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Persistence of COVID-19 symptoms beyond 3 months and the delayed return to the usual state of health in Saudi Arabia: A cross-sectional study

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Abstract

A substantial number of COVID-19 survivors describe ongoing symptoms long after the acute phase. This so-called post-COVID-19 syndrome or long COVID occurs irrespective of initial disease severity.

Objectives: This cross-sectional study aims to describe and characterise the prevalence of persistent COVID-19 symptoms beyond three months and to evaluate the risk factors for the delayed return to the usual state of health.

Methods: An electronic survey was developed, piloted, and conducted during the first wave of the COVID-19 pandemic. The survey consisted of questions exploring socio-demographic data, comorbidities, COVID-19 disease (diagnosis, presenting symptoms, management, and persistent symptoms), and the return to the usual state of health. Participants were users of social media platforms. We received results from 746 respondents. One hundred thirty-six responses were excluded due to a self-diagnosis of COVID-19. Respondents reporting a COVID-19 diagnosis 3 months or more prior to the study (N=213) were included in the analysis. Predictors of the delayed return to the usual state of health were identified by logistic regression.

Results: Three months or more after a COVID-19 diagnosis, almost half of the respondents, 109 (51.2%), had residual symptoms. The five most prevalent persistent symptoms were fatigue (13.6%), altered sense of smell (12.7%), muscle aches (10.3%), headache (9.9%), and body aches (8.5%). When questioned regarding the return to baseline health, 152 (71.4%) answered in the affirmative. The total number of chronic medical conditions was determined as a statistically significant predictor for the delayed return to the usual state of health.

Conclusion: Three months or more after acute COVID-19 infection, 5 out of 10 survivors experienced persistent symptoms, and 3 out of 10 reported a delayed return to baseline health. Considering the overall burden of COVID-19 disease, this can pose health and socio-economic challenges. Therefore, health systems need support in managing long COVID and improving long-term COVID-19 outcomes.

Keywords

SARS-CoV-2, long COVID, chronic COVID syndrome, post-acute sequelae of SARS-CoV-2 syndrome, PASC, post-COVID-19 syndrome

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Introduction

As the COVID-19 pandemic continues to unfold, new insights appear and challenge previously acknowledged facts. One lately scrutinised aspect is the persistence of COVID-19 symptoms among some survivors, irrespective of initial disease severity. As of December 2021, COVID-19 has resulted in more than 289 million confirmed cases and more than five million deaths worldwide.[1] Thereupon, the possibility of the persistence of debilitating symptoms

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among a proportion of those previously affected will likely pose additional stress on an already strained health care system with substantial societal and economic implications. The term 'long COVID' and the cognate term 'long-hauler' were initially coined by patients.[2,3] Other terminologies used in the literature have included 'chronic COVID syndrome',[4] 'coronavirus long-hauler',[5] and 'post-acute sequelae of SARS-CoV-2 infection' (PASC).[6] Due to the lack of a defined, globally accepted description and terminology for this condition, accurate diagnosis and treatment can be difficult.[7] The United Kingdom's National Institute for Health and Care Excellence (NICE) defines post-COVID-19 syndrome as 'signs and symptoms that develop during or after an infection, consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis'.[8] In this definition, long COVID overlaps with two categories, 'ongoing symptomatic COVID-19', which are symptoms lasting for 4 to 12 weeks; and 'post-COVID-19 syndrome', which are symptoms persisting beyond 12 weeks.[9]

Cognitive, mental, and physical health can be affected after COVID-19. This effect can be persistent or occur in an episodic fashion.[10] Furthermore, these sequelae vary in frequency and severity.[11,12] The exact aetiopathogenesis of the condition is unknown. Direct viral tissue damage, endothelial damage, dysregulation of immune responses, and maladaptation of ACE2-related pathways might contribute.[13]

Few studies have been published on the post-COVID-19 syndrome in Saudi Arabia. However, those were restricted to a specific patient population or reported shorter follow-up duration.[14–16] Therefore, in this cross-sectional study, we aim to analyse the persistence of COVID-19 symptoms beyond 3 months or more of disease onset and return to the usual state of health in a mixed population of COVID-19 survivors.

