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OPTIONS OF THE COURSE OF POST-COVID SYNDROME DEPENDING ON AGE, GENDER, COMORBIDITY AND SEVERITY OF THE COURSE OF COVID-19

A – research concept and design; B – collection of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

ABSTRACT. Among residents of Chernivtsi region, the main characteristics, frequency and peculiarities of the occurrence of long-term symptomatic and post-COVID-19 syndrome have not been sufficiently elucidated. **The goal** of the study was set: to evaluate the options for the course of the post-covid syndrome depending on age, gender, comorbidity and severity of the course of COVID-19.

Material and methods. The following research methods were used: electronic questionnaire, epidemiological, clinical and anamnestic, analytical and statistical methods. The study included 214 adult patients who were infected with the SARS-CoV-2 virus (the diagnosis was confirmed by PCR) and who suffered from COVID-19 of varying degrees of severity and were randomized into two groups: the 1st group (main) included – 112 people (ratio of men/women - 56.4 % (n = 63): 47.5 % (n = 49)), comparative (102 people) – patients with a mild and moderate course of COVID-19 who were consulted and were treated on an outpatient basis (male/female ratio – 45.5 % (n = 46): 54.5 % (n = 56)). Statistical processing of the data obtained during the research was carried out using the IBM SPSS Statistics v26.0 program.

Results. It was found that among inpatients there was a significantly significant number of patients older than 60 years old ($p < 0.001$), whereas among outpatients there were significantly more patients aged 18-29, which indicates a connection between the age of the respondents and the need for inpatient treatment presence of COVID-19. In the main group, the following symptoms occurred more frequently ($p < 0.05$): cough OR = 2.023 [CI 1.105-3.703], fever OR = 6.916 [CI 2.061-23.204], difficulty breathing (dyspnea) OR = 4.421 [2.230 -8.764]. In the comparison group, the following prevailed: loss of smell OR = 0.147 [CI 0.077-0.281], fatigue OR = 0.456 [CI 0.226-0.920], increased temperature OR=2.023 [2.061- 23.204]. With a higher frequency, such diseases as: coronary heart disease (OR = 33.088 [CI 9.444-115.930]), arterial hypertension (OR = 13.641 [CI 6.547-28.422]), diabetes (OR = 4.755 [CI 1.915-11.803]), heart failure (OR = 18.504 [CI 8.200-41.752]), obesity (OR = 4.828 [CI 2.433-9.581]).

Conclusions. 1. Among the patients who received inpatient treatment, the vast majority were people over 40 years old, younger men (from 40 years old) were more likely than women (over 60). **2.** In persons with a severe course of COVID-19, the frequency of symptoms of shortness of breath, cough, difficulty breathing, chest pain is more likely to be registered, and in outpatients - loss of smell and fatigue. **3.** With a greater frequency, such diseases as: coronary heart disease (37.5 %), arterial hypertension (57.4 %), diabetes (21.3 %), heart failure (54,1 %), obesity (41.1 %). Smoking and alcohol abuse did not show significant reliable differences. **4.** The combination of 3 pathologies (hypertension, heart failure, obesity) was most common - in 11 people (10 %).

KEYWORDS: *post-Covid syndrome, COVID-19, comorbidity*

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Introduction

Currently, many studies have been conducted on the pathogenesis of coronavirus infection caused by SARS-CoV 2 [1, 2]. Today, scientists all over the world are working hard to create high-quality medicines for COVID-19, in particular, they are conducting research in such areas as preventing the penetration of SARS-CoV 2 into the cell, disrupting the replication processes of the virus, suppressing the activity of an excessive systemic inflammatory reaction, using the blood plasma of patients who have recovered, vaccination, etc. [3, 4].

At the beginning of the COVID-19 pandemic, all attention was focused on the clinical manifestations of the acute course of the viral disease caused by SARS-CoV-2 [5]. However, it was soon discovered that after experiencing a coronavirus infection, patients continue to suffer from life-threatening symptoms associated with having experienced COVID-19 [4, 6, 7].

However, to date, due to various circumstances, no large-scale observational studies have been carried out in full, and clinicians can only obtain information from reports on cases of post-covid complications or small-scale personal observations [4, 8]. Therefore, despite the huge number of scientific publications, a clear picture of the distant consequences of COVID-19 remains insufficiently clarified.

