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ИММУНОЛОГИЧЕСКИЕ МАРКЕРЫ У ПАЦИЕНТОВ С ГАСТРОЭНТЕРОЛОГИЧЕСКИМИ ПРОЯВЛЕНИЯМИ В РАЗЛИЧНЫЕ ПЕРИОДЫ COVID-19

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Immunological Markers in Patients with Gastroenterological Manifestations During Different Periods of COVID-19

Резюме

Цель исследования — оценить уровни иммунологических маркеров у пациентов, перенесших COVID-19 и имеющих гастроэнтерологические симптомы в различные сроки. **Материалы и методы**. На I этапе проведено ретроспективное исследование 785 медицинских карт пациентов, находившихся на стационарном лечении с 05.2020 по 12.2020 г. с диагнозом «Новая коронавирусная инфекция COVID-19» среднего и тяжелого течения. Основной задачей была оценка клинических симптомов с фокусом на выявление гастроэнтерологических проявлений COVID-19. После выписки из стационара через 3, 6 и 12 месяцев было проведено телефонное анкетирование с применением специально разработанного опросника сотрудниками кафедры внутренних болезней ФГБОУ ВО Башкирский государственный медицинский университет (БГМУ) МЗ РФ для выявления гастроэнтерологических симптомов, а также с использованием стандартного опросника оценки желудочно-кишечных симптомов GSRS (Gastrointestinal Symptom Rating Scale — Шкала оценки желудочно-кишечных симптомов) и Бристольской шкалы оценки кала. В опросе приняло участие 247 респондентов, после чего они были разделены на 3 группы по критерию наличия и длительности симптомов со стороны желудочно-кишечного тракта. 1 группа — пациенты, с сохраняющимися желудочно-кишечными симптомами в период от 4 до 12 недель (продолжающийся симптоматический COVID) — 30 человек; 2 группа — пациенты с длительностью желудочно-кишечных симптомов более 12 недель (постковидный синдром) — 75 человек. Контрольную группу (3 группа) составили 151 пациент, переболевший COVID-19 без развития постковидного синдрома. На II этапе в каждой группе пациентов были исследованы сывороточные концентрации иммунологических маркеров (интерлейкины (ИЛ) 4, 6, 8, 18; ревматоидный фактор, антитела к дезоксирибонуклеиновой кислоте (ДНК)). **Результаты.** Отмечается статистически значимое увеличение среднего возраста у пациентов 1 группы и 2 группы ($p=0,02*10^{-4}$ и $p=0,01*10^{-9}$), а также длительности госпитализации у 1-й группы пациентов в сравнении с группой контроля (p=0,04). Женщины преобладали как в 1-й (p=0,01), так и во 2-й группах (p=0,002). Сроки амбулаторного лечения до госпитализации составили в среднем 8,1 дней. В обеих группах пациентов отмечались статистически значимое повышение уровня ИЛ-18 ($p=0,095$; $p=0,88*10^{-9}$), в группе 2 выявлено повышение уровня ревматоидного фактора (p=0,044) в сравнении с группой контроля. Выявлено также статистически значимое повышение уровней ИЛ-6 в обеих исследуемых группах относительно группы контроля (p=0,020; p=0,000017), при этом средние значения находились в пределах референтных интервалов. **Выводы.** Таким образом, пациенты, перенесшие COVID-19 среднетяжёлого и тяжелого течения, подвержены развитию постковидного синдрома, в том числе, с гастроэнтерологическими проявлениями. Впервые выявлен повышенный уровень ИЛ-18 у данной категории пациентов, что может служить как диагностическим биомаркером, так и потенциальной мишенью таргетной терапии.

