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Original article

Persistent COVID-19 symptoms at least one month after diagnosis: A national survey

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Background: Post-acute COVID-19 syndrome (PACS) is an important healthcare burden. We examined persistent symptoms in COVID-19 patients at least four weeks after the onset of infection, participants' return to pre-COVID-19 health status and associated risk factors.

Methods: Cross-sectional study was conducted (December 2020 to January 2021). A validated online questionnaire was sent to randomly selected individuals aged more than 14 years from a total of 1397,386 people confirmed to have COVID-19 at least 4 weeks prior to the start of this survey. This sample was drawn from the Saudi ministry of health COVID-19 testing registry system.

Results: Out of the 9507 COVID-19 patients who responded to the survey, 5946 (62.5%) of them adequately completed it. 2895 patients (48.7%) were aged 35–44 years, 64.4% were males, and 91.5% were Middle Eastern or North African. 79.4% experienced unresolved symptoms for at least 4 weeks after the disease onset. 9.3% were hospitalized with 42.7% visiting healthcare facility after discharge and 14.3% requiring readmission. The rates of main reported persistent symptoms in descending order were fatigue 53.5%, muscle and body ache 38.2%, loss of smell 35.0%, joint pain 30.5%, and loss of taste 29.1%. There was moderate correlation between the number of symptoms at the onset and post-four weeks of COVID-19 infection. Female sex, pre-existing comorbidities, increased number of baseline symptoms, longer hospital-stay, and hospital readmission were predictors of delayed return to baseline health state ($p < 0.05$).

Conclusion: The symptoms of PACS are prevalent after contracting COVID-19 disease. Several risk factors could predict delayed return to baseline health state.

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1. Introduction

SARS-CoV-2 affects several organ systems, including the lungs, heart, brain, liver, kidneys, and gastrointestinal tract [1]. Symptoms associated with post-acute COVID-19 syndrome (PACS) represent a complex systemic disease that affect a significant number of patients who have recovered from acute COVID-19 resulting in impairment of everyday activities beyond the initial acute period [2].

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COVID-19 long-haulers have a profile that differs from acute COVID-19 disease, with chronic symptoms that are not always related to acute COVID-19 severity. Despite recovering from the active viral infection, atypical persistent symptoms such as excessive fatigue, shortness of breath, joint pain, brain fog, and mood swings may continue for weeks or months suggesting an underlying pathology that persists beyond the initial presentation of the disease [3,4].

The terms "long COVID-19" and "post-acute COVID-19 syndrome (PACS)" lack a unified definition. It was described by the National Institute for Health and Care Excellence (NICE) as a set of “signs and symptoms that emerge during or after an infection consistent with COVID-19, persist for more than 12 weeks, and are not explained by an alternative diagnosis” [5]. Another group of investigators defined PACS as chronic symptoms or long-term sequelae of COVID-19 lasting beyond 4 weeks after onset of symptoms [2,6]. This syndrome is subdivided into two categories: 1) subacute, which is defined as ongoing symptoms and abnormalities that last 4–12 weeks after the onset of illness. 2) Chronic, defined as symptoms and abnormalities that last more than 12 weeks after the onset of illness and are not explained by an alternative diagnosis [2,6].

Globally and in Saudi Arabia, the number of patients recovering from COVID-19 infection continues to grow. In a recent systematic review and meta-analysis that included 63 studies, with a total COVID-19 population of 257 348, we found that the most commonly reported symptoms were fatigue, dyspnea, sleep disorder, and difficulty concentrating (32%, 25%, 24%, and 22%, respectively, at 3- to < 6-month follow-up); effort intolerance, fatigue, sleep disorder, and dyspnea (45%, 36%, 29%, and 25%, respectively, at 6- to < 9-month follow-up); fatigue (37%) and dyspnea (21%) at 9 to < 12 months; and fatigue, dyspnea, sleep disorder, and myalgia (41%, 31%, 30%, and 22%, respectively, at > 12-month follow-up) [7].

Little is known about the prevalence of PACS in Saudi Arabia. Therefore, we sought to describe the short term and medium-term symptoms experienced by a nationwide cohort of SARS-CoV-2 infected patients in Saudi Arabia who were diagnosed with COVID-19 disease more than four weeks prior to participation in the study. We aimed to determine the prevalence of COVID-19 associated symptoms 4 weeks or more after the onset of the disease and identify predictors associated with delayed return to baseline health state among these patients.

2. Methodology

2.1. Study design and participants

We conducted a cross-sectional study, targeted randomly selected sample, that represented 10% of confirmed COVID-19 infected patients who were registered in the Saudi Ministry of Health (MOH) COVID-19 registry system. The first survey was sent on 17/12/2020 and a reminder on 21/01/2021. The sample was chosen at the end of November 2020 when there were 1397,386 individuals with laboratory confirmed SARS-CoV2 who were 18 years and older and 2 weeks have passed since their diagnosis. An SMS message was sent to every 10th record totaling to 139,738 messages.

