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Original Article

Predictors of long-term shortness of breath in COVID-19: A prospective study

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ABSTRACT

Persistent symptoms after COVID-19 continue to be actively studied today due to their impact on the quality of life of patients. The symptoms of long-term COVID-19 have a wide range and require long-term monitoring, and even repeated hospitalization due to deterioration of the condition. The study aimed to determine the predictors of the persistence of prolonged shortness of breath in patients in the post-covid period and to analyze their survival. The observational, prospective multicenter cohort study included 252 hospitalized COVID-19 patients (56% women, average age 47), monitored for 48-96 weeks post-infection from 2020 to May 2022. Shortness of breath was assessed via physical activity in a subsample, with risk factors identified using chi-squared, Fisher's exact, and Wilcoxon rank sum tests, and logistic regression for survival analysis. Long-term follow-up (48-96 weeks) of 252 acute COVID-19 patients showed that 90 patient (35.7%) retained practically all acute symptoms, although severity did not affect them. In the 90 patients, 56 (62.2%) developed chronic shortness of breath and were hospitalized again. Prolonged dyspnea in postcovid syndrome was statistically dependent on acute infection severity, neutrophil, fibrinogen, and CRP levels, and lung CT alterations. Predicting the development of dyspnea based on basic markers of inflammation and the CT picture of the lungs can be used in various settings, including the level of primary health care, which can help promote early and effective treatment.

Keywords: Primary health care, Shortness of breath, COVID-19, Postcovid syndrome, Quality of life

Introduction

The acute phase of COVID-19 is characterized by a wide range of clinical symptoms with a spectrum of adverse effects on multiple organ systems. While most individuals recover totally from acute COVID-19, a significant minority has protracted sequelae affecting several physiological systems, including pulmonary, neurological, and cardiovascular domains, as well as mental health [1]. Typically presenting three months post-infection, post-COVID-19 syndrome (or post-acute sequelae of SARS-CoV-2 infection) is defined by the World Health Organisation (WHO) as a condition arising in persons with confirmed or probable SARS-CoV-2 infection, typically manifested three months post-infection, with symptoms persisting for a minimum of two months and not attributable to alternative diagnosis [2].

Acute COVID-19 symptoms could linger or recur, resulting in medium long-term clinical consequences that greatly limit patients' everyday activities [3, 4]. Recent epidemiological studies show that the cumulative prevalence of post-COVID syndrome ranges from 9% to 63%; affected individuals commonly exhibit at least one of several symptoms, including fatigue, dyspnea, cough, cognitive dysfunction, myalgia, thoracic pain, memory impairment, sleep disturbances, changes in olfactory and gustatory senses, cephalalgia, and mood disorders including depression [5, 6]. Crucially, these effects show regardless of the degree of the original illness, the strength of the

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therapeutic measures, or the kind of respiratory assistance given [7]. Still, they are more often seen in middle-aged women, patients showing more acute phase symptoms, and those needing hospitalization than in outpatients [8].

Notwithstanding progress in knowledge and control of acute COVID-19, early identification of individuals at risk for post-COVID syndrome and the use of sensible care techniques still present difficult tasks [9]. Thus, thorough studies are needed to clarify the correlations between acute phase symptomatology and the following development of post-COVID syndrome as well as to find possible predictive elements. This study aims to define factors related to the development of post-COVID problems and methodically assess the long-term repercussions of COVID-19 in a group of individuals with acute SARS-CoV-2 infection.

Materials and Methods

252 COVID-19 patients hospitalized in the period 2020-2022 at the Osh Interregional Clinical Hospital (OMOCB) were under observation Osh region, Kyrgyz Republic. Inclusion criteria for follow-up: persons aged 18 years and older who received inpatient treatment for COVID-19 and had various symptoms of the disease after recovery for at least 24 weeks. The exclusion criteria were: patients with disabilities, patients transferred from another hospital, pregnant women, visitors from other regions, and foreign citizens. The clinical, laboratory, and instrumental data of 252 patients in the acute stage of infection and dynamics over two years were studied. Of these, 90 patients still had symptoms: shortness of breath, myalgia, chest pain, loss of sense of smell, and loss of taste. Patients were observed in family medicine centers at their place of residence after recovery from COVID-19 in 2-3, 6-9, and 12-15 months. Patients filled out questionnaires with questions about persistent symptoms and emerging new symptoms. The study of symptoms was carried out using questionnaires and scales and monitoring their duration.

