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CLINICAL AND LABORATORY PREDICTORS OF THE SEVERITY OF COVID-19 INFECTION IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract

Background: The clinical course of COVID-19 infection varied from mild, sometimes asymptomatic manifestations to severe ones, requiring mandatory hospitalization and emergency care, up to the need for artificial pulmonary ventilation (ALV). Increased risk factors for adverse outcomes included older age and comorbid conditions, including non-alcoholic fatty liver disease (NAFLD). Many studies have focused on the severity of COVID-19 in patients with non-alcoholic fatty liver disease (NAFLD) during the pandemic, but few of them fully reflect the clinical features of COVID-19 infection in hospitalized patients with NAFLD.

Aim: Evaluation of the relationship between laboratory parameters and the severity of COVID-19 infection in hospitalized patients with NAFLD.

Materials and methods: The study design was a retrospective and prospective analysis of 185 medical records of patients hospitalized in infectious diseases hospitals in Moscow from May to August 2021. *Inclusion criteria* were patients with and without NAFLD, aged over 18, hospitalized with COVID-19. *Exclusion criteria* were age under 18 years, alcoholic and viral liver damage. Processing of statistical data was carried out using the SPSS program and Excel application.

Results and discussion: In our study, the group of hospitalized patients with COVID-19 infection and NAFLD were older, their average age was 52.0 (42; 64.0). The dynamics of laboratory parameters of alanine aminotransferase (ALT), aspartate aminotransferase (AST), CRP, glutamylaminotransferase (GGTP) in patients of both groups showed statistically significant differences on days 1, 7 and 21 of hospitalization. In the group of patients with NAFLD, a statistically significant increase in the indicators of cytolysis and inflammation syndrome was observed, and their relationship proportionally correlated with the need for mechanical ventilation.

Conclusion: Cytolytic syndrome in patients with NAFLD hospitalized with COVID-19 infection is a predictor of severe course, longer hospitalization and the need for emergency medical interventions and additional costs.

Keywords: predictors, severity of the course, COVID-19, NAFLD, mechanical ventilation.

Резюме

КЛИНИЧЕСКИЕ И ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ТЯЖЕСТИ ТЕЧЕНИЯ COVID-19 ИНФЕКЦИИ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Введение. Клиника течения COVID-19 инфекции варьировала от легких, порой бессимптомных проявлений до тяжелых, требующих обязательной госпитализации и проведения неотложной помощи, вплоть до необходимости проведения искусственной вентиляции легких (ИВЛ). Факторами повышенного риска неблагоприятных исходов были пожилой возраст, коморбидные состояния, в том числе и неалкогольная жировая болезнь печени (НАЖБП). Тяжести течения COVID-19 у пациентов с неалкогольной жировой болезнью печени (НАЖБП) во время пандемии посвящены многие исследования, однако немногие из них наиболее полно отражают клинические особенности течения COVID-19 инфекции у госпитализированных пациентов с НАЖБП.

Цель исследования: Оценка связи лабораторных показателей с тяжестью течения COVID-19 инфекции у госпитализированных пациентов с НАЖБП.

Материалы и методы исследования: Дизайн исследования – ретроспективный и проспективный анализ 185 историй болезни пациентов, госпитализированных в инфекционные стационары г. Москвы в период с июня по август 2021 года. *Критерием включения* были пациенты с НАЖБП и без НАЖБП, госпитализированные с COVID-19, в возрасте старше 18 лет. *Критерием исключения* были возраст моложе 18 лет, алкогольные и вирусные поражения печени. Обработка статистических данных проводилась с помощью программы SPSS и приложения Excel.

Результаты исследования и обсуждение: В нашем исследовании группа госпитализированных пациентов с COVID-19 инфекцией и НАЖБП были более старшего возраста, их средний возраст составил 52,0(42; 64,0). Динамика лабораторных показателей аланинаминотрансферазы (АЛТ), аспартатаминотрансферазы (АСТ), СРБ, глутамиламинотрансферазы (ГГТП) у пациентов обеих групп показала наличие статистически значимых различий на 1,7 и 21 дни госпитализации. В группе пациентов с НАЖБП наблюдалось статистически значимое превышение показателей синдрома цитолиза и воспаления и их связь пропорционально коррелировала с необходимостью в ИВЛ.

