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ПОСТ-КОВИДНЫЙ ПЕРИОД: СОВРЕМЕННЫЙ ВЗГЛЯД И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ

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Post-COVID 19 Period: Modern State and Clinical Features

Резюме

Коронавирусная болезнь (COVID-19) рассматривается в качестве серьезной проблемы общественного здравоохранения, о чем свидетельствует неуклонный рост вновь зараженных пациентов.

Несмотря на то, что борьба с данной инфекцией длится более года, до сих пор недостаточно изучены малопрогнозируемые последствия COVID-19 в сочетании или без сочетания с сопутствующими хроническими заболеваниями, что несомненно является дополнительной нагрузкой на амбулаторное звено здравоохранения. Данная статья представляет собой обзор, современной доступной литературы, посвященной особенностям течения и длительности пост-ковидного периода. Проанализировано более 15 исследований, в которых авторы оценивали встречаемость симптомов в пост-ковидный период и его клинические характеристики.

Ключевые слова: *COVID-19, пост-ковидный период, одышка, усталость, амбулаторный этап*

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Abstract

Coronavirus disease (COVID-19) has proven to be a major global public health crisis, as evidenced by the steady increase in re-infected patients. In spite of the fight against this infection going on for more than a year, the unpredictable consequences of COVID-19, with or without concomitant chronic diseases, are still insufficiently studied, which undoubtedly is an additional burden on the outpatient health care unit. This article is a review of the available modern literature on the features of the course and duration of the post-COVID period. More than fifteen studies have been analyzed, in which the authors evaluated the incidence of symptoms in post-COVID period and its clinical characteristics.

Key words: *COVID-19, post-COVID 19 period, shortness of breath, fatigue, outpatient stage*

Conflict of interests

The authors declare no conflict of interests

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Introduction

Due to the increase in the incidence of novel coronavirus disease (COVID-19), clinical features of this disease are being studied both in the acute period and in the recovery period after infection [1–5].

There is currently not enough reliable professional information on the medical rehabilitation of COVID-19 patients since this disease is new. The conventional method of obtaining the necessary data from studies was ineffective since the experience of treating patients with coronavirus disease is limited to several months [6].

In the Russian Federation, recommendations were developed on rehabilitation measures after COVID-19 [6]. Experts proposed a scale for determining individual rehabilitation routing of persons with and after COVID-19. This scale allows determining the possibility of rehabilitation measures for patients at different stages of medical care. However, given the ambiguity of the recovery period after a new infection, a comprehensive and personalized algorithm for managing such patients at the outpatient stage should be developed.

Since most complaints of patients are due to respiratory symptoms, the best time for rehabilitation is the first two or three months after the acute period of coronavirus disease. Priority objectives of providing medical care to patients who contracted a new infection as part of rehabilitation measures are to prevent complications and quickly return patients to their previous lifestyle. Post-COVID rehabilitation of patients should start as early as possible. Therefore, there is need for a careful assessment of the clinical and functional status of the patient and choosing a comprehensive treatment plan, with the focus on the restoration of functional activity and return to social life depending on the individual characteristics of a person.

As new information regarding the diagnosis, treatment, and follow-up of patients with COVID-19 becomes available, the approach to coding conditions changes. To record COVID-19 cases, on March 25, 2020, the World Health Organization (WHO) recommended diagnostic criteria and COVID-19 codes according to the International Classification of Diseases, Tenth Revision (ICD-10). These codes were adopted in the Russian Federation on April 08, 2020, by Order of the Ministry of Health of the Russian Federation No. 13-2/I/2-4335, of April 08, 2020, "On the Coding of Coronavirus Disease (COVID-19)" [7]. Later, WHO experts added to the ICD-10 a diagnosis of U09.0 Post COVID-19 condition [8].

Post-COVID Period

The severity of SARS-CoV-2 disease varies from asymptomatic to life-threatening clinical symptoms. According to current estimates, approximately 20 million people in the world have «recovered» [9]; however, many clinicians report persisting symptoms of varying severity, up to significant organ dysfunction. At present, there is indeed insufficient information on the true nature and incidence of post-COVID-19 symptoms in the so-called «post-COVID» period, and there is no consensus on the occurrence and length of this period.

