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The Nature of Changes in Liver Function and Structure in Patients with COVID-19 and End-Stage Chronic Renal Failure Treated at a Repurposed Moscow Clinic

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Abstract: Relevance: Currently, COVID-19 is considered as a systemic disease with impaired immune system function, primarily affecting the lungs, as well as the heart, kidneys, and intestines. The nature of changes in liver function in (COVID-19) is still poorly understood and poorly covered in the available literature. There are no publications on the nature of liver and gastrointestinal tract damage in patients with end-stage chronic kidney disease with COVID-19 virus infection complicated by pneumonia, in the available modern literature. Purpose of the work: To assess the structure of liver pathology in patients with end-stage chronic renal failure (CRF), including chronically receiving hemofiltration procedures, hospitalized with a diagnosis of COVID-19 in a converted emergency hospital in Moscow. Material and methods: We studied 72 patients, including 38 men and 34 women aged 23-86 years, with an average of 58.2±4.8, who were admitted to the hospital for diagnosis and treatment in the period from 10.04.2020 to 02.10.2020 with diagnoses according to ICD-10: U07.1 Coronavirus infection caused by the COVID-19 virus. All patients underwent ultrasound examination of the liver, gallbladder, pancreas and spleen. The level of liver enzyme activity in dynamics, serum albumin concentration, prothrombin time and index were evaluated. Results: Biochemical signs of liver cell cytolysis were detected in 25-57% of patients with viral pneumonia in COVID-19, which complicates the course of terminal forms of chronic kidney disease with hemodialysis. Most often, the disease was accompanied by signs of a decrease in the synthesis of hemostatic proteins of the prothrombin complex and serum albumin, which may be associated with an aggravation of the severity of their existing chronic anemia. hematomegaly and changes in the liver structure were diagnosed in 42-85% of patients with this pathology and were combined with ultrasoundsigns of damage to the pancreas and spleen in 26-38%. In 11-19% of patients with COVID-19 infection, chronic liver damage preceded the development of pneumonia. Regardless of the state of renal function, these changes were accompanied by a worsening of the course of pre-existing liver and pancreatic lesions, including hepatitis and pancreatitis. Conclusion: Assessment of the state of enzyme and protein-producing function of the liver and pancreas should be included in the standards of inpatient examination in patients with end-stage renal failure and hemodialysis, with the development of COVID-19 and viral pneumonia, due to the high prevalence of liver, gallbladder and pancreas pathology.

Keywords: COVID-19, Viral Pneumonia, End-Stage Chronic Kidney Disease, Liver Damage, Pancreas

1. Introduction

Currently, COVID-19 is considered as a systemic disease with impaired immune system function, primarily affecting the lungs, as well as the heart, kidneys, and intestines. Severe forms of the disease are accompanied by hyperimmune inflammation, an imbalance of the renin-angiotensin-aldosterone system, the development of endothelial dysfunction and special forms of vasculopathy (thrombotic microangiopathy and intravascular coagulopathy). This

condition, according to some experts, should be called a thrombo-inflammatory process, or COVID-19-associated coagulopathy [1, 2]. The development of the disease is most often predisposed to:

1) cardiovascular diseases, especially arterial hypertension;
2) diabetes mellitus;
3) chronic lung disease;
4) cancer (in particular, hematological malignancies, lung cancer, and metastasis);
5) chronic kidney disease;
6) obesity;
7) smoking;
8) immunodeficiency states;
9) xchronic liver diseases [3, 4].

It is assumed that, in some patients with chronic diseases of the gastrointestinal tract (GIT) (Crohn's disease, ulcerative colitis) or liver (cirrhosis of the liver), there maybe an increased risk of COVID-19 and more severe forms of diseases [5]. The incidence of liver damage in patients with COVID-19, according to various studies, varies from 14 to 53% [4]. At the same time, changes in liver function in patients with COVID-19 are not mentioned in the list of major complications of this infection [6]. In this list, WHO experts included:

1) acute respiratory distresssyndrome, 15% to 33%;
2) acute respiratory failure, 8%;
3) acute heart failure, 7% to 20%;
4) secondary infection, from 6% to 10%;
5) acute renal failure, from 14% to 53%;
6) septic shock, 4% to 8%;
7) cardiomyopathy, in 33% of critical patients;
8) disseminated intravascular coagulation, 71% of fatalities;
9) pregnancy complications are not excluded.