2.2. Data collection tool, and study variables

An online Arabic and English self-administrated questionnaires were distributed through short message services (SMS) and the emails of the MOHs employees. The survey was initially piloted on 100 adult patients in the community who recovered from COVID-19 (4 weeks and more after recovery). The pilot study did not reveal any problems and thus no changes were made to the questionnaire. The survey was composed of four main parts; 1- demographic data (age, gender, smoking status, nationality), and medical comorbidities, 2- management course including need for hospital admission, oxygen requirement and ICU admission, 3- self-reported COVID-19 symptoms (at the onset of infection and at the follow-up time), 4- the participants’ return to their pre-COVID-19 health status at the survey time and 5- validated questionnaires to assess their exertional dyspnea, exercise tolerance, fatigability, and mental well-being post discharge. These include:

1. Patient self-reported functional status (PCFS) scale [8] which is a new recommended scale to be used during the current pandemic. It assesses the functional sequelae and monitors direct recovery after the SARS-CoV-2 infection at four weeks post-discharge from the hospital. PCFS scale covers the entire range of functional limitations over an average of one-week period,
2. Medical research council (MRC) dyspnea scale used to measure perceived respiratory disability. The MRC breathlessness scale is a questionnaire that has five statements about perceived shortness of breath: grade 1- “I only get breathless with strenuous exercise”; grade 2- “I get short of breath when hurrying on the level or up a slight hill”; grade 3- “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”; grade 4- “I stop for breath after walking 100 yards or after a few minutes on the level”; grade 5- “ I am too breathless to leave the house”. Participants choose the grade that applies to them. Those who selected MRC grades 1 and 2 were classified as having mild dyspnea, those with grades 3 and 4 were considered to have moderate dyspnea and those with grade 5 breathlessness were considered to have severe dyspnea [9].
3. Chronic fatigability syndrome (CFS) questionnaire [10]: Respondents rated the severity of fatigue and the eight ancillary criteria over the past 6 months using an anchored ordinal scale of 0 (no symptom), 1 (trivial), 2 (mild), 3 (moderate), and 4 (severe). The sum of the eight ancillary criteria was calculated and each patient was classified according to the following categories: Normal (Fatigue = none, trivial, or mild; score < 14), chronic idiopathic fatigue (CIF) (Fatigue = moderate or severe; score < 14), CFS-like with insufficient fatigue syndrome (Fatigue = none, trivial, or mild; score ≥14), and CFS (Fatigue = moderate or severe; score ≥14)
4. World Health Organization-five well-being index (WHO-5) which consists of five positively phrased statements that reflect degree of psychological well-being [11]. Participants were asked to rate these statements over the last two weeks on Likert scale from all the time (5 points) to at no time (0 point). Each score item is multiplied by 4 with a total score ranging from 0 to 100. A score of less than 50 indicates poor well-being.
5. Metabolic equivalent of task (MET) score was used to assess exercise tolerance [12]. The activities are divided into 10 variables ranging from at rest, to performing simple activities such as getting dressed and doing routine housework, to highly strenuous sports.

2.3. Statistical analysis

The collected data were coded and analyzed using the software Stata (version 12) Statistical Software, College Station, TX Stata Corp. After cleaning data in the sub-sample, the descriptive statistics were used to summarize the baseline characteristics of the individuals. Frequencies and percentages (%) of the COVID-19 symptoms at onset and after at least 4 weeks after infection were created. To examine, whether there was a significant reduction in the participants reported number of symptoms from the baseline (at onset of covid-19) to at least 4 weeks post covid-19, we used Wilcoxon signed-rank test. To examine, whether there was a significant correlation between the reported number of symptoms at onset and at least 4 weeks post covid-19, we used Spearman's rank correlation coefficient.

Simple logistic regression analysis within the framework of generalized linear model technique was used to examine the association of each potential factor with the binary outcome (return to pre-COVID-19 health status). Independent variables included baseline factor such as participants' age, sex, hospitalization, comorbidities, and number of symptoms at baseline. Next, we fitted a final logistic regression model using a stepwise method to examine the independent associations of each potential factor with the outcome of interest. In the stepwise regression method, first we added into the model all those factors that were significant ($p < 0.05$) in the univariable analyses. Then we retained significant ($p < 0.05$) factors in the model and iteratively tested all non-significant variables in the final model for possible significance in the subsequent steps. We used likelihood ratio tests to examine the statistical significance of each factor. Based on this iterative testing method in the stepwise regression, we retained the following factors in the model: participants' age, gender, healthcare worker, heart failure, cardiac arrhythmia, COPD, asthma, Crohn's disease, ulcerative disease, number symptoms and signs at the onset of infection, admitted to hospital for COVID-19 infection, interaction of the number of symptoms with hospital admission. From the above fitted final model, we estimated the adjusted odds ratios (OR) and 95% confidence intervals (CI). To examine the final model fit, we used Hosmer-Lemeshow test and computed area under the ROC curve as a post-estimation measure.

