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Prognostic model of rapid hepatic fibrosis progression in men with chronic hepatitis C

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of the research was to determine clinical and genetic predictors and to create a prognostic model for the rapid hepatic fibrosis progression in men with chronic hepatitis C.

Materials and methods. A cross-sectional study which included 111 male patients with chronic hepatitis C was conducted. The patient examination program included: assessment of complaints and anamnestic data, physical examination, complete blood count, biochemical test, the stages of hepatic fibrosis according to METAVIR and genetic studies (detecting carriers alleles 11Gln or 11Leu of TLR7 gene in the genome of the examined men).

Results. It was determined that informative predictors of rapid hepatic fibrosis progression in men with chronic hepatitis C are: ethanol use in a dose of more than 40 g/day (OR = 2.40, P = 0.042), presence of chronic cholecystitis in past history (OR = 2.94, P = 0.013), ALT level above 3 upper limit of normal (OR = 2.49, P = 0.031), the levels of AST, GGT exceeding upper limit of normal (OR = 6.94, P < 0.001 and OR = 4.02, P = 0.001 respectively), hyperbilirubinemia (OR = 3.13, P = 0.010) and carrier state of allele 11Gln of TLR7 gene in the genome (OR = 3.62, P = 0.036). In order to optimize the prognosis of rapid hepatic fibrosis progression in men with chronic hepatitis C a model that demonstrated statistical significance (χ^2 = 44.73, P < 0.001) and high operational characteristics (sensitivity – 76.8 %, specificity – 74.5 %, the total number of correct predictions – 75.7 %, AUC of the ROC-curve – 0.828), which indicates the feasibility of its practical use, was proposed.

Conclusions. An effective clinical and genetic prognostic model has been created and allows us to predict the probability of rapid hepatic fibrosis progression in men with chronic hepatitis C with high accuracy and to form a group of patients who need high priority antiviral therapy.

Key words: chronic hepatitis C, hepatic fibrosis, men, prognosis, TLR7 gene.

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Прогностична модель швидкого прогресування фіброзу печінки в чоловіків із хронічним гепатитом С

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Мета роботи – визначити клініко-генетичні предиктори та на їхній основі створити прогностичну модель швидкого прогресування фіброзу печінки в чоловіків із хронічним гепатитом С.

Матеріали та методи. Здійснили крос-секційне дослідження, в яке залучили 111 пацієнтів чоловічої статі з хронічним гепатитом С. Програма обстеження передбачала оцінювання скарг та анамнестичних даних, фізикальний огляд, загальноклінічне дослідження периферичної крові, визначення біохімічних показників сироватки крові, що характеризують функціональний стан печінки, стадії фіброзу печінки за METAVIR і генетичні дослідження (виявлення носійства в геномі обстежених чоловіків алелів 11Gln або 11Leu гена TLR7).

Результати. Інформативними предикторами швидкого прогресування фіброзу печінки в чоловіків із хронічним гепатитом С є вживання етанолу в дозі понад 40 г/добу (OR = 2,40; p = 0,042), наявність хронічного холециститу в анамнезі (OR = 2,94; p = 0,013), показник АЛТ вищий за 3 верхні межі норми (OR = 2,49; p = 0,031), показники АСТ і ГГТП, що перевищують верхню межу норми (OR = 6,94; p < 0,001 та OR = 4,02; p = 0,001 відповідно), гіпербілірубінемія (OR = 3,13; p = 0,010) і носійство в геномі алеля 11Gln TLR7 (OR = 3,62; p = 0,036). Для оптимізації прогнозу швидкого прогресування фіброзу печінки в чоловіків із хронічним гепатитом С запропонована модель, котра продемонструвала статистичну значущість (χ^2 = 44,73; p < 0,001) і високі операційні характеристики (чутливість – 76,8 %, специфічність – 74,5 %, загальна кількість коректних прогнозів – 75,7 %, AUC ROC-кривої – 0,828), що вказує на доцільність її практичного застосування.

Висновки. Створили ефективну клініко-генетичну прогностичну модель, що дало змогу з високою точністю прогнозувати вірогідність швидкого прогресування фіброзу печінки в чоловіків із хронічним гепатитом С і сформувати групу пацієнтів, які потребують першочергового призначення противірусної терапії.