The nature of changes in liver function in (COVID-19) patients is still insufficiently studied and poorly covered in the available literature [7]. There are no publications on the nature of liver and gastrointestinal tract damage in patients with end-stage chronic kidney disease with COVID-19 virus infection complicated by pneumonia, in the available modern literature. Based on this, we set the following goal in our work.

2. Purpose of the Study

To assess the structure of liver pathology in patients with end-stage chronic renal failure (CRF), including chronically receiving hemofiltration procedures, hospitalized with a diagnosis of COVID-19 in a converted emergency hospital in Moscow in the period from April to October 2020.

3. Material and Methods

We retrospectively analyzed the data of 72 patients, including 38 men and 34 women aged 23-86 years, with an average of 58.2±4.8, who were admitted to the hospital for diagnosis and treatment in the period from 10.04.2020 to 02.10.2020 with diagnoses according to ICD-10: B. 34. 2. Unspecified coronavirus infection. U07.1 Coronavirus infection caused by the COVID-19 virus, the virus is identified (confirmed by laboratory testing regardless of the severity of clinical signsor symptoms); U07.2 Coronavirus infection caused by the COVID-19 virus, the virus has not been identified (COVID-19 is diagnosed clinically or epidemiologically, but laboratory tests are inconclusive or unavailable. Medical records of patients were archived in the city computer room system “ЕМИАС” (Unified Information and Analytical system of the Moscow Department of Health). Ultrasound scanning (US) of the liver, spleen, gallbladder, and pancreas in real - time and gray-scale mode was performed in all patients, including 12 patients in the course of treatment. Diagnostic esophagoduodenogastroscopy was performed in 16 patients. In all patients, the level of liver enzyme activity was studied in dynamics, and indicators of protein-synthetic function were evaluated (serum albumin concentration, prothrombin time, and international normalized attitude index (INR) on an automatic analyzer Getpremier spectrophotometer (USA), indicators of pigment metabolism with an assessment of the concentration of total and conjugated bilirubin. Parameters of carbohydrate metabolism were studied (the level of glucose in the blood serum, in the urine, in some patients-the level of glycosylated hemoglobin). The study data were processed using the methods of variation and frequency statistics. From the total sample, patients were 2 groups of patients: the first - with end-stage chronic kidney disease (CKD) - 26 men and 16 women, age from 23 to 84 years, average of 58.3±5.6 years, with CKD stage 4 - 2 patients, 5S stage 1; 5D – 39 patients (classification of CKD, K/DOQI, 2006). Program hemodialysis was performed earlier in 33 patients (78.6%), its duration ranged from 2 months to 26 years. In 6 patients (14.3%), hemodiafiltration procedures (from 2-7) were performed for the first time in the hemodialysis department of our clinic, and in 3 patients (7.1%) with terminal CKD, this method of treatment was not used before the current hospitalization. The main diseases and causes of CKD in patients of this group are given in Table 1.

Table 1. *The nature of kidney pathology as causes of chronic kidney disease and renal failure in 42 patients with COVID-19 infection in group 1.*

n/n	Disease, syndrome	Number of patients (frequency in%)
1.	Chronic glomerulonephritis	7 (16.7%)
2.	Tubulo-interstitial nephritis	3 (7.1%)
3.	IgA-nephropathy	1 (2.4%)
4.	Chronic nephritis	2 (4.8%)
5.	Chronic pyelonephritis	4 (9.5%)
6.	Acute interstitial nephritis	1 (2.4%)

n/n	Disease, syndrome	Number of patients (frequency in%)
7.	Hemolytic-uremic syndrome	2 (4.8%)
8.	Hemorrhagic renal fever	1 (2.4%)
9.	Kidney carbuncle, nephrectomy	1 (2.4%)
10.	Hypertension with nephrosclerosis	4 (9.5%)
11.	Diabetic kidney	6 (14.3%)
12.	Myeloma kidney	1 (2.4%)
13.	Gouty nephritis	2 (4.8%)
14.	Kidney amyloidosis	2 (4.8%)
15.	Congenital malformations of the urinary system of the kidneys	1 (2.4%)
16.	Renal agenesis	1 (2.4%)
17.	Polycystic 2-x kidney disease 2	1 (2.4%)
18.	Kidney malformation	2 (4.8%)
19.	Hypoplasia of 2 kidneys	1 (2.4%)
20.	Bilateral kidney wrinkling	2 (4.8%)
21.	Prostate adenoma	1 (2.4%)
22.	Cadaveric kidney transplantation, transplant rejection	2 (4.8%)
23.	Epicystostoma	1 (2.4%)

The second comparison group included 30 patients, 12 men and 18 women aged 42-86 years, an average of 57.8±4.4 years, with COVID-19 infection, without severe renal failure and need for the procedure hemodiafiltration, with values of GFR in 27 of 30 (88.9%) above 60 ml/min (62 to 125 ml/min). In 3 patients (11.1%) of this group, CKD of the 3rd stage was detected with a GFR level of 34-46 ml/min. The causes of CKD in this group were a combination of diseases such as chronic pyelonephritis-2 cases (7.4%), urolithiasis – 1 (3.7%), diabetic nephropathy – 1 (3.7%), kidney cyst – 1 (3.7%).