Study design

A multicenter, prospective observational cohort study was conducted over two years from 2020 to May 2022. Data analysis included calculations of indicators using n (%), median (IQR), Pearson's chi-squared test, Fisher's exact test, and the Wilcoxon rank sum test. Logistic regression was employed to assess patient survival, and risk factors associated with prolonged shortness of breath were systematically identified.

Statistics

For all indicators, a bilateral p-value of less than 0.05 was deemed statistically significant. All data underwent processing utilizing the R statistical package. Standard methods of descriptive statistics were used for analyzing the data, utilizing mean values along with standard deviations (SD) for continuous variables. A multifactorial logistic regression model was applied to identify the predictors of symptom duration and to forecast patient survival outcomes. An exhaustive model encompassing all indicators was assessed. We employed reverse variable selection to pinpoint the most significant variables within the model. The risk profiles were derived from a model incorporating a selection of variables.

Results and Discussion

The study included 252 individuals diagnosed with acute COVID-19, 56% of them female and with an average age of 47 years. Out of 252 individuals, 90 (35.7%) developed postcovid syndrome after a 48 to 96-96-week period; the most common symptom recorded by 85.5% of those afflicted was overall weakness. Of the patients, 58.1% experienced headache; followed by shortness of breath at 29.7%; chest discomfort at 24.3%; and myalgia at 23.8%). Furthermore reported were loss of taste in 12.6% of people and loss of sense of smell in 6.8% of them. Recorded less often at 5.4% was diarrhea **(Figure 1)**.

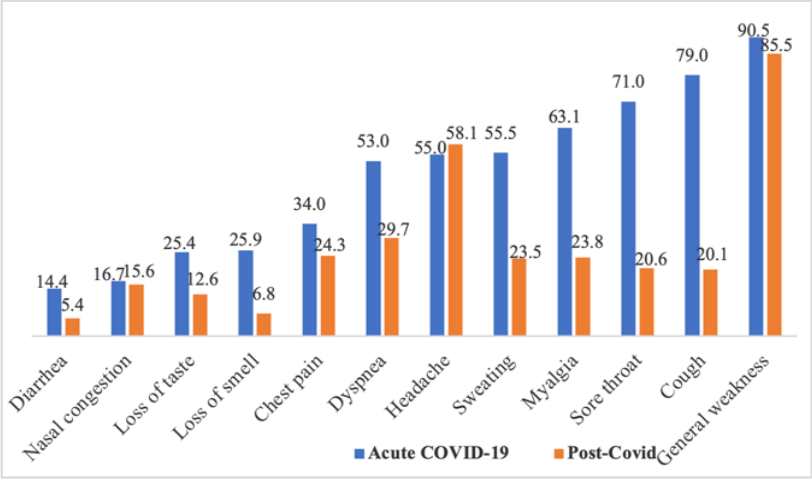

Figure 1. Comparative analysis of symptoms in acute COVID-19 and post-COVID syndrome among patients treated at OMOKB between 2020-2022 (n=252).

Potential predictors for the development of post-COVID syndrome include the severity of the initial COVID-19 infection, extended periods of viremia, and the presence of hyperinflammatory responses during the acute phase of the illness

[10]. A detailed analysis was conducted to explore the clinical symptoms of post-COVID syndrome and their duration. This analysis aimed to determine how these symptoms and their persistence are influenced by the severity of the acute COVID-19 infection **(Table 1)**.

Table 1. The relationship between various indicators in patients with post-COVID syndrome who underwent inpatient treatment at OMOKB from 2020 to 2022 and the severity of their acute COVID-19 infection (n=90) was analyzed.

Indicators		mild, (n = 4[1])	Moderate (n = 30[1])	severe, (n = 56[1])	P-value[2]
Sex	Men	1 (25)	9 (30)	35 (62)	0.007
	Women	3 (75)	21(70)	21 (38)	
Age	15-29 Years	3 (75)	2 (6.7)	1 (1.8)	<0.001
	30-44 Years	1 (25)	6 (20)	5 (8.9)	
	45-59 Years	0 (0)	11 (37)	15 (27)	
	60-74 Years	0 (0)	8 (27)	30 (54)	
	75 + Years	0 (0)	3 (10)	5 (8.9)	
Myailgia		3 (75)	22 (73)	37 (66)	0.8
Dyspnea		0 (0)	15 (50)	41 (73)	0.002
General weakness		4 (100)	27 (90)	55 (98)	0.3
Chest pain		0 (0)	9 (30)	27 (48)	0.073
Nasal congestion		1 (25)	3 (10)	11 (20)	
Loss of taste		1 (25)	6 (20)	16 (29)	0.8
Loss of sense of smell		1 (25)	6 (20)	17 (30)	0.7