3. Results

Of the 101842 patients who received the SMS and opened the survey, 28,983 (28.5%) responded: 9637 did not want to participate, 19346 were willing to participate but 4737 were diagnosed less than 4 weeks and 8633 did not provide complete answers. Out of the 9507 patients who responded to the survey, 5946 (62.5%) of them adequately completed it. Therefore, the analyses were confined to this final sample. To examine the sub-sample for attrition bias, we compared the baseline data (demographics, hospitalization and symptoms) of the studied sample (N = 5946) to the sample of individuals who did not provide adequate data. No significant differences were found between respondents with complete data and incomplete responses.

Clinical characteristics of the study population

The included individuals were predominantly young with 48.7% where in the age group 35–44 years and were males (64.4%). 58.9 hold bachelor's degree and 91.5 were Middle Eastern or North African. 67.1% never smoked. Several comorbidities have been reported by the participants; the most common of which were dyslipidemia which was reported by 20.1% of individuals, followed by hypertension in 15.5% and diabetes in 13.9% [Table 1].

Out of 5946 participants who provided sufficient data, 552 (9.3%) required hospitalization, of whom 283 (51.3%) were hospitalized for one week or less, 171 (31.0) were hospitalized for 2–4 weeks and 26 (4.7%) were hospitalized for more than four weeks. 72 (13.0%) of the participants did not report their hospital length of stay [Table 2].

Among discharged patients with complete data (n = 480), 205 (42.7%) visited a health care facility after discharge and 68 (14.2%) had readmission for COVID-19 disease [Table 2].

Prevalence of symptoms at follow-up

4722 (79.4%) of the participants experienced one or more symptoms at least 4 weeks after acquiring COVID-19 disease. The main symptoms at the onset of the disease were fatigue which was

Table 1
The characteristics of patients with COVID-19 who responded to the survey.

Variables	Total sample (N = 9505) N (%)	Patients who provided adequate data: sample used for the analysis N = 5946 N (%)
Age (y) years:	162(1.7)	101 (1.7)
18 - < 25	892 (9.4)	598 (10.1)
25 - < 35	4397 (46.3)	2895 (48.7)
35 - < 45	2513 (26.4)	1528 (25.7)
45 - < 55	1541 (16.2)	824 (13.9)
55 +		
Sex: Male	5.814 (61.2)	3831 (64.4)
Education:	561 (5.9)	299 (5.0)
Middle school	2211 (23.3)	1290 (21.7)
High school	5444 (57.3)	3500 (58.9)
Degree Bachelor	867 (9.1)	582 (9.8)
Degree Masters	188 (2.0)	130 (2.2)
MBBS	235 (2.5)	145 (2.4)
Degree Doctorate		
Healthcare workers:	1788 (18.8)	1160 (19.5)
Ethnicity:	8635 (90.9)	5439 (91.5)
Middle Eastern,	767 (8.1)	449 (7.5)
North African	64 (0.7)	39 (0.7)
Asian, South Asian,	6 (0.1)	2 (0.0)
Southeast Asian	26 (0.2)	16 (0.3)
Black		
Hispanic, Latino, or		
Spanish Origin		
White		
Smoking status:	6576 (69.2)	3992 (67.1)
Never smoked	1160 (12.2)	714 (12.0)
Previous smoker	1643 (17.3)	1155 (19.4)
Current smoker	126 (1.3)	85 (1.4)
Others (Unknown)		
Chronic diseases:	1426 (15.0)	826 (13.9)
Diabetes Mellitus	1576 (16.6)	923 (15.5)
Hypertension	1992 (21.0)	1196 (20.1)
Dyslipidemia	229 (2.4)	118 (2.0)
Heart failure	117 (1.2)	63 (1.1)
Ischemic heart	616 (6.5)	355 (6.0)
disease	27 (0.3)	10 (0.2)
Cardiac arrhythmia	1380 (14.5)	833 (14.0)
COPD	23 (0.2)	11 (0.2)
Asthma	48 (0.5)	31 (0.5)
Interstitial lung	154 (1.6)	97 (1.6)
disease	502 (5.3)	280 (4.7)
Stroke	418 (4.4)	239 (4.0)
Liver disease	18 (0.2)	7 (0.1)
Crohn's disease		
Ulcerative disease		
On Dialysis		

Table 2
Hospitalization for Covid-19 infection among studied participants.