The presence of COVID-19 infection was confirmed by laboratory methods PCR and ELISA in 26 (61.9%) patients in group 1. During laboratory diagnostics, the virus was not identified in 16 patients (38.1%). Viral infection was complicated by pneumonia in all 42 patients, including bilateral – in 32 (76.2%) and unilateral – in 10 (23.8%). The severity of pneumonia according to the classification of lung damage according to multispiral computed tomography (MSCT) of the chest organs was in the group: grade 1 – CT1 – 20 cases (47.6%), CT2 – in 17 (40.5%) and CT3+CT4 – in 5 (11.9%). In group 2, laboratory testing allowed to verify COVID-19 infection in 76.7% of patients (23 out of 30). Bilateral pneumonia was confirmed by MSCT of the lungs and radiography in 86.7% of patients (26 out of 30), unilateral-in 2 (6.7%) and in two cases (6.7%), with this diagnosis, signs of pneumonia were not detected in patients. Theseverity of pneumonia according to the MSCT classification of the lungs was in the group – CT 1 – 33.3%, CT 2 – 63.3% and CT 3-4 – 3.3%.

4. Research Results

We compared the data of biochemical and instrumental diagnostics of signs of liver damage in 2 selected groups of patients.

Table 2. *Indicators of the frequency (in percent) of changes in the activity of cytoplasmic ALT enzymes, and serum CT, LDH, and CPK in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/n	Indicator	Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
out 1.	Activity of enzyme alanine-amino-transferase (ALT) above 32 u/l	36.8%	38.5%	nd
2.	The activity of enzyme asparagine-amino-transferase-(ACT) is higher than 42 u than 42 u/l	42.2%	60%	p<0.05
3.	The activity of enzyme lactate-dihydrogenase (LDH) activity is higher than 480 u/l	57.7%	77.8%	p<0.03
4.	The activity of enzyme creatinephosphokinase (CPK) activity above 190 u/l	25%	50%	p<0.022

Increased levels of intracellular enzyme activity were found in 25-77. 8% of patients with COVID-19 infection, most often increased activity of the cytoplasmic enzyme LDH. Significantly higher average values were observed in the 2nd group of patients: 17.8% higher activity of the mitochondrial AST enzyme, 20.1% higher activity of the cytoplasmic LDH enzyme, and 25% higher activity of the cytoplasmic muscle cell enzyme, CPK (Tables 1, 2).

Table 3. *Indicators of the frequency of changes in the activity of excretory enzymes ALP, gamma-HT and serum bilirubin (in percent) in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/n	Indicator	Group 1 (n=42)	Group 2 (n=30)	Difference, confidence
1.	The activity of enzyme a alkaline phosphatase (ALP) activity above 360 u/l	27.3%	33.3%	nd
2.	The activity of enzyme a gammama-glutamyl-transpeptidase (gamma-HT) is higher than 55 u/l	42.8%	58.6%	nd
.	Concentration of total bilirubin a over 22 mcg/ml, or bilirubin glucuronide over 3.4 mcmol/l	15.1%	23.8%	nd

The activity of excretory enzymes ALP and gamma-HT was increased in 27.3-58.6% of patients with pneumonia and

COVID-19, and the increased concentration of total bilirubin and bilirubin glucuronide – in 15.1-23.8% (Table 3).

Table 4. *Frequency of changes in prothrombin indicators and prothrombin time, INR and plasma albumin concentration (percentage) in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/n	Indicator	Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
1.	Prothrombin time indicator (PV) over 12 sec	84.2%	73.6%	nd
2.	Indicator INR over 1.10	84.6%	71.4%	nd
3.	Serum albumin concentrations less than 34 mg / l	64.5%	27.3%	p<0.001

Prolongation of prothrombin time and an increase in the international normalized ratio, indicators that characterizet protein-kinetic function of the liver and the synthesis of hemostatic proteins of the prothrombin complex, were detected in 71.4-84.6% of patients with pneumonia and COVID-19, without statistical differences in groups 1 and 2 (Table 4). Signs of hypoalbuminemia were significantly detected 2.36 times more often, in the first group of patients with pneumonia and COVID-19 with terminal CKD.

