

Long-Term Symptoms in Hospitalized COVID-19 Patients: A Prospective 9-Month Follow-up Study

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ABSTRACT

Backgrounds: This study aimed to investigate persistent symptoms of coronavirus disease 2019 (COVID-19) patients admitted to a general tertiary teaching hospital during a 9-month follow-up period.

Materials & Methods: In this study, 400 hospitalized COVID-19 patients in Iran were studied, among them 78 RT-qPCR positive cases were identified from February 19 to March 18, 2020. After excluding readmitted and deceased patients, 75 cases underwent in-hospital follow-up. Out-of-hospital follow-up was done for 57 living patients, of whom four cases were unreachable, and five cases died after discharge. The remaining 48 participants were followed up for nine months, and their symptoms and complaints were checked by regular visits to the infectious disease clinic and telephone calls via a checklist designed by the authors.

Findings: The mean age of RT-qPCR positive hospitalized patients was 54.64 ± 17.42 years, and 38.7% of them were female. Overall, five (10.4%) patients complained of dyspnea, three (6.2%) patients of olfactory nerve complications, three (6.2%) patients of persistent fatigue, and two (4.2%) patients of prolonged cough up to the end of the follow-up period. New-onset symptoms were reported in five (10.4%) patients; in most of them (4 out of 5), these symptoms were neurological (urinary retention, tremor with ataxia, distraction, and insomnia).

Conclusion: A large proportion of patients who recover from COVID-19 infection experience prolonged symptoms. Further investigations should be done to provide more data on the underlying causes and risk factors of developing these post-COVID conditions.

Keywords: COVID-19, Persistent symptoms, Follow-up

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Introduction

Despite the passage of more than one year since the coronavirus disease 2019 (COVID-19) pandemic, a noticeable number of recovered patients still suffer from persistent symptoms and long-term complications of this disease. Despite significant global efforts to vaccinate the public against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the causative agent of COVID-19, a large proportion of the population remains at risk of contracting the virus, especially in less-developed countries. Furthermore, there are concerning reports of breakthrough cases after vaccination around the globe ^[1]. Under these circumstances, the importance of investigating the long-term effects of SARS-CoV-2 infection on the growing number of patients becomes more critical.

Given the devastating number of deceased cases and the priorities of healthcare systems worldwide, the significance of discussing the long-term impact of COVID-19 on the health condition of recovered patients has received less attention than expected. Currently, few studies have investigated these persistent symptoms, and much effort is still needed to fully understand the scale of this matter.

Among the studies focusing on persistent symptoms is a recent study by Garrigues et al. (2020) ^[2], which followed up 120 patients for an average of nearly three months. In their study, fatigue (55%), dyspnea (42%), concentration and sleep disorders (28 and 30.8%, respectively), and loss of memory (34%) were reported as the most prevalent conditions. In another study on a larger sample size in China, fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were reported as the most common symptoms after recovery from COVID-19 ^[3]. On the other hand, Davis et al. (2021) reported that the most prevalent symptoms on average

60.1 days after the onset of symptoms in 143 patients were fatigue, post-exertional malaise, and cognitive dysfunction ^[4]. Interestingly, in another study, 87.4% of cases complained of the persistence of at least one symptom, particularly fatigue and dyspnea ^[5].

Objectives: It is still unclear what the underlying causes of persistent symptoms are, and identifying accurate prognostic factors seems crucial. There is an urgent need for further investigations on this issue. With this aim in mind, in this study, all persistent complaints of patients recovering from COVID-19 infection were recorded during a close 9-month follow-up after discharge.

Materials and Methods

In this prospective cohort study conducted during the initial phase of the COVID-19 pandemic, data were collected from 400 patients admitted to a general teaching hospital in Tehran, Iran. These data were extracted since the announcement of the first COVID-19 case by the Ministry of Health of Iran on February 19, 2020 until March 18, 2020 when the diagnostic and treatment approaches for COVID-19 were renewed by the 5th edition of the national guidelines for diagnosing and treating COVID-19.

The data belonged to all patients admitted to Rasool-e-Akram general teaching hospital based on the admission criteria for COVID-19 patients according to the 4th edition of the national guidelines for diagnosing and treating COVID-19 ^[6]. Cases who died for reasons other than COVID-19 and patients with a history of readmission were excluded from the study. Besides, all patients with a negative RT-qPCR (reverse transcription-quantitative polymerase chain reaction) test for SARS-CoV-2 were also excluded from the study. A nasal swab placed in a tube with viral transport medium was used for RT-qPCR test.