Variable	N (%)
Admitted to a Hospital for COVID-19 infection (n = 5946)	5263 (87.1)
No	552 (9.3)
Yes	112 (1.9)
ER visit without hospitalization	19 (0.3)
Unknown (Not Reported)	
Length of hospital stay (LOS) (in weeks) (n = 552)	283 (51.3)
1 week or less than 1 week	127 (23.0)
2 weeks	35 (6.3)
3 weeks	9 (1.6)
4 weeks	26 (4.7)
More than 4 weeks	72 (13.0)
Unknown (Not reported)	
Hospital readmission for COVID-19 (n = 480)	68 (14.2)
Visiting any health care services after leaving the hospital (n = 480)	205 (42.7)

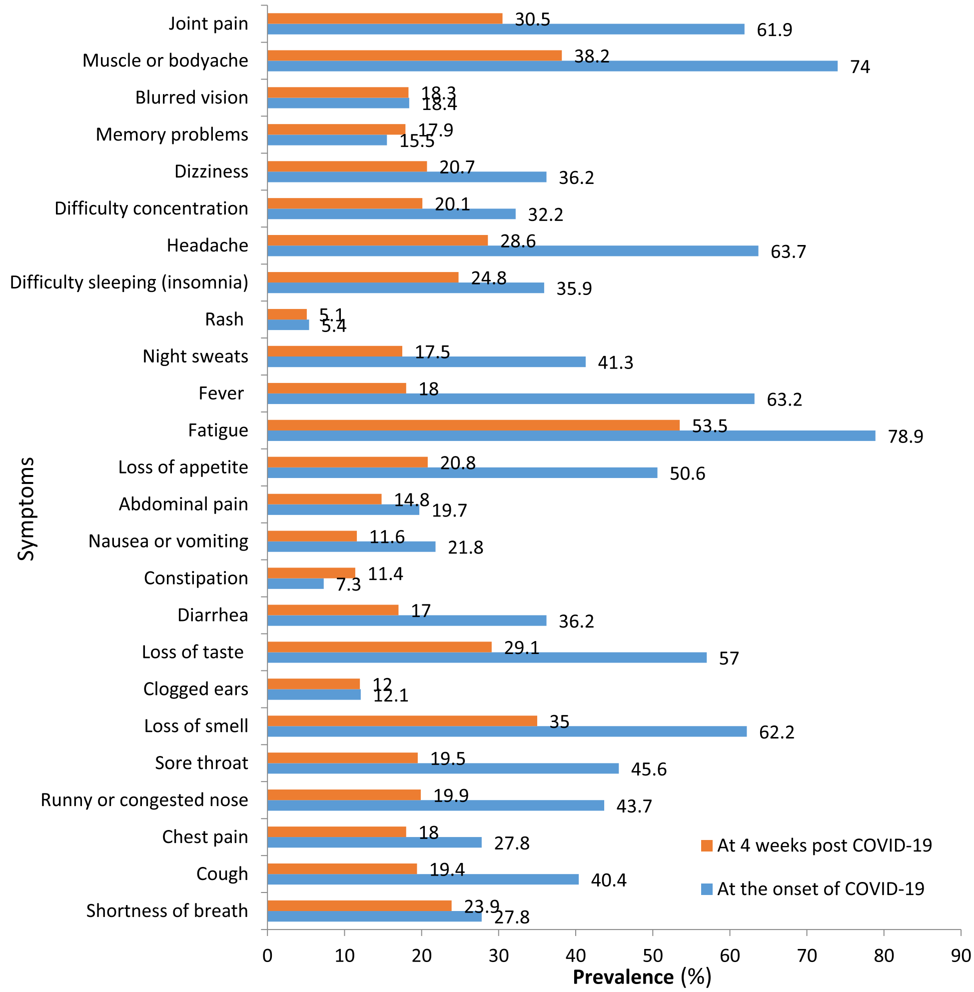

Fig. 1. Prevalence of self-reported COVID-19 symptoms at the onset of infection and after at least four weeks follow up All symptoms showed statistically significant reduction at the percentage of the onset of COVID-19 and after 4 weeks ($p < 0.00^*$) except clogged ears ($p = 0.766$).

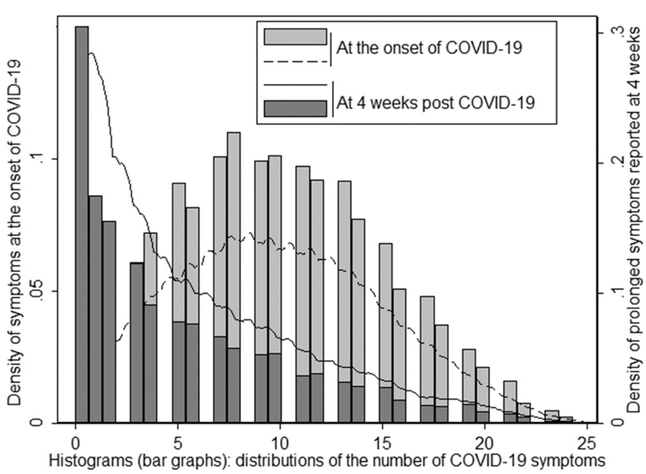

Fig. 2. Histograms of the number of COVID-19 symptoms at the onset of infection and at follow up There was a significant reduction in the median number of symptoms from 10 symptoms (IQR 6–13) at disease onset to three (IQR 1–8) after four weeks ($p < 0.001$).

