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ПОСТКОВИДНЫЙ СИНДРОМ: ПЕРСИСТЕНЦИЯ СИМПТОМОВ И ФАКТОРЫ РИСКА (ПРОДОЛЬНОЕ ОБСЕРВАЦИОННОЕ ИССЛЕДОВАНИЕ)

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Post-COVID Syndrome: Persistence of Symptoms and Risk Factors (Longitudinal Observational Study)

Резюме

Цель исследования: изучение динамики симптомов постковидного синдрома (в зависимости от результатов полимеразной цепной реакции на SARS-CoV-2) и факторов, оказывающих на нее влияние. **Материалы и методы.** Исследование когортное, обсервационное продольное. I этап: одномоментный анализ медицинских карт пациентов с давностью COVID-19 12 мес. (анкета на постковидный синдром, анализы крови). II этап: повторное анкетирование, давность заболевания — 24 мес. Выделены тестовая (положительная полимеразная цепная реакция, 138 чел.) и контрольная (отрицательная полимеразная цепная реакция, 87 чел.) группы. Статистический анализ: пакет Statistica 13.5.0.17. **Результаты.** Через 1 год после COVID-19 частота проявлений постковидного синдрома составила (тестовая *vs* контрольная группы): астения 63 % *vs* 64 %; снижение качества жизни 59 % *vs* 56 %; респираторный синдром 60 % *vs* 49 %; артралгии 55 % *vs* 49 %; кардиальный синдром 47 % *vs* 46 %, (разница не достоверна); симптомы, связанные с женским полом (r=0,231-0,379), тяжестью COVID-19 (r=0,187-0,425); Д-димер (r=0,244-0,328). Через 2 года частота симптомов составила: астения 43 % *vs* 45 %; кардиальные симптомы 23 % *vs* 15 %; респираторные симптомы 18 % *vs* 22 %; кожные проявления 8 % *vs* 12 %; снижение качества жизни 7 % *vs* 9 %, разница не достоверна; симптомы, связанные с возрастом (r=0,208-0,402). На протяжении двух лет симптомы коррелировали с тромбоцитами (r=-0,322-0,403), ферментами печени (r=0,216-0,298), липидами крови (r=0,188-0,257). **Заключение.** Выраженность постковидного синдрома не зависит от результатов полимеразной цепной реакции на SARS-CoV-2. Частота кардиальных и респираторных синдромов через 2 года снижается в 2-3 раза; качество жизни улучшается. Астения — самый долгосрочный синдром. Факторы риска постковидного синдрома в течение 1-го года — тяжесть COVID-19, женский пол, уровень Д-димера; со 2-го года — возраст. В течение двух лет после COVID-19 требуется контроль ферментов печени, липидного спектра, тромбоцитов.

Ключевые слова: *постковидный синдром, динамика, полимеразная цепная реакция, факторы риска*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The aim — studying the dynamics of symptoms of post-COVID syndrome (depending on the results of depending on the results of the polymerase chain reaction for SARS-CoV-2) and the factors influencing it. **Materials and methods.** A study is a cohort, observational longitudinal. Stage I: snapshot analysis of medical records of patients with COVID-19 disease history 12 months. (questionnaire for post-COVID syndrome, blood tests). Stage II: questionnaire repeat, disease history — 24 months. There were test (positive polymerase chain reaction, 138 people) and control (negative polymerase chain reaction, 87 people) groups. Statistical analysis: package Statistica 13.5.0.17. **Results.** 1 year after COVID-19, the frequency of manifestations of post-COVID syndrome was (test vs control group): asthenia 63 % vs 64 %, decreased quality of life 59 % vs 56 %, respiratory syndrome 60 % vs 49 %, arthralgia 55 % vs 49 %, cardiac syndrome 47 % vs 46 % (the difference is not significant); symptoms are associated with female gender (r=0.231-0.379), severity of COVID-19 (r=0.187-0.425), D-dimer (r=0.244-0.328). After 2 years, the frequency of symptoms was: asthenia 43 % vs 45 %, cardiac symptoms 23 % vs 15 %, respiratory symptoms 18 % vs 22 %, skin manifestations 8 % vs 12 %, decreased quality of life 7 % vs 9 %, the difference is not significant; symptoms are associated with age (r=0.208-0.402). During two years, symptoms have been correlating with platelets (r=-0.322-0.403), liver enzymes (r=0.216-0.298), blood lipids (r=0.188-0.257). **Conclusions.** The severity of post-COVID syndrome does not depend on the results of the polymerase chain reaction for SARS-CoV-2. The frequency of cardiac and respiratory syndromes after 2 years decreases by 2-3 times; quality of life improves. Asthenia is the most long-term syndrome. Risk factors for post-COVID syndrome during the 1st year — severity of COVID-19, female gender, D-dimer level; from the 2nd year — age. For two years after COVID-19, monitoring of liver enzymes, lipids, and platelets is required.