The patients were followed up for nine months after discharge to assess their persistent symptoms after COVID-19 infection. Deceased and unreachable patients or those who were not interested in participating in the study were excluded. Each month, trained physicians contacted the participants and used a checklist to collect 9-month out-of-hospital follow-up data. If further examinations were required based on telephone calls, patients were advised to attend their regular visits with specialist physicians.

Persistent symptoms were defined as symptoms that began at the onset of illness and were still present at the time of filling out the questionnaire. Presentation of any late-onset or persistent symptom (yes or no), especially dyspnea, cough, and fatigue; complaints of anosmia or ageusia; improvement (by asking to rate their symptoms from 1 to 10 at baseline and after nine months); complete resolution (having no symptoms); consistency of all symptoms, and data on any re-hospitalization or death (including cause and date) were assessed through a designed checklist.

The variables of this study in the in-hospital stage were age; sex; symptoms at the onset of illness; number of symptomatic days before hospitalization; chief complaint; symptoms during the illness; comorbidities; drug history; results of physical examination (O_2 -saturation and heart rate on admission); laboratory data including creatinine, blood urea nitrogen (BUN), and plasma lactate dehydrogenase (LDH) levels; mechanical ventilation; and intensive care unit (ICU) admission. Also, the patients' clinical condition at the time of discharge, including death and length of hospital stay (LOS), were recorded. During follow-up, shortly post-discharge complaints, their recovery time, new-onset symptoms after discharge, and persistent symptoms were assessed.

Hospital information system reports were used to obtain laboratory data and radiographic findings. The patients were discharged if they were afebrile (temporal temperature $< 38.2^\circ\text{C}$) for 48-72 hours without the use of antipyretics and had a chest X-ray with significant improvement, O_2 sat $>93\%$ without O_2 supplement, and improved respiratory and vital signs based on the physician's opinion. After discharge, all patients were advised to observe home quarantine for 14 days; then they were asked to visit the infectious disease clinic every week for four weeks and then every month to be visited by a specialist.

The sampling method of this study was census.

Statistical analysis: Categorical variables were described as frequencies, and continuous variables were defined as mean and standard deviation (SD) or median and range values when applicable. Means of continuous variables were compared using independent t-tests when data were normally distributed. Proportions of categorical variables were compared using Chi-square test; however, Fisher's exact test was used if data were limited. SPSS software Version 25 for windows (SPSS Inc., Chicago, Illinois) was used to analyze the data.

Findings

Among the 400 hospitalized COVID-19 patients, 78 cases had a positive RT-qPCR for COVID-19 in the first month of the pandemic in Iran. Patients with readmission were excluded ($n=3$), and 75 patients were considered for in-hospital follow-up from admission to discharge or death. For out-of-hospital follow-up, 18 deceased patients were also excluded. Among all patients discharged and transferred to other centers (57 living patients), four patients were unreachable (could not be followed up), and five patients died: one patient after

six months and the other four patients in less than one month after discharge (9.4% post-discharge mortality). All five patients died due to COVID-19 and its complications. Therefore, the remaining 48 participants were followed up for nine months.

Demographic and baseline characteristics:

The mean age of RT-qPCR positive hospitalized patients was 54.64 ± 17.42 years, and 38.7% (29 of 75) of them were female. The median period from symptom onset to hospitalization was 7.00 days (range: 1-22). The patients were referred to the hospital with the chief complaints of dyspnea (57.5%), cough (11%), and fever and chills (8.2%), respectively. Cough was the most common symptom at the onset of the illness (40.3%). The most common symptoms during the illness were cough (69.3%), fever (66.2%), and dyspnea (60%). The prevalence of comorbidities was 66.7%, including hypertension (HTN) (29.3%), diabetes mellitus (DM) (26.7%), and cardiovascular diseases (CVD) (24.0%) (Table 1).

Shortly post-discharge complaints: Out of the 48 participants undergoing a 9-month follow-up, 18 (37.8%) patients experienced dyspnea, 14 (29.1%) patients loss of taste and smell, 12 (25.2%) patients cough, and 10 (22%) patients fatigue.

Post-COVID complaints recovery time:

The mean recovery time of dyspnea was 5.68 ± 11.27 weeks. This figure was 4.09 ± 10.1 weeks for recovery from olfactory nerve complications, and it took 2.74 ± 7.76 weeks for cough to resolve. Finally, the mean fatigue resolution time was 3.13 ± 9.06 weeks.

