Mood Disorders After COVID-19

Anna G. Mikheeva, Mariya P. Topuzova, Valeriya A. Malko, Ekaterina S. Zhilina, Arina A. Mikhailova, Daria I. Lagutina, Tatiana L. Karonova, Tatyana M. Alekseeva

Almazov National Medical Research Centre, St. Petersburg, Russia

Abstract

Introduction. *The COVID-19 pandemic has led to a high prevalence of post-COVID-19 syndrome (PCS), with mood disorders being the most common manifestations.*
Objective: *To study the prevalence of PCS-associated mood disorders and their features.*
Materials and methods. *We examined patients after COVID-19 (n = 91; age: 24–84 years; median time to recovery: 7 months) using the following tools: the BDI and HADS (screening for anxiety and depression); the Starkstein Apathy Scale; FIS and FSS (fatigue assessment); the MoCA, MMSE, and FAB (cognitive assessment); the FIRST, ESS, PSQI, and ISI (sleep disorders evaluation); the EQ5D (quality of life measurement). We designed a special questionnaire to collect data related to a history of COVID-19 and patients' condition after discharge. In addition, we analyzed electronic medical records and discharge summaries and performed neurological examination.*
Results. *Of all the examined patients, 65 (71.4%) participants had signs and symptoms of PCS. Mood disorders were observed in 33 (50.8%) cases, with apathy (78.7%), anxiety (66.7%), and fatigue (60.6%) being the most common. Depressive disorders were found in 12 (36.3%) patients. Cognitive functions were impaired in 7 (21.2%) patients; sleep disorders were observed in 16 (48.5%) cases. We found a positive correlation between depressive disorders and fatigue based on the BDI, FIS, and FSS scores (r_S = 0.711; r_S = 0.453), depressive disorders and anxiety (r_S = 0.366), fatigue and apathy (r_S = 0.350). Anxiety increased the risk of sleep disorders (r_S = 0.683). Quality of life has been shown to decrease in patients with mood disorders due to the negative effect of long-term fatigue and depressive disorders.*
Conclusions. *There is a close connection between different types of mood disorders that develop after COVID-19 and exacerbate symptoms of each other. Early diagnosis and treatment of these disorders can improve patients' quality of life and preserve their ability to work.*

Keywords: *COVID-19; post-COVID-19 syndrome; depression; apathy; anxiety; fatigue*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of Almazov National Medical Research Centre (protocol No. 0212-22, 26 December 2022).

Source of funding. The study was supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2022-301 dated 20 April 2022).

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For correspondence: 197341, Russia, St. Petersburg, Akkuratova str., 2. Almazov National Medical Research Centre.
E-mail: amikheevag@mail.ru. Mikheeva A.G.

For citation: Mikheeva A.G., Topuzova M.P., Malko V.A., Zhilina E.S., Mikhailova A.A., Lagutina D.I., Karonova T.L., Alekseeva T.M. Mood disorders after COVID-19. *Annals of Clinical and Experimental Neurology.* 2023;17(4):17–27.

DOI: https://doi.org/10.54101/ACEN.2023.4.2

Received 03.09.2022 / Accepted 22.03.2023 / Published 25.12.2023

Аффективные нарушения у пациентов, перенёсших COVID-19

А.Г. Михеева, М.П. Топузова, В.А. Малько, Е.С. Жилина, А.А. Михайлова, Д.И. Лагутина, Т.Л. Каронова, Т.М. Алексеева

ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова», Санкт-Петербург, Россия

Аннотация

Введение. *Пандемия коронавирусной инфекции (COVID-19) привела к высокой распространённости постковидного синдрома (ПКС), частым проявлением которого являются аффективные нарушения.*
Цель *исследования — изучение встречаемости аффективных нарушений в рамках ПКС и их особенностей.*
Материалы и методы. *Обследованы пациенты, перенёсшие COVID-19 (n = 91; возраст 24–84 года; медиана выздоровления — 7 мес). Использовались опросники: BDI, HADS (выявление тревоги и депрессии); шкала апатии Starskein; FIS, FSS (оценка усталости); MoCA, MMSE, FAB (оценка когнитивных функций); FIRST, ESS, PSQI, ISI (выявление нарушений сна); EQ5D (оценка качества жизни (КЖ)). Сбор анамнеза заболевания COVID-19, состояния пациентов после выписки проводили с помощью специально разработанного опросника. Дополнительно анализировали электронные истории болезней, выписные эпикризы, выполняли неврологический осмотр.*
Результаты. *В исследуемой группе 65 (71,4%) пациентов имели признаки постковидного синдрома. Аффективные нарушения встречались в 33 (50,8%) случаях, наиболее частые из них: апатия (78,7%), тревожность (66,7%), усталость (60,6%). Депрессивные расстройства выявлены у 12 (36,3%) пациентов. У 7 (21,2%) пациентов снизились когнитивные функции. В 16 (48,5%) случаях наблюдались расстройства сна. Выявлена прямая взаимосвязь между депрессивными расстройствами и усталостью, согласно данным BDI, FIS и FSS (r_S = 0,711; r_S = 0,453), депрессивными расстройствами*

и тревожностью (r_S = 0,366), усталостью и апатией (r_S = 0,350). Наличие тревожности повышало риск развития сомнологических расстройств (r_S = 0,683). Выявлено, что при наличии аффективных нарушений снижается КЖ вследствие негативного влияния длительно сохраняющейся усталости и развития депрессивных расстройств.

Заключение. *Разные виды аффективных нарушений, развивающихся после перенесённого COVID-19, тесно связаны между собой, усугубляя проявления друг друга. Раннее выявление и лечение таких расстройств позволит улучшить КЖ и сохранить трудоспособность пациентов.*

Ключевые слова: *COVID-19; постковидный синдром; депрессия; апатия; тревожность; усталость*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом ФГБУ НМИЦ им. В.А. Алмазова (протокол № 0212-22 от 26.12.2022).

Источник финансирования. Исследование выполнено при финансовой поддержке Министерства науки и высшего образования Российской Федерации (Соглашение № 075-15-2022-301 от 20.04.2022).