Key words: *post-COVID syndrome, dynamics, polymerase chain reaction, risk factors*

Conflict of interests

The authors declare no conflict of interests

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, LDH — lactic dehydrogenase, LDL — low density lipoproteins, NCVI — novel coronavirus infection, PCR — polymerase chain reaction, COVID-19 — COronaVIrus Disease 2019, SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2

Introduction

The term "post-COVID syndrome" is used to describe persistent or new symptoms arising three months after acute COVID-19 and not associated with alternative diagnoses [1, 2]. The incidence of post-COVID syndrome varies significantly — from 10-20 % (according to the WHO) to 60–80 % (meta-analyses and original studies) [3-5]. The significant difference in the information on the incidence of post-COVID syndrome is a result of its high clinical heterogeneity, as well as the lack of a unified and specific definition of this condition.

Various clinical symptoms comprising post-COVID syndrome are grouped into clusters (cognitive, neural and mental, cardiac and respiratory, digestive, asthenic, etc) [6]. Several risk factors of this syndrome have been identified; they are elderly age, higher body mass index, comorbidities, specific symptoms of acute COVID-19 (particularly dyspnoea), number of symptoms during the acute phase, and female sex [3, 7, 8].

It has been demonstrated that over time the incidence of symptoms reduces significantly; however, 6, 12, 18, and 24 months after COVID-19 diagnosis, the share of patients with at least one symptom is 32.3 %, 30.5 %, 25.8 %, and 33.3 %, respectively [9]. According to authors, the most long-lasting consequences of COVID-19 (with the longest follow-up period of 20 months) are sleep disorders, depression, paresthesia [6], hyposmia and fatigue [10], changes of skin and mucous membranes, excessive sweat, oedema [11]; the most long-lasting symptoms were found in women aged 20 years old and over [4].

There are evidences on the relationship between the severity of clinical manifestations of post-COVID syndrome and laboratory test results: D-dimer, markers of inflammation and hepatic cytolysis [8, 12], as well as the presence of positive polymerase chain reaction (PCR) to SARS-CoV-2 during the acute phase of the disease [13]. Therefore, continued observational studies of

post-COVID syndrome are of some interest: identification of its maximum duration and risk factors of symptom persistence.

Study objective: To study the changes in symptoms of post-COVID syndrome (depending on SARS-CoV-2 PCR results) and impacting factors.

Materials and Methods

Study type: cohort, observational longitudinal study. The study was conducted in the City Polyclinic LLC (Perm). The study consisted of two stages.

Stage one: a snapshot analysis of 447 medical records of outpatient patients aged 19 to 91 years old, who underwent comprehensive medical examination during a period from July 2021 to October 2022 (Order No. 698н of the Ministry of Health of the Russian Federation dated 01 July 2021, On the Approval of the Procedure of Citizen Referrals to a Comprehensive Medical Examination, Including Categories of Citizens Who Undergo a Priority Comprehensive Medical Examination. [Digital resource]. Garant.ru, informational and legal web portal, 1990–2021. Electronic data https://www.garant.ru/products/ipo/prime/doc/401344234/ (accessed on 25 January 2024) and had novel coronavirus infection (NCVI). All subjects were divided into two subsets: study subset with positive SARS-COV-2 PCR (227 subjects) and controls — with negative PCR (200 subjects). On the average, subjects had COVID-19 12 months before medical examination. Questionnaires for post-COVID syndrome identification [13], biochemical and clinical test results were evaluated.