Persistent and new-onset symptoms: Five out of 48 (10.4%) patients had dyspnea until the end of the study. Three (6.2%) patients experienced olfactory nerve complications until the end of the 9-month follow-up period. Three out of 48 (6.2%) patients suffered from persistent fatigue, and two

(4.2%) patients complained of prolonged cough up to the end of the follow-up period. New-onset symptoms emerged in five (10.4%) patients after discharge and persisted until the end of the study. In most patients (4 out of 5), these symptoms were neurological (urinary retention, tremor with ataxia, distraction, and insomnia).

In total, 13 (27.0%) patients experienced post-COVID conditions for nine months, they had a mean age of 48.53 ± 13.67 years, and 53.8% of them were female. The mean LOS for them was 6.07 ± 4.17 days. Out of these 13 patients, only three patients were admitted to the ICU, and none of them needed mechanical ventilation during their hospital stay. In addition, 17 other patients experienced post-COVID conditions but reported a resolved condition, they had a mean age of 50.05 ± 13.84 years, and 47.1% of them were female, and the mean LOS for them was 7.64 ± 3.60 days. Of whom, five cases (29.4%) were admitted to the ICU, but none needed mechanical ventilation. History findings, clinical findings, or laboratory data showed no significant differences between patient subgroups (details and relative risks are available in Supplementary Tables 2-4).

Characteristics of deceased cases at the end of hospitalization:

A history of ICU admission during in-hospital follow-up was recorded for 10 (55.5%) of the 18 deceased patients compared to 11 (19.3%) of the 57 survived cases (p -value= .003, OR=5.227, CI: 1.7,16.3). Weakness and LOC symptoms were significantly higher in deceased patients (38.9% vs. 15.8%, p -value= .037, and 27.8% vs. 1.7%, p -value= .003, respectively). History of cardiovascular diseases was also higher among the deceased patients (50.0% vs. 15.8%, p -value= .003, OR=5.333, CI:1.7,17.1). None of the patients who needed mechanical ventilation survived, and the need for mechanical ventilation was significantly higher in deceased cases

Table 1) Basic characteristics of 75 patients with positive RT-qPCR for COVID-19

Symptoms at the Onset of Illness		Symptoms during the Illness		Comorbidities	
Cough	40.3%	Cough	69.3%	HTN [€]	29.3%
Fever	37.6%	Fever	66.2%	DM ^μ	26.7%
Chills	12.5%	Dyspnea	60%	CVD ^α	24.0%
Myalgia	11.2%	Chills	32%	Neuropathy	8.0%
Weakness	6.9%	Myalgia	29.3%	Dialysis	8.0%
Coryza	5.6%	Productive cough	22.7%	CPD ^β	8.0%
Others ¹	4.2%	Nausea	13.3%	HT ^π	5.3%
Chief Complaints		Vomiting	10.7%	Malignancy	4.0%
Dyspnea	57.5%	Diarrhea	8%	Hematology	4.0%
Cough	11%	LOC [£]	8%	Liver disease	1.3%
Fever and chills	8.2%	Abdominal pain	5.3%	Drug history	
Fever	4.1%	Anorexia	5.3%	ASA [©]	17.3%
Fever and cough	4.1%	Runny nose	5.3%	BB [€]	9.3%
Weakness	2.7%	Headache	4%	ARBs [°]	8.0%
Fever and myalgia	1.4%	Chest discomfort	4%	Statins	8.0%
Others ²	11%	Hemoptysis	2.7%	Diuretics	8.0%
		Sore throat	2.7%	CCB [°]	6.7%
		Vertigo	2.7%	Levothyroxine	5.3%
				Anticoagulants	4.0%
				Vitamin D	2.7%
				ACEIs ^α	1.3%
				Steroids	1.3%

1: Anorexia, sore throat or flank pain, 2: headache, nausea and vertigo, hypogastric pain, LOC, back and flank pain, and brain pacemaker replacement, £: loss of consciousness, €: hypertension, μ: diabetes mellitus, α: cardiovascular disease, β: chronic pulmonary disease, π: hypothyroidism, ©: acetylsalicylic acid, €: beta-blockers, °: angiotensin II receptor blockers, °: calcium channel blockers, α: angiotensin-converting enzyme inhibitors.

(44.4% vs. 0%, p -value<0.001). Plasma level of LDH was not statistically significant in case of mortality; however, all patients with normal LDH levels survived.

