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Effect of vitamin D blood levels on the disease in patients with COVID-19

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The danger of COVID-19 infection is its higher contagiousness (several times higher than influenza), a long incubation period (up to 14 days), and is complicated by the fact that patients without any symptoms are carriers of the infection. Currently, the clinical and epidemiological researches on the characteristics of the disease continue, along with the development of the new means of its prevention and treatment. The most important preventive resource is the activation of the antiviral innate immune system. According to the literature, an adequate supply of vitamin D is one of the foundations of the antiviral immune system, including against the influenza virus. No clinical trials have been conducted to determine the relationship between vitamin D blood level and clinical outcome in COVID-19 patients.

To study the effect of blood levels of vitamin D in patients infected with COVID-19 on the course of the disease and the outcome of treatment, a medical history of 19 patients with laboratory-confirmed COVID-19 infection was analyzed. The patients were treated at the «MediClub» LLC between 15.06.2020 - 15.07.2020. «MediClub» hospital was approved by «TABIB» Azerbaijan for the treatment of patients with COVID-19. Data on clinical manifestations and blood 25-hydroxyvitamin D [25(OH)D] levels were obtained from all medical histories.

A retrospective analysis of laboratory-confirmed cases of COVID-19 showed a relationship between the blood level of 25-hydroxyvitamin D [25(OH)D] and the nature of the course of COVID-19 and the development of complications of the disease.

Taking into account the main cause of critical complications of COVID-19 is impaired immunity, and cholecalciferol harmonizes the functioning of the immune system at all its levels, it can be concluded that an adequate level of vitamin D in the blood increases the likelihood of a light course of COVID-19 and its favorable outcome.

Keywords: *Coronavirus infection, pandemic, COVID-19, 25-hydroxyvitamin D [25(OH)D], blood level of vitamin D, volume of lung damage, proinflammatory cytokines, concomitant diseases*

INTRODUCTION

The coronavirus infection COVID-19 was officially registered by the World Health Organization (WHO) on December 31, 2019, when the PRC Ministry of Health reported 44 cases of SARS in Wuhan City, Hubei Province. On February 11, 2020, the WHO determined the official name of the infection caused by the new coronavirus - COVID-19 ("Coronavirus disease 2019"). On February 11, 2020, the International Committee on Taxonomy of Viruses stated the official name of the infectious agent, a SARS-CoV-2. It has been established that COVID-19 is caused by the new coronavirus SARS-CoV-2. Later, on March 11, 2020, WHO declared a COVID-19, a pandemic (Громова и др., 2020; Временные методические рекомендации: профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19), 2020).

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and is complicated by the fact that patients without any symptoms are carriers of the infection. COVID-19 is characterized by a severe course in the presence of the chronic pathology in patients. These COVID-19 features place increased demand on the healthcare system. In particular, the higher contagiousness leads to the simultaneous disease incidence of COVID-19 of the large number of people, which has led to the overload of the health care system in several countries. More severe course of infection in patients with a chronic pathology is associated with use for adaptive lung ventilation (ALV) and with a higher mortality rate (Громова и др., 2020).

Currently, the clinical and epidemiological researches on characteristics of the disease continues, along with the development of the new means of its prevention and treatment. The most common clinical manifestation of the COVID-19 is bilateral pneumonia (diffuse alveolar damage and microangiopathy); acute respiratory distress syndrome (ARDS) was recorded in 3-4% of the patients. Some patients develop hypercoagulable syndrome with thrombosis and thromboembolism, along with the other damage of the organs and systems (the central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), and also sepsis and septic shock may be developed.

Attempts to control the COVID-19 only by quarantine measures (for example, wearing masks, gloves, washing hands, social distancing, self-isolation, and other) do not engage the most important preventive resource such as the activation of antiviral innate immune system. This aspect is especially important in the case of COVID-19, as this infection is highly contagious and can lead to severe pneumonia and acute respiratory failure. To identify risk groups for a severe course of the disease, it is necessary to systematize the features of the pathogenesis of COVID-19, which distinguish it from other coronavirus infections (Alipio, 2020).