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Адрес для корреспонденции: 197341, Россия, Санкт-Петербург, ул. Аккуратова, д. 2. ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова». E-mail: amikheevag@mail.ru. Михеева А.Г.

Для цитирования: Михеева А.Г., Топузова М.П., Малько В.А., Жилина Е.С., Михайлова А.А., Лагутина Д.И., Каронова Т.Л., Алексеева Т.М. Аффективные нарушения у пациентов, перенесших COVID-19. *Анналы клинической и экспериментальной неврологии*. 2023;17(4):17–27.

DOI: https://doi.org/10.54101/ACEN.2023.4.2

Поступила 03.09.2022 / Принята в печать 23.03.2023 / Опубликована 25.12.2023

Introduction

The COVID-19 pandemic has led to a high prevalence of post-COVID-19 syndrome (PCS) that physicians of various fields currently deal with. This condition has 2 phases: (1) subacute symptomatic phase with symptoms present from 4 to 12 weeks after COVID-19 and (2) chronic phase with symptoms persisting beyond 12 weeks and not attributable to an alternative diagnosis [1–3]. The prevalence of PCS accounts for 10–65% and reaches 85% in patients hospitalized for acute COVID-19 [3, 4].

Neurological disorders can occur during the first days of the disease. A USA study conducted in 2020 included 509 patients hospitalized with COVID-19 and found that 82.3% of the participants had neurological disorders at any time during the disease course. The most common disorders were myalgia, headache, encephalopathy, dizziness, dysgeusia, and anosmia [5]. These symptoms are referred to as neurological manifestations of post-acute sequelae of SARS-CoV-2 infection (neuro-PASC) [6]. The most common neuro-PASC include memory and attention disorders, signs of depression, apathy, sleep disorders, fatigue, myalgia, headache, and dizziness [7–10]. Apart from individual post-COVID-19 neurological symptoms, some patients develop more serious neurological complications during or after COVID-19: stroke, seizures, neuromuscular disorders and demyelinating diseases such as myasthenia gravis and Guillain-Barré syndrome, etc. [11–14].

The pathogenesis of PCS has not been entirely investigated despite its high prevalence [2]. Neurotropism of SARS-CoV-2 is thought to be linked to its high affinity to receptors of angiotensin-converting enzyme 2 (ACE2) that is expressed not only on type II pneumocytes but also in neurons and glial cells [11]. Moreover, binding of SARS-CoV-2 to ACE2 receptors in the vascular endothelium can cause endotheliitis, coagulopathy, arterial and venous thromboses resulting in such complications as ischemic strokes, cerebral venous thrombosis, intracerebral or subarachnoid hemorrhage [15]. Mood disorders are hypothesized to develop during or after COVID-19 because neuropsychological disorders may be caused by GABAergic dysfunction due to COVID-19-associated inflammation [16]. The literature shows that newly developed depression may be triggered by cytokine release, e.g., interleukin-6 (IL-6), during acute COVID-19, and it resolves as cytokines return to normal levels, regardless of antidepressant treatment. This suggests that medications that lower cytokine activity can reduce the odds of mood disorders after COVID-19; however, further research is required to better understand this process [17].

Our objective is to study the prevalence of PCS-associated mood disorders and their features.

Materials and methods

Our study involved 91 patients (38 men and 53 women) aged 24–84 years (mean age: 58.7 years). COVID-19 was confirmed by PCR tests. Seventy-one (78%) COVID-19 patients were admitted to the rehabilitation clinic of Almazov National Medical Research Centre that functioned as an infectious disease hospital in the summer of 2021. The median time to recovery was

7 months. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of Almazov National Medical Research Centre (protocol No. 0212-22, 26 December 2022).

We performed clinical neurological examination in the outpatient setting.

We designed a questionnaire to collect data related to a history of COVID-19 and patients' condition after discharge. This questionnaire includes several sections that assess history of acute COVID-19 and condition after discharge, chronic diseases, vaccination, and pre-existing cognitive, mood, and/or sleep disorders.

Cognitive functions were evaluated by the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Frontal Assessment Battery (FAB). Apathy and depression were assessed by the Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), and Starskein Apathy Scale. Fatigue was measured using the Fatigue Impact Scale (FIS) and Fatigue Severity Scale (FSS). In addition, patients completed questionnaires to detect sleep disorders: the Ford Insomnia Response to Stress Test (FIRST), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Insomnia Severity Index (ISI). The EuroQol 5 Dimensions (EQ5D) questionnaire was used to assess quality of life.

The MoCA and MMSE are one of the most commonly used cognitive assessment tools worldwide [18]. The MoCA contains 10 subtests, and the MMSE is composed of 9 subtests. The maximum score in both scales is 30. A score above 26 is considered normal in the MoCA, while a score above 28 is considered normal in the MMSE. Along with these tools, physicians and researchers often use the FAB because it is sensitive to frontal lobe dysfunction and is easy to administer [19]. It consists of 6 subtests, each scored from 0 to 3. A score above 16 is considered normal.

The BDI is a 21-item self-reported questionnaire. Each item is scored on a scale value of 0-3 (maximum total score: 63) [20]. The results are interpreted as follows: 0–9 for no depression, 10–15 for mild depression (minor depression), 16–19 for moderate depression, 20–29 for moderate-to-severe depression, and 30–63 for severe depression [21].

The HADS consists of 2 subscales and detects anxiety and depression. Each subscale includes 7 questions, each scored from 0 to 3. A score of 0–7 indicates no anxiety/depression, a score of 8–10 represents subclinical anxiety/depression, and a score of 11 or above is considered clinically significant anxiety/depression [22].

The Starkstein Apathy Scale includes 14 questions, each scored from 0 to 3. A score of 14 or above indicates clinically significant apathy [23].

The FIS is a 40-item scale that measures the impact of fatigue on patient's quality of life. Each item is scored from 0 to 4 (0: never, 1: once or twice, 2: sometimes, 3: often, 4: every day or almost every day). All statements are divided into 3 subscales: cognitive, physical, and psychosocial (maximum total score of each subscale: 40). An overall score is calculated separately and ranges from 0 to 160. There are no cutoff scores for subscales or the scale as a whole. A higher score indicates greater impact of fatigue on quality of life [24].