Stage two: repeated questionnaires of subjects included in stage one in order to identify symptoms of post-COVID syndrome (phone calls). Response was provided by 138 subjects (61 %) in the PCR-positive subset and 87 subjects (44 %) in the PCR-negative subset, thus defining the final size of the study and control groups for descriptive and comparative statistics. During repeated questionnaires, the average time after recovery after COVID-19 was 24 months. The characteristics of groups are presented in Table 1.

The study group and controls are comparable in terms of age, sex, severity and time of NCVI.

Ethics. All patients provided their written consent for personal data processing upon inclusion in the advanced medical examination program.

Statistical analysis. Quantitative test parameters with non-normal distribution are presented as median (Me), 25(Q25) and 75(Q75) percentiles — Me (Q25–Q75 %), while qualitative variables are presented as percentage of an absolute number of patients in the groups. Statistical data processing was performed using the Kolmogorov–Smirnov test, Mann-Whitney test, Pearson's X^2 (comparison of frequencies in independent groups), McNemar test (comparison of frequencies in repeated questionnaires), Spearman's rank correlation in Statistica 13.5.0.17 application.

Results and Discussion

Laboratory test results from stage one of the study are presented in *Table 2*. Creatinine values in the study group were higher than in controls; nevertheless, they are within the normal range. The blood count was comparable in both groups.

Information from primary (stage one of the study) and repeated questionnaires (stage two of the study), as well as a comparative analysis of the incidence of subjective symptoms of post-COVID syndrome in patients with positive and negative PCR results, is presented in *Table 3*. The most common manifestations in primary questionnaires (on the average, 12 months after COVID-19) in both groups were symptoms of asthenic and respiratory clusters, as well as poorer quality of life and articular syndrome. Also, almost a half of respondents in the study group had anosmia and loss of taste, while the most common symptom in controls was cardiac syndrome.

Repeated questionnaires (on the average, 24 months after acute NCVI) demonstrated similar trends in persistence of post-COVID syndrome manifestations: the top five most common manifestations were asthenic, respiratory clusters, cardiac syndrome, skin symptoms and poorer quality of life. Nevertheless, there was a shift in accents within a set of symptoms: two years after NCVI, cardiac symptoms and respiratory manifestations were on the second place (in terms of incidence) after asthenic syndrome in the study group and controls, respectively. It is also worth mentioning that, while during the first year after acute COVID-19, poorer quality of life (second place in terms of incidence after physical and mental asthenia) was a dominant symptom, two years after the disease it shifted to the fifth place, and articular syndrome was less common than skin manifestations in both groups.

Table 1. *Characterization of the test and control groups*

Parameter	Test group, n=138	Control group, n=87	p
Number of men, *abs. (%)*	27 (20)	18 (21)	>0,1
Age, years, *Me (Q25-75 %)*	61 (47-70)	59 (44-67)	0,199
Mild severity of COVID-19, *abs. (%)*	59 (43)	49 (56)	>0,1

Note: p — level of significance of difference

Table 2. *Blood parameters of patients with laboratory confirmed (test group) and unconfirmed (control group) COVID-19*

Parameter	Test group, n=138	Control group, n=87	p
	Me (Q25-75 %)		
Clinical blood test			
Red blood cells, $x10^{12}$/L	4,4 (4,3-4,8)	4,5 (4,3-4,7)	0,606
Hemoglobin, g/l	134 (125-138)	133 (126-140)	0,769
Platelets, $x10^{9}$/L	235 (210-270)	246 (216-270)	0,041
Leukocytes, $x10^{9}$/L	6,3 (5,6-7,0)	6,2 (5,6-7,3)	0,882
ESR, mm/h	12 (7-15)	10 (7-14)	0,075
Blood chemistry			
ALT, U/L	18,7 (14,9-23,9)	17,4 (12,0-25,5)	0,262
AST, U/L	20,0 (17,2-24,4)	19,2 (17,3-23,0)	0,759
Glucose, mmol/l	5,1 (4,8-5,6)	5,0 (4,6-5,5)	0,102
β-lipoproteins, mmol/l	3,0 (2,3-3,8)	3,3 (2,6-4,0)	0,296
Cholesterol, mmol/l	5,2 (4,5-6,2)	5,4 (4,7-6,1)	0,530
Creatinine, μmol/l	90,0 (83,7-95,0)	89,0 (86,0-97,0)	0,004
LDH, U/L	184,9 (161,3-206,3)	187,5 (164,6-216,3)	0,449
D-dimer, ng/ml	0,36 (0,2-0,5)	0,31 (0,21-0,48)	0,283