[1] N (%)

[2] Fisher's Exact Test

A longitudinal follow-up study, lasting 48 to 96 weeks, of patients who had acute COVID-19 showed that virtually all symptoms from the acute phase remained over time. No substantial link was seen between the duration of these symptoms and the initial severity of the disease. Nevertheless, one symptom was particularly prominent in individuals experiencing post-COVID syndrome: dyspnea [11]. This symptom was significant since it resulted in recurrent hospitalizations, highlighting its possible long-term consequences. Consequently, we choose to concentrate on a more detailed analysis of this specific symptom **(Table 2)**.

The study investigated several predictors, focusing on the relationship between gender, laboratory parameters, lung changes observed through computed tomography (CT), and the presence of shortness of breath. Out of the 90 patients analyzed, 56 individuals (62.2%) experienced prolonged shortness of breath. A comparative analysis between patients with persistent shortness of breath and those without revealed significant findings. The severity of the acute phase of the illness, along with elevated levels of neutrophils, fibrinogen, C-reactive protein (CRP), and notable changes in lung patterns on CT scans, were statistically significant factors associated with the development of post-COVID syndrome.

Table 2. Comparative analysis of various indicators of patients with postcovoid syndrome with and without dyspnea who received inpatient treatment in OMOCB in the period 2020-2022 in % (n=90)

Indicators		Patients with dyspnea (n = 56[1])		Patients without dyspnea, (n = 34[1])		P-value[2]
		n	%	n	%	
Sex	Male	33	59	12	35	0.030
	Female	23	41	22	65	
Age	15-29 Years	1	1.8	5	15	0.11
	30-44 Years	6	11	6	18	
	45-59 Years	19	34	7	21	
	60-74 Years	24	43	14	41	
	75 + Years	6	11	2	5.9	
Severity	Mild	0	0	4	12	0.002
	Average	15	27	15	44	
	Heavy	41	73	15	44	
computed tomography of the lungs	KT-0	0	0	3	8,8	0.009
	KT-1	4	7,1	7	21	
	KT-2	10	18	7	21	

KT-3	28	50	7	21	
KT-4	14	39	10	25	
Concomitant diseases	32	57	14	41	0.14
Neutrophils (%)		65 (60 - 74)		60 (55 - 71)	0.022
CRP(mg/l)		151 (120, 187)		127 (74,179)	0.032
D-dimer (mg/l)		1.24(1.06 - 1.41)		1.25(0.92-1.61)	>0.9
Fibrinogen (g/l)		8,609(7,104-10,660)		7,354 (5,800 -8,888)	0.033
ESR (mm/h)		20 (16 - 26)		24 (16 - 30)	0.4

[1] N (%); Median (Iqr)

[2] Pearson's Chi-Squared Test; Fisher's Exact Test; Wilcoxon Rank Sum Test

In the study, we used logistic regression analysis to comprehensively evaluate how various factors influence the long-term persistence of dyspnea in patients who have recovered from acute COVID-19. Specifically, the analysis examined the roles of gender, age, the severity of the acute COVID-19 illness, and alterations in lung computed tomography (CT) patterns over an extended follow-up period of 48 to 96 weeks **(Table 3)**. The results from the multivariate regression analysis revealed several significant predictors for the long-term retention of dyspnea. Firstly, male patients demonstrated a significantly higher likelihood of experiencing prolonged dyspnea, with a statistical value of p = 0.002. Secondly, individuals aged over 65 years were also at increased risk, as indicated by a p-value of 0.0013. This finding underscores the vulnerability of older adults in the context of post-COVID symptoms. The severity of the acute COVID-19 illness played a crucial role, with severe cases correlating with persistent dyspnea (p = 0.03). This suggests that patients who experienced more intense symptoms during their acute infection are more likely to suffer from ongoing respiratory difficulties. Moreover, the analysis assessed lung damage as observed on CT scans, with classifications CT-3 and CT-4 indicating significant lung involvement. While this factor showed a p-value of 0.7, indicating a lack of statistical significance, it nonetheless highlights the potential for advanced lung lesions to contribute to long-term respiratory issues.

