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THE BURDEN OF RESIDUAL SYMPTOMS THAT COMPLICATE THE LIFE OF PATIENTS WHO HAVE SUFFERED A NEW CORONAVIRUS INFECTION (THROW STUDY)

<i>Aim</i>	To evaluate the prevalence of residual symptoms in patients hospitalized for novel coronavirus infection at 8 months after discharge and the severity of such symptoms depending on demographic characteristics, concurrent diseases, and specific features of the acute period of COVID-19.
<i>Material and methods</i>	This study included the patients who were managed for novel coronavirus infection in a COVID-19 hospital and provided their consent to participate in the study (98 patients). At 8 months after discharge from the hospital, a structured telephone interview was performed.
<i>Results</i>	Only 40% of patients treated for COVID-19 did not have any complaints at 8 months after discharge from the hospital. The most frequent complaints in the long term were fatigue (30.5%), weakness (28.4%), shortness of breath (23.2%), arthralgia (22.1%), myalgia (17.9%), and anosmia (15.8%). The background of chronic diseases and obesity, percentage of lung damage according to CT data, and the requirement for oxygen support during the acute period in our sample were not related with the presence of symptoms in the long term. The presence and severity of symptoms during the long term were not determined by the clinical condition, volume of lung damage, or requirement for oxygen support but were related with the gender and severity of inflammation upon admission.
<i>Conclusion</i>	Independent predictors for persistence of symptoms in the patient sample with severe novel coronavirus infection during the long term included chest and joint pain during the stay in the hospital, female gender, and increased levels of C-reactive protein upon admission.
<i>Keywords</i>	COVID-19; post COVID syndrome; C-reactive protein
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Introduction

The of COVID-19 has spread and affected the lives and health of people worldwide since its outbreak in Wuhan, China. Recent evidence has shown that some symptoms can persist long after the acute SARS-CoV-2 infection. This condition, i.e., signs and symptoms that occur during or after COVID-19 and last more than 4 weeks, is called long COVID or post-COVID syndrome [1]. On October 6, 2021, the World Health Organization (WHO) [2] issued a statement formulating and defining the criteria for post-COVID syndrome: “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of COVID-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis”. Post-COVID syndrome can manifest as fatigue, dyspnea, cardiovascular problems,

cognitive impairment, sleep disturbance, symptoms of post-traumatic stress disorder, muscle pain, trouble concentrating, and headache.

Despite a number of publications [3–5] devoted to post-COVID syndrome, there are very few works that study the severity of long-term symptoms depending not only on demographic characteristics, but on underlying polymorbidity and characteristics of the acute course of the novel coronavirus disease. There are currently no effective drug or non-drug treatments for patients with post-COVID syndrome. A comprehensive description of this population is required to identify potential therapeutic targets, with an emphasis made on identifying the underlying mechanisms of long-term sequelae. Understanding the predictors of post-COVID syndrome and the long-term recovery pathway could allow consistently planning the care for patients with a history of

COVID-19, who currently number more than 17 million in the Russian Federation. (<https://xn--80aesfpebagmfb1c0a.xn--p1ai/information/>).

Objective

Study the prevalence and the severity of long-term symptoms in patients hospitalized for COVID-19 eight months after discharge, depending on their demographic characteristics, the presence of comorbidities and the characteristics of the acute course of COVID-19.

Material and Methods

The study design was retrospective. The protocol was approved by the local ethics committee of the Ethics Committee of the Medical Research and Educational Center of the Lomonosov Moscow State University before the beginning of the study. All patients signed the informed consent to be included in the study.

Patients treated for COVID-19 at the temporary COVID hospital in Medical Research and Educational Center between April and June 2020 were enrolled in the study. Of the 184 patients consistently discharged from the hospital, 98 agreed to participate in the study, 61 patients refused to participate, the contact with 23 patients was lost, and 2 patients died within eight months after discharge.

The inclusion criteria were as follows: hospitalization in the temporary COVID hospital organized in the Medical Research and Educational Center of the Lomonosov Moscow State University for the management of COVID-19; recovery from COVID-19 according to the WHO criteria: no fever for three consecutive days, improvements in the patient's general condition and two negative polymerase chain reaction (PCR) test results for SARS-CoV-2 within 24 hours; signed informed voluntary consent to participate in the study.