Greenhalgh Trisha et al. (2020) were among the first to propose the term «long-COVID», which implies a set of symptoms after the disease that persist for more than three weeks from the onset — «post-acute (probably meaning sub-acute) COVID-19» and for more than 12 weeks — «chronic COVID-19» [10].

Based on the study of the incidence of COVID-19 symptoms that included more than 4 million people in the United States, Britain and Sweden, it is believed that «sub-acute» COVID-19 is the presence of symptoms lasting more than three weeks from the onset, and chronic COVID-19 — symptoms lasting more than 12 weeks [10].

Experts at the National Institute for Health and Care Excellence the Scottish Intercollegiate Guidelines Network of General Practitioners define «post-COVID syndrome» as «a combination of symptoms that develop within 12 weeks after recovery and are not explained by the presence of other diseases» [11]. This document indicates the importance of follow-up in the post-COVID period taking into consideration multisystem disorders associated with COVID-19, which requires:

- Assessment of the general condition, the presence of fatigue and neurological symptoms;
- Assessment and management of persistent dyspnea, concomitant chronic conditions, if any;

- Assessment of the need for oxygen and its delivery;
- Assessment of the need for rehabilitation and its subsequent development;
- Psychosocial assessment (depression, anxiety disorders, post-traumatic stress disorders and subsequent referral to specialists to provide assistance according to indications);
- Assessment of cognitive impairment;
- Diagnosis of previously unverified diagnosis of venous thromboembolism.

The presence of «post-COVID syndrome» is quite natural since any infectious disease has certain consequences of varying duration and severity.

Post-COVID Period Clinical Signs

Long-term effects of COVID-19 are currently being studied, although the results of these studies include few data indicating the persistence of symptoms after the acute period in a certain number of patients (Table 1).

The above data indicate that dyspnea and increased fatigue are the leading symptoms in the post-COVID period and develop in most (up to 70%) patients. Cognitive impairments and headaches are detected in almost one in three (up to 36%) patients. The most analyzed studies provided no information on the time when the symptoms regressed and patients fully returned to their previous lifestyle, which does not allow us to estimate the true average duration of the recovery period after COVID-19. The incidence of COVID-19 symptoms in acute and recovery periods is presented in Table 2.

In one study conducted in Italy, which evaluated the persistence of COVID-19 in 143 patients aged 19 to 84 years (mean age 56.5 years), 53 (37%) were female, 90 (63%) were male, discharged from the hospital, only 18 (12.6%) patients had absolutely no symptoms associated with COVID-19 60 days after the onset of the first symptoms. Among all subjects, arterial hypertension was found in 50 (35%), thyroid diseases — in 26 (18.2%), autoimmune diseases — in 16 (11.2%), chronic obstructive pulmonary disease — in 13 (9.1%), chronic heart failure — in 7 (4.9%) patients [13].

Table 1. *The incidence of symptoms after COVID-19 infection in the recovery period*

