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СТЕПЕНИ ТЯЖЕСТИ ПОСТКОВИДНОГО СИНДРОМА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Severity of Postcovid Syndrome: A Systematic Review

Резюме

Постковидный синдром включает в себя множество состояний и симптомов, как возникших непосредственно в острый период инфекции, так и возникших после его окончания. Целью систематического обзора является определение критериев степеней тяжести постковидного синдрома. Материалы и методы. Для поиска литературных источников использовались следующие ключевые слова: «постковидный синдром», «тяжесть постковидного синдрома», «выраженность постковидного синдрома», «симптомы постковидного синдрома» на русском и английском языках. Для поиска использовались поисковые системы «eLIBRARY.RU — НАУЧНАЯ ЭЛЕКТРОННАЯ БИБЛИОТЕКА» и PubMed.gov. Были включены статьи, в которых представлено исследование пациентов, после подтвержденной лабораторно перенесенной коронавирусной инфекции с остаточными клиническими признаками и/или биохимическими изменениями, проведенное не менее чем через месяц после выздоровления от COVID-19. В анализ включались только публикации последних 3х лет (2020-2023 гг.). Результаты. Всего по двум поисковым системам было найдено 2913 публикаций, после удаления дубликатов, обзоров литературы, клинических исследований лекарственных препаратов, исследований, проведенных на животных, исследований неудовлетворяющих времени проведения после перенесённого COVID-19 и выполненных на лицах, не достигших 18-летнего возраста, для анализа было отобрано 69 статей, удовлетворяющих критериям включения в анализ. Заключение. Анализ литературы последних 3-х лет позволил определить, что наличие и степень тяжести постковидного синдрома, вероятно, может определяться наличием у пациента хотя бы одного признака из представленных в обзоре, развившегося во время или после лабораторно верифицированной инфекции COVID-19 и сохраняющегося в сроки более 4х недель от начала заболевания при условии, что он не может быть объяснен другими причинами.

Ключевые слова: *постковидный синдром, степень тяжести постковидного синдрома, симптомы постковидного синдрома, систематический обзор*

Конфликт интересов

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Abstract

Postcovid syndrome includes many conditions and symptoms, both those that arose directly during the acute period of infection and the appearance of new ones. The purpose of the systematic review is to determine the criteria for the severity of postcovid syndrome. Materials and methods. The following keywords were used to search for literary sources: "postcovid syndrome", "severity of postcovid syndrome", "severity of postcovid syndrome" and "symptoms of postcovid syndrome" in Russian and English. We used the search engines "eLibrary.RU — Scientific Electronic Library" and PubMed.gov. Articles were included that presented a study of patients with laboratory-confirmed coronavirus infection at least a month after recovery from COVID-19 with residual clinical signs and/or biochemical changes. The analysis included only publications from the last 3 years (2020–2023). Results. A total of 2,913 publications were found by two search engines. After removing duplicates, literature reviews, clinical studies of medicines, studies conducted on animals, studies unsatisfactory for time after acute COVID-19, and studies performed on persons under the age of 18, 69 articles were selected for analysis that meet the criteria for inclusion in the analysis. Conclusion. An analysis of the literature of the last 3 years has allowed us to determine that the presence and severity of postcovid syndrome can probably be determined by the presence in a patient of at least one of the signs presented in the review that developed during or after a laboratory-verified COVID-19 infection and persisted for more than 4 weeks from the onset of the disease and that cannot be explained by other reasons.

Key words: *postcovid syndrome, severity of postcovid syndrome, symptoms of postcovid syndrome, systematic review*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, ALT — alanine aminotransferase, AST — aspartate aminotransferase, BA — bronchial asthma, GIT — gastrointestinal tract, CHD — coronary heart disease, MI — myocardial infarction, CT — chest computer tomography, NCVI — novel coronavirus infection, PCS — post-COVID syndrome, PTSD — post-traumatic stress disorder, DM— diabetes mellitus, POTS — postural orthostatic tachycardia syndrome, AF — atrial fibrillation, CKD — chronic kidney disease, CCF — chronic cardiac failure, COVID-19 — novel coronavirus infection, CFQ-11 — The Chalder fatigue scale, EQ-5D — European Quality of Life Questionnaire, HADS — Hospital Anxiety and Depression Scale, mMRC — Modified Medical Research Council, SARS-CoV-2 — severe acute respiratory syndrome coronavirus-2, SF-36 — Health Status Survey

Introduction

Post-COVID-19 condition has been widely studied by academic and medical communities.

Currently, there is no globally recognised definition of post-COVID syndrome (PCS). However, in December 2020, the National Institute for Health and Care Excellence (NICE) release a quick COVID-19 guide in cooperation with the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP), which sets forth clinical definitions of this condition at various stages. According to the document, acute COVID-19 symptoms (ACS) last for up to 4 weeks from disease manifestation; ongoing symptomatic COVID-19 persists for 4–12 weeks from the onset; post-COVID-19 syndrome is signs and symptoms evolving during and after COVID-19 infection, lasting for over 12 weeks and not attributed to any other diagnosis [1].