Ключові слова: хронічний гепатит С, фіброз печінки, чоловіки, прогноз, ген TLR7.

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Прогностическая модель быстрого прогрессирования фиброза печени у мужчин с хроническим гепатитом С

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Цель работы – определить клинико-генетические предикторы и на их основе создать прогностическую модель быстрого прогрессирования фиброза печени у мужчин с хроническим гепатитом С.

Ключевые слова: хронический гепатит С, фиброз печени, мужчины, прогноз, ген TLR7.

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Материалы и методы. Проведено кросс-секционное когортное исследование, в которое вошли 111 пациентов мужского пола с хроническим гепатитом С. Программа обследования включала оценку жалоб и анамнестических данных, физикальный осмотр, общеклиническое исследование периферической крови, определение биохимических показателей сыворотки крови, характеризующих функциональное состояние печени, стадии фиброза печени по METAVIR и генетические исследования (установление носительства в геноме обследованных мужчин аллелей 11Gln или 11Leu гена TLR7).

Результаты. Информативные предикторы быстрого прогрессирования фиброза печени у мужчин с хроническим гепатитом С: употребление этанола в дозе более 40 г/сут (OR = 2,40; p = 0,042), наличие хронического холецистита в анамнезе (OR = 2,94; p = 0,013), показатель АЛТ выше 3 верхних границ нормы (OR = 2,49; p = 0,031), показатели АСТ и ГГТП, превышающие верхнюю границу нормы (OR = 6,94, p < 0,001 и OR = 4,02; p = 0,001 соответственно), гипербилирубинемия (OR = 3,13; p = 0,010) и носительство в геноме аллели 11Gln TLR7 (OR = 3,62; p = 0,036). Для оптимизации прогноза быстрого прогрессирования фиброза печени у мужчин с хроническим гепатитом С предложена модель, которая продемонстрировала статистическую значимость (χ^2 = 44,73; p < 0,001) и высокие операционные характеристики (чувствительность – 76,8 %, специфичность – 74,5 %, общее количество корректных прогнозов – 75,7 %, AUC ROC-кривой – 0,828), что указывает на целесообразность ее практического применения.

Выводы. Создана эффективная клинико-генетическая прогностическая модель, которая позволяет с высокой точностью прогнозировать вероятность быстрого прогрессирования фиброза печени у мужчин с хроническим гепатитом С и формировать группу пациентов, которые нуждаются в первоочередном назначении противовирусной терапии.

It is widely known that the development of fibrotic changes in the liver is an integral part of the pathogenesis and natural course of chronic hepatitis C [1]. Currently, hepatic fibrosis is considered to be a process when a certain number of external factors interact with a unique combination of host factors, which causes significant differences in the course of chronic hepatitis C. There are virus factors (genotype and HCV quasi species, viral load level), host factors (duration of disease, age over 40 years at the time of infection, male gender, co-infection with hepatitis B virus and/or HIV, metabolic disorders – insulin resistance, hepatic steatosis, type II diabetes mellitus, iron metabolism disorders, etc.), as well as external (alcohol abuse, effect of toxins and, in particular, drugs, tobacco smoking and/or cannabinol derivatives) among the factors affecting the rate of hepatic fibrosis progression in chronic hepatitis C [1–4].

Recently, the attention of the researchers has been drawn to the search for genetic determinants that affect the rate of hepatic fibrosis progression in chronic hepatitis C, in particular, the TLR7 gene, which triggers the effector mechanisms of innate immunity and also it effectively regulates the production of IFN Type I which, for its turn, has an antifibrotic effect [5–9]. Conversely, the Gln11Leu polymorphism of the TLR7 gene encodes functionally inferior proteins and is able to reduce the production of IFN-α, thereby disrupting the adaptive immune response, which is realized through the TLR7-dependent signaling pathway [5,7,10,11].

Considering the fact that chronic hepatitis C is detected more often in males, the rate of hepatic fibrosis progression is gender dependent, as well as the availability of data on the influence of the polymorphic 11Leu allele of the TLR7 gene on this process [12–16], scientific and practical interest represents the search for clinical genetic predictors and the creation of a prognostic model for the rapid hepatic fibrosis progression in men.