Author, source	Number of patients, gender, age	Symptoms	Observation period
Arnold et al. 2020 [12]	n=110 median age 60, 49 women (44%) 61 male (56%)	Dyspnea (39%) Fatigue (39%) Insomnia (24%) Myalgia (22%) Anosmia (11%) Arthralgia, headache, abdominal pain, diarrhea (<5%) Combination of multiple symptoms 74%	Median of 83 days after hospital discharge
Carfi et al. 2020 [13]	n=143 median age 56,5 53 women (37,1 %) 90 male (62,9%)/	Fatigue (53,1%) Dyspnea (43,4%) Arthralgia (27,3%) Chest pain (21,7 %) Cough, sputum, joint pain, anosmia, rhinitis, taste disturbance, loss of appetite, Sikki syndrome, redness of the eyes, headache, dizziness, myalgia, diarrhea (< 20%) Combination of 1-2 symptoms — 32% 3 symptoms — 55%	Mean of 60 days after hospital discharge
Cirulli et al. 2020 [14]	n=233 median age 56 148 women (63,6 %) 85 male (36,4%)	Concentration and memory problems, anosmia, ageusia, dyspnea, headache, heart palpitations, chest pain, tachycardia, and cough: - 42,3% - 33,8% - 24,1%	 Symptom lasting for >30 days Symptom lasting for >60 days Symptom lasting for >90 days
Lu et al. 2020 [15]	n=60 median age 45,9	Memory loss (28,3 %) Myalgia (25%) Mood changes (16,7%) Fatigue (6,7%) Numbness in extremities (6,7 %) Combination of symptoms 55%	3 months after hospital discharge
Mandal et al. 2020 [16]	n=384 median age 59,9 146 women (38%) 238 male (62%)	Fatigue (69%) Dyspnea (53%) Cough (34%) Depression (15%)	Median of 54 days after hospital discharge

Author, source	Number of patients, gender, age	Symptoms	Observation period
Miyazato et al. 2020 [17]	n=63 median age 48,1 21 women (33,3 %) 42 male (66,7 %)	Dyspnea (17,5%) Dysosmia (16,1%) Fatigue (15,9%) Cough (7,9%) Dysgeusia (4,8%)	60 days after symptom onset
		Fatigue (9,5%) Cough (6,3%) Dysosmia (9,7%) Dysgeusia (1,6%)	120 days after symptom onset
Paterson et al. 2020 [18]	n=180 median age 39,9 98 women (54%) 82 male (46%)	Fatigue (28,9%) Anosmia (27,2%) Ageusia (15,6%) Joint pain (11,1%) Rhinorrhea (8,9%) Dyspnea (8,3%) Headache (7,2%) Myalgia (7,2%) Nausea (6,1%) Chest tightness (6,1%) Chills (4,4%) Cough (4,4%) Diarrhea (4,4%) Combination of symptoms 55%	125 days after symptom onset
Shah et al. 2020 [19]	n=60 median age 67 20 women (32%) 40 male (68%)	Dyspnea (20%) Cough (20%)	12 weeks after symptom onset
Sollini et al. 2020 [20]	n=10 median age 58 7 women (70%) 3 мужчины/male (30%)	Dyspnea (70%) Fatigue (70%) Ageusia (20%) Joint pain (20%) Chest pain (10%) Headache (10%) Trembling hands (10%)	>30 days after hospital discharge
Stavem et al. 2020 [21]	n=434 median age 49,8 244 women (56 %) 190 male (44%)	Dyspnea (15%) Smell dysfunction (12%) Taste dysfunction (10%) Arthralgia (9%) Myalgia (8,5%) Headache (6%) Dry cough (6%) Sore throat, chills, runny nose, vision disturbance, skin rash, conjunctivitis, ear pain, cramps, wheeze, confusion, gastrointestinal symptoms (<5%)	1,5 — 6 months after symptom onset
Surde et al. 2020 [22]	n=4 182 median age 42,8 2 991 women (71,5 %) 1 191 male (29,5 %)	Symptom lasting for >4 weeks (13,3%) Symptom lasting for >8 weeks (4,5%) Symptom lasting for >12 weeks (2,3%) Symptoms: fatigue, headache, dyspnoea, and anosmia	12 weeks after symptom onset
Townsend et al. 2020 [23]	n=128 median age 49,5 70 women (54%) 58 male (46%)	Fatigue (52,3%)	Median of 10 weeks after symptom onset
Van den Borst et al. 2020 [24]	n=124 median age 59 50 women (40%) 74 male (60%)	Decreased quality of life (72%) Fatigue (69%) Cognitive or mental impairments (36%)	3 months after hospital discharge
Wong et al. 2020 [25]	n=78 median age 62 29 women (36%) 49 male (64%)	Worsened quality of life (51%) Dyspnea (50%) Cough (23%) Combination of symptoms 76%	3 months after symptom onset
Y.M. Zhao et al. 2020 [26]	n=55 median age 47,5 23 women (41,8 %) 32/male (58,2 %)	Gastrointestinal symptoms (30,91%) Fatigue (16,36%) Headache (18,18%) Dyspnoea (14,55%) Cough and sputum (1,81%)	3 months after hospital discharge