According to the French National Board of Health, long-term persistent COVID-19 means one or several initial symptoms persisting for at least 4 weeks after infection onset, where none of the symptoms can be attributable to another cause [2].

In October 2021, the WHO developed a definition of the clinical condition after COVID-19 using the Delphi methodology: the post-COVID-19 condition develops in subjects with a history of possible or confirmed SARS-CoV-2, usually 3 months after the onset, with symptoms lasting at least for 2 months and not attributable to any other diagnosis [3]. Due to the incidence and clinical significance, this syndrome is officially a disease and was included into the new edition of the International Classification of Diseases, 10th Edition, as "post-COVID-19 condition, unspecified", code U09.9; it is also called post-COVID condition or PCS [4].

It is well-known that the term "long COVID" was introduced by patients in social media to describe persistent post-NCVI symptoms; later, the term has become common in mass media and medical community. In scientific literature it is often used as a synonym to PCS or NICE variant 2 and variant 3 of COVID-19, whereas other scientists differentiate between these conditions,

believing that PCS is a complication of the infection that was cured and the latter is a chronic persistent virus in the body. According to the guidelines developed by the Russian Scientific Medical Society of General Practitioners, National Scientific Society of Infectious Disease Specialists and the Rehabilitation Society (2022), long COVID means clinical manifestations of the disease lasting for 4 to 12 weeks from infection onset; whereas chronic COVID and PCS should be used where symptoms persist for over 12 weeks after disease development [5].

Completed studies show that the recorded incidence of long COVID vary between countries and within a country: United Kingdom 1.6–71 %, Germany 35–77 %, China 49–76 %, Africa 68 %, India 22 %, Bangladesh 16–46 %, Denmark 1 %, Italy 5–51 %, USA 16–53 %, Norway 61 % [6].

According to the ACTIV register (analysis of comorbidities in patients surviving SARS-CoV-2 infection), examination of 9,364 patients demonstrated that more than a half of COVID-19 survivors had disturbing symptoms for a long time (up to 1 year); such symptoms are new or are a result of exacerbation of existing symptoms. Feeling unwell made two thirds of patients seeking unscheduled medical advice during 12 months after discharge from the outpatient unit [7].

A prospective cohort study in children and adults with conformed COVID-19 in Moscow revealed the incidence of post-COVID-19 condition after a 6 and 12-month follow-up of previously hospitalised adults and children. This study demonstrated that a half of adults and one in five children had post-COVID-19 condition [8].

The multicenter clinical epidemiological observational program CORTEX revealed that daily up to 5 patients visited healthcare professionals due to complaints associated with past COVID-19 (up to 30 % of the number of outpatient neurological patients) [9].

PCS manifestations are versatile and vary from neurological symptoms to respiratory, cardiovascular and metabolic conditions and GIT manifestations. Symptoms can develop after recovery or persist after initial disease, and can change or reduce over time.

It is known that SARS-CoV-1 and MERS-CoV, which are two previous outbreaks of a viral infection similar to the current COVID-19 pandemic, had long-lasting symptoms after complete recovery from the primary disease. In their meta-analysis, H. Ahmed et al. found out that approximately one third of patients suffered from long-term anxiety, depression and post-traumatic stress disorder (PTSD) for 6 months after infection manifestation. Besides, they found out that 11–45 % of patients had reduced diffusing lung capacity during a one-year follow-up [10].

Currently, there are no PCS classifications to be used by clinicians, therefore, this topic is a matter of academic interest. However, German scientists developed Post-COVID-19 Functional Status scale (PCFS) to identify the degree of functional dependence and disease severity. This scale involves five stages of functional limitations: 0 (no functional limitations), 1 (negligible), 2 (minor), 3 (moderate) and 4 (significant) [11].

The current situation, where the number of patients with clinical signs of a long-term infection grows and healthcare professionals have to face these manifestations, necessitates the development of criteria for PCS severity in order to provide medical professionals with guidelines for the management of such patients. As more scientific data become available, this approach will probably have comprehensive evidences.

Study Objective

The objective of the systematic review is to identify criteria of PCS severity.

Materials and Methods

The following keywords were used for a search in literature sources: “post-COVID syndrome”, “post-COVID syndrome severity”, “post-COVID”, “long COVID”, “Post-COVID-19 Syndrome”, “post-acute COVID-19 syndrome”. For search in Russian literature, eLIBRARY.RU (SCIENTIFIC ONLINE LIBRARY) was used, whereas PubMed.gov was used for search in English literature sources. The review included the articles describing studies in patients over 18 years of age after a laboratory confirmed NCVI with residual clinical signs and/or biochemical changes, at least one month after recovery from COVID-19. The analysis covered papers which had been published during the previous 3 years (2020–2023) and did not include literature reviews, clinical trials and animal studies. All in all, 2,920 publications were found in both search systems; once duplicate papers, literature reviews, clinical trials and animal studies had been removed, 1,617 publications were included in the analysis.

