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ORIGINAL ARTICLE

Retrospective Study

Hepatobiliary system and intestinal injury in new coronavirus infection (COVID-19): A retrospective study

Konstantin V Kozlov, Konstantin V Zhdanov, Anna K Ratnikova, Vyacheslav A Ratnikov, Artem V Tishkov, Vladimir Grinevich, Yuriy A Kravchuk, Panteley I Miklush, Polina O Nikiforova, Vera V Gordienko, Alexander F Popov, Boris G Andryukov

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Konstantin V Kozlov, Konstantin V Zhdanov, Yuriy A Kravchuk, Panteley I Miklush, Polina O Nikiforova, Vera V Gordienko, Department of Infectious Disease, Military Medical Academy Named After SM. Kirov, Saint-Petersburg 194044, Russia

Anna K Ratnikova, Department of Admission, Federal State Budgetary Institution "North-West District Scientific and Clinical Center Named After LG. Sokolov Federal Medical and Biological Agency", Saint-Petersburg 194291, Russia

Vyacheslav A Ratnikov, Department of Roentgenology, Federal State Budgetary Institution "North-West District Scientific and Clinical Center Named After LG. Sokolov Federal Medical and Biological Agency", Saint-Petersburg 194291, Russia

Artem V Tishkov, Department of Physics, Mathematics and Informatics, FSBEI HE IP. Pavlov SPbSMU MOH Russia, Saint-Petersburg 197022, Russia

Vladimir Grinevich, 2nd Department of Therapy (Advanced Medical Education), Military Medical Academy Named After SM. Kirov, Saint-Petersburg 194044, Russia

Alexander F Popov, Boris G Andryukov, School of Medicine, Far Eastern Federal University, Vladivostok 690922, Russia

Corresponding author: Vera V Gordienko, MD, Doctor, Teacher, Department of Infectious Disease, Military Medical Academy named after S.M. Kirov, No. 6 Lebedeva Street, Saint-Petersburg 194044, Russia. ivanovavmeda@gmail.com

Abstract

BACKGROUND

An important area of effective control of the coronavirus disease 19 (COVID-19) pandemic is the study of the pathogenic features of severe acute respiratory syndrome coronavirus 2 infection, including those based on assessing the state of the intestinal microbiota and permeability.

AIM

To study the clinical features of the new COVID-19 in patients with mild and moderate severity at the stage of hospitalization, to determine the role of hepato-biliary injury, intestinal permeability disorders, and changes in the qualitative and

quantitative composition of the microbiota in the development of systemic inflammation in patients with COVID-19.

METHODS

The study was performed in 80 patients with COVID-19, with an average age of 45 years, 19 of whom had mild disease, and 61 had moderate disease severity. The scope of the examination included traditional clinical, laboratory, biochemical, instrumental, and radiation studies, as well as original methods for studying microbiota and intestinal permeability.

RESULTS

The clinical course of COVID-19 was studied, and the clinical and biochemical features, manifestations of systemic inflammation, and intestinal microbiome changes in patients with mild and moderate severity were identified. Intestinal permeability characteristics against the background of COVID-19 were evaluated by measuring levels of proinflammatory cytokines, insulin, faecal calprotectin, and zonulin.

CONCLUSION

This study highlights the role of intestinal permeability and microbiota as the main drivers of gastroenterological manifestations and increased COVID-19 severity.

Key Words: Novel coronavirus infection; COVID-19; SARS-CoV-2; Zonulin; Faecal calprotectin; Microbiota

Core Tip: The clinical course of coronavirus disease 19 (COVID-19) was studied, and the clinical and biochemical features, manifestations of systemic inflammation, and intestinal microbiome changes in patients with mild and moderate severity were identified. Intestinal permeability characteristics against the background of COVID-19 were evaluated by measuring levels of proinflammatory cytokines, insulin, faecal calprotectin, and zonulin. This study highlights the role of intestinal permeability and microbiota as the main drivers of gastroenterological manifestations and increased COVID-19 severity.

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INTRODUCTION

While gaining experience in the diagnosis and treatment of the new coronavirus disease (COVID-19), an increasing number of researchers are focusing on the extremely high prevalence of extrapulmonary symptoms, including gastroenterological manifestations in patients with COVID-19[1]. The frequency of gastrointestinal (GI) symptoms in patients with COVID-19 is variable and depends on the severity of the disease and, probably, the viral strain that causes the disease[2]. The severe form of COVID-19, as a rule, is associated with polysegmental lung damage and liver injury and a steep increase in the intestinal epithelium's permeability with the subsequent transfer of bacterial and fungal products into the blood and the development of systemic inflammation. Bidirectional communication impairment in the intestinal-lung axis is considered a risk factor for the development of severe respiratory disease. It follows the principle of positive feedback and develops due to dysbiotic changes in the intestinal microbiota on the one hand and cytokine storm on the other[3,4].

