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Mental Disorders Among Hospitalized Patients With Covid-19 In Moscow, Russia: A Prospective Cohort Study

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Abstract

We assessed the prevalence of mental disorders in hospitalized patients with the coronavirus disease 2019 (COVID-19) in the Coronavirus Infection Treatment Units nos. 1-4 at Sechenov University (Moscow, Russia). In the first group (n=440), all patients were observed by trained psychiatrists using the Mini-Mental State Examination, Delirium Rating Scale-R-98, Patient Health Questionnaire, General Anxiety Disorder-7, and the Insomnia Severity Index. In the second group (n=455), only patients with identified signs of mental disorders were examined. In total, 237 (53.9%) and 110 (24.2%) patients in the first and second groups showed signs of mental illness, respectively: delirium, 122 (27.8%) and 81 (17.8%); anxiety, 108 (24.5%) and 22 (4.8%); depression, 54 (12.3%) and 6 (1.3%); mild cognitive impairment, 78 (17.8%) and 13 (2, 9%); dementia, 68 (15.5%), and 39 (8.6%) patients, respectively. The prevalence of mental illness among hospitalized patients with COVID-19 is significantly higher than that detected by non-psychiatric clinicians.

Keywords: *COVID-19, mental health, delirium, anxiety, depression.*

Introduction

The impact of the coronavirus disease 2019 (COVID-19) on mental health has attracted the attention of specialists si[1]nce the beginning of the pandemic. The effect of the disease itself, its complications, the methods of therapy used, and psychosocial factors associated with isolation, quarantine measures, social and economic problems, and so on are being studied. It has been shown that the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), in combination with its associated clinical manifestations, can also cause neuropsychiatric symptoms. The neurological manifestations include hyposmia or anosmia, dysgeusia, headache, dizziness, and myalgia. Meanwhile, the neurological complications of COVID-19 include acute cerebrovascular disease, encephalitis, encephalopathy, peripheral nerve autoimmune diseases such as Guillain–Barré and Miller–Fischer syndromes, seizures, ataxia, and cranial nerve neuropathies [1, 2], with delirium being the most formidable complication. Considerable attention has been paid to cognitive decline (including dementia) in COVID-19, anxiety, depression, stress reactions, sleep disorders, and psychotic spectrum disorders [3-5].

The main pathogenetic factors in the development of neuropsychiatric pathology in COVID-19 are the direct neurotropic effect of the virus, brain hypoxia, destruction of the blood-brain barrier during cytokine storm, and cerebral hemodynamic disorders [4, 5, 6]. The neurotropic activity of SARS-CoV-2 is supposedly caused by the invasion of the virus

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into the central nervous system, which occurs via two routes: hematogenous spread due to infection of the endothelium, blood cells, and cerebrospinal fluid, barrier epithelium, transfer using myeloid cells; and retrograde transport of the virus from receptors along the axons of the olfactory, respiratory, and intestinal nervous systems [2, 6]. However, there is currently insufficient evidence regarding the neuroinvasive mechanism of SARS-CoV-2 [3, 7], though it is likely associated with its interaction with angiotensin-converting enzyme type II receptors in the endothelium and blood vessels of the central nervous system and the development of a hyperimmune response with multiple vasculitis of the small and large cerebral vessels. The cerebrovascular mechanism also includes conditions mediated by the pathogenesis of COVID-19 complications, such as cardiogenic cerebral ischemia, coagulopathy (disseminated intravascular coagulation, thrombosis), and septic shock with arterial hypotension [2, 4, 6]. Furthermore, there is also an increased risk of developing mental pathology when using pharmacological drugs (glucocorticosteroids, benzodiazepines, hydroxychloroquine, etc.) or respiratory support [8, 9].

At the start of the pandemic, most mental health research on COVID-19 focused on healthcare workers and the general population [10, 11]. To date, few studies have been conducted on the mental health of patients hospitalized with COVID-19; most of them were retrospective, and data were obtained from patients' self-assessments, which could lead to conflicting results. For example, most studies have revealed an increased incidence of anxiety, post-traumatic stress disorder, depression, and sleep disturbances in hospitalized patients [12, 13]. However, Einvik et al. (2021) showed that the incidence of post-traumatic stress disorder in hospitalized patients was not significantly different from that in patients with COVID-19 under outpatient treatment [14].

