Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal of Infection and Public Health 15 (2022) 21–28

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Original Articles

Long term predictors of breathlessness, exercise intolerance, chronic fatigue and well-being in hospitalized patients with COVID-19: A cohort study with 4 months median follow-up

Imad M. Tleyjeh[a,b,c,d,*], Basema Saddik[e,f,1], Rakhee K. Ramakrishnan[e,f,1], Nourah AlSwaidan[g,1], Ahmed AlAnazi[g,1], Deema Alhazmi[g,1], Ahmad Aloufi[a,1], Fahad AlSumait[g,1], Elie F. Berbari[c], Rabih Halwani[e,f,h]

[a] Infectious Diseases Section, Department of Medical Specialties, King Fahad Medical City, Riyadh, Saudi Arabia
[b] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[c] Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
[d] Division of Epidemiology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
[e] Sharjah Institute for Medical Research, University of Sharjah, Sharjah, United Arab Emirates
[f] College of Medicine, University of Sharjah, Sharjah, United Arab Emirates
[g] Department of Medical Specialties, King Fahad Medical City, Riyadh, Saudi Arabia
[h] Prince Abdullah Ben Khaled Celiac Disease Chair, Department of Pediatrics, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 15 July 2021
Received in revised form 4 November 2021
Accepted 14 November 2021

Keywords:
Post-acute COVID-19 syndrome
PACS
Long COVID
Breathlessness
Exercise intolerance
Chronic fatigue
Well-being

ABSTRACT

Background: Post-acute COVID-19 syndrome (PACS) is an emerging healthcare burden. We therefore aimed to determine predictors of different functional outcomes after hospital discharge in patients with COVID-19.

Methods: An ambidirectional cohort study was conducted between May and July 2020, in which PCR-confirmed COVID-19 patients underwent a standardized telephone assessment between 6 weeks and 6 months post discharge. We excluded patients who died, had a mental illness or failed to respond to two follow-up phone calls. The medical research council (MRC) dyspnea scale, metabolic equivalent of task (MET) score for exercise tolerance, chronic fatigability syndrome (CFS) scale and World Health Organization-five well-being index (WHO-5) for mental health were used to evaluate symptoms at follow-up.

Results: 375 patients were contacted and 153 failed to respond. The median timing for the follow-up assessment was 122 days (IQR, 109– 158). On multivariate analyses, female gender, pre-existing lung disease, headache at presentation, intensive care unit (ICU) admission, critical COVID-19 and post-discharge ER visit were predictors of higher MRC scores at follow-up. Female gender, older age >67 years, arterial hypertension and emergency room (ER) visit were associated with lower MET exercise tolerance scores. Female gender, pre-existing lung disease, and ER visit were associated with higher risk of CFS. Age, dyslipidemia, hypertension, pre-existing lung disease and duration of symptoms were negatively associated with WHO-5 score.

Conclusions: Several risk factors were associated with an increased risk of PACS. Hospitalized patients with COVID-19 who are at risk for PACS may benefit from a targeted pre-emptive follow-up and rehabilitation programs.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

With over 246 million Coronavirus disease 2019 (COVID-19) diagnoses around the world, of which many have required hospital care over the past 23 months, enhanced emphasis is gradually moving to the post-acute care of COVID-19 survivors. Based on recent

* Corresponding author at: Medicine and Epidemiology, Section of Infectious Diseases, King Fahd Medical City, P.O. Box 59046, Riyadh 11525, Saudi Arabia.
E-mail address: Tleyjeh.Imad@mayo.edu (I.M. Tleyjeh).
[1] Equal contributions as second author.

https://doi.org/10.1016/j.jiph.2021.11.016
1876-0341/© 2021 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

data, millions of patients who have recovered from acute COVID-19 are experiencing lingering symptoms, leading to disability and impairment of their daily life activities [1]. Various terms have been used to describe the condition of patients who fail to return to their baseline health state to include post-acute sequelae of COVID-19, post-acute COVID syndrome (PACS), and long COVID. In this article, we use the term PACS henceforth.

The prevalence of various PACS symptoms have been examined in a systematic review of studies published till 6 March 2021 [2]. In the acute post-COVID phase (<12 weeks), the most frequently reported symptoms were fatigue (0.37; 95% CI, 0.20–0.56), dyspnea (0.35; 95% CI, 0.16–0.562) and anxiety (0.29; 95% CI, 0.19–0.40). In the chronic post-COVID phase (≥12 weeks), fatigue (0.48; 95% CI, 0.23– 0.73), sleep disturbance (0.44, 95% CI, 0.08– 0.85), and dyspnea (0.39; 95% CI 0.16– 0.64) were the most prevalent symptoms.

The increasing global burden of COVID-19 suggests that the potential public health effects of PACS are vast even if PACS is experienced by a small proportion of patients recovering from the acute infection. Close follow-up of all patients following hospital discharge may not yet be feasible while healthcare systems worldwide remain burdened with the care of patients with acute and chronic non-COVID diseases. The ability to identify patients at high-risk of PACS and to forecast the medical resource requirements is of significant clinical utility at present times [3].