Table 2. *Symptoms of COVID-19 in the acute and post-infectious periods*

Symptom	Occurrence in the acute period	Occurrence in the recovery period
Fatigue	about 80%	53,1%
Dyspnea	about 70%	43,4%
Arthralgia	about 56%	27,3%
Chest pain	about 40%	21,7%
Cough, sputum, joint pain	about 60%	<20%
Anosmia, rhinitis, taste disturbance	30-50%	<20%
Loss of appetite, Sikki syndrome, redness of the eyes, headache, dizziness, myalgia, diarrhea [13]	40-60%	<20%
Dyspnea	about 70%	39%
Fatigue	39%	39%
Insomnia	<10%	24%
Myalgia	30%	22%
Anosmia	40-50%	11%
Arthralgia, headache, abdominal pain, diarrhea	about 30%	<5%
Fever [12]	about 75%	<5%
Memory loss	13,3%	28,3%
Myalgia	15%	25%
Mood changes	41,7%	16,7%
Повышенная утомляемость/Fatigue	26,7%	6,7%
Impaired mobility [15]	11,7%	6,7%
Fatigue	67,3 — 76,9%	69%
Dyspnea	54,8 — 63,3%	53%
Cough	32,2 — 46,2%	34%
Depression [16]	61,1 — 93,3%	15%
Dyspnea	42,9%	17,5%
Dysosmia	40,3%	16,1%
Fatigue	55,6%	after 60 days — 15,9%, after 120 — 9,5%
Cough	63,5%	after 60 days — 7,9%, after 120 — 6,3%
Dysgeusia [17]	43,5%	after 60 days — 4,8%, after 120 — 1,6%
Dyspnea	57%	15%
Smell dysfunction	64%	12%
Taste dysfunction	68%	10%
Arthralgia	47%	9%
Myalgia	62%	8,5%
Headache	68%	6%
Dry cough [21]	67%	6%

In a telephone survey conducted by the Center for Disease Control and Prevention on a random sample of 292 individuals aged 18+ with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 performed on an outpatient basis, fatigue (71 %), cough (61%) and headache (61%) were the most common symptoms. The authors noted that 26% of persons aged 18–34 years (n = 85), 32% of those aged 35–49 years (n = 96), and 47% of those aged 50 years and above (n = 89) had symptoms that persisted for more than two weeks [27].

Mandal S. et al. (2020) presented data on the incidence of symptoms after novel coronavirus disease [16]. This study included 384 patients (62% — men, 38% — women) with average age of 59.9 years. Patients were observed at three major London clinics for novel coronavirus disease. Changes in their condition were monitored by phone or in person during examination 4–6 weeks after discharge from the hospital. The severity of dyspnea was assessed by the 11-point rating scale of dyspnea (Shortness of Breath Numerical Rating Scale), where a higher score (0–10) indicated serious pathological changes. Patients with abnormal blood tests or significant changes in X-ray examination at discharge were invited for re-examination. X-ray was evaluated using the platform of the British Society of Thoracic Imaging [28]. The severity of depression was established according to the results of the Patient Health Questionnaire-2 (PHQ-2) consisting of two questions and assessing the presence/absence of feelings of depression, hopelessness, interest in activities that previously gave pleasure. The follow-up period averaged 54 (from 47 to 59) days after discharge from the hospital. The average duration of hospital stay was 6.5 days (4–10.75); 14.5% of patients underwent treatment in the intensive care unit. Results of this study revealed that 53% of patients had persistent dyspnea, 34% had cough, 69% reported fatigue, and 14.6% of

subjects had depressive disorders. Out of 273 patients, 7.3% who received treatment in the hospital had persistent lymphopenia in the recovery period; 30.1% of 229 patients had an elevated D-dimer level, and 9.5% of 190 patients had increased C-reactive protein.