The aim of the research

To determine clinical and genetic predictors and to create a prognostic model for the rapid hepatic fibrosis progression in men with chronic hepatitis C.

Materials and methods

To achieve this goal, a cross-sectional study was conducted, which included 111 male patients with chronic hepatitis C, aged 23 to 62 years, median (*Me*) = 39.0 (34.0–46.0). All patients were treated in Poltava regional clinical hospital of infectious diseases in 2011–2018. A comprehensive clinical and laboratory examination, which was carried out according to the informed consent of the patients, was conducted on the basis of this medical institution and in commercial laboratories.

The criterion for inclusion into the study was the established diagnosis of chronic hepatitis C, which was guided by the international classification of diseases of the 10th revision and the international classification of liver diseases (Los Angeles, 1994). The diagnosis was verified by the detection of specific serological markers of HCV by the method of ELISA with the obligatory detection of HCV RNA in the blood serum by PCR method in real time with genotyping and viral load detection, high counted viremia higher than $4.0 \cdot 10^5$ IU/ml [1]. Exclusion criteria – co-infection with other hepatotropic viruses and/or HIV, decompensated somatic diseases, oncopathology.

The patient examination program included: assessment of complaints and anamnestic data, physical examination, complete blood count, determination of biochemical parameters of blood serum, characterizing the functional state of the liver – alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, total bilirubin, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase and the stages of hepatic fibrosis according to METAVIR. Genetic studies were also conducted, the purpose of which was to identify carriers in the genome of the examined male alleles 11Gln (normal) or 11Leu (polymorphic) of TLR7 gene. The frequency of concomitant pathology was established based on the results of anamnesis analysis, outpatient cards, objective examination followed by in-depth clinical and laboratory and instrumental examination, findings of specialists in related specialties.

The duration of HCV infection was determined by the results of anamnestic data analysis (indication of the transferred icteric form of acute hepatitis C, transfusion of blood and its components prior to mandatory screening of donors, initiation of systemic injecting drug

use), in the absence of the anamnesis of these facts – on the basis of clinical and laboratory data (the first detection of antibodies to HCV and/or hepatic transaminases elevation the upper limit of normal (ULN), reflected in outpatient cards).

Biochemical studies were carried out on the automatic biochemical analyzer GBG STAT FAX-1904 (Japan) with Human reagents (Germany).

The hepatic fibrosis stage was assessed on the METAVIR scale using the transient elastometry of shear waves of the liver on the ultrasound scanning device "Ultima PA-Expert" (Ukraine). The rate of hepatic fibrosis progression was calculated by T. Poniard's formula by dividing the stage of hepatic fibrosis by METAVIR for the time, for which it was formed, and measured in units per year (units/year) [3].

The gene TLR7 was genotyped by real-time allele-specific PCR on the "DT Lite" amplifier ("NPO DNA-Technology", LLC, RF) on the basis of the Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics of Ukrainian Medical Stomatological Academy.

Statistical processing of the findings was carried out using the Stata software version 11.0 (StataCorp, College Station, TX, USA, serial number 71606281563). The verification of the normality of the data distribution was analyzed by the Kolmogorov-Smirnov criterion. To determine the central trend, the value of the median with the upper and lower quartiles was used. The probability of differences in quality indicators was determined by analyzing contingency tables using Fisher's exact test and χ^2 test, depending on the conditions of the analysis. To create a prognostic model, 30 indicators ranked in the nominal scale were considered as potential predictors of the rapid hepatic fibrosis progression (1 – sign, 0 – none). The influence of each was estimated by the method of simple logistic regression with the calculation of the odds ratio (OR) and its 95 % confidence interval [95 % CI]. Predictors with a significance level of $P < 0.05$ were included in a systematic multiple logistic regression analysis, which resulted in a clinical prognostic model of the rapid hepatic fibrosis progression in men with chronic hepatitis C. In general, the model assumes that the dependent variable (rapid progression of hepatic fibrosis) is associated with predictors in accordance with the following formula:

$$P = \frac{1}{1 + e^{-y}},$$

where P – is the probability of an error-free prognosis; e – is a mathematical constant, which is equal to 2.72; $y = \alpha + B_1 \cdot X_1 + B_2 \cdot X_2 + ... + B_n \cdot X_n$; α – is the constant of the regression equation; $B_1 .... B_n$ – regression coefficients for independent variables; $X_1 .... X_n$ – independent variables included in the model.

