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Risk Factors and Multidimensional Assessment of Long-COVID Fatigue: A Nested Case-Control Study

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Background. Fatigue is the most prevalent and debilitating long-COVID (coronavirus disease) symptom; however, risk factors and pathophysiology of this condition remain unknown. We assessed risk factors for long-COVID fatigue and explored its possible pathophysiology.

Methods. This was a nested case-control study in a COVID recovery clinic. Individuals with (cases) and without (controls) significant fatigue were included. We performed a multidimensional assessment evaluating various parameters, including pulmonary function tests and cardiopulmonary exercise testing, and implemented multivariable logistic regression to assess risk factors for significant long-COVID fatigue.

Results. A total of 141 individuals were included. The mean age was 47 (SD: 13) years; 115 (82%) were recovering from mild coronavirus disease 2019 (COVID-19). Mean time for evaluation was 8 months following COVID-19. Sixty-six (47%) individuals were classified with significant long-COVID fatigue. They had a significantly higher number of children, lower proportion of hypothyroidism, higher proportion of sore throat during acute illness, higher proportions of long-COVID symptoms, and of physical limitation in daily activities. Individuals with long-COVID fatigue also had poorer sleep quality and higher degree of depression. They had significantly lower heart rate [153.52 (22.64) vs 163.52 (18.53); $P = .038$] and oxygen consumption per kilogram [27.69 (7.52) vs 30.71 (7.52); $P = .036$] at peak exercise. The 2 independent risk factors for fatigue identified in multivariable analysis were peak exercise heart rate (OR: .79 per 10 beats/minute; 95% CI: .65–.96; $P = .019$) and long-COVID memory impairment (OR: 3.76; 95% CI: 1.57–9.01; $P = .003$).

Conclusions. Long-COVID fatigue may be related to autonomic dysfunction, impaired cognition, and decreased mood. This may suggest a limbic-vagal pathophysiology.

Clinical Trials Registration. clinicaltrials.gov; NCT04851561.

Keywords. post-COVID; post-viral fatigue.

Long coronavirus disease (COVID), a late sequela manifesting as ongoing symptoms persisting at least 4 weeks following the onset of acute coronavirus disease 2019 (COVID-19), has been widely reported [1]. It is estimated to affect approximately 10% of the infected individuals [2]. Long-COVID fatigue was reported among 63% and 28% of COVID-19–infected individuals at 6 and 12 months, respectively [3, 4]. The high prevalence reported at 1-year follow-up was similar for individuals with severe and nonsevere acute COVID-19 [4].

The pathophysiology behind long COVID is unknown. The presumed mechanisms include direct and indirect damage to the central nervous system (CNS) secondary to either viral invasion or inflammation, persistent inflammatory response, negative psychosocial aspects associated with the pandemic, direct damage to muscle fibers or neuromuscular junction, and possibly autonomic dysfunction as well as direct or indirect cardiac toxicity [5, 6].

While identifying exclusive risk factors for long-COVID fatigue will assist in detecting populations at risk, unveiling the mechanisms behind this phenomenon is imperative in the search for therapeutic approaches. Nested case-control studies were recommended in order to identify explanatory mechanisms for the major long-COVID manifestations [7]. Accordingly, we

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aimed to assess risk factors for long-COVID fatigue and to implement a multidimensional assessment in order to cast light on its possible pathophysiology.

METHODS

Study Design and Population

We conducted a nested case-control study in a cohort of individuals who attended our COVID recovery clinic at Rabin Medical Center, Beilinson Hospital. Adults (age ≥18 years) who recovered from COVID-19 were invited for a comprehensive medical evaluation (Supplementary Appendix 1). During a clinic visit, all individuals were evaluated by an internist using a preplanned questionnaire and were asked to grade 14 symptoms as 0 (not present) to 3 (severe) scale. In addition, all individuals underwent pulmonary function testing and were evaluated by a pulmonologist.

Using a computerized algorithm, we randomly sampled individuals who visited our clinic and invited them to participate in the current study (Supplementary Appendix 2). In order to meet our inclusion criteria, an individual had to be at least 2 months following a polymerase chain reaction (PCR)–proven diagnosis of COVID-19.

Individuals with debilitating cardiovascular, neurological, muscular, or other conditions were excluded from participation (for detailed exclusion criteria, see Supplementary Appendix 3).

Classification of Cases and Controls

In order to define individuals with clinically significant long-COVID fatigue, we created a classification tool. The tool is based on the Institute of Medicine criteria and case definition for myalgic encephalitis/chronic fatigue syndrome, adopted by the Centers for Disease Control and Prevention (CDC) [8]. We modified the portion on fatigue to suit the time frame and relations with COVID-19.

Cases (ie, having significant long-COVID fatigue) were defined as having a substantial impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persisted for more than 6 weeks and that was accompanied by fatigue, which is often profound, of new onset (appeared after the diagnosis of COVID-19), not the result of ongoing excessive exertion, and not substantially alleviated by rest. These symptoms must have been present for at least half of the daytime, to at least a moderately severe degree. Those who did not meet all of these criteria were defined as controls.