To date, very few studies have evaluated the clinical predictors associated with prolonged and persistent symptoms of PACS. In the herein mentioned systematic review [2], reviewers identified 5 studies that have examined predictors of PACS [4– 8]. In view of the large number of COVID-19 survivors that may require follow-up, determining which patients are at risk of PACS and those who will require close follow-up is crucial. In this study, we therefore aimed to determine predictors of different functional outcomes after hospital discharge using an ambidirectional cohort study design of patients with COVID-19.

Methods

Study design and participants

This study was conducted at King Fahad Medical City (KFMC), Riyadh, Kingdom of Saudi Arabia. We included all patients with Polymerase Chain Reaction (PCR)-confirmed COVID-19 infection of age 18 years or older who were admitted to KFMC between the months of May and July 2020. We excluded patients who died before follow-up, were mentally unfit, were still hospitalized, and were unable to be contacted post discharge.

The study was approved by the Institutional Review Board (IRB) at KFMC (IRB No. 20-557). Verbal informed consent was obtained from all participants.

Data collection procedures

Demographic characteristics (including age, gender, smoking status, nationality), medical comorbidities, and hospital course (including type of admission, oxygen requirement, disease severity and treatment modality) were accessed from the electronic medical records. Participants were divided into intensive care unit (ICU) or general ward admission, and the disease severity was categorized into mild, moderate, severe and critical according to their oxygen need and hemodynamics. Treatment modality included antivirals (Favipiravir, convalescent plasma and triple antiviral therapy (lopinavir/ritonavir + ribavirin + interferonβ-1b)), immunomodulators (corticosteroids and Tocilizumab), and supportive therapy.

Participants were contacted through phone calls by trained physicians from 6 weeks to 6 months after hospital discharge. In order to ensure that data were collected in a scientific and standardized manner, a structured interview process was used to collect information from patients. General interviewer training which covered the basics of interviewing skills, probing, and how to avoid refusals was conducted, in addition to research-specific training including a complete review of the data collection instrument, the time that should be taken to conduct the interview, and how to address questions from patients. All interviewers were trained to follow a set script and protocol of questions to ensure the consistency and structure of questions. A pilot study followed by a debriefing was conducted prior to data collection to identify and minimize potential bias and inconsistency. Additionally, periodic meetings with the research team were held to ensure no divergence among the team and data collection had occurred. On average, the survey took approximately 10 min to complete. The interviews were conducted in Arabic or English based on patients' language fluency. Two patients could only speak other languages and were therefore excluded. The patients were asked to answer self-reported symptom questionnaires including the following four validated scales to assess their exertional dyspnea, exercise tolerance, fatigability, and mental well-being post discharge:

1 Medical research council (MRC) dyspnea scale uses a scoring from 1 to 5 to grade exertional dyspnea from mild to severe, respectively [9].
2 Metabolic equivalent of task (MET) score was used to assess exercise tolerance [10– 12]. The activities are divided into 10 variables ranging from at rest to performing simple activities such as getting dressed and housework to highly strenuous sports, with a score of 1 being the least strenuous to 10 being the most rigorous.
3 Chronic fatigability syndrome (CFS) questionnaire was used to score eight fatigue related symptoms, such as short-term memory problem, sore throat, sore lymph nodes, muscle pain, joint pain, headache, difficulty sleeping, extreme fatigue after exertion [13]. Based on the sum of the scores for these eight variables, the patients were classified according to chronicity into: normal, chronic idiopathic fatigue, CFS-like with insufficient fatigue syndrome and CFS.
4 World Health Organization – five well-being index (WHO-5) was used to measure the mental well-being of participants over the past 2 weeks [14]. Five psychological well-being parameters were scored and multiplied by 4 giving a final score in the range from 0 representing the worst well-being to 100 representing the best well-being.

Statistical analyses

Demographics, clinical characteristics, and symptoms at presentation and follow-up were presented in means (standard deviations [SD]) and medians (interquartile ranges [IQR]) for continuous variables and expressed as absolute values and percentages for categorical variables. For comparison between demographic and clinical characteristics, and ordinal dependent variables (MRC, MET, CFS scores), the Pearson's Chi-Square (χ^2) for categorical data was used. Significant associations found in the univariate analysis were included in cumulative odds ordinal logistic regression with proportional odds to determine the effects of gender, age, pre-existing comorbidities, ICU admission, BMI, COVID-19 severity, O_2 therapy, seven category scale, emergency room (ER) visit and hospital re-admission on the outcome variable MRC. The effects of gender, age, ethnicity, nationality, pre-existing comorbidities, ICU admission, BMI, COVID-19 severity, treatment, seven category scale, ER visit and hospital re-admission on the outcome variable MET was determined. Gender, age, pre-existing comorbidities, BMI, COVID-19 severity, treatment, ICU admission, seven category scale, ER visit and re-admission were assessed against the outcome variable CFS.