The FSS includes 9 statements, each scored on a 7-point scale, from 1 = strongly disagree to 7 = strongly agree. The total score is reported as the mean score of the 9 items. The FSS measures the severity of the patient's fatigue over the past week. The mean score above 4 indicates fatigue [25].

The FIRST includes 9 items asking about the likelihood of sleep disruption due to specific situations. The responses and corresponding scores are as follows: 1 = not likely, 2 = somewhat likely, 3 = moderately likely, and 4 = very likely. The total score ranges from 9 to 36. A higher score indicates a higher likelihood of sleep disruption [26].

The ESS asks patients to rate their likelihood of falling asleep during the day in 8 different situations. Each item is scored on a scale of 0 to 3. The maximum total score is 24. A score above 10 indicates excessive daytime sleepiness [27].

The PSQI is a standardized self-reported questionnaire that assesses sleep quality over the past month. It contains 7 components: sleep duration, disturbances, latency, habitual sleep efficiency, use of sleeping medications, daytime dysfunction due to sleepiness, and overall sleep quality. Each component is scored from 0 to 3, where 0 means no difficulty and 3 means severe difficulty. The maximum total score is 21. A score above 5 indicates sleep disturbances [26].

The ISI is a 7-item self-reported questionnaire that assesses nighttime and daytime components of insomnia. Responses are scored from 0 to 4, where 0 means no problem and 4 means a very severe problem. The maximum total score is 28. The results are interpreted as follows: 0–7 for absence of insomnia, 8–14 for subclinical insomnia, 15–21 for moderate insomnia, and 22–28 for severe insomnia [28].

The EQ5D consists of 6 components: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and comparison of the current health with

that a year ago. Each component is scored from 1 to 3. A higher score indicates more severe problems. A score of 6 means no problems, a score of 7–12 indicates moderate problems, and a score of 13 or above means severe problems [29].

To collect complete and accurate data on a history of acute COVID-19, we analyzed electronic medical records stored in the QMS database (patients treated in the rehabilitation clinic) and discharge summaries (patients hospitalized in other clinics). We performed neurological examination to assess the neurological status.

During appointments blood samples were taken, and blood serum and plasma were further stored in a biobank.

Statistical analysis was performed using IBM SPSS Statistics 23.0. We used the descriptive statistics, *t* test, Spearman's rank correlation coefficient, linear regression, and odds ratios.

All patients were grouped based on diagnosed disorders. The control group included 26 (28.6%) participants without complaints and objectively diagnosed neurological disorders during the study. Mood disorders were diagnosed in 33 (36.3%) patients. Cognitive disorders during COVID-19 were found in 19 (20.9%) participants. Seven patients had both mood and cognitive disorders. Sleep disorders were observed in 19 (20.9%) participants. During the study, we discovered that 7 patients (7.7%) had the onset of peripheral nervous system diseases after COVID-19; stroke during COVID-19 developed in 3 (3.3%) patients; 3 (3.3%) participants had onset of demyelinating diseases (2 cases of multiple sclerosis and 1 case of acute disseminated encephalomyelitis); onset of the neuromuscular disorder (myasthenia) was reported in 1 (1.1%) patient, and 2 (2.2%) participants presented with persistent anosmia. Patients that experienced onset of neurological disorders during COVID-19 were included only in one group of patients with the corresponding nosology and could not be included in other groups.

This article analyzes data of patients with mood disorders ($n = 33$).

Results

Patient characteristics and features of acute COVID-19 are presented in Tables 1–3.

Table 1. Characteristics of patients from the control and study groups, *n* (%)

Parameter	Control group (*n* = 26)	Patients with mood disorders (*n* = 33)
Sex:		
male	14	10
female	12	23
Mean age, years	60,5 ± 14,1	53,0 ± 14,3
Vaccination:		
no	15	27
before COVID-19	2	4
after COVID-19	9	2
Disease severity:		
mild	5	3
moderate	17	20
severe	4	9
Time after recovery (median), months	7	7
Acute COVID-19 treatment:		
antiviral agents	0 (0%)	2 (6%)
oxygen therapy	19 (73%)	23 (69,7%)
glucocorticoids	18 (69,2%)	23 (69,7%)
Janus kinase inhibitors	3 (11,5%)	11 (33,3%)
monoclonal antibodies	2 (7,6%)	0 (0%)
IL-6 inhibitors	3 (11,5%)	9 (27,3%)
Intensive care unit treatment	1	4

Table 2. Features of the COVID-19 course: symptoms during acute COVID-19, *n* (%)

Symptoms	Control group (*n* = 26)	Patients with mood disorders (*n* = 33)
Fever	21 (80,8%)	32 (97%)
Fatigue	23 (88,4%)	30 (90,9%)
Cough	15 (57,7%)	23 (69,6%)
Dyspnea	19 (73,1%)	21 (63,6%)
Reduced appetite	13 (50%)	22 (66,6%)
Sweating	17 (65,3%)	20 (60,6%)
Chest pain	6 (23,1%)	11 (33,3%)
Rhinitis	5 (19,2%)	7 (21,2%)

Table 3. Features of the COVID-19 course: neurological and somatic symptoms during acute COVID-19 and at the time of examination, *n* (%)

Disorders	Control group (*n* = 26)		Patients with mood disorders (*n* = 33)	
	during COVID-19	at the time of examination	during COVID-19	at the time of examination
Memory impairment (subjective)	8 (30,8%)	7 (26,9%)	16 (48,5%)	15 (45,4%)
Sleep disorder	13 (50%)	6 (23,1%)	24 (72,7%)	18 (54,5%)
Anxiety and depression (subjective)	6 (23,1%)	3 (11,5%)	18 (54,5%)	18 (54,5%)
Headache	10 (38,5%)	5 (19,2%)	15 (45,4%)	5 (15,1%)
Muscle weakness	9 (34,6%)	4 (15,4%)	14 (42,4%)	8 (24,2%)
Back and limb pain	5 (19,2%)	1 (3,8%)	11 (33,3%)	11 (33,3%)
Muscle pain	4 (15,4%)	0 (0%)	11 (33,3%)	3 (9,1%)
Anosmia	13 (50%)	0 (0%)	22 (66,6%)	4 (12,1%)
Ageusia	11 (42,3%)	0 (0%)	19 (57,6%)	3 (9,1%)