A separate study is required for patients hospitalized with COVID-19 since mental illnesses can significantly affect the behavior of patients and the implementation of medical recommendations. In addition, the development of delirium is a criterion for severe COVID-19 infection and a possible sign of an unfavorable outcome. Therefore, the study of mental disorders in patients hospitalized with COVID-19 and the development of standardized diagnostic and therapeutic programs are urgent tasks. This problem requires a comprehensive study of the mental health of patients in hospital due to COVID-19, with a thorough psychopathological and psychometric examination and prospective follow-up.

This study was conducted to determine the prevalence of mental disorders in patients hospitalized with a diagnosis of COVID-19, study their clinical characteristics, and determine the timing of their development.

Materials and Methods

In 2020-2021, a large-scale scientific study on the mental health of patients with COVID-19 was conducted at the Clinical Center of Sechenov University (Moscow, Russia). In the first stage (December 2020 to February 2021), a prospective cohort comparative study of mental disorders was conducted among patients undergoing inpatient treatment for COVID-19. The study included patients aged >18 years who were admitted to the clinic. The Tareeva University Clinical Hospital No. 3 (UCB 3) diagnosed with COVID-19. Two observation groups were formed according to the study design (Fig. 1). Group 1 included all patients admitted to the Coronavirus Infection Treatment Units nos. 1-2. All patients were examined by a psychiatrist on the first, fifth, and fifth days of hospitalization and on the day of discharge. If a mental pathology is detected, the frequency of observation could be higher in accordance with the clinical situation. Group 2 included patients admitted to the Coronavirus Infection Treatment Units nos. 3-4, and psychopathological examination was carried out only for patients in whom the attending physician identified signs of mental disorders and invited a psychiatrist for consultation. The frequency of observation of these patients was set individually by a psychiatrist. The exclusion criteria for both groups were as follows: patient's refusal to participate and the absence of a diagnosis of COVID-19 confirmed by the attending physician (confirmed case of COVID-19 and probable [clinically confirmed] case of COVID-19, in accordance with the Interim Guidelines of the Ministry of Health of the Russian Federation, version 9 of 10/26/2020, 10 of 08.02. 2021). Clinical data were obtained from clinical examinations and electronic health records. The mental state was assessed by a psychiatrist using clinical and psychopathological

examinations. With the preservation of verbal contact, the following psychometric methods were used: Patient Health Questionnaire, Generalized Anxiety Disorder Screening Questionnaire-7, Mini-Mental State Examination, and Insomnia Severity Index. If signs of delirium were present, the Delirium Severity Rating Scale (DRS-R-98) was used. Demographic indicators (sex, age, employment), clinical and anamnestic parameters (comorbid somatic diseases, previous psychiatric history), clinical features of COVID-19 (clinical variants, severity of pneumonia), duration of the disease and hospitalization, and disease outcome were also obtained.

Statistical analysis

Data were entered into an electronic database (Access, 2019), based on algorithms for recoding clinical information into quantitative and qualitative signs. The normality of the distribution was tested using the Kolmogorov–Smirnov test. Data analysis was carried out by sequential statistical processing of the array of primary data using descriptive statistics (shares, median, and interquartile range). Group comparisons were made using the Student's t-test or Mann–Whitney U-test for continuous variables and χ^2 for categorical variables. The strength of the associations was assessed using odds ratios with a 95% confidence interval. The significance level was set at $p<0.05$. Statistical analyses were performed using STATISTICA (version 10.0).

