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НЕИНВАЗИВНЫЕ ПРЕДИКТОРЫ ВЫРАЖЕННОЙ ГИСТОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ПЕЧЕНИ: РОЛЬ МАТРИКСНЫХ МЕТАЛЛОПРОТЕИНАЗ

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A Noninvasive Predictors of Significant Histological Activity in Chronic Liver Diseases: The Role of Matrix Metalloproteinases

Резюме

Цель исследования: изучение прогностической значимости клинико-лабораторных маркеров печеночной патологии, в том числе компонентов системы матриксных металлопротеиназ (ММП), для выявления умеренной/выраженной активности при хронических заболеваниях печени (ХЗП). **Материалы и методы.** Обследовано 76 пациентов ХЗП вирусной или алкогольной этиологии в возрасте от 18 до 64 лет. Минимальная (индекс гистологической активности — ИГА 1-3 балла), слабовыраженная (ИГА 4-8 баллов), умеренная (ИГА 9-12 баллов) и выраженная морфологическая активность (ИГА более 12 баллов) выявлялись в 19 (25,0 %), 34 (44,7 %), 14 (18,4 %) и 9 (11,9 %) случаев соответственно. Методом иммуноферментного анализа определяли содержание в крови ММП-1, ММП-9, тканевого ингибитора матриксных металлопротеиназ-1 (ТИМП-1), рассчитывали соотношение ТИМП-1/ММП-1, ТИМП-1/ММП-9. **Результаты.** По данным многофакторной логистической регрессии, умеренная/выраженная гистологическая активность ХЗП была ассоциирована с показателями γ-глютамилтранспептидазы (ГГТ) (отношение шансов (ОШ) 1,016; 95 % доверительный интервал (ДИ) (1,006-1,024), p=0,001), международного нормализованного отношения (МНО) (ОШ 1,079; 95 % ДИ (1,028-1,132), p=0,002), соотношения ТИМП-1/ММП-9 (ОШ 0,554; 95 % ДИ (0,380-0,809), p=0,002). Комбинация этих параметров имела чувствительность 82,6 %, специфичность 92,5 % и точность 89,5 % в выявлении ИГА 9 и более баллов. **Заключение.** Увеличенные значения ГГТ и МНО, а также сниженное соотношение ТИМП-1/ММП-9 являются независимыми факторами риска умеренной/выраженной гистологической активности при ХЗП, что обусловлено их участием в процессах печеночного воспаления.

Ключевые слова: *хронические заболевания печени, гистологическая активность, матриксная металлопротеиназа-9, тканевой ингибитор матриксных металлопротеиназ-1, γ-глютамилтранспептидаза, международное нормализованное отношение*

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Abstract

Aim of investigation. To study the prognostic significance of clinical and laboratory markers of liver pathology, including components of the matrix metalloproteinase (MMP) system, to identify moderate/significant activity in chronic liver diseases (CLD). **Materials and methods.** 76 patients with CLD of viral or alcoholic etiology aged from 18 to 64 years were examined. Minimal (histological activity index — HAI 1-3 points), minor (HAI 4-8 points), moderate (HAI 9-12 points) and significant morphological activity (HAI more than 12 points) were detected in 19 (25.0 %), 34 (44.7 %), 14 (18.4 %) and 9 (11.9 %) of cases, respectively. Enzyme immunoassay was used to determine the blood levels of MMP-1, MMP-9, tissue inhibitor of matrix metalloproteinases-1 (TIMP-1), and the of TIMP-1/MMP-1, TIMP-1/MMP-9 was calculated. **Results.** According to multivariate logistic regression data, moderate/significant histological activity of CLD was associated with γ-glutamyltranspeptidase (GGT) (odds ratio (OR) 1.016; 95 % confidence interval (CI) (1.006-1.024), p=0.001), international normalized ratio (INR) (OR 1.079; 95 % CI (1.028-1.132), p=0.002), and TIMP-1/MMP-9 ratio (OR 0.554; 95 % CI (0.380-0.809), p=0.002). The combination of these parameters had sensitivity of 82.6 %, specificity of 92.5 % and accuracy of 89.5 % in detecting HAI of 9 or more points. **Conclusion.** The increased values of GGT and INR, as well as a reduced ratio of TIMP-1/MMP-9, are independent risk factors for moderate/significant histological activity in CLD, due to their participation in the processes of hepatic inflammation.

Key words: *chronic liver diseases, histological activity, matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinases-1, γ-glutamyltranspeptidase, international normalized ratio*

Conflict of interests

Co-author of the article Yagoda A.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Yagoda A.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics

The study was approved by the local ethics committee of Stavropol State Medical University (protocol No. 100 dated 17.06.2020). All patients signed informed consent.

