UDC 616.36-02:[616.98:578.834C0V]-06:616.24-002]-07
DOI: 10.14739/2310-1237.2024.3.302921

Features of liver damage in patients with coronavirus disease (COVID-19) with pneumonia in relation to indicators of inflammation taking into account oxygen dependence

O. V. Riabokon*[A,E,F], I. O. Kuliesh[B,C,D]

Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

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

Keywords: coronavirus disease, COVID-19, pneumonia, oxygen dependence, liver damage, diagnosis.

Pathologia. 2024;21(3):220-225

***E-mail:** ryabokonzsmu@ukr.net

Aim. The purpose of the work is to analyze the biochemical indicators of liver function in relation to indicators of inflammation in patients with coronavirus disease (COVID-19) with pneumonia, taking into account the development of oxygen dependence.

Material and methods. 123 patients with COVID-19 with pneumonia were examined. The diagnosis was confirmed by isolation of RNA-SARS-CoV-2 from the nasopharyngeal mucus by polymerase chain reaction. The presence of pneumonia in all patients was confirmed by X-ray or computer tomography of the chest organs. The patients were divided into groups: I group – 32 patients with a moderately severe course without oxygen dependence; II group – 91 patients with a severe course with oxygen dependence. Exclusion criteria from the research were: the presence of infection with hepatotropic viruses and the presence of previously diagnosed other chronic liver diseases. Statistical data processing was carried out in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. In 45.5 % of patients with COVID-19 with pneumonia at the time of hospitalization by 9.0 [7.0; 12.0] days of the disease, liver damage with the development of cytolytic syndrome was confirmed. The frequency of liver damage in patients with COVID-19 with pneumonia increased with the appearance of oxygen dependence (25.0 % vs. 52.7 %, $p = 0.007$). Biochemical signs of the syndrome of intrahepatic cholestasis were weakly expressed, with the appearance of oxygen dependence, they were characterized by an increase the number of patients with an elevated level of gammaglutamyltranspeptidase (59.7 % vs. 24.0 %, $p = 0.002$) in the absence of statistically significant changes in the median indicators activity of gammaglutamyltranspeptidase and alkaline phosphatase ($p > 0.05$). The relationship between liver damage and the development of oxygen dependence in patients with COVID-19 with pneumonia is confirmed by the correlation between the activity index of alanine aminotransferase (ALT) and the oxygen saturation index ($r = -0.31$, $p < 0.05$). In patients with COVID-19 with pneumonia in the dynamics after a week in presence of oxygen dependence, a higher level of activity of ALT remained ($p < 0.05$) and the frequency of detection of increased activity of ALT remained higher (62.6 % vs. 37.5 %, $\chi^2 = 6.07$, $p = 0.01$), the activity of aspartate aminotransferase is higher ($p < 0.05$), compared to patients with COVID-19 with pneumonia without oxygen dependence.

A higher frequency of liver damage in patients with COVID-19 with pneumonia in presence of oxygen dependence is combined with more pronounced changes in acute inflammatory parameters, namely a higher level of C-reactive protein (CRP) in blood serum ($p < 0.01$), more frequent ($p = 0.001$) and more pronounced ($p = 0.004$) absolute lymphopenia, a higher level of absolute neutrophilia ($p = 0.03$) and, accordingly, a higher coefficient of N/L ratio ($p = 0.0001$). The oxygen saturation indicator correlates with the indicators: CRP ($r = -0.37$, $p < 0.05$), relative ($r = +0.36$, $p < 0.05$) and absolute ($r = +0.23$, $p < 0.05$) number of lymphocytes, the absolute number of neutrophils ($r = -0.32$, $p < 0.05$) and the ratio of N/L ($r = -0.42$, $p < 0.05$).

Conclusions. Liver damage with the development of cytolytic syndrome was established in 45.5 % of patients with COVID-19 with pneumonia at the time of hospitalization. The dependence of the frequency of liver damage with the appearance of oxygen dependence, as well as the relationship with acute inflammatory indicators, was demonstrated.