Zonulin is a modulator and serum marker of intestinal permeability, which, when connected to the receptors of intercellular tight junctions, causes contraction of the cytoskeleton of epithelial cells and, therefore, facilitates the transport of macromolecules[5-7]. High serum zonulin levels have been associated with severe COVID-19 in several studies[7]. Thus, one of the possible therapeutic goals in treating severe COVID-19 may be to prevent the pathological increase in zonulin-mediated intestinal permeability[8,9]. The combination of low-grade endotoxemia (an increase in the concentration of lipopolysaccharide secreted by the microbiota) with an increased level of zonulin may indicate an increase in intestinal permeability, which is one of the mechanisms underlying the pathogenesis of COVID-19 and its gastroenterological manifestations[10]. It is also known that intestinal dysfunction

and microbial translocation strongly correlate with increased systemic inflammation and complement activation decreased metabolic function of the intestine, and higher mortality rate[11].

According to research data dedicated to the study of cytokine levels in patients with severe and sometimes fatal forms of COVID-19, it was found that plasma concentrations of interleukin (IL) -1-beta, 6, 7, 8, 9, and 10, and tumor necrosis factor-alpha (TNF-α) were increased[12].

The intestinal microbiome of patients with COVID-19 is characterized by the enrichment of opportunistic microorganisms and depletion of normal intestinal microflora with immunomodulatory potential, such as Faecalibacterium prausnitzii, Eubacterium rectale, and bifidobacteria[13]. At the same time, the disturbed composition of the microbiota correlated with the severity of the disease, corresponding to increased concentrations of inflammatory cytokines and markers of inflammation in the blood (including C-reactive protein and lactate dehydrogenase), which was most likely due to the modulation of the immune response[14].

MATERIALS AND METHODS

The study was carried out at the North-Western District Scientific and Clinical Center named after LG Sokolov FMBA of Russia (SZONKTS named after LG Sokolov) between July 2020 to March 2021. It included 80 hospitalized patients with COVID-19, whose median age was 45 years (range: 39–56 years). All patients provided informed consent to participate in the study; 19 (23.8%) of them had mild, and 61 (76.2%) had moderate severity of COVID-19. The diagnosis of the disease in all the patients was verified by detecting severe acute respiratory syndrome-related etoronavirus 2(SARS-CoV-2) RNA using nucleic acid amplification. Patients were hospitalized on the 7th day of illness (range: 5.0–9.0), which corresponded to the peak period of the infectious process. As a control, a group of 17 healthy individuals, with an average age of 41 years (range: 22.0–59.5 years), who underwent examination at the outpatient dispensary of SZONKTS (named after LG Sokolov), were included. The patient groups did not differ in terms of their demographic and clinical characteristics. The study did not include patients with chronic viral hepatitis (B and C), anemia of any etiology, or patients whose treatment required transfer to the intensive care unit.

On admission, all patients with COVID-19 underwent standard examination and treatment protocol, and the severity of the disease was determined in accordance with the current versions of the Temporary Guidelines of the Ministry of Health of the Russian Federation on the prevention, diagnosis, and treatment of new coronavirus infections[15]. Computed tomography (CT) of the chest was supplemented with post-processing and assessment of qualitative and quantitative criteria for defining the state of the parenchymal and hollow organs of the GI tract, which were visualized during the chest CT scan, was done.

To assess the complaints related to the GI tract, a questionnaire was developed that included a detailed assessment of abdominal pain syndrome according to a visual analogue scale, an assessment of the presence of symptoms of dyspepsia, and the presence and duration of concomitant gastroenterological pathology. All patients completed the questionnaire based on the main questionnaire and 36-Item Short Form Survey quality of life questionnaire.

To assess the state of the intestinal barrier, qualitatively and quantitatively assess the state of the microbiota and hepatobiliary system, as well as evaluate systemic inflammation indicators that develop during COVID-19, the scope of the survey was supplemented with an analysis of a biomarker complex: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, zonulin in feces and blood, and calprotectin in feces. TNF and IL1-beta, 6, 8, 10, and insulin levels were also examined in the blood. To assess insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) index was used. The index was calculated using the formula: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. Indirect determination of the composition of the intestinal microbiota was performed using an Agilent 7890 gas chromatograph with mass selective and flame ionization detectors (Agilent Technologies, United State of America). The proposed method of gas chromatography combined with mass spectrometry makes it possible to detect in blood and then, to the contents of the intestine, extrapolate components of cells of a wide range of microorganisms of normal and pathogenic human microbiota.

Blood and stool samples were collected on day 8 (range: 5–11.5 d) of the COVID-19 illness. The healthy individuals in the control group underwent similar examinations.

The entire spectrum of the obtained data was transformed into an information base, represented by 720 parameters for assessing the condition of each patient, adapted for subsequent mathematical and statistical processing. The statistical analysis was carried out using the IBM SPSS 20.0 program using parametric and nonparametric statistical methods. Descriptive statistics for the samples that fit the normal distribution are represented by the arithmetic mean and standard deviation. Descriptive statistics for non-Gaussian distributions included the median and upper bounds for the 1st and 3rd quartiles. The differences between the two numerical samples were determined using Student's t-test in the case of a normal distribution and the Mann-Whitney test in the case of a non-Gaussian distribution. To compare related samples, the paired Student's t-test was used if the samples were normally

distributed, and the Wilcoxon test was used for non-Gaussian samples. The normality of the samples was checked using the Kolmogorov-Smirnov test with Lilliefors correction.