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGT — γ-glutamyl transpeptidase, CI — confidence interval, HAI — histological activity index, INR — international normalised ratio, MMP — matrix metalloproteinase, OR — odds ratio, MPTI — matrix metalloproteinase tissue inhibitor, CLD — chronic liver diseases, Ac — accuracy, AUC — area under ROC-curve, HBV — hepatitis B virus, HCV — hepatitis C virus, HDV — hepatitis D virus, MCV — mean corpuscular volume, NPV — negative predictive value, PPV — positive predictive value, RDW — red blood cell distribution width, Se — sensitivity, Sp — specificity

Introduction

Chronic liver diseases (CLD) constitute a serious health-related issue, which is associated with high prevalence, morbidity, and mortality, low quality of life, enhanced patient disability, and increased organ transplant requirements. CLDs are mainly represented by infections associated with hepatitis B (HBV) (29 %) and C (HCV) (9 %) viruses, alcoholic (2 %) and non-alcoholic (59–60 %) fatty liver disease; autoimmune, hereditary, and drug-induced lesions (1 %) are rare [1].

Despite the vaccination and use of nucleos(t)ide analogues, chronic HBV infection is diagnosed in 240–296 million people, which is more commonly diagnosed in China (29 %), India (6.6 %), and Nigeria (5.8 % of cases). 1.5 million new HBV infection cases are diagnosed annually; every year, 800–820 thousand people die from its complications (liver cirrhosis and hepatocellular carcinoma) [1, 2, 3].

Approximately 58–113 million people globally are infected with HCV (0.8–1.1 %); 1.5–1.8 million new cases are detected annually, which exceeds the number of deceased and recovered patients. Half of all infection cases are reported in China, Pakistan, India, Egypt, Russia, and the USA [1, 2].

12 million patients with the HDV infection have been diagnosed globally; anti-HDV antibodies are detected in 4.5–16.4 % of HBsAg-positive persons. Mongolia is the first in the list of HBsAg-positive and HDV-infected population (36.9 %), followed by Guinea-Bissau (23.9 %), Gabon (22 %), Mauritania (19.4 %), Togo (18.5 %), and Moldova (15 %) [4].

The exact prevalence of alcoholic liver disease is unknown, while its trend can be followed with the alcohol consumption per capita. Alcohol consumption leads to 3.3 million deaths annually, 5.3–10 % of premature deaths among people of working age [5]; alcohol is associated with a high risk of mortality from liver diseases (27 %) and hepatocellular carcinoma (20–30 %) [1, 2].

Determining the severity of necrotic & inflammatory changes in the liver is important to optimize the patient management from the point of prognosis and timely therapeutic decisions. Transcutaneous liver biopsy followed

by the morphological study is a golden standard of evaluating the hepatic inflammation severity. However, biopsy is an invasive diagnostic method, which is not available in the limited resource setting, but rather associated with the low patient compliance, unfavorable risks, variability of results, insufficient representativeness, and impossibility of monitoring changes [6].

Currently almost no non-invasive markers and scales exist that help to diagnose hepatic inflammation, especially in patients with stably normal aminotransferase activity. Actitest (BioPredictive, France) including six parameters (alanine aminotransferase, bilirubin, γ-glutamyl transpeptidase, haptoglobin, alpha-2 macroglobulin, apolipoprotein A1) is positioned as a non-invasive tool in the diagnosis of hepatic disease activity. Along with that, some data demonstrate the insufficient Actitest concordance with morphological signs of chronic hepatitis [7, 8], while several parameters of the scale are not used routinely, which limits its use.

Besides controlling the accumulation and degradation of the extracellular matrix components, matrix metalloproteinases (MMP) and their tissue inhibitors (MPTI) actively participate in the inflammatory process, angiogenesis, and hepatic regeneration [9]. MMPs affect the replication, penetration, and spread of hepatotropic viruses, release the membrane-bound pro-inflammatory cytokines, destroying the basal membrane markers, and promote white blood cell transfer to tissues [9, 10]. Increased MMP-2 and MMP-9 expression is associated with white blood cell extravasation and infiltration, enhanced inflammation in the setting of the ischemic-reperfusion liver injury [11]. MMP-8 deficiency in the acute hepatitis model impaired white blood cell migration and chemokine release, which can prove the role of this matrix metalloproteinase in the regulation of inflammation [9].

However, the association of serum MMP and MPTI levels and the histological activity of chronic liver diseases has not been always detected [12, 13, 14]. TIMP-1, MMP-3 parameters have been more commonly used in the non-invasive diagnosis of fibrosis [6], while the prognostic ability of metalloproteinases and their inhibitors regarding the severity of inflammation in patients with hepatic diseases have not been analyzed at all.

The study is aimed at analyzing the diagnostic significance of clinical & laboratory parameters, including the components of the matrix metalloproteinase system, in the prediction of moderate/significant morphological activity in chronic liver diseases.