In the Russian search system, 964 sources were found. 840 articles were excluded because subjects had been examined less than a month after recovery; 116 articles were removed because the mean age of subjects was less than 18 years. Thus, the final analysis included 8 articles in Russian.

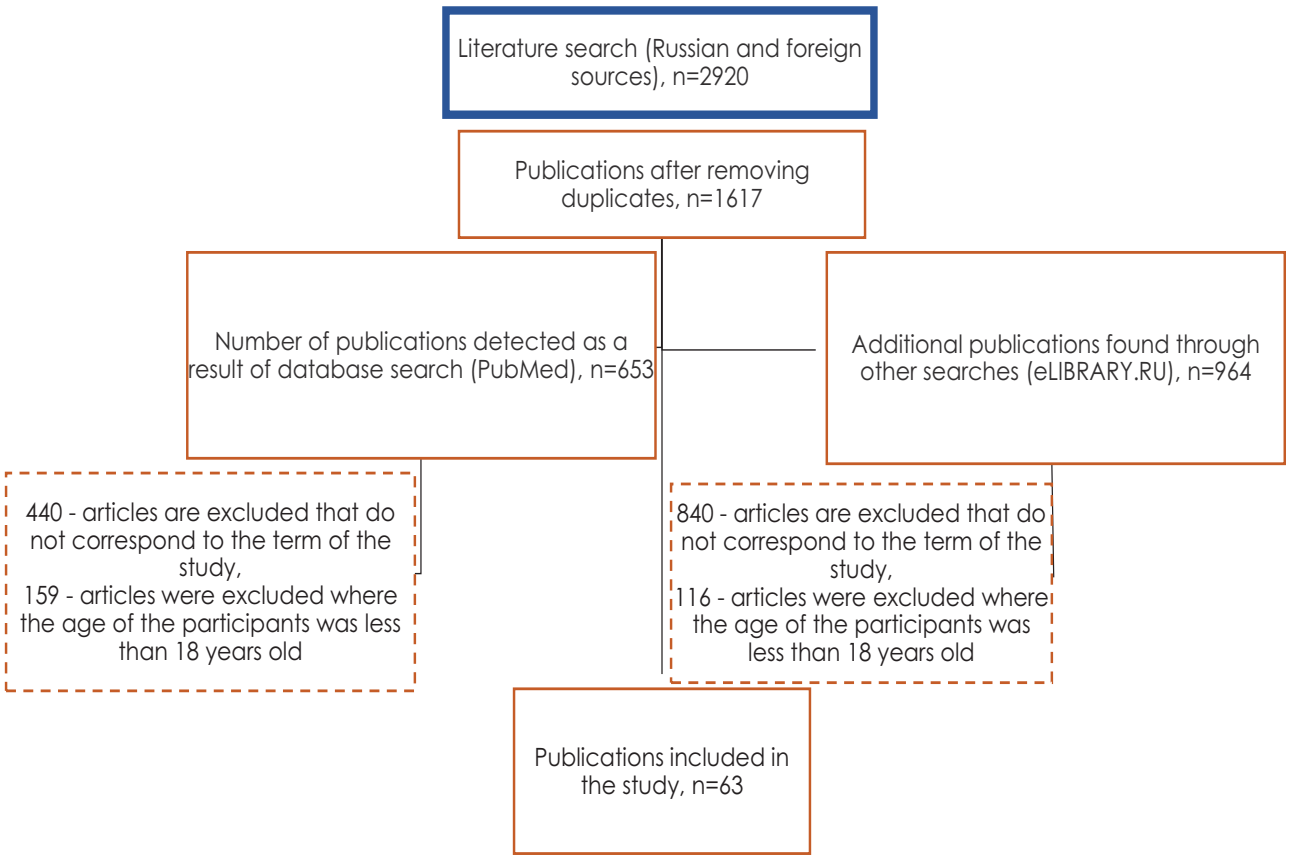

Figure 1. *Research Flowchart*

In the English search system, 653 sources were found. 440 articles were excluded because subjects had been examined less than a month after recovery; 159 articles were removed because the mean age of subjects was less than 18 years. Thus, the final analysis included 54 articles in English.

All in all, 63 articles from the Russian and global systems were selected, which met the inclusion criteria (Fig. 1).

Results

PCS comprises a number of conditions and symptoms, developing both during the acute phase of the infection and after its resolution.

Dominic L. Sykes et al. determined that 86 % of post-COVID-19 patients reported at least one symptom during follow-up [12].

A Swedish study demonstrated that out of 431 COVID-19 patients, 40 % needed another visit to a healthcare provider (GP, emergency room, hospitalisation) 6–8 month after infection onset. In 18 % of cases, a new diagnosis was made. The most common post-COVID-19 conditions were respiratory diseases (56 %), neurological and cognitive disorders (30 %), cardiovascular (11 %) and skin (11 %) diseases [13].