Among the participants with mood disorders, depressive disorders and apathy were objectively diagnosed in 12 (36.3%) and 26 (78.7%) patients, respectively. Anxiety was observed in 22 (66.7%) participants, of which 13 (59.1%) and 9 (40.9%) patients had subclinical and clinically significant anxiety, respectively. Fatigue was objectively diagnosed in 20 (60.6%) patients. Signs of mood disorders developed in the study group despite more frequent use of preemptive therapy. This category of patients was prescribed Janus kinase inhibitors 2.9 times more often than the controls (33.3% vs 11.5%, respectively), and IL-6 inhibitors were prescribed 2.4 times more often compared with the control group (27.3% vs 11.5%, respectively). Prescription rates of antiviral agents, oxygen therapy, glucocorticoids, and monoclonal antibodies were almost similar(see percentages in Table 1). We calculated odds ratios for mood disorders development, depending on different symptoms of acute COVID-19. Thus, sleep disorders during the acute phase increased the risk of mood disorders by 2.7 times, the risk of anxiety and depression (subjective) by 2.8 times, the risk of hyposmia or anosmia by 2 times, and the risk of hypogeusia or ageusia by 1.8 times.

Table 4. Results of mood disorders assessment in the examined groups, scores ($M \pm \sigma$)

Screening tool	Control group (n = 26)	Patients with mood disorders (n = 33)	p
BDI	3,885 ± 3,410	10,545 ± 7,268	< 0,001
Starskein Apathy Scale	6,077 ± 4,335	15,909 ± 6,090	< 0,001
HADS (anxiety)	3,962 ± 2,584	8,788 ± 3,959	< 0,001
FIS	36,077 ± 21,779	61,848 ± 29,416	< 0,001
FSS	3,341 ± 1,688	4,278 ± 1,409	0,027

Table 5. Cognitive assessment results in the examined patients, scores ($M \pm \sigma$)

Screening tool	Control group (n = 26)	Patients with mood disorders (n = 26)	Patients with mood and cognitive disorders (n = 7)
MMSE	29,1 ± 1,1	29,5 ± 1,0	27,1 ± 0,9
MoCA	27,6 ± 1,2	28,1 ± 1,3	25,6 ± 2,0
FAB	17,7 ± 0,6	17,6 ± 0,8	17,1 ± 1,2

Table 6. Mean scores for sleep disorders assessment, scores ($M \pm \sigma$)

Screening tool	Control group (n = 26)	Patients with mood disorders (n = 33)	p
FIRST	14,235 ± 3,133	18,167 ± 6,418	0,014
ESS	5,364 ± 3,831	4,962 ± 3,572	–
PSQI	9,118 ± 8,298	14,333 ± 7,883	–
ISI	2,647 ± 2,448	10,625 ± 6,439	< 0,001

It is worth noting that the patients from the study group did not retrospectively report mood disorders before COVID-19. Mean scale scores of the patients from the study and control groups are given in Table 4.

Seven (21.2%) patients were found to have both mood disorders and decreased cognitive functions. Table 5 shows mean cognitive assessment scores in the patients with only mood disorders, those with both cognitive and mood disorders, and the controls. Comparison of cognitive assessment results revealed no significant differences between the patients with mood disorders and the control group.

In addition, the patients were given sleep disorders questionnaires. Among the patients with mood disorders, sleep disorders were observed in 48.5% of cases (16 of 33 patients): of them, 87.5% of the cases (14 patients) were insomnias, and 12.5% of the cases (2 patients) were parasomnias. It should be noted that 56.2% of the patients (9 of 16) retrospectively reported sleep disorders before COVID-19. Our findings are presented in Table 6.

During the data analysis, we found a positive correlation between the BDI, FSS, and FIS scores:

1) BDI and FIS (psychosocial subscale) — high ($r_s = 0.724$; $p < 0.001$);
2) BDI and FIS (cognitive subscale) — moderate ($r_s = 0.544$; $p < 0.001$);
3) BDI and FIS (overall score) — high ($r_s = 0.711$; $p < 0.001$);
4) BDI and FSS — moderate ($r_s = 0.453$; $p = 0.008$).

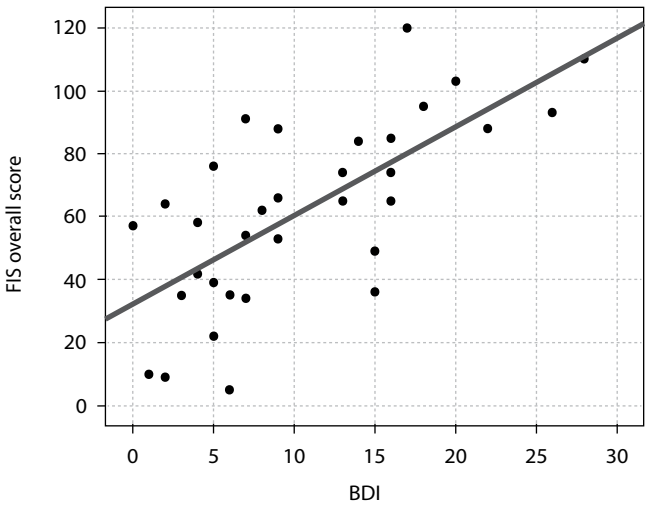

Fig. 1. Correlation of the impact of overall fatigue on quality of life (FIS overall score) and the depression severity (BDI).

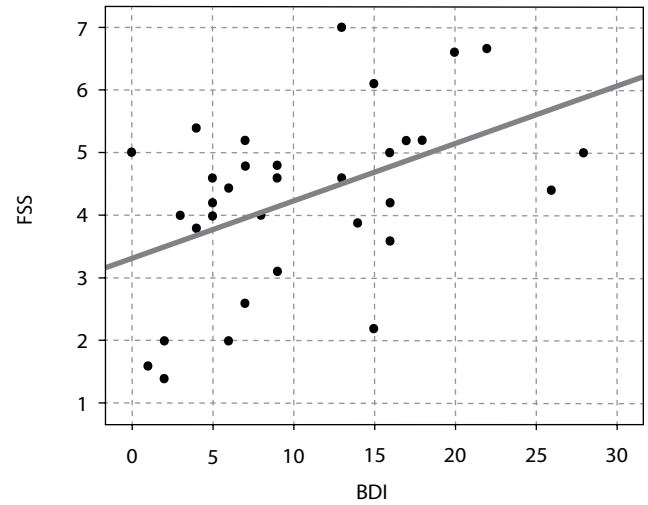

Fig. 2. Correlation of the fatigue severity (FSS score) and the depression severity (BDI score).