Table 1
Summary of findings from 4 validated questionnaires.

	N = 222	n (%)
WHO – 5 well-being score	Mean ± SD 85.36 ± 18.77	
	Median [IQR] 92 [76– 100]	
MRC exertional dyspnea	No shortness of breath (SOB)	107 (48.2)
	Mild	76 (34.2)
	Moderate	31 (14.0)
	Severe	8 (3.6)
MET exercise tolerance	<2 poor	7 (3.2)
	2–3 below average	30 (13.5)
	4–9 average	138 (62.2)
	>10 excellent	47 (21.2)
Chronic fatigability syndrome	Normal	163 (73.4)
	CFS-like: chronic fatigue like with sufficient fatigue	6 (2.7)
	CIF: chronic idiopathic fatigue	40 (18.0)
	CFS: chronic Fatigue Syndrome	13 (5.9)

A multiple linear regression was used to examine the effects of significant variables in the univariate analysis on the outcome variable WHO well-being score. The model included gender, age, nationality, pre-existing comorbidities, disease severity, triple antiviral treatment, ER visits and duration of symptoms. The sign of the estimates predicted the direction of association between the outcome and the independent variable. The overall fit of the model was measured through the F statistic and the collinearity among the variables by the Eigen method and index condition.

All statistical analyses were performed using IBM SPSS version 26 (Chicago, IL) software. A two-tailed $p < 0.05$ was considered statistically significant.

Results

The cohort included 461 patients hospitalized with PCR-confirmed SARS-CoV-2 infection between May and July 2020. We excluded 86 patients on account of the study exclusion criteria. The remaining 375 patients were contacted for the phone interviews and 153 of them failed to respond. Fig. 1 details the flow diagram of the study participants. A comparison of patients' characteristics did not show any significant difference between the 2 groups of respondents and non-respondents. The median timing for the follow-up phone calls after discharge was 122 days (IQR, 109– 158 days).

Baseline clinical characteristics of the cohort

A total of 222 patients discharged from the hospital post-acute COVID-19 infection responded to the follow-up phone survey. The demographic and clinical characteristics of these patients are summarized in Table S2. 125 patients (56.3%) experienced unresolved symptoms after a month of discharge and 28.8% of the cohort had not returned to their pre-COVID baseline state after a median 4 months of follow-up.

Summary of the results of the validated questionnaires at follow-up

Validated questionnaires were used to assess exertional dyspnea, exercise tolerance, fatigability, and mental well-being of the patients at follow-up (Table 1). Nearly half of our study cohort experienced varying degrees of exertional dyspnea, with 76 patients (34.2%) reporting mild, 31 (14%) moderate and 8 (3.6%) severe dyspnea. The patients in our cohort also demonstrated an above average exercise tolerance with 47 (21.2%) having a MET score >10 and 138 (62.2%) a score between 4–9. 30 patients (13.5%) experienced below average and 7 (3.2%) poor exercise tolerance. While 163 patients (73.4%) experienced no fatigue at follow-up, 40 patients (18%) reported chronic idiopathic fatigue and 13 (6%) chronic fatigue syndrome. From a WHO-5 well-being score ranging from 0 to 100, with 0 being the worst and 100 being the best imaginable well-being, our cohort demonstrated a median value of 92 (IQR, 76– 100). Variables independently associated with MRC, MET and CFS scores are displayed in Fig. 2.

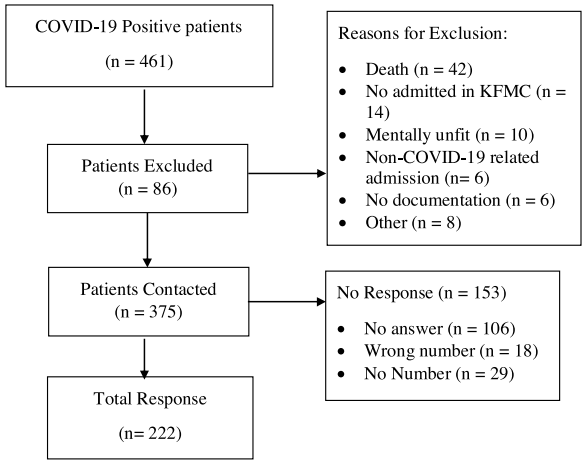

Fig. 1. Flow diagram of COVID-19 patients hospitalized at KFMC between May and July, 2020.