Since the risk factors for long COVID remain largely unknown, we decided to perform an unmatched rather than a matched case-control study in order to facilitate maximal identification of possible risk factors.

During the first study visit (see below), each participant independently filled out a designated form in which she/he was requested to answer on the aforementioned criteria (Supplementary Appendix 4). The research team was blinded to participants' answers and consequent case definition at the time of recruitment and during the study visit.

Hypothetical Mechanisms for Fatigue

In order to assess the explanatory pathophysiology for long-COVID fatigue we assumed 4 hypothetical mechanisms: neurocognitive, psychosocial, neuromuscular, and cardiopulmonary. We have also considered several other potential contributing factors for fatigue, among these were thyroid dysfunction, iron or vitamin B-12 deficiency, and cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection. We planned our multidimensional assessment based on the aforementioned mechanisms, while examining all possible manifestations for each mechanism.

Evaluation Protocol of Cases and Controls

All participating individuals (cases and controls) were assessed following the study protocol. The detailed assessment procedure, including questionnaires, physical examination, blood tests, cognitive evaluation, and exercise physiology evaluation including a cardiopulmonary exercise test (CPET), is detailed in Supplementary Appendix 5.

The variables deriving from the questionnaires were assessed as potential predictors of fatigue or used to characterize it but were not used for classification of cases and controls.

Data Collection

We collected demographic data (including socioeconomic status following the classification of the state Central Bureau of Statistics [9]), habits, physical activity before COVID-19 and afterward, comorbidities, and pharmacotherapy. These data were extracted from the questionnaires completed during the first study visit. Missing data were managed by re-approaching the patients to complete absent details.

Acute COVID-19 history (disease severity according to the World Health Organization criteria [10], symptoms of the acute phase, need for hospitalization, complications, pharmacotherapy directed at COVID-19) and long-COVID symptoms as well as pulmonary function tests on COVID recovery clinic visit were extracted from hospital's electronic medical charts.

Statistical Analysis

The dependent variables were compared between individuals with long-COVID fatigue (cases) and those without (controls) using Student's *t* test or the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Correlations between the independent variables were assessed using the Spearman's rank correlation coefficient.

Multivariable analysis was implemented using logistic regression models. Independent variables were selected to be included in the multivariable model based on the bivariate

analysis and clinical logic ($P < .05$). Collinearity was assessed using variance inflation factor (VIF) and bivariate correlations. Variables with suspected collinearity (VIF >3.0 or correlation coefficient >0.4) were assessed in separate models. We used the Akaike information criterion (AIC) and identified the optimal multivariable model as the model for which the AIC was minimal. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from the logistic regression models.

Sensitivity analyses were performed to assess the classification of cases and controls. We implemented the same long-COVID fatigue classification tool (see above), while using 2 alternative classification definitions: (1) a more restrictive definition, by which an individual was classified as a case if the symptoms were not substantially alleviated by rest, in addition to all other requirements (see Supplementary Appendix 4), and (2) a more liberal definition, by which an individual was classified as a case even if the symptoms did not persist beyond 6 weeks and/or were present less than half of the time, and/or at a mild degree.

For all analyses, $P < .05$ was considered statistically significant.

Data analysis was undertaken using IBM SPSS version 27 (IBM Corporation, Armonk, NY, USA).

Compliance With Research Ethics and Guidance

The Research Ethics Committee at Rabin Medical Center approved the study protocol (RMC-0834-20). All participants signed an informed consent prior to participation. All methods were performed in accordance with the relevant guidelines and regulations. The study was registered at clinicaltrials.gov (NCT04851561).

Role of the Funding Source

The funding was served for covering the expenses of CPET and blood tests. The funders had no role in the study's design, conduct, and reporting.

RESULTS

A total of 144 individuals were recruited between 2 March and 30 June 2021. Following recruitment, 3 individuals appeared to have an exclusion criterion and were therefore excluded (Figure 1). Accordingly, 141 individuals were included for analysis. The mean age of the study population was 47 (SD: 13) years and 83 (59%) were women. The first study visit occurred at an average of 212 (SD: 74) days following COVID-19 diagnosis. The CPET was conducted at an average of 28 (SD: 19) days following the first study visit. By applying our long-COVID fatigue classification tool, 66 individuals (46.8%) were classified as having long-COVID fatigue.

Sociodemographic and Clinical Characteristics

Those with long-COVID fatigue had more children [2.80 (SD: 1.81) vs 2.09 (SD: 1.67); $P = .023$] and a lower proportion of hypothyroidism [3 (4.5%) vs 11 (14.7%); $P = .045$]. No other sociodemographic or clinical background characteristics differed between the groups (Table 1). Acute sore throat was the only acute illness variable that differed between those with long-COVID fatigue and those without, the proportion among the former was 3.8 times higher [17 (26.6%) vs 5 (7.0%); $P = 0.002$] (Table 2).

On their first visit at the recovery clinic, 60 (90.9%) of those with long-COVID fatigue reported at least 1 significant symptom apart from fatigue, compared with 57 (76.0%) of those without fatigue ($P = 0.019$). Those with fatigue tended to have a higher prevalence of the other long-COVID symptoms (Table 3). The heart rate and saturation at rest as well as pulmonary function tests during the clinic visit were similar between the 2 groups.

