

Physical and Mental Fatigue in Subjects Recovered from COVID-19 Infection: A Case–Control Study

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Purpose: Much effort has been directed toward studying COVID-19 symptoms; however, the post–COVID-19 phase remains mysterious. The aim of this work was to conduct a clinical and neurophysiological evaluation of physical and mental fatigue in COVID-19 long-haulers and to study whether markers of COVID-19 severity are able to predict the likelihood of developing postinfectious fatigue syndrome (PIFS) in such patients.

Patients and Methods: This case–control study was conducted on 46 COVID-19 long-haulers who met the criteria for PIFS and 46 recovered COVID-19 subjects without any residuals. Clinical assessment of fatigue was done using a fatigue questionnaire. Repetitive nerve stimulation and single-fiber electromyography were done after excluding neuropathy and myopathy.

Results: The median value for physical fatigue was 4 (IQR 2–7), while that for mental fatigue was 2 (IQR 0–3). Each day’s increase in the period of COVID-19 illness increased the odds of PIFS in COVID-19 long-haulers 1.104-fold, and each unit increase in ferritin increased the odds of PIFS 1.006-fold. A significant decrement in at least one muscle was observed in 50% of patients. Patients with PIFS had significantly higher mean consecutive difference (MCD) in the extensor digitorum communis than the control group. There were statistically significant positive correlations between MCD values and physical, mental, and total fatigue scores.

Conclusion: Higher ferritin levels and prolonged COVID-19 infection were independent predictors of PIFS in COVID-19 long-haulers. There was electrophysiological evidence of abnormalities in the peripheral portion of the motor unit in COVID-19 long-haulers with PIFS.

Keywords: COVID-19, fatigue, COVID-19 long-haulers, single-fiber EMG, ferritin

Introduction

Since the beginning of the SARS-CoV2 pandemic, health-care professionals have been challenged by its variable clinical manifestations. Much effort has been directed toward studying the prevalence and patterning of COVID-19 symptoms.¹ Nevertheless, the post-COVID phase is still worth exploring.

SARS-CoV2 was recently reported to be a potential trigger for postinfectious fatigue syndrome (PIFS).² PIFS refers to severe, disabling, and persistent/recurrent physical and/or mental fatigue following infectious triggers, such as viruses, bacteria, and parasites.³ The terms myalgic encephalomyelitis (ME), chronic FS (CFS) and postviral FS (PVFS) are also used to describe this condition.⁴

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Health-care professionals should be aware of such disorder because it greatly affects functional status and quality of life of the patients comparably with other diseases, such as depression, cancer, multiple sclerosis, rheumatoid arthritis, HIV, heart disease, and end-stage renal diseases^{5–7} The economic impact of PIFS on society is also substantial, because this disorder may result in decreased productivity and loss of employment.⁸ As such, rehabilitation care for COVID-19 survivors with PIFS must be focused on and delivered by multidisciplinary teams. This may decrease the consequences of fatigue and improve functional outcomes in activities of daily living.^{9–13}

The etiology of PIFS remains elusive; however, a number of mechanisms have been suggested, such as immunodysfunction, neuroinflammation, enhanced oxidative stress, mitochondrial dysfunction, neuroendocrine disorder, and hereditary predisposition.⁴ The hallmarks of PIFS include easy fatigability, postexertional malaise, pains, sleep abnormalities, and autonomic dysfunction that must be present or recurrent for at least 6 months. The patient's functional level must decrease by more than 50% compared with preillness levels.^{3,14} No cure currently exists; therefore, treatment of PIFS aims mainly at alleviating symptoms and improving functional status.¹⁵

Electrophysiological studies remain an extension of clinical assessment and help in accurate localization, thus providing guidance for proper management, especially when dealing with subjective complaints.¹⁶ Several electrophysiological studies have been done to localize sites of abnormality in motor units in patients with CFS. Reduced recruitment of voluntary motor units and jitter abnormalities were reported in some patients.^{17–19}

Aim of This Work

This study aimed to evaluate physical and mental fatigue and their neurophysiological correlate in subjects recovered from COVID-19 and to study whether clinical, laboratory, and radiological markers of COVID-19 severity can predict the likelihood of developing PIFS in COVID-19 long-haulers.