Materials and Methods

A total of 76 patients with chronic liver diseases (27 females, 49 males) aged 18 to 64 years (41 (31; 48) years). Inclusion criteria: histologically confirmed CLDs of viral or alcoholic origin; age over 18 years; signed informed consent to participate in the study, including the liver biopsy. Exclusion criteria: liver diseases of any other etiology; acute and chronic (exacerbated) clinically significant somatic diseases; drug abuse; psychic diseases; pregnancy and lactation; malignancies.

Study design: open-label cross-sectional study.

Clinical characteristics of patients with CLDs are presented in Table 1.

Chronic hepatitis was detected in 59 (77.6 %) cases (HBV — 16, HCV — 30, HDV — 13), liver cirrhosis (Child-Pugh Class A) — in 17 (22.4 %) patients: that of viral etiology — in 13 (17.1 %) patients (HBV — 2, HCV — 8, HDV — 3), alcoholic cirrhosis — in 4 (5.3 %) cases.

The viral etiology of hepatic diseases was established based on the presence of HBsAg and HBV DNA (HBV infection), anti-HCV antibodies and HCV RNA (HCV infection), anti-HDV antibodies and HDV RNA (HDV infection). The alcoholic etiology of hepatic diseases was diagnosed based on the history, AUDIT test (> 8 points), detection of alcoholic stigmata and laboratory markers (AST elevation > ALT, increased mean corpuscular volume (MCV), γ-glutamyl transpeptidase activity).

Depending on the ALT and/or AST parameters, biochemical CLD activity was divided into minimal (increase < 3 x upper limit of normal (ULN)), moderate (3–5 fold increase), and severe (> 5 x ULN), which were observed in 57 (75.0 %), 11 (14.5 %), and 8 (10.5 %) patients, respectively.

Mesenchymal-inflammatory syndrome was diagnosed based on increased erythrocyte sedimentation rate (ESR), C-reactive protein, a- and g-globulin, fibrinogen levels; its manifestations were detected in 19 (25 %) patients. Cholestatic syndrome detected in 7 (9.2 %) cases was determined with the increased alkaline phosphatase, γ-glutamyl transpeptidase, and conjugated bilirubin levels.

To evaluate the histological activity, all patients underwent the transcutaneous liver biopsy in the morning in the fasting condition under ultrasound guidance with the 18G needle, obtaining the liver sample 1.5 mm wide and ≥ 1.5 cm long (the sample should have contained at least six portal tracts). Biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxyline-eosin. All liver specimens were analyzed by the pathologist not knowing the clinical patient characteristics.

Based on the histological activity index (HAI) (R.J. Knodell et al., 1981), the morphological activity was stratified into minimal (1–3 points), mild (4–8 points), moderate (9–12 points), and severe (> 12 points), which were detected in 19 (25.0 %), 34 (44.7 %), 14 (18.4 %), and 9 (11.9 %) cases, respectively. Liver fibrosis (V. Desmet et al.) F0, F1, F2, F3, F4 was detected in 8 (10.5 %), 20 (26.3 %), 18 (23.7 %), 13 (17.1 %), 17 (22.4 %) cases, respectively.

The gender- and age-matched control group consisted of 72 almost healthy persons.

Table 1. *Clinical characteristics of patients with CLD*

Parameters	Patients with CLD, n=76
Gender (women/men, n (%))	27 (35,5) / 49 (64,5)
Age (years)	41,0 (31,0; 48,0)
AST (u/l) (reference values: men 0-40 u/l, women 0-31 u/l)	43,0 (25,9; 81,0)
ALT (u/l) (reference values: men 0-41 u/l, women 0-32 u/l)	56,5 (28,0; 99,9)
GGT (u/l) (reference values: men 8-61 u/l, women 7-32 u/l)	51,0 (33,5; 95,5)
Alkaline phosphatase (u/l) (reference values: men 40-130 u/l, women 36-106 u/l)	111,0 (70,0; 210,0)
Total bilirubin (μmol/l) (reference values: 0-17 μmol/l)	15,9 (11,9; 25,45)
Conjugated bilirubin (μmol/l) (reference values: 0-5 μmol/l)	3,7 (3,0; 7,1)
ESR (mm/h) (reference values: men 2-10 mm/h, women 2-15 mm/h)	8,0 (5,0; 12,0)
C-reactive protein (mg/l) (reference values: 0-5 mg/l)	0,7 (0,2; 4,4)
Fibrinogen (g/l) (reference values: 2.2-3.97 g/l)	2,63 (2,23; 3,55)
Albumin (g/l) (reference values: 34-48 g/l)	45,0 (42,0; 47,0)
Prothrombin time (sec) (reference values: 9.1-12.1 sec)	16,19 (12,65; 17,45)
Prothrombin index (%) (reference values: 90-105 %)	91,0 (88,0; 97,5)
INR (reference values: 0.85-1.15)	1,13 (1,02; 1,2)
Total cholesterol (mmol/l) (reference values: 0-5.17 mmol/l)	4,28 (3,75; 4,65)
Platelets (x10^9/l) (reference values: 150-400x10^9/l)	187,5 (150,5; 238)
Moderate/severe biochemical activity n (%)	19 (25,0)
Mesenchymal inflammatory syndrome n (%)	19 (25,0)
Cholestatic syndrome n (%)	7 (9,2)