Вывод: Цитолитический синдром у госпитализированных с COVID-19 инфекцией пациентов с НАЖБП является предиктором тяжелого течения, более длительной госпитализации и необходимости неотложных медицинских вмешательств и дополнительных затрат.

Ключевые слова: предикторы, тяжесть течения, COVID-19, НАЖБП, ИВЛ.

Түйіндеме

АЛКОГОЛЬСІЗ МАЙЛЫ БАУЫР АУРУЫ БАР НАУҚАСТАРДА COVID-19 ИНФЕКЦИЯСЫНЫҢ АУЫРЛЫҚ ДӘРЕЖЕСІНІҢ КЛИНИКАЛЫҚ ЖӘНЕ ЗЕРТХАНАЛЫҚ БОЛЖАУШЫЛАРЫ

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Кіріспе. COVID-19 инфекциясының клиникалық ағымы көп жағдайларда жеңіл, кейде асимптоматикалық көріністерден, кей жағдайларда міндетті ауруханаға жатқызуды және жедел медициналық көмекті қажет ететін ауыр көріністерге дейін, өкпенің жасанды вентиляциясын (АЖЖ) қажет ететінге дейін өзгерді. Жағымсыз нәтижелердің жоғарылауы тәуекел факторларына егде жастағы және ілеспелі жағдайлар, соның ішінде алкогольсіз майлы бауыр ауруы (NAFLD) кіреді. Көптеген зерттеулер пандемия кезінде алкогольсіз майлы бауыр ауруы (NAFLD) бар науқастарда COVID-19 ауырлығына бағытталған, дегенмен, зерттеулерде (NAFLD) бар госпитализацияланған науқастардағы COVID-19 инфекциясының клиникалық ерекшеліктерін толық көрсетілмеген.

Зерттеу мақсаты: NAFLD бар ауруханаға жатқызылған пациенттердегі зертханалық көрсеткіштер мен COVID-19 инфекциясының ауырлығы арасындағы байланысты бағалау.

Материалдар мен зерттеу әдістері: Зерттеу дизайны: 185 пациенттердин 2021 жылдың мамыр мен тамыз айларында Мәскеудегі жұқпалы аурулар ауруханаларында емделген ауру тарихтарынын ретроспективті және перспективалық талдау. *Қосылу критерийлері* 18 жастан асқан, Ковид-19 ауруханасына жатқызылған NAFLD бар

және онсыз науқастар болды. *Шығарудың критерийлері* 18 жасқа дейінгі жас, алкогольдік және вирустық бауыр зақымдануы болды. Статистикалық мәліметтерді өңдеу SPSS бағдарламасы мен Excel бағдарламасының көмегімен жүзеге асырылды.

Зерттеу нәтижелері: Біздің зерттеуімізде COVID-19 инфекциясы және NAFLD бар ауруханаға жатқызылған пациенттер тобы жастары үлкенірек болды, олардың орташа жасы 52,0 (42; 64,0) болды. Аланинаминотрансфераза (АЛТ), аспартатаминотрансфераза (АСТ), СРП, глутамиламинотрансфераза (ГТП) зертханалық көрсеткіштерінің динамикасы екі топтағы емделушілерде госпитализацияның 1, 7 және 21-ші күндерінде статистикалық маңызды айырмашылықтарды көрсетті. NAFLD бар науқастар тобында биохимиялық қан көрсеткіштерінің статистикалық маңызды жоғарылауы байқалды және олардың арақатынасы механикалық желдету қажеттілігімен пропорционалды корреляцияланды. NAFLD бар науқастар тобында биохимиялық қан көрсеткіштерінің статистикалық маңызды жоғарылауы байқалды және олардың арақатынасы механикалық желдету қажеттілігімен пропорционалды корреляцияланды.

Қорытынды: COVID-19 инфекциясымен ауруханаға жатқызылған NAFLD бар науқастардағы цитолитикалық синдром ауыр ағымның, ұзақ ауруханаға жатқызудың және қосымша медициналық араласулар мен қосымша шығындардың қажеттілігінің болжамы болып табылады.

Түйінді сөздер: болжаушылар, ауырлығы, COVID-19, NAFLD, механикалық желдету.

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Introduction

The COVID-19 pandemic has posed a significant challenge to humanity, resulting in the loss of more than 7 million lives worldwide [7]. The course of the infection can vary from mild, with sometimes asymptomatic symptoms, to severe cases that require mandatory hospitalization and even artificial lung ventilation, incurring additional costs.