Materials and methods

This cross-sectional study was conducted in Saudi Arabia between 11 November 2020, and 11 December 2020, during the first wave of the pandemic (approximately 8 months after the first confirmed case of COVID-19 in the country, which was announced on 2 March 2020). Participants were users of social media platforms (Twitter and WhatsApp). They were invited online to participate in this study assessing long-term, persistent COVID-19 symptoms, and the return to the usual state of health. Inclusion criteria were an age of 18 years or above and a self-reported diagnosis of COVID-19 based on the assessment of a healthcare worker or a positive COVID-19 test. The exclusion criterion was a self-diagnosis of COVID-19 with no confirmatory testing.

An ad hoc web-based survey was developed in Arabic utilising SurveyMonkey (surveymonkey.com). Local studies on COVID-19[17] and studies on long COVID[18–20] were referred to during the development of the study instrument. Ultimately, the survey consisted of 19 open and close-ended questions divided into four parts. Part one explored socio-demographic data. Comorbidities were documented in part two using a checklist of 18 conditions (modified from the Charlson Comorbidity Index[21] and other studies).[19] In addition, respondents were given the option to document other comorbidities not listed. The number of comorbidities was then categorised as 0, 1, 2, or $\geqslant 3$ comorbidities. COVID-19 diagnosis, presenting symptoms, management, and persistent symptoms were examined in part three. These were extrapolated from previous studies.[17,19] Finally, participants were asked about the return to the usual state of health in part four. A pilot test involving 14 participants was conducted to confirm the clarity of questions and the reproducibility of answers. Based on the feedback, unclear questions were modified, and minor changes to the survey were made.

The study objectives were described to the participants, and written informed consent was obtained from all participants before the study. Anonymity was ensured as no identifying information was collected. No incentives were provided for answering the survey. The study was approved by the Research Ethics Committee at the University of Ha'il (Reference Number 00127/CM-UOH.04/20).

Sample size

The sample size (n = 663) was calculated using the formula: $n = N \times X/(X + N - 1)$. In this formula, $X = Z\,\alpha/22 \times p \times (1 - p)/MOE2$, and $Z\alpha/2$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 99%, α is 0.05, and the critical value is 1.96), N is the population size, p is the sample proportion (set at 50%), and MOE is the margin of error (set at 5%). The population size was estimated based on the total COVID-19 cases in Saudi Arabia as of 11 November 2020 (N = 352,200 cases). The electronic survey was online for a duration of 10 days to reach the calculated sample size. All responses received during this period were included. The NICE definition is used to define the duration of persistent symptoms.[8] Thus, responses reporting a past COVID-19 diagnosis 3 months prior to the study are included in the analysis.

Statistical analysis

Data were entered and analysed using IBM SPSS Statistics (version 26). Means and standard deviations were used to describe the continuous data. Frequencies and percentages were used to describe categorical data. Statistical significance was set at $p < 0.05$ (two-tailed). Binomial logistic regression was performed to determine the effects of gender, age, the total number of chronic medical conditions, and the total number of initial symptoms on the likelihood that respondents do not return to their usual state of health. The linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell

procedure. There were no significant outliers in the data. Model fit was assessed using the Hosmer and Lemeshow goodness of fit test. The model explained 5.1% (Nagelkerke R^2) of the variance in the return to the usual state of health and correctly classified 70.4% of cases.

Results

We received results from 746 respondents. The average time to complete the survey was around 4 min. One hundred thirty-six responses were excluded due to a self-diagnosis of COVID-19. Of the remaining 610 responses, only those from respondents reporting a COVID-19 diagnosis 3 months prior to the study (N = 213) were included in the analysis for the post-COVID-19 syndrome. Of these, 162 (76.1%) were female, and 192 (90.1%) were less than 45 years of age. Table 1 summarises the demographic data and clinical characteristics of respondents.