Footnote: quantitative data are presented as Me (Q1; Q3), categorical data as n (%)
Abbreviations: ALT — alanine aminotransferase, AST — aspartic aminotransferase, CLD — chronic liver diseases, GGT — γ-glutamyltranspeptidase, ESR — erythrocyte sedimentation rate, INR — international normalized ratio

The study was approved by the Local Ethics Committee of the University (Protocol No. 100 dated 17/06/2020).

The immunoenzymatic method was used to detect the blood levels of MMP-1 (RayBiotech, USA), MMP-9 (Bender MedSystems GmbH, Austria), MPTI-1 (Aviscera Bioscience, USA), with subsequent calculation of MPTI-1/MMP-1 and MPTI-1/MMP-9 ratios.

The results were statistically processed (StatTech v. 3.1.7; StatTech LLC, Russia). Quantitative values with the distribution other than normal are presented as medians (Me) and the interquartile range (Q1; Q3). Differences were detected using the Mann-Whitney test. Categorical data presented as percentages (%) were evaluated using the χ^2 test with Yates' correction for continuity. The Spearman rank correlation coefficient, odds ratio (OR), and its 95 % confidence interval (CI) were calculated. The following was calculated: sensitivity, specificity, positive and negative predictive value, accuracy. The association of independent variables and the dependent variable (HAI ≥ 9 points) was analyzed using the logistic regression analysis method. ROC analysis and model informativity were evaluated using the area under ROC curve. Differences were considered statistically significant with $p < 0.05$.

Results

Patients with chronic liver diseases compared to the control group had MPTI-1 (565 (478; 691) ng/mL and 387.5 (284.5; 482.0) ng/mL, $p < 0.00001$) and MMP-1 (22 (12.75; 33.63) ng/mL and 4.95 (2.64; 14.25) ng/mL, $p < 0.00001$) in blood; MPTI-1/MMP-9 (3.02 (1.3; 6.7) U and 1.40 (0.95; 2.05) U, $p = 0.00002$) were higher, while plasma MMP-9 levels (188.0 (95.15; 407.0) ng/mL and 320.0 (200.0; 362.0) ng/mL, $p = 0.056$) and MPTI-1/MMP-1 (23.95 (15.0; 53.15) U and 67.90 (24.10; 139.85) U, $p < 0.00001$) were lower than in healthy persons. The parameters analyzed did not depend on the sex and age of persons in the study.

Changes in the matrix metalloproteinase system parameters were unidirectional for the alcoholic and viral CLD etiology, without statistically significant differences.

Maximum MPTI-1, MPTI-1/MMP-1 and MPTI-1/MMP-9 ratios, and minimum MMP-1 values were reported in the patient group with the F4 fibrosis vs. the F0-F3 fibrosis.

Blood MMP and MPTI levels in patients with CLD were not associated with hepatitis B/C virus replication, besides the direct correlation of serum MMP-9 values with the HBV (r = 0.65; p = 0.004) and HCV (r = 0.39; p = 0.02) viremia level. Histological activity index parameters in CLD did not correlate with the HBV (r = 0.22; p > 0.05) and HCV (r = 0.15; p > 0.05) viremia level.

Higher serum levels of aspartate (AST) and alanine (ALT) aminotransferases, gamma-glutamyl transpeptidase (GGT), total bilirubin, higher ESR, international normalised ratio (INR) levels, lower platelet count were observed with the moderate and severe histological activity of liver diseases compared to the minimal one; moderate/high cytolysis and mesenchymal inflammation syndromes were also more common among the former ones. In this patient group, blood MPTI-1 and MMP-9 levels were higher, while the MPTI-1/MMP-9 ratio was lower than in minimum morphological activity cases (Table 2).