Having an O₂sat less than 93% on admission was the only physical examination finding that was significantly different between the deceased and survived patients (88.2% vs. 49.1%, p -value= .005, OR=7.778 CI: 1.6,37.3). At the end of hospitalization, 42.85% of patients with at least one underlying disease died; in patients without any known underlying condition, this frequency was 13.63% (p -value= .150).

The mean age of deceased patients was higher than that of survived cases (66.61 years vs. 50.86 years, p -value= .001).

Discussion

In the present study, the mean age of all RT-qPCR positive admitted patients was 54.64 ± 17.42 years, which is more than that reported in a systematic review with a total of 5057 patients [7]. Male cases constituted 61.3% (46 of 75) of the study population, similar to the findings of a study by Nasiri et al. (2020) [7]. Cough (69.3%), fever (66.2%), and dyspnea (60%) were found to be the

Table 2) Differences between dead and alive patients in terms of the variables investigated in this study

		Death		P-Value	Odds Ratio (OR)
		No	Yes		
Gender	Female	25	4	.164	
	Male	32	14		
ICU ^Ω	No	46	8	.003	5.227
	Yes	11	10		
Weakness	No	48	11	.037	3.394
	Yes	9	7		
LOC ^ε symptom	No	56	13	.003	21.538
	Yes	1	5		
Cardiovascular	No	48	9	.003	5.333
	Yes	9	9		
Anticoagulant	No	57	15	.012	-
	Yes	0	3		
LOC ^ε	No	56	11	< .001	35.63
	Yes	1	7		
Mechanical ventilation	No	57	10	< .001	-
	Yes	0	8		
Creatinine Q ^α	Normal	41	8	.012	4.193
	Raised	11	9		
LDH [£] Q ^α	Normal	8	0	.081	-
	Raised	16	8		
O ₂ sat W/O [◊] Q	>93%	28	2	.005	7.778
	<93%	27	15		
Underlying disease	No	22	3	.150	
	Yes	35	15		

^Ω: intensive care unit, ^ε: loss of consciousness, ^α: qualitative, [£]: lactate dehydrogenase, [◊]:saturation without oxygen therapy

most prevalent symptom on admission, which are slightly different from the results of a review study that reported fever as the most common symptom [7]. Although very close incidence rates were found for fever and cough, the difference may be due to inaccurate measurement of patients' body temperature and small sample size. The prevalence of comorbidities was higher in the present study than in a systematic review by Nasiri et al. (2020) [7]; however, the order of the most prevalent underlying conditions was similar in both. This difference in results

may be due to examining only hospitalized patients in the current study.

As far as we know, this study investigated persistent COVID-19 symptoms in RT-qPCR positive hospitalized patients during the longest follow-up period. The most significant finding of this study was that cough, fatigue, dyspnea, and decreased sense of taste and smell were found to be the most prevalent symptoms persisting from the onset of the disease up to nine months after COVID-19 infection. There are still many uncertainties about the reasons behind the

Table 3) Differences between dead and alive patients in terms of the variables investigated in this study

	Mean $\pm$ SD		P-Value
	Alive	Dead	
Age	50.86 $\pm$ 16.21	66.61 $\pm$ 15.98	.001
HR [¥]	94.94 $\pm$ 22.37	82.83 $\pm$ 15.51	.039
O ₂ sat W/O [◊]	90.78 $\pm$ 7.84	76.65 $\pm$ 15.17	.002
BUN ^β	16.73 $\pm$ 11.20	24.52 $\pm$ 17.09	.033
LDH [£]	696.95 $\pm$ 277.49	954.12 $\pm$ 326.11	.038

¥: heart rate, ◊: saturation without, β: blood urea nitrogen, £: lactate dehydrogenase

Table 4) Relative risks calculated for 4 and 12 weeks of follow-up

	Prolonged Symptoms of more than 4 Weeks		Prolonged Symptoms of more than 12 Weeks	
	Relative risk (CI ^Ξ)	P-value	Relative risk (CI ^Ξ)	P-value
Sex (F)	1.513 (0.776-2.949)	.221	1.415 (0.614-3.263)	.414
ICU [¥] admission	1.069 (0.583-1.960)	1	0.781 (0.539-1.132)	.461
Cough	0.663 (0.324-1.357)	.200	0.817 (0.485-1.337)	.481
Dyspnea	1.496 (0.932-2.402)	.107	1.102 (0.747-1.628)	.753
Asthma	-	.176	1.378 (0.340-5.586)	.541
Respiratory past medical history	2.419 (0.435-13.433)	.298	1.395 (0.514-3.791)	.583

