148M – Patatin-Like Phospholipase Domain Containing 3; n.s. – not significant.
Примечание: КПХЗП – компенсированное продвинутое хроническое заболевание печени; АЛТ – аланиновая аминотрансфераза; АСТ – аспарагиновая аминотрансфераза; КПЗУ – контролируемый параметр затухания ультразвука; *PNPLA3* I148M – Patatin-Like Phospholipase Domain Containing 3, пататин-подобный домен фосфолипазы, содержащий белок-3; n.s. – not significant, не значимо.

influence of T2DM, obesity, AH, and dyslipidemia on the risk of developing cirrhosis and HCC in the American population was studied. The lowest risk of progression was observed in patients with one or no sign of metabolic dysfunction. It was noted that each additional metabolic factor increased the risk of liver cirrhosis and HCC: in the presence of AH and dyslipidemia, the risk increased by 1.8 times; a combination of T2DM, obesity, dyslipidemia, and AH increased the risk by 2.6 times [22].

In the Mexican population, logistic multivariate regression analysis showed that T2DM, AH, high total cholesterol, and hypertriglyceridemia increased the risk of liver fibrosis, but only T2DM and hypertriglyceridemia significantly increased the risk of cirrhosis [23].

The AMORIS study, conducted on a Swedish cohort of patients, showed that obesity was associated with the development of HCC, but not cirrhosis, while other metabolic factors (dyslipidemia, hyperglycemia, T2DM) were associated with a high risk of both HCC and cirrhosis [24].

In a European cohort of patients, T2DM was shown to be an independent risk factor for the progression of NAFLD to HCC or cirrhosis, while obesity and AH in this population did not significantly affect the development of adverse outcomes [25], which is consistent with our data.

As of interest, although the *PNPLA3* gene polymorphism is associated with the progressive course of MASLD, our study has found it less

Table 2. **Cardiometabolic factors and *PNPLA3* I148M polymorphism in a model for detecting compensated advanced chronic liver disease**

Таблица 2. **Кардиометаболические факторы и полиморфизм *PNPLA3* I148M в модели выявления компенсированного продвинутого хронического заболевания печени**

Factor / Фактор	Unadjusted OR (95% CI) / Нескорректированное ОШ (95% ДИ) /	*p*-value / Значение *p*	Adjusted OR (95% CI) / Скорректированное ОШ (95% ДИ)	*p*-value / Значение *p*
Arterial hypertension / Артериальная гипертензия	5.58 (1.21–25.71)	0.016	3.28 (0.62–17.33)	n.s.
Type 2 diabetes mellitus / Сахарный диабет 2-го типа	4.58 (1.59–13.21)	0.005	3.09 (1.05–9.92)	0.047
Obesity / Ожирение	3.13 (1.1–8.9)	0.02	1.21 (0.23–6.34)	n.s.
Waist circumference, cm / Окружность талии, см	1.08 (1.02–1.15)	0.006	1.05 (1.01–1.11)	0.018
Dyslipidemia / Дислипидемия	6.12 (1.33–28.19)	0.015	5.89 (1.21–28.67)	0.028
CAP, dB/m^2 / КПЗУ, дБ/м^2	1.01 (1.00–1.03)	0.002	1.01 (0.99–1.02)	n.s.
PNPLA3 I148M (IM+MM)	3.9 (1.28–11.88)	0.018	1.29 (0.63–2.63)	n.s.

Note: OR – odds ratio; CI – confidence interval; CAP – controlled attenuation parameter; *PNPLA3* I148M – Patatin-Like Phospholipase Domain Containing 3; n.s. – not significant.
Примечание: ОШ – отношение шансов; ДИ – доверительный интервал; КПЗУ – контролируемый параметр затухания ультразвука; *PNPLA3* I148M – Patatin-Like Phospholipase Domain Containing 3, пататин-подобный домен фосфолипазы, содержащий белок-3; n.s. – not significant, не значимо.

significant comparatively to T2DM, dyslipidemia and waist circumference. In some studies, it was gene polymorphisms that played a leading role in the development of fibrosis in non-alcoholic steatohepatitis, compared to cardiometabolic risk components [26, 27]. Thus, according to a large study involved 13,298 US residents, the presence of *PNPLA3* gene polymorphism was associated with excess fat accumulation in the liver, development of fibrosis and an increase in mortality from liver disease [26]. At the same time, a meta-analysis did not reveal a significant association between *PNPLA3* gene polymorphism and simple steatosis in the Asian population, while a strong association was found in Europeans. The same meta-analysis of the relationship between polymorphism and the development of non-alcoholic steatohepatitis has obtained a convincing data on the influence of the polymorphic allele on the development of progressive forms of liver disease in both the European and Asian populations. In Europeans, the odds of developing non-alcoholic steatohepatitis were higher than in Asians: 3.11 (95% CI: 1.82–5.33, $p < 0.0001$) versus 2.33 (95% CI: 1.83–2.96, $p < 0.00001$), respectively [28].