None of the participating individuals had a major finding on physical examination. Results of the comprehensive blood tests performed were similar between the 2 groups, including thyroid function tests and vitamin B-12 levels (Supplementary Tables 1–5). There was no evidence for an acute or recent CMV or EBV infection in our study population (Supplementary Table 6).

Neurocognitive, Sleep, and Mood

Individuals with significant long-COVID fatigue reported substantially higher proportions of physical limitations and different manifestations of fatigue (Table 4). The sleep assessment revealed that those with long-COVID reported difficulties in all aspects of sleep: they had poorer sleep quality [global Pittsburgh Sleep Quality Index score of 11.30 (SD: 4.14) vs 6.32 (SD: 3.03); $P < .001$]; higher scores of sleepiness [total Epworth Sleepiness Scale score of 12.11 (SD: 5.25) vs 8.39 (SD: 4.46); $P < .001$]; and higher insomnia scores [total Insomnia Severity Index score of 17.82 (SD: 5.93) vs 8.65 (SD: 5.66); $P < .001$]. The population of individuals with long-COVID fatigue also had approximately 3 times higher scores in the Patient Health Questionnaire-9 assessing depression (while excluding the components on fatigue and sleep disorders): 9.71 (SD: 4.53) versus 3.32 (SD: 3.46) ($P < .001$).

Individuals with long-COVID fatigue also had a higher proportion of subjective report of cognitive impairment [58 (87.9%) vs 34 (45.9%); $P < .001$] (Table 4). However, when adjusted for age, the 2 groups performed similarly in the cognitive fatigue task, and those with long-COVID fatigue did not exhibit signs of cognitive fatigue (Supplementary Table 7).

Cardiopulmonary Exercise Testing

The performance on CPET is presented in Table 5. Although being able to complete the test in terms of work rate, heart rate, and respiratory exchange ratio requirements, individuals with long-COVID fatigue had significantly lower heart rate [153.52 (SD: 22.64) vs 163.52 (SD: 18.53) beats/minute; $P = .038$] and oxygen consumption per kilogram [27.69 (SD: 7.52) vs 30.71 (SD: 7.52); $P = .036$] at peak exercise.