Descriptive statistics for non-numeric data are represented by the number of objects with corresponding values as well as the proportion (percentage) of representation of each value in the sample. To find differences in the counting data, Fisher's exact test and Pearson's χ^2 test were used.

In all cases of hypothesis testing, the critical significance level was considered to be equal to or less than 0.05.

RESULTS

Patients with mild COVID-19 showed no evidence of lung damage on CT in addition to the clinical, virological, and clinical laboratory manifestations of the disease; however, all of these patients exhibited symptoms of mild general infectious intoxication (low-grade fever in 13 (68.4%) patients), anosmia was detected in 6 (31.6%) patients and hyposmia in 1 (6%) patient. With an average disease severity, the most frequent clinical manifestation of COVID-19 was low-grade fever, which was observed in 57 (93.4%) patients; anosmia was observed in 29 (48%) patients and hyposmia in 6 (9.8%) patients. A respiratory rate of > 22 *per* minute, shortness of breath during physical exertion, a decrease in hemoglobin oxygen saturation to 95% -93%, and characteristic signs of viral lung damage on CT involving more than 25% of lung tissue were observed in 49 (80%) patients.

Abdominal CT analysis showed localized or diffuse low liver density (signs of steatosis) and adipose tissue accumulation around the gallbladder.

According to survey data, the frequency and severity of most GI symptoms during the peak of the infectious process caused by SARS-CoV-2 did not vary with disease severity. Dyspeptic syndrome was found in 67 (83.8%) patients with mild to moderate severity, with flatulence and stool instability being the most common (51.25%, 41 patients). A decreased appetite was observed in 41 patients (51.25%). Abdominal pain syndrome was detected in 36 (45%) patients. However, patients with COVID-19 do not typically experience localized pain. The most distinctive pains were in the epigastrium: 6.0 points (4.5-6.5), in the lower abdomen: 6.0 points (5.0-7.0) and night pains: 5.5 points (3.0-7.0). At the same time, the duration of the manifestations of dyspepsia in patients with moderate severity was significantly longer: 15.0 d (range: 10.5–21.0 d) than that in patients with mild severity: 13.5 d (range: 9.0-15.0 d, $P = 0.041$). The study of the anamnesis of the disease showed that patients with moderate severity at the pre-hospital stage more often took azithromycin ($P = 0.003$) and non-steroidal anti-inflammatory drugs ($P = 0.004$) than patients with mild severity, which could have also contributed to the appearance of GI symptoms.

As shown in Table 1, Compared with control group, patients with COVID-19 had increased level of ALT (35; 43.7%), AST (45; 56.2%) and total bilirubin (32; 39.4%).

As shown in Table 2, after first CT, the lower of liver density < 45 hounsfield unit (HU) was noted in 28 (34.7%). Patients with moderate severity had significantly lower liver density 42.6 HU (39.2-47.8), compare with patients with mild COVID-19 48.5 HU (43.7-52.1) ($P < 0.05$). The liver/spleen density ratio was also lower in moderate severity group, 0.87 (0.69-0.98) and 1.02 (0.92-1.09) ($P < 0.05$) suggest.

One of the most characteristic changes in patients with mild and moderate COVID-19 compared with the control group was a statistically significant increase in insulin content up to 19.10 mIU/L (8.90-34.575) [(control group: 6.90 mIU/L (4.325-15.4)], $P = 0.0026$, as well as an insignificant trend towards an increase in the insulin resistance index to 1.70 (1.08-2.97), $P = 0.88$. At the same time, in patients with COVID-19 with moderate severity, the level of insulin was 1.8 times higher than in patients with mild severity of the disease ($P = 0.0026$). The analysis of indicators of systemic inflammation in patients with COVID-19 on the first day of hospitalization showed that the average level of TNF, as well as IL 1-beta, 6, 8, and 10, did not differ statistically significantly from those in the control group. However, upon further study, it was found that by the 7th day of hospitalization with moderate severity of COVID-19, the TNF content was significantly higher: 1.00 pg/mL (range: 1.00–3.00 pg/mL), IL6: 13.0 (range: 1.0-18.0, $P < 0.001$)- and there was also a tendency for an increase in the content of IL 1-beta, 8, and 10.

A set of indicators reflecting intestinal permeability and inflammatory activity in patients with mild to moderate COVID-19 compared to the control group at the initial examination is presented in Table 3.

As shown in Table 3, the faecal calprotectin content in the control group and patients with COVID-19 did not differ significantly. The concentration of zonulin in the feces of patients with COVID-19 was significantly higher than that in the control group ($P = 0.003$). Simultaneously, the zonulin content in the blood of patients with COVID-19 was lower than that in the control group ($P = 0.046$).