The subjects were interviewed by telephone between December 2020 and February 2021, i.e., 8–9 months after discharge from the hospital, to identify symptoms believed to be related to post-COVID syndrome. A structured questionnaire was used, which was developed based on the available questionnaires used in other clinical studies of post-COVID syndrome [3]. The draft questionnaire was later supplemented with questions clarifying clinical manifestations of post-COVID syndrome. The full version of the questionnaire is provided in the Appendix (Appendix 1 published in the journal website).

NEWS-2 and SHOCS-COVID scores [6] were used, taking into consideration the percentage of lung damage as shown by computed tomography (CT) scanning, to assess the severity of patient condition during hospital treatment for acute coronavirus infection. Moreover, the in-hospital

results of complete blood count and biochemical blood tests were analyzed.

The data obtained were processed in R-Studio using the R programming language. Parametric quantitative indicators are described as the means and standard deviations, nonparametric indicators are expressed as the medians and interquartile range [25th percentile; 75th percentile].

Quantitative variables were compared using Student's t-test in case of normal distribution, and the Mann-Whitney test was used for non-normally distributed quantitative variables. The qualitative indicators were compared using the chi-squared test and two-tailed Fisher's exact test. The correlations between indicators were assessed using the Spearman's rank correlation coefficient. Logistic regression was used to assess the factors associated with the likelihood of long-term post-COVID symptoms. The critical significance threshold for the statistical hypotheses was set as 0.05.

Results

The final analysis included 98 patients. Sequentially discharged patients (those who were included in the study ($n = 98$) and those who refused to participate ($n = 61$)) were included in the analysis of the baseline data to demonstrate the absence of bias in the selection of subjects of the telephone survey. The comparative characteristics of respondents ($n = 159$) are presented in Table 2a (Appendix 2 in the journal website). There were no statistically significant inter-subgroup differences in any parameter.

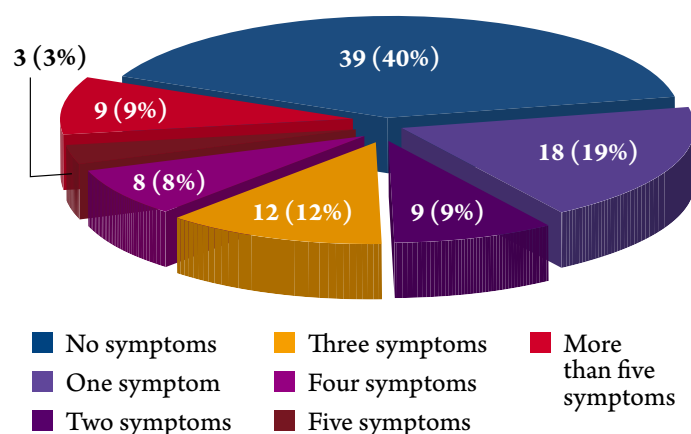
The analysis of the study results showed that, eight months after discharge from the hospital, no complaints were reported by 39 respondents, 1 symptom – 18 (19%) patients, 2 symptoms – 9 (9%), 3 symptoms – 12 (12%), 4 symptoms – 8 (8%), 5 symptoms – 3 (3%), 6 symptoms – 2 patients, 7 symptoms – 3 patients, 8 symptoms – another 3 patients, and only 1 patient complained of 10 symptoms after eight months (6 or more long-term complaints had 9% of patients; Figure 1).

The frequency of detecting symptoms at admission and eight months after discharge is presented in Figure 2. The most frequent complaints in the long term were fatigue (30.5%), asthenia (28.4%), dyspnea (23.2%), arthralgia (22.1%), myalgia (17.9%), anosmia (15.8%).

Further, subjects were divided into two groups: patients without symptoms and patients with symptoms eight months after discharge. Patients were assigned to the group with symptoms, if they still had ≥ 1 symptom. The comparative characteristics of patients is provided in Table 1.

Female patients were more likely to report having symptoms 8 months after COVID-19 ($p=0.010$). Older

Figure 1. Percentage of patients reporting the symptoms in 8 months



patients and patients with higher levels of C-reactive protein (CRP) at admission tended to have more symptoms. The groups did not differ in clinical status (SHOCS-COVID and NEWS-2 scores), volume of lung damage, and whether or not oxygen support was required.

The number and nature of complaints made during hospital stay was evaluated in patients with and without symptoms eight months after discharge from the hospital (Table 2).