A Dutch retrospective study demonstrated that out of 1,886 subjects in various ethnic groups, 483 patients (26 %, 95 % CI 24–28 %) had lasting symptoms 12 weeks after discharge from the hospital after COVID-19. The most common symptoms reported 3 months after discharge were shortness of breath and fatigue (16 %). It is worth noting that during a one-year follow-up, 40 (14 %) patients still had lasting COVID-19 symptoms [14].

Results of a 6-month follow-up from the global ACTIV register showed that 5.6 % and 6.4 % patients were diagnosed with new diseases during 3 and 6 months post-hospitalisation, respectively. As for the patients with newly diagnosed diseases during 3 and 4–6 months of follow-up, patients with arterial hypertension (AH) were prevailing; they accounted for 41.5 % and 46.7 % in the structure of newly diagnosed diseases. Of note, as compared to the first 3 months, a share of patients with AH increased over 4–6 months of follow-up. Also, the number of patients with newly diagnosed coronary

heart disease (CHD) grew over 4–6 months (22.1 %) as compared to 3 months (9.7 %). Cases of myocardial infarction (MI) were more numerous over 4–6 months as compared to the first 3 months (3.9 % vs 0.8 %). Similar changes were observed for arthritis: growth of 5.2 % over 4–6 months as compared to 4.9 % over the first 3 months; and for newly diagnosed chronic cardiac failure (CCF): growth of 0.8 % of newly registered cases during the first 3 months and 1.3 % of cases over 4–6 months. The remarkable fact is that a share of such newly diagnosed diseases as type 2 diabetes mellitus (DM), atrial fibrillation (AF), stroke, bronchial asthma (BA), cancer, chronic kidney disease (CKD) and DM1 in the total number of newly diagnosed diseases dropped during 4–6 months as compared to the first 3 months [7].

In their meta-analysis, Qing Han et al. found out that fatigue/weakness (28 %, 95 %), shortness of breath (18 %), myodynia (26 %), depression (23 %), anxiety (22 %), memory loss (19 %), impaired concentration (18 %) and insomnia (12 %) were the most common symptoms during a 1-year follow-up [15].

For better understanding the symptoms and conditions, PCS should be divided into groups.

1. Cardiovascular manifestations

In foreign sources, cardiac manifestations of COVID-19 are described with the term "acute COVID-19 cardiovascular syndrome", comprising a wide array of pathologies.

A large US study which included 690,892 COVID-19 survivors and 690,892 controls without NCVI demonstrated that COVID-19 survivors had a higher risk of cardiovascular complications, such as stroke (OR 1.618, 95 % CI 1.545–1.694), AF (OR 2.407, 95 % CI 2.296–2.523), myocarditis (OR 4.406 95 % CI 2.890–6.716), ischemic cardiomyopathy (OR 2.811, 95 % CI 2.477–3.190), cardiac failure (OR 2.296, 95 % CI 2.200–2.396), pulmonary artery thromboembolia (OR 2.648, 95 % CI 2.443–2.870) [16].

A meta-analysis of over 2 million people showed that COVID-19 survivors had an additional 90 % risk of heart failure during 9 months after an acute infection [17].

In a study by Pogosova N. V. et al. under the "COVID-19: a remote follow-up" program, newly diagnosed AH and CHD were recorded in 4.2 % and 1.9 % of patients, respectively [18]. A study of 153 patients a month after COVID-19 showed that both systolic and diastolic blood pressure was higher during the post-COVID-19 period than upon admission in the acute period [19]. In their study, Ayoubkhani D. et al. present data on newly diagnosed cardiovascular complications (MI, stroke, death due to cardiovascular diseases) in 4.8 % of cases after discharge from the hospital after COVID-19 [20].

Maestre-Muñiz M evaluated PCS in persons who were hospitalised with COVID-19, one year after recovery. It was found out that 56.9 % of patients still had PCS a year after an acute infection, while 2 % had newly diagnosed AH and CCF de novo [21].

In 2020–2022, a clinical prospective observational study was conducted to identify the incidence and demonstrate the features of development of newly diagnosed CCF in post-NCVI patients with shortness of breath. The study gradually enrolled 368 patients with shortness of breath, who came to the outpatient clinic; mean time after COVID-19 recovery was 3.5 [1.5; 22.4] months. It was found out that the CCF incidence among post-COVID-19 patients with shortness of breath was statistically higher than in patients without a history of this pathology and made 19.0 % vs 9.8 % ($p = 0.021$). One out of five patients with shortness of breath had a more severe CCF 3.5 months after COVID-19, both as confirmed by clinical tests and blood NT-proBNP levels [22].