Ключові слова: коронавірусна хвороба, COVID-19, пневмонія, киснева залежність, ураження печінки, діагностика.

Патологія. 2024. Т. 21, № 3(62). С. 220-225

Особливості ураження печінки у хворих на коронавірусну хворобу (COVID-19) та пневмонію у взаємозв'язку з показниками запалення, враховуючи кисневу залежність

О. В. Рябоконь, І. О. Кулєш

Мета роботи – проаналізувати біохімічні показники функції печінки у взаємозв'язку з показниками запалення у хворих на коронавірусну хворобу (COVID-19) та пневмонію, враховуючи розвиток кисневої залежності.

Матеріали і методи. Обстежили 123 хворих на COVID-19 і пневмонію. Діагноз підтверджено виділенням RNA-SARS-CoV-2 із носоглоткового слизу методом полімеразної ланцюгової реакції. Пневмонію в усіх хворих підтверджено методом рентгенографії або комп'ютерної томографії органів грудної клітки. Хворих поділили на групи: I – 32 пацієнти з середньотяжким перебігом без кисневої залежності; II – 91 пацієнт із тяжким перебігом і кисневою залежністю. Критерії виключення з дослідження – інфікування гепатотропними вірусами та раніше діагностовані інші хронічні хвороби печінки. Статистично дані опрацювали в програмі Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. У 45,5 % хворих на COVID-19 із пневмонією на час госпіталізації на 9,0 [7,0; 12,0] дня хвороби підтверджено ураження печінки з розвитком цитолітичного синдрому. Частота ураження печінки у хворих на COVID-19 із пневмонією збільшувалася в разі виникнення кисневої залежності (25,0 % проти 52,7 %, $p = 0,007$). Біохімічні ознаки синдрому вну-

трішньопечінкового холестазу виражені слабо; в разі виникнення кисневої залежності зафіксовано збільшення кількості пацієнтів із підвищеним рівнем гамма-глутамілтрансферази (59,7 % проти 24,0 %, p = 0,002), при цьому не зафіксовано статистично значущих змін медіан показників активності і гамма-глутамілтрансферази, і лужної фосфатази (p > 0,05). Взаємозв'язок між ураженням печінки та розвитком кисневої залежності у хворих на COVID-19 і пневмонію підтверджує кореляція між показником активності аланінамінотрансферази (АлАТ) і рівнем сатурації кисню (r = -0,31, p < 0,05).

За наявності кисневої залежності у хворих на COVID-19 і пневмонію в динаміці через тиждень вищим залишався рівень активності АлАТ (p < 0,05), а також частота виявлення підвищеної активності АлАТ (62,6 % проти 37,5 %, χ^2 = 6,07, p = 0,01), зафіксовано вищу активність аспартатамінотрансферази (p < 0,05) порівняно з хворими на COVID-19 і пневмонію без кисневої залежності.

Вища частота ураження печінки у хворих на COVID-19 і пневмонію за наявності кисневої залежності поєднувалася з вираженішими змінами гострозапальних показників, зокрема з вищим рівнем С-реактивного білка (СРБ) у сироватці крові (p < 0,01), частішою (p = 0,001) та більш вираженою (p = 0,004) абсолютною лімфопенією, вищим рівнем абсолютного нейтрофільозу (p = 0,03) та, відповідно, вищим коефіцієнтом співвідношення N/L (p = 0,0001). Показник сатурації кисню корелював із СРБ (r = -0,37, p < 0,05), відносною (r = +0,36, p < 0,05) та абсолютною (r = +0,23, p < 0,05) кількістю лімфоцитів, абсолютною кількістю нейтрофілів (r = -0,32, p < 0,05) і коефіцієнтом співвідношення N/L (r = -0,42, p < 0,05).

Висновки. Ураження печінки з розвитком цитолітичного синдрому виявлено у 45,5 % хворих на COVID-19 і пневмонію під час госпіталізації. Встановлено залежність частоти ураження печінки і виникнення кисневої залежності, а також взаємозв'язки з гострозапальними показниками.