COVID-19 has become a crucial factor influencing the course and outcomes of existing chronic conditions.

According to numerous epidemiological studies, among hospitalized patients with COVID-19, there was a high prevalence of concomitant diseases such as obesity, diabetes mellitus, cardiovascular diseases, hypertension and chronic obstructive pulmonary disease. Studies have also shown that patients with liver disease make up from 1 to 11%, among whom the majority suffer from non-alcoholic fatty liver disease[19]

In recent decades, there has been a trend towards a significant increase in the number of patients with non-alcoholic fatty liver disease. Recent meta-analyses show that over 30% of people worldwide suffer from non-alcoholic fatty liver disease [13]. By 2030, according to experts, it is expected that the proportion of patients with NAFLD will increase by 63%, given the pandemic increase in the incidence of obesity and type 2 diabetes among the American population [8].

COVID-19 infection has significantly worsened the current situation along with the global increase in the prevalence of NAFLD. During the COVID-19 pandemic, patients with NAFLD were at high risk of adverse outcomes

due to the presence of "aggravating factors such as dyslipidemia, hypertension, and overweight [14].

In the South Korean cohort (74,244 examined), among 2,251 patients with a positive test for COVID-19 (45 of whom died and 438 had severe COVID-19 infection), patients with pre-existing non-alcoholic liver damage showed a higher susceptibility to infection (11-23%), as well as an increased risk of severe course by 35-40%[12].

Currently, with the continued spread of COVID-19 infection, there remains a risk of susceptibility and adverse outcomes among patients with NAFLD. It remains relevant to identify and comprehensively assess the clinical and morphological predictors of severe COVID-19 infection in patients with NAFLD.

Based on the fact that patients with NAFLD are a fairly common cohort and require close attention in the context of the ongoing spread of COVID-19 infection, the purpose of our study was to evaluate clinical and laboratory parameters in patients with NAFLD hospitalized with COVID-19 infection and identify their connection with the need for additional oxygen support (ventilator).

Materials and methods

A controlled retrospective and prospective study was conducted based on the analysis of primary medical records (medical histories, extracts from medical records and data from outpatient records) of patients hospitalized with COVID-19 infection in repurposed infectious diseases hospitals in Moscow in the period from June to August 2021.

Sample formation. Out of the total number of medical records, 185 medical records were selected by random

sampling, the data of which were analyzed to obtain reliable values.

The design and methodology of the study were reviewed and approved by the local Bioethics Committee at the Russian National Research University named after N.I. Pirogov.

The criteria for inclusion of patients in the study were: patients over 18 years of age; positive PCR test for COVID-19; hospitalization in infectious disease department; presence of non-alcoholic fatty liver disease in patients of the main group (clinical, laboratory, and instrumental criteria)

Criteria for excluding patients: Patients with existing clinical, laboratory, immunological, and instrumental signs of liver damage of autoimmune, viral, alcoholic, or hereditary origin.

The results of a general blood test were extracted from the primary medical records of all patients:

-the results of a biochemical blood test and their dynamics on days 1, 7 and 21 of hospitalization (ALT, AST, GGTP, CRP, ferritin, D-dimer);

-ultrasound data of abdominal organs (size, structure, echogenicity, contour of the liver); information about hospitalization in the ICU; data on concomitant diseases.

Height and weight were measured in all patients of groups I and II, and BMI was calculated using the formula:

$$BMI = \text{Weight (kg)} / \text{Height (m)}^2.$$

All patients were conditionally divided into two groups:

1 - the main group of 88 patients with NAFLD;

2- the control group of 97 patients without NAFLD.

The results were evaluated according to the criteria of the disease outcome: clinical and laboratory parameters, duration of hospitalization, and the need for artificial lung ventilation (ventilator).

Statistical analysis of the results

Statistical data processing was performed using the software "STATISTICA 10" (StatSoft, 2010). The mean value± standard deviation was used to describe quantitative variables with a normal distribution, and quantitative variables with an abnormal distribution were expressed as a median with an interquartile range. Categorical data were presented as a percentage frequency. Pearson's chi-squared criterion was used to identify the relationship between qualitative variables. The unpaired t-test/Wilcoxon rank sum test was used to compare quantitative characteristics between the two groups. Statistical hypotheses were tested at the significance level (p<0.05).

Results

General characteristics of the sample

The average age of the patients included in the study was 46.0 (33-58) years.

The average number of days of hospital stay was 30.0 days.

