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Etiological factors of Post COVID-19 Syndrome fatigue

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To my parents and my son for their unconditional and true support.

To Prof. Marta Drummond, a true inspiration, who never doubted that this thesis would be possible.

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This thesis is dedicated to Marcelo Bruno Pires, my dear brother who was studying medicine and had dreams like me, having died prematurely without the opportunity to make them come true. I hope to honour his legacy as a person and humanist.

Table of contents

1.
List of publications

This PhD thesis is based in the following publications:

Table 1: List of publications

CITATION	QUARTIL	IF*
Pires L, Reis C, Mesquita Facão AR, Moniri A, Marreiros A, Drummond M, Berger-Estilita J. Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study. JMIR Res Protoc. **2024 Jan** 19;13:e51820. doi: 10.2196/51820.	Q2 General Medicine	1.46
Pires, Ligia MD[a,b]; Marreiros, Ana PhD[c,d,e]; Saraiva, Cátia MD[a]; Reis, Cláudia MD[f]; Neves, Djamila MD[a]; Guerreiro, Cláudia MD[a]; Tomé, José Boleo MD[g]; Luz, Maria Inês MD[g]; Pereira, Margarida Isabel MD[g]; Barroso, Ana Sofia MD[h]; Ferreira, Jorge MD, PhD[h]; Gonzalez, Lucía Méndez RN[h]; Moniri, Armin MD, PhD[b,d,i,j]; Drummond, Marta MD, PhD[k]; Berger-Estilita, Joana MD, PhD[l,m,*]. Association of acute COVID-19 severity and long COVID fatigue and quality of life: Prospective cohort multicenter observational study. Medicine 104(36):p e42891, **September 05, 2025.** | DOI: 10.1097/MD.0000000000042891	Q2 Medicine, General & Internal	1.60
Pires L, Moniri A, Marreiros A, Belchior I, Fatal T, Ribeiro AR, Chaves Ramos H, Cunha K, Ferreira J, Barroso AS, Méndez Gonzalez L, Guimarães MJ, Conde B, Dias C, Ferreira-da-Silva R, Berger-Estilita J, Drummond M. Newly diagnosed Obstructive Sleep Apnea in long COVID-19 patients: a Prospective Cohort Multicenter Observational Study. **Per review in Pulmonology Journal**	Q1 Respiratory	11.70

Legend: *IF – Impact factor

2.

List of abbreviations

AHT – Arterial Hypertension

ALS – Amyotrophic Lateral Sclerosis

ANOVA – Analysis of Variance test

AASM – American Academy of Sleep Medicine

ACE – Angiotensin-Converting Enzyme

ACE2 – Angiotensin-Converting Enzyme 2

AHI – Apnea Hypopnea Index

AHT – Arterial Hypertension

AT2R – Angiotensin 2 Receptor

BMI – Body Mass Index

CFQ-11 – Chalder Fatigue Scale (11-item version)

CFS – Chronic Fatigue Syndrome

CRP – C-Reactive Protein

COVID-19 – Coronavirus Disease 2019

HADS – Hospital Anxiety and Depression Scale

DM – Diabetes Mellitus

DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

HRQoL – Health-Related Quality of Life

EQ-5D – EuroQol-5D

EQ-VAS – EuroQol Visual Analog Scale

ICD-10 – International Classification of Diseases, Tenth Revision

ICU – Intensive Care Unit

IQR – Interquartile Range

L-6 – Interleukin-6

MasR – Mas Receptor

ORCID – Open Researcher and Contributor ID

OSA – Obstructive Sleep Apnea

PACS – post-acute COVID-19 syndrome

PASC – Post-Acute Sequelae of COVID-19

PCSF – post COVID-19 syndrome fatigue

POD – Postoperative Delirium

PROMs – Patient-Reported Outcome Measures

PSG – Polysomnography

PSG 3 – Type 3 Polysomnography

PTSD – Post-Traumatic Stress Disorder

PTSS-14 – Post-Traumatic Stress Scale, 14-item version

RAAS – Renin-Angiotensin-Aldosterone Aystem

RT-PCR – Reverse Transcription Polymerase Chain Reaction

SAOS – Sindrome de Apneia Obstrutiva do Sono

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

SD – Standard Deviation

SLE – Systemic Lupus Erythematosus

SPSS – Statistical Package for the Social Sciences

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

T1 – Timepoint 1 (Three months post-infection)

T2 – Timepoint 2 (Six months post-infection)

TNF-α – Tumor Necrosis Factor Alpha

TRAG – Rapid Antigen Testing

WHO – World Health Organization

ULS – Local Health Unit (Unidade Local de Saúde)

3.
Abstract

3.1. Abstract

Background

The emergence of long COVID - a post-viral syndrome characterized by persistent symptoms such as fatigue, neuropsychiatric disturbances, and sleep disorders - has posed a significant challenge to healthcare systems worldwide. While fatigue is a consistently reported feature, its interaction with mental health (notably depression, anxiety, and PTSD) and sleep disturbances such as obstructive sleep apnea (OSA), as well as the impact of acute COVID-19 severity, remain incompletely understood. Better delineating these interrelationships is critical for developing targeted interventions and optimizing the long-term outcomes of COVID-19 survivors.