During the coronavirus disease (COVID-19) pandemic, attention was drawn to the fact that in addition to respiratory symptoms of COVID-19, which primarily determined the severity of the disease, some patients had clinical and laboratory signs of damage to gastrointestinal tract, in particular the liver [1,2,3]. According to the data of a systematic analysis of 11 research, in which the functional state of the liver was assessed by biochemical indicators in 2541 patients, it was demonstrated that the appearance of cytolytic syndrome was recorded in 25 % of patients with COVID-19, but an increase bilirubin occurred in isolated cases, and the development of intrahepatic cholestasis syndrome was not recorded according to the results of the research of alkaline phosphatase activity [4]. According to the results of the meta-analysis, it was demonstrated that the cumulative prevalence of acute liver damage in patients with COVID-19 is 23.7 % [2].

Today, several mechanisms of liver damage by the SARS-CoV-2 coronavirus are discussed, namely: the direct effect of the virus on liver cells due to the expression of the angiotensin-converting enzyme 2 (ACE2) receptor on their membranes, immune-mediated mechanisms of damage in the context of the development of a "cytokine storm"; liver damage due to ischemia; in addition, when assessing liver damage, attention is paid to the need to exclude adverse hepatotoxic effects of drugs used [4,5,6,7,8].

When studying the direct effect of the virus on liver cells, certain features were established, namely, the level of ACE2 expression on hepatocytes was 0.31 %, in contrast to cholangiocytes, on the membrane of which the level of ACE2 expression was 20 times higher [5]. It is believed that one of the main mechanisms of liver damage can be an excessive inflammatory immune reaction, so-called "cytokine storm" [1]. The research [6] demonstrated that in patients with COVID-19, non-specific inflammatory changes were found in hepatocytes (hyperplasia of Kupffer cells, edema and steatosis of hepatocytes, mild infiltration by lymphocytes), the appearance and degree of which were correlated with a significant increase pro-inflammatory cytokines (interleukin-2 and interleukin-6) and, accordingly, with the severity of the course of the coronavirus disease (COVID-19).

Research [7,8] also demonstrated the relationship between the development of cytolytic syndrome and hypoalbuminemia with an increase the level of acute inflammatory indicators, in particular C-reactive protein (CRP) and ferritin, and, accordingly, the relationship with the adverse course of COVID-19. In addition to the above-mentioned acute inflammatory markers of the adverse course of the coronavirus disease and the development of multiorgan lesions of COVID-19, such hematological changes as the development of absolute lymphopenia [9] and an increase in the ratio of the absolute number of neutrophils to the absolute number of lymphocytes (N/L) [10] are also included.

However, researchers [3,11] believe that the liver is not a target for significant inflammatory damage in COVID-19. Histopathology of the liver in severe respiratory insufficiency of COVID-19 indicates primarily vascular changes, which are secondary to systemic changes caused by the virus, in particular in damage to the endothelium and hypercoagulation play a significant role in the pathogenesis of hepatitis in COVID-19 [11].

The above, in our opinion, requires further research to clarify the specifics of liver damage in hospitalized patients with coronavirus disease (COVID-19) with pneumonia.

Aim

The purpose of the work is to analyze the biochemical indicators of liver function in relation to indicators of inflammation in patients with coronavirus disease (COVID-19) with pneumonia, taking into account the development of oxygen dependence.

Material and methods

The research included 123 patients with coronavirus disease (COVID-19) with pneumonia. Patients underwent inpatient treatment at the Communal Non-Commercial Enterprise "Regional Infectious Clinical Hospital" of Zaporizhzhia Regional Council. In all patients, the diagnosis was confirmed by isolation of RNA-SARS-CoV-2 from nasopharyngeal mucus by the polymerase chain reaction method. The presence of pneumonia in all patients

was confirmed by imaging methods (x-ray or computer tomography of the chest organs).