Ключевые слова: *COVID-19, постковидный синдром, желудочно-кишечный тракт, ИЛ-18*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Materials and Methods. A retrospective study of 785 medical records of patients hospitalized between 05.2020 and 12.2020 with a diagnosis of moderate to severe new coronavirus COVID-19 infection was performed in phase I. The study was conducted. The primary objective was to evaluate clinical symptoms with a focus on detecting gastroenterologic manifestations of COVID-19. After discharge from the Covid hospital in 3, 6 and 12 months, a telephone questionnaire was conducted using a specially developed questionnaire by the staff of the Department of Internal Medicine of the FSBEU VO BSMU of the Ministry of Health of the Russian Federation to identify gastroenterological symptoms, as well as using the standard questionnaire for the assessment of gastrointestinal symptoms GSRS (Gastrointestinal Symptom Rating Scale) and the Bristol Stool Assessment Scale. 247 respondents took part in the survey, after which they were divided into 3 groups according to the criterion of presence and duration of gastrointestinal symptoms. Group 1 — patients with persisting gastrointestinal symptoms in the period from 4 to 12 weeks (ongoing symptomatic COVID) — 30 people; Group 2 — patients with duration of gastrointestinal symptoms more than 12 weeks (post-COVID syndrome) — 75 people. The control group (group 3) consisted of 151 patients who had survived COVID-19 without the development of postcoviral syndrome. At stage II, serum concentrations of immunologic markers (interleukins 4, 6, 8, 18; rheumatoid factor, antibodies to DNA,) were studied in each group of patients. **Results.** There was a statistically significant increase in the mean age in group 1 and group 2 patients (p=0.02*10-4 and p=0.01*10-9), as well as in the duration of hospitalization in group 1 patients compared to the control group (p=0.04). Women predominated in both groups 1 (p=0.01) and 2 (p=0.002). The time of outpatient treatment before hospitalization averaged 8.1 days. In both groups of patients there was a statistically significant increase in IL-18 level (p=0,095; p=0,88*10-9), in group 2 there was an increase in rheumatoid factor level (p=0,044) in comparison with the control group. A statistically significant increase in IL-6 levels was also revealed in both studied groups in comparison with the control group (p=0,020; p=0,000017), while the mean values were within the reference intervals. **Conclusions.** Thus, patients who have had moderate to severe COVID-19 are susceptible to the development of post-Covid syndrome, including gastroenterological manifestations. For the first time, an elevated level of IL-18 was detected in this category of patients, which can serve as both a diagnostic marker and a potential target for targeted therapy.

Key words: *COVID-19, long-covid, gastrointestinal tract, IL-18*

Conflict of interests

The authors declare no conflict of interests

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WHO — World Health Organisation, IL — interleukin, TNF — tumour necrosis factor, ACE2 — angiotensin converting enzyme, CBC — complete blood count, BBA — biochemical blood assay, AST — aspartate aminotransferase, ALT — alanine aminotransferase, CRP — C-reactive protein, PCR — polymerase chain reaction, ECG — electrocardiography, CT — computer tomography, GSRS — Gastrointestinal Symptom Rating Scale LDH — lactic dehydrogenase, PCS — post-COVID syndrome, RF — rheumatoid factor

Introduction

The World Health Organisation (WHO) has officially announced the end of the coronavirus infection 2019 (COVID-19) pandemic; however, currently there are still a lot of open questions about the health condition of patients who had acute COVID-19. Up to a half of patients still have symptoms, which they had not had before the novel coronavirus infection, and symptoms can last for a long period of time after the infectious process resolution. According to the recommendations of the National Institute for Health and Care Excellence (NICE), ongoing (symptomatic) COVID is diagnosed in the presence of symptoms 4 to 12 weeks after disease onset; post-COVID syndrome (long COVID) is diagnosed if symptoms persist for over 12 weeks [1]. According to the definition by the WHO, the term "post-COVID syndrome" is used to define a totality of various long-lasting symptoms in some individuals after past COVID-19; usually, they are diagnosed by a healthcare professional at least 3 months after disease onset [2]. GIT clinical symptoms of COVID-19 include nausea, abdominal pain, loss of appetite, heartburn and constipations [3], and the majority of initial symptoms resolve in 3–6 months. However, according to a multicentre, retrospective study conduced in New York (2021), 20.5 % of subjects with long COVID had persistent diarrhoea, while 13.7 % of patients with long COVID experienced loss of appetite even 7 months after infection [4, 5]. A number of studies demonstrated that both mild and severe COVID-19 can result in a hyperinflammatory reaction, which manifests with higher levels of multiple cytokines, including interleukin-6 (IL-6), IL-8 and tumour necrosis factor (TNF-α) [6, 7]. Nevertheless, the data on changes in the cytokine regulation system are fragmented and relate mainly to the acute stage of disease. Developing knowledge in this area will ensure better understanding of the pathogenesis of post-COVID syndrome in order to develop prevention and therapy methods.

Objective: To assess levels of immunological markers in post-COVID-19 patients who had GIT symptoms at a various stage of the disease.