Table 3. Regression analysis examining the influence of various factors on the presence of shortness of breath over a follow-up period of 48 to 96 weeks in patients (n=90) who received inpatient treatment at OMOC from 2020 to 2022

Characteristic	Standard Error (SD)	t - value	*p*-value
Male	0,3	0,002	0,03
Age	>0,9	0,0013	0,11
Severity	0,6	0,03	0,002
CT of lung	0,7	0,7	0,009

Examining the survival rates of patients suffering post-COVID syndrome with dyspnea using multivariate regression analysis shown in the ROC curve **(Figure 2)** indicated a noteworthy association between age and mortality risk. More especially, the results show that older age groups have a higher mortality risk. Especially, individuals showing little dyspnea during the initial phase of COVID-19 have a nil mortality risk. The mortality risk increases by 3 to 4 times, on the other hand, for individuals 75 years of age or older who have moderate to severe symptoms during the acute phase of illness.

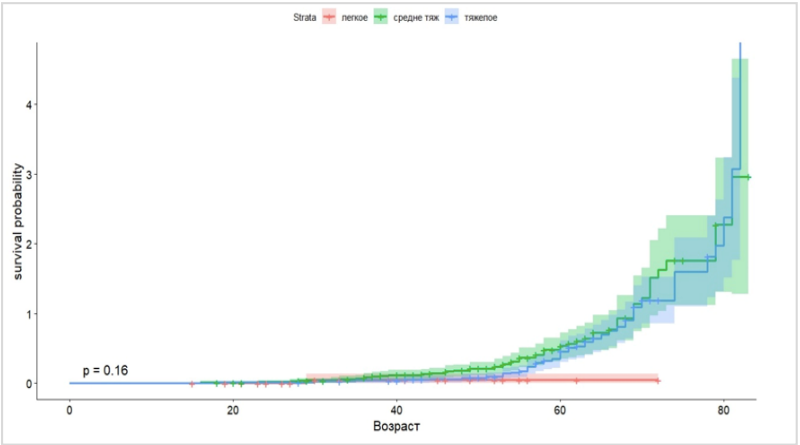

Figure 2. Multifactorial regression analysis of the survival rate of patients with postcovid syndrome with shortness of breath who received inpatient treatment in the OMOCB in the period 2020-2022 (n=90)

It is well-established that patients who have recovered from COVID-19 may continue to experience a range of persistent symptoms. Several longitudinal studies with a follow-up period of up to seven months have identified common manifestations of post-COVID syndrome, including fatigue, weakness, impaired concentration, and shortness of breath, which were also observed in our study [1, 12-14]. Following acute COVID-19 infection, we followed the members of our group for up to 96 weeks. We recorded the continuation of symptoms influencing the respiratory, cardiovascular, musculoskeletal, gastrointestinal, and neurological systems over this period. Regardless of the severity of that initial sickness, 70.3% of patients had at least one lasting clinical symptom 48 to 96 weeks after infection. General weakness (85.5%), headaches (58.1%), dyspnea (29.7%), chest discomfort (24.3%), and myalgia (23.8%), were the most often mentioned symptoms. Complications either from the viral infection itself or from the activation of inflammatory pathways—especially the production of cytokines in reaction to the virus—probably contributed to the continuation of these symptoms [15]. These findings draw attention to how COVID-19 affects patient health even after the acute phase of the illness has passed [16, 17]. Our results match data showing people with both moderate and severe COVID-19 may have a wide range of persistent symptoms—often neurological, cognitive, or psychological—that show up weeks to months after the acute phase of infection. Shortness of breath was found by clinical analysis as the main cause of frequent hospital visits, greatly compromising patients' quality of life as follow-up showed no improvement in symptom intensity. Post-COVID dyspnea has a complex etiology including central origins, respiratory and cardiovascular system diseases, or poor oxygen transport efficiency [18].