It is interesting to note that postural orthostatic tachycardia syndrome (POTS) in post-COVID-19 patients is a separate OCS type which is characterised by sinus tachycardia, postural tachycardia and inadequate sinus tachycardia [23]. Swedish scientists described a series of case studies in 3 patients with POTS 3 months after initial COVID-19 infection [24]. This syndrome is more common in women and is an autoimmune reaction to SARS-CoV-2 infection [25]. Miglis MG et al. described a case study of POTS in a 26-year-old nurse after infection with SARS-CoV-2. Symptoms of vegetative disorders persisted and aggravated for several months after recovery from COVID-19 [26].

A. S. Bagdasaryan et al. found out that, 12 weeks and more after COVID-19, post-COVID tachycardia was diagnosed in 100 % of cases, manifesting as POTS in 64.6 % and as inadequate sinus tachycardia in 19.1 % [27].

A study of 104 patients at the scientific and practical centre for PCS management at the University Clinic of the Federal State Educational Institution of Higher Education Tver Medical State University during a period from September 2021 to August 2022 revealed that, in a majority of patients with PCS, a standard tilt test gives an inadequate response, which is usually an increase in the heart rate by more than 30 bpm and raised systolic blood pressure by more than 20 mm Hg when the patient gets up from the bed [28].

The objective of the study in German COVID-19 survivors was to determine serological markers of cardiac damage (high-sensitivity troponin T and NT-proBNP tests) and to perform highly standardised cardiac imaging using magnetic resonance imaging. Median period between positive COVID-19 test and patient examination was 71 (64–92) days. It was found out that the highly sensitive troponin T values of over 3 pg/mL were recorded in 71 patients (71 %) and were significantly higher (over 13.9 pg/mL) in 5 patients (5 %). If compared to healthy controls, COVID-19 survivors had lower left and right ventricle ejection fraction, higher left ventricle volume and raised native T1 and T2 values as demonstrated by magnetic resonance tomography results [29].

2. Respiratory symptoms

Available data show that lungs are an organ which is most susceptible to COVID-19-induced pathophysiological changes, including diffuse destruction of alveolar epithelium, hyaline membrane formation, vascular damage and, thus, bleeding, fibrous proliferation and lung consolidation [5].

According to a retrospective cohort study conducted in England from January 1 to September 30, 2020, which analysed 47,780 patients, it was found out that respiratory disorders were diagnosed in 14,140 persons (29.6 %) after discharge, and 6,085 of them were newly diagnosed conditions [20].

A Chinese study to evaluate long-term symptoms in COVID-19 survivors 6 months after discharge demonstrated that a majority (22–56 % using various severity scores) of subjects had reduced diffusing lung capacity, as determined by spirography. The analysis included 1,733 patients, and during examination (with the mean follow-up period of 186 days) over a half of them still had abnormal chest computer tomography (CT) results, which independently correlated with lung involvement during the acute phase [30].

Similar data were presented in a study by You J et al., where a month after discharge 83.3 % of patients had abnormal chest CT results with a high share of pulmonary fibrosis. Pulmonary function assessment (spirometry) demonstrated prevailing restrictive disorders (reduced total lung capacity to < 80 % of the normal value or forced vital capacity to < 80 % of the normal value, with normal or increased ratio of forced vital capacity to 1 second forced expiratory volume and reduced diffusing lung capacity to < 80 % of the normal value) [31].

During a 6-month follow-up after recovery from COVID-19, Caruso D et al. found out that 72 % of patients had fibrous changes on CT [32].

Puja Mehta et al. proposed to use the term "post-COVID interstitial lung pathologies (ILD)" for patients with respiratory symptoms (cough, shortness of breath) lasting for over 3 months after acute COVID-19, whereas pulmonary tissue induration should be > 10 % of the lung area [33]. In a majority of cases, post-COVID pulmonary fibrosis does not progress; however, persistent interstitial changes in lungs are often associated with chronic respiratory failure and hypoxaemia, induced by physical load; thus, they impair quality of life and prognosis for patients and require adequate treatment.

In a French prospective cohort study, patients were examined 4 months after hospitalisation with COVID-19. During a phone call, 244 patients reported at least one symptom that they had not had before COVID-19, and newly diagnosed shortness of breath was recorded in 16 %. Chest CT was performed in 171 patient and demonstrated fibrous damage and ground-glass in 19.3 % and 42.4 % of patients, respectively [34].

Also, during the first study in the United Kingdom which reported long-lasting symptoms in COVID-19 survivors, it was found out that newly diagnosed shortness of breath was reported in 65.6 % of cases in ICU patients and in 42.6 % in therapeutic patients [35].

In a single-site prospective cohort study, 183 patients reported persistent symptoms 35 days after recovery from COVID-19, including 58 patients with shortness of breath and 46 patients with cough [36].

Lindahl A. et al. found out that 90 % of patients had several symptoms six months after inpatient treatment of COVID-19. According to available information, shortness of breath and cough were recorded in 66 patients (70 %) and 57 patients (61 %), respectively. Shortness of breath was assessed using mMRC score; the majority of men reported grade 1, while the majority of women — grade 2 [37].