In the next stage of the study, the levels of these indicators were assessed depending on the severity of the infection caused by SARS-CoV-2.

As shown in Table 3, with an average severity of COVID-19, a statistically significant increase in faecal calprotectin content was observed, as well as a tendency toward an increase in zonulin content in the feces.

In accordance with the purpose of this study, a comparative analysis of some indicators characterizing the qualitative and quantitative composition of the intestinal microbiota and the functional state

Table 1 Changes of alanine aminotransferase, aspartate aminotransferase and serum bilirubin in patients with coronavirus disease 19 compared with the control group, depending on the severity of the disease

Indication	COVID-19 patients (*n* = 80)	Control Group (*n* = 17)	*P* value	COVID-19-patients, mild severity (*n* = 19)	COVID-19-patients, moderate severity (*n* = 61)	*P* value
ALT, IU/L	75 (21-96)	21 (5-30)	< 0.05	57 (16-65)	89 (79-96)	< 0.05
AST, IU/L	81 (26-112)	26 (8-35)	< 0.05	60 (20-69)	102 (90;112)	< 0.05
Total bilirubin, μmol /L	63.2 (13.8-70.2)	22.1 (5.4-25.3)	< 0.05	41.3 (22.8-62.1)	72.4 (35.2-89.2)	< 0.05

Compared with control group, patients with COVID-19 had increased level of ALT (35; 43.7%), AST (45; 56.2%) and total bilirubin (32; 39.4%). COVID-19: Coronavirus disease 19; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Table 2 Changes of liver/spleen density in patients with coronavirus disease 19, depending on the severity of the disease

Indication	Density, HU		*P* value
	COVID-19 patients, mild severity (*n* = 19)	COVID-19 patients, moderate severity (*n* = 61)	
Liver	48.52 (43.7-52.1)	42.63 (39.2-47.8)	< 0.05
Spleen	47.41 (42.1-51.5)	48.78 (43.4-52.8)	0.47
Liver/spleen ratio	1.02 (0.92-1.09)	0.87 (0.69-0.98)	< 0.05

After first CT, the lower of liver density < 45 HU was noted in 28 (34.7%). Patients with moderate severity had significantly lower liver density 42.6 HU (39.2-47.8), compare with patients with mild COVID-19 48.5 HU (43.7-52.1) ($P < 0.05$). The liver/spleen density ratio was also lower in moderate severity group, 0.87 (0.69-0.98) and 1.02 (0.92-1.09) ($P < 0.05$) suggest. COVID-19: Coronavirus disease 19; HU: Hounsfield unit; CT: Computed tomography.

Table 3 Factors characterizing intestinal permeability in patients with coronavirus disease 19 compared with the control group, depending on the severity of the disease Me (UQ; LQ)

Indication	COVID-19 patients (*n* = 80)	Control Group (*n* = 17)	*P* value	COVID-19 patients, mild severity (*n* = 19)	COVID-19 patients, moderate severity (*n* = 61)	*P* value
Fecal calprotectin (mg/g)	87.5 (53.525-227.75)	109.65 (23.275-213.75)	0.97	53.1 (21.0-153.0)	105.0 (58.2-236.0)	0.018
Zonulin, feces (ng/mL)	141 (110-180)	64.4 (32.1-74.8)	0.003	134.9 (78.8-167.5)	143 (119-155.9)	0.74
Zonulin, blood (ng/mL)	67.9 (20.3-77.8)	85.7 (23.0-98.1)	0.039	67.9 (20.3-76.1)	71.1 (20.0-81.7)	0.55

The content of fecal calprotectin in the control group and in patients with COVID-19 did not differ statistically significantly. At the same time, the concentration of zonulin in feces in patients with COVID-19 was statistically significantly higher than in the control group ($P = 0.003$). At the same time, the content of zonulin in the blood in patients with COVID-19 was lower than in the control group ($P = 0.046$). COVID-19: Coronavirus disease 19.

of the intestine in patients with COVID-19 was carried out (Table 4).

As shown in Table 4, Propionibacterium/Cl. Subterminale, content of fungi, and lactobacilli ratios significantly changed among patients with mild and moderately severe COVID-19 compared with the control group. It is extremely important to note a significant (more than three times) and statistically significant ($P = 0.0000779$) increase in the endotoxin content. At the same time, the endotoxin content in the feces of patients with mild to moderate severity of the new coronavirus infection did not differ significantly.

To study the interdependence of the indicators of the intestinal microbiota and the most commonly used indicators in clinical and biochemical studies, a correlation matrix was built (Figure 1).