At the time of diagnosis, 5 (2%) of the respondents were asymptomatic, 66 (31%) reported one to five symptoms, 70 (33%) had six to ten symptoms, and 72 (34%) had more than 10 symptoms. The most frequent presenting symptoms were headache 132 (62%), loss of smell and fatigue 130 (61%) each, body aches 117 (54.9%), and fever 115 (54%). COVID-19 diagnosis and management among respondents are summarised in Table 2.

More than 13 comorbid conditions were identified among the respondents, with 82 (38.5%) reporting one or more comorbid conditions. The number of comorbid conditions ($p < 0.007$), and in particular being overweight ($p < 0.021$), were significantly associated with developing persistent symptoms (see Table 1).

Table 1. Socio-demographic characteristics of the respondents.

	Total (N = 213) (%)	Persistent COVID-19 symptoms beyond 3 months		p-value§
		No (N = 105) (%)	Yes (N = 108) (%)	
Gender				0.224
Female	162 (76.1)	77 (73.3)	85 (78.7)	
Male	51 (23.9)	28 (26.7)	23 (21.3)	
Age (years)				0.252
18–24	64 (30)	36 (34.3)	28 (25.9)	
25–34	82 (38.5)	42 (40)	40 (37)	
35–44	46 (21.6)	20 (19)	26 (24.1)	
45–54	14 (16.6)	5 (4.8)	9 (8.3)	
55–64	6 (2.8)	1 (1)	5 (4.6)	
65 +	1 (0.5)	1 (1)	0 (0)	
Marital status				0.008
Single	79 (31.7)	49 (46.7)	30 (27.8)	
Married	125 (58.7)	54 (51.4)	71 (65.7)	
Divorced/separated	4 (1.9)	2 (1.9)	2 (1.9)	
Widowed	5 (2.3)	0 (0)	5 (4.6)	
Education				0.021
Primary	5 (2.3)	3 (2.9)	2 (1.9)	
Secondary	4 (1.9)	0 (0)	4 (3.7)	
Tertiary	204 (95.8)	102 (97.1)	102 (94.4)	
Employment				0.004
Student	50 (23.5)	31 (29.5)	19 (17.6)	
Governmental sector	60 (28.1)	29 (27.6)	31 (28.7)	
Private sector	20 (9.4)	11 (10.5)	9 (8.3)	
Homemaker/unemployed	83 (39)	34 (32.4)	49 (45.4)	
Monthly income (SAR*)				0.226
<5000	60 (28.2)	31 (29.5)	29 (26.9)	
5000–10,000	55 (25.8)	23 (21.9)	32 (26.9)	
>10,000–15,000	44 (20.7)	18 (17.1)	26 (24.1)	
>15,000–20,000	22 (10.3)	12 (11.4)	10 (9.3)	
>20,000–25,000	17 (8)	10 (9.5)	7 (6.5)	
>25,000	15 (7)	11 (10.5)	4 (3.7)	

(Continued)

Table 1. (Continued)