Patients and Methods

Design and Participants

This case-control study was conducted between November 1, 2020 and February 1, 2021. Study subjects

were COVID-19 long-haulers who were diagnosed as having PIFS according to the US National Academies of Sciences, Engineering, and Medicine,²⁰ and another sample of age- and sex-matched volunteers who had recovered from COVID-19 infection without any residuals. In order to fulfill the definition of PIFS,²⁰ patients had to have persistent fatigue for at least 6 months after recovery. The patient group was recruited from the COVID-19 Clinic, Beni-Suef University Hospital. Health workers who had recovered from COVID-19 without any residuals were recruited as a control group.

According to the World Health Organization,²¹ recovery from COVID-19 infection is defined as improvement in all symptoms of COVID-19, absence of fever for 3 consecutive days and negative results for two consecutive SARS-CoV2 tests at a 24-hour interval.

We excluded patients with a history of CFS preceding the onset of COVID-19, any medical disorder known to be associated with fatigue (eg, cardiac disorders, hypothyroidism, malignancy), any central or peripheral neurological disorder, and depressive disorders according to the *Diagnostic and Statistical Manual of Mental Disorders* fifth edition.²²

Measures

Data on duration of COVID-19 infection, including symptomatology, steroid intake, initial laboratory markers (serum CRP, ferritin, and neutrophil-lymphocyte ratio), and results of chest imaging, were obtained from Beni-Suef University Hospital medical records. The COVID-19 Reporting and Data System (CO-RADS)²³ was used for radiological grading of pulmonary involvement.

All participants underwent face-to-face interviews for data collection, including demographics, smoking status, and body-mass index (BMI), as well as detailed general and neurological examinations.

At enrollment, fatigue was assessed using a fatigue questionnaire.²⁴ This was an eleven-item scale to assess physical and mental fatigue. Items 1–7 represent physical fatigue, while items 8–11 represent mental fatigue. Each item was scored using a bimodal response system: better than usual or no more than usual = 0, worse than usual or much worse than usual = 1.

Patients were also assessed for any other associated long COVID-19 manifestations, such as musculoskeletal pains, insomnia, dizziness, sore throat, and tender lymph nodes.

Neurophysiological Assessment

Neurophysiological assessment was carried out for both groups at the Neurodiagnostic Research Center, Beni-Suef University using a Nihon Kohden apparatus. Motor and sensory nerve-conduction studies were done for the upper limbs (both ulnar nerves and left median nerves) and the lower limbs (both common peroneal nerves and right tibial nerve) to exclude any neuropathy. Electromyography (EMG) examinations of distal and proximal muscles were carried out to exclude any myopathy.

Slow (3 Hz) repetitive nerve stimulation (RNS) was performed for the ulnar and spinal accessory nerves while recording the abductor digiti minimi (ADM) and trapezius muscles, respectively, using surface electrodes at 1, 2, 3, and 4 minutes. RNS is positive when there is a decrement in compound muscle action potential amplitude and/or area >10% between the first and fourth responses.²⁵

Volitional single-fiber EMG (SFEMG) was carried out using a concentric facial needle. The band pass was 1–10 kHz (values of low- and high-frequency filters, respectively). Patients were asked to contract the muscle minimally and maintain this contraction. Four insertions were made to record 10–20 pairs of single muscle fibers. The needle was moved until locating a single muscle-fiber potential of amplitude >200 μ V and rise time <300 μ s. The needle was then moved slightly to get a second potential that was time-locked to the first potential, denoting that it was from the same motor unit. Multiple consecutive firings of muscle-fiber action-potential were then recorded. By recording 50–100 subsequent potentials, the mean consecutive difference (MCD), a measure of jitter, was taken. Mean MCD was taken by repeating the procedure until collecting an adequate number of single-fiber pairs. SFEMG data (mean MCD and percentage of blocking) were measured from the extensor digitorum communis (EDC) muscle.²⁶

Sampling

Because our study was the first study to use SFEMG for assessment of post-COVID fatigue, we calculated the sample size based on the results of a pilot study we performed before starting our study. The sample-size calculation was done using G*Power 3.1.9.2. The probability of type I error (α) was 5%, effect size 0.761, noncentrality parameter $\lambda=3.65$, critical $t=1.987$, and $df=90$. A total sample of 46 patients in each group was required to achieve statistical power ($1-\beta$) of 95%.