Aims

Aim 1 - To design a Multidisciplinary Protocol to assess post-COVID-19 Fatigue and Mental Disorders

Aim 2 - To quantify the prevalence and severity of physical and psychological fatigue in long COVID and examine their correlation with mental health disorders, including depression, anxiety,and PTSD

Aim 3 - To explore the association between fatigue subtypes, neuropsychiatric symptoms, and health-related quality of life (HRQoL) in individuals with post-COVID-19 condition, stratified by acute disease

Aim 4 - To determine the prevalence of newly diagnosed OSA in adults with long COVID, evaluate its association with persistent symptoms (particularly fatigue) and COVID-19 acute severity, and investigate gender-specific clinical patterns

Methods

A protocol to assess post-COVID-19 mental changes (Article 1) and two prospective, multicentre cohort studies were conducted in Portuguese hospitals, including adults with confirmed SARS-CoV-2 infection for at least six months ago. In Article 2, participants underwent standardized face-to-face clinical assessments. Fatigue was measured using the Chalder Fatigue Scale (CFQ-11). At the same time, symptoms of depression, anxiety, and post-traumatic stress were assessed using the Hospital Anxiety and Depression Scale (HADS) and the 14-item Post-Traumatic Stress Scale (PTSS-14). Quality of life was evaluated using the EuroQol-5D (EQ-5D). In the study focused on OAS (Article 3), level 3 sleep studies (at six months post-acute illness) were conducted to determine the prevalence and severity of OSA (according to the AHI), with stratification by sex and severity of previous acute COVID-19. Statistical analyses examined correlations and group differences in outcomes across all studies.

Results

In the fatigue and mental illness cohort, both physical and psychological fatigue were highly prevalent post-COVID-19, with significant positive correlations with depression and anxiety; PTSD symptoms were also persistent in a relevant subset. Patients with higher depression and anxiety symptoms reported more severe fatigue and lower HRQoL, underscoring the psychological impact of long COVID. This study revealed that fatigue remained the predominant symptom in the post-acute phase, with a strong association to anxiety and depression. Notably, individuals who had mild or moderate acute illness experienced higher levels of both physical and mental fatigue and poorer HRQoL compared to those who had severe disease. This unexpected pattern challenges previous studies assumptions, that greater acute severity predicts worse long-term impairment, and emphasises the importance of considering neuropsychiatric comorbidities in prognostication and care planning .

The third study found that the prevalence of newly diagnosed OSA at six months post-infection was substantially higher in the long COVID population than community estimates, particularly amongst those with persistent fatigue - 77.9% of fatigued patients met OSA diagnostic criteria. Marked gender differences emerged: OSA was more prevalent and severe in men, especially following severe acute illness, whereas in women, increasing OSA severity correlated with

higher BMI and milder acute COVID-19. Persistent fatigue, memory loss, brain fog, and hypersomnolence overlapped clinically with OSA symptoms, complicating the attribution of these features to either condition in long COVID patients.

Conclusions

Long COVID is a complex, multifactorial syndrome in which fatigue - both physical and psychological - is closely linked to mental health symptoms (depression, anxiety, PTSD) and, in a substantial proportion, to newly identified OSA. The impact on quality of life is profound, particularly among women and those who experienced less severe acute disease. The findings indicate that acute COVID-19 severity does not straightforwardly predict long-term burden or HRQoL. Instead, persistent neuropsychiatric symptoms and unrecognized OSA underpin much of the chronic morbidity. These results emphasize the necessity for holistic, multidisciplinary post-COVID-19 care, including routine screening for sleep pathology and mental health, early intervention for modifiable contributors to fatigue, and the development of integrated care pathways to optimize long-term recovery and well-being.

3.2. Resumo

Racional

O surgimento da COVID longa – uma síndrome pós-viral caracterizada por sintomas persistentes como fadiga, distúrbios neuropsiquiátricos e distúrbios do sono – representou um desafio significativo para os sistemas de saúde em todo o mundo. Embora a fadiga seja uma característica consistentemente relatada, a sua interação com a saúde mental (nomeadamente depressão, ansiedade e stress pós-traumático), a apneia obstrutiva do sono (AOS) e o impacto da gravidade aguda da COVID-19, permanecem pouco compreendidos. Carificar essas inter-relações é fundamental para desenvolver intervenções direcionadas e otimizar os resultados de longo prazo dos sobreviventes da COVID-19.

Objetivos

Primeiro: Realizar um protocolo multidisciplinar para avaliar a fadiga e distúrbios mentais pós-COVID-19;

Segundo: Quantificar a prevalência e a gravidade da fadiga física e psicológica na COVID longa e examinar a sua correlação com transtornos de saúde mental, incluindo depressão, ansiedade e stress pós-traumático;

Terceiro - Explorar a associação entre subtipos de fadiga, sintomas neuropsiquiátricos e o seu impacto na qualidade de vida, em indivíduos com condição pós-COVID-19, estratificada pela gravidade da doença aguda.

Quarto - Determinar a prevalência de AOS recém-diagnosticada, em adultos com COVID longa, avaliar a sua associação com: sintomas persistentes (particularmente fadiga), gravidade aguda de COVID-19 e padrões clínicos específicos de genero.

Métodos

Foram realizados um protocolo para avaliar alterações mentais pós-COVID-19 (1º Artigo) e dois estudos de coorte prospetivos e multicêntricos em hospitais portugueses, incluindo adultos com infeção confirmada a SARS-CoV-2 há pelo menos seis meses.

No 2º Artigo, os participantes foram submetidos a avaliações clínicas presenciais padronizadas. A fadiga foi medida usando a Escala de Fadiga de Chalder (CFQ-11), enquanto os sintomas de depressão, ansiedade e stress pós-traumático foram avaliados usando a Escala Hospitalar de Ansiedade e Depressão (HADS) e a Escala de Stress Pós-Traumático de 14 itens (PTSS-14). A qualidade de vida foi avaliada utilizando o EuroQol-5D (EQ-5D).

No estudo focado na SAOS (3º Artigo), foram realizados estudos polissonográficos nível três (PSG 3), aos seis meses pós-doença aguda, para determinar a prevalência e gravidade da SAOS (segundo o IAH), com estratificação por sexo e gravidade da COVID-19 aguda prévia. As análises estatísticas examinaram correlações e diferenças de grupo nos resultados em todos os estudos.