	Total (N = 213) (%)	Persistent COVID-19 symptoms beyond 3 months		p-value§
		No (N = 105) (%)	Yes (N = 108) (%)	
Number of medical conditions				0.007
0	131 (61.5)	78 (74.3)	53 (49.1)	
1	52 (24.4)	19 (18.1)	33 (30.6)	
2	18 (8.5)	4 (3.8)	14 (13)	
⩾3	12 (5.6)	4 (3.8)	8 (7.4)	
Individual medical conditions				
Hypertension	14 (6.6)	5 (4.8)	9 (8.3)	0.220
Diabetes	8 (3.8)	4 (3.8)	4 (3.7)	0.624
Coronary artery disease	1 (0.5)	1 (1)	0 (0)	0.493
Overweight	32 (15)	10 (9.5)	22 (20.4)	0.021
Anxiety	20 (9.4)	6 (5.7)	14 (13)	0.056
Depression	10 (4.7)	2 (1.9)	8 (7.4)	0.055
Other mental health disorder	4 (1.9)	0 (0)	4 (3.7)	0.064
Asthma	25 (11.7)	9 (8.6)	16 (14.8)	0.114
Immunosuppressive condition	2 (0.9)	0 (0)	2 (1.9)	0.256
Drug-induced immune suppression	4 (1.9)	1 (1)	3 (2.8)	0.321
Chronic kidney disorder	1 (0.5)	0 (0)	1 (0.9)	0.507
Chronic haematological disorder	4 (1.9)	0 (0)	4 (3.7)	0.064
Hypothyroidism	4 (1.9)	2 (1.9)	2 (1.9)	0.679
Others	5 (2.3)	1 (1)	4 (3.7)	0.193
Total number of initial symptoms				0.014
0	5 (2.3)	5 (4.8)	0 (0)	
1	18 (8.5)	10 (9.5)	8 (7.4)	
2	4 (1.9)	3 (2.9)	1 (0.9)	
3	14 (6.6)	10 (9.5)	4 (3.7)	
4	17 (8)	11 (10.5)	6 (5.6)	
5	13 (6.1)	5 (4.8)	8 (7.4)	
⩾6	142 (66.7)	61 (58.1)	81 (75)	

Data are presented as n, or n (%).
§Respondents who reported persistent symptoms and respondents who reported no persistent symptoms were compared using the chi-square test or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. p-values < 0.05 indicate significant differences.

Table 2. COVID-19 diagnosis and management among respondents.

	Total (N = 213) (%)	Return to baseline health		p-value
		No (N = 61) (%)	Yes (N = 152) (%)	
Diagnosis				0.777
Throat swab	65 (30.5)	20 (32.8)	45 (29.6)	
Nasopharyngeal swab	137 (64.3)	38 (62.3)	99 (65.1)	
Through a physician (no investigation)	11 (5.2)	3 (4.9)	8 (5.3)	
Management				
Advice from MOH hotline	157 (73.7)	50 (82%)	107 (70.4)	0.083
Outpatient care	127 (59.6)	35 (67.4)	92 (60.5)	0.672
Hospital admission	18 (8.5)	5 (8.2)	13 (8.6)	0.933
ICU admission	4 (1.9)	4 (1.9)	0 (0)	0.001
Required oxygen therapy	31 (14.6)	14 (23)	17 (11.2)	0.028

ICU: intensive care unit; MOH: Ministry of Health.