Table 2. *The relationship of markers of liver pathology and components of the matrix metalloproteinase system with HAI*

Parameters	Patients with CLD, n=76		P Value
	HAI <9 points, n=53	HAI ≥9 points, n=23	
Gender (women/men, n (%))	17 (32,1) / 36 (67,9)	10 (43,5) / 13 (56,5)	p>0,05
Age (years)	40,0 (29,5; 44,0)	45,0 (35,0; 47,0)	p>0,05
AST (u/l) (reference values: men 0-40 u/l, women 0-31 u/l)	39,9 (22,5; 55,5)	67,2 (28,0; 95,0)	p=0,016
ALT (u/l) (reference values: men 0-41 u/l, women 0-32 u/l)	49,0 (25,35; 66,95)	97,4 (39,0; 113,0)	p=0,007
GGT (u/l) (reference values: men 8-61 u/l, women 7-32 u/l)	37,0 (21,5; 60,0)	91,0 (55,0; 107,2)	p<0,001
Alkaline phosphatase (u/l) (reference values: men 40-130 u/l, women 36-106 u/l)	90,0 (68,5; 163,0)	210,0 (70,0; 210,0)	p=0,061
Total bilirubin (μmol/l) (reference values: 0-17 μmol/l)	15,0 (11,15; 18,5)	21,9 (14,0; 34,2)	p=0,003
Conjugated bilirubin (μmol/l) (reference values: 0-5 μmol/l)	4,0 (3,0; 5,8)	3,0 (1,7; 5,0)	p>0,05
ESR (mm/h) (reference values: men 2-10 mm/h, women 2-15 mm/h)	5,0 (4,5; 12,0)	9,0 (8,0; 9,0)	p=0,013
C-reactive protein (mg/l) (reference values: 0-5 mg/l)	0,6 (0,2; 2,4)	1,03 (0,2; 4,8)	p>0,05
Fibrinogen (g/l) (reference values: 2.2-3.97 g/l)	2,6 (2,29; 3,5)	3,0 (1,7; 5,0)	p>0,05
Albumin (g/l) (reference values: 34-48 g/l)	45,0 (42,0; 47,0)	43 (40,5; 47,0)	p>0,05
Prothrombin time (sec) (reference values: 9.1-12.1 sec)	15,9 (12,35; 17,0)	16,5 (13,0; 17,2)	p>0,05
Prothrombin index (%) (reference values: 90-105 %)	91,0 (88,0; 97,5)	91,0 (79,0; 95,0)	p>0,05
INR (reference values: 0.85-1.15)	1,1 (1,0; 1,15)	1,17 (1,11; 1,3)	p<0,001
Total cholesterol (mmol/l) (reference values: 0-5.17 mmol/l)	4,28 (3,75; 4,59)	4,28 (3,75; 4,54)	p>0,05
Platelets (x10^9/l) (reference values: 150-400x10^9/l)	210 (143; 238)	161 (104; 172)	p=0,008
Moderate/severe biochemical activity n (%)	9 (17,0)	10 (43,5)	p=0,031
Mesenchymal inflammatory syndrome n (%)	9 (17,0)	10 (43,5)	p=0,031
Cholestatic syndrome n (%)	3 (5,7)	4 (17,4)	p>0,05
TIMP-1 (ng/ml)	528,0 (429,0; 621,0)	664,0 (564,0; 713,0)	p<0,001
MMP-1 (ng/ml)	21,0 (13,88; 30,6)	25,3 (10,1; 31,35)	p>0,05
MMP-9 (ng/ml)	119,0 (73,65; 254,0)	576,0 (200,0; 790,0)	p<0,001
TIMP-1/MMP-1	22,36 (14,89; 35,95)	25,4 (15,71; 36,4)	p>0,05
TIMP-1/MMP-9	3,5 (1,9; 6,8)	1,2 (0,6; 2,8)	p<0,001

Footnote: quantitative data are presented as Me (Q1; Q3), categorical data as n (%); criterion Yates's chi-squared test, Mann-Whitney criterion
Abbreviations: ALT — alanine aminotransferase, AST — aspartic aminotransferase, CLD — chronic liver diseases, GGT — γ-glutamyltranspeptidase, ESR — erythrocyte sedimentation rate, HAI — histological activity index, INR — international normalized ratio, MMP — matrix metalloproteinase, TIMP — tissue inhibitor of matrix metalloproteinases

Increased risk (IHA ≥ 9 points) was associated with the following parameters: ESR ≥8 mm/h, GGT ≥ 53.8 U/L, INR ≥ 1.11, total bilirubin ≥ 20.5 μmol/L, ALT ≥ 70.5 U/L, alkaline phosphatase ≥ 189 U/L, AST ≥ 53 U/L, platelet count ≤ 187x10^9/L, as well as with moderate/high biochemical activity, mesenchymal-inflammatory syndrome. Blood MPTI-1 levels ≥ 554 ng/mL, MMP-9 levels ≥ 410 ng/mL, and MPTI-1/MMP-9 ratio ≤ 1.59 U were also associated with the increased risk of significant inflammation. The most optimal area under curve was detected in cases of MMP-9 levels ≥ 410 ng/mL (0.82±0.05), GGT ≥ 53.8 U/L (0.81±0.05), MPTI-1 ≥ 554 ng/mL (0.74±0.06), MPTI-1/MMP-9 ≤ 1.59 U (0.74±0.06), INR ≥ 1.11 (0.73±0.06). Sensitivity and specificity values for the aforementioned parameters were as follows: MMP-9 — 60.9 % and 92.5 %, GGT — 91.3 % and 69.8 %, MPTI-1 — 87.0 % and 58.5 %, MPTI-1/MMP-9 — 60.9 % and 83.0 %, INR — 87.0 % and 54.7 %, respectively (Table 3).