Predictors of exertional dyspnea at follow-up as measured by MRC Exertional Dyspnea score

Table S3 summarizes the results of univariate comparisons between different MRC score categories. Results of the ordinal logistic regression model to identify predictors of exertional dyspnea are displayed in Table 2. In our cohort, females were at higher risk of exertional dyspnea when compared to males (OR = 4.36; 95% CI, 2.25– 8.46). Patients with pre-existing lung disease (OR = 4.41; 95% CI, 1.81– 10.77), those who reported headaches at presentation (OR = 8.50; 95% CI, 2.04– 35.48) and those with ICU admission (OR = 2.44; 95% CI, 1.42– 4.19) were more likely to report higher scores of MRC. The severity of COVID-19 was also found to be associated with higher MRC scores with critical patients at the highest risk (OR = 23.67; 95% CI, 3.04– 84.41). Patients who visited the ER (OR = 4.71; 95% CI, 2.00– 11.06), those with seven category scale 5–6 (OR = 5.85; 95% CI, 2.04– 16.77) and scale 4 (OR = 3.12; 95% CI, 1.14– 8.58) were also predictors for higher MRC scores at follow-up.

Predictors of exercise tolerance at follow-up as measured by MET Exercise Tolerance score

Table S4 summarizes the results of univariate comparisons between different MET score categories. Results of the ordinal logis-

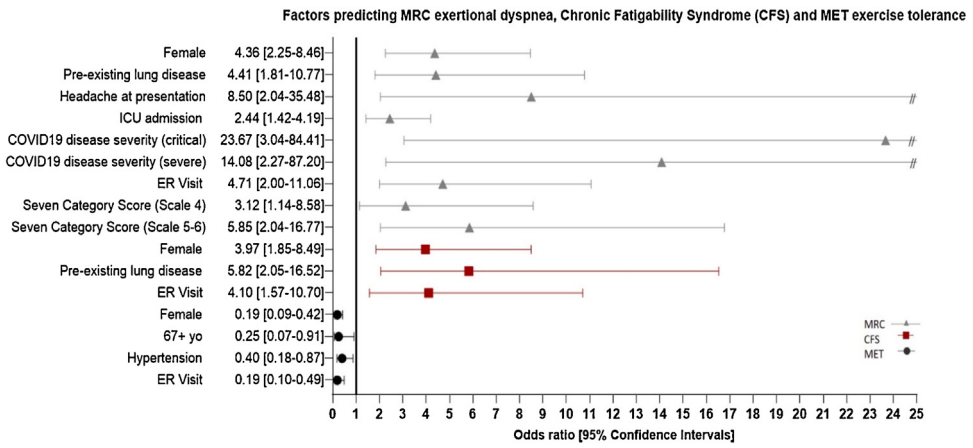

Fig. 2. Forest plot of odds ratios and 95% CIs of variables independently associated with medical research council (MRC) dyspnea scale, metabolic equivalent of task (MET) score for exercise tolerance, and chronic fatigability syndrome (CFS) scale.

Table 2
Ordinal logistic regression model for factors associated with MRC exertional dyspnea score.

		n (%)	OR (95% CI)
Gender	Female	51 (23.1)	**4.36 (2.25– 8.46)**
	Male[a]	170 (76.9)	**1**
Pre-existing lung disease	Yes	22 (10.0)	**4.41 (1.81– 10.77)**
	No[a]	198 (90.0)	1
SOB at presentation	Yes	204 (92.3)	1.63 (0.43– 6.64)
	No[a]	17 (7.7)	1
Headache at presentation	Yes	8 (3.6)	**8.50 (2.04– 35.48)**
	No[a]	212 (96.4)	**1**
Dizziness at presentation	Yes	3 (1.4)	7.12 (0.74– 68.86)
	No[a]	217 (98.6)	1
Type of admission	ICU	67 (30.5)	**2.44 (1.42– 4.19)**
	Ward[a]	153 (69.5)	1
Disease severity	Critical	44 (20.0)	**23.67 (3.04– 84.41)**
	Severe	48 (21.8)	**14.08 (2.27– 87.20)**
	Moderate	101 (45.9)	2.43 (0.48– 12.24)
	Mild[a]	27 (12.3)	1
ER visit	Yes	39 (17.7)	**4.71 (2.00– 11.06)**
	No [a]	181 (82.3)	1
Readmission to hospital	Yes	15 (6.8)	2.40 (0.69– 8.38)
	No [a]	205 (93.2)	1
Seven category score	Scale 5–6	70 (31.8)	**5.85 (2.04– 16.77)**
	Scale 4	128 (58.2)	**3.12 (1.14– 8.58)**
	Scale 3 [a]	22 (10.0)	1

[a] Reference group, *OR* odds ratio, *CI* confidence interval. MRC scale: No SOB; Mild; moderate; severe. Model Fit: ***-2Log-Likelihood 168.822 Likelihood Ratio Chi-Square 96.273 (df = 13, p-value≤0.001)***.