Note: p — level of significance of difference

Table 3. *Survey data of patients with laboratory confirmed (test group) and unconfirmed (control group) COVID-19 to identify post-COVID syndrome*

Parameter	Test group, n=138	Control group, n=87	p
Primary survey			
Fatigue, muscle pain, dysautonomia, cognitive deficit, %	63,0	64,4	0,841
Decreased quality of life and performance, %	59,4	56,3	0,558
Shortness of breath, exercise intolerance, cough, %	56,5	49,4	0,115
Joint pain, %	55,1	49,4	0,409
Anosmia, ageusia, %	50,7	42,5	0,707
Chest pain, tachycardia, leg swelling, %	48,6	46,0	0,707
Hair loss, skin rash, %	42,0	32,2	0,139
Diabetes mellitus: newly diagnosed, unstable hyperglycemia, %	14,5	12,6	0,695
Temperature increase, %	13,8	14,9	0,806
Repeated survey			
Fatigue, muscle pain, dysautonomia, cognitive deficit, %	42,8	44,8	0,760
Chest pain, tachycardia, leg swelling, %	23,2	14,9	0,132
Shortness of breath, exercise intolerance, cough,%	18,1	21,8	0,493
Hair loss, skin rash, %	8,0	11,5	0,376
Decreased quality of life and performance, %	7,2	9,2	0,600
Joint pain, %	6,5	4,6	0,547
Anosmia, ageusia, %	5,1	2,3	0,301
Diabetes mellitus: newly diagnosed, unstable hyperglycemia, %	0,0	0,0	-
Temperature increase, %	0,0	0,0	-

Note: p — level of significance of difference

Changes in subjective manifestations of post-COVID syndrome during the year are presented in Figures 1 and 2. Study and control subjects had significantly fewer symptoms (even high temperature and hyperglycemia resolved), except for physical and mental asthenia. The examined cohort demonstrated similar changes in symptoms.

The most significant reliable relations between post-COVID syndrome manifestations and examined factors are presented in *Table 4*. Of note, the existence of symptoms one year after acute COVID-19 is greatly impacted by being a female in the study group, severity of past NCVI and D-dimer values in both groups.