All patients in the main (I) and control (II) groups had their height and weight measured, as well as their BMI calculated. The average body mass index was 28.2± 4.95.

The comparative characteristics of groups I and II are presented in Table 1

Table 1.

Comparative characteristics of groups I and II by age, BMI, number of days of hospitalization.

	with NAFLD	without NAFLD	P
Age (Me, Q1;Q3)	52,0(42;64,0)	38,0(29; 50)	0,001
number of days of hospitalization (Me, Q1;Q3)	27 (29,2;35,4)	25 (26,1;29,7)	0,023
Body Mass Index(Me, Q1;Q3)	30,5 (25,4; 33,0)	25,9 (23,8; 28,9)	0,001

As can be seen from the data presented in Table 1, patients with NAFLD were older, had an increased body mass index, and had a longer hospitalization compared with patients without NAFLD.

Laboratory results:

Analysis of blood biochemical parameters ALT, AST, GGTP, C-reactive protein, ferritin, D-dimer in patients included in the study showed a statistically significant difference of 1.7 and 21 days of hospitalization.

Laboratory blood counts at 1.7 and 21 days are shown in Table 2

Table 2.

Comparative characteristics of laboratory parameters in patients of groups I and II on days 1, 7, 21 of hospitalization.

Indicators	with NAFLD n1=88	without NAFLD n2=97	P
ALT_ (Me, Q1;Q3)	175,2(175,1; 175,6)	34,8 (23,4; 52,4)	<0,001
ALT_7 (M, Q1;Q3)	175,4 (175,1; 175,7)	56,0 (37,5; 91,2)	<0,001
ALT_21 (Me,Q1;Q3)	175,3(175,1;175,7)	54,3 (40,6;80,6)	<0,001
AST (Me, Q1;Q3)	56,8(36,2;90,8)	30,2 (20,4;38,8)	<0,001
AST_7 (Me, Q1;Q3)	106,4(56,4;183,6)	44,4 (29,8;84,3)	<0,001
AST_21 (Me,Q1;Q3)	75,2(42,4;96,0)	46,8 (34,7;71,8)	<0,001
GGTP (Me, Q1;Q3)	68,7(48,8;115,4)	42,4(32,0;54,8)	<0,001
GGTP 7(Me, Q1;Q3)	119,4 (79,7;210,8)	54,0(40,5;101,3)	<0,001
GGTP 21(Me,Q1;Q3)	100,4(78,4;132,8)	64,6(45,3; 89,8)	<0,001
CRP_ (Me,Q1;Q3_)	12,7(7,7;23,8)	7,6(5,4;11,6)	<0,001
CRP 7_(Me,Q1;Q3)	76,5(18,2;153,5)	27,9(18,4;56,1)	<0,001
CRP 21_(Me,Q1;Q3)	20,2(9,6;35,4)	10,4(8,1;19,4)	<0,001
Ferritin (Me, Q1;Q3)	119,4(92,2;156,3)	164,4(118,7;187,0)	<0,001
Ferritin_7(Me,Q1;Q3)	210,4(128,9; 324,0)	214,6(196,5;300,2)	<0,195
Ferritin_21(Me,Q1;Q3)	223,2(114,6;391,0)	178,0(147,7;215,3)	<0,039

According to the data presented in Table 2, initially, from the first days of hospitalization, patients with NAFLD showed a significant increase in biochemical parameters: ALT, AST, GGTP, CRP, which indicates that they have chronic inflammatory process, which is aggravated during COVID-19 viral infection (Fig. 1);

ALT, AST indicators increase significantly by the 7th day of hospitalization, and remain high throughout hospitalization, which indicates significant cytolysis and hyperfermentemia in patients with NAFLD compared with patients without NAFLD (Fig. 2).

The severity of the inflammatory process and a significant immune response reflect the indicators of CRP on the first day of hospitalization, which initially differ statistically significantly in patients with NAFLD compared with the indicators of CRP in patients without NAFLD (Fig. 3).

Of 185 patients with COVID-19 infection, 44 (23.7%) underwent artificial lung ventilation (ventilator). Data on the degree of lung damage and the number of ventilators performed in patients of groups I and II are shown in Table 3.