According to the global ACTIV register, 9,364 patients were interviewed 3 months after recovery from COVID-19, and it has been shown that 38.7 % of respondents complained of shortness of breath [7].

An examination of 65 students from Tver State Medical University aged 18 to 25 years in post-COVID period demonstrated that the incidence of cough and shortness of breath was 7.7 % [38].

Xiong Q et al. showed that after a mean period of 79 ± 17 days (a period between first signs of COVID-19 and completion of questionnaire about persistent long-term symptoms after recovery), respondents reported a symptom — sore throat [39]. During the follow-up after 6 months after discharge from hospital after COVID-19, this symptom was recorded in 4 % of cases (69 patients out of 1,655 examined subjects) [30].

3. GIT manifestations

Literature sources mainly present information on aggravation of chronic gastrointestinal (GIT) diseases, such as gastroesophageal reflux disease, stomach ulcer, irritable bowel syndrome [40-42]. The main manifestations of GIT disorders are diarrhea and abdominal pain, which can persist for up to 4 weeks after the acute period of COVID-19 and are non-specific [43]. A number of Russian and foreign studies demonstrated that the incidence of bowels motor function disorders (diarrhea, constipation) varied from 3.6 % to 48 %, abdominal pain of any location — from 9 % to 32 % [44-46].

Hepatobiliary involvement is also temporary and is characterised by the development of acute hepatitis, drug-induced liver injury and aggravation of chronic hepatobiliary disorders [47]. Increased ALT, AST and bilirubin levels are temporary and are directly associated with the severity and therapy of COVID-19 [48]. Persistent liver changes are observed in pre-existing diseases [49]. Thus, these studies mainly present GIT changes during the acute phase of continuing COVID-19 and rarely last for more than 12 weeks.

4. Endocrine manifestations

It is well known that fasting glucose levels in COVID-19 patients are significantly higher than in patients with bacterial pneumonia, both in patients with and without DM [50]. Mechanisms of carbohydrate metabolism in COVID-19 patients are versatile and include virus affinity with pancreatic endocrine cells [51], insulin resistance caused by systemic pro-inflammatory reaction due to cytokine storm [52] and management of COVID-19 infection. A large cohort study (47,780 COVID-19 survivors) in England showed that DM after NCVI was diagnosed in 4.9 % of respondents [53].

In their study, Ruggeri RM et al. described a case study of a woman who developed subacute thyroiditis with thyrotoxicosis six weeks after SARS-COV-2 onset [54]. In a study of a large cohort of patients to identify persistent changes in thyroid gland functions after recovery from COVID-19, Bernard Khoo et al. found that, on the average during 79 days of follow-up, two patients were diagnosed with subclinical hypothyroidism, 4 patients had secondary hypothyroidism and 2 patients developed subclinical hypothyroidism without any prior thyroid disorders [55].

5. Neurological manifestations

A meta-analysis to study the incidence of long COVID-19 symptoms, which included 7 studies (47,910 patients aged 17 to 87 years), demonstrated that the most common symptoms were fatigue (58 %), headache (44 %) and poor concentration (27 %) [56].

A large meta-analysis of persistent neurological manifestations in 9,944 patients reports that the most common symptom in patients with a history of COVID-19 infection was fatigue (52.8 %); then cognitive disorders (35.4 %); paresthesia (33.3 %); sleep disorders (32.9 %); and dizziness (26.4 %) [57].

During examination of patients 4 weeks after recovery and a negative COVID-19 PCR test, the most common symptom reported by patients was fatigue 84.8 % (n = 420). The incidence of this symptom in 12 weeks was 82.9 % (n = 295) [58].

In their article, Rudroff T et al. define post-COVID-19 fatigue as reduced physical and/or mental capacity as a result of changes in central, psychological and/or peripheral mechanisms caused by COVID-19 [59].

In ICD-10, this PCS manifestation is included in G93.3 Postviral Fatigue Syndrome.

Data from a cohort study of outpatient patients (n = 458) showed a high incidence (46 %) of persistent feeling of tiredness 4 months after recovery, when Chalder Fatigue Scale (CFQ-11) was used [60]. Also, this scale was used to analyse the incidence of this symptom in a study of 128 subjects (49.5 ± 15 years old; 54 % were females), where a majority of patients reported persistent fatigue (67 subjects, 52.3 %) on the average 10 weeks after first symptoms of COVID-19 [61].

Halpin S et al. found out that fatigue after discharge (4–8 weeks later) was reported by 72 % of patients who were treated in ICU during the acute phase, and by 60.3 % of subjects who were treated in the therapeutic unit [35].

As evident from results of numerous studies, the most common and persistent signs of PCS, in addition to asthenia, are cognitive disorders, primarily poor attention and concentration, mental block.