Table 5. *Ultrasound examination of signs of changes in the liver, spleen, gallbladder and pancreas, frequency of changes in the activity of the alpha-amylase enzyme in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/a number	Indicator	Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
Liver				
1.	Anterior-posterior size of the right lobe of the liver more than 15 cm	50%	51.8%	nd
2.	Anterior-posterior size of the left lobe of the liver is more than 7 cm	42.8%	37%	nd
3.	Changing the echo structure of the liver:			
	heterogeneity	11.9%	18.5%	nd
	cysts	7.1%	3.7%	nd
	focal formations	2.4%	0	nd
	fine-grained design	2.4%	0	nd
	calcinates	2.4%	0	nd
	venous plethora	0	3.7%	nd
	steatosis	0	3.7%	nd
	Total:	30.9%	29.6%	nd
4.	Echogenicity of the liver parenchyma:			
	theprice is too high	85.7%	77.8%	nd
	average	11.9%	22.2%	nd
	not changed	2.4%	0	nd
5.	Intrahepatic vessels:			
	not changed	95.2%	85.1%	nd
	expanded	4.8%	14.9%	nd
6.	Intrahepatic bile ducts:			
	not changed	95.2%	100%	nd
	expanded	4.8%	0	nd
7.	Portal vein diameter: greater than 1.3 cm:	11.9%	3.7%	nd
	not expanded	88.1%	96.3%	nd
8.	Inferior vena cava:			
	not extended	90.5%	96.3%	nd
	dilated	9.5%	3.7%	nd
Gallbladder (LC)				
9.	Thickening of the LC wall more than 2 mm	11.9%	7.4%	nd
10.	Inflection, deformation of the LC	16.7%	25.9%	nd
11.	Concretions of LC	23.8%	22.2%	nd
12.	Change эхогенностиin bile echogenicity	7.1%	7.4%	nd
13.	Polyps in LC	9.5%	14.8%	nd
14.	Total pathology of LC	69%	63%	nd
The pancreas (PJ)				
15.	Head magnification pancreas more than 3 cm	19%	18.5%	nd
16.	Body augmentation pancreas more than 2.5 cm	2.4%	7.4%	nd
17.	Tail augmentation pancreas more than 2 cm	0	3.7%	nd
18.	Increasing all structures PJ	21.4%	29.6%	nd
19.	Changes to the echo structure PJ:			
	heterogeneity	14.3%	14.8%	nd
	fuzziness	9.5%	7.4%	nd
	polygons			
	uneven outline	7.1%	14.8%	nd
	education in the head	2.4%	3.7%	nd
	steatosis	2.4%	3.7%	nd
	thickening	2.4%	0	nd

n/a number	Indicator	Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
	glands			
	fluid in the stuffing box	2.4%	0	nd
	in the bag			
	Total:	26%	44.4%	p<0.05
	Echogenicity PJ:			
20.	increased price	59.5%	88.9%	p<0.01
	average	2.4%	11.1%	nd
	not changed	19%	0	p<0.05
21.	Pancreas is notvisualized	19%	18.5%	nd
22.	Serum alpha-amylase in blood serum activity above 115 u/l	22.7%	44.4%	p<0.03
Spleen				
23.	Increasing the size organ size increase	38.1%	11.1%	p<0.01
24.	Additional lobule	7.1%	0	nd
25.	Extension of the village-zenochnaya square meter range veins larger than 8 mm	7.1%	3.7%	nd
26.	Free fluid in the abdominal, cavity	19%	14.8%	nd

An increase in the size of the liver during ultrasound scanning was detected in more than 37% of patients, including 50-51.8% of patients – the right lobe, y 37-42% - the left lobe. Diffuse changes in the liver parenchyma and increased echogenicity of its structure were detected in 77.8-85.6% of patients, and structural changes in 29.6-30.5% of patients, with approximately similar frequency in groups 1 and 2 (Table 5). Changes in intrahepatic vessels and bile ducts were detected by this method much less frequently – in 4.8-14.9% of patients and did not differ significantly in the frequency of the sign in the groups, as well as signs of changes in the portal and inferior vena cava. Pathology of the gallbladder was detected frequently in 63-69% of patients, most often signs of concretion and changes in the properties of bile – in 29.6-30.2% of patients, without significant differences in the groups. Increasing the ultrasound size of different parts of the pancreas (RJ) was detected in 21.4-29.6% of patients. Changes to the echo structure pancreas was diagnosed in 26-44% of patients with COVID-19, 18.4% (significantly) more often in the 2nd group of patients. Gland echogenicity was also more often increased in the group of patients without hemodialysis, by 29.7% (significantly), as well as the frequency of increased activity of the organ-specific enzyme alpha-amylase by 21.7% (significantly). Signs of pathological enlargement of the spleen, on the contrary, were more often detected in the 1-st group of patients with hemodialysis, by 27% (significantly).