Table 3
Ordinal logistic regression model for factors associated with MET exercise tolerance score.

		n (%)	OR (95% CI)
Gender	Female	50 (22.8)	**0.19 (0.09– 0.42)**
	Male[a]	169 (77.2)	1
Age group	18–34[a]	19 (8.7)	1
	35–49	67 (30.6)	0.59 (0.19– 1.79)
	50–66	98 (44.7)	0.38 (0.13– 1.18)
	67+	35 (16.0)	**0.25 (0.07– 0.91)**
Nationality	Saudi	85 (38.8)	0.69 (0.32– 1.49)
	Non-Saudi	134 (61.2)	1
Ethnicity	European	6 (2.7)	1.36 (0.21–8.75)
	Pakistani	16 (7.3)	2.58 (0.77– 8.67)
	Filipino	22 (10.0)	0.45 (0.15– 1.35)
	Indian	41 (18.7)	1.21 (0.48– 3.03)
	Arab[a]	134 (61.2)	1
Existing co-morbidities	Yes	138 (63.0)	0.93 (0.35– 2.45)
	No[a]	81 (37.0)	1
Pre-existing cardiac disease	Yes	26 (11.9)	1.03 (0.47– 2.25)
	No[a]	193 (88.1)	1
Hypertension	Yes	88 (40.2)	**0.40 (0.18– 0.87)**
	No[a]	131 (59.8)	1
Steroids treatment	Yes	180 (82.2)	0.85 (0.40– 1.80)
	No[a]	39 (17.8)	1

Table 3 (*Continued*)

		n (%)	OR (95% CI)
ER visit	Yes	39 (17.8)	**0.19 (0.10– 0.49)**
	No[a]	180 (82.2)	1
Readmission to hospital	Yes	15 (6.8)	1.18 (0.30– 4.67)
	No[a]	204 (93.2)	1

[a] Reference group, *OR* odds ratio, *CI* confidence interval. MET scale: <2 poor; 2–3 below average; 4–9 average; <10 excellent. Model Fit: ***-2Log-Likelihood 274.034 Likelihood Ratio Chi-Square 74.729 (df = 15, p-value≤0.001)***.

Table 4
Ordinal logistic regression model for factors associated with chronic fatigability syndrome (CFS)* score.

		n (%)	OR (95% CI)
Gender	Female	50 (22.7)	**3.97 (1.85– 8.49)**
	Male[a]	170 (77.3)	1
Age	18–34[a]	19(9.1)	1
	35–49	63(30.3)	2.98 (0.65–13.61)
	50–66	93 (44.7)	2.27 (0.52– 9.96)
	67+	33(15.9)	3.04 (0.62– 14.86)
Dyslipidemia	Yes	11 (5.0)	1.04 (0.35– 4.34)
	No[a]	209 (95.0)	1
Lung disease	Yes	22 (10.0)	**5.82 (2.05– 16.52)**
	No[a]	198 (90.0)	1
COVID19 disease severity	Critical	44 (20.0)	0.07 (0.02– 3.42)
	Severe	48 (21.8)	0.38 (0.04– 3.36)
	Moderate	101 (45.9)	0.78 (0.16– 3.83)
	Mild[a]	27 (12.3)	1
ER visit	Yes	39 (17.7)	**4.10 (1.57– 10.70)**
	No[a]	181 (82.3)	1
Readmission to hospital	Yes	15 (6.8)	3.07 (0.79– 11.94)
	No[a]	205 (93.2)	1

[a] Reference group, *OR* odds ratio, *CI* confidence interval.
* CFS scale: normal; CFS-like: chronic fatigue like with sufficient fatigue; CIF: chronic idiopathic fatigue; CFS: chronic fatigue syndrome; Model Fit: ***-2Log-Likelihood 222.664 Likelihood Ratio Chi-Square 58.595 (df = 16, p-value ≤ 0.001)***.

tic regression model to identify predictors of exercise tolerance are displayed in Table 3. Female gender (OR = 0.19; 95% CI, 0.09– 0.42), older age >67 years (OR = 0.25; 95% CI, 0.07– 0.91), arterial hypertension (OR = 0.40; 95% CI, 0.18– 0.87) and ER visit (OR = 0.19; 95% CI, 0.10– 0.49) were associated with lower MET exercise tolerance scores at follow-up.

Predictors of fatigability at follow-up as measured by CFS questionnaire

Table S5 summarizes the results of univariate comparisons between different CFS score categories. Results of the ordinal logistic regression model to identify predictors of CFS are displayed in Table 4. Our analysis identified female gender (OR = 3.97; 95% CI, 1.85– 8.49), pre-existing lung disease (OR = 5.82; 95% CI, 2.05–16.52), and ER visit (OR = 4.10; 95% CI, 1.57– 10.70) to be associated with higher risk of CFS.

Predictors of wellbeing at follow-up as measured by WHO-5 well-being index

Table 5 summarizes the results of univariate and multivariate associations between WHO-5 scores and different variables. Age (B = −2.84; 95% CI, −5.57 to −0.11; p = 0.042), dyslipidemia (B = −24.85; 95% CI, −35.98 to −13.72; p < 0.001), arterial hypertension (B = −9.96; 95% CI, −15.50 to −4.42; p = 0.001), pre-existing lung disease (B = −9.39; 95% CI, −16.60 to −2.18; p = 0.011) and duration of symptoms (B = −4.39; 95% CI, −6.19 to −2.59; p< = 0.001) were found to negatively impact the well-being score.

