

Fatigue in Post-COVID-19 Syndrome: Clinical Phenomenology, Comorbidities and Association With Initial Course of COVID-19

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ABSTRACT

INTRODUCTION: Post-COVID-19 syndrome affects approximately 10-25% of people suffering from COVID-19 infection, irrespective of initial COVID-19 severity. Fatigue is one of the major symptoms, occurring in 30-90% of people with post-COVID-19 syndrome. This study aims at describing factors associated with fatigue in people with Post-COVID-19 seen in our newly established Post-Covid clinic.

METHODS: This retrospective single center study included 42 consecutive patients suffering from Post-COVID-19 syndrome treated at the Department of Neurology, University Hospital Bern, between 11/2020 and 05/2021. Clinical phenomenology of Post-COVID-19 syndrome with a special focus on fatigue and risk factor identification was performed using Mann-Whitney U Test, Pearson Correlation, and Chi-Quadrat-Test.

RESULTS: Fatigue (90.5%) was the most prevalent Post-COVID-19 symptom followed by depressive mood (52.4%) and sleep disturbance (47.6%). Fatigue was in mean severe (Fatigue severity scale (FSS) mean 5.5 points (95% Confidence interval (95CI) 5.1 - 5.9, range .9 - 6.9, n = 40), and it was unrelated to age, COVID-19 severity or sex. The only related factors with fatigue severity were daytime sleepiness and depressed mood.

CONCLUSION: Fatigue is the main symptom of the Post-COVID-19 syndrome in our cohort. Further studies describing this syndrome are needed to prepare the healthcare systems for the challenge of treating patients with Post-COVID-19 syndrome.

KEYWORDS: SARS-CoV2, corona virus, post infectious, long-term symptoms, neuropsychiatric symptoms, viral infection

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Introduction

The SARS-CoV2 pandemic is a major health concern. Not all of the infected people completely recover, as 10 - 22% remain symptomatic even months after the initial COVID-19 infection¹ and subsequently develop a Post-COVID-19 syndrome. Post-COVID-19 or Long-COVID-19 syndrome - in the

following named Post-COVID-19 syndrome - is defined as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis".² Despite the large amount of affected people and even though post infectious syndromes have been described since decades, eg as the von



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Economo's syndrome,³ our knowledge on post-infectious fatigue syndrome is still limited. Post-infectious fatigue has been also reported in other infectious diseases, such as Epstein-Barr-Virus (EBV), Q-Fever, Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) and Ross River Virus (RRV).⁴ Post-COVID-19 syndrome is characterized by multiple symptoms including headache, fatigue, dyspnoea, anosmia, and cough.⁵ Fatigue is one of the most prevalent symptoms occurring after acute COVID-19 in 30-90%.^{4,6}

Fatigue is defined as a debilitating feeling of mental and/or physical loss of energy⁴ and can be accompanied especially in the Post-COVID-19 syndrome by a post exertional malaise.⁶

Post-COVID-19 syndrome and fatigue affects the social wellbeing. Studies on non-hospitalized patients with COVID-19 showed that between 12 - 23% remain absent from work even 3 - 7 months after COVID-19.⁷ Still, it is unclear how many of them will remain unable to work and eventually need invalidity pensions. The therapy of the Post-COVID-19 syndrome remains challenging. Despite its fundamental role in the Post-COVID-19 syndrome, a clinical study on fatigue in patients with Post-COVID-19 syndrome is still missing. Thus, the aim of our study is to characterize Post-COVID-19 syndrome with a special focus on Post-COVID-19 fatigue.

Methods

In this retrospective single center study we included 42 consecutive patients seen at our Neuroimmunological Post-COVID-19 clinic between 11/2020 and 05/2021 who consented to participate in the established prospective neuroimmunological registry and who met the definition of Post-COVID 19 syndrome.² The patients were seen during the Post-COVID-19 consultation at department of neurology university hospital Bern, Switzerland. This consultation included a detailed history of the course of the acute infection and current symptoms, physical examination, completion of questionnaires on fatigue (fatigue severity scale (FSS), Fatigue Scale of Motor and Cognitive Function (FSMC)), mood (Beck Depression Index II (BDI II)) and daytime sleepiness (Epworth Sleepiness Scale (ESS)), and a detailed laboratory evaluation to exclude secondary causes of fatigue (supplement table 1). Severity of COVID-19 was classified by initial symptomatology into asymptomatic, mild, moderate, severe and critical following a previously described definition (supplement table 2).² Fatigue was defined as a mean FSS score ≥ 4 points.⁸ Fatigue was further characterized with the FSMC.⁹ Secondary causes of fatigue were evaluated as routinely examined in our neuroimmunological patients taken into account in the analysis of the result (supplement table 1).