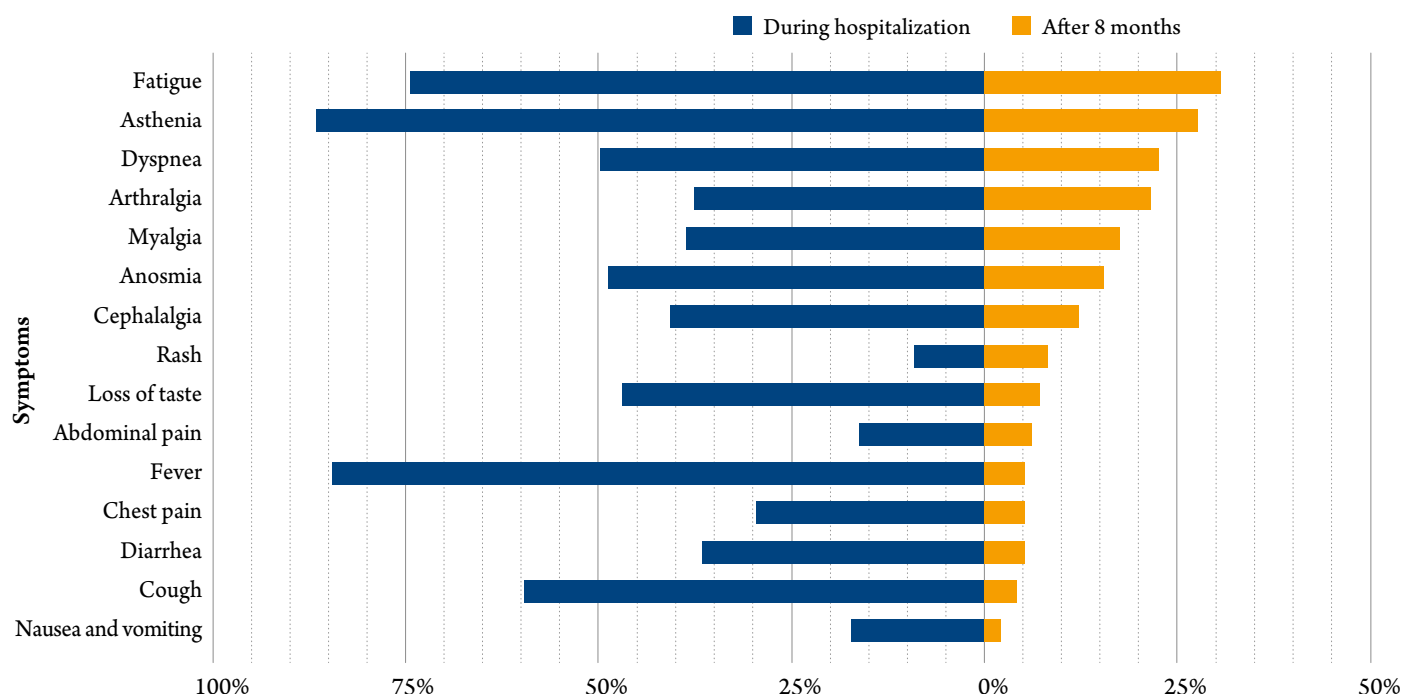
The results showed that patients without long-term symptoms eight months after discharge recalled less complaints during hospital stay (5.38 ± 2.61 versus 7.69 ± 2.74 , respectively).

The sex-specific analysis of long-term symptoms was later conducted. In our sample, male and female patients differed statistically significantly only in age. Female patients were older than male patients (60.7 ± 12.6 years and 51.6 ± 14.1 years, respectively; $p=0.001$). No differences were revealed in the severity of acute disease.

Table 3a present the comparative characteristics of two subgroups of patients hospitalized for COVID-19 (male ($n=56$) and female ($n=42$) patients) by long-term symptoms and frequency of detection during hospital stay and after eight months (Appendix 3 in the journal website). During hospital stay, female patients complained of the mean of 1 symptom more than male patients: women had the mean of 3 symptoms, and men had the mean of 2 symptoms ($p=0.005$), a statistically significant difference persisted in the long-term period. After eight months, 76.2% of female and 48.2% of male patients had complaints ($p=0.01$).

For the age-specific analysis of symptoms experienced by patients after eight months, the enrolled patients ($n=98$) were divided into two subgroups: patients older than the median age ($n=47$) and patient of median age and younger than the median age ($n=51$). The median age was 57 years. Patients did not statistically differ significantly in the number and nature of symptoms during hospital stay and differed only in one symptom after eight months. Patients older than 57 years complained of continuing asthenia after discharge twice as often as younger patients (38.3% versus 17.6%, respectively; $p=0.039$). A multivariate

Figure 2. Frequency of detecting symptoms at admission and eight months after discharge





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1. *Journal of the American Medical Association*, 1997; 277: 1039-1043.

