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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

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A B S T R A C T

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 fatigue 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.

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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
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 + interferon-β1b)), 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 ($\chi^2$) 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.
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.

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 fatigue 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                     | 170 (76.9)| 1           |
| Pre-existing lung disease|           |             |
| Yes                      | 22 (10.0) | 4.41 [1.81–10.77] |
| No                       | 198 (90.0)| 1           |
| SOB at presentation      |           |             |
| Yes                      | 204 (92.3)| 1.63 [0.43–6.64] |
| No                       | 17 (7.7)  | 1           |
| Headache at presentation |           |             |
| Yes                      | 8 (3.6)   | 8.50 [2.04–35.48] |
| No                       | 212 (96.4)| 1           |
| Dizziness at presentation|           |             |
| Yes                      | 3 (1.4)   | 7.12 [0.74–68.86] |
| No                       | 217 (98.6)| 1           |
| Type of admission        |           |             |
| ICU                      | 67 (30.5) | 2.44 [1.42–4.19] |
| Ward                     | 153 (69.5)| 1           |
| Critical                 | 44 (20.0) | 23.67 [3.04–84.41] |
| Disease severity         |           |             |
| Severe                   | 48 (21.6) | 14.08 [2.27–87.20] |
| Moderate                 | 101 (45.9)| 2.43 [0.48–12.24] |
| Mild                     | 27 (12.3) | 1           |
| ER visit                 |           |             |
| Yes                      | 39 (17.7) | 4.71 [2.00–11.06] |
| No                       | 181 (82.3)| 1           |
| Readmission to hospital  |           |             |
| Yes                      | 15 (6.8)  | 2.40 [0.69–8.38] |
| No                       | 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                  | 22 (10.0) | 1           |

* 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                     | 169 (77.2)| 1           |
| Age group                |           |             |
| 18–34                    | 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           |
| European                 | 6 (2.7)   | 1.36 [0.21–8.75] |
| Pakistani                | 16 (7.3)  | 2.58 [0.77–8.67] |
| Ethnicity                |           |             |
| Filipino                 | 22 (10.0) | 0.45 [0.15–1.35] |
| Indian                   | 41 (18.7) | 1.21 [0.48–3.03] |
| Arab                     | 134 (61.2)| 1           |
| Existing co-morbidities  |           |             |
| Yes                      | 138 (63.0)| 0.93 [0.35–2.45] |
| No                       | 81 (37.0) | 1           |
| Pre-existing cardiac disease |       |             |
| Yes                      | 26 (11.9) | 1.03 [0.47–2.25] |
| No                       | 193 (88.1)| 1           |
| Hypertension             |           |             |
| Yes                      | 88 (40.2) | 0.40 [0.18–0.87] |
| No                       | 131 (59.8)| 1           |
| Steroids treatment       |           |             |
| Yes                      | 180 (82.2)| 0.85 [0.40–1.80] |
| No                       | 39 (17.8) | 1           |
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.

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

| Gender          | n (%) | OR (95% CI) |
|-----------------|-------|-------------|
| Female          | 50 (22.7) | 3.97 (1.85–8.49) |
| Male*           | 170 (77.3) | 1 |
| Age             |       |             |
| 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*             | 209 (95.0) | 1 |
| Lung disease    |       |             |
| Yes             | 22 (10.0) | 5.82 (2.05–16.52) |
| No*             | 198 (90.0) | 1 |
| COVID19 disease severity | | |
| Severe          | 48 (21.8) | 0.38 (0.04–3.36) |
| Moderate        | 101 (45.9) | 0.78 (0.16–3.83) |
| Mild*           | 27 (12.3) | 1 |
| ER visit        |       |             |
| Yes             | 39 (17.7) | 4.10 (1.57–10.70) |
| No*             | 181 (82.3) | 1 |
| Readmission to hospital | | |
| Yes             | 15 (6.8) | 3.07 (0.79–11.94) |
| No*             | 205 (93.2) | 1 |

* 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).

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, fatigueability, 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 postacute sequelae of COVID-19 [21]. Although multiple studies have examined the burden of PACS symptomatology [22,22,23], 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.

| WHO-5 well-being score | Median [IQR] | Mean rank | Test statistic | P value* | R (95% CI) | P value* |
|------------------------|-------------|-----------|----------------|---------|------------|---------|
| Gender                 |             |           |                |         |            |         |
| Male                   | 92 [76–100] | 121.05    | 2727.50        | <0.001  | 8.32 (3.28–13.37) | 0.001  |
| Female                 | 96 [80–100] | 79.48     |                |         |            |         |
| Age                    |             |           |                |         |            |         |
| 18–34                  | 100 [84–100]| 133.95    | 10.95          | 0.012   | –2.64 (–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 |         |           |                |         |            |         |
| Dyslipidemia           | 68 [44–88]  | 55.18     | 4831.50        | 0.048   | 5.17 (–0.62 to 10.96) | 0.080  |
| Diabetes               | 90 [76–100] | 108.08    | 541.00         | 0.002   | –24.85 (–35.98 to –13.72) | <0.001  |
| Hypertension           | 85 [86–100] | 94.39     | 5780.50        | 0.440   | –9.96 (–15.50 to –4.42) | 0.001  |
| Cardiac disease        | 80 [60–100] | 88.69     | 4400.00        | 0.001   | –2.21 (–9.24 to 4.82) | 0.535  |
| Renal disease          | 75 [69–97]  | 80.81     | 2016.50        | 0.041   | –              |         |
| Lung disease           | 80 [65–91]  | 78.21     | 510.50         | 0.154   | –              |         |
| BMI                    |             |           |                |         |            |         |
| Underweight            | 96 [92–100] | 141.00    | 1577.00        | 0.005   | –9.39 (–16.60 to –2.18) | 0.011  |
| Moderate               | 92 [76–100] | 108.13    | 1352.00        | 0.717   | –              |         |
| Normal                 | 82 [80–100] | 106.39    |                |         |            |         |
| Overweight             | 88 [72–100] | 100.76    |                |         |            |         |
| Disease severity       |             |           |                |         |            |         |
| Mild                   | 88 [74–100] | 107.91    | 9.066          | 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 1     | 88 [76–100] | 107.39 | 0.269   | 0.874   | –         |
| Scale 2                | 92 [76–100] | 110.69    |                |         |            |         |
| Scale 3–5              | 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  |
| Favipiravir            | 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     |                |         |            |         |

* Using Mann–Whitney and Kruskal Wallis tests.

Using multiple linear regression $F(12.193) = 9.893, p < 0.001$ 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 post 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 disease. 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.

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Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not required.

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