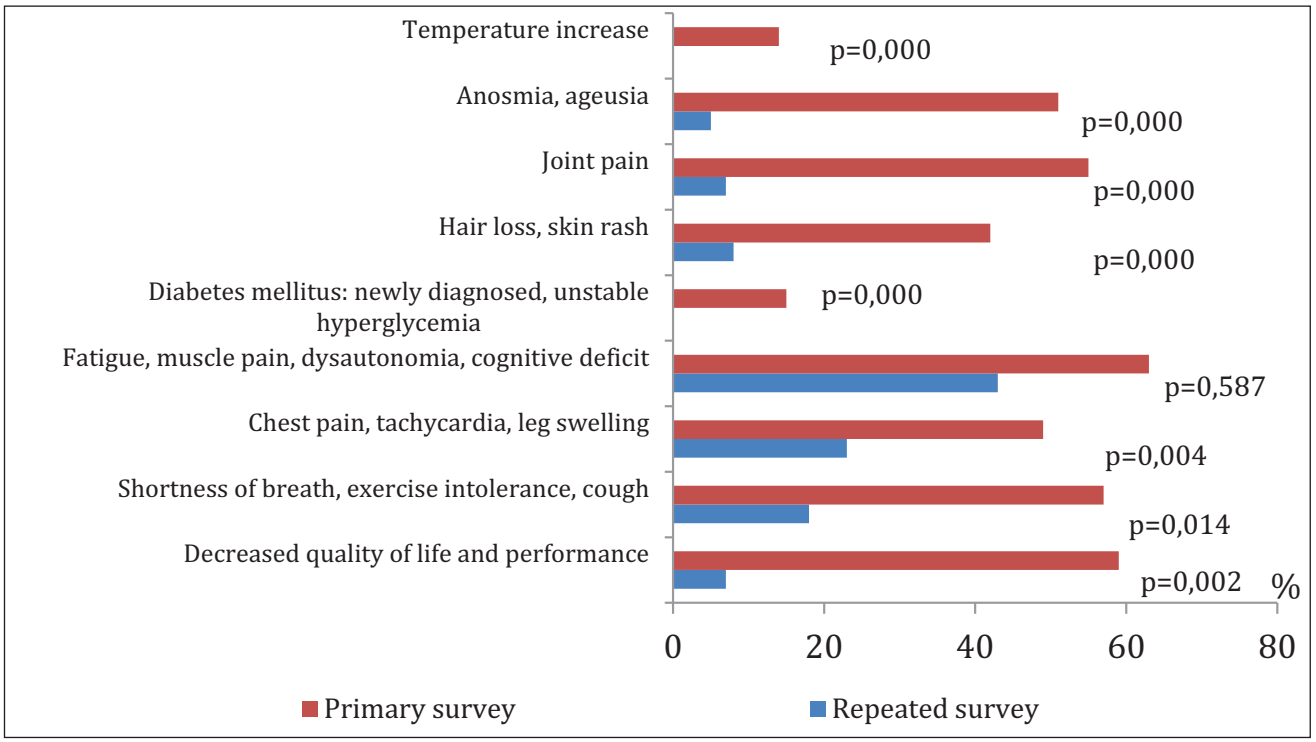

Figure 1. *Dynamics of symptoms of post-Covid syndrome in laboratory-confirmed (test group) SARS-CoV-2 infection*