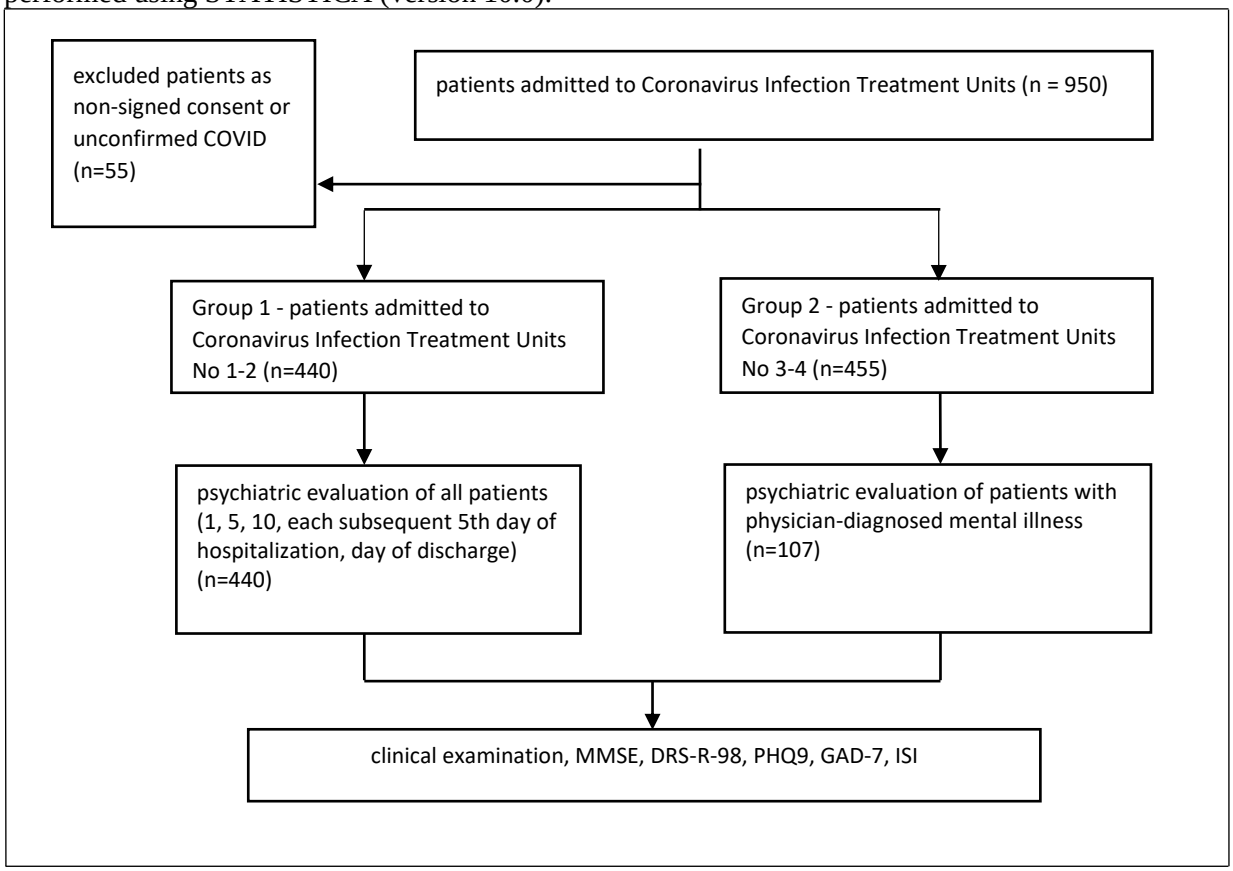

Figure 1. Flow diagram of study procedure.

MMSE - Mini-Mental State Examination, DRS-R-98 - Delirium Rating Scale-R-98, PHQ9 - Patient Health Questionnaire-9, GAD-7 - General Anxiety Disorder-7, ISI - Insomnia Severity Index

Results

Demographic and clinical characteristics of patients

From December 1, 2020, to February 17, 2021, 950 patients were treated in the Coronavirus Infection Treatment Units nos. 1-4. A total of 895 patients were included in the study: 440 in Group 1 and 455 in Group 2 (Table 1).

The median ages in the groups were 69.0 and 72.0, respectively. In Group 1, patients aged 60–69 (26.4%), 70–79 (25.4%), 80–89 (20%), and 50–59 (16.1%) years were most often represented. In Group 2, the age distribution did not differ significantly as most were 70–79 (30.7), 80–89 (24.8%), 60–69 (18.7%), 50–59 (13%) years old. The distribution according to sex also did not differ significantly: 42.3% and 41.1% of men and 57.7% and 58.9% of women, respectively. No differences were found in the distribution of employed and pensioners/disabled people.

SARS-CoV-2 infection was verified via reverse transcriptase-polymerase chain reaction in 83.2% and 85.9% of the patients, respectively. The length of hospital stay was significantly different, with a median duration of hospitalization of 12 and 14 days in Groups 1 and 2, respectively ($p=0.001$). The hospitalization outcome did not differ significantly between the groups (mortality rates of 5.9% and 5.7%, respectively). The severity of respiratory failure did not also differ significantly between the groups.