Resultados

Na coorte fadiga e doença mental, fadiga física e psicológica foram altamente prevalentes pós-

COVID-19, com correlações positivas e estatísticamente significativas com depressão e ansiedade. Os sintomas de stress pós-traumático também foram persistentes num subgrupo relevante. Doentes com mais sintomas de depressão e ansiedade relataram fadiga mais grave e menor qualidade de vida, ressaltando o impacto psicológico da COVID longa.

O 2º estudo, revelou que a fadiga permaneceu como sintoma predominante no pos-COVID-19, com forte associação à ansiedade e depressão. Notavelmente, os indivíduos que tiveram COVID-19 aguda ligeira ou moderada sentiram níveis mais altos de fadiga física e mental e pior qualidade de vida, em comparação com aqueles que tiveram doença grave. Este padrão inesperado desafia as observações de estudos anteriores, de que uma maior gravidade da doença aguda prediz pior desfecho clínico a longo prazo, e enfatiza a importância de considerar as comorbilidades neuropsiquiátricas no prognóstico e no plano para " seguimento e assistência a estes doentes".

O 3º estudo revelou que a prevalência de SAOS recém-diagnosticada aos seis meses após a infeção aguda foi substancialmente maior na população com sintomas persistentes pos-COVID-19 do que as estimativas de prevalência na população geral, particularmente quando existe fadiga persistente - 77,9% dos pacientes com fadiga pós-COVID-19 apresentaram critérios de diagnóstico de SOS na PSG 3. Diferenças significativas entre os sexos emergiram: a SAOS foi mais prevalente e grave nos homens, especialmente após doença aguda grave; enquanto nas mulheres, o aumento da gravidade da SAOS correlacionou-se com maior IMC e COVID-19 inicial ligeira. Fadiga persistente, perda de memória, névoa cerebral e hipersonolência, sobrepuseram-se clinicamente aos sintomas de SAOS, complicando a atribuição dessas características à sindrome pós-COVID-19 ou COVID longa.

Conclusões

A COVID longa é uma síndrome complexa e multifatorial na qual a fadiga - tanto física quanto psicológica - está intimamente ligada a sintomas de saúde mental (depressão, ansiedade e stress pós-traumático) e, em uma proporção substancial, à SAOS recém-identificada e não tratada.

O impacto na qualidade de vida é profundo, particularmente entre as mulheres, especialmente as que sofreram doença aguda menos grave. Os resultados indicam que a gravidade aguda da COVID-19 não prevê diretamente a persistência de sintomas a longo prazo e o seu impacto na qualidade de vida

4.
Introduction

4.1 Investigator's Perspective

The pandemic burden and post-COVID-19 syndrome

In Portugal, the SARS-CoV-2 pandemic reached its peak in new daily cases on January 28, 2021, with the diagnosis of 16,432 new cases (DGS, 2021). At that time, it was the country in the world with the highest number of cases per 100,000 inhabitants.

In the world, the cumulative numbers of SARS-CoV-2-infected patients is 778 million (WHO May 2025).

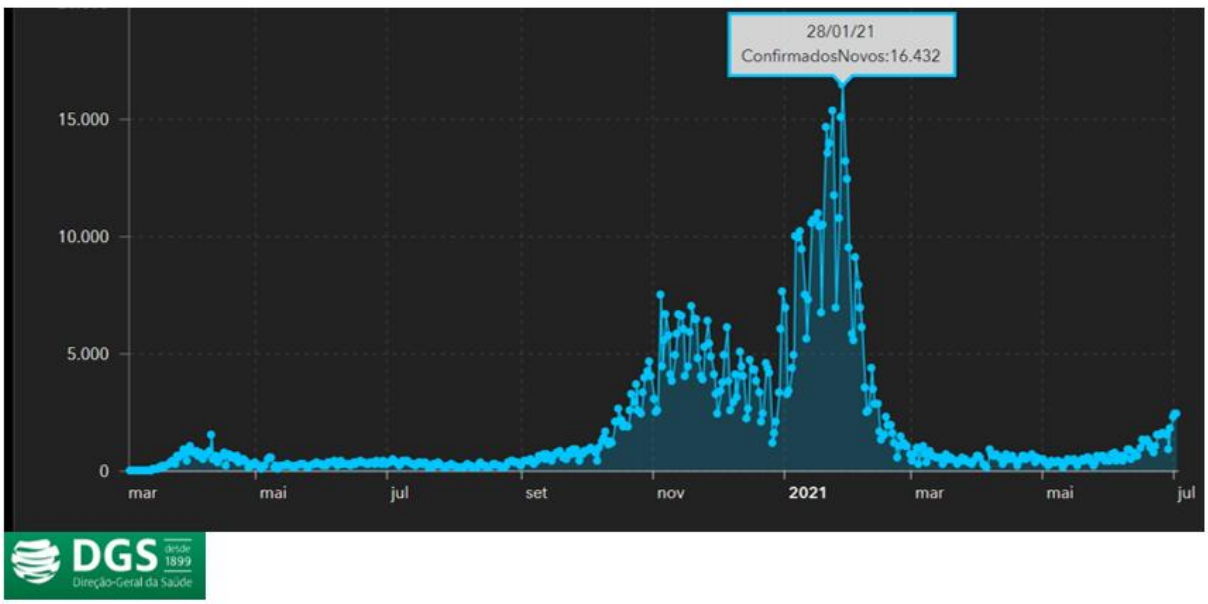


FIGURE 1 - SARS-CoV-2 pandemic peak in Portugal, the (DGS, 2021)