Materials and Methods

The COVID Hospital of the Clinics at the Bashkir State Medical University hosted a retrospective study of medical records of 785 patients who were undergoing inpatient treatment for moderate and severe novel coronavirus infection COVID-19 from May 2020 till December 2020. The mean age was 59 years old, including 571 (72.3 %) patients with moderate and 214 patients (27.2 %) with severe disease. In order to confirm COVID-19, all patients had an oropharynx+nasopharynx swab for SARS-CoV-2 by real-time polymerase chain reaction (PCR) (Intifica SARS-CoV-2 kit, Alkor Bio LLC, Russia). On the average, patients were hospitalised on day 7 after first symptoms. 341 subjects (43 %) were males. The most common comorbidities before COVID-19 infection were hypertensive disease (40 %), ischemic heart disease (17 %), and diabetes mellitus (types 1 and 2) (17 %). The main characteristics of subjects are presented in Table 1.

The study was conducted in two stages. At stage I, electronic medical records were analysed to assess clinical symptoms, mostly to identify GIT signs of COVID-19. During inpatient treatment, all patients had standard laboratory and instrumental tests, included in the Global Clinical Recommendations for Prevention, Diagnosis and Treatment of the Novel Coronavirus Infection, Version 1 (January 29, 2020). Laboratory tests included complete blood count (CBC); biochemical blood assay (BBA)(creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, electrolytes, albumin); C-reactive protein (CRP); polymerase chain reaction (PCR) tests for SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2, formerly 2019-nCoV) — enveloped virus single-strand (+) RNA virus. Instrumental examinations included lung computer tomography (CT), electrocardiography (ECG). Also, biological materials were sampled (an informed voluntary consent form was signed for research and biological material sampling); a biobank for biological material storage at -80° C was created; and a database was registered (Database Registration Certificate No. 2021620499 dated March 16, 2021). 3, 6 and 12 months after acute COVID-19 infection, a phone survey was conducted in accordance with a dedicated questionnaire developed by the staff of the Chair of Internal Diseases at the Bashkir State Medical University of the Ministry of Health of Russia, and also using a validated Russian version of the Gastrointestinal Symptom Rating Scale (GSRS) and the Bristol Stool Form Scale. The original questionnaire and the validated version of GSRS were used to find out common complaints and specific chronic or acute symptoms, which are typical for GIT involvement. The survey included 247 respondents, who were divided into study groups: group 1 — patients with GIT symptoms of COVID-19 persisting 4 to 12 weeks (current symptoms of COVID), 30 subjects; group 2 — patients with GIT symptoms lasting over 12 weeks (post-COVID syndrome), 75 subjects; group 3 — controls, no GIT symptoms, 151 subjects (stage I).

The main objective of stage II was to identify patients with genuinely GIT symptoms, since initially formed groups (stage I) had both current GIT symptoms and other symptoms (joint pain, shortness of breath, etc.); therefore, patients only with persistent GIT symptoms (gastroenterological monosyndrome) were selected for the study of immunological markers (measurement of interleukins (IL) 4, 6, 8, 18, rheumatoid factor (RF), anti-DNA antibodies). Immunological markers were measured by enzyme-linked immunosorbent assay (ELISA) using human blood sample using Vektor-Best reagent kit (Vektor-Best JSC, Novosibirsk, Russia) in order to determine IL-4 levels (sensitivity: 0.4 pg/mL, measurement range: 0–100 pg/mL (reference values: 0.00–4.00)), IL-6 (sensitivity: 0.5 pg/mL, measurement range: 0–300 pg/mL (reference values: 0.00–10.00)), IL-8 (sensitivity: 2.0 pg/mL, measurement range: 0–250 pg/mL (reference values: 0.00–12.00); IL-18 (sensitivity: 2.0 pg/mL, measurement range: 0–1,000 pg/mL (reference values: 0.00–260.00); RF (reference values: 0.00–10.00); and anti-DNA antibodies (reference values: 0.00–20.00). Tests and assessments were conducted at the unit of clinical laboratory diagnostics of the Clinics at the Bashkir State Medical University.

As a result, 20 patients from group 1 and 38 patients from group 2 were included in stage II; 30 patients were controls. Inclusion criteria for stage II of the study were: male and female patients aged 18 to 80 years old; persisting GIT symptoms lasting 4 to 12 weeks and 12 and over weeks after acute COVID-19 infection without any other signs of post-COVID syndrome (shortness of breath, joint pain, fever, etc.). Non-inclusion criteria for stage II were: age of over 80 years old; patients with a history

Table 1. *Characteristics of the total sample*

Options	General sample N=785
Age, years, Me [IQR]	59 [49; 67]
Hospitalization, days, Me [IQR]	11 [9; 14]
Time from the onset of symptoms to hospitalization, days, Me [IQR]	7 [6; 10]
Men, N (%)	♂341(43)

Note: N — Total quantity; Me [IQR] (Me is the median, IQR is the first and third quartiles).