Table 4 Intestinal microbiota indications in coronavirus disease 19 patients compared with the control group Me (UQ; LQ)

Symptom	Patients with COVID-19 (*n* = 80)	Control group (*n* = 17)	*P* value
Eubacterium/Cl. Coccoides, amt. × 10^5/r	6849 (3380-7987)	8211 (2996-10987)	0.17
Herpes, amt. × 10^5/r	0.00 (0.00-1808.25)	3610 (1914-5316)	0.001
Propionibacterium/Cl. Subterminale, amt. × 10^5/r	2706 (1614-3476)	1992 (704-2118)	0.0016
Bifidobacteria, amt. × 10^5/r	3768 (2000-4678)	4614 (1653-6123)	0.13
Fungus, amt. × 10^5/r	1200 (423-1851)	540 (384-774)	0.0406
Lactobacillus, amt. × 10^5/r	7488 (4221-8790)	4309 (2521-5198)	0.0016
The ratio of anaerobic to aerobic flora	1.801 (0.718-3.01)	1.983 (0.637-3.09)	0.39
The ratio of beneficial flora to opportunistic	1.009 (0.359-2.110)	0.992 (0.300-1.990)	0.86
Beneficial flora, amt. × 10^5/r	20953 (5508-36018)	19126 (3930-35764)	0.18
Sum, amt. × 10^5/r	44651 (8152-97098)	42566 (6297-89016)	0.33
Large intestine (anaerobes), amt. × 10^5/r	26171 (7088-44099)	24964 (4423-43871)	0.44
Small intestine (aerobes), amt. × 10^5/r	15944 (4620-19087)	13570 (3692-20114)	0.06
Opportunistic flora, amt. × 10^5/r	21927 (5493-25900)	19849 (3690-23983)	0.11
Cytomegalovirus, amt. × 10^5/r	0.00 (0.00-40.00)	0.00 (0.00-0.00)	0.12
Endotoxin (sum), amt. × 10^5/r	2.44 (1.21-6.11)	0.689 (0.490-1.11)	0.0000779

Propionibacterium /Cl. Subterminale, content of fungi, lactobacill ratios significantly changed among mild and moderate COVID-19 patients compared with the control group. It is extremely important to note a significant (more than 3 times) and statistically significant (P = 0.0000779) increase in endotoxin content. At the same time, the content of endotoxin in feces in patients with mild to moderate severity of new coronavirus infection did not differ significantly. COVID-19: Coronavirus disease 19.

DISCUSSION

According to the study results, it was found that the majority of GI symptoms during the peak of the infectious process did not differ depending on the severity of the infection caused by SARS-CoV-2. The data obtained regarding the symptoms of GI tract damage among patients with COVID-19 are generally consistent with the results of previous studies, which confirms the relevance of improving approaches to the early diagnosis of gastroenterological manifestations of the disease, identifying the pathogenetic mechanisms of their development, and finding effective treatment[16,17].

In the course of this work, new data were also obtained that supplement the opinion of several researchers regarding the duration of manifestations of dyspepsia during the inpatient treatment of patients with COVID-19. Therefore, among patients with moderate severity, dyspepsia lasted significantly longer than in those with mild severity, which could be linked, among other things, to the administration of nonsteroidal anti-inflammatory drugs and antibiotics at the pre-hospital stage.

One of the most characteristic changes in patients with COVID-19 of mild and moderate severity compared with the control group was a statistically significant increase in liver aminotransferases, bilirubin, and insulin levels, as well as a trend towards an increase in the insulin resistance index. At the same time, it is important to note that in patients with COVID-19 with moderate severity, the insulin level was 1.8 times higher than that in patients with mild disease severity. The data obtained can provide evidence for the need to monitor insulin resistance during treatment.

According to many authors, indicators of systemic inflammation play a fundamental role in patients with COVID-19. Several studies have shown that the severity of COVID-19 positively correlates with the level of inflammatory cytokines, and in patients with severe disease, there is also a significant decrease in the number of lymphocytes[18,19]. However, data pertaining to patients with mild to moderate COVID-19, especially during hospitalization, is limited. In this regard, the obtained data seem important, as they complement the clinical picture of SARS-CoV-2 infection.

In the professional literature, there is an active discussion of the role of the functional intestinal-lung axis as a bidirectional communication network. Many respiratory infections are often accompanied by symptoms of GI tract pathology or intestinal dysfunction[20]. It is also known that acute lung injury disrupts the microbiota of the respiratory tract, causing transient translocation of bacteria into the bloodstream and increased bacterial load in the caecum. In addition, normal microbiota maintains tolerogenic immunomodulatory effects in the intestine and protects against systemic inflammatory diseases[21]. Moreover, among several scientists, there is an opinion that the state of the intestinal