The nature of the gastrointestinal pathology that was present before hospitalization and revealed during the current study period had certain features and differences in the two selected groups of patients with COVID-19 and pneumonia (Table 6).

Table 6. *The nature and frequency of diagnosis of gastrointestinal pathology in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/n	Pathology and disease	groups Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
Liver pathology				
1.	Viral hepatitis B	4.8%	3.7%	nd
2.	Viral hepatitis C	7.1%	0	nd
3.	Liver steatosis	0	3.7%	nd
4.	Cirrhosis of the liver, class A	2.4%	3.7%	nd
5.	Chronic hepatitis	2.4%	0	nd
6.	Polycystic liver and kidney disease	2.4%	0	nd
Pathology of the gallbladder and ducts				
7.	Gallstone cholelithiasis	14.3%	33.3%	p<0.05
8.	Chronic cholecystitis	2.4%	3.7%	nd
9.	Postcholecystectomy syndrome	4.8%	0	nd
10.	Choledochal stenosis	0	3.7%	nd
11.	Jaundice	4.8%	3.7%	nd
Pathology of the pancreas				
12.	Chronic pancreatitis	0	11.1%	nd
13.	Acute edematous pancreatitis	0	7.4%	nd
Pathology of the stomach and duodenum				
14.	Chronic gastritis, bulbitis	7.1%	7.4%	nd
15.	Duodenal ulcer	4.8%	0	nd
16.	Chronic gastric ulcer with gastrointestinal tract	2.4%	0	nd
17.	Duodenogastric reflux	4.2%	0	nd
Pathology of the small and large intestines				
18.	Umbilical, femoral hernias plasty	0	7.4%	nd
19.	Crohn's disease, bowel resection	2.4%	0	nd
20.	Intestinal obstruction	4.8%	0	nd

n/n	Pathology and disease	groups Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differences, p
21.	Hemorrhoids, bleeding	2.4%	0	nd
22.	Chronic colitis	0	3.7%	nd
23.	Constipation	0	3.7%	nd
24.	Antibiotic-associated diarrhea (pseudomembranous colitis)	9.5%	0	nd

Table 7. *Concomitant diseases in two groups of patients with COVID-19 and pneumonia with end-stage CRF and dialysis (group 1) and preserved renal function (group 2).*

n/n	a Diseases, pathology	Group 1 (n=42)	Group 2 (n=30)	Difference, significance of differen-ces, p
Cardiovascular pathology				
	Hypertensive disease (GD):			
1.	2 degrees of severity	4.8%	16.7%	nd
	3 degrees of severity	40.8%	22.2%	p<0.05
2.	Ischemic Heart Disease (IHD): tension angina 2 FC	2.4%	7.4%	nd
3.	IHD: cardiosclerosis, atrial fibrillation	7.1%	25.9%	p<0.05
4.	IHD: post-infarction cardiosclerosis, EC	2.4%	3.7%	nd
5.	Degenerative calcification of the aortic, mitral, and tricuspidal heart valves	4.8%	0	nd
6.	Deep vein thrombosis of the lower extremities (PE)	2.4%	3.7%	nd
Pathology of the central nervous system				
7.	Cerebrovascular disease (CVD). Chronic cerebral ischemia (HIGM).	11.9%	7.4%	nd
8.	CVD. Consequences of acute cerebrovascular accident (ONMC)	2.4%	7.4%	nd
9.	Mixed-origin encephalopathy	4.8%	3.7%	nd
10.	Operated on meningioma	2.4%	0	nd
11.	Mental retardation	2.4%	0	nd
Respiratory pathology				
12.	Lung cancer, pulmonectomy	0	3.7%	nd
13.	Chronic obstructive pulmonary disease (COPD)	0	14.8%	nd
14.	Emphysema of the lungs	0	3.7%	nd
Pathologists of the system of hematopoiesis				
	Anemia: mild	61.9%	0	p<0.001
15.	moderate severity	21.4%	3.7%	p<0.05
	heavy	11.9%	0	nd
16.	Without anemia	4.8%	96.3%	p<0.001
Pathology of the endocrine system				
	Diabetes mellitus:			
17.	Type 1	2.4%	0	nd
	2 types	9.5%	14.8%	nd
18.	Grade 3 obesity	4.8%	0	nd
19.	Nodular goiter, hypothyroidism	4.8%	0	nd
20.	Thyroid cancer that was operated	operated on 2.4%	0	nd
21.	Hyperparathyroidism with bone-mineral defects and mineral disorders	2.4%	0	nd
Diseases of the musculoskeletal system				
22.	Dorsopathy of the cervical spine	2.4%	0	nd
23.	Coxarthrosis, aseptic necrosis of the femoral	head 0	10%	nd
24.	Purulent bursitis of the elbow joint	2.4%	0	nd
25.	Gout, arthritis	2.4%	0	nd
Chronic infections				
25.	HIV infection	0	3.7%	nd