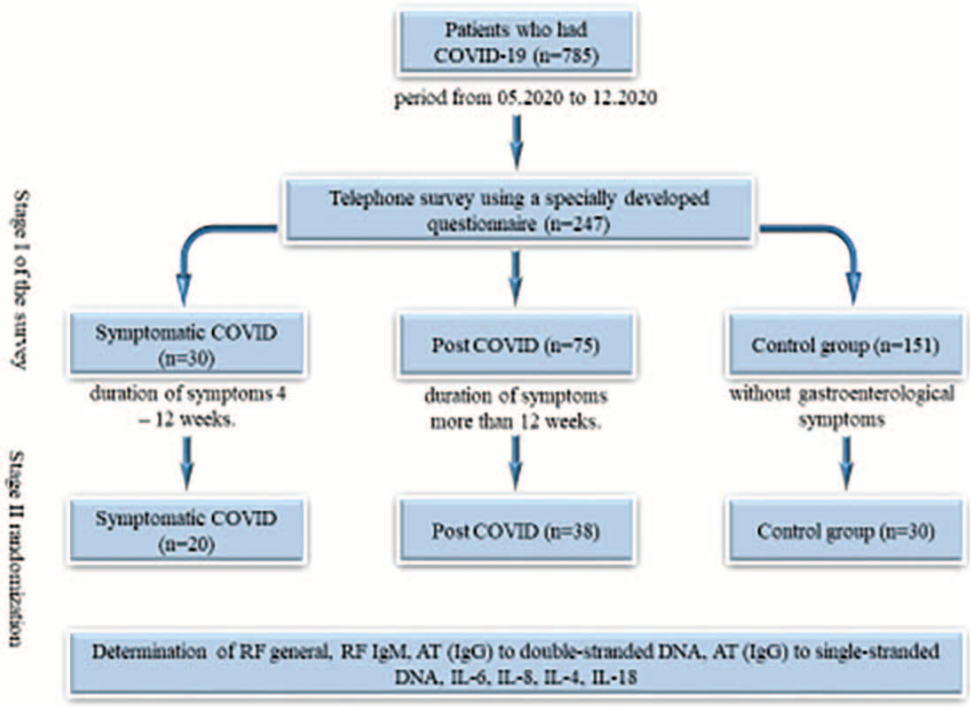

Figure 1. *Study design*
Note: Rheumatoid factor (RF), immunoglobulin G (IgG), antibodies (AT) IgG, interleukin (IL)

of GIT diseases before acute COVID-19; patients with other persistent symptomatic and post-COVID manifestations (shortness of breath, joint pain, fever, etc.); a history of/suspected malignancy in any location, any immunodeficiency; pregnancy, breastfeeding, a history of mental disorders; refusal from taking part in the study.

A schematic representation of the study is presented in Figure 1.

An informed consent form for the use of medical data for research purposes was signed both during inpatient treatment and, later, for the phone survey. The study was approved by the Local Ethics Committee at the Bashkir State Medical University (Minutes No. 4 dated April 21, 2021).

Statistical data processing was performed using Microsoft Excel 2010, Statistica 12.0. The normality of parameter distribution was assessed using Kolmogorov–Smirnov test. Depending on the normality of distribution, data are presented as median with quartiles and mean values with standard deviations. Intergroup pair-wise comparison of two independent samples was performed using Student t-test (for normal distribution) and Mann–Whitney U test (for distribution other than normal); statistically significant level was at $p < 0.05$. For qualitative data, 2x2 cross tables were used with Yates corrected $\chi 2$, if the frequency in at least one cell of the table was equal or less than 5. The degree of associations was assessed with the help of odds ratio (OR).

Results

Complaints of GIT problems, including abnormal bowel patterns and abdominal pain, were recorded in 11 % and 8 % of cases, respectively; the duration of symptoms was 4 [3; 4] and 2 [1; 2] weeks. The results are presented in Table 2.