Laboratory examination and treatment of patients were carried out in accordance with the Order of the Ministry of Health of Ukraine dated March 28, 2020 No. 722 "Organization of medical care for patients with coronavirus disease (COVID-19)". Depending on the severity of the course and the presence of oxygen dependence, patients with COVID-19 with pneumonia were divided into groups: I group – 32 patients with a medium-severe course without oxygen dependence; II group – 91 patients with a severe course with the presence of oxygen dependence. Exclusion criteria from the research were: presence of infection with hepatotropic viruses (patients were examined for markers of viral hepatitis, namely HBsAg, anti-HCV, IgM anti-HAV) and the presence of previously diagnosed other chronic liver diseases. Patients are included in the research with informed consent.

For statistical processing of the received data, we created a database of patients in the Excel program. Statistical data processing was carried out in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J). The normality of the distribution was assessed using the Shapiro–Wilk test, taking into account the difference of the distribution of the investigated characteristic from the normal law of distribution, non-parametric methods of statistical processing of the obtained data were used. The results of quantitative data were presented in form of the median and interquartile ranges of Me [Q25; Q75]. The Mann–Whitney test was used to determine the differences between quantitative characteristics in independent groups, the Wilcoxon test was used in dependent groups, and the χ^2 test was used between qualitative characteristics. Spearman's correlation was used to establish relationships between quantitative traits. Differences at $p < 0.05$ were considered to be reliably significant.

Results

According to the results of the conducted research, we established that at the time of hospitalization by 9.0 [7.0; 12.0] day of the disease, liver damage in patients with coronavirus disease (COVID-19) with pneumonia occurred in 45.5 % (56 out of 123) of patients, which was evidenced by an increase activity of alanine aminotransferase (ALT) in blood serum from 43.0 U/L to 333.0 U/L.

However, it should be noted that the frequency of liver damage depended on the appearance of oxygen dependence, namely, during the specified period of observation, the frequency of increased activity of ALT in the blood serum of patients of the II group was statistically significantly higher than of the patients of the I group (52.7 % vs. 25.0 %, $\chi^2 = 7.35$, $p = 0.007$). The activity index of aspartate aminotransferase (AST) in blood serum during the specified period of observation was not statistically different in the patients of the researched groups ($p > 0.05$). When comparing the activity of enzymes that reflect the development of intrahepatic cholestasis, at the time of hospitalization, the median activity of alkaline phosphatase (ALP) in blood serum remained within the reference values, while among patients of the I group, in no case was an increase in this indicator recorded, and among patients of the II group 18.1 % had an increase in the activity of this enzyme by 1.2–1.3 times the upper limit of the norm. The median activity of gammaglutamyltranspeptidase (GGT) in the blood serum of patients of the II group had a tendency ($p > 0.05$) to a higher level, compared to the patients of the I group, however, the frequency of increasing the activity of GGT in the blood serum was statistically significantly higher in the patients of the II group, compared to patients of the I group (59.7 % versus 24.0 %, $\chi^2 = 9.47$, $p = 0.002$). Violation of pigment metabolism with an increase the level of total bilirubin was recorded only in individual patients (7 out of 123, 5.7 %) in the range from 21.9 μmol/l to 68.0 μmol/l, while the median of this indicator did not differ ($p > 0.05$) in patients of the studied groups *(Table 1)*.

In the dynamics of observation during the week, the frequency of increased activity of ALT in blood serum had a tendency to increase, but this was not statistically significant: in patients of the I group from 25.0 % to 37.5 % ($\chi^2 = 1.16$, $p > 0,05$) and in patients of the II group from 37.5 % to 62.6 % ($\chi^2 = 1.82$, $p > 0.05$). The median activity of ALT in the dynamics of observation during the week did not change statistically significantly ($p > 0.05$). Among patients of the I group, the proportion of patients with increased activity of GGT increased dynamically ($\chi^2 = 9.47$, $p = 0.002$), and intensity of the mesenchymal-inflammatory reaction according to the indicator of thymol test increased in the patients of the II group ($p < 0.01$) *(Table 1)*.