Clinical phenomenology of fatigue and comorbidities as well as serological findings were analysed using Mann-Whitney U Test (MWU), Pearson Correlation and Chi-Quadrat-Test, respectively. Adjustment for multiple testing was performed by Bonferroni procedure with regards to each domain.

Data sharing statement: Following an open data approach, anonymized data of the cohort can be requested via the corresponding author.

Ethicsstatement: The prospective registry was approved by Ethics Committee of the Canton of Bern, Switzerland (approval no. 2017-01369). All participants provided written informed consent.

Results

Characteristics of the Cohort

The majority of patients were female (23/42 (54.8%)) and the mean age was 44.8 years (95% Confidence interval (95CI) 40.4 - 49.3, range 16.4 - 82.0, n=42). The patients were seen 28.0 weeks (mean, 95%CI 23.6 - 32.3, range 13.0 - 56.6, n=42) after acute COVID-19 infection. Acute COVID-19 course was mild/moderate in 32/42 (76.2%) and severe/critical in 10/42 (23.8%) of included patients. Further characteristics of the cohort are given in Table 1A. The three most prevalent Post-COVID-19 symptoms in this preselected cohort were fatigue (38/42, 90.5%), depression (22/42, 52.4%) and sleep disturbance (20/42, 47.6%). Sleep disturbance consisted of insomnia including difficulties in initiating (13/20, 65%) and maintaining sleep (7/20, 35%; figure 1). Laboratory analysis at the time of first consultation was available in 40 patients (95.2%). Despite normal C-reactive protein (CRP) serum levels, ferritin serum levels were elevated (207.1 $\mu\text{g/l}$, 95%CI 133.8 - 280.4, range 5 - 963, reference range: 10 - 120 $\mu\text{g/l}$; Table 1A).

Characterizing Fatigue in Patients With Post-COVID-19 Syndrome

In those patients reporting fatigue, fatigue severity was in mean 5.6 points (95%CI 5.3 - 5.9, range 4.0 - 6.9, n=38). No sex difference or difference in the severity of COVID-19 infection were present between patients with and without fatigue (Table 1C). Neither time between acute infection to fatigue assessment (corr. -.17, P=.285, n=38), nor age (corr. -.24, P=.146, n=38) or Body Mass Index (BMI) (corr. .31, P=.864, n=33) correlated with FSS score (Table 1B).

Increased daytime sleepiness (defined by ESS ≥ 11 points) was reported in 11/34 (32.4%, 4 missing values) and affective symptoms classifying for at least a mild depressive mood (definite by BDI II ≥ 14 points) were present in 21/38 (55.3%) of the patients with fatigue. Fatigued patients with daytime sleepiness differed from patients without daytime sleepiness as sleep disorders during acute infection were more frequently observed and BDI II scores were significantly higher (P=.031) (supplementary table 3). Of the conditions routinely tested for secondary causes of fatigue, only iron deficiency (defined as ferritin $< 50 \mu\text{g/l}$ and transferrin saturation $< 20\%$ following Swiss internal medicine guidelines¹⁰) was found in 2/38 (5.3%) patients as possible aggravating factor of Post-COVID-19 fatigue. CRP and ferritin values were not differentially distributed in patients with and without fatigue. However we found significantly higher ferritin serum levels in patients with fatigue without confounders of fatigue (daytime sleepiness, iron deficiency, and depression) compared to the remaining population (342.7 $\mu\text{g/l}$, 95%CI 169.1 - 516.4, range

Table 1. Characteristics of patients with Post-COVID-19 syndrome. A: Characteristics of all patients with Post-COVID-19 syndrome. B: Correlation analyses to investigate associations with FSS score in fatigued patients with Post-COVID-19 syndrome. C: Comparison of fatigued and not-fatigued patients with Post-COVID-19 syndrome.