Discussion

In this first post-COVID-19 hospitalization follow-up cohort study in the Middle East and North Africa (MENA) region, we assessed predictors of exertional dyspnea, exercise intolerance, fatigability, and mental well-being, in PCR-Confirmed COVID-19 patients at a median of 4 months after hospital discharge. We observed that a sizeable proportion of patients experienced moderate to severe exertional dyspnea, below average to poor exercise tolerance and moderate to severe fatigue at follow-up. Overall, patients reported positive well-being, although longer duration of symptoms predicted lower scores on the WHO-5 well-being scale. The female gender was identified as an independent predictor across all four questionnaires.

Previous studies have reported the long-term sequelae of COVID-19 in Asian [15], American [16] and European [17– 20] populations. A recent systematic review identified functional mobility impairments, pulmonary abnormalities, neurological disorders and mental health disorders as common long-term persistent post-acute sequelae of COVID-19 [21]. Although multiple studies have examined the burden of PACS symptomatology [2,22,23], studies detailing predictors of functional outcomes after more than 2 months of hospital discharge are very limited [2,24,25].

In a cohort study from China, which included 1733 discharged COVID-19 patients with a median follow-up time after symptom onset of 186 (175– 199) days, fatigue, or muscle weakness (63%) and sleep difficulties (26%) were the most common symptoms [15]. Being the most prevalent symptomology associated with post-acute COVID-19, we examined the predictors of long-term breathlessness, exercise intolerance, chronic fatigue, and mental well-being in our study to help identify COVID-19 patients who need close evaluation after hospital discharge. The findings from our study are in line with those from the Chinese cohort, where 76% of patients reported at least one symptom at 6 months follow-up, and the proportion was higher in women. After multivariable adjustment, women had an increased odds of anxiety or depression [OR 1.80 (1.39– 2.34)], and for fatigue or muscle weakness [OR 1.33 (1.05– 1.67)] compared with men. Severity of COVID-

Table 5
Patients' characteristics and symptoms associated with the WHO-5 well-being score.

		Median [IQR]	Mean rank	Test statistic	*P* value[a]	*B* (95% CI)	*P* value[*]
WHO-5 well-being score		92 [76–100]					
Gender	Male	96 [80–100]	121.05	2727.50	**<0.001**	8.32 (3.28– 13.37)	**0.001**
	Female	80 [68–92]	79.48				
Age	18–34	100 [84–100]	133.95	10.95	**0.012**	−2.84 (−5.57 to −0.11)	**0.042**
	35–49	92 [80–100]	116.41				
	50–66	92 [80–100]	114.35				
	67+	80 [68–95]	82.61				
Nationality	Saudi	88 [72–100]	98.74	4762.50	**0.014**	0.10 (−1.83 to 2.03)	0.917
	Non-Saudi	96 [80–100]	119.72				
Pre-existing Co-morbidities		88 [72–100]	105.27	4831.50	**0.048**	5.17 (−0.62 to 10.96)	0.080
	Dyslipidemia	68 [44–88]	55.18	541.00	**0.002**	−24.85 (−35.98 to −13.72)	**<0.001**
	Diabetes	90 [76–100]	108.08	5780.50	**0.440**	–	
	Hypertension	85 [68–100]	94.39	4400.00	**0.001**	−9.96 (−15.50 to −4.42)	**0.001**
	Cardiac disease	80 [60–100]	88.69	2016.50	**0.041**	−2.21 (−9.24 to 4.82)	0.535
	Renal disease	75 [69–97]	80.81	510.50	**0.154**	–	
	Lung disease	80 [65–91]	78.21	1577.00	**0.005**	−9.39 (−16.60 to −2.18)	**0.011**
BMI	Underweight	96 [92–100]	141.00	1.352	**0.717**		
	Normal	92 [76–100]	108.13				
	Overweight	92 [80–100]	106.39				
	Obese	88 [72–100]	100.76				
Disease severity	Mild	88 [74–100]	107.91	10.966	**0.012**	1.09 (−1.15 to 3.33)	0.339
	Moderate	88 [72–100]	102.27				
	Severe	100 [85–100]	137.38				
	Critical	92 [73–100]	107.09				
Severity category Scale	Scale 3	88 [76–100]	107.39	0.269	0.874	–	
	Scale 4	92 [76–100]	110.69				
	Scale 5–6	92 [80–100]	114.34				
Therapy	Triple Antiviral	100 [91–100]	138.87	2119.00	**0.016**	2.93 (−3.06 to 8.91)	0.336
	Favipravir	94 [80–100]	114.66	4142.00	**0.682**	–	
	Plasma	96 [80–100]	118.83	1172.00	**0.673**	–	
	Tocilizumab	88 [70–100]	101.20	2778.50	**0.301**	–	
	Steroids	92 [80–100]	114.04	3178.00	**0.193**	–	
ICU admission		92 [80–100]	112.25	5142.50	0.906	–	
Hospital re-admission		75 [57–100]	90.94	1319.00	0.168	–	
ER visit		76 [60–100]	79.54	2322.00	**<0.001**	−4.76 (−10.79 to 1.26)	0.121
Duration of symptom	1–7 days	100 [92–100]	133.95	35.33	**<0.001**	−4.39 (−6.19 to −2.59)	≤**0.001**
	8–14 days	92 [85–100]	109.82				
	15–21 days	84 [78–94]	86.30				
	>21 days	80 [68–100]	77.73				