An analysis of numerous published studies showed that the active phase of the coronavirus disease lasts up to 14 days in most patients. A more severe form of the disease, which requires hospitalization and intensive therapy, can last up to 3-6 weeks. Many people, even after recovery, continue to experience individual symptoms that last from a month to six months. To define this situation, a new term appeared, which quickly made it into the top news headlines - "post-covid syndrome" [9].

- It was practically the first to be used in Great Britain, where the National Institute for Health Care (NICE) proposed a sequential grading of post-covid syndrome (PSS). According to the National Institute for Health and Care Excellence (NICE) of Great Britain, the guideline "Treatment of long-term effects of COVID-19" (NG188) uses the following clinical definitions for primary disease and persistent COVID-19 depending on when they

occurred and during which they are stored:

- acute COVID-19 – signs and symptoms of COVID-19 are determined within 4 weeks;
- symptomatic COVID-19 that persists – signs and symptoms of COVID-19 persist from week 4 to week 12.
- "post-covid syndrome – signs and symptoms occurring during or after infection with COVID-19 persist for more than 12 weeks and are not explained by another alternative diagnosis. Usually, this is a group of symptoms that often repeat, can vary, change over time and affect any of the body's systems [10]. Post-covid syndrome can be observed from 2 to 6 months, and the possibility of an alternative underlying disease is also periodically evaluated [11].

Thus, the post-COVID syndrome is a multisystem syndrome characterized by a long course and can occur even after a relatively mild course of the acute period of COVID-19.

Currently, there are several variations of the definitions of this condition, which are worth mentioning, since they are quite often found in scientific publications. The Infectious Diseases Society of America (IDSA) distinguishes between "prolonged COVID", "post-COVID syndrome" and "post-acute COVID-19 syndrome". Harvard Medical School uses the definition of "long haulers." Post-COVID long-hauler («truck driver») – any person diagnosed with COVID-19, caused by SARS-CoV 2, who has not returned to their normal level of health and functioning 6 months after the illness. The term "chronic" or "long-term" course of an infectious disease implies long-term persistence of the pathogen [4].

Long-COVID – multisystem multiorgan disease: scientists identify more than 200 post-covid symptoms in 10 organ systems. Long-COVID-19 masks have a single multifactorial pathogenesis of complications:

- pathophysiological syndromes: endotheliitis, systemic inflammation and damage to the nervous system, damage to the respiratory system (pneumonitis) and pronounced asthenic syndrome [2, 6, 12].

Admittedly, we still don't know why most of the symptoms of post-covid syndrome develop. Actually, this causes serious difficulties in the

treatment of this condition. At the same time, observations indicate that most complaints and symptoms can pass on their own after a certain period of time.

However, an analysis of available scientific sources has shown that the consequences of transferred COVID-19 depend on the prevalence and severity of viral lesions in different cell types and organ systems [7, 13, 14].

In connection with the above, as well as the fact that the main characteristics, frequency and peculiarities of the occurrence of long-term symptomatic and post-COVID-19 syndrome among the residents of Chernivtsi region have not been sufficiently clarified, **we set the goal of the study:** evaluate options for the course of the post-Covid syndrome depending on the age, gender, comorbidity and severity of the course of COVID-19.

Material and methods

Our study used the NICE definition for post-covid syndrome [9], as one of the most frequently used definitions in the literature. The following research methods were used: electronic questionnaire, epidemiological, clinical and anamnestic, analytical and statistical methods.

Statistical processing of the data obtained during the research was carried out using the IBM SPSS Statistics v26.0 program. To assess the reliability of the difference between statistical data presented in percentages (nominal data), the Pearson's Chi-square test was used, and in the case when the number of measurements was less than 5, the Fisher's exact method was used. Values of $p < 0.05$ were considered reliable. In the process of statistical processing of the research results, the type of data distribution, the probability of the obtained results and other types of analyzes were determined. For the data corresponding to the normal distribution, the arithmetic mean of the sample (M), the value of the standard deviation (s) and the standard error (m), the maximum and minimum values were determined. Student's test (t) was used to compare the data of two groups with a normal distribution. A difference of $p < 0.05$ was considered significant. The assessment of the degree of influence of factor characteristics was carried out using the ratio of odds (OR) with the determination of a confidence interval of 95 % in order to assess the possibility of further use of the obtained results in the general population.

We conducted a cross-sectional observational study of long-term symptomatic COVID-19 and post-covid syndromes in residents of Bukovyna with a confirmed diagnosis of COVID-19 using a survey methodology and included patients who were ill with acute COVID-19 during the second and third waves of the pandemic.