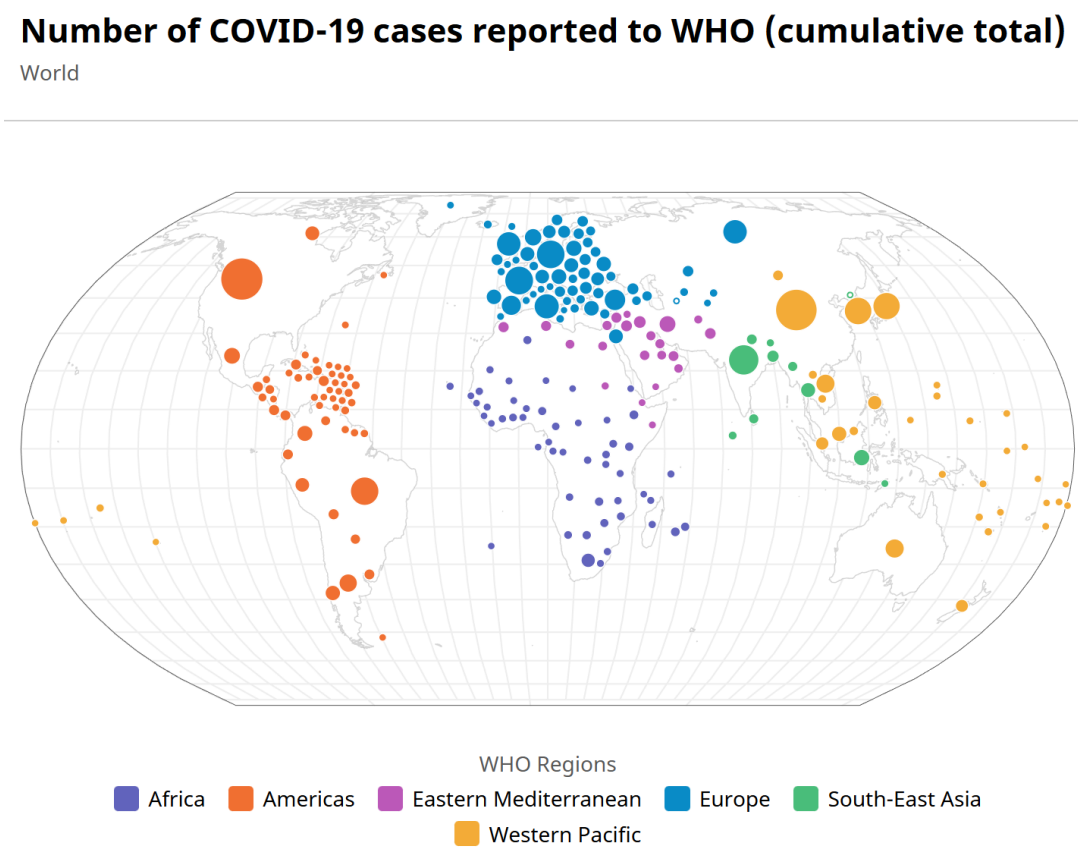
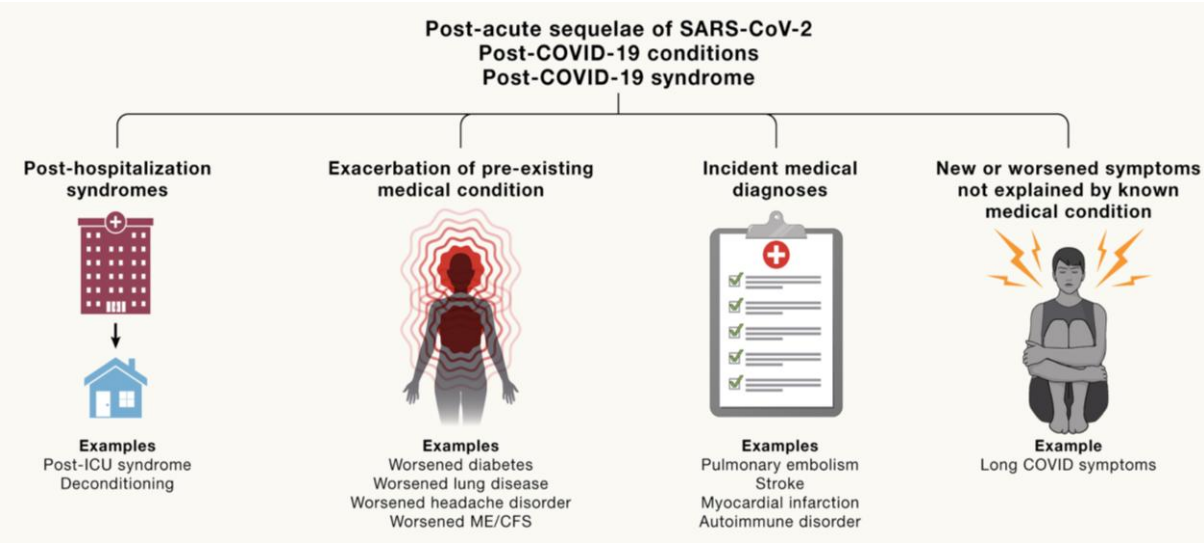


FIGURE 2 - Cumulative numbers of SARS-CoV-2-infected patients reported by WHO

In most individuals COVID-19 is self-limited, but a proportion of those infected, experience post-acute sequelae including: the post-hospital or post-intensive care unit (ICU) syndrome characterized by muscle weakness, fatigue, and cognitive dysfunction (Nalbandian et al. 2021); newly developed or exacerbated medical conditions such as diabetes mellitus, cerebrovascular events, and autoimmune disease; and/or the emergence of medically unexplained symptoms that affect every day functioning and quality of life. Patients with SARS-CoV-2 infection are still increasing, which may reflect a high number of survivors who can develop long-term sequelae (Carfi et al. 2020; Fauci 2020; Richardson et al. 2020): the post-COVID-19 condition. The term is synonymous with other designations such as “long COVID”, “post-acute sequelae of SARS-CoV-2” infection (PASC), and “post-acute COVID syndrome” (PACS).