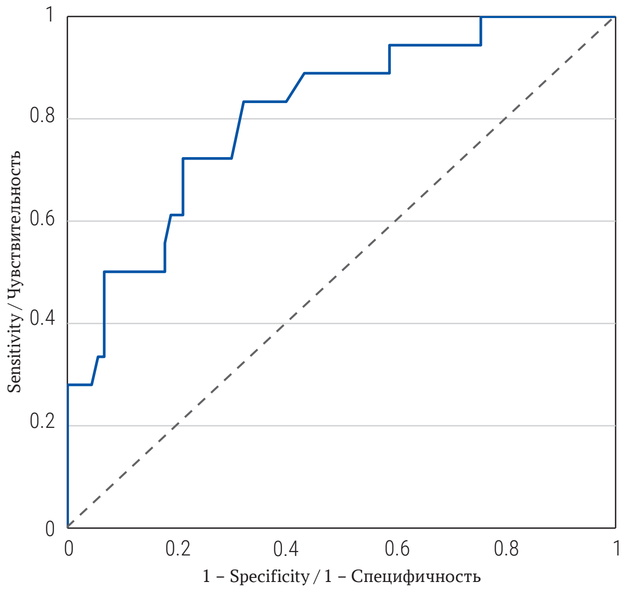

FIG. 2. ROC curve for detection of compensated advanced chronic liver disease.
РИС. 2. ROC-кривая выявления компенсированного продвинутого хронического заболевания печени.

Data from another meta-analysis also demonstrate different odds of developing NAFLD in different populations: the odds ratio and 95% CI for Caucasian, Asian, and Hispanic populations were 3.29 (2.47–4.39), 2.43 (2.06–2.87), and 3.98 (2.71–5.86), respectively, all $p < 0.001$ [29].

We created a prognostic model for identifying NAFLD, which includes non-invasive parameters (the presence of T2DM, dyslipidemia, and waist circumference values). Thus, our model does not include laboratory data, but is based on anamnesis and on a single anthropometric parameter, unlike the most screening indices for determining the risk of the late stages of the disease (FIB-4 index (Fibrosis-4 index)) and NFS (Nonalcoholic Fatty Liver Disease Fibrosis Score), that are commonly accepted [9] and recommended for use in the Russian Federation [15, 27, 30]. Therefore, it can be used for screening to identify high-risk groups for progressive MASLD in common clinical practice. In addition, this model was created for the first time in a study of a cohort of patients meeting the new criteria for MASLD, not NAFLD, and is also aimed specifically at identifying cACLD. It is important that it was developed based on data of patients living in the Russian Federation. The model is characterized by average sensitivity and specificity and requires validation and further evaluation in patients from other regions of the country.

The limitations of the study are a small sample of patients, assessment of the effect of only one mutation of the *PNPLA3* I148M rs738409 C>G gene. In further studies, it is advisable to evaluate the contribution of polymorphisms of other genes that are important for the formation of MASLD (such as TM6SF2, MBOAT7, HSD17B13, GCKR, APOB) in patients residing in different regions of the Russian Federation.

CONCLUSIONS

The results of the study demonstrated that T2DM, dyslipidemia and waist circumference are the determining factors associated with diagnosing cACLD in Russian patients with MASLD. The polymorphism of the *PNPLA3* I148M gene does not play a leading role in the development of progressive MASLD in the studied cohort.

AUTHOR CONTRIBUTIONS

Veronika P. Gomonova and Karina L. Raikhelson contributed equally to this work and should be considered first co-authors.

Veronika P. Gomonova: study concept and design, data collection and analysis, statistical analysis, the interpretation of the results, drafting of the manuscript. Karina L. Raikhelson: study concept and design, data collection and analysis, the interpretation of the results, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Ekaterina V. Pazenko, Maria K. Prashnova, Sergey V. Lapin, Vladimir D. Nazarov, and Darya V. Sidorenko data collection and analysis, manuscript revision. All authors approved the final version of the article before publication.

ВКЛАД АВТОРОВ

В.П. Гомонова и К.Л. Райхельсон в равной степени внесли вклад в данную работу и должны считаться первыми соавторами.

В.П. Гомонова внесла существенный вклад в концепцию и дизайн исследования, сбор и анализ данных, статистический анализ, интерпретацию результатов и составление текста рукописи. К.Л. Райхельсон внесла существенный вклад в концепцию и дизайн исследования, сбор и анализ данных, интерпретацию результатов и внесение в рукопись важных правок с целью повышения научной ценности статьи. Е.В. Пазенко, М.К. Прашнова, С.В. Лапин, В.Д. Назаров и Д.В. Сидоренко внесли существенный вклад в сбор и анализ данных, внесение в рукопись важных правок. Все авторы одобрили финальную версию статьи перед публикацией.

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