	msEuClCocc	msHerpes	msPropClSubterm	msBifido	msMyco	msLacto	msAnaeroAero	msUsefulPatho	msUseful	msSum	msAnaero	msAero	msPatho	msCytomeg	msEndotox
glu1	0.109	-0.011	-0.124	0.057	-0.140	0.054	-0.029	-0.111	0.101	0.193	0.144	0.178	0.238	-0.155	-0.099
alt1	0.066	0.064	0.036	0.013	-0.087	0.042	-0.040	0.083	0.051	0.016	0.004	0.027	-0.012	-0.069	-0.260
ast1	-0.026	-0.012	-0.012	0.090	-0.092	0.105	-0.058	0.058	0.057	-0.009	-0.020	0.105	0.000	-0.110	-0.187
dercf1	-0.177	-0.108	-0.049	-0.025	0.068	0.030	-0.022	-0.151	-0.112	-0.085	-0.080	0.044	0.023	0.065	0.220
bil1	-0.041	0.060	0.121	-0.056	-0.032	-0.023	0.143	0.058	0.047	-0.005	0.075	-0.139	-0.064	0.209	0.145
bilp1	-0.102	0.093	0.054	-0.082	-0.016	0.067	0.009	0.017	0.027	-0.001	0.008	-0.011	-0.045	0.233	0.071
crea1	-0.131	0.065	0.070	0.138	-0.044	0.196	-0.073	0.176	0.145	-0.030	-0.055	0.102	-0.134	-0.055	0.149
ckdepi1	-0.071	0.184	-0.048	-0.285	-0.092	-0.168	-0.033	-0.159	-0.261	-0.220	-0.207	-0.130	-0.127	0.037	-0.233
urea1	0.055	-0.059	0.120	0.094	0.082	0.060	0.167	0.157	0.135	0.042	0.088	-0.057	-0.072	0.111	0.129
crp1	0.131	-0.060	-0.058	0.033	-0.045	0.135	0.000	0.089	0.180	0.185	0.142	0.132	0.128	-0.146	0.015
fer1	-0.027	-0.126	0.070	0.048	0.055	0.176	-0.053	-0.021	0.126	0.161	0.106	0.178	0.164	0.135	0.070
ldg1	-0.042	0.027	0.006	0.003	-0.153	0.122	-0.114	0.124	0.102	0.034	-0.016	0.136	-0.028	-0.106	-0.084
sodium1	-0.005	-0.088	0.083	-0.072	0.176	0.038	-0.020	-0.037	0.038	0.047	-0.020	0.037	0.007	-0.025	-0.145
potasium1	-0.074	-0.087	-0.047	-0.027	0.145	-0.041	-0.021	-0.033	-0.050	-0.074	-0.097	0.006	-0.073	0.168	0.071
chlor1	0.053	-0.170	0.064	-0.090	0.294	-0.090	0.139	0.070	-0.082	-0.116	-0.068	-0.229	-0.189	0.139	-0.095
hemog1	-0.017	0.169	0.054	-0.084	-0.086	0.027	-0.070	-0.157	0.048	0.141	0.088	0.239	0.189	0.061	-0.017
erythr1	0.034	0.123	0.135	0.043	-0.133	-0.052	0.044	-0.138	0.106	0.193	0.223	0.166	0.230	-0.061	0.027
hematoc1	0.065	0.056	0.099	0.051	-0.063	0.016	0.015	-0.099	0.144	0.223	0.215	0.219	0.242	-0.018	0.045
mch1	-0.118	0.050	-0.180	-0.256	0.004	0.182	-0.253	-0.010	-0.110	-0.172	-0.310	0.109	-0.149	0.146	-0.090
rdw1	0.089	0.075	-0.102	0.085	-0.018	-0.123	0.044	-0.048	-0.096	-0.002	0.012	-0.104	-0.009	-0.081	-0.162
mcv1	0.044	-0.153	-0.069	-0.123	0.090	0.127	-0.062	0.055	0.016	-0.021	-0.071	0.039	-0.026	-0.011	0.073
plt1	0.107	0.034	-0.226	-0.284	0.026	-0.021	0.003	0.105	-0.074	-0.207	-0.187	-0.145	-0.250	-0.058	-0.195
leu1	-0.026	-0.025	-0.177	-0.069	-0.143	-0.074	0.022	-0.068	-0.040	-0.085	-0.031	0.009	-0.006	-0.016	0.032
segmne1	0.034	-0.128	-0.188	0.001	-0.081	-0.099	0.091	-0.061	-0.021	-0.056	0.037	-0.045	0.035	-0.019	0.115
segmnePerc1	0.084	-0.186	-0.109	0.028	-0.002	-0.053	0.101	-0.024	0.028	0.025	0.102	-0.034	0.096	-0.092	0.119
stabne1	-0.089	0.092	-0.106	-0.075	-0.173	0.011	-0.084	-0.143	-0.186	-0.049	-0.060	0.024	0.074	-0.035	-0.099
stabnePerc1	-0.123	0.087	-0.102	0.001	-0.176	0.075	-0.129	-0.117	-0.154	-0.022	-0.066	0.073	0.072	-0.079	-0.113
eo1	0.089	0.152	-0.104	-0.170	0.063	-0.202	0.082	-0.057	-0.161	-0.176	-0.098	-0.182	-0.103	0.133	-0.107
eoPerc1	0.004	0.081	-0.009	-0.183	0.127	-0.096	0.020	-0.026	-0.119	-0.146	-0.129	-0.133	-0.112	0.180	-0.123
baso1	0.070	-0.173	0.089	0.037	0.047	-0.093	0.223	0.053	0.058	-0.103	0.092	-0.179	-0.120	-0.093	0.125
basoPerc1	0.036	-0.002	0.034	-0.180	0.064	0.015	-0.045	-0.019	-0.053	-0.117	-0.135	-0.083	-0.114	-0.024	-0.239
lym1	0.014	0.178	-0.088	0.008	-0.039	-0.084	0.021	-0.010	-0.015	-0.082	-0.067	-0.048	-0.129	0.018	-0.036
lymPerc1	-0.034	0.200	0.074	0.008	0.125	-0.019	-0.048	-0.003	-0.022	-0.002	-0.074	0.000	-0.084	0.093	-0.093
mono1	0.109	0.101	-0.032	-0.046	-0.219	-0.069	0.069	0.068	-0.027	-0.140	-0.021	-0.122	-0.138	0.025	-0.121
monoPerc1	0.013	0.053	0.097	-0.014	-0.090	0.090	-0.068	0.141	0.006	-0.074	-0.089	-0.014	-0.133	0.061	-0.087
soe1	0.130	-0.018	-0.152	0.171	-0.068	0.081	0.076	0.099	0.140	0.152	0.154	0.017	0.097	-0.112	-0.029
aptt1	-0.052	0.052	-0.106	-0.160	-0.074	0.146	-0.193	-0.013	-0.057	-0.091	-0.196	0.136	-0.035	-0.109	-0.218
protro1	-0.034	0.037	-0.167	-0.049	0.117	-0.062	-0.138	-0.134	-0.090	0.045	-0.097	0.096	0.120	-0.073	-0.274
inr1	-0.038	0.034	0.133	0.079	-0.088	0.164	0.029	0.081	0.141	0.023	0.061	0.066	-0.037	0.105	0.229
fibr1	0.398	0.022	0.197	0.220	0.170	-0.116	0.296	0.088	0.224	0.319	0.403	-0.062	0.215	-0.059	0.035
trotime1	-0.241	-0.050	-0.451	-0.164	0.282	0.077	-0.473	-0.419	-0.282	0.073	-0.264	0.333	0.387	0.153	-0.314
antitro1	-0.201	0.344	0.092	0.243	-0.611	-0.569	0.555	-0.159	-0.477	-0.469	-0.059	-0.569	-0.444	-0.298	0.059
dd1	0.090	0.115	-0.044	0.122	-0.155	0.243	-0.104	0.179	0.236	0.178	0.079	0.140	0.039	-0.096	-0.088