A) VARIABLE	POST-COVID-19 SYNDROME PATIENTS	N
Age, years, mean (95%CI)	44.8 (40.4-49.3)	42
Female, n (%)	23 (54.8)	42
BMI, mean (95%CI)	24.8 (23.4-26.3)	36
Education ≥13 years*, n (%)	28 (66.7)	42
Duration of acute infection, days, mean (95%CI)	19.4 (15.5-24.0)	42
Time between onset of acute infection and consultation, weeks, mean (95%CI)	28.0 (23.6-32.3)	42
Symptoms of acute COVID-19, n (%)		
Headache	20 (47.6)	42
Fever	21 (50.0)	42
Anosmia	25 (59.5)	42
Dyspnoea	23 (54.8)	42
Cough	25 (59.5)	42
Cold	22 (52.4)	42
Pain	25 (59.5)	42
Gastrointestinal symptoms	3 (7.1)	42
Fatigue	24 (57.1)	42
Sleep disturbance	20 (47.6)	42
Severity of COVID-19, n (%)		
Asymptomatic	0 (0)	42
Mild	18 (42.9)	42
Moderate	14 (33.3)	42
Severe	8 (19.1)	42
Critical	2 (4.8)	42
Hospitalisation, n (%)		
Pneumonia	6 (14.3)	42
Sepsis	2 (4.8)	42
Pulmonary embolism	2 (4.8)	42
Myelitis	1 (2.4)	42
Intubation, n (%)	2 (4.8)	42
Diagnosis of COVID-19		
Positive PCR test, n (%)	40 (95.2)	42
Positive IgG-Antibody n (%)	2 (4.8)	42
Comorbidities, n (%)		
Hypertension, n (%)	4 (9.5)	42
Metabolic syndrome, n (%)	3 (7.1)	42
Depression, n (%)	1 (2.4)	42
Stroke, n (%)	1 (2.4)	42
Autoimmune disorders, n (%)	6 (14.3)	42
Multiple sclerosis (MS), n (%)	1 (2.4)	42
Guillain Barré syndrome	1 (2.4)	42
Hashimoto thyroiditis	2 (4.8)	42
Spondylarthritis	1 (2.4)	42
Asthma bronchiale	1 (2.4)	42
Long-term immunotherapies, n (%)	4 (9.6)	42
Post-COVID symptoms		
Fatigue, n (%)	38 (90.5)	42
Depressive mood, n (%)	22 (52.4)	42
Sleep disturbance, n (%)	20 (47.6)	42
Headache, n (%)	11 (26.2)	42
Pain, n (%)	9 (21.4)	42
Dyspnoea, n (%)	8 (19.1)	42
Dizziness, n (%)	5 (11.9)	42
Autonomic dysfunction, n (%)	6 (14.3)	42
Hair loss, n (%)	1 (2.4)	42

(Continued)

Table 1. Continued.