Chronic diffuse and focal liver diseases in the anamnesis occurred in 11.1-19.1% of patients, and cholelithiasis was significantly more often detected - by 19% - in the second group of patients. Acute and chronic forms of pancreatitis were diagnosed only in the group of patients without end – stage CKD-in 18.5% ($p<0.05$, significantly). Gastric and duodenal ulcers, including those with duodenogastric reflux, were detected only in patients with end-stage CKD and dialysis - in 11.4% of patients. Lesions of the small and large intestines weres lightly more often diagnosed in patients in group 1 - in 19.1% of patients, and in the second – in 7.4%, but the difference was unreliable, and pseudomembranous colitis was detected only in group 1 patients with hemodialysis - in 9.5%.

Abbreviations in the table: Hypertensive disease (GD),

IHD – coronary heart disease, FC- functional class, EX – electrocardiostimulator, PE – pulmonary embolism, CVD – cerebrovascular disease, HIGM – chronic cerebral ischemia, ONMC – acute cerebrovascular accident, COPD – chronic obstructive pulmonary disease, HIV – acquired immunodeficiency virus.

When analyzing the nature of concomitant pathology in 2 groups of patients with COVID-19 and pneumonia, differences were found in the frequency of existing cardiovascular diseases, respiratory and hematopoietic pathologies (Table 7). The incidence of stage 3 hypertension

was significantly 18.6% higher in group 1, and IHD, cardiosclerosis complicated by atrial fibrillation, was 18.8% higher in group 2 without hemodialysis. Chronic respiratory pathology, most often COPD, was diagnosed only in the 2nd group of patients – in 22.2% (the difference was significant, $p<0.02$). Anemia in group 1 of patients with end-stage CKD affected more than 95% of patients, in contrast, in group 2 of patients without hemodialysis, normal indicators of erythroid hematopoiesis were detected in 96% of patients, the difference is highly significant. Thyroid and parathyroid gland lesions were typical only for patients in the hemodialysis group and were detected in 9.6% of patients, but the difference from group 2 was not significant.

5. Discussion of the Results

These study data suggest that viral infection in patients with COVID-19 and pneumonia had a multifactorial impact on the function and structure of the liver in patients with terminal phases of CKD and hemodialysis, and patients with preserved kidney function, were detected especially in reaction invalid on this impact depending on the nature of the flow of the main pathological process.

It is known from the literature that typical for systemic viral infections is that they are often accompanied by a transient increase in transaminases, which reflects general immune activation, hyperimmune inflammation against the background of circulating cytokines in the absence of liver function disorders. This phenomenon is referred to in the english literature as bystander (witness) hepatitis [8].

According to our data, signs of this syndrome could occur, in at least 35% of patients in the selected groups with increased aminotransferase activity. At the same time, there was a significant excess of cases of hyperfermentemia, with an increase in cytoplasmic (LDH) and mitochondrial (AST) enzymes in the group of patients with preserved renal function (group 2). We tried to explain this difference in the frequency of hyperfermentemia by the nature of the main infectious process and the severity of pneumonia. Indeed, pneumonia CT of 2 severity, assessed by the results of the study of the lung structure by MSCT, was 22.8% (significantly, $p <0.03$) more often detected in the second group of patients, as well as cases of bilateral pneumonia – by 10.5%. That is, in patients of the second group, bilateral pneumonia developed more often and proceeded with a larger area of damage to the respiratory structures of the lungs.