In our study, we investigated key inflammatory markers during acute COVID-19, including ESR, neutrophils, D-dimer, fibrinogen, CRP, and procalcitonin, in 56 patients (62.2%) who developed dyspnea in the post-COVID period. Statistical analysis revealed significant associations between initial levels of neutrophils ($p=0.022$), fibrinogen ($p=0.033$), CRP ($p=0.032$), and lung CT patterns ($p=0.009$) with the development of dyspnea. Our data suggest that post-infectious dyspnea in these patients is driven by elevated CRP, fibrinogen, and leukocyte levels, and a direct correlation with lung imaging findings. Hyperinflammation and hypercoagulation, along with complement activation, platelet-leukocyte interactions, and the release of pro-inflammatory cytokines, contribute to conditions favorable for chronic thromboembolic pulmonary hypertension, which underlies the persistence of dyspnea [19]. Furthermore, elevated levels of acute-phase inflammatory markers were associated with ongoing symptoms, identifying predictors of post-COVID complications: the severity of the initial infection, the presence of hyperinflammation or autoimmune responses, and persistent viremia during the acute phase [20].

A comprehensive regression analysis was performed to evaluate the long-term influence of various clinical and demographic factors on the occurrence of dyspnea in patients recovering from COVID-19. This study tracked individuals over a follow-up period of 48 to 96 weeks and identified several statistically significant risk factors. Specifically, male sex ($p=0.003$), age greater than 65 years ($p=0.11$), a severe clinical course of acute COVID-19 ($p=0.002$), and extensive pulmonary involvement as assessed by chest computed tomography (CT) at stages 3 and 4 ($p=0.009$) emerged as key determinants. These factors were strongly correlated with an increased likelihood of persistent dyspnea in the context of post-COVID-19 syndrome. The data suggest that older adults and male patients, particularly those who experienced severe acute COVID-19 and demonstrated significant lung pathology, are at elevated risk for developing prolonged respiratory symptoms.

The present study aligns with existing literature that underscores the role of these factors in post-COVID respiratory sequelae [21-23]. Our findings provide additional evidence to support their classification as predisposing elements for the development of post-COVID dyspnea. These results also suggest that clinicians should remain vigilant when managing patients who fit this risk profile [24]. Importantly, we propose that predictive models incorporating basic inflammatory biomarkers and detailed lung imaging via CT scans can serve as valuable tools for the early identification of patients at risk for persistent dyspnea. Such models could be applied across multiple healthcare settings, including primary care, enabling timely interventions. Continuous monitoring of post-COVID patients with dyspnea is essential, as early referral to pulmonary rehabilitation and the initiation of supportive therapies, including physical and respiratory therapy, can significantly improve outcomes. Proactive management strategies will be crucial in mitigating the long-term respiratory burden associated with COVID-19, particularly in high-risk populations [25-27].

Conclusion

Widespread and clinically important, persistent dyspnea after COVID-19 severely and permanently affects patients' quality of life. Our study shows that those who had severe acute infection are more likely to have post-COVID dyspnea; we also find significant correlations between this condition and severe lung damage seen on CT scans as well as with raised inflammatory markers including neutrophil count, fibrinogen, and C-reactive protein (CRP). These results highlight the need to realize these elements as the main determinants of the emergence and continuation of respiratory problems in the post-COVID era. Furthermore, in patients 75 years of age and above, especially those who have a severe acute infection and show persistent shortness of breath, the post-COVID death risk is considerably greater. Emphasizing the requirement of early diagnosis and aggressive therapy of high-risk patients, the early start of dyspnea is a major predictor of its continuation. This emphasizes how important increased clinical alertness is to controlling post-COVID respiratory consequences. Beyond Kyrgyzstan, these results have consequences for other low- and middle-income nations (LMICs), where the burden of long-term COVID-19 problems might aggravate already existing healthcare issues, and healthcare resources are typically restricted. Not only in high-

resource environments but also in LMICs, where proactive management of post-COVID conditions is essential to improving patient outcomes and lowering the long-term strain on healthcare systems, early intervention including pulmonary rehabilitation and targeted treatment strategies should be prioritized here as well. In the identification and management of post-COVID dyspnea, the integration of inflammatory biomarkers and cutting-edge imaging technologies such as CT scans into standard clinical practice is ultimately crucial. Especially in disadvantaged groups and in areas where healthcare infrastructure may encounter extra difficulties, early and efficient treatments are essential in reducing the long-term effects of COVID-19 on respiratory health. These approaches will be essential for both global and LMIC prediction and prevention of severe post-COVID respiratory outcomes [28-32].

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Ethics statement: The Local Ethics Committee of the Osh State University of the Ministry of Health of the Kyrgyz Republic approved the study (Protocol No.1-FHD/05.09.24) dated 01.03.2024. Informed permission was waived since the culture findings were obtained anonymously from the laboratory's computerized database, with no patient characteristics identified.

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