The statistical significance of the obtained model was determined by the χ^2 criterion, the evaluation of diagnostic power – using the analysis of the operating characteristics of diagnostic tests (ROC), which included calculations of sensitivity, specificity, the total number of correct predictions and the construction of the ROC-curve with the definition of the area under it (AUC). The delimitation point, according to generally accepted criteria, was taken as threshold value P = 0.5 in which the sensitivity and specificity of the model were optimal (P > 0.5 is considered as a positive prognosis of the event − risk group). Differences were considered significant at the level of $P < 0.05$.

Table 1. Comparative characteristics of the examined male patients with chronic hepatitis C, abs. number (%)

Characteristics	Patients with chronic hepatitis C		P
	Rapid hepatic fibrosis progression, n = 56	Slow hepatic fibrosis progression , n = 55	
1 genotype of HCV	36 (64.3)	28 (50.9)	0.154
High viral load	32 (57.1)	23 (58.2)	0.912
Age older 40	29 (51.8)	23 (41.8)	0.239
Type II diabetes mellitus	5 (8.9)	1 (1.8)	0.206
Ethanol use in a dose of more than 40 g/day	21 (37.5)	11 (20.0)	0.042
Tobacco smoking	16 (28.6)	23 (41.8)	0.144
Smoking cannabiol derivatives	11 (20.0)	5 (9.1)	0.175
Intravenous drug abuse	5 (8.9)	2 (3.6)	0.437
Overweight, BMI ≥25 kg/m^2	10 (17.9)	6 (10.9)	0.419
Carrier state of the 11Leu TLR7 allele	4 (7.1)	12 (21.8)	0.033

P: is the significance level obtained using the Fisher's exact test and the χ^2 criterion, depending on the analysis conditions.

Results

The study found that the examined men with chronic hepatitis C had various stages of hepatic fibrosis, without predominance of any of them. Thus, there were 7 patients (6.3 %) without fibrosis, 19 (17.1 %) with F_1 stages, F_2 – 33 (29.7 %), F_3 – 23 (20.7 %) and F_4 – 29 (26.1 %). By the duration of HCV infection, the patients were divided as follows: less than 5 years − 39 (35.1 %), from 5 to 10 − 24 (21.6 %) and more than 10 − 48 (43.3 %). Based on the obtained data, the median rate of hepatic fibrosis progression was determined and amounted to 0.222 (0.125–1.000) units/year. Depending on the rate of hepatic fibrosis progression, patients with rapid (fibrosis progression rate ≥0.222 units/year) – 56 (50.5 %) and slow (fibrosis progression rate <0.222 units/year) hepatic fibrosis progression – 55 (49.5 %) were identified.

Further, the main characteristics of the examined men with rapid and slow progression of hepatic fibrosis were analyzed, taking into account the well-known risk factors affecting this process and genetic markers (*Table 1*).

According to the data presented in table 1, alcohol abuse – 37.5 % (with slow hepatic fibrosis progression – 20.0 %, P = 0.041) and carrier state of the 11Leu TLR7 allele − 7.1 % (with slow hepatic fibrosis progression – 21.8 %, P = 0.033) were significantly more frequent identified among patients with a rapid hepatic fibrosis progression. No statistically significant differences were found for the remaining characteristics.

Further, a simple logistic regression analysis was carried out for 30 indicators (data of general clinical, biochemical and molecular-genetic tests), as a result of the study we have determined that significant predictors of rapid hepatic fibrosis progression in men with chronic hepatitis C are: ethanol use in a dose of more than 40 g/day (OR = 2.40 [95 % CI 1.02–5.63], P = 0.042), presence of chronic cholecystitis in past history (OR = 2.94 [95 % CI

Table 2. Resulting prognostic model of rapid hepatic fibrosis progression in men with chronic hepatitis C