At the time of the first visit to the hospital, chest X-ray was performed for 333 of 384 (87%) patients. No pathological or infiltrative changes in lungs were found in 15%; 56% of patients had pathological changes typical for the acute period of disease; 29% had no identified pathology or had pathology not typical for COVID-19. Control X-ray was performed for 66% of patients: 151 (62%) had results consistent with the physiological picture; 66 (27%) showed significant improvement; the signs in 4 (2%) patients remained unchanged; 23 (9%) patients showed a significant deterioration on X-ray associated with pulmonary fibrosis.

Halpin S. et al. (2021) in January 2021, for the first time in the UK, provided data on the incidence of post-COVID-19 symptoms [29]. This study included 100 patients who were discharged from the largest university clinic (Leeds Teaching Hospitals NHS Trust) in Europe, with a capacity of about 1,800 beds. A telephone survey was conducted with recovering patients 4–8 weeks after discharge from the clinic, using the adapted questionnaire EQ-5D that included five questions and assessed subjective sensations of the patient's physical and mental state (mobility, personal care, daily activities, pain/discomfort, anxiety/depression). Patients were followed-up by a multidisciplinary team of specialists: physiotherapists, therapists, rehabilitation therapists, neuropsychologists. Follow-up period averaged 48 ± 10.3 days (from 29 to 71 days) after discharge from the hospital. The patients were divided into two groups. Group 1 included 32 patients (59.4% men) aged 58.5 (34–84) years who underwent intensive care; group 2 included 68 patients (51.5% men) aged 70.5 (20–93) years who received conventional therapy.

The most common symptoms during recovery were fatigue (in 72% of patients of group 1 and in 60.3% of group 2); dyspnea (in 65.6% and in 42.6% of patients, respectively) and psychological disorders (in 46.9% and in 23.5% of patients, respectively). According to the EQ-5D questionnaire, a clinically significant drop in quality of life was observed in 68.8% of patients in the intensive care group and in 45.5% in the conventional therapy group. Therefore, fatigue, shortness of breath and psychological stress associated with this disease were reported on average seven weeks after discharge from the hospital, which led to a significant drop in quality of life. These symptoms were present in patients regardless of intensive care, with a higher frequency in individuals of group 1.

As for the persistence of symptoms during the recovery period after COVID-19, these symptoms lasted longer than symptoms after community-acquired pneumonia. Wootton D. et al. (2017) showed that, on average, 97% of patients after pneumonia recovered by the 10-11th day of the disease [30]. Wyrwich K. et al. (2015) confirmed that dyspnea disappears, on average, 14 days after the onset of the first symptoms of pneumonia, and fatigue — after 20 days in a group of 201 patients (mean age 62.4 years, 45% men). The hospitalization period averaged 6.8 days, 91.4% of patients were hospitalized on the first day of the onset of pneumonia symptoms. The authors noted that chills, sweating and fever lasted less than a week, and fatigue, weakness and shortness of breath — less than three weeks. Other symptoms (headache, decreased appetite, dizziness, dyspepsia, body aches, sleep disturbance) persisted for 1-2 weeks [31]. The results indicate a longer period of symptoms after novel coronavirus disease compared with that of pneumonia, which requires further study of the post-COVID-19 recovery period.

Need for Individual Post-COVID Recovery Program

There are currently no approaches to consistent monitoring of the functional state of patients after novel coronavirus disease [10]. Of course, the lack of reliable information on the management of patients in the recovery period, specifically in the first three months of the disease, creates certain challenges in assessing dynamic changes in the clinical picture and in the development of therapeutic and preventive measures for physicians who work in outpatient health care.

The workload on the primary care unit requires rational approaches to the management of patients in the post-COVID period, given that, according to the World Health Organization, as of December 27, 2020, more than 79.2 million cases of the diseases had been registered in the world, and over 1.7 million were fatal [32].