[a] Using Mann– Whitney and Kruskal Wallis tests.
[*] Using multiple linear regression $F(12,193) = 9.893$ $p \leq 0.001$ adjusted $R^2 = 0.34$.

19 was also associated with persistent symptoms [OR 2.42 (1.15–5.08)].

The female gender, pre-existing comorbidities, COVID-19 severity and ER visits constituted the independent predictors of functional outcomes that were assessed in our study. These findings are consistent with similar observations reported from studies conducted in Spain and Brazil. In the Spanish study which followed up patients over a mean of 7 months after hospital discharge, female gender, duration of hospital stay, multiple medical comorbidities and number of acute COVID-19 symptoms at hospital admission were significantly associated with multiple long-term post-COVID symptoms [25].

Similarly in Brazil, where health-related quality of life (HRQoL) was assessed in COVID-19 patients at 3 months' post-hospital discharge, the female gender and intensive care unit admission were independently associated with worse HRQoL [24].

Notably, female gender was an independent predictor of unresolved symptoms in our study. This is in agreement with similar studies which observed that female patients more frequently reported moderate or severe fatigue and breathlessness than male patients [26,27]. The association between female gender and long-COVID [15,28], post-exertional polypnea [29], persisting fatigue [15,29,30], anxiety or depression [15,31] and decreased rates of recovery [31] have also been reported in the literature. These findings further highlight the gender differences in immunological response, as illustrated by the higher representation of women in autoimmune diseases [32], which may explain divergent findings between acute COVID-19 and post-COVID-19 syndrome. However, there remains no clear pathophysiology of why females are more susceptible to prolonged effects of the disease than males and further research on biological determinants and immunological responses in females could investigate this further.

Furthermore in our study, pre-existing lung disease, disease severity, ICU admission and ER visits were associated with an increased risk of exertional dyspnea at follow-up. Patients with airways disease are likely to experience comorbidities relevant to COVID-19 pathogenesis and its multisystem disease manifestations. In fact, pre-existing airway disease is known to affect health outcomes in COVID-19 survivors and can as a result lead to complications after hospital discharge [33]. The association between increased disease severity during hospital stay and high dyspnea prevalence at 6 months of follow-up have also been previously reported [15]. Similarly, females under the age of 50, in particular those with severe disease in the acute stage mandating critical care experienced poor long-term outcomes even after adjusting for severity of the acute illness [27].

We also observed that patients who needed to visit the ER after discharge had poorer mental well-being. Understandably ER visits post hospital discharge is a sign of poor long-term effects related to post-viral syndrome, post-critical care syndrome, and superimposed infection. Thus, many of our findings are in accordance with recent studies that have reported a similar pattern in the global population [27].

In addition to the direct effects of the virus, a dysregulated immune response, including hyperinflammation, cytokine storm syndrome, immune-mediated multi-system damage, or a combination of these [1] could reinforce the persistence of these symptoms or emergence of new ones. We recently hypothesized potential immunopathological mechanisms underlying multi-organ long-term manifestations of COVID-19, namely, a) COVID-19 survivors with persistent symptoms may harbor the virus in several potential tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs, b) delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue repair, c) cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity, d) mitochondrial dysfunction and impaired immunometabolism, e) alterations in microbiome, and f) imbalance in renin angiotensin system leading to the long-term health consequences of COVID-19 [34]. Furthermore, the upregulation in the expression of several oxidative stress genes in blood as well as lung tissue relative to COVID-19 severity reflects the SARS-CoV-2-induced reactive oxygen species generation and associated tissue injury [35].

To the best of our knowledge, our study is the first of its kind in the MENA region and one of very few studies worldwide to examine for predictors of commonly encountered functional outcomes in COVID-19 patients following hospitalization. Nevertheless, our study has several limitations. First, this was a single-centre study. On the other hand, being the largest public hospital in the country, the patients' population is representative of those living in Saudi Arabia. Second, because participants were asked to self-report health-related symptoms, measurement bias due to subjective reporting cannot be ruled out among those who suffered severe illness. Third, we could not measure the different functional outcomes at baseline prior to COVID-19 infection. At the same time, the presence of pre-existing comorbidities may have influenced these functional outcomes. However, we believe that recall bias would have inflicted such measurements at follow-up. Despite the wide confidence interval, we have reported the statistically significant associations as they were found to be valid and clinically meaningful. Nevertheless, these results need to be interpreted with caution. Finally, we did not perform objective assessments such as pulmonary imaging or 6 min' walk test at follow-up. The different questionnaires we have used were previously validated in different populations against objective outcomes, but none have been specifically validated in COVID-19.