When comparing the biochemical indicators of liver function after a week of complex treatment, it was noted that the patterns established during the hospitalization of patients with COVID-19 with pneumonia were preserved. During the specified period of observation, patients of the II group who had oxygen dependence had a higher level of ALT activity in the blood serum compared to patients of the I group ($p < 0.05$), and the frequency of detection of elevated ALT activity remained higher (62.6 % vs. 37.5 %, $\chi^2 = 6.07$, $p = 0.01$). It should be noted that during this period of observation, a higher median activity of AST in blood serum was noted in patients of the II group, compared to patients of the I group ($p < 0.05$), which indicated the deepening of liver damage in oxygen-dependent patients. At the same time, no statistically significant differences ($p > 0.05$) were found in the dynamics of treatment when comparing the median parameters of intrahepatic cholestasis and the indicator of pigment metabolism in the patients of the investigated groups ($p > 0.05$) *(Table 1)*.

We established a higher frequency of liver damage in patients with COVID-19 with pneumonia in the presence of oxygen dependence was combined with more pronounced changes in acute inflammatory indicators. Thus, at the time of hospitalization, the content of CRP in blood serum was 2.5 times higher in patients of the II group ($p < 0.01$), absolute lymphopenia was more often detected (82.4 % versus 46.9 %, $\chi^2 = 15.23$, $p = 0.001$) and the absolute number of blood lymphocytes was lower ($p = 0.004$), the level of the absolute number of neutrophils was higher ($p = 0.03$) and the N/L ratio was correspondingly higher ($p = 0.0001$) *(Table 2)*.

Table 1. Biochemical indicators of liver function in patients with coronavirus disease (COVID-19) with pneumonia, taking into account the development of oxygen dependence in the dynamics of the disease, Me [Q25; Q75]

Indicator, units of measurement	During hospitalization		In dynamics after 7 days	
	I group, n = 32	II group, n = 91	I group, n = 32	II group, n = 91
Total bilirubin, μmol/l	10.0 [8.1; 11.8]	10.0 [8.5; 12.5]	9.5 [7.9; 10.7]	11.9 [9.8; 16.8]
ALT activity, Units/l	29.3 [20.6; 41.6]	40.4 [30.6; 58.0][1]	33.9 [28.8; 75.1]	51.1 [32.0; 98.4][1]
Increase ALT activity, abs. (%)	8 (25.0)	48 (52.7)[1]	12 (37.5)	57 (62.6)[1]
Activity of AST, Units/l	43.0 [27.9; 48.9]	46.3 [31.4; 65.9]	26.0 [20.8; 40.0]	42.6 [30.3; 73.0][1]
Activity of ALP, Units/l	52.8 [54.1; 72.6]	77.6 [61.7; 97.3]	68.1 [64.1; 82.6]	89.1 [71.6; 104.0]
Increase ALP activity, % (abs.)	0.0 (0 of 25)	18.1 (13 of 72)	0.0 (0 of 24)	30.2 (16 of 53)
GGT activity, Units/l	48.1 [44.6; 62.5]	72.9 [34.9; 111.5]	78.1 [56.7; 78.6]	82.2 [51.0; 113.0]
Increase GGT activity, % (abs.)	24.0 (6 of 25)	59.7 (43 of 72)[1]	54.2 (13 of 24)[2]	60.4 (32 of 53)
Thymol test, unit	1.8 [1.4; 3.1]	2.1 [0.9; 3.0]	2.9 [1.5; 4.6]	5.0 [1.5; 7.9][2]

[1]: the difference is significant, compared to patients of the I group in the corresponding period of observation ($p < 0.05$); [2]: compared with hospitalization of patients of the corresponding group ($p < 0.05$).