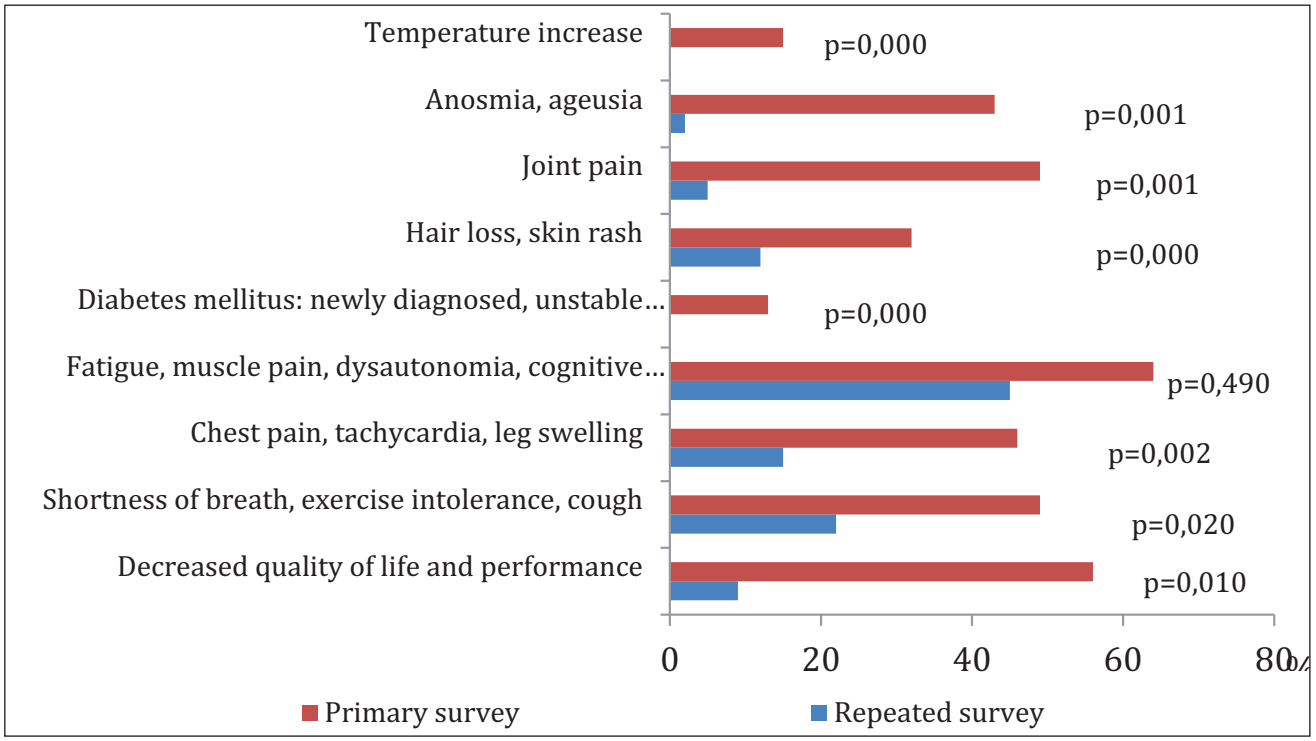

Figure 2. *Dynamics of symptoms of post-Covid syndrome in laboratory-unconfirmed (control group) SARS-CoV-2 infection*

Table 4. *Correlation analysis of manifestations of post-COVID syndrome in patients with laboratory confirmed (test group) and unconfirmed (control group) SARS-CoV-2 infection*

Parameter	Correlation coefficients in the test group/control group, *r, p <0,05*						
	Fatigue, muscle pain, dysautonomia, cognitive deficit	Decreased quality of life and performance	Shortness of breath, exercise intolerance, cough	Joint pain	Chest pain, tachycardia, leg swelling	Anosmia, ageusia	Hair loss, skin rash
Gender	0,379/-	0,374/-	0,231/-	0,289/-	0,296/-	0,281/-	0,309/ 0,230
Age	0,402/ 0,223	-	-	-	0,208/ 0,235	-/0,237	-
Severity of COVID-19	-/0,329	0,285/ 0,349	-/0,406	0,187/ 0,425	0,182/ 0,311	-/0,265	0,288 /0,226
Platelets	-/-0,370 -0,403/-	-	-/-0,347	-	-/-0,322	-	-
Alaninaminotransferase, Aspartataminotransferase, Lactate dehydrogenase	0,216/-	-/0,229 0,249/-	-/0,258	-/0,298	-/0,220 0,244/-	-	-/0,222
Cholesterol, β-lipoproteins	-/0,224	0,257/-	0,188/-	0,212/-	-	-	-
D-dimer	0,244/-	-	0,308/0,315	-	-/0,328	-	-/0,328

Note: correlation coefficients identified at the 2nd stage of the study are highlighted in red

Two years later, symptom prolongation is affected by age (asthenic, cardiac syndromes in both groups, loss of taste and anosmia in controls). During a two-year follow-up period, platelet count, hepatic enzymes and blood lipids still impact subjective manifestations of post-COVID syndrome. Lower platelet count in controls is associated with asthenic and respiratory syndromes during the first year, with cardiac syndrome two years after the acute phase; in the study group — with asthenia persisting for two years. Hepatic cytolysis is related to the major symptoms during the first year in controls and the second year in the study group; the quality of life and cardiac syndrome are affected the most. Total cholesterol and LDL levels are related to the quality of life, respiratory and articular syndromes in the study group and with asthenic syndrome in the control group (two years after NCVI).

Overall, the results of our study did not conflict to the literature data; however, there are some clarifications and updates. According to available reviews, during the first year after acute NCVI, the incidence of the most common signs of post-COVID syndrome are: physical and mental asthenia is recorded in 46–67 %, loss of taste and anosmia — in 27–41 %, respiratory symptoms — in 15–37 %, cardiac symptoms — in 31 % [6, 10, 11], joint pain — in 39 % [5]. In examined patients, the incidence of symptoms was slightly higher than the mentioned value and did not depend on SARS-CoV-2 PCR results. The high incidence of post-COVID syndrome resulted in significantly lower quality of life and disability during the first year after NCVI in over a half of patients.