At each of the stages, the survey was conducted in two ways: online - based on the results of consulted patients through the BSMU system. Heli (medical consultation center of the Bukovyna State Medical University) and through physical examination during direct contact with patients during face-to-face appointments at the clinical base of the department of phthisiology and pulmonology of the BSMU (KNP "Chernivetsk Regional Antituberculosis Dispensary"). No personal data was used during the survey, the survey was voluntary, open, and no remuneration was offered for participation in the survey. The obtained data were automatically (in the case of an online survey) and manually (in the case of a physical survey) entered into Excel tables and protected by a password.

Based on literature data, regarding the most frequent manifestations of long-term symptomatic COVID-19 and post-covid syndromes, we included in the questionnaire grouped questions about demographic information, the presence of comorbid conditions and laboratory confirmation of a case of COVID-19, a list of respiratory, digestive, and nervous symptoms (neurological symptoms and psychological manifestations), musculoskeletal system and dermatological manifestations. In addition to the questionnaire, a standardized scale "POST-COVID-19 FUNCTIONAL STATUS SCALE (PCFS)" was added in order to assess in more detail the degree of reduction in patients' working capacity [5, 15].

In total, 214 adult patients infected with the SARS-CoV-2 virus (diagnosis confirmed by PCR) and suffering from COVID-19 of varying degrees of severity were included in the study, who were randomized into two groups: 1st group (main) included - 112 people; 2nd group (control) - 102 people. The study period lasted from February 2021 to February 2022.

Criteria for inclusion in the study: persons, residents of Bukovyna, who have reached the age of 18 and older, who had preserved post-covid

symptoms after a laboratory-confirmed case of COVID-19.

Exclusion criteria from the study: laboratory-unconfirmed case of COVID-19; a laboratory-confirmed case of COVID-19, but without existing post-covid symptoms; persons younger than 18 years.

Results

During the research, the respondents were divided into two groups: the main one - patients with a severe course of COVID-19, who were consulted after the inpatient stage of the acute course of the coronavirus infection (n=112 (male/female ratio -

56.4% (n=63)): 47.5% (n=49)), comparative - patients with a mild and moderate course of COVID-19 who were consulted and treated on an outpatient basis (n=102 (male/female ratio - 45.5% (n=46): 54.5% (n=56)).

It was found that among inpatients there was a significantly significant number of patients older than 60 years old ($p < 0.001$), whereas among outpatients there were significantly more patients aged 18-29, which indicates a connection between the age of the respondents and the need for inpatient treatment presence of COVID-19, (table 1).

Table 1. Distribution of patients depending on the treatment option for COVID-19 by age

Age	Stationary (n=112)	Outpatient (n=102)	P
	%	%	
18-29	3,3	41,3	<0,001
30-39	6,6	28,7	<0,001
40-49	32,8	19,2	0,030
50-59	27,9	10,8	<0,001
Older than 60	29,5	0	<0,001

For the purpose of a more detailed analysis, a division into age categories was also carried out depending on the gender of the respondents. It was established that in the group of outpatient respondents there was a significantly higher percentage of women aged 18-29 years and men in the age subgroup 30-39 years compared to the group

of inpatients ($p < 0.05$) (Table 2). In the group of inpatients, there was a significantly higher percentage of women over 60 years of age, and the number of male respondents in the age subgroup of 40-49 years old significantly prevailed ($p < 0.05$) (Table 2).

Table 2. Age categories of patients depending on the gender of the respondents (%)

Age	Stationary women (n=27, %)	Outpatient women (n=88, %)	P	Stationary, men (n=27, %)	Outpatient, men	P
18-29	3,5	48,3	<0,001	3,1	31,6	0,002
30-39	10,3	24,2	0,111	3,1	34,2	<0,001
40-49	20,7	18,7	0,811	43,8	21	0,017
50-59	20,7	8,8	0,083	34,4	13,2	0,011
Older than, 60	44,8	0	<0,001	15,6	0	<0,001

Evaluating the symptoms of acute COVID-19 (see Table 3), we established the dependence of the growth of COVID-19 on the course of the acute disease of COVID-19 and found out that in the main group (inpatient) the following symptoms occurred more frequently ($p < 0.05$): cough OR = 2.023 [CI 1.105-3.703], fever OR = 6.916 [CI 2.061-23.204], difficulty breathing (shortness of

breath) OR = 4.421 [2.230-8.764]. In the comparison group (ambulatory), the following prevailed: loss of smell OR = 0.147 [CI 0.077-0.281], fatigue OR = 0.456 [CI 0.226-0.920], increased temperature OR = 2.023 [2.061-23.204]. It can also be observed that symptoms such as sore throat, headache, and muscle pain are almost equally common in the main and comparative groups ($p > 0.05$).