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1. **Introduction**

1. **Introduction**

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1. *Journal of the American Medical Association*, 2000; 283: 2686-2692.

1. *Journal of the American Medical Association*, 2000; 283: 2689-2694.

Abstract

СОХРАНИТЬ САМУ
ЖИЗНЬ



Запатентованный механизм от 1 октября 2021 года
ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК*

3 года с 2017*

ФОРСИТА – единственный*
препарат, доказавший
замедление* прогресси-
рования ХБП на 39%¹⁻⁴

↓ 39% замедление*
прогрессирования
ХБП

по сравнению с плацебо
в исследовании



1 мг



1 мг



1 мг



1 мг

Table 1. Main characteristics at admission to the hospital depending on whether or not symptoms are present in 8 months

Parameter	Total of the subjects (n = 98)	Symptoms are not present in 8 months (n = 39)	Symptoms are present in 8 months (n = 59)	p
Age, years	55.5 ± 14.2	52.4 ± 13.8	57.5 ± 14.1	0.077
Male	56 (57.1)	29 (74.4)	27 (45.8)	0.010
BMI, kg/m ²	29.0 [25.5; 32.3]	28.5 [25.5; 32.6]	29.8 [25.5; 32.0]	0.610
Obesity (BMI ≥ 30 kg/m ²)	42 (43.8)	14 (36.8)	28 (48.3)	0.371
Arterial hypertension	44 (45.4)	16 (41.0)	28 (48.3)	0.620
CAD	11 (11.3)	4 (10.3)	7 (12.1)	1.000
Diabetes mellitus	13 (13.4)	3 (7.69)	10 (17.2)	0.271
Cancer	2 (2.08)	0	2 (3.51)	0.495
Any chronic comorbidities	46 (47.9)	17 (43.6)	29 (50.9)	0.621
RR, breaths per min	19.0 [18.0; 20.0]	20.0 [18.0; 21.5]	19.0 [18.0; 20.0]	0.265
HR, bpm	87.8 ± 15.0	89.1 ± 16.7	87.0 ± 13.9	0.512
SBP, mm Hg	120 [115; 132]	120 [115; 130]	123 [117; 133]	0.377
SO ₂ , %	95.0 [94.0; 98.0]	95.5 [93.2; 97.8]	95.0 [94.0; 98.0]	0.926
Any oxygen support	24 (24.5)	9 (23.1)	15 (25.4)	0.980
CRP, mg/dL	51.2 [13.2; 99.0]	25.8 [8.87; 90.8]	67.5 [17.0; 99.7]	0.103
D-dimer, µg/mL	0.50 [0.30; 0.96]	0.41 [0.28; 0.86]	0.53 [0.37; 0.98]	0.133
GFR (CKD EPI), mL/min/1.73 m ²	74.0 [61.0; 87.0]	78.0 [64.5; 87.0]	72.5 [61.0; 86.8]	0.680
Glucose, mmol/L	5.88 [5.30; 6.54]	5.72 [5.30; 6.47]	6.04 [5.28; 6.67]	0.425
Fibrinogen, g/L	5.51 ± 1.59	5.34 ± 1.47	5.61 ± 1.66	0.402
Platelets, × 10 ⁹ /L	210 [172; 257]	207 [172; 278]	211 [173; 250]	0.922
Lymphocytes, × 10 ⁹ /L	1.17 [0.84; 1.56]	1.17 [0.90; 1.65]	1.19 [0.83; 1.47]	0.571
Neutrophils, × 10 ⁹ /L	4.07 [2.59; 5.07]	4.14 [2.58; 5.23]	3.85 [2.59; 4.92]	0.584
NLR	3.01 [1.91; 4.68]	2.90 [1.98; 5.21]	3.13 [1.90; 4.67]	0.922
LCR	23.7 [8.35; 130]	43.5 [10.8; 149]	17.6 [8.24; 67.0]	0.130
CT stage				
1	64 (70.3)	29 (76.3)	35 (66.0)	0.196
2	20 (22.0)	5 (13.2)	15 (28.3)	
3	7 (7.69)	4 (10.5)	3 (5.66)	
SHOCS-COVID, score	5.00 [3.25; 7.00]	5.00 [3.00; 8.00]	5.00 [4.00; 7.00]	0.701
NEWS-2, score	3.00 [1.00; 5.00]	4.00 [2.00; 5.00]	3.00 [1.00; 4.00]	0.195