Table 2. *Analysis of symptoms in patients who have had COVID-19*

Symptoms	N	%	Duration, weeks Me[IQR]
Weight loss (kg)	33	13	**7 [5; 10]**
Loss of smell	27	11	**4 [4; 12]**
Weight gain (kg)	27	11	**7 [5; 10]**
Abnormal stool (constipation/diarrhea)	27	11	**4 [3; 4]**
Loss of taste	22	9	**1 [1; 2]**
Stomach ache	21	8	**2 [1; 2]**

Table 3. *Results of a comparative analysis of clinical and anamnestic characteristics in the study groups at stage II*

Options	Group 1 N=20	Group 2 N=38	Control group N=30
Age, years	59,2±7,8* p=0,02x10^{-4}	56,2±6,5** p=0,01x10^{-9}	55,8 ±5,4
Hospitalization, days (Me±SD)	15,5±4,2* p=0,04	14±4,6	11,1±2,1
Time from the onset of symptoms to hospitalization, days Me [IQR]	**7 [5; 9]**	**7 [6; 10]**	**6 [5; 8]**
Men, N (%)	1(5)* p=0,01	6 (15,7)** p=0,04	12 (40)
Women, N (%)	19(95)	32 (84,3)	18 (60)

Note: N — Total quantity; p — statistical significance; Me+SD — mean + standard deviation; Me [IQR] (Me is the median, IQR is the first and third quartiles).
* Comparison of group 1 with the control group
** Comparison of group 2 with the control group

Table 4. *Analysis of the intensity of gastroenterological syndromes in the formed groups 12 months after acute COVID-19 infection*

Syndromes	Intensity, points Me [IQR]	
	Group 1 N=30	Group 2 N=75
Dyspeptic syndrome	**5 [5; 6]**	**5 [4; 6]**
Reflux syndrome	**5 [5; 7]**	**5 [4; 6]**
Abdominal pain syndrome	**6 [5,5; 6]**	**5 [4; 5]**
Constipation syndrome	**6 [6; 7]**	**6 [4; 7]**
Diarrheal syndrome	**5 [5; 6]**	**7 [5; 7]**

Note: N — Total quantity; Me [IQR] (Me is the median, IQR is the first and third quartiles).

Table 5. *Results of comparative analysis of immunological markers*

Options	Reference values	Group 1 N=20	Group 2 N=38	Control group N=30
RF total, U/ml M [Q1; Q3]	0,00-10,00	14,81; [13,63;20,59]* p=0,067	17,71; [13,39;21,21]** p=0,044	10,94; [7,64;18,3]
RF IgM, IU/ml	0,00-14,00	3,43; [1,45;13,01]	2,24; [1,32;4,36]	3,181; [1,78;4,11]
AT (IgG) to double-stranded DNA IU/ml	0,00-20,00	3,16; [1,89;9,54]	3,98; [1,54;7,24]	2,881; [1,45;5,12]
AT (IgG) to single-stranded DNA, IU/ml	0,00-20,00	2,88; [2,46;4,61]	3,86; [2,54;5,02]	3,885; [1,98;5,52]
IL-6, pg/ml	0,00-10,00	3,86; [2,27;4,29]* p=0,020	4,02; [3,32;4,2]** p=0,00017	0,96; [0,96;1,16]
IL-8, pg/ml	0,00-12,00	0,16; [0,01;1,37]	0,32; [0,01;1,78]	0,41; [0,01;1,78]
IL-4, pg/ml	0,00-4,00	0,48; [0,01;0,6]	0,48; [0,01;0,82]	0,20; [0,01;1,14]
IL-18, pg/ml	0,00-260,00	394,74*; [192,62;505,39] p=0,095	378,32*; [351,2;513,96] p=0,88x10^{-9}	121,16; [88;210,56]

Note: M[Q1; Q3] — median, first and third quartiles; N — Total Rheumatoid factor (RF), immunoglobulin G (IgG), antibodies (AT) IgG, interleukin (IL), deoxyribonucleic acid (DNA), international unit per milliliter (IU/ml), picogram per milliliter (pg/ml)
* Comparison of group 1 with the control group
** Comparison of group 2 with the control group

Statistically significant increase in the mean age of patients in group 1 and group 2 ($p = 0.02*10^{-4}$ and $p = 0.01*10^{-9}$), as well as duration of hospitalisation in group 1 vs controls ($p = 0.04$) were recorded. Females prevailed both in group 1 ($p = 0.01$) and group 2 ($p = 0.04$). Before hospital admission, outpatient treatment lasted on the average for 7 days. A comparative analysis of the study groups at stage II is presented in Table 3.