Mann-Whitney U criterion for independent samples

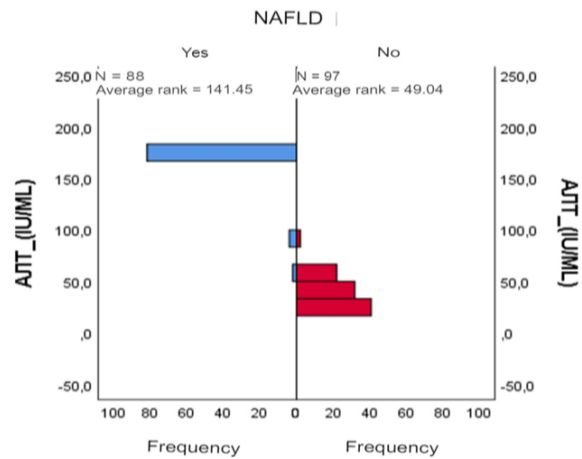


Figure 1. Average ALT values in patients of groups I and II on day 1 of hospitalization.

Mann-Whitney U criterion for independent samples

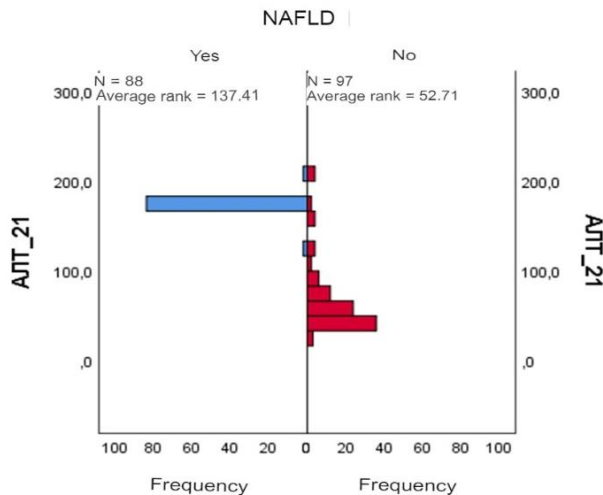


Figure 2. Average ALT values in patients of groups I and II on the 21st day of hospitalization.

Mann-Whitney U criterion for independent samples

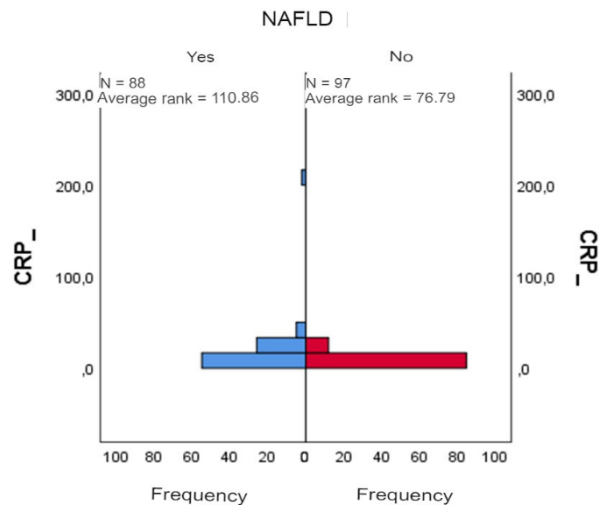


Figure 3. Indicators of CRP in patients of groups I and II on day 1 of hospitalization.

Table 3.

Comparative characteristics of the degree of lung damage and the number of ventilators performed in patients of groups I and II.

Indicators	With NAFLD n=88	Without NAFLD n=97	P
CT scan of the degree of lung damage			
Initial	12 (13,6%)	24 (24,7%)	< 0,171
moderate	44(50,0%)	49 (50,5%)	
Medium heavy	22(25,0%)	16 (16,5%)	
Heavy	10 (11,3%)	8 (8,2%)	
VENTILATOR	With NAFLD	Without NAFLD	< 0,08
There was no	62(72,5%)	79(81,4%)	
There was	26(29,5%)	18 (18,6%)	

As can be seen from the data presented in Table 3, moderate (50%) and moderate-severe (25%) lung lesions were more common among patients with NAFLD compared with patients without NAFLD, in whom initial (24.7%) and moderate (50.5%) lung lesions prevailed.

Among patients requiring artificial lung ventilation for patients with NAFLD was higher (29.5%) than among patients without NAFLD (18.6%).

Comparing whether there is a link between an increase in body mass index and the need for artificial ventilation in

patients of both groups in our study, we had a statistically significant difference between the groups, namely in the group with NAFLD it was higher (Fig. 4; Table 4)

To investigate the association between BMI and the requirement for mechanical ventilation in patients with NAFLD, a correlation analysis was conducted, as presented in Table 4.