Vitamin D is one of the most important immunity regulators. Adequate supply of vitamin D is one of the foundations of anti-viral immune system, including against the influenza virus. It has been proven that vitamin D reduces the risk of acute respiratory viral infection (ARVI) (Rondanelli et al., 2018). Vitamin D deficiency is associated with impaired functioning of innate and adaptive immune systems, also with increased risk of viral and bacterial diseases. A patient of any age with vitamin D deficiency develops chronic inflammation, which significantly reduces the body's resistance to bacterial and viral diseases (ARVI, influenza, rhinitis, bronchitis, obstructive pulmonary diseases) (Громова и др., 2020). In addition, vitamin D increases cell-mediated immunity (Cantorna, 2010), modulates adaptive immune system (Sharifi et al., 2019) and increases the expression of genes encoding the antioxidant enzymes (Lei et al., 2017). Therefore, several authors have proposed the use of vitamin D for the prevention and treatment of COVID-19 (Alipio, 2020). No clinical trials have been conducted to determine the ability of vitamin D to suppress the COVID-19 virus. There is a lack of tests for the statistically significant relationship between vitamin D levels and clinical outcome in COVID-19 patients. In this article, we have used vitamin D status to predict clinical outcomes in patients infected with COVID-19. The analysis was based on the level of 25-hydroxyvitamin D [25(OH)D], a measure of the amount of vitamin D in the body.

Purpose of the study: To study the effect of blood levels of vitamin D in patients infected with COVID-19 on the course of the disease and the outcome of treatment.

MATERIALS AND METHODS

We analyzed medical history of 19 patients with laboratory confirmed COVID-19 infection. The patients were treated at the «MediClub» LLC between 15.06.2020 - 15.07.2020. Hospital «MediClub» was approved by «TABIB» Azerbaijan for the treatment of patients COVİD-19. Data on clinical manifestations and blood 25-hydroxyvitamin D [25(OH)D] levels were obtained from all medical histories. It should be noted that the patients we analyzed were inpatients. They were hospitalized due to the severity of the physical condition. Thus, all the patients had respiratory failure and increased body temperature. The clinical analyzes were obtained from the patients, presentation of pulmonary infection on computer tomography (CT). It was important to obtain the level of 25-hydroxyvitamin D [25(OH)D in the blood of the patients and to assess their clinical condition in accordance with the obtained data.

RESULTS AND DISCUSSION

A total of 19 patients with COVID-19 enrolled to this study, where 11 were men and 8 were women (Fig. 1). Most of the patients were men (58%).

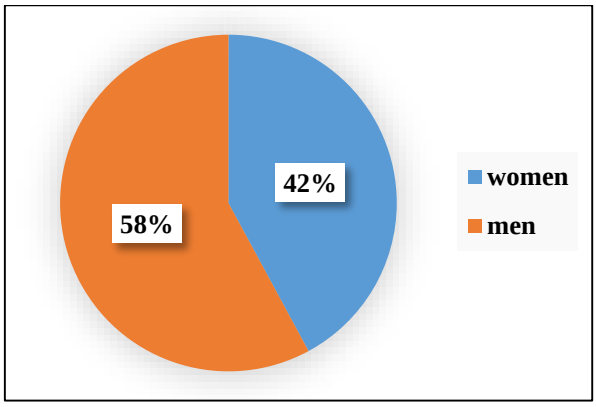

Fig. 1. The total number of patients participating in the study (total 19 patients).

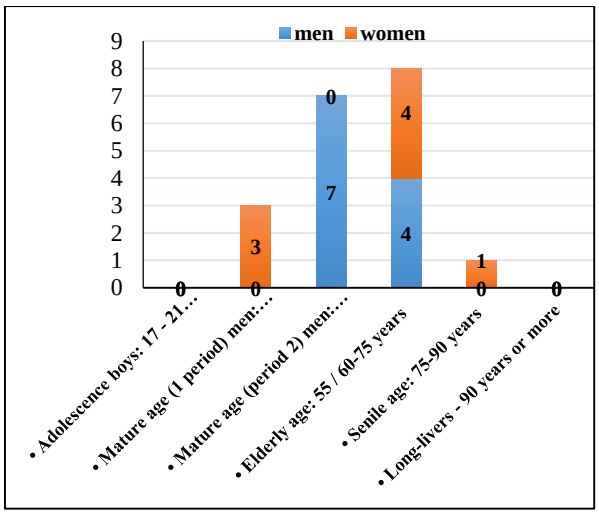

Fig. 2. Distribution of patients participating in the study by age (total 19 patients).