We conducted a regression analysis and derived simple linear regression equations for the FIS and FSS scores:
1) Y (FIS overall score) = 2.817 × *x*(BDI) + 32.145;
2) Y (FSS) = 0.091 × *x*(BDI) + 3.324.

Thus, when the BDI score increases by 1, the FIS overall score and the FSS score are expected to increase by 2.817 (Fig. 1) and 0.091 (Fig. 2), respectively, i.e., depressive disorders and fatigue correlate. Patients with higher fatigue levels have more severe depression and vice versa.

The group of patients with anxiety and depression during acute COVID-19 had a significantly higher BDI score at the time of examination (13.3 ± 7.6 and 7.2 ± 5.3; $p = 0.011$).

We found a medium positive correlation between the Starskein Apathy Scale score and the FIS overall score, as well as the FIS psychosocial subscale score ($r_s = 0.350$, $p = 0.046$; $r_s = 0.394$, $p = 0.023$). We conducted a regression analysis and derived a simple linear regression equation:

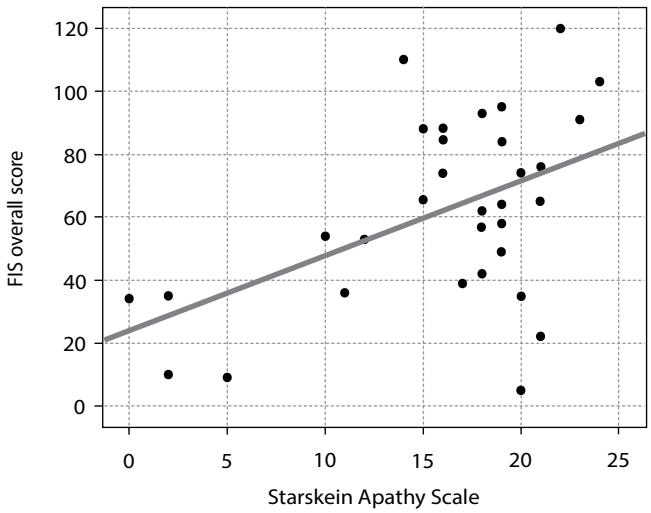

Fig. 3. Correlation of the impact of overall fatigue on quality of life and the apathy severity.

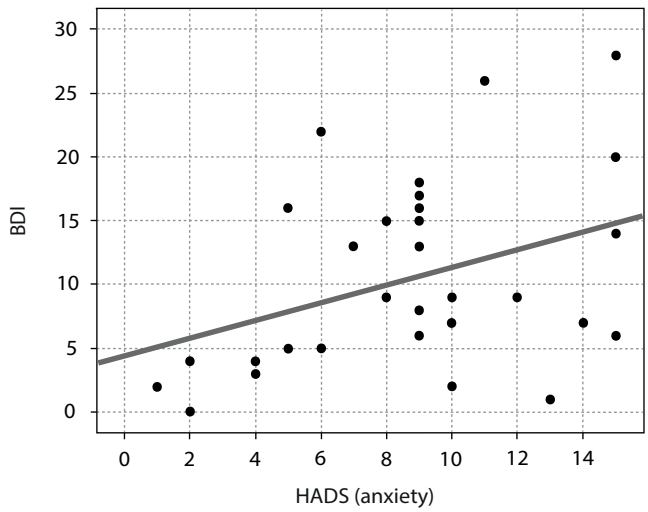

Fig. 4. Correlation of the depression and anxiety severity.

Y (FIS overall score) = 2.356 × *x*(Starskein) + 24.224.

Thus, when the Starskein Apathy Scale score increases by 1, the FIS overall score is expected to increase by 2.365 (Fig. 3), i.e., the impact of fatigue on patients' usual activities increases as apathy becomes more severe, indicating that apathy has a direct negative impact on the fatigue level and quality of life.

We found that based on the HADS (anxiety) and BDI scores, anxiety and depressive disorders have a direct correlation and negatively impact each other ($r_s = 0.366$; $p = 0.036$). Anxiety increased the risk of sleep disorders:

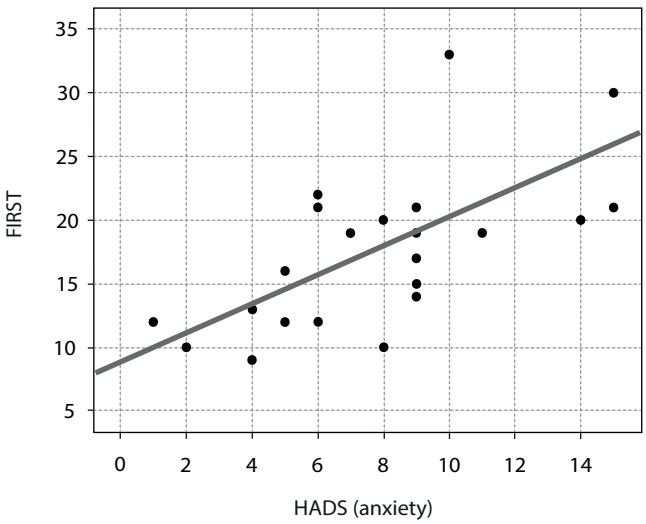

Fig. 5. Relationship between the likelihood of sleep disturbances and anxiety.

there was a significant positive correlation between the HADS (anxiety) and FIRST scores (r_s = 0.683; p = 0.001). However, we found no correlation between depressive disorders and apathy.

After the regression analysis we derived simple linear regression equations for the BDI and FIRST scores:
1. Y (BDI) = 0.686 × x(HADS [anxiety]) + 4.521;
2. Y (FIRST) = 1.143 × x(HADS [anxiety]) + 8.831.