A)		POST-COVID-19 SYNDROME PATIENTS		N
VARIABLE				
Laboratory parameters				
Ferritin serum level, µg/l, mean (95%CI)		207.1 (133.8-280.4)		40
Iron serum level, µmol/l, mean (95%CI)		16.6 (14.5-18.7)		40
Transferrin serum level, g/l, mean (95%CI)		2.7 (2.5-2.8)		40
Transferrin saturation, %, mean (95%CI)		25.9 (22.2-29.6)		40
CRP serum level, mg/l, mean (95%CI)		3.2 (2.8-3.6)		40
IgG serum level, g/l, mean (95%CI)		10.4 (9.8-11.1)		40
IgG-anti-nucleocapsid-antibodies positive, n (%)		17 (48.6)		35
IgG-anti-spike-antibodies positive, n (%)		28 (80.0)		35
IgG-anti-nucleocapsid-antibodies, serum index, mean (95%CI)		2.2 (1.7-2.7)		35
IgG-anti-spike-antibodies, serum AU/ml mean (95%CI)		94.4 (58.3-130.4)		35
Symptom assessment batteries				
MoCA test, mean (95%CI)		27.5 (26.9-28.0)		34
SDMT, mean (95%CI)		56.6 (52.8-60.3)		33
FSS, mean (95%CI)		5.2 (4.7-5.7)		42
FSMC total, mean (95%CI)		68.7 (61.3-76.1)		39
FSMC cognition, mean (95%CI)		34.2 (30.3-38.1)		39
FSMC motor, mean (95%CI)		34.5 (30.8-38.2)		39
ESS, mean (95%CI)		7.6 (6.1-9.0)		38
BDI II, mean (95%CI)		15.2 (12.3-18.1)		39
B)				
VARIABLE	CORRELATION FACTOR (FSS)	P-VALUE		N
Age	-.24	.146		38
Time between acute infection and consultation	-.17	.285		38
BMI	.31	.864		33
BDI II	.47	.003		39
FSMC total	.64	<.001		36
FSMC motor	.61	<.001		36
FSMC cognition	.55	.001		36
Ferritin serum level, µg/l	.12	.469		38
C)				
VARIABLE	FATIGUED (FSS ≥4) (N=38)	NOT FATIGUED (FSS <4) (N=4)		P-VALUE
Patient characteristics				
Age, years, mean (95%CI), n)	45.7 (40.9-50.5), 38	35.8 (14.5-57.1), 4		.157
Female, n (%)	22/38 (57.9)	1/4 (25)		.313
BMI, mean (95%CI), n	24.9 (23.3-26.5), 33	23.9 (14.0-33.7), 3		.667
Autoimmune disease, n (%)	5/38 (13.2)	2/4 (50)		.123
Time variable				
Duration acute infection, days, mean (95%CI), n	18.5 (15.9-21.1) 38	31.5 (-30.8-93.8), 4		.591
Time between acute infection and consultation, weeks, mean (95%CI), n	26.9 (22.4-31.4), 38	38.2 (14.1-62.3), 4		.118
Symptoms of acute COVID-19, n (%)				
Headache, n (%)	17/38 (44.7)	3/4 (75)		.333
Fever, n (%)	21/38 (55.3)	0/4 (0)		.107
Anosmia, n (%)	23/38 (60.5)	2/4 (50)		1.0
Dyspnoea, n (%)	22/38 (57.9)	1/4 (25)		.313
Cough, n (%)	24/38 (63.2)	1/4 (25)		.286
Cold, n (%)	21/38 (55.3)	1/4 (25)		.333
Pain, n (%)	23/38 (60.5)	2/4 (50)		1.0
Gastrointestinal symptoms, n (%)	3/38 (7.9)	0/4 (0)		1.0
Fatigue, n (%)	23/38 (60.5)	1/4 (25)		.297
Sleep disturbance, n (%)	23/38 (60.5)	1/4 (25)		.297

(Continued)

Table 1. Continued.

C) VARIABLE	FATIGUED (FSS ≥4) (N=38)	NOT FATIGUED (FSS <4) (N=4)	P- VALUE
Severity of COVID-19			
Mild, n (%)	15/38 (39.5)	3/4 (75)	.418
Moderate, n (%)	14/38 (36.8)	0/4 (0)	
Severe, n (%)	7/38 (18.4)	1/4 (25)	
Critical, n (%)	2/38 (5.3)	0/4 (0)	
Laboratory parameters			
Ferritin serum level, µg/l, mean (95%CI), n	206.8 (129.7-284.0), 38	211.00 (-754.7-1176.7), 2	.420
CRP serum level, mg/l, mean (95%CI), n	3.2 (2.8-3.7), 38	2.9 (2.9-2.9), 2	.684
Iron deficiency, n (%)	2/38 (5.3)	0/38 (0)	.739
IgG-anti-nucleocapsid-antibodies, serum index, mean (95%CI), n	2.4 (1.8-2.9), 31	1.3 (1.3-1.3), 4	.058
IgG-anti-spike-antibodies, serum AU/ml mean (95%CI), n	100.6 (60.4-140.8), 31	46.1 (-8.1-100.2), 4	.406
Scores			
ESS, mean (95%CI), n	7.8 (6.3-9.2), 36	3.5 (-28.3-35.3), 2	.179
BDI II, mean (95%CI), n	15.6 (12.6-18.6), 36	10.3 (-12.1-32.7), 3	.509

Abbreviations: 95%CI: 95% Confidence interval; AU: Arbitrate Units; BDI II: Beck Depression Index II; BMI: Body Mass Index; CRP: C-reactive protein, CU: chemiluminescent units; ESS: Epworth Sleepiness Scale; FSMC: Fatigue Scala for Motor and Cognitive Function; FSS: Fatigue Severity Score; PCR: Polymerase chain reaction, MoCA: Montreal Cognitive Assessment Test; SDMT: Symbol Digit Modalities Test (number of correct answers in 90 seconds). Iron deficiency is defined as ferritin <50 µg/l and transferrin saturation <20%. *Education over 13 years corresponds to compulsory schooling (9 years) and job training (3 years) in Switzerland.