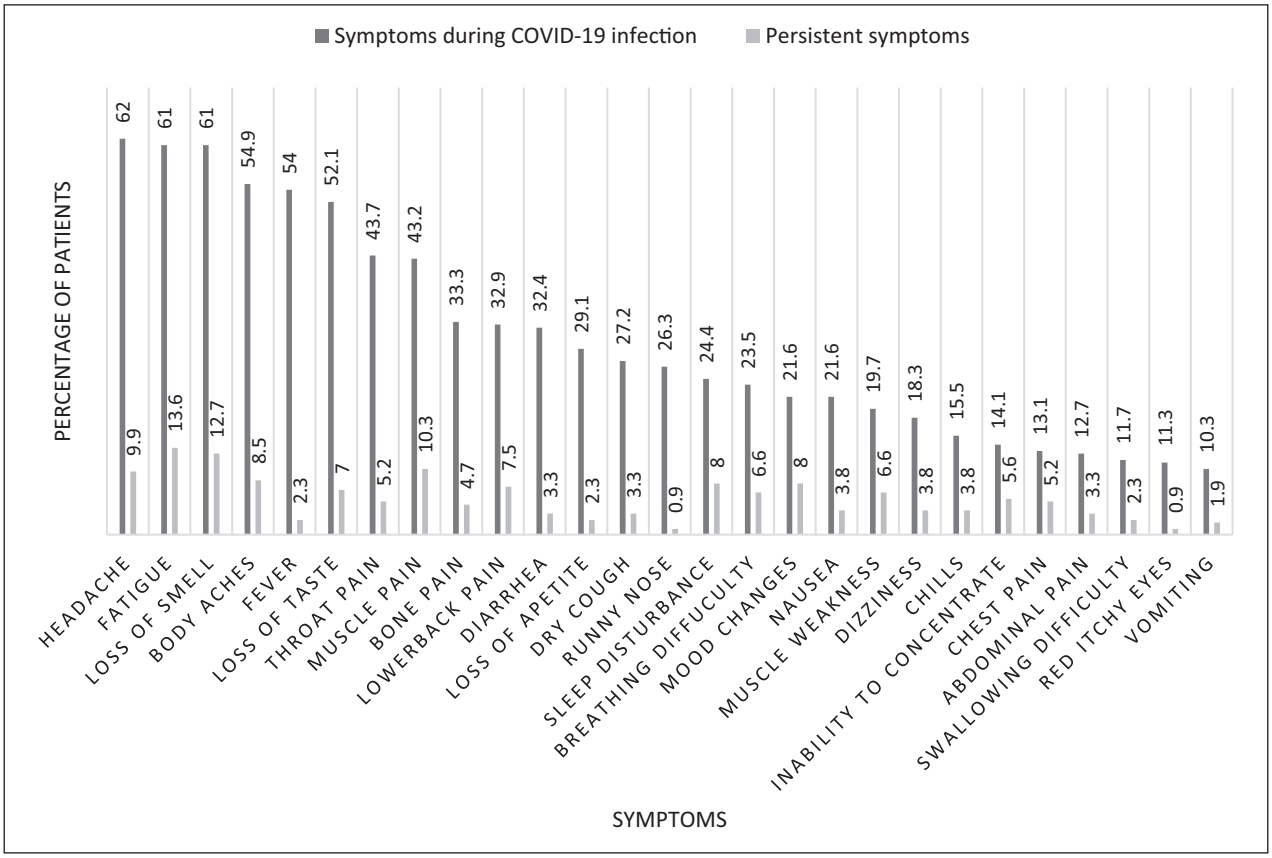

Figure 1. Symptoms reported during COVID-19 diagnosis and persistent symptoms ⩾ 3 months later (N = 213).

Table 3. Logistic regression for predicting the likelihood of not returning to baseline health based on gender, age, the total number of chronic medical conditions, and the total number of symptoms at disease onset.

	B	SE	Wald	Df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Gender	0.068	0.373	0.033	1	0.855	1.071	0.515	2.225
Age	0.082	0.152	0.290	1	0.590	1.085	0.806	1.462
Total number of chronic medical conditions	−0.286	0.147	3.765	1	0.052	0.751	0.563	1.003
Total number of symptoms at disease onset	−0.042	0.026	2.614	1	0.106	0.959	0.911	1.009
Constant	1.295	0.420	9.496	1	0.002	3.652		

Three months or more after a COVID-19 diagnosis, almost half of the respondents, 109 (51.2%), had residual symptoms. The five most reported persistent symptoms were fatigue 29 (13.6%), altered sense of smell 27 (12.7%), muscle aches 22 (10.3%), headache 21 (9.9%), and body aches 18 (8.5%). Figure 1 shows symptoms at diagnosis and persistent symptoms beyond 3 months of COVID-19 diagnosis.

When questioned regarding the return to the usual state of health, 152 (71.4%) answered in the affirmative. Of the four predictor variables for the delayed return to the usual state of health, only one was statistically significant: the total number of chronic medical conditions (Table 3).