The multivariate regression analysis was arranged to detect the most significant factors associated with moderate and high histological activity (HAI ≥ 9 points). It included 13 factors (AST, ALT, GGT, total bilirubin, alkaline phosphatase, ESR, INR values, platelet count, moderate/high biochemical activity, mesenchymal inflammatory syndrome, blood MMP-9 and MPTI-1 levels, MPTI-1/MMP-9 ratio) which were associated with a high risk of severe morphological hepatic changes based on the univariate analysis.

According to the multivariate analysis results, association with HAI ≥ 9 points was detected for parameters of the MPTI-1/MMP-9 ratio (OR 0.554; 95 % CI (0.380–0.809), p = 0.002), GGT (OR 1.016; 95 % CI (1.006–1.024), p = 0.001), INR (OR 1.079; 95 % CI (1.028–1.132), p = 0.002). The odds of moderate/severe histological activity decreased 1.805-fold with MPTI-1/MMP-9 increase by 1 U and increased 1.016-fold with GGT increase by 1 U/L, 1.079-fold with INR increase by 1.

The association observed was described by the following equation:

$$z = -9.077 - 0.590 \times X_{\text{MPTI-1/MMP-9}} + \\ + 0.015 \times X_{\text{GGT}} + 7.599 \times X_{\text{INR}},$$

where z is the value of the logistic regression function; $X_{\text{MPTI-1/MMP-9}}$ is a value of the MPTI-1/MMP-9 ratio (U); X_{GGT} is a value of the GGT activity (U/L); X_{INR} is the INR value; –9.077 is a regression constant; –0.590; 0.015; 7.599 are regression coefficients for corresponding variables.

Table 3. *Diagnostic significance of liver pathology markers and components of the matrix metalloproteinase system in the detection of HAI ≥9 points*

Parameters	OR (95 % CI)	AUC (M±SE)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Ac (%)
AST ≥53.0 u/l	4,8 (1,7-13,5) p=0,0035	0,65±0,07 p=0,033	65,2	71,7	50,0	82,6	69,7
ALT ≥70.5 u/l	6,4 (2,2-18,7) p=0,0007	0,68±0,07 p=0,015	65,2	77,4	55,6	83,7	73,7
GGT ≥53.80 u/l	24,3 (5,1-116,1) p=0,0001	0,81±0,05 p<0,001	91,3	69,8	56,8	94,9	76,3
Alkaline phosphatase ≥189 u/l	5,3 (1,8-15,3) p=0,0019	0,64±0,07 p=0,049	60,9	77,4	53,8	82,0	72,4
Total bilirubin ≥20.5 μmol/l	7,2 (2,4-21,2) p=0,0004	0,70±0,06 p=0,007	65,2	79,2	57,7	84,0	75,0
ESR ≥8 mm/h	61,0 (3,5-1057,0) p=0,0047	0,66±0,07 p=0,026	100	56,6	50,0	100	69,7
INR ≥1.11	8,1 (2,1-30,4) p=0,0021	0,73±0,06 p=0,002	87,0	54,7	45,5	90,6	64,5
Platelets ≤187x10^9/l	4,3 (1,5-12,7) p=0,008	0,67±0,07 p=0,016	73,9	60,4	44,7	84,2	64,5
Modeate/severe biochemical activity	3,8 (1,3-11,2) p=0,0175	0,62±0,07 p=0,017	43,5	83,0	52,6	77,2	71,1
Mesenchymal inflammatory syndrome	3,8 (1,3-11,2) p=0,0175	0,62±0,07 p=0,017	43,5	83,0	52,6	77,2	71,1
TIMP-1 ≥554 ng/ml	9,39 (2,48-35,55) p=0,001	0,74±0,06 p=0,001	87,0	58,5	47,6	91,2	67,1
MMP-9 ≥410 ng/ml	19,06 (5,1-71,27) p=0,001	0,82±0,05 p<0,001	60,9	92,5	77,8	84,5	82,9
TIMP-1/MMP-9 ≤1,59	7,6 (2,53-22,9) p=0,0003	0,74±0,06 p<0,001	60,9	83,0	60,9	83,0	76,3

Abbreviations: Ac — accuracy, ALT — alanine aminotransferase, AST — aspartic aminotransferase, AUC — area under the ROC curve, CI — confidence interval, GGT — γ-glutamyltranspeptidase, ESR — erythrocyte sedimentation rate, HAI — histological activity index, INR — international normalized ratio, MMP — matrix metalloproteinase, NPV — negative predictive value, OR — odds ratio, PPV — positive predictive value, Se — sensitivity, Sp — specificity, TIMP — tissue inhibitor of matrix metalloproteinases

The probability of HAI ≥ 9 points is calculated using the formula: $p = 1 : (1 + e^{-z})$, where e is the base of the natural algorithm (2.72), p is the probability of HAI ≥ 9 points.

