

Persistence of symptoms after improvement of acute COVID-19 infection, a longitudinal study

Mona Mohammed Abdelrahman¹  | Noha Mohammed Abd-Elrahman¹ |
Tasneem Mohammed Bakheet²

¹Tropical medicine and Gastroenterology Department, Faculty of Medicine, Sohag University, Sohag, Egypt

²Public Health and Community Medicine Department, Faculty of Medicine, Sohag University, Sohag, Egypt

Correspondence

Mona Mohammed Abdelrahman, Tropical medicine and Gastroenterology Department, Faculty of Medicine, Sohag University, Sohag 82524, Egypt.
Email: monamhamed@med.sohag.edu.eg

Abstract

With the number of coronavirus disease 2019 (COVID-19) infected patients increasing all over the world, a large number of survivors have reported changes in their quality of life or experienced re-infection. So, we aimed to detect the percentage, type, and risk factors of persistent symptoms after improvement from acute COVID-19 infection and to detect the percentage of COVID-19 re-infection and degree of severity of the second infection. One hundred seventy-two (59 male, 113 female) patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were followed up via mobile phone every 2 months for 8 to 10 months. After recovery, 105 patients (61%) (30 male, 75 female) reported one or more COVID-19 persistent symptoms. Fatigue, dyspnea, and depression were the most common persistent symptoms representing 37.3%, 22%, 22%, respectively. We found that age was independently related to the persistence of symptoms. During the follow-up, six females (3.5%) had laboratory-confirmed COVID-19 re-infection. Their mean age was 35.7 ± 11 years. The mean interval from the complete recovery of the first infection to the onset of the second one was 53 ± 22.2 days and ranged from 30 to 90 days. The second infection was milder in severity than the first infection in 83.33% of cases. There was a high percentage of patients who complained of persistent symptoms after recovery from COVID-19. Fatigue and headache were the most common persistent symptoms. Age was considered a risk factor for persistent symptoms. Re-infection with SARS-CoV-2 can occur after recovery.

KEYWORDS

COVID-19, persistent symptoms, re-infection, risk factors, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection has been spread rapidly all over the world, affecting millions of patients over the last few months.¹ COVID-19 illness has a wide range of symptoms from mild disease to severe one. Fever, cough, dyspnea, and fatigue are the most commonly reported symptoms of COVID-19 illness.² The course of illness ranges from 2 weeks for a mild illness to 3-6 weeks for those with a severe or critical illness.³

Numerous studies have reported that one or more symptoms of COVID-19 persist for more than a month after recovery.^{1,4-6} Fatigue and dyspnea have been reported as the most common persistent complaints after recovery from COVID-19.^{4,7} Several studies have indicated that the persistence of symptoms is not linked to a certain age, gender, or severity of the disease.^{1,2} However, another study noticed those elderly patients and those with chronic health issues were associated with higher percentages of persistent symptoms.^{3,4}

Re-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported in several studies.^{5,6} The severity of the second attack varies over all the studies. Prado-Vivar et al.⁵ reported that the second infection is more severe than the first one while Chen et al.⁶ documented that 75% of patients with re-infection were asymptomatic.

So, we aimed to detect the percentage, type, and risk factors of persistent symptoms after improvement from acute COVID-19 infection and to detect the percentage of COVID-19 re-infection and degree of severity of the second infection.

2 | PATIENTS AND METHODS

Out of 250 patients who tested positive for SARS-CoV-2 in Sohag University COVID-19 isolation hospital during the period from 15th May 2020 to 25th July 2020, 172 (59 male, 113 female) patients improved and agreed to be recruited in the present study. Their age range was 17–80 years. Of them, 22 patients needed hospital admission in Sohag University COVID-19 isolation department and 150 patients received treatment in home isolation. The severity of COVID-19 infection was evaluated according to the COVID-19 management protocol of the Ministry of Health, Egypt.⁸ Patient improvement and discharge criteria included 10 days from symptom onset in addition to 3 days free of fever and respiratory symptoms.⁹ Patients with severe complex illness, pregnant or lactating females, and patients who refused to participate or give a complete detailed history were excluded from the study. The study protocol was approved by Sohag University Ethical Committee for medical research with the registration number (Soh-Med-21-2-46).