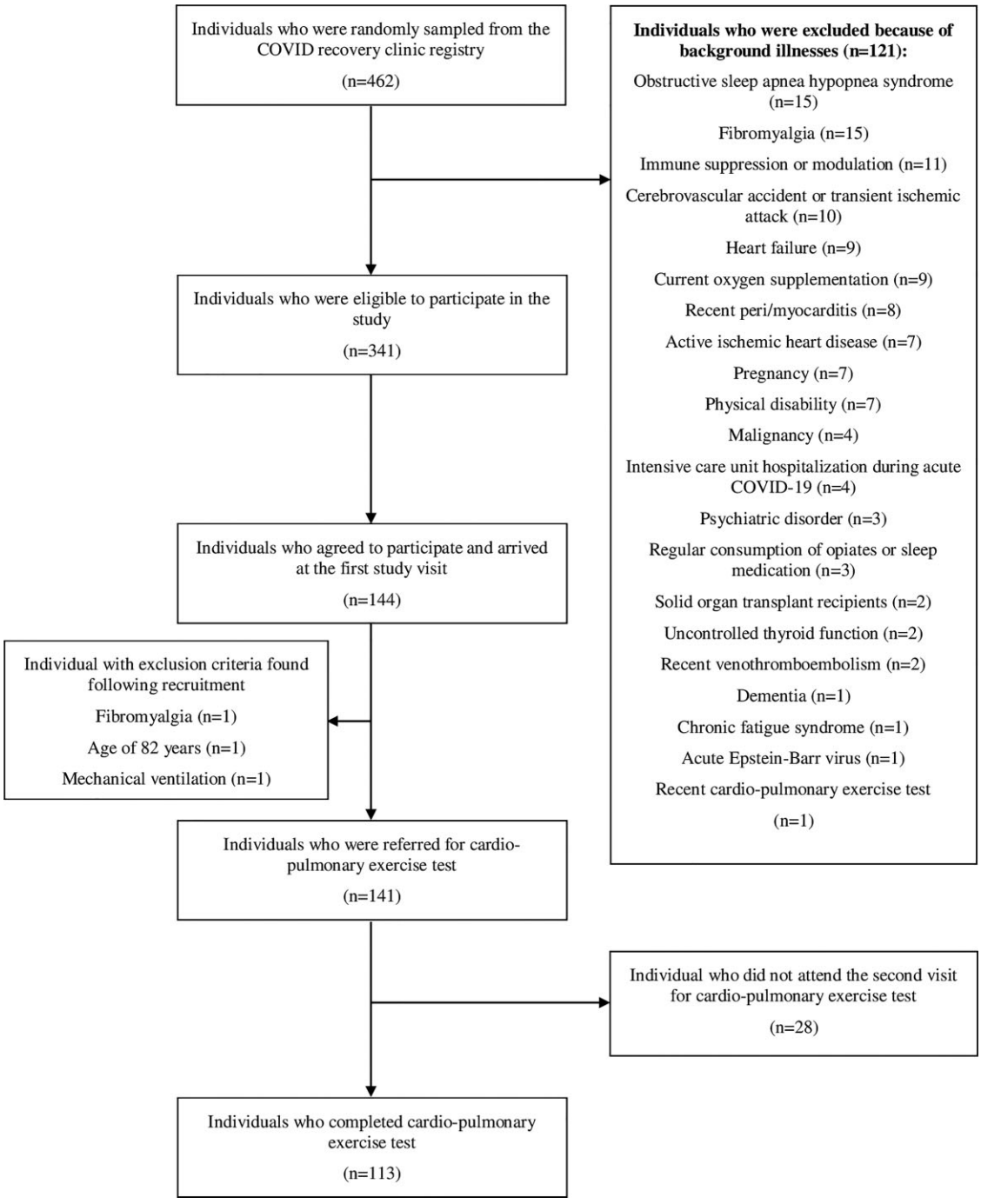

Figure 1. Participant flow diagram. Abbreviations: COVID, coronavirus disease; COVID-19, coronavirus disease 2019.

These differences were not noted at rest; however, they were evident at the anaerobic threshold (Supplementary Table 8). All other CPET components were similar between the 2 groups.

Multivariable Analysis

Since long-COVID fatigue highly correlated with sleep disturbances and with the degree of depression ($\rho > 0.5$, $P < .001$ for all), we did not introduce these variables into the multivariable model.

Two independent risk factors were identified for significant long-COVID fatigue: peak exercise heart rate (OR: .79 per 10 beats/minute; 95% CI: .65–.96; $P = .019$) and long-COVID memory impairment (OR: 3.76; 95% CI: 1.57–9.01; $P = .003$).

Sensitivity Analyses

A total of 43 and 76 individuals were classified as having significant long-COVID fatigue using the restrictive and liberal

Table 1. Demographics and Clinical Characteristic of the Study Population

	Nonsignificant Fatigue (n = 75; 53.2%)	Long-COVID Fatigue (n = 66; 46.8%)	P^a
Women, n (%)	43 (57.3)	40 (60.6)	.694
Age at enrollment, mean (SD), years	45.21 (14.45)	48.85 (11.51)	.211
Born in Israel, n (%)	61 (81.3)	57 (86.4)	.420
Marital status, n (%)			.053[φ]
Single	20 (26.7)	8 (12.1)	
Married	48 (64.0)	44 (66.7)	
Divorced	6 (8.0)	10 (15.2)	
Widow	1 (1.3)	4 (6.1)	
Relationship	53 (70.7)	54 (81.8)	.122
Number of children, mean (SD)	2.09 (1.67)	2.80 (1.81)	.023
Age of the oldest child, mean (SD), years	23.59 (12.38)	24.00 (12.53)	.889
Age of the youngest child, mean (SD), years	16.45 (10.81)	16.37 (11.20)	.930
Age of youngest child <5 years, n (%)	11 (20.0)	9 (15.8)	.561
Living alone, n (%)	8 (10.7)	5 (7.6)	.527
Type of residence, n (%)			.959
Apartment	41 (54.7)	36 (54.5)	
Two-family dwelling	9 (12.0)	7 (10.6)	
Private home	25 (33.0)	23 (34.8)	
Unemployed, n (%)	6 (8.0)	8 (12.1)	.414
Healthcare workers, n (%)	10 (13.3)	5 (7.6)	.269
Socioeconomic status (deciles of city of residence according to the CBS), mean (SD)	6.95 (1.72)	6.73 (1.67)	.443
Smoking status, n (%)			.219
Never smoked	53 (70.7)	39 (59.1)	
Past smoker	16 (21.3)	16 (24.2)	
Current smoker	6 (8.0)	11 (16.7)	
Cigarette pack-years, mean (SD)	12.29 (12.63)	14.09 (19.55)	.936
Use of cannabis, n (%)	3 (4.1)	5 (7.7)	.473[φ]
Use of alcohol, n (%)	35 (46.7)	32 (48.5)	.867
Alcohol servings per week, mean (SD)	1.40 (1.35)	1.10 (1.45)	.247
Body mass index, mean (SD), kg/m^2	27.46 (5.15)	27.54 (4.96)	.935
Body fat percentage, mean (SD)	30.97 (7.78)	33.34 (8.13)	.120†
Recreational physical activity			
Prior to COVID-19, mean (SD), minutes/week	144.80 (218.91)	140.15 (114.36)	.379
Following COVID-19, mean (SD), minutes/week	49.18 (84.69)	49.28 (121.13)	.457
The ratio (%) of physical activity pre-and post-COVID-19,[b] mean (SD)	36.06 (45.59)	33.87 (76.49)	.169
Decline in physical activity, n (%)	40 (53.3)	43 (65.2)	.155
Background illnesses, n (%)			
Diabetes mellitus	6 (8.0)	6 (9.1)	.817
Hypertension	10 (13.3)	9 (13.6)	.958
Ischemic heart disease	2 (2.7)	2 (3.0)	1.000[φ]
Hypothyroidism	11 (14.7)	3 (4.5)	.045
Veno-thromboembolism	0	1 (1.5)	.468[φ]
Chronic kidney disease	0	1 (1.5)	.468[φ]
Asthma	4 (5.3)	5 (7.6)	.734[φ]
Dyslipidemia	14 (18.7)	13 (19.7)	.877
Charlson comorbidity score, mean (SD)	0.13 (0.38)	0.17 (0.41)	.589
Regular use of medications			
Any medication, N (%)	40 (53.3)	37 (56.1)	.746
Types of regular medications, n (%)			
Aspirin	7 (9.3)	4 (6.1)	.470
Beta-blockers	3 (4.0)	5 (7.6)	.474[φ]
Statins	16 (21.3)	14 (21.2)	.986
ACEi	5 (6.7)	5 (7.6)	1.000[φ]
Angiotensin receptor blockers	4 (5.3)	3 (4.5)	1.000[φ]
Calcium channel blockers	5 (6.7)	6 (9.1)	.592