Table 2. Indicators of an acute inflammatory reaction in patients with the coronavirus disease COVID-19 with pneumonia depending on the development of oxygen dependence in dynamics of the disease, Me [Q25; Q75]

Indicator, units of measurement	During hospitalization		In dynamics after 7 days	
	I group, n = 32	II group, n = 91	I group, n = 32	II group, n = 91
CRP, mg/l	40.1 [18.4; 82.0]	100.5 [44.2; 175.1][1]	8.4 [5.0; 15.0][2]	36.5 [16.0; 111.5][1,2]
Leukocytosis, abs. (%)	8 (25.0)	26 (28.6)	4 (12.5)	56 (61.5)[1,2]
Leukocytes, $\times 10^9$/l	6.0 [4.6; 7.1]	7.1 [4.9; 9.5]	7.5 [6.1; 8.6]	10.8 [7.6; 18.4][2]
Neutrophils, $\times 10^9$/l	4.3 [3.5; 6.9]	6.2 [4.0; 8.7][1]	4.8 [3.5; 6.3]	9.1 [6.2; 17.3][1,2]
Lymphopenia, abs. (%)	15 (46.9)	75 (82.4)[1]	1 (3,1)[2]	57 (62.6)[1,2]
Lymphocytes, $\times 10^9$/l	1.1 [0.8; 1.5]	0.8 [0.6; 1.0][1]	1.8 [1,3; 2,2][2]	1.0 [0.7; 1.3][1,2]
N/L	3.7 [2.7; 7.0]	8.3 [4.9; 12.1][1]	2.5 [1.9; 3.8][2]	9.0 [5.1; 22.4][1,2]

[1]: the difference is significant, compared to patients of the I group in the corresponding period of observation ($p < 0.05$); [2]: compared with hospitalization of patients of the corresponding group ($p < 0.05$).

During the first week of observation, the opposite dynamics of acute phase indicators were noted in the patients of the investigated groups. Thus, in patients of the I group who did not develop oxygen dependence, a decrease the CRP level ($p = 0.0001$), a decrease the frequency of lymphopenia ($\chi^2 = 16.33$, $p = 0.001$) and a decrease the severity of absolute lymphopenia ($p = 0.001$) and, accordingly, a decrease the ratio of N/L ($p = 0.001$). On the contrary, in patients with COVID-19 with pneumonia of the II group who had oxygen dependence during the week, an increase in the frequency of detection of leukocytosis was noted ($\chi^2 = 19.98$, $p = 0.0001$) and the level of leukocytosis ($p = 0.001$), absolute neutrophilia ($p = 0.001$), of the ratio of N/L ($p = 0,02$) despite the decrease in the level of CRP ($p = 0.001$), decrease in the frequency of absolute lymphopenia ($\chi^2 = 8.93$, $p = 0.003$) and decrease in the severity of absolute lymphopenia ($p = 0.001$) *(Table 2)*.

Comparison of acute phase indicators after a week of complex treatment showed that laboratory signs of immune inflammation were significantly more pronounced in patients of the II group than in patients of the I group. Namely, the level of CRP remained higher ($p = 0.001$), the frequency of leukocytosis was higher ($\chi^2 = 22.79$, $p = 0.0001$), the level of expressiveness of absolute neutrophilia ($p = 0.0001$), the frequency of absolute lymphopenia was higher ($\chi^2 = 33.65$, $p = 0.0001$) and the level of the absolute number of lymphocytes is lower ($p = 0.0001$) and, accordingly, the coefficient of the ratio N/L is higher ($p = 0.0001$) *(Table 2)*.

The correlation analysis of the investigated parameters at the time of hospitalization confirmed the existence of a relationship between the development of the cytolytic syndrome and the appearance of oxygen dependence, namely, the inverse correlation of the activity indicator of ALT in blood serum with the oxygen saturation indicator in the air upon admission was established ($r = -0.31$, $p < 0.05$). Direct correlations were also recorded between indicators of cytolytic syndrome, namely between ALT and AST ($r = +0.54$, $p < 0.01$), as well as between the activity index of ALT and the thymol test index, which reflects the degree of expression of the mesenchymal inflammatory reaction ($r = +0.26$, $p < 0.05$). Statistically significant correlations were also established between the index of oxygen saturation on admission and acute phase indicators, which confirm the role of immunoinflammatory changes in the formation of oxygen dependence in patients with coronavirus disease (COVID-19) with pneumonia.