In a study conducted at the State Budgetary Healthcare Institution of the Novosibirsk Region State Novosibirsk Regional Clinical Hospital to characterise neurological variants of PCS (neurology patients with a history of confirmed COVID-19), toxic and metabolic encephalopathy was prevailing — 412 subjects out of 455. This pathology manifested primarily with confused and depressed consciousness in 211 subjects (51.2 %), cognitive disorders (moderate cognitive disorders, dementia) in 201 subjects (48.8 %). Also, there was a case of a cerebrovascular pathology in the form of acute cerebrovascular accident (ischaemic type) in a 36-year-old woman without any history of vascular risk factors [62].

In an examination of a Spanish cohort during 6 months after discharge from the hospital after COVID-19, neurological manifestations were recorded in 20.8 % of cases. The most common symptoms were persistent anosmia and dysgeusia (7.2 %), headache (5.3 %), confused consciousness (2.6 %). 3.4 % of subjects had symptoms of paresthesia and tremor [63].

A prospective Italian study showed that one year after COVID-19, 22.0 % of subjects reported deterioration of olfaction or taste (67 patients out of 161) [64].

Out of 356 persons who reported persistent symptoms of COVID-19 12 weeks after diagnosis, 12 (3.4 %) patients noted loss of taste, 8 (2.2 %) patients — persistent headache, 18 (5.1 %) patients — anosmia [58].

The data from SF-36 quality of life questionnaire in a study by Arnold DT demonstrate low values both for physical and mental health after NCVI [65].

In a study by van den Borst, all SF-36 scores were reduced, especially physical and general health. Also, the Hospital Anxiety and Depression Scale (HADS) demonstrated abnormal values in 10 % and 12 % of subjects for respective parameters [66].

Deteriorated quality of life was recorded in 44.1 % of patients on EQ–5D scale, on the average 60.3 days after the first symptom of COVID-19 [67]. The most common symptoms in patients with PCS were anosmia, loss of taste and fatigue, when patients were observed 4 and 7 months after onset of COVID-19 symptoms [68].

6. Mental and behavioural disorders

In a study by Romero-Duarte Á. et al., the incidence of symptoms of mental disorders was 12.2 % after hospitalisation for COVID-19. The scientists recorded a high incidence of anxiety (6.8 %), sleep disorders (4.9 %) and symptoms of depression (4.4 %), primarily in women [63]. Similar data were reported in a Chinese study: sleep disorders were recorded in 26 % (437 subjects out of 1,655), anxiety or depression were recorded in 23 % of patients [30].

A large meta-analysis of the incidence of mental changes during the post-COVID period, which included 66 articles (3 to 266,586 subjects), demonstrated that 40 studies reported anxiety and/or depression, 20 studies — PTSD symptoms, 27 studies — cognitive deficit, 32 — fatigue during observation, and 23 studies reported sleep disorders. The identified risk factors were the severity, duration of symptoms and female sex [69].

7. Changes in other organs and systems

In a study by Romero-Duarte Á. et al., the most common symptom was exanthematous disease (3.1 %). High incidence of alopecia (3.0 %), especially in women, is of special interest [63]. In an article by Augustin M. et al., 9 patients (2.5 %) out of 353 reported alopecia after 7 months of follow-up [68].

35 days after discharge from hospital after COVID-19, 51 % of respondents reported permanent muscle pain [36]. According to guidelines developed by the Russian Scientific Medical Society of General Practitioners, "Features of long-COVID infection. Therapy and rehabilitation", post-COVID arthritis is diagnosed in 22.6 % of COVID-19 survivors, where articular syndrome is easily arrested with non-steroidal anti-inflammatory drugs. In patients with undifferentiated arthritis, rheumatoid disease was verified in 49 % of cases during 3–6 months (undifferentiated arthritis with antinuclear antibodies — 10 cases (26.3 %), Sjogren disease — 2 cases (5.2 %), systemic lupus erythematosus — 1 case (2.6 %), unspecified autoimmune disease — 1 case (2.6 %), rheumatoid arthritis — 2 cases (5.2 %), undifferentiated arthritis — 2 cases (5.2 %)) [5].

Results of available studies demonstrate long-lasting haemostasis changes after NCVI. However, currently, the clear pathogenesis of changes in these parameters is unknown. Several papers described increased D-dimer, C-reactive protein, ferritin in post-COVID period [70,71,72].

Artemyeva G. A. et al. examined 100 COVID-19 convalescents (55 patients 70–116 days (median: 99) after hospitalisation, 45 patients — 139–173 days (median: 160)). 37 subjects were controls. All patients underwent coagulation testing, aggregometry, thrombodynamics examination and clot dissolution test. Results demonstrated that 2–6 months after disease, patients had normalised clotting parameters, but clot dissolution was excessively activated [73]. In their study, Liam Townsend et al. found out that increased D-dimer levels persisted 2 months after recovery from acute COVID-19 infection and were observed in a cohort of predominantly young patients [70]. Venturelli S et al, reported several cases of pulmonary artery thromboembolia, with D-dimer levels of over 2,000 ng/mL, 80 days after discharge from the hospital after COVID-19 [74]. However, it is worth mentioning that studies of clinical manifestations of post-COVID clotting disorders are very few; they are limited to the number of observations and usually last maximum for a month after acute COVID-19 period. In their systematic review, Nalbandian A et al. assumed that the incidence of post-COVID venous thromboembolism was less than 5 % [75].