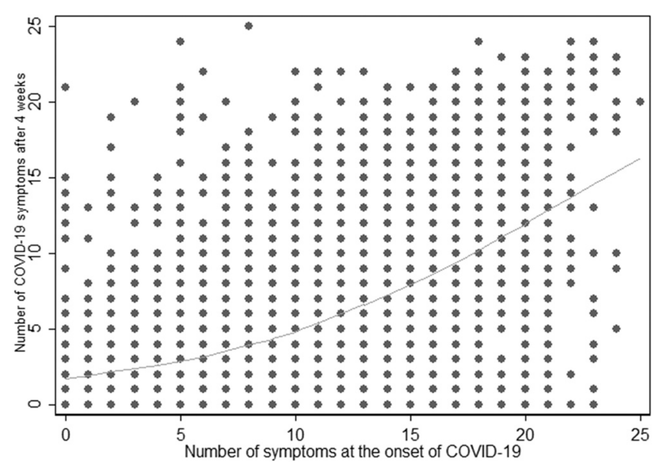

Fig. 3. Scatter diagram the correlation between the number of COVID-19 symptoms at the onset of infection and at follow up The Scatter plot shows a moderate correlation between the number of symptoms at the onset of COVID-19 infection and at the post four weeks ($r = 0.461$, $p < 0.001$).

reported by 78.9% of individuals, muscle and body aches 74.0%, headache 63.7%, fever 63.2%, loss of smell 62.2% and joint pain 61.9%.

The rates of reported symptoms at least four weeks after the infection onset were fatigue 45.2%, muscle and body aches 38.2%, loss of smell 35.0%, joint pain 30.5%, loss of taste 29.1% and headache 28.6%. Other important symptoms that were reported by at least 20% of individuals included: dyspnea, insomnia, dizziness, difficulty in concentration and loss of appetite [Fig. 1]. There was a significant reduction in the median number of symptoms from 10 symptoms (IQR 6–13) at disease onset to three (IQR 1–8) after four weeks

Table 3
Summary results of validated questionnaires.

	(N = 5946)	n (%)
WHO – 5 Well-being score	Mean ± SD 60.3 ± 21.8	
	Median [IQR] 64 [48–76]	
	Proportion with score < 50	1623 (27.3)
MET Exercise tolerance (N = 5939	< 2, Poor	143 (2.4)
	2–3, Below average	996 (16.8)
	4–9, Average	4022 (67.7)
	> 10, Excellent	778 (13.1)
MRC exertional dyspnea	No shortness of breath (SOB)	4528 (76.1)
	Mild	325 (5.5)
	Moderate	842 (14.2)
	Severe	251 (4.2)
Fatigue		2686 (45.1)
Chronic Fatigability Syndrome (N = 2686)	Normal	663 (24.7)
	CFS-like: Chronic Fatigue like with sufficient fatigue	7 (0.3)
	CIF: Chronic idiopathic fatigue	985 (36.7)
	CFS: Chronic Fatigue Syndrome	1031 (38.4)
Self-reported Functional Status (PCFS)	Grade 0: No functional limitations	4216 (70.9)
	Grade 1: Negligible functional limitations	842 (14.0)
	Grade 2: Slight functional limitations	272 (5.0)
	Grade 3: Moderate functional limitations	558 (9.4)
	Grade 4: Severe functional limitations	58 (0.9)
Symptomatic status at follow-up	Asymptomatic	1224 (20.6)
	Unresolved symptoms	4722 (79.4)

($p < 0.001$) [Fig. 2]. The Scatter plot [Fig. 3], shows a moderate correlation between the number of symptoms at the onset of COVID-19 infection and at the post four weeks ($r = 0.461$, $p < 0.001$).

Post COVID-19 functional status scale (PCFS)

The majority of the participants 70.9% reported no functional status limitation after recovery from COVID-19 disease and 29.1% reported functional limitations of different degrees. 842 (14.2%) reported negligible functional status limitation, 272 (4.6%) had mild limitation, 558 (9.4) had moderate limitation, and 58 (0.9) had severe limitation [Table 3].

Post COVID-19 shortness of breath

5946 participants answered the MRC exertional dyspnea scale. Of whom, 4022 (76.7) reported no shortness of breath at follow-up. 325 individuals (5.5%) had mild, 842 (14.2%) had moderate and 251 (4.2%) had severe shortness of breath at follow-up [Table 3].

Post COVID-19 chronic fatigue syndrome related symptoms

2686 (45.1%) of total participants answered the 8-item CFS questionnaire. Among these patients, 663 (24.7%) were classified as normal, 7 (0.3%) had chronic fatigue like syndrome, 985 (36.7%) had idiopathic chronic fatigue and 1031 (38.4%) fulfilled the criteria for chronic fatigue syndrome [Table 3].