The indicator of oxygen saturation correlated with indicators: CRP ($r = -0.37$, $p < 0.05$), relative ($r = +0.36$, $p < 0.05$) and absolute ($r = +0.23$, $p < 0.05$) number of lymphocytes, the absolute number of neutrophils ($r = -0.32$, $p < 0.05$) and the ratio of N/L ($r = -0.42$, $p < 0.05$). A number of correlations were also established between acute phase indicators, namely, the level of CRP in blood serum was correlated with indicators of relative ($r = -0.38$, $p < 0.05$) and absolute ($r = -0.26$, $p < 0.05$) number of lymphocytes, the absolute number of neutrophils ($r = +0.23$, $p < 0.05$) and the ratio of N/L ($r = +0.32$, $p < 0.05$). In the dynamics, after 7 days of treatment, a direct correlation was established between the activity indicators of ALT and GGT ($r = +0.65$, $p < 0.05$) in blood serum.

Discussion

Today, there are more and more research devoted to the detection of liver damage in patients with COVID-19 [12,13,14]. In the research [12] with inclusion of 5700 patients with COVID-19, in which biochemical indicators of the state of the liver were analyzed, the development of cytolytic syndrome with increased activity of ALT in blood serum was demonstrated in 39.0 % of patients. According to the results of a meta-analysis, it was demonstrated that the adverse course of COVID-19 is accompanied by a significant increase activity of ALT, AST, and bilirubin [13].

The data obtained during our research also showed that in 45.5 % of patients with coronavirus disease (COVID-19) with pneumonia at the time of hospitalization by 9.0 [7.0; 12.0] day of the disease, there were biochemical signs of liver damage, which was confirmed by the development of cytolytic syndrome. In addition, with a severe course with the development of oxygen dependence, a higher frequency of increased activity of ALT ($p < 0.05$) and a higher level of activity of this enzyme ($p < 0.05$) was established, compared to patients with COVID-19 with pneumonia without oxygen dependence. We confirmed the role of oxygen dependence in increasing the frequency of liver damage in patients with COVID-19 with pneumonia by the presence of a correlation between the oxygen saturation indicator and the activity of ALT ($r = -0.31$, $p < 0.05$). In the presence of oxygen dependence, we also established a higher activity of AST in blood serum ($p < 0.05$).

Other researchers also paid attention to a certain prognostic value of increasing the activity of AST in the blood serum of patients with COVID-19, namely, a high frequency of increasing the activity of this enzyme in hospitalized patients and a further increase of this indicator in conditions of an adverse course of the disease was demonstrated [14]. An assumption was made that mitochondrial proteins can directly interact with SARS-CoV-2, which can lead to an increase AST activity in blood serum [15].

According to the results obtained by us, biochemical signs of intrahepatic cholestasis syndrome are weakly expressed in patients with COVID-19 with pneumonia, namely, in the absence of statistically significant changes in the median indicators of activity of GGT and ALP ($p > 0.05$). The appearance of oxygen dependence was accompanied by only a certain increase in the number of patients with an elevated level of GGT (59.7 % vs. 24.0 %, $p = 0.002$). The features of biochemical changes we established regarding the syndrome of intrahepatic cholestasis in patients with COVID-19 with pneumonia are confirmed by the results of other research. Thus, the authors demonstrated an increase activity of GGT in the blood serum of patients with a severe course in the absence of changes in the activity index of ALP [16].

Today, it is believed that immune-mediated mechanisms of damage not only to the lungs, but also to other organs, including the liver, are involved in the formation of a "cytokine storm" [4,8]. According to the results of our research, it was demonstrated that a higher frequency of liver damage in patients with COVID-19 with pneumonia in the presence of oxygen dependence is combined with more pronounced changes in acute inflammatory indicators, namely, a higher level of CRP in blood serum ($p < 0.01$), more frequent ($p = 0.001$) and more pronounced ($p = 0.004$) absolute lymphopenia, a higher level of absolute neutrophilia ($p = 0.03$) and, accordingly, a higher ratio of N/L ($p = 0.0001$).