The age distribution of the patients was following (Fig. 2):

- adolescence boys: 17-21 years, girls: 16-20 years;
- mature age (1 period) men: 21-35 years, women: 20-35 years;
- mature age (period 2) men: 35-60 years, women: 35-55 years;
- advanced age: 55/60-75 years;
- senior adult: 75-90 years;
- long-livers - 90 years or more.

In our study, the overwhelming number of patients (15 patients) belongs to mature age (period 2), 37% and to old age, 43%, which amounted to 80% in general.

The patients' distribution by the volume of lung damage is presented in the Fig. 3.

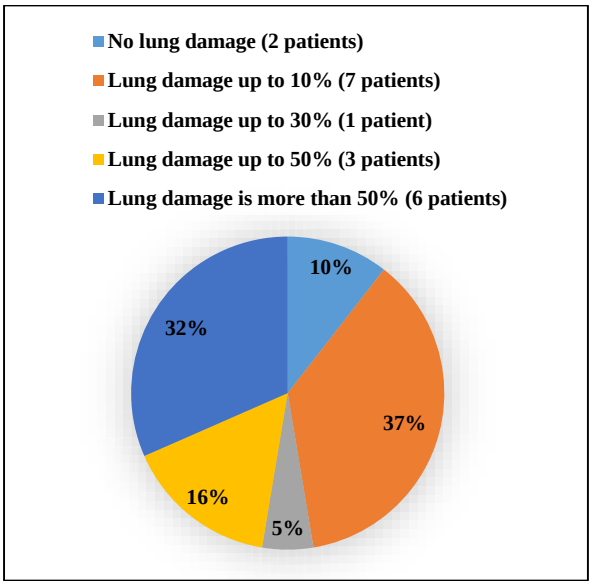

Fig. 3. Distribution of patients participating in the study by the volume of lung damage (19 patients in total).

According to the volume of lung damage, confirmed by CT of the chest, the cases were classified as follows:

- COVID-19 infected patients with clinical manifestations, without lung involvement;
- COVID-19 infected patients with clinical manifestations, the volume of lung damage was up to 10%;
- COVID-19 infected patients with clinical manifestations, the volume of lung damage was up to 30%;
- COVID-19 infected patients with clinical manifestations, the volume of lung damage was up to 50%;
- COVID-19 infected patients with clinical manifestations, the volume of lung damage was more than 50%.

Patients with severe clinical manifestations (hypoxia (oxygen saturation below 93%), with respiratory impairment or deviations in the results of laboratory blood gas analyzes (PaCO2> 50 mm Hg Art.), and respiratory failure requiring intensive monitoring of the patient) accounted for 48% (9 patients) of the total number of the patients. These were patients whose volume of lung damage was up to 50% (3 patients - 16% of the total number of patients) and patients whose lung damage was more than 50% (6 patients - 32% of the total number of patients).

An important criterion, in the presence of which the health status of COVID-19 patients is aggravated, is the presence of concomitant diseases. It is known that the presence of any chronic inflammation in a patient (glomerulonephritis, cholestasis, atherosclerosis, obesity, diabetes mellitus, bronchial asthma, endothelial dysfunction in hypertension, and other) stimulates more rapid increase in the synthesis of proinflammatory cytokines. We analyzed the relationship between the presence of concomitant diseases with the spread of the pathological process in the lungs (Fig. 4).

Eight patients (42%) had concomitant diseases, which is a serious complication associated with COVID-19. Six patients with severe lung damage (lung damage is more than 50%) and, thus, with a severe clinical course of COVID-19, suffered for many years from various somatic diseases, such as diabetes mellitus, atherosclerosis, coronary heart disease, coronary angioplasty, arterial hypertension, chronic renal failure, obesity. All patients had severe respiratory failure, 4 out of 6 patients had acute respiratory distress syndrome (RDS). All patients at certain stages of treatment were connected to the AVL. Two of these patients with volume of lung damage up to 95% and 100% died.