Parametric quantitative indicators are expressed as the means and standard deviations (M ± SD), non-parametric indicators are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]), qualitative indicators are expressed as the absolute numbers and percentages (n (%)). BMI, body mass index; CAD, coronary artery disease; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SO₂, blood oxygen saturation; CRP, C-reactive protein; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; CT, computed tomography; SHOCS-COVID, Symptomatic Hospital and Outpatient Clinical score for COVID-19; NEWS-2, National Early Warning Score 2.

logistic regression analysis was performed to assess the correlation between the parameters of interest and the maintenance of symptoms eight months after discharge from the hospital. The final models are presented in Table 3.

Chest and joint pain in the acute period of COVID-19, irrespective of sex and levels CRP at admission, were predictors of long-term maintenance of symptoms in the sample of patients with severe COVID-19.

Independent predictors of long-term maintenance of symptoms in the sample of patients with severe COVID-19 were chest and joint pain during hospital stay, female sex, and higher levels of CRP at admission to the hospital.

Discussion

Since 2020, dozens of studies have been published providing evidence that many patients had persistent symptoms within a year after COVID-19 [3, 7–9]. There are evidence signs that even patients with a history of mild or moderate COVID-19 have subclinical multi-organ involvement associated with lung, heart, and kidney dysfunction, as well as deterioration in the quality of life [10]. We made an attempt to estimate the prevalence of long-term symptoms after eight months in patients hospitalized for COVID-19 and analyze early predictors of post-COVID syndrome.

Among our patients, 60% had at least one complaint eight months after discharge from the hospital. Fatigue

(30.5%), asthenia (28.4%), and dyspnea (23.2%) were the most common symptoms. In the Italian study [3], which is most consistent with ours in design and the included population, the presence of fatigue, dyspnea, joint pain, and chest pain was reported by 53.1%, 43.4%, 27.3% and 21.7% of patients, respectively, two months after discharge from the hospital. The cross-sectional study by Belgian and Dutch researchers showed that fatigue persists 79 days after the onset of the disease in 92.9% and 93.5% of hospitalized and outpatient patients with COVID-19, respectively [11].

We did not find any relationship between the severity of the acute course of COVID-19 and the presence of complaints in the long term. The inclusion of only hospitalized patients in obvious serious condition definitely limits the possibility of assessing the impact of the disease severity on the onset of long-term symptoms. Some publications reported the detection of long-term symptoms even in the outpatient course of the disease, but the percentage of complaining patients was usually lower. In the study including 410 Swiss outpatients with mild COVID-19, 39% of subjects reported persistent symptoms seven to nine months after the onset of infection. At the same time, the range of symptoms was comparable to that observed in our study: the most frequent symptoms were fatigue (21%), loss of taste or smell (17%), dyspnea (12%), and headache (10%) [12]. In another study, 19% of outpatients with symptomatic infection had one to two persistent symptoms after six months, 14% had ≥ 3 persistent symptoms, and 29% reported a deterioration in the quality of life [7].

In 2022, the prospective longitudinal cohort study PHOSP-COVID, which included patients with COVID-19 discharged from the hospital, was published [13]. The recovery was assessed five and twelve months after discharge. After five months, 501 (25.5%) of the 1,965 patients felt fully recovered, 385 (19.6%) hesitated, and 1,079 (54.9%) did not recover. After twelve months, 232 (28.9%) of the 804 patients felt fully recovered and 392 (48.8%) did not recover. The percentage of patients reporting complete recovery did not change between the cutoff points of five months (25.5%) and twelve months (28.9%). Factors associated with a lower likelihood of full recovery after twelve months were female sex (odds ratio (OR) 0.68; 95% confidence interval (CI) 0.46–0.99), obesity (OR 0.50; 95% CI 0.34–0.74), and invasive mechanical ventilation (OR 0.42; 95% CI 0.23–0.76).

In our study, female sex was also associated with a higher likelihood of having symptoms in the long term.