The baseline data was collected from the Sohag University isolation hospital of COVID-19, then, the researchers conducted interviews with all participants through the mobile phone after the improvement of acute COVID-19. After that, we followed the patients up through mobile phones every 2 months for 8–10 months.

Informed consent was taken from all participants. Then, the researchers asked about demographic criteria, current chronic medical diseases, the presentation of COVID-19 at the test time, whether these symptoms improved by the interview time, and whether the patients had reverted to their normal health status at the interview date and during follow up. Any residual or newly reported symptoms not related to previous illness or underlying chronic medical condition was considered as persistent symptoms of COVID-19 infection.³ A complete detailed history was taken for the reported persistent symptoms. We also asked if there was a re-infection with COVID-19 and the interval between the first and second infection.

3 | STATISTICAL ANALYSIS

Data were analyzed using SPSS version 25. Continuous variables were analyzed as mean \pm SD when normally distributed or as median (interquartile range) when not normally distributed. Categorical variables were represented as a number (%). χ^2 tests were used to

TABLE 1 Socio-demographic and clinical characters of the studied population

Parameters		COVID-19 positive cases, N = 172	
		No.	(%)
Age	Mean \pm SD	41.8+	17.6
Sex	Male	59	34.3%
	Female	113	65.7%
Residence	Urban	71	41.3%
	Semi-urban	57	33.1%
	Rural	44	25.6%
Occupation	Physicians	47	27.3%
	Working in medical field; not physicians	21	12.2%
	Not working in medical field	30	17.4%
	Not working	74	43.0%
Smoking	Active smoker	6	3.5%
	Non smoking	151	87.8%
	X-smoker	15	8.7%
Comorbid diseases	Diabetes mellitus	24	13.9%
	Hypertension	37	21.5%
	Chronic obstructive lung diseases	10	5.8%
	Chronic renal failure	4	2.3%
	Ischemic heart disease	12	7%
	Others	10	5.8%

Abbreviation: COVID-19, coronavirus disease 2019.

compare differences between the two groups. Multivariate logistic regression analysis was used to detect the potential risk factors associated with the persistence of symptoms.

4 | RESULTS

From May 2020 to March 2021, 172 COVID-19 infected patients participated in our study and were followed up for 8 to 10 months. The principal characteristics of the participants and their clinical parameters are shown in Table 1. Twenty-two positive cases were hospitalized (12.8% of COVID-19 cases), seven of them were admitted to the intensive care unit (31.8% of hospitalized patients and about 4% of COVID-19 cases).

The median duration of COVID-19 infection was 15 days and the interquartile range was 10–21 days. The clinical presentation of acute COVID-19 infection in our patients involved multiple systems, however, generalized malaise, fever, headache, and cough were the most common presenting symptoms as shown in Figure 1.