This post-infectious condition, which has garnered substantial discussion among clinicians, researchers, public health agencies, and patients due to its evolving terminology and diagnostic criteria, which research is on-going concerning its mechanisms and clinical findings. The WHO (Soriano et al., 2021) arrived at its clinical case definition through a global consensus process (using a Delphi methodology), incorporating perspectives from patients, clinicians, and researchers, resulting in a working definition that may continue to evolve. "Post-COVID-19 condition" occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

Common symptoms of "Post-COVID-19 condition" include fatigue, shortness of breath, and cognitive dysfunction, but also others that generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from acute COVID-19 or persist from the initial illness and may fluctuate or relapse over time. This consensus definition is subject to updates.



Peluso MJ, Deeks SG. Cell. 2024 Oct 3;187(20)

FIGURE 3 – Proposed framework for defining PASC

Post–COVID–19 fatigue depends on conditional and psychophysiological factors, including the individual's task, environment, physical, and mental capacity, as well as the disease's central, psychological, and peripheral aspects (Rudroff et al., 2020). These aspects have also been found in some chronic autoimmune diseases, as systemic lupus erythematosus (SLE), and anxiety, depression and fatigue are common symptoms of SLE that substantially contribute to the decreased quality of life of these patients. Figueiredo-Braga et al. 2018, found a correlation between physical markers and psychiatric health in a Portuguese systemic lupus erythematosus cohort. Regarding the variables examined in this study, fatigue (using the Chalder Fatigue Scale) was the strongest predictor of depression in SLE patients. On the other hand chronic fatigue syndrome can also have an association with neuropsychological disturbances (Komaroff and Bateman 2021).

Physiological plausibility for OSA and post-COVID-19 fatigue

SARS-CoV-2 primarily infects individuals through the respiratory epithelium by entering cells that carry the ACE-2 receptor and TMPRSS2 coreceptor in the nasal or upper respiratory epithelium (Melms et al. 2021; Shang et al. 2020; Sungnak et al. 2020; Yan et al. 2020). Other cells including neurons in the brain are also observed to be infected and may express low levels of ACE-2 or may use alternative coreceptors (Song et al. 2021).

There is a physiological plausibility for OSA being a causal factor in COVID-19 morbidity and fatigue by intermittent nocturnal hypoxemia, endothelial dysfunction, low-grade systemic inflammation, oxidative stress, microaspiration and cardiac dysfunction (Miller et al. 2021). OSAS activates the renin-angiotensin-aldosterone system (RAAS) and angiotensin-converting enzyme 2 (ACE2), which is the entry receptor for SARS-CoV-2 (Zhang et al. 2020; Maas et al. 2020).

4.2 Motivation for the present research

The motivation for this PhD thesis stems from the urgent need to understand the mechanisms underpinning **post-COVID-19 syndrome fatigue** —a condition that significantly impairs quality of life and functional independence in millions of survivors globally. Despite growing

recognition, the pathophysiology of PCSF remains poorly defined, and effective treatments are lacking.

This study seeks to investigate potential explanatory models for PCSF, particularly focusing on the role of **obstructive sleep apnea** as a modifiable contributing factor. By identifying clinical, physiological, and behavioural correlates of fatigue in post-COVID-19 individuals, we aim to contribute evidence that may inform the development of targeted, personalised interventions to mitigate long-term functional impairment.

5.
Background

This section reviews the literature on fatigue in PCSF. Four main themes are presented: (1) Prevalence and risk factors, (2) Symptomatology and impact , (3) Clinical findings and diagnostic features, and (4) Theoretical perspectives on fatigue mechanisms

5.1 Prevalence and risk factors

The presence of fatigue up to 6-7 months after acute COVID-19 has been reported as the most frequent post-COVID-19 symptom (Townsend et al. 2020) and it is similar to myalgic encephalomyelitis/chronic fatigue syndrome (Institute of Medicine of the National Academies, USA 2015), observed after other viral infections (Rasa et al. 2018). For example, studies have found rates as high as 52-77% months after acute COVID-19, with marked reductions in work capacity and daily functioning (Komaroff et al. 2021; Santos et al. 2024). The precise explanation for what causes post-viral fatigue remains uncertain. Several studies have found that more than half of patients report persistent fatigue for weeks or even months post-infection, regardless of the severity of the initial illness.

Greater risk of PCSF has been associated with female gender, high BMI, previous hospitalisation during acute infection, coexisting comorbidities like autoimmune diseases and diabetes, sleep disorders and neuropsychological conditions (Santos et al. 2024).

Factors such as dyspnoea and comorbidities (e.g., hypertension) were likely risk factors for fatigue in the short term. In contrast, psychological factors appeared to be more strongly associated with fatigue in the long term.

The determinant of post-illness fatigue in older age is inconsistent across several studies. Being over 50 years was associated with fatigue severity in some studies (Qin et al. 2022; Daugherty et al. 2021), but not in others (Karaarslan et al. 2021; Hossain et al. 2021).

Kim Poole-Wright et al. (2023) conducted a systematic review and meta-analysis of fatigue outcomes following COVID-19, which included 147 eligible records, involving 48,466

participants. The pooled prevalence was 41%, but a higher proportion of fatigue was found in studies using a valid scale. Gender was investigated by 46 studies and 30 studies reported a significant association of female gender with fatigue.