The blood levels of vitamin D in patients with COVID-19 in the study has been classified based on serum 25 (OH) D levels:

- <10 ng/ml (severe vitamin D deficiency);
- 10-20 ng / ml (vitamin D deficiency);
- 20-30 ng / ml (vitamin D insufficiency);
- 30-100 ng / ml (adequate level of vitamin D);
- 100 ng / ml (excess vitamin D).

The obtained data of blood levels of vitamin D in patients is presented in the Fig. 5.

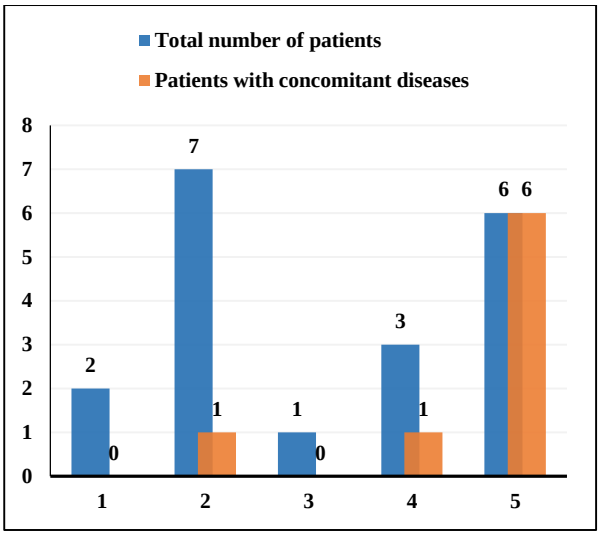

Fig. 4. Patients with the presence of concomitant diseases, respectively, the spread of the pathological process in the lungs (19 patients in total).

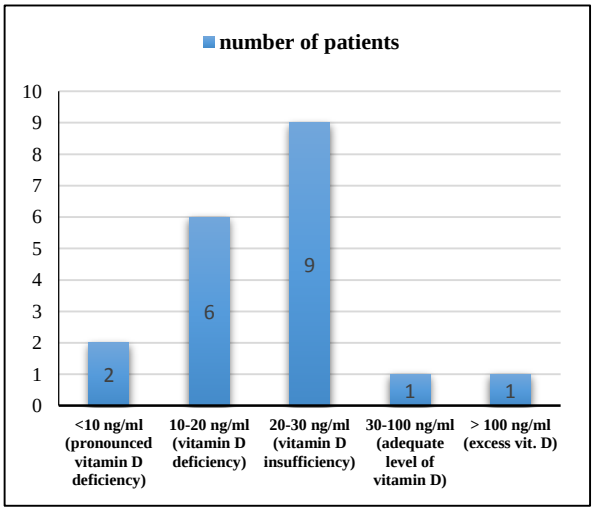

Fig. 5. Vitamin D status in the blood of the studied patients (total 19 patients).

The analysis showed that 15 (79%) of the total number of patients had a deficiency (6 patients - 32%) and insufficiency (9 patients - 47%) of vitamin D in the blood. Two patients (11%) had a (pronounced vitamin D deficiency (<10 ng/ml).

The relationship between the blood levels of vitamin D with the volume of lung damage is presented in Table 1.

Table 1. Vitamin D status in the blood of the studied patients, depending on the degree of lung damage (19 patients in total)

	<10 ng/ml	10-20 ng/ml	20-30 ng/ml	30-100 ng/ml	> 100 ng/ml
No lung damage (2 patients)	0	0	2	0	0
Lung damage up to 10% (7 patients)	0	4	2	0	1
Lung damage up to 30% (1 patient)	0	0	1	0	0
Lung damage up to 50% (3 patients)	0	0	2	1	0
Lung damage is more than 50% (6 patients)	2	2	2	0	0

Table 2. Statistical analysis results.

Number of observatrions	17
degrees of freedom	15
correlation coefficient	-0,581
t-statistic	2,765
p-value	0,014

We employ statistical analysis to examine the relation between the level of vitamin D and the lung damage of the 19 observed patients. Due to possible distortions, we exclude the 2 outliers with the vitamin D level of 100 and 38.6, because they used drugs containing vitamin D for prophylactic purposes long before they became infected with COVID-19. This leaves us with the population of 17 observations.