The p threshold in the cut off point was 0.457. HAI ≥ 9 points was predicted with p over or equal to this value. Parameters of the diagnostic significance for p ≥ 0.457 were as follows: sensitivity — 82.6 %, specificity — 92.5 %, positive predictive value — 82.6 %, negative predictive value — 92.5 %, accuracy — 89.5 %. The regression model was statistically significant ($p < 0.001$), with area under ROC-curve of 0.911±0.043 (95 % CI: 0.828–0.995), which proved an excellent model quality.

Discussion

Thus, chronic liver diseases are accompanied by increased blood MMP-1, MPTI-1 levels, and the MPTI-1/MMP-9 ratio, with decreased MPTI-1/MMP-1 levels. Based on our data, the matrix metalloproteinase system plays an important role in the development of necroinflammatory lesions in hepatic diseases. Thus, moderate and significant morphological activity of chronic liver diseases was associated not only with cytolysis, inflammation, and cholestasis markers, INR values, and platelet count, but also with increased serum MPTI-1, MMP-9 levels and decreased MPTI-1/MMP-9 ratio.

Older age, higher ALT, AST, GGT, alkaline phosphatase, prothrombin time, INR values, lower albumin levels and platelet count were typical for patients with chronic viral hepatitis and significant inflammation that was confirmed morphologically [15]. Severe hepatic inflammation during the HBV infection was associated with the increased rate of the male sex, HBeAg positivity, increased total bilirubin, ALT, AST, alkaline phosphatase, GGT, prothrombin time, INR, viremia, mean platelet volume and mean corpuscular volume vales, as well as with low albumin levels, platelet and white blood cell counts [16, 17, 18, 19]. It is presumed that the Golgi 73 protein, antibodies to the core hepatitis B antigen, globulins, and red blood cell distribution width (RDW) are associated with the histological activity of chronic liver diseases; however, their predictive values have not been validated [19–22].

Aminotransferase parameters are widely used in routine practice for the indirect evaluation of hepatic inflammation in chronic hepatitis; however, their correlation with the process activity is limited by the effects of various factors [16, 23]. It is considered that AST better predicts inflammatory changes in the liver (due to slower excretion and mitochondrial damage associated with severe inflammation), but ideal values for the cutoff point have not been defined. Besides, the predictive aminotransferase value is negatively affected by periodic fluctuations of their levels.

The association of platelets with lesion and inflammation severity in liver diseases is based on the participation in white blood cell recruitment and accumulation (CD8+ T-cells) in parenchyma; interaction with Kupfer cells mediated by the von Willebrand factor-GP1b complex; ability to preserve viruses from degradation or, vice versa, to present them to immune cells; sinusoidal blood flow modulation due to the secreted serotonin [24].

MMP-1 plays a role in the regression of inflammation, fibrosis, and liver regeneration, cleaving collagen and proteoglycans, interleukin-1β, and tumor necrosis factor-α, activating MMP-2 and -9, participating in the white blood cell migration, facilitating the molecule release from storage pools. In liver diseases, MMP-1 is expressed predominantly by stellate and inflammatory cells [9, 25, 26]. Blood MMP-1 levels increased in chronic hepatitis C [27]; however, some data demonstrate its generally decreased levels in CLD [13], including in the setting of viral, alcoholic hepatitis, and cirrhosis, as well as in late stages of the primary biliary cholangitis [28]. One cannot exclude the presence of normal serum MMP-1 levels in alcoholic and non-alcoholic fatty liver disease, early stages of primary biliary cholangitis [28, 29].

MMP-9 is secreted by endotheliocytes, Kupfer cells, white blood cells, and macrophages [28, 30]. It destroys type IV collagen, elastin, fibronectin, increases the permeability and white blood cell extravasation and infiltration, promotes inflammation, impairs liver regeneration [30]. MMP-9 expression and activity increased with ischemic-reperfusion damage, chronic hepatitis C, alcoholic liver [9, 27]. Blood MMP-9 levels increased in acute alcoholic intoxication [31], chronic hepatitis B [32]. In other studies serum MMP-9 levels decreased in viral or alcoholic hepatitis and cirrhosis, primary biliary cholangitis [28], but were normal in alcoholic or non-alcoholic fatty liver disease [28, 29].