Table 1. Continued

	Nonsignificant Fatigue (n = 75; 53.2%)	Long-COVID Fatigue (n = 66; 46.8%)	P^a
Thiazide	1 (1.3)	3 (4.5)	.340$^{\varphi}$
Proton pump inhibitors	6 (8.0)	3 (4.5)	.502$^{\varphi}$
Metformin	5 (6.7)	5 (7.6)	1.000$^{\varphi}$
GLP-1 agonists	3 (4.0)	2 (3.0)	1.000$^{\varphi}$
Levothyroxine	10 (13.3)	2 (3.0)	.029
SSRIs	5 (6.7)	5 (7.6)	1.000$^{\varphi}$
ICS/LABA inhaler	3 (4.0)	2 (3.0)	1.000$^{\varphi}$
Tamsulosin	2 (2.7)	1 (1.5)	1.000$^{\varphi}$
Vitamin B-12	15 (20.0)	20 (31.3)	.128
Vitamin D	17 (22.7)	21 (32.8)	.181
Vitamin C	5 (6.7)	6 (9.4)	.555

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; CBS, Israel Central Bureau of Statistics; COVID, coronavirus disease; COVID-19, coronavirus disease 2019; GLP-1, glucagon-like peptide 1; ICS/LABA, inhaled corticosteroids plus long-acting beta agonist; SSRI, selective serotonin reuptake inhibitor.

[a]Calculated using Mann-Whitney *U* test or Student's *t* test (†) for continuous variables and chi-square test or Fisher's exact test ($^{\varphi}$) for categorical variables.

[b]Calculated for those with physical activity >0 minutes per week prior to COVID-19.

Table 2. Characteristics of the Acute Illness (COVID-19)

	Nonsignificant Fatigue (n = 75; 53.2%)	Long-COVID Fatigue (n = 66; 46.8%)	P^a
COVID-19 severity, n (%)			.492$^{\varphi}$
Mild	64 (85.3)	51 (77.3)	
Moderate	7 (9.3)	9 (13.6)	
Severe	4 (5.3)	6 (9.1)	
Admission to hospital, n (%)	8 (10.7)	6 (9.1)	.755
Length of in-hospital stay, mean (SD),[b] days	9.25 (6.16)	8.83 (6.74)	.950
Symptomatic acute infection, n (%)	73 (97.3)	65 (98.5)	1.000$^{\varphi}$
Duration (in days) of acute symptoms, mean (SD)[c]	10.81 (6.16)	11.35 (4.79)	.262
Fever ≥38°C, N (%)	44 (60.3)	38 (58.5)	.829
COVID-19 symptoms,[d] n (%)			
Sore throat	5 (7.0)	17 (26.6)	.002
Nasal congestion	14 (19.2)	19 (29.7)	.151
Fatigue	54 (74.0)	47 (73.4)	.943
Headache	40 (54.8)	38 (59.4)	.589
Anosmia/dysgeusia	32 (44.4)	32 (50.0)	.517
Cough	34 (46.6)	33 (52.4)	.499
Dyspnea	27 (38.0)	28 (44.4)	.451
Chest pain	18 (25.4)	25 (39.1)	.088
Gastrointestinal symptoms	16 (22.5)	16 (25.0)	.737
Myalgia	39 (53.4)	41 (66.1)	.134
Infiltrates on chest radiogram, n (%)	9 (47.4)	8 (40.0)	.643

Abbreviations: COVID, coronavirus disease; COVID-19, coronavirus disease 2019.

[a]Calculated using Mann-Whitney *U* test for continuous variables and chi-square test or Fisher's exact test ($^{\varphi}$) for categorical variables.

[b]Calculated only for those who were hospitalized.

[c]Calculated only for those who had symptoms.