Well-being index and physical activity after recovery from acute COVID-19

The mean WHO-5 wellbeing score was 60.3 (SD= 21.8) and the median was 64 (IQR= 48–76). However, 1236 out of 5946 individuals who completed the WHO-5 questionnaire (27.3%) had a score that was less than 50 indicating poor wellbeing [Table 3].

Among 5939 participants who provided information on exercise tolerance, the majority (4022, 67.7%) were able to engage in moderate exercise of 4–9 METs such as performing heavy household activities, running a short distance and engaging in moderately strenuous sports. 996 (16.8%) had below average exercise tolerance of 2–3 METS and only 778 (13.1%), were able to perform heavy sports equivalent to 10 or more METs. 143 (2.4%) participants had poor exercise tolerance and were able to only engage in activities with less than 2 METs [Table 3].

Predictors of return to baseline health status after COVID-19 disease

Table 5 summarizes the results of the univariate and multivariate analyses for predictors of return to baseline health status prior to acquiring the COVID-19 disease. On univariate analysis, young age, female sex, smoking, comorbidities (Heart failure, cardiac arrhythmias, COPD, asthma, Crohn's disease, ulcerative colitis), number of symptoms, hospitalization and length of stay were all negative predictors of return to baseline health status ($p < 0.05$ for all comparisons) [Table 4].

We then used multivariable logistic regression analysis to identify independent risk factors that were associated with participants' return to pre-COVID-19 disease baseline health status. The logistic regression was adjusted for age, sex, being a healthcare worker, comorbidities, baseline number of COVID-19 symptoms at the onset of infection, hospitalization, and ER visit [Table 4]. The independent predictors of lack of return to pre-COVID-19 disease baseline health status at least 4 weeks after the disease onset were age; using the age group 25–34 years as a reference, for every 10 years of increased age the odds of returning to the pre-infection states increases with people who are above 54 years of age had the highest chance of returning to their baseline health status (OR 2.60, CI 1.59–4.25, $p = 0.001$). Compared to males, females were less likely to return to their pre-COVID-19 health state (OR 0.72, CI 0.63–0.82, $p < 0.001$)). Other important independent predictors include hospital admission (OR 0.35, CI 0.21–0.59, $p < 0.001$), number of symptoms (OR 0.91, CI 0.89–0.92, $p < 0.001$) and certain comorbidities; cardiac arrhythmias (OR 0.60, CI 0.46–0.77, $p < 0.001$), asthma (OR 0.74, CI 0.62–0.88, $p < 0.001$) and ulcerative colitis (OR 0.67, CI 0.49–0.90, $p = 0.009$) [Table 4].

4. Discussion

This study is to our knowledge, the first national study from Saudi Arabia that addresses the problem of post-acute COVID-19 syndrome and that includes both hospitalized and non-hospitalized COVID-19 patients. Our study contributes to the international efforts trying to understand the long-term effects of COVID-19 disease

Table 4
Factors associated with the return to pre-COVID-19 disease baseline health status.

Variables	Univariable Analyses		Multiple logistic regression model (adjusted ORs) (aOR)	
Demographics:	OR (95% CI)	P	OR (95% CI)	P
Age (y):	Reference	-	-	-
18 - < 25	1.67 (1.07–2.62)	0.025[a]	1.73 (1.06–2.82)	0.028[a]
25 - < 35	1.79 (1.18–2.72)	0.007[a]	1.77 (1.13–2.80)	0.014[a]
35 - < 45	2.20 (1.43–3.38)	< 0.001	2.16 (1.36–3.45)	0.001[a]
45 - < 55	2.68 (1.71–4.20)	< 0.001	**2.60 (1.59–4.25)**	< 0.001
55 +				
Sex: Female	0.55 (0.48–0.61)	< 0.001	0.72 (0.63–0.82)	< 0.001
Healthcare worker:	0.83 (0.72–0.97)	0.023a	0.93 (0.79–1.10)	0.392
Smoking status:	Reference	-	–	–
Never smoked	1.22 (1.00–1.49)	0.050		
Previous smoker	1.23 (1.05–1.45)	0.012[a]		
Current smoker	1.01 (0.60–1.69)	0.975		
Unknown				
Health Issues (suffer from diseases):	0.50 (0.34–074)	< 0.001[a]	0.75 (0.47–1.19)	0.219
Heart failure	0.44 (0.36–0.56)	< 0.001[a]	0.60 (0.47–0.77)	< 0.001[a]
Cardiac arrhythmia	0.27 (0.08–0.94)	0.040a	0.47 (0.15–1.50)	0.203
COPD	0.59 (0.50–0.69)	< 0.001[a]	0.74 (0.63–0.89)	0.001[a]
Asthma	0.57 (0.44–0.74)	< 0.001[a]	0.82 (0.61–1.09)	0.168
Crohn's disease	0.51 (0.38–0.67)	< 0.001[a]	0.67 (0.49–0.91)	0.011
Ulcerative disease				
Number symptoms at the onset of infection:	0.89 (0.88–0.91)	< 0.001	0.91 (0.90–0.92)	< 0.001
Hospitalization:				
Admitted to a Hospital for COVID-19 infection (n = 5946)*	Reference	< 0.001	0.36 (0.22–0.61)	< 0.001
No hospitalization	0.51 (0.42–0.62)	< 0.001	0.45 (0.19–1.09)	0.076
Hospitalization	0.56 (0.41–0.76)			
ER visit without hospitalization				
Interaction of the number of symptoms with:			1.04 (1.00–1.08)	0.042a
hospitalization			1.05 (0.98–1.11)	0.167
ER visit without hospitalization				
LOS (weeks) (n = 552)**	Reference	0.014[a]	–	–
1 week or less	0.57 (0.37–0.89)	0.537		
2 weeks	0.79 (0.37–1.68)	< 0.001[a]		
3 weeks	0.24 (0.12–0.50)	0.250		
4 weeks or more	0.72 (0.41–1.26)			
Unknown (Not reported)				
Hospital readmission for COVID-19 (n = 552)**	0.39 (0.23–0.66)	< 0.001[a]	–	–