A burden of at least one concomitant somatic disease was detected in 75.2% and 77.6% of patients, respectively. Most often, the patients were diagnosed with hypertension (51.4% of all patients with comorbid somatic pathology) and coronary heart disease (34.4%). Previous mental disorders were confirmed in 10.9% of patients in Group 1, with anxiety disorders and depression (observed in 47.9% of patients with a psychiatric history) being the most common. The following were also detected: organic mental disorders in 22.9%, recurrent depression in 12.5%, addiction in 8.4%, schizophrenia in 4.2%, and bipolar affective disorder in 4.2% of patients. In Group 2, anamnesis was obtained only in 102 patients. Of these, 12.7% had a psychiatric history. The distribution of nosologies between the groups did not differ significantly.

Psychiatric disorders in patients hospitalized with COVID-19

In the group with continuous observation by a psychiatrist, 440 patients were examined. Meanwhile, 115 patients were examined in Group 2.

In Group 1, the most frequent complaints (excluding somatic complaints) were weakness and fatigue (69.5%) and sleep disorders (58.6%). Mental disorders during the hospital stay were observed in 237 (53.9%) patients (Table 2). Impaired consciousness was observed in 122 patients (27.8%). Furthermore, 108 (24.5%) patients had disorders with predominant anxiety symptoms. Cognitive impairments that did not reach the level of dementia were identified in 78 patients (17.8%), while dementia of various origins (vascular, atrophic, mixed, and unspecified) was detected in 68 patients (15.5%). Clinical depression was detected in 54 (12.3%) patients.

Mental disorders were detected in 110 patients (24.2%) in Group 2. Most often, a psychiatrist was called upon the appearance of signs of delirium, which was confirmed in 81 (17.8%) patients. The next most common reason for consultation was dementia, which was detected in 39 (8.6%) patients. Twenty-two (4.8%) patients were examined for symptoms of anxiety. Thirteen (2.9%) patients had mild cognitive impairment, and six (1.3%) had depression.

Comparative analysis of the characteristics of delirium in groups

We also conducted a separate analysis of the patients who developed delirium during hospitalization. We included those with subsyndromal delirium, defined as a condition with an acute or subacute onset, a fluctuating level of consciousness, the presence of 1-3 key symptoms of delirium, which do not allow for the diagnosis of delirium [15].

In the group with constant supervision by a psychiatrist, the incidence of delirium was 27.8% (122 patients), whereas it was 17.8% (81 patients) in the other group. The comparison showed a significant difference ($p<0.001$) (Table 2). The age and sex composition of the patients with delirium did not differ significantly between the groups (Table 3). The median age of the patients was 77 and 78 years, respectively. There were slightly more women with delirium in both groups. The median day of stay in the hospital,

on which delirium was detected, was day 4.0 (2.0–10.0) in Group 1 and day 6.0 (3.0–15.0) in Group 2 (p=0.08).
The severity of delirium, assessed using the DSR-R-98, was 18.5 (13.0-24.5) and 22.5 (16.0-28.5), respectively (p=0.01). The duration of delirium in the group with constant psychiatric supervision was also lower (4.0 days [2.0–7.0] vs. 5.5 days [4.0–7.0]) (p=0.03). The distribution of clinical variants differed significantly between groups (p=0.007). In both groups, the mixed type of delirium was more prevalent (49.2% and 61.7%, respectively). However, in Group 1, the prevalence of the hypoactive type was significantly higher (42.6% compared to 22.2%), while the hyperactive type was less prevalent (8.2% compared to 16.0%). The severity of COVID-19 pneumonia (p=0.81) and the proportion of concomitant somatic pathology (p=0.78) did not differ significantly between the groups.