Klok F. et al. (2020) proposed a scale for assessing the functional state of patients after COVID-19 [33] (Fig. 1).

This scale can be used to assess the effect of symptoms on the functional state of a person and allows assessing the changes in the post-COVID-19 recovery period. This scale is intended for use at various stages of the post-COVID period, which allows assessing the functional status and changes in the patient's recovery [33].

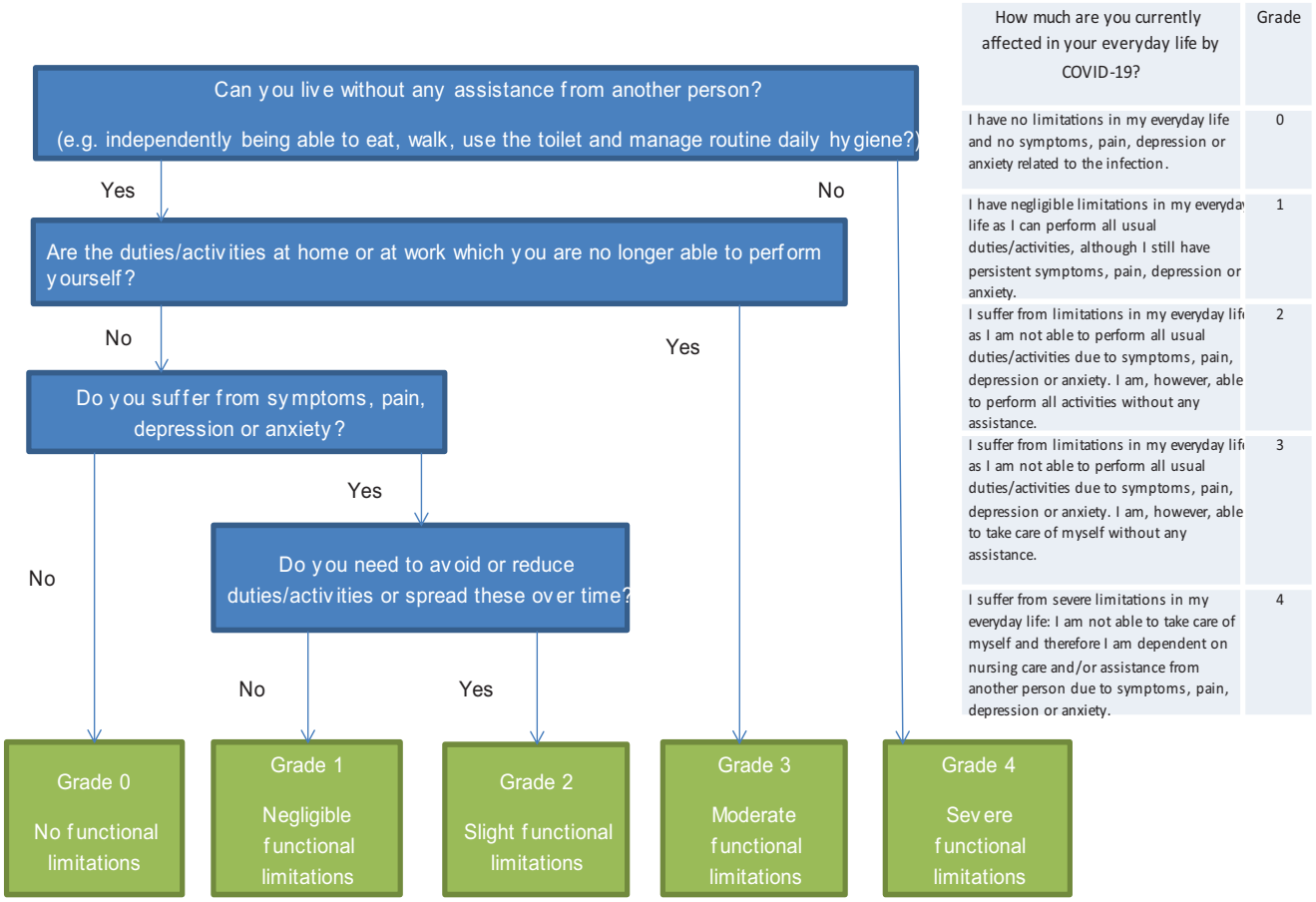

Figure 1. *The Post-COVID-19 Functional Status (PCFS) Scale (Klok et al., 2020)*

The main objective in the early days of the pandemic was the treatment and follow-up of patients in the acute period of the disease. Given that most patients are followed up on an outpatient basis, there is currently a need for management algorithms since many patients have residual symptoms after infection. Clear algorithms for the management of patients during the post-COVID period will surely not only reduce the burden on the outpatient unit but will also help reduce the number of re-hospitalizations, avoiding the complications associated with COVID-19 and improving the quality of life.

The Authors' Opinion on the Principles of Rehabilitation and Treatment of Patients after COVID-19

From our point of view, planning rehabilitation programs (rehabilitation treatment plan) should start during hospitalization (or in the acute period in the case of outpatient treatment) in order to further monitor the clinical condition of recovering patients and optimize their functional recovery. The continuity of hospital and outpatient stages plays a critical role in this process. Post-COVID-19 rehabilitation at the outpatient stage should start as early as possible and should include the following aspects:

- restoration/maintenance of functional status *(aimed at regression of clinical symptoms and their consequences)*,
- monitoring the course of chronic non-communicable diseases *(if any)*,
- maintaining mobility and mental health *(especially in elderly people)*,
- vaccine prophylaxis of acute infectious respiratory diseases.

When examining a patient at the outpatient stage after coronavirus disease, the general condition, respiratory symptoms and their severity, anthropometric and hemodynamic parameters, exercise tolerance *(possibly using a six-minute walk test)*, bad habits, risk factors, and the level of adherence to a healthy lifestyle should be assessed.

Depending on the severity of the condition, it is necessary to resolve the issue of dispensary follow-up of the patient on an individual basis. One should take into