[d]Individuals who reported symptom intensity of moderate to severe were counted as positive.

definitions, respectively (Supplementary Tables 9–18). Multivariable analysis revealed the same independent risk factors using both definitions: using the restrictive definition—peak exercise heart rate (OR: .60 per 10 beats/minute; 95% CI: .47–.78; $P < .001$) and long-COVID memory impairment (OR: 3.03; 95% CI: 1.17–7.85; $P = .023$); using the liberal definition—peak exercise heart rate (OR: .81 per 10 beats/minute; 95% CI: .67–.99; $P = .037$) and long-COVID memory impairment (OR: 4.16; 95% CI: 1.65–10.49; $P = .003$).

DISCUSSION

In this multidimensional assessment of long-COVID fatigue we compared recovered individuals with and without significant fatigue, at an average of approximately 8 months following acute illness. Most individuals were recovering from mild (82%) or nonsevere (93%) COVID-19. Those with significant long-COVID fatigue had decreased peak exercise heart rate and reported a higher rate of cognitive symptoms, predominantly memory impairment.

Those with long-COVID fatigue achieved the CPET requirements in terms of work rate and respiratory exchange ratio and met the expected values for all test parameters. Nonetheless, when compared with those without fatigue, individuals with long-COVID fatigue had lower peak oxygen consumption per weight and significantly decreased peak heart rate, at an average of 10 beats per minute lower than those without fatigue. No differences in heart rate were noted while at rest. These findings suggest that individuals with significant long-COVID fatigue experience a slightly impaired chronotropic response.

It was previously suggested that autonomic dysfunction may play a role in the pathophysiology of long-COVID, particularly in symptoms resulting from the cardiovascular system [5]. This assumption was derived from several reports on orthostatic hypotension and postural tachycardia syndrome occurring following the acute disease [11, 12]. Long-COVID may also involve other components of the autonomic nervous system, such as the sudomotor, gastrointestinal, and pupillomotor functions

Table 3. Characteristics of Long COVID at Time of Recovery Clinic Visit

	Nonsignificant Fatigue (n = 75; 53.2%)	Long-COVID Fatigue (n = 66; 46.8%)	P^a
Time interval (in days) from COVID-19 diagnosis to clinic visit, mean (SD)	113.68 (52.84)	126.49 (81.57)	.812
Long-COVID symptoms,[b] n (%)			
At least 1 long-COVID symptom	57 (76.0)	60 (90.9)	.019
Headache	4 (5.5)	9 (14.3)	.082
Anosmia/dysgeusia	12 (16.0)	18 (27.3)	.103
Cough	3 (4.0)	12 (18.2)	.006
Dyspnea	24 (32.9)	27 (40.9)	.326
Chest pain	13 (17.3)	22 (33.3)	.028
Palpitations	5 (6.8)	6 (9.1)	.608
Paresthesia	6 (8.2)	14 (21.2)	.029
Concentration impairment	7 (9.6)	30 (45.5)	<.001
Memory impairment	13 (17.8)	31 (47.0)	<.001
Irritability	6 (8.0)	18 (27.7)	.002
Emotional distress	8 (10.7)	23 (34.8)	.001
Myalgia	20 (26.7)	31 (47.7)	.010
Arthralgia	2 (2.7)	10 (15.6)	.007
Weakness	9 (12.0)	12 (18.5)	.286
Rash	0	1 (1.5)	.285φ
Hair loss	7 (9.3)	11 (17.7)	.147
Insomnia	11 (14.7)	29 (43.9)	<.001
Vital signs, mean (SD)			
Heart rate, beats/minute	76.61 (11.21)	78.02 (12.93)	.470
Saturation, %	98.69 (1.20)	98.75 (1.87)	.293
Infiltrates on chest radiogram, n (%)	8 (12.5)	3 (6.0)	.342φ
Pulmonary function tests, mean (SD)			
FEV_1, % of expected	95.20 (14.82)	95.27 (14.11)	.979†
FVC, % of expected	97.02 (14.63)	96.64 (13.24)	.884†
FEV_1/FVC	0.83 (0.07)	0.83 (0.06)	.643
TLC, % of expected	96.50 (18.91)	96.36 (12.45)	.441
DLCO, % of expected	88.30 (15.76)	86.16 (14.46)	.526
Blood parameters, mean (SD)			
White blood cells, K/μL	6.61 (1.73)	6.82 (2.07)	.611
Hemoglobin, g/dL	13.66 (1.18)	13.66 (1.30)	.839
Thyroid-stimulating hormone, mIU/L	2.02 (1.24)	2.17 (1.27)	.374
Fasting serum glucose, mg/dL	94.65 (15.38)	97.44 (16.99)	.336
Creatinine, mg/dL	0.78 (0.14)	0.77 (0.16)	.538
Creatine phosphokinase, U/L	150.50 (237.59)	114.23 (77.92)	.954
C-reactive protein, mg/dL	0.39 (0.52)	0.29 (0.28)	.898
Hemoglobin A1c, %	5.51 (0.63)	5.69 (0.56)	.587

Abbreviations: COVID, coronavirus disease; COVID-19, coronavirus disease 2019; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume; FVC, forced vital capacity; TLC, total lung capacity.

[a]Calculated using Mann-Whitney *U* test or Student's *t* test (†) for continuous variables and chi-square test or Fisher's exact test (φ) for categorical variables.