Predictors	B	χ^2 Wald	P	OR	95 % CI
Carrier state of allele 11Gln TLR7	1.97	7.02	0.008	7.23	1.67–31.28
AST level above ULN	2.22	12.41	<0.001	9.25	2.68–31.87
GGT level above ULN	1.10	5.17	0.023	3.02	1.16–7.83
Hyperbilirubinemia	1.58	7.69	0.006	4.88	1.59–14.96
Ethanol use in a dose of more than 40 g/day	1.18	4.87	0.027	3.28	1.14–9.42
Constant (α)	−4.67	19.81	<0.001		

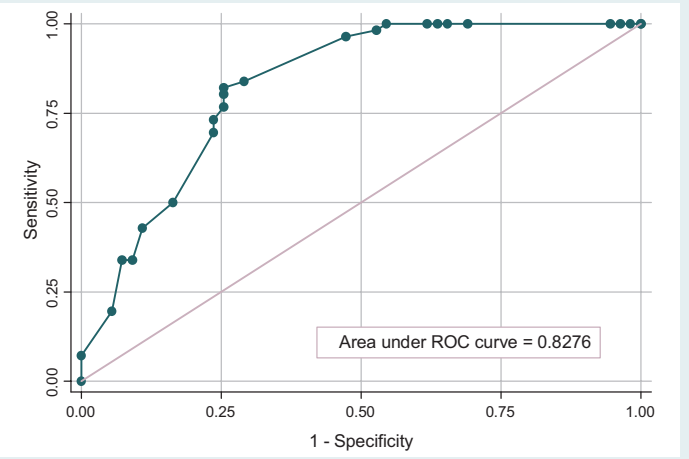

Fig. 1. ROC curve of the resulting prognostic model of rapid hepatic fibrosis progression in men with chronic hepatitis C.

1.25–6.87], P = 0.013), ALT level above 3 ULN (OR = 2.49 [95 % CI 1.08–5.74], P = 0.031), the levels of AST and GGT elevation above ULN (OR = 6.94 [95 % CI 2.55–18.86], P < 0.001 and OR = 4.02 [95 % CI 1.82–8.87], P = 0.001 respectively), hyperbilirubinemia (OR = 3.13 [95 % CI 1.31–7.46], P = 0.010) and carrier state of allele 11Gln of TLR7 gene in the genome (OR = 3.62 [95 % CI 1.09–12.06], P = 0.036). All of them were included in the systematic multiple logistic regression analysis, which resulted in a statistically significant predictive model (χ^2 = 44.73; P < 0.001) of 5 predictors (*Table 2*).

The conducted ROC analysis determined the high operational characteristics of the model: sensitivity – 76.8 %, specificity – 74.5 %, the total number of correct predictions – 75.7 %. The AUC of the ROC-curve model was 0.828, which, according to the generally accepted expert scale, indicates "very good" predictive ability and proves its effectiveness for practical use (*Fig. 1*).

The proposed prognostic model assumes that after entering the numerical values of the regression coefficients in the appropriate formula, the probability (P) of assigning the patient to the risk group of the rapid hepatic fibrosis progression can be calculated as follows:

$$P = \frac{1}{1 + e^{-(-4.67 + 1.97 \cdot X1 + 2.22 \cdot X2 + 1.1 \cdot X3 + 1.58 \cdot X4 + 1.18 \cdot X5)}},$$

where: −4.67 − is the constant of the regression equation; X_1 − carrier state of allele 11Gln TLR7, X_2 − ethanol use in a dose more than 40 g/day, X_3 – AST level above ULN, X_4 – GGT level above ULN, X_5 – hyperbilirubinemia (if there is a predictor, the number 1 is added, if it is absent – 0).

Here is an example of calculation for a patient with the presence of all the specified predictors:

$$P = \frac{1}{1 + e^{-(-4.67 + 1.97 \cdot 1 + 2.22 \cdot 1 + 1.1 \cdot 1 + 1.58 \cdot 1 + 1.18 \cdot 1)}} = 0.970$$

Thus, in this case, the probability of rapid hepatic fibrosis progression is 97.0 %.