Table 3. Evaluation of symptoms during the acute phase of the disease of COVID-19 (%)

№	Feature	Stationary (n=112)	Outpatient (n=102)	OR	CI
	Indicators	%	%		
1	Cough *	63,9	46,7	2.023	1.105-3.703
2	Increase in temperature *	95,1	73,7	6.916	2.061-23.204
3	Difficulty breathing*	78,7	45,5	4.421	2.230-8.764
4	Pain in the throat *	21,3	25,7	0.781	0.386-1.579
5	Headache *	44,3	43,1	1.048	0.580-1.892
6	Pain in the muscles*	45,9	49,1	0.880	0.489-1.583
7	Anosmia *	31,1	75,4	0.147	0.077-0.281
8	Fatigue *	72,1	85	0.456	0.226-0.920
9	Diarrhea *	1,6	10,2	0.147	0.019-1.130
10	Sweating *	27,9	32,9	0.787	0.412-1.501
11	Chills *	27,9	22,2	1.357	0.696-2.648

Note: * $p < 0,05$; # $p > 0,05$

We evaluated the dependence of the manifestations of long-term symptomatic COVID-19 and post-covid syndromes on comorbid pathology (see Table 3). It was investigated that in the main group there is a higher probability of combination with comorbid pathology than in the comparison group (ambulatory patients). With a higher

frequency, such diseases as: coronary heart disease (OR = 33.088 [CI 9.444-115.930]), arterial hypertension (OR = 13.641 [CI 6.547- 28.422]), diabetes (OR = 4.755 [CI 1.915-11.803]), heart failure (OR = 18.504 [CI 8.200-41.752]), obesity (OR = 4.828 [CI 2.433-9.581]). Smoking and alcohol abuse did not show significant reliable differences.

Table 4. Assessment of the course of post-covid syndrome depending on comorbid pathology

№	Feature	Stationary (n=112)	Outpatient (n=102)	OR	CI
	Indicators	%	%		
1	Bronchial asthma	13,1	4,2	3.450	1.194-9.967
2	Coronary heart disease	37,7	1,8	33.088	9.444-115.93
3	Arterial hypertension	57,4	9	13.641	6.547-28.422
4	Diabetes	21,3	5,4	4.755	1.915-11.803
5	Heart failure	54,1	6	18.504	8.200-41.752
6	Overweight	41	12,6	4.828	2.433-9.581
7	Smoking	31,1	25,7	1.305	0.686-2.482
8	Alcohol abuse	1,6	1,2	1.375	0.122-15.442

In the course of the study, 49 people with a combination of comorbid pathology were also selected and the indicators were evaluated using Euler's circles. It is shown that the combination of all 5 diseases was present in the 1st person. A combination of 4 different pathologies in 6 people, 3 - in 9 people, 2 - in 21 people, one separate pathology - in 12 people. It is also worth noting that the combination of 3 pathologies (hypertension, heart failure, obesity) was most often encountered - the number of persons was 11.

Thus, prolonged symptomatic COVID-19 and post-covid syndrome is increasingly recognized as a new clinical manifestation in the context of SARS-CoV-2 disease. The pathogenesis of this syndrome is multicomponent, more than one mechanism may be involved in the formation of some clinical manifestations. Long-term inflammation plays a key role in the pathogenesis of post-covid syndrome and may be the driving force behind the appearance of distant consequences of the disease [3, 16].

Therefore, the experienced acute disease of COVID-19 often does not mean a full recovery and causes many remote consequences from various body systems. Taking into account the multifactorial pathogenetic features of the infection caused by SARS-CoV 2 (inflammation,

dysfunction of the nervous system, endothelial damage, thromboembolism), after the transfer of the acute phase of COVID-19, it is necessary to conduct further monitoring of the condition of patients in order to find out the prevalence and level of morbidity, clinical spectrum, consequences and the subsequent prognosis of the post-COVID syndrome.