During the second year after acute COVID-19, the incidence of subjective symptoms was considerably lower, except physical and mental asthenia, which can be considered the most prolonged manifestation of post-COVID syndrome. Lower severity of manifestations and adaptation to the condition over time made socialisation of post-NCVI patients possible, thus the number of patients who reported poorer quality of life dropped 6–7-fold. Unfortunately, the number of studies with the longest follow-up period of post-COVID-19-patients of 20–24 months is limited; nevertheless, they also demonstrate long-lasting signs of fatigue and cognitive disorders [3, 6]. Long-lasting post-COVID symptoms also include cardiac, respiratory and skin clusters. The latter is less common than articular syndrome during the first year after recovery; however, it is more persistent. Long-lasting NCVI manifestations are associated with delayed immune clearance of SARS-CoV-2 antigen or a high viral load during acute COVID-19 [14]. The latter is doubtful, since we have not found any difference in manifestation of post-COVID syndrome in patients with laboratory-proven and not confirmed SARS-CoV-2 infection. However, negative PCR results during the acute phase can be caused not only by test system faults, but also a low viral load.

There are some indications in literature that subjective signs of post-COVID manifestations last for 7–12 months in hospitalised patients and 4 months in non-hospitalised patients, thus confirming the relationship between symptoms persistence and severity of the acute phase [4]. This study has also established the relationship between post-COVID syndrome and NCVI

severity in both groups. On the other hand, acute phase severity matters only for the number of manifestations of post-COVID syndrome during the first year, thus probably explaining the difference in test results: some studies claim that disease severity does not impact long-lasting COVID-19 [9, 10].

In our study, female sex, which the majority of authors include in risk factors of post-COVID syndrome [2, 4, 7, 9], is a risk factor only during the first year after an acute infection; during the second year, persistent symptoms (particularly astehnia, cardiac symptoms, anosmia, loss of taste) are associated with age, which can be due to slower recovery and adaptation in older patients.

It is worth mentioning that, 12 months after NCVI, blood counts, blood biochemistry and D-dimers normalise, irrespective of baseline values during the acute phase and laboratory confirmation of NCVI. However, persistent post-COVID syndrome is affected by platelets count (negative correlation coefficient), LDH, AST, ALT, cholesterol and LDL, D-dimer (positive correlation coefficients), while the latter impacts the presence of subjective symptoms only during the first year after NCVI, all other parameters — during two years. These parameters make sense for several years for the purposes of assessing the long-term residual organ damage (lungs, heart, central nervous system, peripheral nervous system), since, for instance, it has been proven that the cardiovascular risk rises even one year after an acute disease, irrespective of long-lasting symptoms of COVID-19 [15].

Currently, multicenter, cohort studies are ongoing, which assess post-NCVI patients [2], the results of which will add to the data on the duration and signs of post-COVID syndrome, standardise test methods and identify approaches to patient management.

Conclusions

1. The incidence of signs of post-COVID syndrome does not depend on PCR results during acute SARS-CoV-2 infection.
2. Symptoms of post-COVID syndrome persist for at least two years; during the entire follow-up period, the main signs are: asthenia, cardiac and respiratory clusters, poorer quality of life, articular syndrome (the latter is less common than skin manifestations after the first year).
3. Physical and mental asthenia is the most long-lasting manifestation of post-COVID syndrome, its incidence does not reduce after two years after the acute phase and persists practically in a half of all patients.
4. After two years after COVID-19, the incidence of the main manifestations of post-COVID syndrome (cardiac and respiratory clusters) drops 2–3-fold; poorer quality of life is 6–7 times less common.
5. The risk factors for post-COVID syndrome are severity of acute NCVI and female sex during the first year, after that — age.
6. D-dimer is associated with subjective signs of post-COVID syndrome during one year after the acute phase; hepatic enzymes, lipid profile and platelet count should be monitored for at least two years.

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Author Contribution:

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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