[b]Individuals who reported symptom intensity of moderate to severe were counted as positive.

[13]. Suggested mechanisms for long-COVID, including direct viral invasion, endothelial dysfunction and inflammation, microthrombosis, and capillary congestion, may affect the central and peripheral nervous system by either direct viral activity or by vascular compromise and demyelination [5, 13].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) shares similarities with long-COVID fatigue not only in terms of symptoms such as persistent exhaustion and pain but also with respect to its association with autonomic dysfunction [14, 15]. A meta-analysis comparing CPET results of individuals with ME/CFS with healthy controls demonstrated that the former exhibit impaired chronotropic response [16]. The impairment in chronotropic response in our study was more subtle than that demonstrated in ME/CFS, with small deviations within the range of normal, and results in a discrepancy between the severe symptoms reported by those with long-COVID fatigue and the absence of overt findings on routine clinical tests.

The close association between long-COVID fatigue and cognitive symptoms implies a common pathophysiology. Individuals with fibromyalgia, a syndrome that shares similarities with long-COVID, exhibit low heart rate variability (HRV) [17]. It was assumed that their symptoms are related to a low vagal tone, responsible for the low HRV and consequent affective

Table 4. Assessment at First Study Visit

	Nonsignificant Fatigue (n = 75; 53.2%)	Long-COVID Fatigue (n = 66; 46.8%)	P^a
Time interval (in days) from COVID-19 diagnosis to first study visit, mean (SD)	207.55 (67.11)	218.03 (80.63)	.585
Assessment of functional capacity (SF-36 component on physical limitation),[b] n (%)			
Vigorous activities	46 (63.0)	56 (87.5)	.001
Moderate activities	10 (13.3)	37 (56.1)	<.001
Lifting or carrying groceries	10 (13.3)	38 (58.5)	<.001
Climbing several flights of stairs	36 (48.0)	54 (83.1)	<.001
Climbing 1 flight of stairs	12 (16.0)	22 (33.8)	.014
Bending, kneeling, or stooping	10 (13.3)	26 (39.4)	<.001
Walking more than 1 kilometer	20 (27.0)	42 (64.6)	<.001
Walking several blocks	19 (25.7)	39 (60.0)	<.001
Walking 1 block	3 (4.1)	20 (30.8)	<.001
Bathing or dressing yourself	1 (1.3)	8 (12.1)	.013φ
Subjective report on fatigue, n (%)			<.001
Yes, even before COVID-19	19 (25.3)	3 (4.5)	
Yes, after I was diagnosed with COVID-19	38 (50.7)	63 (95.5)	
Not at all	18 (24.0)	0	
Characteristics of fatigue,[c] n (%)			
Morning waking up	25 (43.9)	43 (65.2)	.018
Need for siesta	32 (57.1)	49 (75.4)	.033
Feeling fatigued throughout the entire day	21 (36.8)	60 (90.9)	<.001
Feeling fatigued during the evening	44 (77.2)	62 (93.9)	.007
Need for longer sleeping hours	28 (50.9)	54 (81.8)	<.001
Need for more coffee servings per day	8 (14.0)	19 (28.8)	.049
Fatigue burdens me with daily home tasks	14 (25.0)	50 (75.8)	<.001
Fatigue burdens me with employment tasks	13 (22.8)	49 (74.2)	<.001
Fatigue burdens me with sport activities	29 (55.8)	53 (80.3)	.004
Subjective impression of cognitive decline, n (%)	34 (45.9)	58 (87.9)	<.001
Sleep assessment, mean (SD)			
Global PSQI score	6.32 (3.03)	11.30 (4.14)	<.001
Total ESS score	8.39 (4.46)	12.11 (5.25)	<.001
Total ISI score	8.65 (5.66)	17.82 (5.93)	<.001
Depression assessment, mean (SD)			
Total PHQ-9 score[d]	3.32 (3.46)	9.71 (4.53)	<.001

Abbreviations: COVID, coronavirus disease; COVID-19, coronavirus disease 2019; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-item Short Form Survey.

[a]Calculated using Mann-Whitney *U* test for continuous variables and chi-square test or Fisher's exact test (φ) for categorical variables.

[b]For each category, individuals who responded a moderate or severe limitation were counted as positive.

[c]Excluding those who responded that they do not experience fatigue. For each category, individuals who responded on moderate or severe limitation were counted.

[d]For the current calculation, the questions on fatigue or sleep were omitted.

disorders through the vagal ventral branch [17]. Reduced vagal tone was also associated with cognitive impairment among individuals with ME/CFS [18]. It is therefore possible that long-COVID fatigue is mediated through CNS involvement of the limbic system, responsible for cognitive and emotional symptoms, as well as for low vagal tone. This can be somewhat supported by a recent study that reported nonspecific magnetic resonance imaging (MRI) alternations in the thalamus [19].