Ethics Statement

Written informed consent was obtained from all participants. Ethics approval for this study was obtained from the research-ethics committee of Beni-Suef University (FMBSUREC/03012021/Hussein). The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

SPSS 25 was used to analyze the data. The Kolmogorov–Smirnov test was used to test data normality. Categorical variables, ie, sex, smoking status, COVID and post-COVID symptoms, steroid intake, CO-RADS staging, and occurrence of decremental responses are expressed as numbers and percentages. Abnormally distributed quantitative variables, such as age, BMI, duration of illness, laboratory markers, and MCD, are expressed as medians and IQRs. Normally distributed quantitative variables, eg, percentage of decremental response, are expressed as means \pm SD. For comparisons between the fatigue and nonfatigue group on categorical variables, Chi square tests were used, whereas the Mann–Whitney U test was used for quantitative abnormally distributed variables. Correlations between fatigue scores and MCD were assessed using the Spearman correlation test. Stepwise binary logistic regression was used to identify predictors of occurrence of PIFS after being adjusted for their potential mutual confounding effect. $P\leq 0.05$ was considered statistically significant. All tests were two-tailed.

Results

This was a case-control study that was conducted on 46 patients with PIFS (fatigue group) and 46 recovered COVID-19 subjects without fatigue (control group). The two groups were matched for age and sex ($P=0.063$ and 0.075 respectively).

Clinical assessment of fatigue in patients with PIFS using the fatigue questionnaire revealed that median values for physical fatigue, mental fatigue, total fatigue scores, were 4, 2, and 6, respectively. In sum, 36 patients (78.3%) had post-COVID musculoskeletal pain, 31 (67.4%) orthostatic intolerance, 30 (65.2%) insomnia, 12 (26.1%) sore throat, and five (10.9%) tender lymph nodes (Table 1).

Clinical, Laboratory, and Radiological Parameters of COVID-19 Infection in Relation to Occurrence of PIFS

On comparing the clinical, laboratory, and radiological parameters between the two groups, we found that patients with

Table 1 Assessment of fatigue and other associated post-COVID-19 symptoms in patients with PIFS

		Fatigue group (n=46)	
Fatigue questionnaire	Physical, median (IQR)	4 (2–7)	
	Mental, median (IQR)	2 (0–3)	
	Total, median (IQR)	6 (3–9)	
Associated post-COVID symptoms	Musculoskeletal pain	Yes, n (%)	36 (78.3%)
		No, n (%)	10 (21.7%)
	Orthostatic intolerance	Yes, n (%)	31 (67.4%)
		No, n (%)	15 (32.6%)
	Insomnia	Yes, n (%)	30 (65.2%)
		No, n (%)	16 (34.8%)
	Sore throat	Yes, n (%)	12 (26.1%)
		No, n (%)	34 (73.9%)
Tender LNs	Yes, n (%)	5 (10.9%)	
	No, n (%)	41 (89.1%)	

Abbreviation: LNs, lymph nodes.

PIFS had significantly longer disease duration than controls ($P<0.001$). The frequency of fever, respiratory manifestations, gastrointestinal tract symptoms, fatigue, and musculoskeletal pain were significantly higher in patients with PIFS ($P=0.024$, <0.001 , 0.001 , 0.005 , and <0.001 , respectively). Frequency of steroid intake was significantly higher in patients with PIFS than controls ($P<0.001$). Radiological findings for COVID-19 were significantly worse in patients with PIFS than controls ($P<0.001$). Patients with PIFS had significantly higher CRP and ferritin levels than controls ($P=0.014$ and <0.001 , respectively; [Table 2](#)).

Predictors of PIFS in COVID-19 Long-Haulers

Stepwise binary logistic regression was done to identify predictors of PIFS. Duration of COVID-19 illness, fatigue, musculoskeletal pain, CO-RADS, CRP, and ferritin during the period of COVID-19 illness were used as the independent variables.