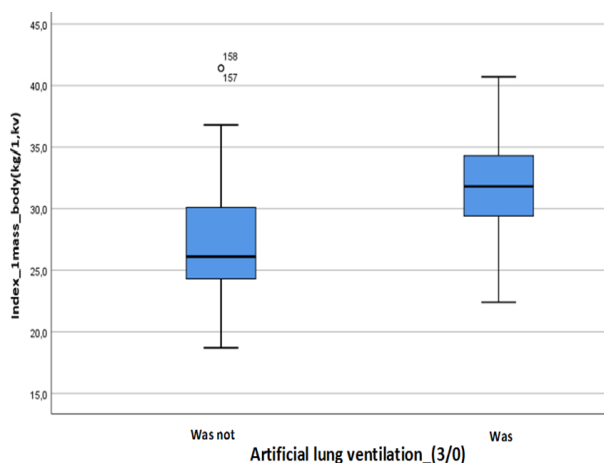


Figure 4. The relationship between BMI and the need for ventilation in patients included in the study.

Table 4.

Association of BMI in patients with NAFLD with the need for ventilation.

	The ventilator		
	was	not	all
The BMI			
1(<20,0)	1	0	1
2(<25,0)	12	0	12
3(>25,0)	49	26	75
All			88

According to the data presented in Fig. 4 and Table 4, the need for artificial lung ventilation was more often needed by patients with elevated BMI (asymptotic significance of Pearson $p < 0.041$) this indicates the severity of COVID-19 infection and longer hospitalization in these patients.

In our study, we found a statistically significant association between levels of ALT and AST at 1.7 and 21 days after admission to the hospital and the need for mechanical ventilation in patients with non-alcoholic fatty liver disease (NAFLD) ($p < 0.0001$).

Discussion of the results

The results of the study revealed that in patients with NAFLD hospitalized with COVID-19 infection, predictors of severe course are older age, high BMI, elevated biochemical parameters (ALT, AST, GGTP, CRP) upon admission and their significant (2-3 fold) increase by day 7, which persists until day 21 of hospitalization.

The results of our study are confirmed by previous data from other researchers. Thus, in a retrospective study by Chinese scientists [11], patients with older NAFLD, with a high BMI and with a higher percentage of concomitant diseases had a progressive course. In addition, patients with NAFLD had a higher risk of disease progression (6.6% vs. 44.7%; $p < 0.0001$) and a longer virus release time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days; $p < 0.0001$) compared with

patients without NAFLD. It was also noted that NAFLD is an independent risk factor for the progression of COVID-19 disease [11]. In a large randomization Mendelian analysis [18], an association was noted between an increased BMI in NAFLD and the severity of COVID-19.

The course of COVID-19 infection in patients with NAFLD, as well as in most patients with COVID-19, can vary from an asymptomatic course and mild flu-like manifestations, initially in the form of headache, myalgia, fever, dry cough and fatigue, to moderate and severe, which are complicated by shortness of breath of varying severity. COVID-19 infection has a favorable prognosis in most patients, but some patients have a high risk of complications and critical conditions, up to fatal outcomes [22].

According to previous studies [4,9], liver damage was observed from 14 to 53% in patients with COVID-19, and manifested by elevated ALT and AST levels, and the incidence of liver damage in severe patients with COVID-19 was significantly higher than in patients with mild severity [27].

In our study, dynamics of biochemical parameters in 1,7,21 days of hospitalization show that patients with NAFLD have elevated ALT and AST levels at the onset of COVID-19 disease, which indicates an existing chronic inflammation that significantly affects the course and severity of COVID-19 infection. Thus, the severity of the cytolytic syndrome is an indicator of the degree of activity of the pathological process in the liver.

Liver damage in COVID-19 infection has a multifactorial character, in particular as a result of direct viral exposure and mediated by hyperactivation of proinflammatory mechanisms, in addition, drug-induced effects are also important. The entrance gate of the SARS-cov-2 virus

It is the epithelial cells of the respiratory tract, hepatobiliary tract, and intestines due to the high affinity of the coronavirus protein S to the angiotensin converting enzyme (ACE) receptor. A number of studies have noted that COVID-19 infection significantly enhances the expression of ACE receptors [26], which contributes to an increased immune response, which leads to damage to hepatocytes [24].