Conclusions

- Among the patients who received inpatient treatment, the vast majority were people over 40 years of age, younger men (from 40 years old) clearly prevailed, as opposed to women (over 60).
- In persons with a severe course of COVID-19, the frequency of symptoms of shortness of breath, cough, difficulty breathing, chest pain is more likely to be recorded, and in ambulatory patients - loss of smell and fatigue.
- With greater frequency in persons treated inpatient, such diseases as: coronary heart disease (37.5 %), arterial hypertension (57.4 %), diabetes (21.3 %), heart failure (54.1 %), obesity (41.1 %). Smoking and alcohol abuse did not show significant reliable differences.
- The combination of 3 pathologies (hypertension, heart failure, obesity) was most common - in 11 people (10 %).

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ВАРІАНТИ ПЕРЕБІГУ ПОСТКОВІДНОГО СИНДРОМУ ЗАЛЕЖНО ВІД ВІКУ, СТАТІ, КОМОРИДНОСТІ ТА ВАЖКОСТІ ПЕРЕБІГУ COVID-19

A – концепція та дизайн дослідження; B – збір даних; C – аналіз та інтерпретація даних; D – написання статті; E – редагування статті; F – остаточне затвердження статті

АНОТАЦІЯ. Серед мешканців Чернівецької області недостатньо з’ясовані основні характеристики, частота та особливості виникнення тривалого симптомного перебігу та постковідного синдрому.

Мета дослідження: оцінити варіанти перебігу постковідного синдрому залежно від віку, статі, супутньої патології та тяжкості перебігу COVID-19.

Матеріал і методи. Використовували такі методи дослідження: електронне анкетування, епідеміологічний, клініко-анамнестичний, аналітичний та статистичний методи. У дослідженні взяли

участь 214 дорослих пацієнтів, які були інфіковані вірусом SARS-CoV-2 (діагноз підтверджено за допомогою ПЛІР) і хворіли на COVID-19 різного ступеня тяжкості та були рандомізовані на дві групи: 1-ша група (основна) включала 112 осіб (співвідношення чоловіки/жінки - 56,4 % (n=63): 47,5 % (n=49)), група порівняння включала 102 особи – пацієнти з легким та середньотяжким перебігом COVID-19, які отримували лікувалися амбулаторно (співвідношення чоловіки/жінки – 45,5 % (n=46): 54,5 % (n=56)). Статистичну обробку даних, отриманих під час дослідження, проводили за допомогою програми IBM SPSS Statistics v26.0.

Результати. Встановлено, що серед стаціонарних пацієнтів достовірно вищою була кількість осіб старше 60 років ($p < 0,001$), тоді як серед амбулаторних – достовірно більше осіб віком 18-29 років, що свідчить про зв'язок віку респондентів із потребами в стаціонарному лікуванні з приводу COVID-19. В основній групі частіше ($p < 0,05$) виникали такі симптоми: кашель OR = 2,023 [CI 1,105-3,703], лихоманка OR = 6,916 [CI 2,061-23,204], утруднене дихання (диспное) OR = 4,421 [CI 2,230 - 8,764]. У групі порівняння переважали: втрата нюху OR = 0,147 [CI 0,077-0,281], втомлюваність OR = 0,456 [CI 0,226-0,920], підвищення температури OR=2,023 [CI 2,061-23,204]. З більшою частотою спостерігаються такі захворювання як: ішемічна хвороба серця (OR = 33,088 [CI 9,444-115,930]), артеріальна гіпертензія (OR = 13,641 [CI 6,547-28,422]), цукровий діабет (OR = 4,755 [CI 1,915-11,803]), серцева недостатність (OR = 18,504 [CI 8,200-41,752]), ожиріння (OR = 4,828 [CI 2,433-9,581]).

Висновки. 1. Серед хворих, які перебували на стаціонарному лікуванні, переважну більшість становили люди старші 40 років, частіше зустрічалися чоловіки молодшого віку (від 40 років), ніж жінки (старше 60). 2. В осіб із тяжким перебігом COVID-19 частіше реєструється поява таких симптомів як задуха, кашель, утруднене дихання, біль в грудній клітці, а в амбулаторних пацієнтів – втрата нюху та втома. 3. З більшою частотою зустрічались такі захворювання як: ішемічна хвороба серця (37,5%), артеріальна гіпертензія (57,4%), цукровий діабет (21,3%), серцева недостатність (54,1%), ожиріння (41,1%). Куріння та зловживання алкоголем не мали суттєвих достовірних відмінностей. 4. Найчастіше зустрічалось поєднання 3 патологій (гіпертонічна хвороба, серцева недостатність, ожиріння) – у 11 осіб (10%).

Ключові слова: пост-ковідний синдром, КОВІД-19, коморбідність

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