Statistic: Clinical phenomenology of fatigue and present comorbidities as well as serological findings were analysed using Mann-Whitney U Test (MWU), Pearson Correlation and Chi-Quadrat-Test, respectively. Adjustment for multiple testing was performed by Bonferroni procedure in regard to each domain independently; part B: *P*-value < .007, part C: patient characteristics: *P*-value < .0125, time variable: *P*-value < .025, acute infection: *P*-value < .006, severity of COVID-19 infection: *P*-value < .0125, laboratory parameters: *P*-value < .01, scores: *P*-value < .025.

41-963, *n*=15 vs 125.6 µg/l 95%CI 85.3 - 166.0, range 5 - 287 *n*=25, *P*=.031). No significant difference of serum CRP levels comparing these two groups.

Discussion

This is the first study focusing on the role of fatigue in patients with Post-COVID-19 syndrome in a tertiary care centre in Switzerland. The main findings of the study are: 1. Fatigue is the predominant symptom of Post-COVID-19 syndrome, being present in >90% of patients approximately 7 months after acute COVID-19 infection. 2. Depression and daytime sleepiness were frequently found as possible aggravating factors of fatigue in this previously non-fatigued population. 3. The elevated ferritin levels support the hypothesis of an underlying immunological cause responsible for the fatigue in Post-Covid-19 syndrome. Considering the pandemic with millions of cases worldwide, health care systems have to prepare for this patient population, which will remain an important part of our daily medical care even after controlling the acute infections with SARS-CoV2.

Regarding the demographic characteristics of our study population, the majority of patients were women, between 40 - 50 years of age and not hospitalized due to the initial COVID-19 course, which is in line with the contemporary literature.^{7,11}

Sleep disturbances and depressive mood were two other common symptoms in our cohort occurring with a frequency of 47.6% and 52.4% respectively. The frequency of these symptoms in our study is comparable to previously published studies (sleep disorders 57 - 78%, depressive mood 31 - 88%).^{7,11} Concerning the mode of measurement of

fatigue, most previously published studies used telephone interview, questionnaire and information from medical records, however standardized questionnaires are yet not investigated in this setting. If questionnaires were used the FSS, the Somatic and Psychological Health Report, the Fatigue Impact Scale or the PROMIS Scale-Global Health were chosen.¹² Thus we decided to use two questionnaires for evaluation of fatigue the FSS as well as the FSMC, both available and validated in German language^{8,9} to note not in the setting of the Post-COVID-19 syndrome, which is to the best of our knowledge not given for any fatigue questionnaire. One advantage of the FSMC is that it differentiates between cognitive and physical fatigue, which was interestingly equally pronounced.

The impact of a depression in fatigue in general is a difficult to answer question as both are often simultaneously present. During the pandemic SARS-CoV-2 infection rates and mobility reduction due to gathering restrictions, were associated with increased prevalence of major depressive and anxiety disorders.¹³ In our study we evaluated a presence of a depressive mood by using the BDI-II, highlighting that a depressive mood is a common symptom occurring in 22/42 patients. However restricting the analysis only on patients with a BDI-II value below the cut-off of minor depressive symptoms (BDI II < 14 points) still 17/20 Post-COVID-19 patients experienced fatigue, highlighting that also beside depression as a comorbidity fatigue appears to be frequently present in Post-COVID-19 patients. In our cohort, laboratory analyses showed elevated average ferritin and normal CRP serum levels in Post-COVID-19 patients. In the group of fatigued patients without potential additional causes of fatigue ferritin serum concentration was higher compared to the non-fatigued group (*P*=.031), giving evidence of the initial viral