Table 1 Patient demographics and clinical characteristics

	Group 1, n=440	Group 2, n=455	p
Age (years), n (%) 20-29 30-39 40-49 50-59 60-69 70-79 80-89 >90 M (IQR)	 2 (0,5) 10 (2,3) 25 (5,7) 71 (16,1) 116 (26,4) 112 (25,4) 88 (20,0) 16 (3,6) 69,0 (60,0-79,4)	 6 (1,3) 14 (3,1) 28 (6,2) 59 (13,0) 85 (18,7) 140 (30,7) 113 (24,8) 10 (2,2) 72,0 (60,7-80,6)	 0,11
Sex, n (%) Male Female	 186 (42,3) 254 (57,7)	 187 (41,1) 268 (58,9)	0,72
Ocupation, n (%) Employed Self-employed Retired/retired on disability	 116 (26,4) 40 (9,1) 284 (64,5)	 112 (24,6) 45 (9,9) 298 (65,5)	0,66
COVID diagnosis, n (%) COVID19, virus identified COVID19, virus not identified	 366 (83,2) 74 (16,8)	 391 (85,9) 64 (14,1)	0,25
Chronic comorbidities, n (%)	331 (75,2)	353 (77,6)	0,45
Pre-COVID-19 mental disorders, n (%)	48 (10,9)	13 (12,7) (n=102)	0,64
Length of stay (days), M (IQR)	12,0 (10,0-16,0)	14,0 (11,0-18,0)	0,001
Severity of respiratory failure (at admission), n (%) 0 0-1 1 1-2 2 2-3 3	 11 (2,5) 19 (4,3) 84 (19,1) 62 (14,1) 209 (47,5) 28 (6,4) 27 (6,1)	 13 (2,9) 23 (5,1) 81 (17,8) 69 (15,2) 208 (45,7) 36 (7,8) 25 (5,5	0,72
In-hospital death, n (%)	26 (5,9)	26 (5,7)	0,95

M – median, IQR – interquartile range (25-75%)

Table 2 Prevalence of mental illness

	Group 1 (n 440), n (%)	Group 1 (n 455), n (%)	Odds ratio (95% confdence interval); p
Mental illness	237 (53,9)	110 (24,2)	3,7 [2,8; 4,9]; <0,001
Anxiety	108 (24,5)	22 (4,8)	6,4 [4,0; 10,3]; <0,001
Mild cognitive impairment	78 (17,8)	13 (2,9)	7,3 [4,0; 13,4]; <0,001
Delirium	122 (27,8)	81 (17,8)	1,8 [1,3; 2,4]; <0,001
Dementia	68 (15,5)	39 (8,6)	2,0 [1,3; 3,0]; 0,003
Depression	54 (12,3)	6 (1,3)	10,5 [4,5; 24,6]; <0,001

Table 3 Characteristics of patients with delirium

	Group 1, n=122	Group 2, n=81	p
Age (years), M (IQR)	77,0 (66,7-85,4)	78 (67,7-88,2)	0,73
Sex, n (%) Male/Female	 57 (46,7)/65 (53,3)	 35 (43,2)/46 (56,8)	0,62
Day of onset, M (IQR)	4,0 (2,0-10,0)	6,0 (3,0-15,0)	0,08
DSR-R-98, M (IQR)	18,5 (13,0-24,5)	22,5 (16,0-28,5)	0,01
Duration, M (IQR)	4,0 (2,0-7,0)	5,5 (4,0-7,0)	0,03
Delirium subtypes, n (%) hyperactive hypoactive mixed	 10 (8,2) 52 (42,6) 60 (49,2)	 13 (16,0) 18 (22,2) 50 (61,7)	0,007
Severity of respiratory failure (at admission), n (%): 1 1-2 2 3	 23 (18,9) 20 (16,4) 53 (43,4) 26 (21,3)	 13 (16,1) 15 (18,5) 32 (39,50 21 (25,9)	0,81
Chronic comorbidities, n (%)	104 (85,2)	71 (87,7)	0,78

M – median, IQR – interquartile range (25-75%), DSR-R-98 - Delirium Rating Scale-R-98

Discussion

The results of the present study showed a high prevalence of mental illness among hospitalized patients with COVID-19. In the group with continuous psychopathological examination, signs of mental illness were observed in more than half of the patients, with 58.6% of the hospitalized patients complaining of sleep disorders. Very often, patients presented with affective complaints: 24.5% of patients had anxiety symptoms (ranging from a state of increased anxiety to anxious agitation in the form of adjustment disorders, other neurotic anxiety disorders, and organic anxiety disorder). A total of 12.3% of patients

had depressive symptoms. Most patients had a combination of various psychopathological symptoms and syndromes, such as anxiety and cognitive impairment, whereas the severity and dynamics of disorders of one spectrum did not always correspond to disorders of another spectrum.

The most severe psychopathological symptoms were observed in patients with delirium (27.8% in the permanent observation group and 17.8% in the selective observation group). In general, the frequency of delirium in this study was higher than that reported in the literature (11%) [16], which might be explained by the prompt identification of psychopathological symptoms by a psychiatrist in our study and the confusion of terms and definitions of delirious states (delirium, confusion, altered consciousness, encephalitis, etc.). In the present study, all states of disturbed consciousness were considered, including subsyndromal delirium. In the study by Ticinese et al. (2020), delirium was prospectively studied by qualified physicians, including using scales, and the frequency of delirium was comparable to our results (33%) [17].