(y): Years, (OR): Odds Ratio, (aOR): adjusted ORs, (CI): Confidence Interval, Length of stay (LOS)
*There were 19 missing observations in the variable of “admitted to a Hospital for COVID-19 infection”. As the odds of these observations were very similar to the “no hospitalization”, in the model we assumed they were not hospitalized.
** Of the 552 hospitalized patients, 72 did not provide information on “LOS”. We kept them as a separate category in the logistic regression.
[a] Statistically significant with at least 5% of the significance level

[13,14]. Previous studies from Saudi Arabia were relatively small, single center and included only hospitalized patients [15].

Main findings and comparison to other studies

Our main finding is the persistence of symptoms at least 4 weeks post infection which was reported by 79.4% of individuals. The most common symptoms were fatigue (45.2%) and muscle aches (38.2%). These findings are consistent with our previous findings from a smaller cohort of hospitalized COVID-19 patients where fatigue was reported by almost 30% of patients at longer follow-up of 4 months [15]. These findings are also similar to previous reports from different parts of the world. In a recent meta-analysis conducted by our group that included 257,348 patients from 63 studies with at least 12 week follow up, fatigue was the most prevalent symptom at all time points up to more than a year after acquiring COVID-19 disease [7]. The prevalence of fatigue was 32%, 36%, 37% and 41% at 3–6, 6–9, 9–12 and > 12 months respectively [7].

Because viral infections have been linked to CFS [16,17], we used the 8-item CFS questionnaire to explore further the nature of fatigue in post-COVID-19 state and found out that 38.4% of patients who reported fatigue at least 4 weeks post-COVID-19 onset fulfilled the criteria for CFS. Limited data on CFS in the context of COVID-19 are available. In a small study, Simani et al. observed that only 3 out of 120 patients they had studied fulfilled the criteria for CFS [18]. On the other hand, in a recent meta-analysis addressing CFS symptoms in COVID-19 disease that included 21 studies, 25 of 29 CFS symptoms were reported by at least one COVID-19 study [19]. Furthermore, similar finding to ours have been reported after recovery from SARS. Lam et al. reported that 27.1% of recovered SARS patients fulfilled the criteria for CFS [20].

Among other important findings that we observed was shortness of breath that was reported by 23.9% and joint pains by 30.5% of participants. Several other symptoms have been reported by more than 20% of patients which include, loss of smell and taste, insomnia, loss of appetite, difficulty in concentration, headaches and dizziness. Persistence of multiple symptoms among our patients is similar to what has been reported by Davis et al. in an international cohort study where they traced 66 symptoms over 7 months after acquiring COVID-19 disease [21]. These findings were confirmed in a recent meta-analysis of 15 studies with 47,910 patients where 50 long-term effects of COVID-19 disease were documented; the most prevalent of which were fatigue 58%, headache 44%, attention disorder 27%, hair loss 25% and dyspnea 24% [22].

Of note, there are some important consequences of the observed increase in the prevalence of post-COVID-19 symptoms among our patients. These include the feeling of poor wellbeing that was evident in 27.3% of patients, impaired functional status in 29.1% and reduced exercise tolerance in 32.3%. These self-reported health limitations have far-reaching implications since over 90% of our patients had mild disease that did not require hospitalization.