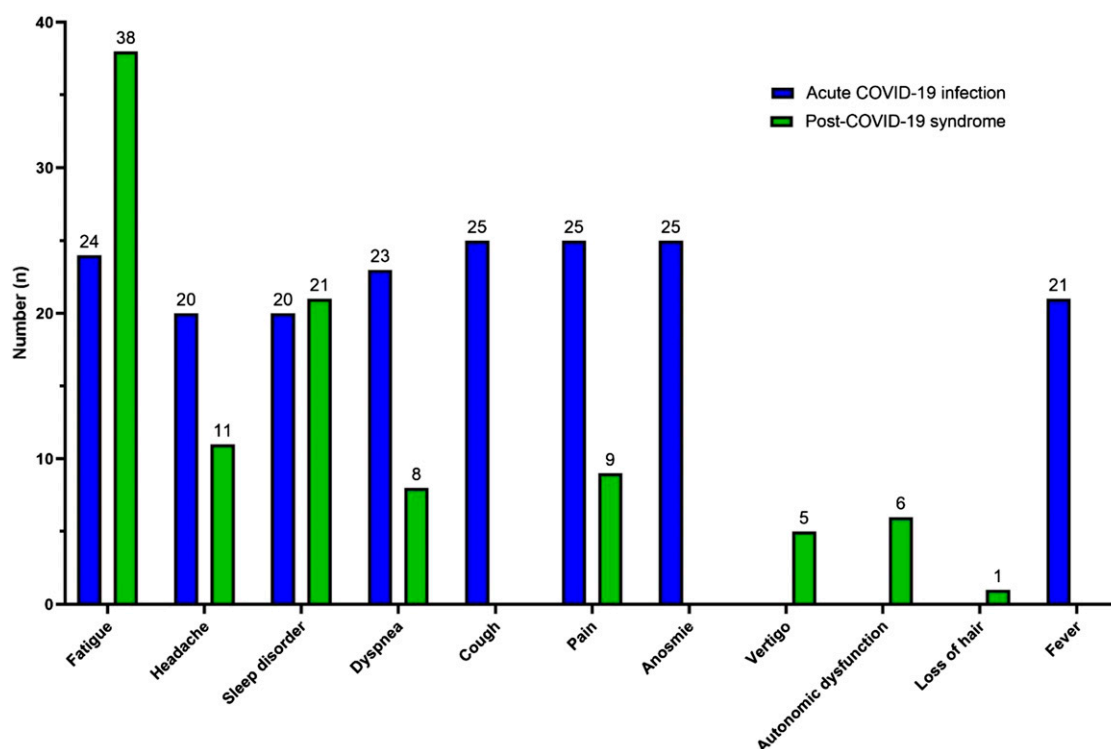


Figure 1. Number of patients with COVID-19 related symptoms during the acute phase of the disease (blue) and during Post-COVID-19 syndrome (green).

cause.^{14,15} Taking into account the limitations of small sample size, our finding nevertheless provides insight into post infectious origin and speculative involved immunological mechanisms of fatigue in patients with Post-COVID-19 syndrome. In detail, ferritin is an acute phase protein, being elevated during infections irrespective of agents and has been described by others to remain elevated in patients with Post-COVID-19 syndrome.¹⁴ Considering the cytokine dysregulation during COVID-19, especially the link between increased IL-6 serum concentration and elevated ferritin levels should be mentioned.^{16,17} As this might bear therapeutic opportunities, it is therefore important to follow this research track and substantiate this hypothesis by longitudinal laboratory data, which is out of the scope of our present study, and by prospective clinical trials, which is out of the scope of our present study. Our study has several limitations. First, the small sample size of 42 patients has to be taken into account. Second, a referral bias cannot be excluded, which might explain the small sample size and high rate of fatigued patients, as the main reason for referral to our neurological clinic was mainly fatigue and not non-neurological complaints such as cardiopulmonary symptoms. Nevertheless, high prevalence of fatigue have been reported also by other studies justifying our finding.^{4,6,7}

Concluding, fatigue appears to be the main symptom of the Post-COVID-19 syndrome in patients referred to a neurological tertiary care hospital. Further studies describing this syndrome as well as providing treatment recommendations are

urgently needed to prepare the healthcare systems for the challenge of treating patients with Post-COVID-19 syndrome.

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