The presence of cytolysis associated with COVID-19 and pneumonia in patients could also be assumed in such liver structures as biliary epithelial cells of the bile ducts, since the level of excretory enzymes such as ALP and gamma -HT was increased in more than 25% of the studied individuals in both groups. According to the study, could be most frequently exposed to viral pneumonia hepatocytes synthesizing prothrombin complex proteins. Thus, wefound a longer prothrombin time and an increase in the international normalized ratio, indicators that characterize protein-synthetic liver function with the formation of hemostatic prothrombin complex proteins, in more than 70% of patients with pneumonia and COVID-19. It is likely that anticoagulant therapy was also involved in the depression of prothrombin synthesis in the liver, since low-molecular-weight heparin therapy was prescribed in 37-44% of the studied patients.

According to previously published literature data, the risk of liver damage in patients with COVID-19, estimated in various clinical studies, varies from 14 to 53% [4]. A higher incidence of liver damage is observed in severe patients with SARS-CoV2 infection. Extremely severe COVID-19 is an independent risk factor for liver damage. In cases of COVID-19 with a fatal outcome, the incidence of liver damage can reach 58.1-78% [9]. As for cholestatic liver damage, it has notyet been proven that SARS-CoV-2 infection worsens the course of cholestasisa [10].

In our sample of patients studied, biochemical signs of cholestasis, assessed by impaired pigment metabolism with an increase in the concentration of total and bilirubin - glucuronide in peripheral blood, were detected in groups of patients with a frequency of 15-23%.

Several possible mechanisms of damaging effects of coronavirus infection on the liver are considered in the available literature [10-13], including the direct effect of SARS-CoV-2 on the structures of this organ. It is stated that the mechanisms of direct exposure of the SARS-CoV-2 virus to the liver (direct cytotoxicity due to active replication of the virus in liver cells) are insufficiently studied. In earlier studies involving infection with betacoronavirus (SARS-CoV), (2002-2003) and MERS-CoV (2012), liver damage was quite common and associated with the severity of the disease [14, 15]. However, it is not entirely clear whether liver damage can be caused directly by the SARS-CoV-2 coronavirus. Previous data on RNA-seq sequencing in the human protein atlas database confirm the expression of ACE2 in the SARS-CoV liver [16]. At the same time, a low frequency of ACE2 expression is observed only in cholangiocytes, but not in hepatocytes, Kupffer's cells or endothelial cells [17]. In addition, SARS-CoV is able to induce apoptosis in cell lines of various organs (including lungs, kidneys, and liver) via a specific protein 7a in a caspase-dependent way. This indicates the possibility of direct exposure to SARS-CoV on liver tissue.

When analyzing the data obtained in our study of instrumental diagnostics of the state of liver structures, we tried to assess the severity of damage to the organ parenchyma by changing its density for ultrasound radiation (echogenicity). Liver echogenicity was diffusely increased in more than 75% of the studied patients with pneumonia and COVID-19, and the size of the right and left significantly exceeded normal in 37-51% of the studied patients.

Literature data on in vivo studies of the liver in patients with viral pneumonia of this type allowed us to assess the nature of morphological changes in the organ. Liver biopsy in patients with SARS-CoV and SARS-SARS pneumonia revealed pronounced mitoses, acidophilic bodies, and cells

Kupffer's balloon - like hepatocytes. This suggested that SARS-CoV induces apoptosis of liver cells and thereby contributes to its damage [14]. The results of post-mortem biopsies in patients with COVID-19 showed moderate microvesicular steatosis, moderate lobular and portal activity. The researchers concluded that the damage could have been caused by SARS-CoV-2 infection, but it is not possible to exclude its drug damage, as well as the development of processes associated with hypoxic conditions. Liver autopsy results were verified for hepatomegaly, hepatocyte degeneration, focal necrosis, neutrophilic, lymphocytic, and monocytic infiltration, sinusoidal dilation, stasis, and microthrombosis. However, histological signs of liver damage leading to liver failure, bile duct damage were not observed in the cited studies [9, 18, 19].

Multiple organ involvement, according to the literature, is characteristic of pneumonia in COVID-19. Previously, it was shown that пautopsy of patients with SARS-CoV by the method of OTT-PCR of the SARS-CoV genome was detected not only in the lungs, but also in parenchymal cells, including hepatocytes, and vascular endothelium of various organs [18, 19].