Thus, when the HADS (anxiety) score increases by 1, the BDI score and the FIRST score increase by 0.686 (Fig. 4) and 1.143 (Fig. 5), respectively, i.e., anxiety increases the severity of depressive and sleep disorders, with sleep being affected to a greater extent.

The anxiety severity (based on the HADS [anxiety] score) had no correlation with the impact of fatigue on quality of life (FIS overall score).

In the analyzed group, the severity of depressive disorders, anxiety, and apathy did not depend on sex, age, COVID-19 severity, vaccination, treatment, and cognitive functions. Quality of life decreased both in the patients with mood disorders and the controls (based on the EQ5D score); however, the decline was more significant in the patients with mood disorders (Table 7).

We found a medium positive correlation between the EQ5D and FIS scores (r_s = 0.440; p = 0.01), FSS (r_s = 0.362; p = 0.039). Moreover, there was a medium positive correlation between the EQ5D and BDI scores (r_s = 0.369; p = 0.035). Thus, fatigue and signs of depression negatively impact quality of life in patients with mood disorders.

We found that decline in quality of life did not depend on sex, age, COVID-19 severity, time after recovery, and vaccination in any group.

Discussion

Mood disorders are relatively common PCS manifestations. Huang et al. found that 6 months after recovery, 23% (367 of 1617) of patients reported anxiety or depression [30]. Chen et al. demonstrated that 3 months after recovery, the prevalence of depression and anxiety among 898 patients was 21% and 16.4%, respectively [31]. Our findings show that 36.2% of the patients (33 of 91) developed mood disorders after COVID-19.

Post-COVID-19 fatigue was found to affect up to 65% of patients, with its level correlating with anxiety (HADS score) [10]. Among the examined patients, fatigue was objectively diagnosed in 60.6% of the cases, which is consistent with the literature data. Our correlations, on the other hand, differed slightly: fatigue, depression, and apathy exacerbate symptoms of each other. Nevertheless, we found no statistically significant correlation between fatigue and anxiety.

Table 7. Quality of life assessment in the examined groups, scores (M ± σ)

EQ5D score	Control group (n = 26)	Patients with mood disorders (n = 33)	p
Mobility	1,303 ± 0,467	1,154 ± 0,368	–
Self-care	1,091 ± 0,292	1,038 ± 0,196	–
Usual activities	1,455 ± 0,506	1,154 ± 0,368	0,01
Pain/discomfort	1,697 ± 0,637	1,346 ± 0,485	0,02
Anxiety/depression	1,818 ± 0,584	1,115 ± 0,326	< 0,001
Health comparison	2,545 ± 0,564	2,5 ± 0,51	–
Total score	9,879 ± 1,746	8,308 ± 1,32	< 0,001

Apathy during acute COVID-19 affects up to 92% of patients [32]. This disorder also demonstrates a high prevalence after COVID-19. Calabria et al. assessed apathy after COVID-19 and compared their findings to retrospective self-reported data. The study included 136 COVID-19 patients. The number of patients reporting apathy increased from 23 (16.9%) before COVID-19 to 85 (62.5%) after COVID-19 [33]. Our findings revealed that apathy was reported in 28.6% of the cases (26 of 91 patients) and was the most common mood disorder. The study group included patients without preexisting disorders according to the retrospective self-reported data.

Neuroinflammation and increased cytokine levels are said to be key mechanisms underlying mood disorders during COVID-19 [16, 17]. However, we discovered that these disorders developed in the study group despite more frequent use of preemptive therapy, including IL-6 inhibitors. Cytokine levels might have decreased due to conservative therapy but did not return to the normal range, thus, leading to symptoms of depression, anxiety, and apathy. It is important to note that such medications as Janus kinase inhibitors, IL-6 inhibitors, and monoclonal antibodies, are often prescribed in case of severe deterioration of the general condition that definitely affect person's mood. To make our findings objective, we plan to measure blood serum levels of IL-6 at the first appointment and at 6 months.

The severity of mood disorders is expected to gradually decrease over time. Huang et al. investigated the prevalence of anxiety and depression among 511 patients at 6 and 12 months after COVID-19. The prevalence of anxiety decreased from 13.31% (at 6 months) to 6.26% (at 12 months), whereas the prevalence of depression decreased from 20.35% to 11.94% [34]. We observed a slightly higher prevalence of anxiety 7 months after COVID-19 and a lower prevalence of depressive disorders: 24.1% (22 of 91 patients) and 13.1% (12 of 91 patients), respectively. To assess changes in mood disorders over time, the repeated appointment is scheduled 6 months after the first appointment.

Ortelli et al. showed a direct correlation between apathy and depression [16]; however, we found no such correlation.

Conclusion

Of 91 examined patients, 65 (71.4%) had PCS. Mood disorders occurred in 33 (50.8%) patients, with apathy (26 patients, 78.7%) and anxiety (22 patients, 66.7%) being the most common. Depression was less common: 12 (36.3%) cases.

Risk factors for mood disorders as PCS manifestations include sleep disorders, anxiety and depression, hyposmia and anosmia, hypogeusia and ageusia during acute COVID-19. The fatigue level correlates with the seve rity of depressive disorders and apathy. In the patients from the study group, the anxiety severity had a direct correlation with the depression severity. Patients with anxiety had an increased risk of sleep disorders. The severity of depressive disorders and fatigue negatively impacted patients' quality of life. We should also note that the patients did not report any mood disorders before COVID-19.

Due to the high prevalence of mood disorders among PCS manifestations and their impact on quality of life, these disorders should be diagnosed and treated early on, involving psychiatrists and sleep physicians if needed.