¥: intensive care unit, Ξ: confidence interval

prolongation of some COVID-19 symptoms. However, some studies have suggested that persistent viremia^[8], reinfection^[9], specific immune reactions^[10, 11], and psychological factors^[12] may all contribute to this issue as observed in previous and more investigated coronavirus epidemics, such as SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)^[13-15]. Recently, a few articles have been published on COVID-19 persistent symptoms. Although our findings on persistent symptoms are in line with those of recent studies^[2, 5, 16-18], we found much lower frequencies for symptoms, which could be due to the longer follow-up period compared to similar investigations. However, the findings of Stavem et al.'s (2021)^[16] study with a 6-month follow-up are more similar to the present study results.

At the time of designing the current study, there were no reports of olfactory nerve complications; therefore, the subjects were asked about the changes in their sense of taste and smell in the midst of the follow-up period. Thus, inconsistencies between taste and smell findings may be due to recall bias, which is inevitable in a retrospective, questionnaire-based study design. Therefore, the results of symptom recovery intervals might also be different from those of similar studies like Boscolo-Rizzo et al. (2020)^[18] due to the same reason. The most prevalent new-onset symptoms were neurological complaints, which is in accordance with another recent study that reported concentration and sleep disorders and loss of memory as the most common persistent symptoms^[2].

The findings showed that the incidence of death in patients with at least one underlying disease was nearly three times higher than in patients without any known underlying condition. After discharge, 9.4% of patients died because of COVID-19 and its complications: four cases within one month and one case after six months.

Post-discharge mortality rate in this study was higher than the findings of several other studies [3, 19, 20], probably due to several reasons: firstly, healthcare professionals worldwide had limited knowledge and skills in managing COVID-19 patients at the beginning of the pandemic. Secondly, due to the limited number of equipment required to manage severely ill respiratory patients, the discharge threshold was lower than standard to make room for the rapidly growing number of patients. Finally, the lack of specific treatment options in the early phase of the study certainly significantly influenced the mortality rate.

Limitations and strength

The most important limitation of this study was its small sample size.

To the best of our knowledge, this study investigated COVID-19 persistent symptoms during the longest possible follow-up time since the first month of the epidemic. All data were collected by only one physician, which makes the sensitivity of data entry uniform.

Conclusion

In conclusion, this study, encompassing a 9-month follow-up of hospitalized COVID-19 patients, sheds light on persistent symptoms and reveals that a noticeable proportion of patients who recover from COVID-19 suffer from persistent health problems and symptoms such as cough, fatigue, dyspnea, and decreased sense of taste and smell. Neurological complaints emerge as common new-onset symptoms. The elevated post-discharge mortality rate

obtained in this study is attributed to early pandemic challenges and limited treatment options. Despite the small sample size, the long-term follow-up and uniform data collection in this study provided valuable insights. It is recommended to conduct further investigations to focus more on the long-term effects of COVID-19 infection on the recovered patients' health conditions in order to identify prognostic factors and methods to prevent the incidence of post-COVID conditions and its long-term impact.

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Ethical considerations: All patients were identified only by their national code, and no personal data were revealed to any party during data extraction or analysis. The Medical Ethics Committee of Iran University of Medical Sciences approved this study under the code: IR.IUMS.REC.1399.192.

Conflicts of interests: The authors declare no conflict of interest.

Authors' contributions: Parmida Shahbazi: idea of the study, writing the proposal, literature review, data extraction, interpretation of data, writing the manuscript, revising the manuscript, confirming final draft, and guaranteeing all details of the project; Mahshid Talebi-Taher: idea of the study, revising the proposal, interpretation of data, revising the manuscript, confirming final draft, and guaranteeing all details of the project; Behrooz Banivaheb: idea of the study, writing the proposal, literature review, data clearing, data analysis, interpretation of data, writing the manuscript, revising the manuscript,

confirming final draft, and guaranteeing all details of the project; Zeynab Yassin: idea of the study and revising the proposal; Ashkan Yahyavi: literature review, interpretation of data, writing the manuscript, revising the manuscript, confirming final draft, and guaranteeing all details of the project; and Nima Hemmati: literature review, interpretation of data, writing the manuscript, revising the manuscript, confirming final draft, and guaranteeing all details of the project.

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