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Figure 1 Correlation matrix of interdependence of a number of indicators of the intestinal microbiota (presented horizontally, in columns from B to P) and the most frequently used clinical and biochemical indicators (in rows from 2 to 44). Correlation values are presented as absolute values, their strength is determined by both the value of the indicated values and the color intensity. In this case, direct correlation has shades of red, inverse correlation has shades of blue and a negative value. The main indicators of the intestinal microbiota were in a rather weak direct (from 0.023 to 0.229) and inverse (from -0.012 to -0.274) interdependence. However, as shown by a detailed analysis of the results presented in the table, in particular, lines No. 41-43, a significant dependence of a number of microbiota indicators was discovered on the content of fibrinogen (line 41), thrombin time (line 42), the content of antithrombin-III (line 43). It was found that the most significant inverse correlation was observed between the content of antithrombin-III and the number of fungi (-0.611), the number of lactobacilli (-0.569), the number of aerobes in the small intestine (-0.569). Moreover, a direct correlation was established (0.555) between the content of antithrombin-III and the ratio of anaerobic flora to aerobic.

microbiota and intestinal permeability are the driving factors of pathogenic processes that can determine the features of the course of COVID-19[22]. With these data in mind, the key indicators of intestinal permeability were analyzed in this study. Thus, the faecal calprotectin content in the control group and in patients with COVID-19 did not differ, and zonulin in feces was significantly higher in patients with COVID-19. At the same time, zonulin content in the blood of patients with COVID-19 was significantly lower than that in the control group. In addition, in patients with moderately severe COVID-19, a statistically significant increase in faecal calprotectin content and a tendency towards an increase in faecal zonulin content were observed. The data obtained generally agree with the opinion of Fasano (2012) on the role of zonulin in the pathogenesis of intestinal permeability disorders[6]; however, they contradict the opinion of many researchers who believe that the level of zonulin in the blood and feces, both synergistically increase in all patients with COVID-19[10]. It is likely that an increase in the level of zonulin in feces during the peak period is a more subtle marker of changes in intestinal permeability and requires further study.

Undoubtedly, the state of the intestinal target organ functional axis plays a special role in the pathogenesis of COVID-19[23]. The understanding that the human intestine is an ecological niche for a large population of intestinal microbiota is based on the idea that it is dominated by Bacteroidetes and Firmicutes[24], which produce several metabolites to maintain intestinal homeostasis[25]. The gut microbiota plays an important role in defense against pathogens as well as in the differentiation and proliferation of the intestinal epithelium[26]. In this regard, any deviation from the normal microbial composition of the intestine is defined as "microbial dysbiosis", which is characterized by a change in the role of pathobionts and instability or reduction in populations of "key" taxon such as Bacteroidetes and Firmicutes[27].