Only duration of COVID-19 illness and serum ferritin were retained as independent predictors occurrence of PIFS. Each day's increase in period of COVID-19 illness increased the odds of PIFS 1.104-fold and each unit

increase in ferritin increased the odds of PIFS 1.006-fold ([Table 3](#)).

Neurophysiological Assessment

A significant decrement in at least one muscle was observed in 23 patients in the fatigue group (50%). Mean values for decremental response were $11.8\% \pm 0.837\%$ in ADM and $11.5\% \pm 0.648\%$ in trapezius muscles. Patients with PIFS had significantly higher MCD in the EDC than controls ($P<0.001$, [Table 4](#)). None of our patients showed blocking.

There were statistically significant positive correlations between MCD in the EDC and physical, mental, and total fatigue scores ($P=0.003$, 0.029 , and <0.001 , respectively; [Table 5](#), [Figure 1](#)).

Discussion

Fatigue is considered one of the most common complaints in COVID-19 patients. It has been found to be a presenting symptom in 44%–69.6% of patients infected with COVID-19.²⁷ The rates of post-COVID fatigue have been reported to be much higher than those previously reported following Q fever Epstein–Barr virus and Ross River virus.²⁸ Nevertheless, a recent Iranian study reported that the prevalence of CFS among patients with COVID-19 was similar to that in the general population.²⁹

Many researchers believe that the abnormal amplified immunoresponse triggered by a specific pathogen may have a significant role in the pathophysiology of PIFS. They have deemed the PIFS a failure state to “downregulate” the immune system, where inflammatory cytokines that are primarily released to attack viral agents invade dorsal root ganglia and muscles. This in turn promotes fatigue, a principal symptom of CFS and pain.^{30,31}

For that purpose, markers of infection severity were investigated in this study as possible risk factors of PIFS. We found that patients with PIFS had significantly longer disease duration, higher levels of CRP and ferritin, and higher CORADS grading than the control group. However, only higher levels of ferritin and longer infection were found to be independent predictors of PIFS in recovered COVID-19 subjects.

Our results were in agreement with a previous study that revealed that PIFS was predicted principally by severity of infection, regardless of the causative viral pathogen.³² On the other hand, Townsend and Dyer²⁸ reported that post-COVID fatigue was not correlated with initial disease severity.

Table 2 Demographics, clinical, radiological, and laboratory characteristics of the study population

		Recovered COVID-19 subjects (n=92)		P	
		Fatigue group (n=46)	Nonfatigue group (n=46)		
Age (years), median (IQR)		54.5 (45.75–62)	51 (37–58)	0.063	
Sex	Male, n (%)	11 (23.9%)	19 (41.3%)	0.075	
	Female, n (%)	35 (76.1%)	27 (58.7%)		
Smoking	Yes, n (%)	2 (4.3%)	4 (8.7%)	0.398	
	No, n (%)	44 (95.7%)	42 (91.3%)		
BMI, median (IQR)		28.04 (25.07–31.68)	29.22 (27–32.4)	0.656	
Duration of illness (days), Median (IQR)		23 (14–45)	14 (11–19.5)	<0.001*	
Symptoms during COVID-19 infection	Fever	Yes, n (%)	44 (95.7%)	37 (80.4%)	0.024*
		No, n (%)	2 (4.3%)	9 (19.6%)	
	Respiratory manifestations	Yes, n (%)	41 (89.1%)	18 (39.1%)	<0.001*
		No, n (%)	5 (10.9%)	28 (60.9%)	
	GIT symptoms	Yes, n (%)	29 (63%)	13 (28.3%)	0.001*
		No, n (%)	17 (37%)	33 (71.7%)	
	Headache	Yes, n (%)	39 (84.8%)	33 (71.7%)	0.129
		No, n (%)	7 (15.2%)	13 (28.3%)	
	Fatigue	Yes, n (%)	42 (91.3%)	31 (67.4%)	0.005*
		No, n (%)	4 (8.7%)	15 (32.6%)	
	Musculoskeletal pain	Yes, n (%)	36 (78.3%)	13 (28.3%)	<0.001*
		No, n (%)	10 (21.7%)	33 (71.7%)	
Steroid intake	Yes, n (%)	32 (69.6%)	15 (32.6%)	<0.001*	
	No, n (%)	14 (30.4%)	31 (67.4%)		
CO-RADS staging	I, n (%)	3 (6.5%)	5 (10.9%)	<0.001*	
	II, n (%)	0	5 (10.9%)		
	III, n (%)	5 (10.9%)	25 (54.3%)		
	IV, n (%)	11 (23.9%)	2 (4.3%)		
	V, n (%)	27 (58.7%)	9 (19.6%)		
Laboratory workup	NLR, median (IQR)	3.053 (2.054–4.53)	2.67 (1.615–4.55)	0.768	
	CRP (mg/L), median (IQR)	25.5 (12–92)	24 (12–38)	0.014*	
	Ferritin (ng/mL), median (IQR)	406 (297.5–535)	124 (79–236)	<0.001*	