Several studies demonstrated increased serum levels of several matrix metalloproteinases in liver diseases associated with the increased histological activity [12, 14]. Blood MMP-7 levels or its expression in the biliary epithelium directly correlated with morphological signs of inflammation in primary sclerosing cholangitis and biliary atresia [14]. MPTIs expressed by stellate cells and macrophages also negatively affect the inflammation severity [33]. Thus, MPTI-1 hyperexpression is an indicator of stellate cell activity, which is associated with necroinflammatory changes in the liver [34]. With that, one cannot exclude negative correlation or the absence of association of serum matrix metalloproteinase values and their inhibitors with the hepatic inflammation severity. Blood MMP-1 levels in children or adults with liver diseases did not depend on the morphological activity degree [12, 13].

Currently, non-invasive markers reflecting the intensity of hepatic inflammation are almost lacking. The multivariate regression analysis has demonstrated that increased GGT activity, INR values, and decreased MPTI-1/MMP-9 ratio had independent effects on the development of moderate and severe histological activity (HAI ≥ 9 points).

Prior logistic regression data established that combinations of GGT and prothrombin time with the alkaline phosphatase activity [15], ALT and HBV viremia levels [17] or AST and anti-HB core levels [16] were independent predictors of significant inflammation in chronic viral hepatitis B. Prognostic models developed based on these parameters evaluated the hepatic inflammation (≥ G2) with moderate sensitivity (61.0–80.8 %) and specificity (60.8–84.2 %) (area under ROC curve 0.714–0.767) [15, 16, 17]. Besides ALT, AST, and GGT activity, platelet count and HBsAg levels in blood [18], RDW, platelet count, and albumin levels [19] had significant effects on inflammation severity in HBV infection. Based on the multivariate regression analysis, necroinflammation predictors in autoimmune hepatitis included Golgi 73 protein and GGT levels in blood, while in patient with primary biliary cholangitis those included serum Golgi 73 protein, alkaline phosphatase, IgM levels, and the platelet count [21].

Being a microsomal enzyme of hepatic ductal and canalicular epithelium, GGT controls the metabolism of glutathione, the main antioxidant molecule in cells. In this aspect, the association of GGT with the inflammation severity is caused by the modulating enzyme effects on the pro-oxidant activity and endothelial dysfunction [35], which plays some role in hepatic injury and inflammation [36, 37]. It is proposed that unlike ALT, GGT is a more sensitive marker of necroinflammatory changes in chronic liver diseases [16].

The association of increased INR levels with the CLD activity detected in our study is caused the ability of inflammation and cellular necrosis to cause the activation and consumption of blood coagulation factors. On the other hand, activated coagulation proteases may modulate the inflammatory activity with receptors on mononuclear or endothelial cells, on platelets, altering the production of pro-inflammatory cytokines, adhesins, or causing the apoptosis of inflammatory cells. Besides, the prolonged prothrombin time (and INR, respectively) reflects the impaired synthetic hepatocyte function worsened by the severity of inflammatory hepatic lesions [16].

The detected predictive significance of decreased MPTI-1/MMP-9 ratio (with MMP-9 prevailing over MPTI-1) regarding the histological activity is based on the ability of MMP-9 produced by immune cells (among others) to impair regeneration processes, enhance the parenchymatous inflammation due to the activation of pro-inflammatory cytokines and enhanced white blood cell migration. It is presumed that MMP-9 reflects the inflammatory process in the liver more than fibrogenesis [28]. Thus, in ischemic-reperfusion liver injury MMP-9 provided extravasal white blood cell migration and promoted inflammation [11].

Thus, the imbalance in the matrix metalloproteinase system is associated with the morphological activity in chronic liver diseases in the form of MMP-9 hyperproduction associated with enhanced inflammation severity. The inclusion of risk factors (GGT, INR, MPTI-1/MMP-9) into a simple mathematical model facilitates the personified prediction of moderate/severe activity in patients with chronic liver diseases.

Conclusion

The study has demonstrated that increased GGT and INR parameters, as well as decreased MPTI-1/MMP-9 ratio values are independent predictors of moderate/severe inflammation in chronic liver diseases. Their association with the inflammation severity is related to the effects on endothelial dysfunction, activity of proinflammatory cytokines, migration of immune cells into the hepatic parenchyma. The combination of GGT, INR, and MPTI-1/MMP-9 is of high significance in the diagnosis of histological activity index ≥ 9 points; thus, it can be used in chronic liver diseases as a non-invasive marker of significant inflammation.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Yagoda A.V.: the concept and design of the study, scientific advice, editing the article, approval of the final version of the manuscript

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