5.2 Symptomatology and impact

Fatigue in the post-COVID context is multidimensional, with patients experiencing physical, cognitive ("brain fog"), mental, and emotional exhaustion. This fatigue is often disproportionate to exertion and is not adequately relieved by rest or sleep (Thomas et al. 2024). Alongside pervasive tiredness, individuals report dyspnoea (shortness of breath), muscle weakness, sleep disturbances, cognitive dysfunction, anxiety, and depressive symptoms. The combination of fatigue with these symptoms profoundly impairs quality of life and the ability to perform daily tasks or return to work.

5.3 Clinical findings and diagnostic features: Multiple dimensions

Fatigue definitions in long COVID research reflect a complex, multi-systemic disorder:

a. Physical - Sensation of weakness, reduced muscle strength and endurance
b. Cognitive/Mental - Impaired attention, memory, processing information, and concentration
c. Emotional/Psychosocial - Feelings of frustration, low motivation, and emotional instability
d. Post-exertional Symptom Exacerbation - Worsening of symptoms after physical or mental activity

Reports on objective evaluations of these individuals with persistent post-COVID fatigue demonstrate:

a. Normal pulmonary function in most cases, despite severe subjective dyspnoea
b. Reduced peripheral and inspiratory muscle strength
c. Higher levels of anxiety and reduced quality of life

d. No consistent laboratory markers; however, some show elevated platelet counts (within normal range) and evidence of chronic low-grade inflammation

5.4 Theoretical perspectives in fatigue mechanisms

The exact causes of underlying mechanisms remain unclear, but proposed mechanisms include:

a. Persistence of SARS-CoV-2 viral RNA and proteins in several tissues, including the respiratory tract, blood, GI tract, olfactory mucosa, and the central nervous system. The mechanisms of persistence may involve replication or the action of viral replication machinery (Craddock et al. 2022) (Mohandas et al. 2023). A meta-analysis indicates that shedding of the virus (as detected by PCR) can persist for prolonged periods in a broad sample of the population recovering from SARS-CoV-2 infection (Cevik et al., 2022).
b. Chronic inflammation: Ongoing inflammation, activation of cytokines (IL-6, IL-1β, TNF-α), and neuroinflammation leading to altered energy metabolism and muscle/brain dysfunction (Russel et al. 2019) (Schultheib et al. 2022). Brain inflammation, interaction of autoantibodies with antigens on neuronal cells membrane, and cytokine expression triggering neurotransmitter dysfunction have been regarded as possible causes of depression in SLE, in rodent SLE models (Lawrence et al. 2007), and this can be similar to post-COVID-19 mental disorders.
c. Direct organ/system injury: Possible involvement of the hypothalamic–pituitary–adrenal axis, mitochondrial dysfunction, and microvascular injury (Saito et al. 2024; Hakem et al. 2023). Recent studies suggest clear and significant links between SARS-CoV-2 infection and mitochondrial dysfunction, autophagy, innate immune response and cellular metabolic function (Ward and Schlichtholz 2024).
d. Autonomic dysfunction: Disruption of the autonomic nervous system, influencing cardiovascular, gastrointestinal, and thermoregulatory responses. One of the proposed pathophysiological mechanisms is cytokine- and hypoxia-induced injury, leading to neuronal apoptosis and affecting the white matter fibre bundles, which causes impaired neurological function. Another hypothesis is that inflammation could lead to autonomic

and small fibre neuropathies, as previously observed in viral infections caused by herpes simplex and infectious mononucleosis (Haloot et al. 2023).

e. Sleep and mental disorders: Sleep apnoea, anxiety, and depression can both cause and worsen fatigue. These disorders are the main themes to be developed by this thesis.

6.
Open questions regarding post COVID-19 fatigue

6.1 Gaps in current literature on the long-term effects of COVID-19 on mental health

Despite a growing body of research about COVID-19 and its aftermath, significant knowledge gaps remain regarding its long-term mental health effects.

Lack of Standardized Definitions and Characterization

The definition of "long COVID" is still evolving and sometimes is unclear, especially regarding its neuropsychiatric and psychological manifestations. This hinders consistent identification and comparison of cases across studies, making it challenging to understand the full spectrum of persistent symptoms, such as anxiety, depression, PTSD, and fatigue.

There is also variation and inconsistency in the reported duration, frequency, and severity of persistent symptoms, which limits the generalizability of findings.

Limited Objective, Longitudinal Data

Much of the existing research relies on self-reported symptoms collected through questionnaires (often administered remotely during pandemic restrictions), which may lack objectivity and be vulnerable to recall bias. There is a notable absence of baseline (pre-COVID) assessments in most studies. Without these data, it is difficult to distinguish which mental health symptoms are new since infection and which may have been pre-existing. Longitudinal studies following patients beyond the acute and subacute stages, particularly across multiple years, are sparse, resulting in limited understanding of the chronicity and resolution of mental health impacts.

Insufficient Exploration of Correlation and Causation

While associations between mental health symptoms (depression, anxiety, PTSD) and fatigue in post-COVID patients are commonly reported, the causal relationships, mediating factors, and potential bidirectional effects remain largely unexplored. Specific risk factors, such as demographic or disease severity variables, also need more precise delineation. Studies often amalgamate self-reported mental symptoms but rarely dissect the interrelationships among various conditions.

6.2 Measurement and research gaps

Measurement Challenges

Definitions and measurement tools for post-COVID fatigue are inconsistent. Most studies rely on self-reported questionnaires, and use dyspnoea rather than fatigue scales (mMRC, Borg). Only a few fatigue scales incorporate objective fatigability (measured decline in performance).

Need for Consensus

The lack of standardization in both fatigue conceptualization and measurement hinders progression in understanding and managing the condition. A holistic, multidimensional approach that captures all facets of fatigue is recommended for future research and clinical assessment.