During the survey 12 months after acute COVID-19 infection, patients who had GIT symptoms, underwent an additional assessment of the nature and severity of complaints using the GSRS scale. The most common symptoms were heartburn (24 %), pain and discomfort in the upper section of abdomen (20 %), bloating (15 %), constipations (14 %), abdominal murmur (13 %), burping and bloating (9 %), hard stool (7 %); acid reflux (5 %), nausea and liquid stool (4 %). Also, the groups were assessed for the severity of GIT syndromes. The results are presented in Table 4.

Evaluation of the results of immunological biomarker assessment in group 1 and group 2 showed a statistically significant increase in serum IL-18 concentrations vs controls ($p = 0.095$ *and* $p = 0.88x10^{-9}$), respectively.

IL-18 levels were higher than the reference values in 8 patients (72 %) from group 1 ($p = 0.019$) and in 15 patients (88 %) from group 2 ($p = 0.014$).

It is important to note a higher serum IL-6 concentrations in the study groups ($p = 0.020$; $p = 0.000017$) vs controls, although they are within the reference range.

Total RF concentrations were statistically higher in group 2 patients ($p = 0.044$) vs controls. In group 1 patients vs controls, total RF levels demonstrated a trend ($p = 0.067$). The summary data on the comparative analysis of biological markers is presented in Table 5.

17 patients out of 20 in group 1 had higher rheumatoid factor values vs reference values ($p = 0.008$; OR = 7.41 (95 % CI 1.78–30.77), in group 2 patients — 32 patients out of 38 ($p = 0.001$; OR = 6.97 (95 % CI 2.24–21.63) vs controls.

Discussion

The study conducted in San-Paolo (Milan, Italy) in 377 patients has proven that over a half of individuals who had acute COVID-19 reported persistent symptoms for a certain period of time. Symptoms can last for 6–7 months and longer. In a multifactor analysis, female sex and elderly age were predictors of long COVID (OR = 3.3 and OR = 1.03, respectively), correlating with our results [8]. According to a systematic review and a meta-analysis by Choudhury A. et al. (2022), GIT symptoms of a past acute COVID-19 infection include abdominal pain (2.7 %), nausea and vomiting (4.6–10.3 %), diarrhoea (7.4–13.2 %) [9]. In this study, abdominal pain was recorded more frequently (8 %); the frequency of bowel disorders was comparable (11 %) with that of earlier studies. A majority of initial symptoms (abdominal pain, nausea, vomiting and diarrhoea) resolve in 3–6 months (in 90.5 % and 89.4 % of cases, respectively) [4]. In this study, complaints persisted for 5.17 ± 4.94 and 2.61 ± 2.34 weeks, respectively.

According to literature, patients with post-COVID symptoms had higher IL-6, SRP and TNF-α levels; and a higher IL-6 value was higher in all patients during 7 months after discharge from the hospital [10], correlating with our results. Also, we have found out higher rheumatoid factor values in patients with GIT symptoms of post-COVID syndrome. According to literature, higher levels of this biomarker were observed in patients with coronavirus infection both during the acute phase and for some time after the infectious process had resolved [11]. At the same time, the importance of RF assessment requires additional evaluation, since there is positive cross-reaction between rheumatoid factors and antibodies to Sars-Cov-2 virus [12].

According to Satış H. et al. (2021) [13], in patients with COVID-19, IL-18 levels correlated with IL-6 concentration, while baseline IL-18 values were a prognostic marker of severe disease. However, available literature does not contain any data on IL-18 levels in patients during various periods after COVID-19. In this study, evaluation of immunological biomarker assessment in group 1 and group 2 showed a statistically significant increase in serum IL-18 concentrations vs controls ($p = 0.095$ and $p = 0.88x10-9$), respectively. IL-18 levels were higher than the reference values in 8 patients (72 %) from group 1 ($p = 0.019$) and in 15 patients (88 %) from group 2 ($p = 0.014$).

Therefore, our results make it possible to better understand the immunopathogenesis of post-COVID syndrome; patients after the novel coronavirus infection had higher delayed IL-18 levels. Measurement of this biomarker is justified in this category of patients (invention patent No. 2807947. Method of Forecasting GIT Symptoms in Post-COVID Syndrome Using Immunological Markers) [14].

Conclusions

Therefore, patients who had moderate and severe COVID-19, are susceptible to post-COVID syndrome, including GIT manifestations. A higher IL-18 level in this category of patients has been identified for the first time; therefore, it can be used both as a diagnostic marker and a potential target in target therapy.

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