Discussion

Nowadays, hepatic fibrosis is considered as a process when a number of extraneous factors interact with a unique combination of the host's ones and causes significant differences in a natural course of chronic hepatitis C. Progression of the disease into cirrhosis occurs over several decades, on average – 20–30 years from the time of infection [1]. The prognosis of chronic hepatitis C is based on the idea of the rate of hepatic fibrosis progression, which is proposed to be calculated by dividing the stage of hepatic fibrosis (in units) by the duration of the disease (in years) from the moment of infection to the study. Such calculations that indicate the stability of the rate of hepatic fibrosis progression are the basis for predicting the period of cirrhosis formation. Summarizing the data of a large-scale study, T. Poynard (1997) identified three options for the progression of fibrosis, each of which is observed in about a third of patients with chronic hepatitis C: rapid (cirrhosis develops within 20 years after HCV-infection), average (cirrhosis develops in 30 years after HCV-infection) and slow rate (cirrhosis develops in more than 50 years) [3]. But a number of other researchers divide this process exclusively into rapid and slow [17–20]. The rate of hepatic fibrosis progression is the main characteristic of the patient since the patients with the rapid progression of fibrosis to cirrhosis are the first candidates for antiviral therapy of chronic hepatitis C. Along with universally recognized risk factors that have an influence on the rate of hepatic fibrosis progression, significant role belongs to genetic markers. Comparison of genetic studies with clinical materials demonstrated the existence of a significant effect of the genetic polymorphism on this process in patients with chronic hepatitis C, however, the analysis of the complex impact of clinical data and genetic polymorphism was carried out in only a few works [2,13,17,20–23].

As a result of our study we have created the prognostic model of the rapid progression of hepatic fibrosis in men with chronic hepatitis C. The predictors included in the model are consistent with data from the scientific literature. Thus, the study confirmed the well-known fact of influence on the rate of hepatic fibrosis progression of such a factor as alcohol abuse [1,3]. There are no doubts about the data on the influence of increased levels of such functional indicators as AST, GGT and total bilirubin, because they are non-direct biochemical markers of fibrogenesis – they indicate activity of inflammation in liver tissues and disruption of its synthetic function and allow indirectly estimate a hepatic fibrosis stage [24–25]. To date, studies of the influence of TLR7 gene Gln11Leu polymorphism on the rate of hepatic fibrosis progression are limited. The results of our study are in line with a number of scientific studies [12,13,15,16], but they contradict the data of F. Z. Fakhir (2018), who describes

the 11Leu allele as a profibrogenic factor, and E. Ascar (2010), who denies the influence of this polymorphism on fibrogenesis in chronic hepatitis C [10,14].

The use of the proposed clinical and genetic prognostic model allows predicting the probability of rapid hepatic fibrosis progression in men with chronic hepatitis C with high accuracy and forming a group of patients who need to receive antiviral therapy in the first place on the basis of simple characteristics, most of which are used in a routine clinical practice.

Conclusions

1. Informative predictors of rapid hepatic fibrosis progression in men with chronic hepatitis C are: ethanol use in a dose of more than 40 g/day (OR = 2.40 [95 % CI 1.02–5.63], P = 0.042), presence of chronic cholecystitis in past history (OR = 2.94 [95 % CI 1.25–6.87], P = 0.013), ALT level above 3 ULN (OR = 2.49 [95 % CI 1.08–5.74], P = 0.031), the levels of AST and GGT exceeding ULN (OR = 6.94 [95 % CI 2.55–18.86], P < 0.001 and OR = 4.02 [95 % CI 1.82–8.87], P = 0.001 respectively), hyperbilirubinemia (OR = 3.13 [95 % CI 1.31–7.46], P = 0.010) and carrier state of allele 11Gln of TLR7 gene in the genome (OR = 3.62 [95 % CI 1.09–12.06], P = 0.036).

2. In order to optimize the prognosis of rapid hepatic fibrosis progression in men with chronic hepatitis C a model that demonstrated statistical significance (χ^2 = 44.73, P < 0.001) and high operational characteristics (sensitivity – 76.8 %, specificity – 74.5 %, the total number of correct predictions – 75.7 %, AUC of the ROC curve – 0.828), which indicates the feasibility of its practical use, was proposed.

Prospects for further research are to study the pathogenetic mechanisms of the influence of the TLR7 gene on the course of chronic hepatitis C.

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