In addition, a number of studies report a long-lasting increase in blood cytokines, such as interleukin-6,

Table 1. *Characteristics of the severity of post-COVID syndrome*

System	Postcovid syndrome of mild severity	Postcovid syndrome of moderate severity
Cardiovascular system [16-29]	Non-physiological sinus tachycardia	De novo development/decompensation: – Coronary heart disease, including the development of myocardial infarction in the acute and post-acute period of COVID-19 – AF – CHF
	Elevation of high-sensitivity troponin T without myocardial infarction clinic	
	Post-COVID tachycardia syndrome (POTS, inadequate sinus tachycardia)	
	De novo development/aggravation of hypertension	
Bronchopulmonary system [5, 20, 30-39]	CT changes (not affecting quality of life)	CT changes affecting quality of life with a predominance of restrictive disorders according to spirometry
	Spirometry changes (not affecting quality of life)	Development of reversible and irreversible bronchial obstruction
	Dyspnea grade 0-1 (mMRC)	Dyspnea grade 2-5 (mMRC)
	Chronic cough	Development of interstitial lung disease
Gastrointestinal manifestations [40-49]	Abdominal pain	Exacerbation of the course of chronic diseases: – Gastroesophageal reflux disease – Peptic ulcer disease – Irritable bowel syndrome – Exacerbation of diseases of the hepatobiliary system
	Diarrhea/constipation	
	Functional dyspepsia syndrome	
		Drug-induced liver injury
Endocrinological manifestations [50-55]	Prediabetes	De novo development/decompensation of DM
		Subacute thyroiditis
	Subclinical hypothyroidism	Manifest hypothyroidism
		Subclinical Hyperthyroidism and Manifest Thyrotoxicosis
Neurological manifestations [35, 56-68]	Fatigue syndrome after a viral infection	Acute cerebrovascular accident and/or transient ischemic attack in the acute and post-acute periods of COVID-19.
	Paresthesias	
	Tremor	
	Vertigo	
	Cognitive disorders (attention disorders and decreased concentration, a feeling of «brain fog»)	
	Parosmia	Long-term persistent anosmia/dysgeusia
	Headache	
Mental and behavioral disorders [30, 63, 66, 69]	Development of subclinical anxiety/depression (HADS score 8-10, Spielberger scale less than 45)	Development of clinically significant anxiety/depression (HADS score of 11 or more, Spielberger scale greater than 45 points)
	Sleep disorders	Development of PTSD
Changes in other organs and systems [5, 36, 63, 68, 70-77]	Exanthema	Alopecia
	Muscle pain	Development of de novo rheumatological diseases.
	Disorders in the hemostasis system without clinical manifestations and with a low probability of thrombosis (IMPROVEDD score <2 points)	High risk of thromboembolic complications (IMPROVEDD score ≥2 points)

Note: AF — atrial fibrillation, CHF — chronic heart failure, hypertension — arterial hypertension, CT — computed tomography of the chest, PTSD — post-traumatic stress disorder, DM — diabetes mellitus

tumour necrosis factor alpha, nerve cell growth factor, etc. [76, 77]. However, this data are mostly fundamental, since routine clinical testing of these biomarkers is very expensive.

Hence, it can be concluded that identification of PCS severity is advisable not only in terms of classification and consolidation of available information, but also for the development of preventive and therapeutic measures. Taken analysed, available studies, it is assumed that PCS division into two severity stages is the most rational: mild PCS (development of potentially reversible conditions) and moderate PCS (development of a chronic condition or aggravation of a pre-existing disease). The impact of symptoms on the quality of patient's life should be taken into account as well. For instance, severe anxiety disorder has a more negative impact on the quality of patient's life than mild depression; even marked fibrous changes in lungs seen on CT not always impact the quality of life in some patients, but cause significant restrictive ventilation disorders in other persons.

Proposed PCS characteristics depending on severity are presented in Table 1.

Conclusion

Summing up the analysed data from available studies evaluating PCS in patients who had laboratory confirmed NCVI, at least 1 month after recovery, two stages of PCS severity were identified depending on the presence of identified signs, symptoms, newly diagnosed diseases and decompensation of pre-existing conditions (Table 1).

We believe that the presence and severity of PCS will depend on the presence of at least one sign from Table 1, which develops during or after verified COVID-19 infection and persists for over 4 weeks from disease onset; provided that it cannot be attributed to other reasons.

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