consideration the reluctance to follow the physician's recommendations and poor adherence to a healthy lifestyle *(non-compliance with the principles of healthy nutrition, active lifestyle, and behavioral risk factors)* of outpatients of working age due to their formal attitude to preventive examinations and delayed response to examination results due to the lack of time because of work.

In the recovery period, it is important to recommend physical activity of any type depending on the individual characteristics of the person — breathing exercises, walking, exercise therapy. Aerobic exercises for 20-30 minutes are indicated at least three times a week for 8-12 weeks, taking into consideration weather conditions, the patient's condition and physical capabilities. Patients should be trained to monitor the effectiveness and safety of physical exertion, to know the "red flags" [5]. It is recommended to provide the patient with a leaflet/booklet containing recommendations on a healthy lifestyle, dietary habits, aerobic exercises, breathing exercises, etc. The set of measures should include a fixed date for the next follow-up visit to the physician or health center. Because the long-term consequences of new infections are still being studied, the determination of the frequency and indications for consultations with specialists (physiotherapy physician, rehabilitation physician, dietitian, physiotherapist, etc.) seems promising at the outpatient stage.

Conclusion

Literature and clinical data show a variety of clinical manifestations in the post-COVID period in both young and elderly people. On average symptoms persist for about 2-3 months, which physicians in the management of outpatients should consider.

Almost all authors emphasize the need for thorough monitoring and analysis of the clinical picture during the post-COVID period. Colleagues abroad suggest the gradation of this period by the duration of symptoms, dividing it into post-acute (sub-acute) and chronic. Considering that the pathogenesis of this disease is not fully understood, the exact duration and features of the post-COVID period require further study.

It is extremely important that the provision of medical care to this vulnerable group of patients be based on an interdisciplinary approach and the continuity of the inpatient and outpatient stages. Moreover, this approach will allow to effectively and consistently implement therapeutic measures to improve the physical and mental health of most patients recovering from COVID-19.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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