In our study, the detected increase in the activity of the CPK enzyme in 25-50% of patients with pneumonia and COVID-19 may reflect damage to myocytes in the skeletal muscles and structures of the cardiovascular system. According to our data, instrumental signs of changes in the parenchyma and sizes parenchymatous organs are also often observed in patients and in the pancreas, and spleen, echogenicity of the pancreas was diffusely increased more than 60% of the patients, statistically significantly more often in patients with preserved renal function, which was associated with the inclusion of this group of data of 5 patients with a complication of pneumonia acute edematous pancreatitis and exacerbation of chronic pancreatitis. More than 20% of patients in both groups showed an increase in organ size, and 22-44% showed an increase in the activity of the enzyme alpha-amylase, a marker of damage and necrosis of pancreatic secretory cells.

Similar data were obtained нами when estimating the size of the spleen. Splenomegaly was diagnosed in 11-38% of patients, with a significant prevalence of this trait in the 1st group of patients with CKD and hemodialysis. The reasons for this difference are difficult to explain and may be related to the response of the spleen's lymphoid tissue to the hemo-ultrafiltration procedure. At the same time, according to the authors who evaluated changes in lymphoid organs in patients based on autopsy results, secondary destruction of lymphoid tissues was detected in patients with COVID-19. Spleen atrophy was observed in all reported cases with a reduced number of lymphocytes. Significant cell degeneration, focal hemorrhagic necrosis, proliferation and phagocytosis of macrophages were detected in the spleen. Lymph node atrophy was noted, accompanied by necrosis. An immunohistochemical study showed a sharp decrease in the number of CD4 and CD8 T cells inthe liver and lymph nodes [20].

In our study, lymphopenia was detected in the group of patients with terminal chronic renal failure and hemodialysis in 66.7%, and preserved kidney function – in 37.1% of patients, which was significantly higher and may be due, in our opinion, with the processes of atrophy of the lymphoid system and the application of cytostatics in patients with chronic renal failure, in the development of COVID-19 infection.

According to the literature, with a view of the high burden of chronic liver disease (CKD) in the world: non-alcoholic fatty liver disease (NAFLD) in the metabolic syndrome (diabetes, obesity), liver cirrhosis in the outcome of chronic viral hepatitis B, C and other diseases can be the main causes of liver damage in patients with COVID-19. It is possible that patients with CKD are more susceptible to liver damage from SARS-CoV-2. However, there is currently limited evidence of a direct effect of pre-existing liver disease on the course of COVID-19 and vice versa. In a number of studies, 2-11% of COVID-19 patients had CKD [21, 22].

According to our study, signs of CKD in patients in the age group from 23 to 86 years were detected with approximately similar frequency to the literature data - in 11-19% of patients.

Other liver-damaging factors in patients with COVID-19 and pneumonia could be hypoxia factors. The literature describes a variant of hypoxic hepatitis due to anoxia, which is of ten foundin severe cases. Severe hypoxia, anoxia, and hypovolemia are considered the main cause of ischemic / hypoxic liver damage in cases of COVID-19 with acute pulmonary insufficiency and / or shock. This liver damage is associated with metabolic acidosis, calcium overload, and changes in mitochondrial membrane permeability, and is usually characterized by high cytolysis [23].

In our sample of patients with COVID-19 and pneumonia, respiratory failure (RF) occurred only in 3 cases (in 4.2%), with RF1- 2 and RF2- 1 cases, and apparently was not a significant factor in the detected liver damage in the studied patients.

6. Conclusions

1. Biochemical signs of liver cell cytolysis are detected in 25-57% of patients with viral pneumonia in COVID-19, which complicates the course of terminal forms of chronic kidney disease with hemodialysis. Most often, the disease is accompanied by signs of a decrease in the synthesis of hemostatic proteins of the prothrombin complex and serum albumin, which may be associated with an aggravation of the severity of their existing pathology. у них chronic anemia.
2. Hepatomegaly and changes in the liver structure are diagnosed in 42-85% of patients with this pathology and are combined with ultrasound-signs of damage to the pancreas and spleen in 26-38%. In 11-19% of patients with COVID-19 infection, chronic liver damage precedes the development of pneumonia. Regardless of the state of renal function, these changes

may be accompanied by a worsening of the course of pre-existing liver and pancreatic lesions, including hepatitis and pancreatitis.

3. Diagnostics of the state of enzyme and protein-producing functions of the liver and pancreas and their monitoring in patients with end-stage renal failure and hemodialysis, with the development of acute viral infections, due to the importance of detecting their violation for the prognosis of the disease, it is advisable to include in the standards of inpatient examination of patients.

Conflicts of Interest

All authors have no possible conflicts of interest.

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