Modern literature data on the possible relationship between changes in intestinal microbiota and the severity of COVID-19 manifestations[28] served as an incentive for this study. Significant differences were found in the parameters of the intestinal microbiota in patients with COVID-19 compared to the control group in terms of the Propionibacterium/Cl. Subterminale ratio and the content of fungi and lactobacilli. It is important to note a statistically significant (more than 3 times) increase in the total endotoxin content in the blood of patients with COVID-19, which certainly enhances the body's general inflammatory response to SARS-CoV-2.

To study the interdependence of the indicators of the intestinal microbiota and the most commonly used indicators of clinical and biochemical studies, a correlation matrix was built, which showed that the main parameters of the microbiota are interrelated with many clinical and biochemical indicators, including the fibrinogen content, thrombin time, and antithrombin III content. The most significant inverse correlation was found between the antithrombin-III content and the number of fungi, lactobacilli, and aerobes in the small intestine. A direct correlation was also established between the antithrombin III content and the ratio of anaerobic flora to aerobic flora.

The data obtained in the course of this work are relatively contradictory. They may indicate not only the important role of the pathogen in the genesis of GI lesions but also the importance of drugs used in treating patients with COVID-19 and affecting inflammation, microcirculation, and blood clotting[17]. Nevertheless, the issues raised in this study require further study.

CONCLUSION

Currently, success in the fight against COVID-19 is associated with a complex of anti-epidemic measures and an increase in the rate of immunization of the population, as well as with a deep systemic study of the pathogenetic mechanisms of the development of the disease, the search for effective therapies, and methods of preventing complications[29].

The mechanisms of various gastroenterological manifestations of COVID-19 are largely mediated by impaired intestinal permeability and homeostasis of the human microbiome. The search for new criteria for the early detection of changes in the intestinal microflora, as well as intestinal permeability, requires the study of this problem at all stages of medical care, including hospitalization.

The approaches proposed in this study to assess the clinical and laboratory manifestations of COVID-19, microbiota, and intestinal permeability indicators are of scientific and practical interest not only in the context of determining the pathogenic mechanisms of the new coronavirus infection and polymorphism of its clinical manifestations, but also for developing predictive models for the course of COVID-19, the introduction of new methods of treatment, and the prevention of complications, including post-COVID syndrome.

ARTICLE HIGHLIGHTS

Research background

An important area of effective control of the coronavirus disease 2019 (COVID-19) pandemic is the

study of the pathogenic features of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection, including those based on assessing the state of the intestinal microbiota and permeability.

Research motivation

To study the clinical features of the COVID-19 in patients with mild and moderate severity at the stage of hospitalization.

Research objectives

The objective of this clinical study was to determine the role of hepatobiliary injury, intestinal permeability disorders, and changes in composition of the microbiota in the development of systemic inflammation in patients with SARS-CoV-2 infection.

Research methods

The study was performed in 80 patients with mild and moderate severity of COVID-19. The scope of the examination included traditional clinical, laboratory, biochemical, instrumental, and radiation studies, as well as original methods for studying microbiota and intestinal permeability.

Research results

The clinical and biochemical features, manifestations of systemic inflammation, and intestinal microbiome changes in patients with mild and moderate severity were identified.

Research conclusions

This study highlights the role of intestinal permeability and microbiota as the main drivers of gastroenterological manifestations and increased COVID-19 severity.

Research perspectives

Our study showed that there is a change in the composition of the intestinal microflora, an increase in zonulin in feces, and intestinal dysfunction, which might be connected to COVID-19. We believe that additional studies should give more promising results. We also suggest that the use of probiotics, prebiotics, short chain fatty acids might show the success in treating intestinal dysbiosis caused by SARS-CoV-2 infection. If the effectiveness of these drugs is confirmed, the results can be used to complement the algorithms for COVID-19 treatment.

FOOTNOTES

Author contributions: Kozlov KV, Zhdanov KV, Ratnikova AK, Ratnikov VA, Tishkov AV, Grinevich V, Kravchuk YA, Miklush PI, Nikiforova PO, Gordienko VV, Popov AF, Andryukov BG wrote the manuscript, reviewed and agreed to the final version of the manuscript.

Institutional review board statement: The present study was reviewed and approved by the independent ethics committee of the Military Medical Academy named after SM. Kirov, protocol (Approval No. 246).

Informed consent statement: Informed written consent was obtained from the patient and her family for publication of this report and any accompanying images.

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Country/Territory of origin: Russia

ORCID number: Konstantin V Kozlov 0000-0002-4398-7525; Konstantin V Zhdanov 0000-0002-3679-1874; Anna K Ratnikova 0000-0003-3279-6448; Vyacheslav A Ratnikov 0000-0002-9645-8408; Artem V Tishkov 0000-0002-4282-8717; Panteley I Miklush 0000-0002-5668-462X; Vera V Gordienko 0000-0003-2078-2196; Boris G Andryukov 0000-0003-4456-808X.

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