To identify factors associated with return to pre-illness status, we performed univariate and multivariate analyses and identified a few independent predictors associated with return to pre-illness status. Female sex was associated with the lack of return to baseline pre-illness status with OR of 0.72 (95% CI 0.63–0.82, $p < 0.001$). This observation has been documented universally in multiple studies [23–28]. The reason for the consistent observation of increased risk among females for developing post-COVID-19 syndrome is not entirely clear but may reflect part of the known sex dimorphism observed with certain conditions such as autoimmune diseases [29]. Unexpectedly, for every 10 years increase in age when we used the age group 25–34 as a reference, there was a steady increase in the odds of returning to the baseline pre-illness status with the highest OR was noted with those above 54 years of age (OR 2.60, 95% CI 1.59–4.25, $p = 0.001$). This finding is in contradiction with our previous finding in a smaller cohort of hospitalized COVID-19 patients and with all other studies [7,15,24]. This might be due to selection bias where only a certain group of healthier older patients could have participated in this online survey. It could also be due to chance or other unidentified factors. Nonetheless, this needs to be explored further in future studies. We have also showed that hospital admission (OR 0.35, CI 0.21–0.59, $p < 0.001$) and number of symptoms (OR 0.91, CI 0.89–0.92, $p < 0.001$) and certain comorbidities such as arrhythmias, and asthma were associated with lack of return to pre-illness baseline state. These findings again are in agreement with previous reports [15,24–27].

We have also demonstrated in this study that among hospitalized patients, 42.7% visited health care facility after discharge and 14.2% required readmission. Several studies reported comparable readmission rates with ours ranging between 10% and 19.9% within 60 days of discharge from the hospital [30–34]. Several factors were associated with increased risk of readmission. In a recent meta-analysis, the most important predictors of readmission were, the age, male sex and comorbidities such as cardiovascular disease, cerebrovascular disease, cancer, kidney disease, COPD, diabetes and hypertension [35].

Another important observation is the high rate of patients seeking medical attention after acute illness. In our study, 42.7% of patients visited a health care facility. Similar observations were reported by Menges et al. where 40% of their patients had at least one visit to a general practitioner related to COVID-19% and 63% reported at least one visit for any reason after their discharge from the hospital [30]. Chopra et al. reported 78% primary care visits within 60 days of discharge [33]. High revisits to emergency department (ED) have also been documented even among those patients who did not require admission. Husain reported 24.3% return to ED within 30 days of initial contact in ED [36] and Menditto et al. reported. 22.9% return to ED within 14 days of the initial visit to ED [37].

Healthcare resources and economic implications

The high rates of medium to long-term persistence of COVID-19 related symptoms of more than 79%, and increased revisits to healthcare facilities after hospital discharge (42.7%) and readmission (14.2%) prove that long-term complication of COVID-19 disease pose huge burden on the health care system. Besides, persistence of symptoms, decreased exercise tolerance and poor wellbeing that we have reported have economic implications as affected patients are less likely to return to full time work. This contention is supported by the findings of Davis et al. who reported that 45.2% of their patients required reduced work load and 22.3% were not able to return to work after recovering from COVID-19 disease [21]. Similar observation was also reported by Heightman et al. in a one-year single center study where they observed that only less than half of employed patients were able to return to full time work [38].

Strengths and limitations

Our study is the largest national study that addressed the post-COVID-19 sequalae. Our study included both hospitalized and non-hospitalized patients. We were able to document the magnitude of the problem and to identify a number of predictors of lack of return to baseline health state. Our study also used multiple tools to identify the medium to long-term consequences of COVID-19 disease. We were also able to measure parameters related to healthcare resource utilization such as revisit rates to healthcare facilities and readmissions. However, our study has a number of limitations. First, our study has all the limitations of observational studies such as bias and confounding issues. Second, the study employed online self-administered survey which reduces the accuracy of collected data because of recall and availability bias. Further, this type of surveys is associated with missing data and in our study, we encountered missing data of up to 37.5%. Third, our study included patients from earlier wave of the COVID-19 disease. The lack of awareness about the long-term effects of COVID-19 during this period may have affected reporting of relevant information. Fourth, we did not perform assessment of the pre-COVID-19 baseline health, it is not possible to differentiate the pre-existing problems from those related to COVID-19 disease. Despite these limitations, our findings are supported by the observations from multiple international studies.

Conclusion

Persistent symptoms specially, fatigue, muscle aches, dyspnea and joint pains were experienced by over 79% of patients at least 4 weeks post-COVID-19 disease onset. This was associated with reduced exercise tolerance, poor wellbeing and lack of return to pre-illness baseline state. female sex, hospital admission, number of symptoms at disease onset and pre-existing comorbidities were associated with lack of return to pre-illness baseline state.

Ethical considerations

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Central 2nd Health Cluster, Ministry of Health, KSA. Protocol log number 20–649, approved 7 October 2020 with IRB registration number at KACST, KSA H-01-R-012 of exempt type.

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Informed consent statement

Patients were informed about the study objectives and asked if they are willing to participate in the online survey prior to filling the survey.

Data availability statement

The datasets used during the current study are available from the corresponding author or the principal investigator on reasonable request.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data confidentiality

The collected data were managed privately, and the identity was anonymous. Patients were informed about the study objectives and asked if they are willing to participate in the online survey prior to filling the survey. No patients' identities collected.

Brief summary

Almost 80% of the participants in this study had long-term symptoms at least 30 days from diagnosis. Participants are most likely to report persistent fatigue, muscle and body ache, loss of smell, and joint pain. There are several risk factors that could predict delayed return to baseline health state.

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