7.

Aims

The main aim of this project is to identify possible etiological factors for PCSF. For this purpose, we use different approaches with the same methodologies – particularly related to the classification and quantification of PCSF, within the same time frame of clinical assessments and the same tools for self-reported symptoms.

Aim 1

To describe a Multidisciplinary Protocol to assess post-COVID-19 Fatigue and Mental Disorders

Aim 2

To quantify the prevalence and severity of physical and psychological fatigue in long COVID and examine their correlation with mental health disorders, including depression, anxiety, and PTSD

Aim 3

To explore the association between fatigue subtypes, neuropsychiatric symptoms, and health-related quality of life (HRQoL) in individuals with post-COVID-19 condition, stratified by acute disease

Aim 4

To determine the prevalence of newly diagnosed OSA in adults with long COVID, evaluate its association with persistent symptoms (particularly fatigue) and COVID-19 acute severity, and investigate gender-specific clinical patterns

Aim 1:

To describe a Multidisciplinary Protocol to assess post-COVID-19 Fatigue and Mental Disorders

8.

Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicentre Observational Study

Pires L, Reis C, Mesquita Facão AR, Moniri A, Marreiros A, Drummond M, Berger-Estilita J. Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study. JMIR Res Protoc. **2024** Jan 19;13:e51820. doi: 10.2196/51820.

This first paper describes a protocol for post-COVID-19 mental disorders and fatigue. This protocol was crucial due to several key reasons, all rooted in the current gaps in knowledge and the significant impact these conditions have on individuals' health and quality of life.

8.1 Persistent and Complex Symptomatology in post-COVID-19

Long-Lasting Symptoms

Many individuals experience persistent symptoms after recovering from the acute phase of COVID-19, with fatigue (both physical and psychological), anxiety, depression, and PTSD frequently reported. These symptoms can last for months, significantly reducing quality of life and daily functioning.

Symptom Overlap

Fatigue is not only a physical issue but also deeply connected to a range of mental health disorders. The overlapping and interconnected nature of these symptoms requires a systematic approach to accurately define, detect, and treat them.

8.2 Knowledge Gaps and Methodological Limitations

Lack of Standardisation

Current literature is limited by varying definitions, inconsistent data collection methods, and subjective (often self-reported) measures. A protocol establishes clear, standardized criteria for identifying and measuring post-COVID conditions, improving comparability and reliability of findings.

Need for Longitudinal, Objective Data

Most studies lack pre-infection baselines or do not follow patients for a sufficient period. A protocol guides a structured, prospective approach to observe patients over time, offering objective insights into the evolution of symptoms and risk factors.

8.3 Clarifying Associations and Causal Links

Understanding Correlations

There is a significant need to clarify how mental health issues such as depression, anxiety, and PTSD relate to the experience of fatigue in post-COVID patients. A research protocol enables systematic evaluation of these associations, identifying at-risk groups and informing targeted interventions.

Guiding Integrated Care

By exploring the interrelationship between mental health symptoms and physical fatigue, protocols can advance integrated care models—ensuring that both aspects are addressed in patient management.

8.4. Addressing Ethical and Methodological Rigor

Standardised Assessment Tools

Using validated scales (like the Chalder Fatigue Scale, Hospital Anxiety and Depression Scale, and EQ-5D) ensures robust, reproducible, and ethically sound research, leading to more substantial evidence for future care guidelines.

Ethical Oversight

Clearly defined protocols include ethical considerations and patient protections, which are critical in studying vulnerable populations.

8.5 Contribution to Public Health and Scientific Literature

Filling Research Gaps

Protocol-driven studies directly address the lack of systematic, reliable data on long-term mental health and fatigue outcomes in post-COVID patients—crucial as the pandemic moves into its chronic phase.

Global Relevance

The findings can inform public health strategies worldwide, preparing healthcare systems for the continuing challenges of long COVID.

8.6 Summary

In essence, a protocol is necessary to produce high-quality, systematic evidence about the prevalence, severity, and relationship of post-COVID fatigue and mental disorders. This evidence enforms the foundation for integrated care, policymaking, resource allocation, and ultimately, better patient outcomes in the ongoing global response to the long-term effects of COVID-19.

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Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study

Ligia Pires[1]; Cláudia Reis[2]; Ana Rita Mesquita Facão[2]; Armin Moniri[3, 4, 5, 6]; Ana Marreiros[4]; Marta Drummond[7]; Joana Berger-Estilita[8, 9, 10]

Abstract

Background:
The aftermath of the COVID-19 pandemic continues to affect millions worldwide, resulting in persisting postvirus complaints and impacting peoples' quality of life. Long COVID, characterized by lingering symptoms like fatigue and mental illness, can extend beyond a few months, necessitating further research to understand its implications.

Objective:
This study aims to quantify the degree of physical and psychological fatigue in patients following COVID-19 infection and examine its correlation with mental health disorders.

Protocol

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Abstract

Background: The aftermath of the COVID-19 pandemic continues to affect millions worldwide, resulting in persisting postvirus complaints and impacting peoples' quality of life. Long COVID, characterized by lingering symptoms like fatigue and mental illness, can extend beyond a few months, necessitating further research to understand its implications.

Objective: This study aims to quantify the degree of physical and psychological fatigue in patients following COVID-19 infection and examine its correlation with mental health disorders.