In the modern literature, there are research that also demonstrate the connection between the degree of expressiveness of the activity of liver enzymes and indicators of immune inflammation. Thus, in the research [17], the authors paid attention to the relationship between higher activity of ALT and GGT, lower albumin level, higher ferritin level, lower level of CD4+ T- and B-lymphocytes in the blood with a more severe course of COVID-19. The role of liver damage in the formation of the adverse course of COVID-19 is confirmed by the data of research in which an increase in the level of interleukin-6, ferritin, CRP and ALT was demonstrated during the progression of the disease [8,18].

Morphological changes of liver parenchyma in COVID-19 are described in the literature as autopsy results. Thus, the pathomorphological research [19] showed moderate microvesicular steatosis, portal and moderate lobular inflammatory activity. However, viral inclusions in liver tissue were not identified [19,20]. Therefore, it should be noted that the mechanism of liver damage due to damage to the endothelium and the development of systemic microthrombosis is also being considered [11,21]. Thus, according to the results of a demonstrated acute damage of the portal intrahepatic system with the presence of thrombotic ectasia, and the intrahepatic blood vessels had an abnormal configuration.

Conclusions

1. In 45.5 % of patients with coronavirus disease (COVID-19) with pneumonia at the time of hospitalization by 9.0 [7.0; 12.0] day of the disease, liver damage occurs with the development of cytolytic syndrome. The frequency of liver damage in patients with COVID-19 with pneumonia increases with the appearance of oxygen dependence (25.0 % vs. 52.7 %, $p = 0.007$). Biochemical signs of the syndrome of intrahepatic cholestasis are weakly expressed, with the appearance of oxygen dependence they are characterized by an increase the number of patients with an elevated level of GGT (59.7 % vs. 24.0 %, $p = 0.002$) in the absence of statistically significant changes in the median indicators of activity GGT and ALP ($p > 0.05$). The relationship between liver damage and the development of oxygen dependence in patients with COVID-19 with pneumonia is confirmed by the correlation between the activity index of ALT and the oxygen saturation index ($r = -0.31$, $p < 0.05$).

2. In patients with COVID-19 with pneumonia in the dynamics after a week in the presence of oxygen dependence, a higher level activity of ALT remains ($p < 0.05$) and the frequency of detection of increased activity of ALT remained higher (62.6 % vs. 37.5 %, $\chi^2 = 6.07$, $p = 0.01$), the activity of AST is higher ($p < 0.05$), compared to patients with COVID-19 with pneumonia without oxygen dependence.

3. A higher frequency of liver damage in patients with COVID-19 with pneumonia in the presence of oxygen

dependence is combined with more pronounced changes in acute inflammatory indicators, namely a higher level of CRP in blood serum ($p < 0.01$), more frequent ($p = 0.001$) and more pronounced ($p = 0.004$) absolute lymphopenia, a higher level of absolute neutrophilia ($p = 0.03$) and, accordingly, a higher ratio of N/L ($p = 0.0001$). The oxygen saturation indicator correlates with the indicators: CRP ($r = -0.37$, $p < 0.05$), relative ($r = +0.36$, $p < 0.05$) and absolute ($r = +0.23$, $p < 0.05$) number of lymphocytes, the absolute number of neutrophils ($r = -0.32$, $p < 0.05$) and the ratio of N/L ($r = -0.42$, $p < 0.05$).

Prospects for further research. The prospects for further research in this direction, in our opinion, are to clarify the clinical-pathogenetic role of endothelial dysfunction in liver damage in patients with coronavirus disease (COVID-19) with pneumonia and to find optimal methods of drug correction.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 01.05.2024
Після доопрацювання / Revised: 13.05.2024
Схвалено до друку / Accepted: 05.06.2024

Information about authors:
Riabokon O. V., MD, PhD, DSc, Professor, Head of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0002-7394-4649
Kuliesh I. O., MD, Graduate Student of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-5575-9901

Відомості про авторів:
Рябоконь О. В., д-р мед. наук, професор, зав. каф. інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.
Кулєш І. О., аспірант каф. інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.

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