The state of sluggish chronic inflammation in patients with NAFLD leads to hypoxia of adipocytes and their dysfunction. In turn, this contributes to the increased release of pro-inflammatory cytokines such as IL-6, IL-8, C-reactive protein, TNF- α and activation of the macrophage system, cellular and humoral immunity. This condition is aggravated by the viral load of COVID-19 infection and the response of systemic activation of immune defense mechanisms, which increases the ongoing inflammation of hepatocytes, and leads to extensive damage to hepatocytes. Also, insulin resistance in patients with NAFLD is one of the factors of inflammation progression [6].

Along with these, dysfunction of the intestinal barrier contributes to the intensification of these inflammatory processes, which in turn leads to the translocation of bacteria or bacterial components into the portal circulation and the induction of liver inflammation [19].

Manifestations of the metabolic syndrome, in particular obesity, lead to increased secretion of proinflammatory leptin, interleukin (IL)-6 and tumor necrosis factor (TNF)- α

from peripheral adipose tissue [1]. Severe dyslipidemia due to an imbalance between lipolysis, oxidation, secretion and absorption of lipids between adipose tissue and the liver contributes to liver steatosis, as well as lipotoxicity, affecting key cellular elements such as the endoplasmic reticulum or mitochondrial function.

Due to the occurrence of a vicious circle, metabolic pathways in the liver are disrupted and further enhance the imbalance in lipid metabolism [10] and, consequently, lipotoxicity. Then, stellate cells are activated and cytokines are produced by Kupfer cells, where IL-1 β , TNF- α , IL-6, interferon (IFN)- γ , nuclear factor-kappa β and reactive oxygen species are key pro-inflammatory factors that support chronic sluggish inflammation and contribute to the development of fibrosis [2, 8, 23].

The data from previous studies are consistent with the results of our study, in which ALT values in patients with NAFLD initially significantly (4-5 times) ($p < 0.001$) exceeded ALT values in patients without NAFLD on the first day and remained high throughout the entire period of hospitalization, which is confirmed by pronounced cytolytic syndrome and hyperfermentemia in these patients on the background of COVID-19 infection (Table 2).

Cytolysis syndrome occurs due to a violation of the structure of liver cells, primarily hepatocytes. The peroxide oxidation of membrane lipids increases, which becomes permeable to some substances, including intracellular enzymes.

AST indicators were also increased in patients with NAFLD on day 1 of hospitalization and these indicators increased 2-fold on day 7 compared with AST indicators in patients without NAFLD ($p < 0.001$) and decreased slightly by day 21. Also, the indicators of C reactive protein in patients with NAFLD were initially high on day 1 and significantly (5 times) increased by day 7 of hospitalization ($p < 0.001$), which confirms the severity of the inflammatory process and activation of the immune response.

The results of our study are consistent with previous studies, for example, in a large review it was shown that COVID-19 leads to an increase in liver enzyme levels in about 17-58% of patients, while an increase in transaminase levels ("hepatitis") prevails, and cholestatic conditions are much less common, indicating predominantly hepatocytic damage [3, 5, 8, 25].

According to previous studies, hospitalized patients with COVID-19 have both direct viral cytotoxic damage to hepatocytes and cholangiocytes, as well as indirect drug damage and an increased immune response due to increased production and excess of cytokines, and as a result, an exacerbation of existing liver disease occurs [10].

In another retrospective study by scientists from Turkey involving 614 patients with COVID-19 infection, an association was found between an increase in ALT, AST and the severity of the infection [18]. Similarly, our study revealed a statistically significant association between elevated ALT and AST values in patients with NAFLD and the need for artificial lung ventilation.

Thus, the presence of metabolic risks and NAFLD in hospitalized patients with COVID-19 infection is an unfavorable prognostic sign of the severity of the infection, requiring careful examination and the need to identify early

symptoms (both clinical and laboratory) of liver tissue damage and its involvement in the pathological process.

Conclusions:

Important predictors of severe course in patients with NAFLD hospitalized with COVID-19 infection in this study were old age, high body mass index, elevated ALT, AST, CRP on the first and subsequent days of hospitalization. The presence of cytolytic syndrome upon admission in patients with NAFLD hospitalized with COVID-19 is one of the important prognostic factors of severe infection.

Contributors. All the authors equally participated in the selection, assessment, and analysis of the selected studies. All of them have approved the final article.

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