Conclusion

In this ambidirectional evaluation at 4 months post hospitalization, female gender, pre-existing comorbidities, or high severity of acute COVID-19 disease were more likely to be associated with worse functional outcomes. Future multicentre studies should develop and validate prediction models to identify COVID-19 patients who might require close follow-up and pre-emptive targeted intervention after hospital discharge.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not required.

Acknowledgements

We would like to acknowledge the support of COVID-19 research grant (CoV19-0307); Seed grant (Grant code: tel:2001090275); collaborative research grant (Grant code: tel:2001090278 and 2001090283); Sandooq Al Watan Applied Research & Development grant (SWARD-S20-007); Al Jalila Foundation Seed Grant (AJF202019); and Prince Abdullah Ben Khalid Celiac Disease Research Chair, under the Vice Deanship of Research Chairs, King Saud University, Riyadh, Kingdom of Saudi Arabia to RH, University of Sharjah, UAE.

References

[1] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(4):601–15.
[2] Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: a systematic review and meta-analysis. EClinicalMedicine 2021;36:100899.
[3] Sudre CH, Lee KA, Lochlainn MN, Varsavsky T, Murray B, Graham MS, et al. Symptom clusters in COVID-19: a potential clinical prediction tool from the COVID symptom study app. Sci Adv 2021;7(12).
[4] Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect 2021;27(2):258–63.
[5] Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 2020;6(4).
[6] Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients with uncomplicated COVID-19 have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic. Clin Infect Dis 2021.
[7] Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. Int J Environ Res Public Health 2021;18(4).
[8] D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Res 2021;7(1).
[9] Paladini L, Hodder R, Cecchini I, Bellia V, Incalzi RA. The MRC dyspnoea scale by telephone interview to monitor health status in elderly COPD patients. Respir Med 2010;104(7):1027–34.
[10] Böhmer AB, Wappler F, Zwissler B. Preoperative risk assessment—from routine tests to individualized investigation. Dtsch Arztebl Int 2014;111(25):437–45, quiz 46.
[11] Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116(17):e418–99.
[12] Holt NF. Perioperative cardiac risk reduction. Am Fam Physician 2012;85(3):239–46.
[13] Timbol CR, Baraniuk JN. Chronic fatigue syndrome in the emergency department. Open Access Emerg Med 2019;11:15–28.
[14] Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 well-being index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167–76.
[15] Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet (London, England) 2021;397(10270):220–32.
[16] Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021.
[17] Gautam N, Madathil S, Tahani N, Bolton S, Parekh D, Stockley J, et al. Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection. Clin Infect Dis 2021.
[18] Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 2021;325(15):1525–34.
[19] Meije Y, Duarte-Borges A, Sanz X, Clemente M, Ribera A, Ortega L, et al. Long-term outcomes of patients following hospitalization for coronavirus disease 2019: a prospective observational study. Clin Microbiol Infect 2021.
[20] Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324(6):603–5.
[21] Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. JAMA Netw Open 2021;4(10):e2128568.

[22] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv: the preprint server for health sciences 2021.
[23] Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021;4(5):e2111417.
[24] Todt BC, Szlejf C, Duim E, Linhares AOM, Kogiso D, Varela G, et al. Clinical outcomes and quality of life of COVID-19 survivors: a follow-up of 3 months post hospital discharge. Respir Med 2021;184:106453.
[25] Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Rodrúez-Jiménez J, Palacios-Ceña M, Velasco-Arribas M, et al. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: a multicenter study. J Infect 2021.
[26] Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol 2021;93(2):1013–22.
[27] Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: a prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Europe 2021;8:100186.
[28] Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med 2021;27(4):626–31.
[29] Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin Microbiol Infect 2021;27(1):89–95.
[30] Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 2020;15(11):e0240784.
[31] Menges D, Ballouz T, Anagnostopoulos A, Aschmann HE, Domenghino A, Fehr JS, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: a population-based cohort study. PLoS One 2021;16(7):e0254523.
[32] Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol 2014;35(3):347–69.
[33] Adeloye D, Elneima O, Daines L, Poinasamy K, Quint JK, Walker S, et al. The long-term sequelae of COVID-19: an international consensus on research priorities for patients with pre-existing and new-onset airways disease. Lancet Respir Med 2021.
[34] Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the mystery surrounding post-acute sequelae of COVID-19. Front Immunol 2021;12(2574).
[35] Saheb Sharif-Askari N, Saheb Sharif-Askari F, Mdkhana B, Hussain Alsayed HA, Alsafar H, Alrais ZF, et al. Upregulation of oxidative stress gene markers during SARS-COV-2 viral infection. Free Radic Biol Med 2021;172:688–98.