Note: *P≤0.05 is considered significant.

Abbreviations: BMI, body mass index; CO-RADS, COVID-19 Reporting and Data System; GIT, gastrointestinal tract; NLR, neutrophil:lymphocyte ratio.

Table 3 Stepwise logistic regression to detect predictors of PIFS

	β	Wald Chi square	P	Odds ratio	95% CI	
					Lower	Upper
Duration of illness, days	0.099	6.109	0.013*	1.104	1.021	1.195
Ferritin (ng/mL)	0.006	7.377	0.007*	1.006	1.002	1.010
Constant	-3.324	13.686	0	0.036		

Notes: Nagelkerke $R^2=0.523$; dependent variable — occurrence of PIFS; * $P \leq 0.05$ is considered significant.

The important point to clarify is that a significantly higher proportion of patients with PIFS were using steroids during the period of COVID-19 illness than the control group. This does not actually dampen the fact that immunodysfunction is a potential mechanism for PIFS. The possibility remains that steroid use primarily indicates a patient’s poor clinical condition.

It should be noted that the aforementioned mechanism cannot alone elucidate the occurrence of CFS. There must be another central mechanism that underpins mental fatigue. Mental fatigue in CFS may be related to impaired regulation of global and regional cerebral blood flow, particularly during challenging mental tasks.^{33,34}

It is well known that decremental responses in RNS are not conclusive for neuromuscular junction disorders, but can sometimes be seen in disorders that affect

peripheral nerve, muscle, or even anterior horn cells.^{35,36} However, the low rate of decremental response (11%–13%) in our patients does not negate any of these possibilities.^{36,37}

SFEMG may provide a more accurate evaluation of the neuromuscular junction than RNS and thus may provide a better determination of the true condition of neuromuscular status. In this study, the fatigue group had significantly higher MCD than the control group, and none showed blocking. These results are in line with published data on PVFS caused by other viruses.^{17–19} Abnormal jitter points to a disturbance in the peripheral part of the motor unit, in either the terminal axon branches, the motor end plate, or the muscle fiber.^{26,38} However, we cannot determine a definite locale because fiber density cannot be reliably assessed using concentric needles.³⁹

The disturbance in the muscle fiber of patients with PVFS was documented at pathological base. Behan et al⁴⁰ were the first to examine muscle biopsies obtained from patients with PVFS, and found varying atrophy of type II fibers, with evident mitochondrial degeneration. After that, successive studies proved that mitochondrial dysfunction plays a fundamental role in the pathophysiology of PVFS.^{41,42}

Many researchers believe that rehabilitation of post-COVID patients is crucial for recovering from fatigue and improving functional status. It is also mandatory to manage residual post-COVID deficits of these patients, even after their discharge, through telerehabilitation.^{9,12}

Table 4 Neurophysiological findings in patients with and without PIFS

		Recovered COVID-19 subjects (n=92)		P
		Fatigue group (n=46)	Nonfatigue group (n=46)	
MCD for EDC, median (IQR)		40.7 (36.70–44.8)	33.6 (28.20–36.48)	<0.001*
Decremental response in ADM	Yes, n (%)	6 (13.0%)	0	0.011*
	No, n (%)	40 (87.0%)	46 (100%)	
Decremental response in trapezius	Yes, n (%)	20 (43.5%)	0	<0.001*
	No, n (%)	26 (56.5%)	46 (100%)	

Note: * $P \leq 0.05$ is considered significant.