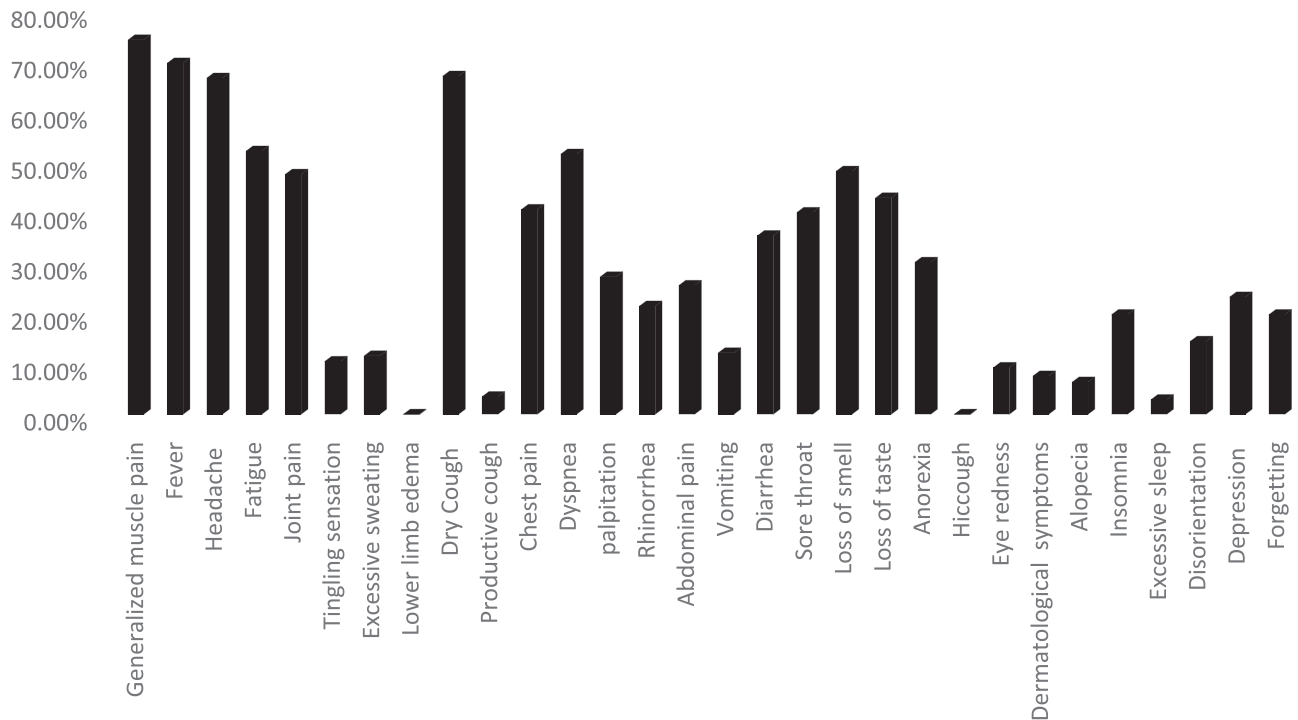


FIGURE 1 Acute symptoms of 172 COVID-19 patients. COVID-19, coronavirus disease 2019

After recovery, 105 patients (61%) (30 male, 75 female) reported one or more persistent COVID-19 symptoms. The median duration of persistent symptoms was 30 days with a range of 10–120 a day. Twenty-two patients (12.8%) reported one persistent complaint, 24 patients (14%) reported two persistent complaints, and 59 patients (34.3%) reported three or more persistent complaints. Impairment of quality of life was noticed in 41.9% of patients.

Fatigue, dyspnea, and depression were the most common persistent symptoms representing 37.3%, 22%, 22% respectively. This was followed by insomnia (13.4%), Joint pain (12.2%), headache (10.5%), alopecia (10.5%), forgetting (9.9%), dry cough (8.1%), and chest pain (7.6%). The authors found that fatigue, joint pain, and headache were the most common persistent general manifestations. As regards the respiratory system, we noticed that dyspnea, dry cough, and chest pain were the most frequent persistent complaint. Loss of smell and taste were the most frequent persistent gastrointestinal complaints. Depression and insomnia were the most frequently reported persistent neurological complaints (Table 2).

During follow-up, newly emerged symptoms, such as disorientation, forgetting, and alopecia were reported in 11%, 9.9%, and 10.5% of our patients, respectively (Table 3).

In assessing risk factors for persistent symptoms, The researchers found that age was independently related to the persistence of symptoms. The severity of illness, sex, and co-morbidity were not risk factors for the persistence of symptoms (Table 4).

During the follow-up, six females (3.5%) had laboratory-confirmed COVID-19 re-infection. Their mean age was 35.7 ± 11 years. The mean interval from the complete recovery of the first infection to the onset of the second one was 53 ± 22.2 days with a

range from 30 to 90 days. The second infection was milder in severity than the first infection, in 83.33% of cases.

5 | DISCUSSION

In the present study, after recovery, 61% of patients reported one or more persistent COVID-19 symptoms. Similarly, the percentage of persistent symptoms in previous studies among SARS-CoV-2 positive patients ranged from 35% to 89.2%.^{2-4,10-14} In our research, 22 patients (12.8%) reported one persistent complaint, 24 patients (14%) reported two persistent complaints, and 59 patients (34.3%) reported three or more persistent complaints. These results were in concordance with Carfi et al.¹⁰ and Rosales-Castillo et al.¹¹ findings.