A third of the patients had cognitive impairment, while the severity of the disorders reached the degree of dementia in 15.5%. Mild cognitive impairment, which is often associated with COVID-19 according to previous studies, occurred in 17.8% of patients in Group 1, which exceeds the prevalence rates in the general population. According to the literature, the frequency of cognitive impairment in people aged >60 years varies from 2.2% to 7.8% [18]. However, when extrapolating the obtained data to all patients with COVID-19, it is worth considering the older age of the hospitalized patients in the study group. In addition, cognitive impairment was often detected in combination with anxiety or depressive symptoms, which could be an independent cause of cognitive decline. Furthermore, to a greater extent, this can be explained by stress factors associated with the disease, hospitalization, and severe physical condition, rather than by any specific effect of COVID-19 on the central nervous system.

In addition, the present study showed a significantly higher prevalence of psychiatric illnesses among patients hospitalized with COVID-19 detected by psychiatrists than by non-psychiatric physicians. The most common reasons for psychiatric consultations were delirium (17.8%), dementia (8.6%), and severe anxiety (4.8%), accompanied by severe behavioral disorders. However, their frequency when compared with the group with constant psychiatric observation was significantly lower. Such a significant difference in the frequency of detected disorders of consciousness can be explained by the fact that the symptoms of incipient delirium are often defined by patients or their therapists as increased anxiety without a qualified assessment of the level of attention and consciousness. Psychiatric consultations due to cognitive impairments were performed in 17.8% in Group 1 and 2.9% of patients in Group 2, while depressive disorders prompted consult in 12.3% and 1.3% of patients, respectively.

A comparison of the delirium characteristics also showed significant differences between the groups. With constant monitoring, the psychiatrist detected disturbances of consciousness earlier (day 4 vs. day 6) and delirium proceeded with fewer complications, with the average DSR-R-98 scores being 18.5 and 22.5, respectively. Furthermore, the duration was shorter in Group 1 (4.0 vs. 5.5 days, respectively). In both groups, a mixed variant of delirium was more often observed. However, in the continuous observation group, a larger proportion of hypoactive forms of delirium and a smaller proportion of hyperactive forms were recorded. Furthermore, there were no differences in the age and sex composition, severity of respiratory failure, and the proportion of concomitant somatic pathology between the groups. It can be assumed that the identified differences in the severity and duration of delirium in the groups were explained by the timely detection and early implementation of adequate psychopharmacological treatment.

Conclusion

Given the clinical significance of disorders of consciousness occurring with COVID-19, the association of delirium with a likely adverse outcome, early diagnosis, and identification of preclinical forms are extremely important during the hospital treatment of

infected patients, primarily to prevent or reduce the risk of developing delirium. The high frequency of cognitive disorders, impaired consciousness, and anxiety in patients hospitalized with COVID-19 leads to the incorrect assessment of their condition and non-compliance with medical instructions, which is especially important when performing non-invasive respiratory support procedures. To improve the ability of non-psychiatric doctors in detecting psychiatric illnesses, it is advisable to use adequate diagnostic tools and clearly differentiated therapeutic and diagnostic algorithms.

Data Availability

The relevant data generated and (or) analyzed in the current study is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

M Kinkulkina contributed to the conceptualisation, writing—review and editing, project administration. M Brovko contributed to the writing—original draft preparation, writing—review and editing, project administration. Y Tikhonova contributed to the conceptualisation, software, writing—original draft preparation, writing—review and editing, A Volkov contributed to the formal analysis and investigation. V Sysoeva contributed to the writing—review and editing and visualization. T Avdeeva contributed to the validation, resources, writing—original draft preparation. O Lavrinenko contributed to the validation, resources, writing—original draft preparation. S Moiseev contributed to the conceptualisation, methodology, software, validation, formal analysis, investigation. D Golovkina contributed to the resources, visualization and funding acquisition. G Krenkel contributed to the resources and visualization. N Ivanets contributed to the conceptualisation, validation, formal analysis and supervision. E Efremova contributed to the data curation and visualization. V. Zaborova contributed to the methodology, data curation, writing—review and editing, supervision and funding acquisition.

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Supplementary Materials

There is no supplementary materials.

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