As both variables are continuous, we utilize the Pearson correlation test. We obtain the Pearson correlation coefficient of -0.581 (negative correlation). The t-statistic of the corresponding two-tailed test is 2.765, with the respective p-value of 0.014. As the p-value is substantially less than 0.05, we can conclude that the correlation is significant (Table2).

One patient had blood levels of vitamin D more than 38.2 ng / ml and only one patient had the vitamin D level > 100 ng/ml. It was noted that patients used drugs containing vitamin D for prophylactic purposes long before they became infected with COVID-19. The remaining 17 patients (89,5 % of total) had blood levels of vitamin D below 30 ng/ml (vitamin D deficiently).

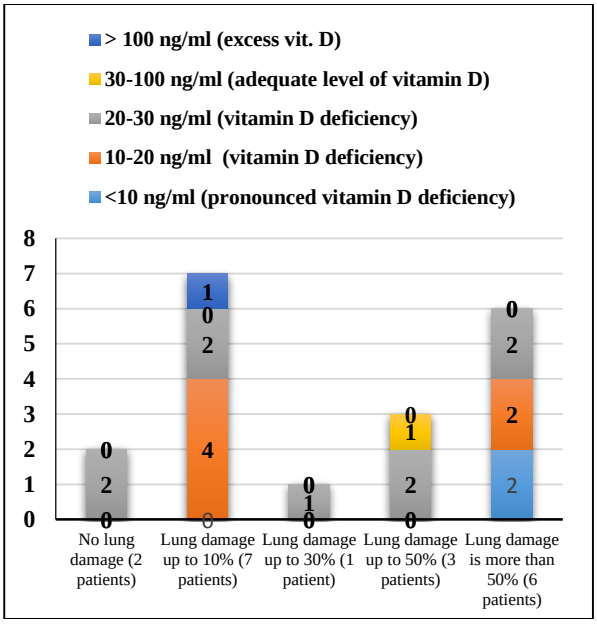

Fig. 6. Vitamin D status in the blood of the studied patients, depending on the degree of lung damage (19 patients in total)

The patients' blood levels of vitamin D with lung damage of more than 50% and, thus, severe clinical course of the disease showed critically low levels: of the six patients in this group, 2 had a pronounced vitamin D deficiency (<10 ng/ml), and another 2 had a vitamin D deficiency (10–20 ng/ml); the remaining 2 patients had blood levels of vitamin D insufficiency (20-30 ng/ml) (Fig. 6).

CONCLUSION

A retrospective analysis of laboratory-confirmed cases of COVID-19 in our study found a relationship between the blood level of 25-hydroxyvitamin D [25 (OH) D and the nature of the course of COVID-19 and the development of complications of the disease. Taking into account the main cause of critical complications of COVID-19 is impaired immunity, the systemic inflammatory response due to the "cytokine storm", and cholecalciferol harmonizes the functioning of the immune system at all its levels, it can be concluded that an adequate level of vitamin D in the blood increases the likelihood of a light course of COVID-19 and its favorable outcome. According to the literature, Vitamin D supplements are recommended for all infected and healthy people.

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Covid-19 xəstələrinin qaninda D vitaminin səviyyəsinin xəstəliyin qedişinə təsiri

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COVID-19 infeksiyasının təhlükəsi onun daha yüksək yoluxdurucu qabiliyyəti olmaqdadır (qripdən bir neçə dəfə yüksək), uzun bir inkubasiya müddəti (14 günə qədər) və heç bir simptomu olmayan xəstələrin infeksiya daşıyıcısı olması ilə əlaqələndirilir. Hal-hazırda, xəstəliyin xüsusiyyətlərinə dair klinik və epidemioloji tədqiqatlar, həmçinin qarşısının alınması və müalicəsi üçün yeni vasitələrin inkişafı davam edir. Ən vacib profilaktik vasitə antiviral immunitet sisteminin aktivləşdirilməsidir. Ədəbiyyat mənbələrinə əsasən, insanın orqanizmində D vitaminin yetərli tərkibi qrip virusuna qarşı da daxil olmaqla antiviral immunitet sisteminin əsaslarından biridir. COVID-19 olan xəstələrdə D vitamini səviyyələri ilə klinik nəticə arasında statistik baxımdan əhəmiyyətli məlumat yoxdur. Bu məqsədlə COVID-19-a yoluxan xəstələrin qanında D vitamini səviyyələrinin xəstəliyin gedişinə və müalicənin nəticələrinə təsirini öyrənmək olmuşdur. Laboratoriya tərəfindən təsdiqlənmiş COVID-19 infeksiyası olan 19 xəstənin xəstəlik tarixlərini təhlil etdik. Xəstələr 15.06.2020 - 15.07.2020 tarixləri arasında «MediClub» MMC-də müalicə alırdılar. «MediClub»