Abbreviations: ADM, abductor digiti minimi; EDC, extensor digitorum communis; MCD, mean consecutive difference.

Table 5 Correlation between scores on fatigue questionnaire and MCD for EDC in patients with PIFS

	Physical fatigue score		Mental fatigue score	
	r	P	r	P
MCD for EDC	0.425	0.003*	0.321	0.029*

Note: * $P \leq 0.05$ is considered significant.

Abbreviations: EDC, extensor digitorum communis; MCD, mean consecutive difference.

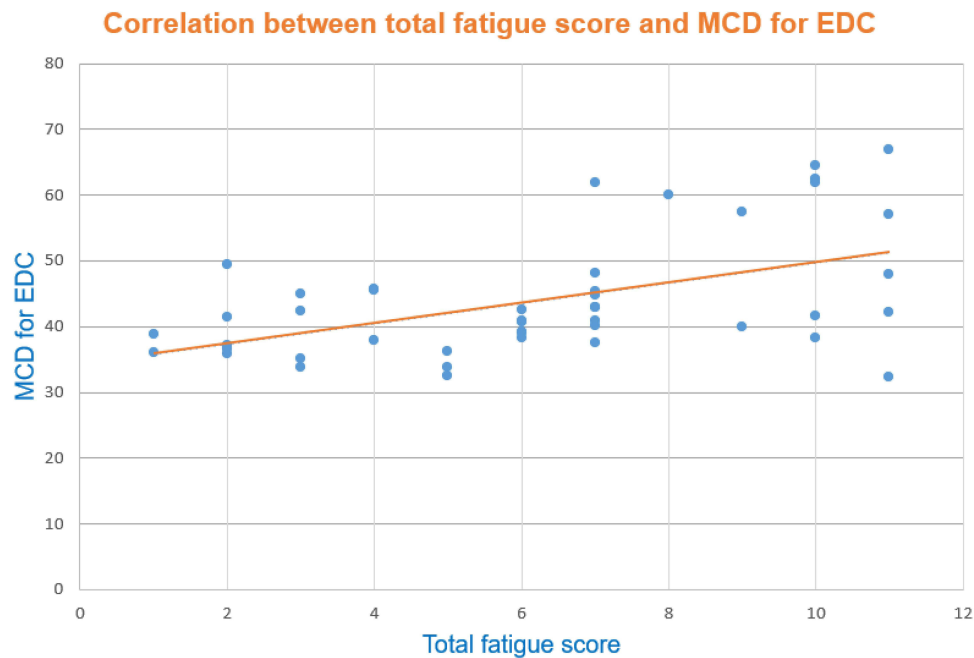


Figure 1 Correlation between total fatigue scores and MCD for EDC in patients with PIFS.
Abbreviations: EDC, extensor digitorum communis; MCD, mean consecutive difference.

The strength of our study is that it is the first to provide both clinical and neurophysiological assessment of fatigue in COVID-19 long-haulers. The main limitation is that we did not assess the levels of any circulating proinflammatory cytokines or markers of peripheral immunoactivation in our patients.

This study might pave the way for future research on the possible mechanisms underlying PIFS in COVID-19 long-haulers. Additionally, follow-up of such subjects to identify long-term outcomes is mandatory.

Conclusion

Higher ferritin levels and prolonged COVID-19 infection were found to be independent predictors of PIFS in COVID-19 long-haulers. Moreover, this study presents clear electrophysiological evidence of abnormalities in the peripheral portion of the motor unit in COVID-19 long-haulers with PIFS. Such abnormalities were demonstrated in the patients despite the fact that they did not have neuropathy or myopathy either clinically or electrophysiologically.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Patient Consent

Written informed consent was obtained from all participants. Ethics approval for this study was obtained from the research-ethics committee of Beni-Suef University (FMBSUREC/03012021/Hussein). The study was performed in accordance with the Declaration of Helsinki.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

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