Список источников / References

1. Szekanecz Z., Vályi-Nagy I. Post-acute COVID-19 syndrome. *Orv. Hetil.* 2021;162(27):1067–1078. DOI: 10.1556/650.2021.32282
2. Dixit N.M., Churchill A., Nsair A., Hsu J.J. Post-acute COVID-19 syndrome and the cardiovascular system: what is known? *Am. Heart J. Plus.* 2021;5:100025. DOI: 10.1016/j.ahjo.2021.100025
3. Carod-Artal F.J. Post-COVID-19 syndrome: epidemiology, diagnostic criteria and pathogenic mechanisms involved. *Rev. Neurol.* 2021;72(11):384–396. DOI: 10.33588/rn.7211.2021230
4. Pavli A., Theodoridou M., Maltezou H.C. Post-COVID syndrome: incidence, clinical spectrum, and challenges for primary healthcare professionals. *Arch. Med. Res.* 2021;52(6):575–581. DOI: 10.1016/j.arcmed.2021.03.010
5. Liotta E.M., Batra A., Clark J.R. et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. *Ann. Clin. Transl. Neurol.* 2020;7(11):2221–2230. DOI: 10.1002/acn3.51210
6. Moghimi N., Di Napoli M., Biller J. et al. The neurological manifestations of post-acute sequelae of SARS-CoV-2 infection. *Curr. Neurol. Neurosci. Rep.* 2021;21(9):44. DOI: 10.1007/s11910-021-01130-1
7. Anaya J.M., Rojas M., Salinas M.L. et al. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun. Rev.* 2021;20(11):102947. DOI: 10.1016/j.autrev.2021.102947
8. Nalbandian A., Sehgal K., Gupta A. et al. Post-acute COVID-19 syndrome. *Nat. Med.* 2021;27(4):601–615. DOI: 10.1038/s41591-021-01283-z
9. Schilling C., Meyer-Lindenberg A., Schweiger J.I. Cognitive disorders and sleep disturbances in long COVID. *Nervenarzt.* 2022;16:1–8. DOI: 10.1007/s00115-022-01297-z
10. Sperling S., Fløe A., Leth S. et al. Fatigue is a major symptom at COVID-19 hospitalization follow-up. *J. Clin. Med.* 2022;11(9):2411. DOI: 10.3390/jcm11092411
11. Camargo-Martínez W., Lozada-Martínez I., Escobar-Collazos A. et al. Post-COVID-19 neurological syndrome: implications for sequelae's treatment. *J. Clin. Neurosci.* 2021;88:219-225. DOI: 10.1016/j.jocn.2021.04.001
12. Mao L., Jin H., Wang M. et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683–690. DOI: 10.1001/jamaneurol.2020.1127
13. Siegler J.E., Cardona P., Arenillas J.F. et al. Cerebrovascular events and outcomes in hospitalized patients with COVID-19: the SVIN COVID-19 Multinational Registry. *Int. J. Stroke.* 2021;16(4):437–447. DOI: 10.1177/1747493020959216
14. Harapan B.N., Yoo H.J. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). *J. Neurol.* 2021;268(9):3059–3071. DOI: 10.1007/s00415-021-10406-y
15. Román G.C., Spencer P.S., Reis J. et al. The neurology of COVID-19 revisited: a proposal from the Environmental Neurology Specialty Group of the World

Federation of Neurology to implement international neurological registries. *J. Neurol. Sci.* 2020;414:116884. DOI: 10.1016/j.jns.2020.116884
16. Ortelli P., Ferrazzoli D., Sebastianelli L. et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J. Neurol. Sci.* 2021;420:117271. DOI: 10.1016/j.jns.2020.117271
17. Alpert O., Begun L., Garren P., Solhkhah R. Cytokine storm induced new onset depression in patients with COVID-19. A new look into the association between depression and cytokines -two case reports. *Brain Behav. Immun. Health.* 2020;9:100173.
DOI: 10.1016/j.bbih.2020.100173
18. Ciesielska N., Sokołowski R., Mazur E. et al. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatr. Pol.* 2016;50(5):1039–1052.
DOI: 10.12740/PP/45368
19. Hurtado-Pomares M., Carmen Terol-Cantero M., Sánchez-Pérez A. et al. The frontal assessment battery in clinical practice: a systematic review. *Int. J. Geriatr. Psychiatry.* 2018;33(2):237–251.
DOI: 10.1002/gps.4751
20. Jackson-Koku G. Beck depression inventory. *Occup. Med. (Lond).* 2016;66(2):174–175. DOI: 10.1093/occmed/kqv087
21. Тарабрина Н.В. Опросник депрессивности Бека (Beck Depression Inventory — BDI). В кн.: Тарабрина Н.В. «Практикум по психологии посттравматического стресса». СПб.; 2001:182–183. Tarabrina N.V. Beck Depression Inventory — BDI. In: Tarabrina N.V. Handbook on psychology of post-traumatic stress. St. Petersburg; 2001:182–183.
22. Snaith R.P. The Hospital Anxiety and Depression Scale. *Health Qual. Life Outcomes.* 2003;1:29. DOI: 10.1186/1477-7525-1-29
23. Garofalo E., Iavarone A., Chieffi S. et al. Italian version of the Starkstein Apathy Scale (SAS-I) and a shortened version (SAS-6) to assess "pure apathy" symptoms: normative study on 392 individuals. *Neurol. Sci.* 2021;42(3):1065–1072. DOI: 10.1007/s10072-020-04631-y
24. Lundgren-Nilsson Å., Tennant A., Jakobsson S. et al. Validation of Fatigue Impact Scale with various item sets — a Rasch analysis. *Disabil. Rehabil.* 2019;41(7):840–846. DOI: 10.1080/09638288.2017.1411983
25. Ozyemisci-Taskiran O., Batur E.B., Yuksel S. et al. Validity and reliability of fatigue severity scale in stroke. *Top Stroke Rehabil.* 2019;26(2):122–127.
DOI: 10.1080/10749357.2018.1550957
26. Gelaye B., Zhong Q.Y., Barrios Y.V. et al. Psychometric evaluation of the Ford Insomnia Response to Stress Test (FIRST) in early pregnancy. *J. Clin. Sleep Med.* 2016;12(4):579–587. DOI: 10.5664/jcsm.5696
27. Lee J.L., Chung Y., Waters E., Vedam H. The Epworth sleepiness scale: reliably unreliable in a sleep clinic population. *J. Sleep Res.* 2020;29(5):e13019.
DOI: 10.1111/jsr.13019
28. Morin C.M., Belleville G., Bélanger L., Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* 2011;34(5):601–608. DOI: 10.1093/sleep/34.5.601
29. Liu T.H., Ho A.D., Hsu Y.T., Hsu C.C. Validation of the EQ-5D in Taiwan using item response theory. *BMC Public Health.* 2021;21(1):2305.
DOI: 10.1186/s12889-021-12334-y
30. Huang C., Huang L., Wang Y. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397(10270):220–232. DOI: 10.1016/S0140-6736(20)32656-8
31. Chen Y., Huang X., Zhang C. et al. Prevalence and predictors of posttraumatic stress disorder, depression and anxiety among hospitalized patients with coronavirus disease 2019 in China. *BMC Psychiatry.* 2021;21(1):80.
DOI: 10.1186/s12888-021-03076-7
32. Абрамов В.Г., Гайгольник Т.В., Фетисов А.О. и соавт. COVID-19: Внелёгочные проявления у пациентов (собственные данные инфекционного госпиталя ФГБУ ФСНКЦ ФМБА России). *Медицина экстремальных ситуаций.* 2020;(3):19–25. Abramov V.G., Gaygolnik T.V., Fetisov A.O. et al. COVID-19: extrapulmonary impairments (own data of infection hospital of FSBI FSSCC FMBA of Russia) and experience of use different profile specialists to working in hospitals. *Medicine of extreme situations.* 2020;3(22):19–25.
DOI: 10.47183/mes.2020.013
33. Calabria M., García-Sánchez C., Grunden N. et al. Post-COVID-19 fatigue: the contribution of cognitive and neuropsychiatric symptoms. *J. Neurol.* 2022;269(8):3990–3999. DOI: 10.1007/s00415-022-11141-8
34. Huang X., Liu L., Eli B. et al. Mental health of COVID-19 survivors at 6 and 12 months postdiagnosis: a cohort study. *Front. Psychiatry.* 2022;13:863698.
DOI: 10.3389/fpsyt.2022.863698