Table 2. Frequency of detecting symptoms during hospitalization in the groups with the presence and absence of long-term symptoms

Parameter	Symptoms are not present in 8 months (n = 39)	Symptoms are present in 8 months (n = 59)	p
Cough	19 (48.7)	39 (66.1)	0.133
Fever	35 (89.7)	48 (81.4)	0.400
Dyspnea	13 (33.3)	36 (61.0)	0.013
Chest pain	5 (12.8)	24 (40.7)	0.006
Loss of taste	16 (41.0)	30 (50.8)	0.455
Anosmia	18 (46.2)	30 (50.8)	0.804
Asthenia	31 (79.5)	54 (91.5)	0.157
Nausea and vomiting	3 (7.69)	14 (23.7)	0.075
Myalgia	10 (25.6)	28 (47.5)	0.050
Arthralgia	7 (17.9)	30 (50.8)	0.002
Cephalalgia	12 (30.8)	28 (47.5)	0.151
Skin rash	1 (2.56)	8 (13.6)	0.090
Diarrhea	9 (23.1)	27 (45.8)	0.039
Abdominal pain	6 (15.4)	10 (16.9)	1.000
Fatigue	25 (64.1)	48 (81.4)	0.093
Total number of complains	5.38 $\pm$ 2.61	7.69 $\pm$ 2.74	< 0.001

Parametric quantitative indicators are expressed as the means and standard deviations (M $\pm$ SD), non-parametric indicators are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile], qualitative indicators are expressed as the absolute numbers and percentages (n (%)).

Table 3. Predictors of the presence of symptoms eight months after discharge Data of the multivariate binary logistic regression analysis

Parameter	OR	95% CI	p
Arthralgia at admission	4.81	1.63–15.93	0.006
Chest pain at admission	4.26	1.25–17.01	0.027
Dyspnea at admission	2.36	0.80–7.20	0.132
Diarrhea at admission	1.69	0.57–5.17	0.344
Female	3.14	1.11–9.54	0.034
CRP at admission (< 51/> 51 mg/dL)	3.62	1.31–10.81	0.016

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein. The accuracy, sensitivity, and specificity of the model was 0.765, 0.847, and 0.641, respectively.

At the same time, obesity, severity of lung damage shown by CT scanning, and whether or not oxygen support was required, were not associated with the development of post-COVID syndrome. We did not assess the effect of mechanical ventilation separately due to the small number of patients in the sample who were subjected to this procedure.

The mechanisms underlying the long-term maintenance of symptoms are not known for certain. The main hypothesis is that hyperinflammation does not resolve in the acute period of COVID-19 and leads to a persistent inflammatory condition associated with immune dysregulation and multi-organ dysfunction. In the above mentioned PHOSP-COVID study, elevated levels of CRP and interleukin-6 were established, which, after five and twelve months, were higher in patients with greater severity of post-COVID manifestations than those with minimal health problems. In our study, CRP was estimated only at admission to the hospital. It has been shown that patients with higher levels of CRP were more likely not to feel fully recovered eight months after discharge. These findings may also provide a support for the suggestion of the inflammatory nature of post-COVID syndrome. Higher levels of CRP at admission to the hospital may be indicative of a contribution of inflammation to the development of post-COVID syndrome and the need for active preemptive anti-inflammatory therapy during the acute infectious process in hospitalized patients with COVID-19.

We did not find publications that analyzed the association of long-term symptoms with symptoms observed during hospitalization. Our work shows that joint and chest pain during hospital stay are independent predictors of the presence of long-term complaints, irrespective of the CRP levels, patient's sex and age. Perhaps, the presence of these symptoms in the acute period would be the ground for considering a patient a higher risk for developing post-COVID syndrome. Of course, this suggestion requires additional verification, but the relevance of a symptom screening questionnaire for rehabilitation planning was shown by other researchers [9].

Limitations

First of all, the study is limited by a small sample size, one investigational site, a potential bias due to the fact that the symptoms are reported by the patients. Moreover, the study design did not allow separating the new complaints that appeared after COVID-19 from the complaints that could have been present before COVID-19. However, our and other studies show that the health effects of COVID-19 go far beyond acute infection, even among patients with a history of mild disease. Long-term and large studies will definitely be required to assess the systemic impact of this viral pathogen.

Conclusion

Only 40% of patients included in our study had no complaints eight months after discharge from the hospital. The presence and severity of symptoms in the long term were not determined in hospitalized patients by clinical status (SHOCS-COVID and NEWS-2 score), volume of lung damage, and whether or not oxygen support was required. Independent predictors of maintenance of symptoms after eight months in the sample of patients with severe COVID-19 were chest and joint pain during hospital stay, female sex, and higher levels of C-reactive protein at admission to the hospital.

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