Fatigue and dyspnea was the most common persistent symptoms in our patient. Similar results were noticed in several previous research.^{4,10,11,15-17} The pathogenesis of persistent symptoms is not well known; however, multiple theories have been postulated. It may be due to the direct effect of the virus, immune reaction, and loneliness.¹⁶ Bornstein et al.¹⁸ indicated that antibodies against β -adrenergic and muscarinic receptors due to viral or autoimmune etiology might be a cause for persistence of symptoms. Residual inflammation, organ injury, the nonspecific impact of the hospital admission or mechanical ventilation, or the effect on pre-existing health issues could all be risk factors for the persistence of symptoms.¹ Yong supposes that SARS-CoV-2 invasion of the brain stem plays a major role in the persistence of symptoms and could explain multiple systems' involvements as the brain stem controls the functions of several organs.²

TABLE 2 Percentage of persistent symptoms in 172 COVID-19 patients

Symptoms	Persistent symptoms among COVID-19 cases	
	No.	%
Generalized muscle pain	19	11%
Headache	18	10.5%
Fatigue	64	37.3%
Joint pain	21	12.2%
Tingling sensation	13	7.6%
Excessive sweating	13	7.6%
Dry cough	14	8.1%
Productive cough	10	5.8%
Chest pain	13	7.6%
Dyspnea	38	22%
palpitation	1	0.6%
Abdominal pain	2	1.2%
Vomiting	0	0%
Diarrhea	8	4.7%
Sore throat	5	2.9%
Loss of smell	12	7.0%
Loss of taste	11	6.4%
Anorexia	11	6.4%
Eye redness	5	2.9%
Insomnia	23	13.4%
Depression	38	22%

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 3 symptoms that emerged during follow up

Symptom	Persistent symptoms among COVID-19 cases	
	No.	%
Hiccough	1	0.6%
Alopecia	18	10.5%
Lower limb edema	3	1.75
Excessive sleep	3	1.7%
Disorientation	19	11%
Forgetting	17	9.9%

Abbreviation: COVID-19, coronavirus disease 2019.

In assessing risk factors for persistent symptoms, the authors found that old age was independently related to the persistence of symptoms. The severity of illness, sex, and comorbidities are not risk factors for the persistence of symptoms. However, Kamal et al.⁴ reported that severity of illness and co-morbid diseases are risk

TABLE 4 Logistic regression of factors that may cause persistent symptoms after recovery from acute COVID-19

Potential risk factors	Odds ratio	95% Confidence interval		p value
		Lower	Upper	
Age	1.03	1.01	1.05	0.01
Sex	1.72	0.78	3.79	0.18
Smoking	1.56	0.51	4.75	0.44
Comorbidity	0.65	0.31	1.38	0.26
Fever degree	1.1	0.54	2.25	0.8
Severity	2.23	0.28	17.9	0.45
Hospital admission	2.32	0.79	6.87	0.13

Abbreviation: COVID-19, coronavirus disease 2019.

factors for the persistence of symptoms. Although Huang et al.¹⁶ reported that the severity of illness and female sex are risk factors for persistent symptoms. Tenforde et al.¹² documented that age more than 65 years and co-morbid diseases are risk factors of persistent symptoms. Stavem et al.¹³ also showed that co-morbidities and the number of symptoms during acute COVID-19 are risk factors for the persistence of symptoms.

During the follow-up, six females (3.5%) had laboratory-confirmed COVID-19 re-infection. The mean interval from the complete recovery of the first infection to the onset of the second one was 53 ± 22.2 days with a range from 30 to 90 days. The second infection was milder in severity than the first infection in 83.33% of cases. Adrielle dos Santos et al.¹⁹ revealed that 90.9% of re-infection occurs among females with a time interval between first and second infection of 18–134 days. They also reported that the severity and frequency of symptoms were higher in the second attack.

6 | LIMITATIONS OF THE STUDY

The relatively small sample size, single-center study, and absence of direct contact and physical examination of the patients were the main limitations in the current study.

6.1 | Recommendation

Long-term follow-up of patients who have recovered from COVID-19 infection is recommended especially in the elderly.

7 | CONCLUSION

There is a high percentage of patients who complained of persistent symptoms after recovery from COVID-19. Fatigue and headache are the most common persistent symptoms. Age is considered a risk

factor for persistent symptoms. Re-infection with SARS-CoV2 can occur after recovery.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data of this study is available under request to the corresponding author.

ETHICAL STATEMENT

The study protocol was accepted by the Ethical Committee of Scientific Research, Faculty of Medicine, Sohag University. Protocol serial number: Soh-Med-21-02-46.

CLINICALTRIALS. GOV IDENTIFIER

NCT04764773.

ORCID

Mona Mohammed Abdelrahman  <http://orcid.org/0000-0002-8784-848X>

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