Discussion

The long-lasting effects of COVID-19 are increasingly recognised. This cross-sectional study found that 5 out of 10 COVID-19 survivors experienced persistent symptoms 3 months beyond the initial disease onset, and 3 out of 10 reported a delayed return to the usual state of health. In our study, 109 (51.2%) had residual symptoms. Other studies

that sampled a similar population of hospitalised and non-hospitalised COVID-19 survivors and used 3 months as a cut-off point for defining long COVID have found similar percentages of 51.4%[22] and 53.1%.[23] On the other hand, a higher percentage of persistent symptoms, 67%[24] and 93%,[25] were described in cohorts of post-hospitalised patients. A recent meta-analysis has shown that there is a disease burden in the paediatric population, with a reported prevalence of 25.24%.[26]

A recent scoping review has reported more than 100 persistent SARS-CoV-2 symptoms pooled from 50 studies.[11] In the review, the significant variability in the prevalence of persistent symptoms among studies was speculated to be related to unknown cohort-specific factors. Fatigue, lost or altered sense of smell, muscle aches, headache, and body aches are the most frequently reported symptoms in our study. A living systematic review identified the following persistent symptoms 12 weeks or more post-COVID-19 as the most common symptoms reported: weakness (41%), general malaise (33%), fatigue (31%), concentration impairment (26%), and breathlessness (25%) as the most common symptoms reported.[12] However, more than half of the studies included in the review (67%) were cohorts of post-discharge hospitalised patients.

Fatigue is the most frequently reported residual symptom in our study. Similarly, in several studies with similar follow-up duration, fatigue was described among the most common residual symptoms of COVID-19.[22,23,27–29] Fatigue is also among the most frequent symptoms described in follow-ups extending beyond 6 months.[30] Loss or altered sense of smell is the second most reported symptom experienced by 12.7% of the respondents. Other studies have reported similar results of 12%[24] and 14.7%.[31] One study reported a higher percentage (45%) when objective tests were used to detect hyposmia/anosmia; however, self-reported hyposmia/anosmia was lower (17%) for the same patients.[32]

Morbidity persists with 28.6% of the respondents attesting not returning to their usual state of health. Townsend et al.[18] reported a higher percentage of 62% when patients were followed up at a median of 75 days after diagnosis; however, 48% of the cohort were hospitalised (26% of which were in the intensive care unit). The number of comorbid conditions was a statistically significant variable when assessing the return to the usual state of health. Being overweight, in particular, was associated with a delayed return to the usual state of health ($p = 0.021$). Tenforde et al.[19] also reported that obesity was associated with more than twofold odds of not returning to usual health; however, the median interval from diagnosis to interview was 16 days in their study.

Our study is novel in characterising persistent COVID-19 symptoms in hospitalised and home-isolated patients; thus, survivors with variable disease severity were included. However, a limitation of this study is the sample size of the pilot study (N = 14, less than 10% of the projected sample size), and the small subgroups; hence, our findings should be confirmed in a larger cohort. Another limitation is the self-report nature of the study, as well as the inherent limitations of surveys. Therefore, studies supplemented with clinical assessment will be of value, in addition to patient-reported outcomes.

Conclusion

In conclusion, our study presents evidence supporting the emerging literature on the persistence of symptoms among COVID-19 survivors. In our cohort, 5 out of 10 COVID-19 survivors experienced persistent symptoms 3 months after the initial disease onset, and 3 out of 10 reported a delay in return to the usual state of health. Given the disease burden, priorities for the detection, management, and rehabilitation of this condition are urgently needed. In addition, due to the various possible persistent symptoms, multidisciplinary collaborative care, including primary healthcare providers, specialists, and occupational medicine, is required. Finally, the control of acute COVID-19 infection rates will ultimately reduce the prevalence of its post-acute sequelae.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Informed consent

Written informed consent was obtained from all participants before the study.

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Supplemental material

Supplemental material for this article is available online.

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