Xəstəxanası, COVIB-19 xəstələrinin müalicəsi üçün «TƏBIB» Azərbaycan tərəfindən təsdiq edilmişdir. 25-hidroksivitamin D[25(OH)D]-nin klinik təzahürləri və qan səviyyələri haqqında məlumatlar xəstəlik tarixlərindən əldə edilmişdir. Laborator təsdiqlənmiş COVID-19 hallarının retrospektiv analizi qanda 25-hidroksivitamin D[25(OH)D] səviyyəsi ilə koronavirus xəstəliyinin gedişatını və xəstəliyin fəsadlarının inkişafı arasındakı əlaqə barədə inamla danışmağa imkan verdi. COVID-19-un kritik ağırlaşmalarının əsas səbəbinin toxunulmazlığın zəifləməsi və xolekalsiferolun immunitet sisteminin işini bütün səviyyələrində uyğunlaşdırması olduğunu nəzərə alsaq, qanda kifayət qədər D vitamini səviyyəsinin COVID-19-un mülayim gedişatını və əlverişli nəticəsini artırdığı qənaətinə gəlmək olar.

Açar sözlər: *Koronavirus infeksiyası, pandemiya, COVID-19, 25-hidroksivitamin D[25(OH)D], D vitamininin qanda səviyyəsi, ağciyər zədələnməsinin həcmi, proinflamatuar sitokinlər, yanaşı xəstəliklər*

Влияние уровня витамина D в крови пациентов с COVID-19 на течение болезни

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Опасность заражения COVID-19 заключается в его более высокой контагиозности (в несколько раз выше, чем у гриппа), длительном инкубационном периоде (до 14 дней) и осложняется тем, что пациенты без каких-либо симптомов являются носителями инфекции. В настоящее время продолжаются клинико-эпидемиологические исследования характеристик заболевания, а также разработка новых средств его профилактики и лечения. Самый важный профилактический ресурс – это активация противовирусной врожденной иммунной системы. Опираясь на литературные данные, остаточное количество витамина D - одна из основ противовирусной иммунной системы, в том числе против вируса гриппа. Клинических испытаний для определения взаимосвязи между уровнем витамина D в крови и клиническим исходом у пациентов с COVID-19 не проводилось. Изучено влияние уровня витамина D в крови пациентов, инфицированных COVID-19, на течение заболевания и исход лечения. Проанализированы истории болезни 19 пациентов с лабораторно подтвержденной инфекцией COVID-19. Пациенты проходили лечение в ООО «MediClub» с 15.06.2020 по 15.07.2020. Госпиталь «MediClub» был одобрен «TABIB»Азербайджан для лечения пациентов с COVID-19. Данные о клинических проявлениях и уровнях гидроксивитамина D[25(OH)D] в крови были получены из историй болезни. Ретроспективный анализ лабораторно подтвержденных случаев COVID-19 позволил с уверенностью говорить о взаимосвязи между уровнем 25-гидроксивитамина D [25(OH)D] в крови, характером течения COVID-19 и развитием осложнений болезни. Учитывая, что основной причиной критических осложнений COVID-19 является нарушение иммунитета, а холекальциферол гармонизирует работу иммунной системы на всех ее уровнях, можно сделать вывод, что адекватный уровень витамина D в крови увеличивает вероятность легкого течения COVID-19 и его благоприятный исход.

Ключевые слова: *Коронавирусная инфекция, пандемия, COVID-19, 25-гидроксивитамин D[25(OH)D], уровень витамина D в крови, объем поражения легких, провоспалительные цитокины, сопутствующие заболевания*