The strong positive correlation between fatigue and sleep disturbances is not surprising considering the significant interrelations between fatigue, the autonomic nervous system, and sleep [20]. Individuals with ME/CFS have poorer sleep quality and tend to experience insomnia [21, 22]. Sleep disorders and poor sleep quality have been suggested as risk factors for fibromyalgia and other chronic pain syndromes [23]. Accordingly, it is possible that individuals with poorer sleep quality are at increased risk for long-COVID fatigue. Depression, which was present to some extent in most individuals with long-COVID fatigue, is almost always associated with poorer sleep quality [24]. The interaction of the autonomic nervous system with several stressors and immune imbalances has been suggested as the pathophysiology leading to depression [25]. Sleep disturbances and mood disorders might interact with long-COVID's autonomic dysfunction to aggravate fatigue.

Our study has several limitations. Residual confounding is a concern, particularly since we did not measure anxiety, a

Table 5. Cardiopulmonary Exercise Test: Exercise Peak Parameters

	Nonsignificant Fatigue (n = 63; 55.8%)	Long-COVID Fatigue (n = 50; 44.2%)	P^a
Time interval (in days) from COVID-19 diagnosis to CPET, mean (SD)	238.92 (69.35)	242.66 (87.48)	.892
Maximum work rate, mean (SD), Watts			
Expected	200.97 (59.10)	187.70 (70.04)	.113
Observed	192.67 (73.00)	172.70 (76.83)	.096
Percent of expected	98.48 (32.31)	95.92 (34.16)	.615
Oxygen consumption, mean (SD), L/minute			
Expected	2.31 (0.59)	2.18 (0.70)	.113
Observed	2.29 (0.60)	2.06 (0.66)	.042
Percent of expected	100.17 (17.17)	96.37 (18.31)	.207
Oxygen consumption, mean (SD), % of normal	99.60 (17.40)	96.07 (18.33)	.327
Oxygen consumption per weight, mean (SD), $V'O_2$/kg	30.71 (7.52)	27.69 (7.52)	.036†
Respiratory exchange ratio, mean (SD)	1.08 (0.06)	1.07 (0.09)	.250†
Heart rate, mean (SD), beats/minute			
Expected	154.87 (14.18)	149.44 (11.21)	.060
Observed	163.52 (18.53)	153.52 (22.64)	.038
Percent of expected	105.95 (11.14)	102.69 (12.93)	.239
Oxygen pulse, mean (SD), mL	14.25 (3.90)	13.17 (3.35)	
Expected	14.97 (3.63)	14.50 (4.07)	.343
Observed	14.25 (3.90)	13.17 (3.35)	.206
Percent of expected	95.62 (18.50)	93.69 (13.68)	.960
Systolic blood pressure, mean (SD), mmHg	175.48 (16.87)	173.98 (19.82)	.880
Diastolic blood pressure, mean (SD), mmHg	74.29 (5.60)	75.51 (5.97)	.331
Minute ventilation, mean (SD), L/minute			
Expected	100.91 (19.83)	93.68 (25.09)	.047
Observed	83.54 (22.89)	75.34 (28.88)	.065
Percent of expected	83.16 (16.78)	80.50 (22.37)	0.486†
Tidal volume, mean (SD), L	2.01 (0.61)	1.84 (0.58)	.122
Breathing frequency (times per minute), mean (SD)			
Expected	32.78 (4.39)	31.56 (3.92)	.116
Observed	43.24 (8.81)	42.02 (8.47)	.493†
Percent of expected	133.09 (30.60)	131.53 (28.53)	.752
Minute ventilation/CO_2 output, mean (SD)	31.32 (3.67)	31.28 (3.62)	.961†

Abbreviations: COVID, coronavirus disease; COVID-19, coronavirus disease 2019; CPET, cardiopulmonary exercise test.

[a]Calculated using Mann-Whitney *U* test or Student's *t* test (†).

commonly reported long-COVID symptom [3]. However, since we assessed depression and considering the strong correlation reported for both conditions, this limitation is unlikely to change the results. A few other components were also missing, mainly the assessment of HRV at rest and brain functional MRI. Additionally, since we assessed manifold parameters, one may argue that adjustment for multiple comparisons is required. Some experts advocate against multiple comparisons [26], particularly in observational studies and when an in-depth assessment includes multiple variables that share similar thematic fields. However, in the absence of correction for multiple comparisons, our findings should be considered preliminary and further validation in another population is warranted.

Another potential limitation is the nonuniform interval between the acute illness (COVID-19) and study recruitment. However, no differences in the time interval between diagnosis and recruitment were noted among those with long-COVID fatigue and those without. Accordingly, it is implausible to significantly affect the results.

All participating individuals were sampled from the cohort of individuals who attended the COVID recovery clinic. The study is lacking a control group of recovered individuals who do not have long-COVID. Future studies should aim to include a non–COVID-infected control group in order to control for possible sequelae of lockdowns and stress associated with the pandemic [27].

Our study implies that long-COVID fatigue results from mild autonomic dysfunction. Future rehabilitation programs and other interventions should take into account subtle changes in the chronotropic competence of symptomatic recoverees.

Further studies are warranted to establish these novel preliminary findings and to elucidate the role of the limbic system and vagus nerve in the pathophysiology of long-COVID fatigue.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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