Information about the authors

Anna G. Mikheeva — postgraduate student, Department of neurology with the clinic, Medical Education Institute, laboratory assistant-researcher, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0002-1478-6580
Mariya P. Topuzova — Cand. Sci. (Med.), Associate Professor, Department of neurology with the clinic, Medical Education Institute, senior researcher, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0002-0175-3085
Valeriya A. Malko — postgraduate student, Department of neurology with the clinic, Medical Education Institute, junior researcher, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0000-0003-2230-3750
Ekaterina S. Zhilina — resident, Department of neurology with the clinic, Medical Education Institute, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0002-9020-3287
Arina A. Mikhailova — laboratory research assistant, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, resident, Department of endocrinology, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0001-6066-3525
Daria I. Lagutina — laboratory research assistant, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, resident, Department of endocrinology, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0001-6198-5278
Tatiana L. Karonova — D. Sci. (Med.), Head, Research laboratory of new coronavirus infection and postcovid syndrome, Center for Personalized Medicine, chief researcher, Clinical endocrinology laboratory, professor, Department of internal medicine, V.A. Almazov Federal National Medical Research Centre, St. Petersburg, Russia,
https://orcid.org/0000-0002-1547-0123
Tatyana M. Alekseeva — D. Sci. (Med.), Head, Department of neurology with the clinic, Medical Education Institute, V.A. Almazov Federal National Medical Research Centre,
https://orcid.org/0000-0002-4441-1165

Author contribution. *Mikheeva A.G.* — concept and design of the study, conduct of the study, data curation, data analysis, text writing; *Topuzova M.P.* — concept and design of the study, research management, text writing and editing; *Malko V.A.* — data curation, data analysis; *Zhilina E.S.* — data curation, data analysis; *Mikhailova A.A., Lagutina D.I.* — data curation; *Karonova T.L.* — concept and design of the study, research management; *Alekseeva T.M.* — concept and design of the study, research management, text editing.

Информация об авторах

Михеева Анна Геннадьевна — аспирант каф. неврологии с клиникой Института медицинского образования, лаборант-исследователь НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины» ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия, https://orcid.org/0000-0002-1478-6580
Топузова Мария Петровна — к.м.н., доцент каф. неврологии с клиникой Института медицинского образования, старший научный сотрудник НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины» ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия,
https://orcid.org/0000-0002-0175-3085
Малько Валерия Алексеевна — аспирант каф. неврологии с клиникой Института медицинского образования, м.н.с. НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины» ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия, https://orcid.org/0000-0003-2230-3750
Жилина Екатерина Сергеевна — ординатор каф. неврологии с клиникой Института медицинского образования ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия, https://orcid.org/0000-0002-9020-3287
Михайлова Арина Алексеевна — лаборант-исследователь НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины», ординатор каф. эндокринологии ИМО ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия,
https://orcid.org/0000-0001-6066-3525
Лагутина Дарья Ивановна — лаборант-исследователь НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины», ординатор каф. эндокринологии ИМО ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия,
https://orcid.org/0000-0001-6198-5278
Каронова Татьяна Леонидовна — д.м.н., зав. НИЛ новой коронавирусной инфекции и постковидного синдрома НЦМУ «Центр персонализированной медицины», г.н.с. НИЛ клинической эндокринологии Института эндокринологии, профессор каф. эндокринологии ИМО ФГБУ Национальный медицинский исследовательский центр им. В.А. Алмазова», Санкт-Петербург, Россия, https://orcid.org/0000-0002-1547-0123
Алексеева Татьяна Михайловна — д.м.н., зав. каф. неврологии с клиникой Института медицинского образования ФГБУ «НМИЦ им. В.А. Алмазова», Санкт-Петербург, Россия, https://orcid.org/0000-0002-4441-1165

Вклад авторов. *Михеева А.Г.* — создание концепции и дизайна исследования, проведение исследования, курирование данных, анализ данных, написание текста; *Топузова М.П.* — создание концепции и дизайна исследования, руководство научно-исследовательской работой, написание и редактирование текста; *Малько В.А.* — проведение исследования, курирование данных; *Жилина Е.С.* — проведение исследования, курирование данных; А.А. Михайлова, Д.И. Лагутина — проведение исследования; *Т.Л. Каронова* — создание концепции и дизайна исследования, руководство научно-исследовательской работой; *Алексеева Т.М.* — создание концепции и дизайна исследования, руководство научно-исследовательской работой, редактирование текста.