Methods: Using a consecutive nonrandom sampling technique, we will conduct a prospective cohort multicenter observational study in 5 Portuguese hospitals. Symptomatic adult patients with previous COVID-19 attending follow-up consultations will be enrolled. We will include patients who had mild, moderate, and severe acute disease. We will assess clinical outcomes related to COVID-19, including the type of respiratory support such as high-flow nasal cannula, noninvasive ventilation, and invasive mechanical ventilation. The exclusion criteria will include previous severe psychiatric disorders confirmed by a psychiatrist; refusal or inability to respond to the questionnaire; concomitant neurological disorder; persistent fatigue symptoms during the 6 months before infection; and the need for invasive mechanical ventilation during COVID-19 infection due to a high prevalence of postintensive care syndrome. Our primary outcome is the prevalence of fatigue in patients with post–COVID-19 depression and/or anxiety, as measured by the Chalder Fatigue Scale (CFQ-11) and the Hospital Anxiety and Depression Scale (HADS). The secondary outcomes will include an assessment of health-related quality of life via the EQ-5D questionnaire and an exploration of the prevalence of symptoms of posttraumatic stress disorder (PTSD) using the 14-item Posttraumatic Stress Scale (PTSS-14). We will also examine the association between mental health symptoms and the severity of acute COVID-19. The post–COVID-19 data will be collected at least 6 months after the positive test and no longer than 9 months during the clinical appointment.

Results: We expect our multicenter study on patients post COVID-19 to reveal a significant link between mental illness symptoms and both physical and psychological fatigue. Patients with heightened depression and anxiety may report increased levels of

fatigue. Additionally, we expect to find persistent PTSD symptoms in a subset of participants, indicating the enduring psychological impact of the virus.

Conclusions: This study may underscore the need for integrated care addressing physical and mental health in patients post COVID-19. The observed connections emphasize the importance of considering mental well-being for long-term health outcomes. Despite study limitations, our findings contribute valuable insights for future treatment strategies and highlight the necessity for comprehensive mental health support in post–COVID-19 care. This research provides valuable insights into the mental health implications of COVID-19 and its impact on post–COVID-19 fatigue and the overall well-being of affected individuals.

Trial Registration: ClinicalTrials.gov NCT05323318; https://clinicaltrials.gov/study/NCT05323318

International Registered Report Identifier (IRRID): DERR1-10.2196/51820

(JMIR Res Protoc 2024;13:e51820) doi: 10.2196/51820

KEYWORDS

SARS-CoV-2; coronavirus; COVID; long COVID; fatigue; tired; tiredness; anxiety; depression; PTSD; stress; quality of life; mental health; post-COVID-condition; neuropsychological; neuropsychology; psychological; long COVID-19; COVID-19; myalgia; correlation; impairment

Introduction

Despite the World Health Organization (WHO) declaration marking the end of the COVID-19 pandemic on May 5, 2023 [1], millions of people continue to have postvirus complaints. Moreover, the virus remains endemic in many parts of the world. Confirmed COVID-19 cases have exceeded 430 million globally, with 200 million in Europe alone [2]. The causative agent of COVID-19 is the novel SARS-CoV-2 [3]. Although, as the name implies, respiratory symptoms are acute, the term long COVID (or post-COVID syndrome or long-haul COVID-19) began gaining recognition in the scientific and medical communities after the first descriptions of long-lasting symptoms related to mental health, such as anxiety or stress after the first infection [4]. While the definition of long COVID is unclear, the most frequent symptoms are fatigue and dyspnea [5,6]. Other less typical symptoms include cognitive and mental disorders, headache, myalgia, chest and joint pain, smell and taste dysfunction, cough, hair loss, insomnia, wheezing, rhinorrhea, sputum, and cardiac and gastrointestinal issues [4]. These symptoms may persist for up to 6 months after hospital discharge, severely impacting patients' quality of life [7]. Since July 2021, long COVID is considered a disability under the *Americans With Disabilities* Act [8].

Per its definition, long COVID appears within 3 months after the onset of COVID-19, with symptoms lasting for at least 2 months that an alternative diagnosis [9] cannot explain, including, myalgic encephalomyelitis and chronic fatigue syndrome. However, studies have reported different persistent symptoms in contrasting durations and frequencies among survivors of long COVID [10,11]. Long COVID appears like other postviral syndromes observed in other coronavirus diseases. For example, symptoms of fatigue, myalgia, and psychiatric impairments have affected survivors of Middle East respiratory syndrome (MERS) and those with severe acute respiratory syndrome (SARS) for up to 4 years [10,12,13]. Even at 7-year and 15-year follow-ups, pulmonary and bone radiological complications were evident among a proportion of survivors of SARS who were predominantly younger than 40 years [10,14,15]. This is unsettling, as it implies that long COVID may extend beyond just a few months.

Fatigue, a primary persistent symptom of long COVID, has been reported in 10% to 70% of patients [16-19]. It is defined as "a decrease in physical or mental performance that results from changes in central, psychological, or peripheral factors due to the COVID-19 disease" [20]. Thus, post–COVID-19 fatigue depends on conditional and psychophysiological factors comprising the individual's task, environment, physical, and mental capacity, as well as the disease's central, psychological, and peripheral aspects [20].

While fatigue is not traditionally considered a neuropsychiatric disorder, it can be a symptom of many mental health conditions, such as depression, anxiety, and posttraumatic stress disorder (PTSD) [21,22]. Therefore, it is often included in discussions of mental health symptoms in post–COVID-19 syndrome [23]. The term "neuropsychiatric" often refers to a wide range of disorders affecting the brain and mental health. In contrast, "neuropsychological" refers to studying the relationship between brain function and behavior [24]. The primary focus of this study is on psychiatric symptoms, particularly depression and anxiety. However, we will also investigate PTSD, which is a neuropsychiatric disorder involving both neurological and psychiatric aspects. In addition, the health-related quality of life (HRQoL) assessment includes a section that evaluates aspects related to anxiety and depression. While not designed for diagnosing psychiatric disorders, this assessment can help gauge how these symptoms affect a person's overall quality of life, making it more of a general health assessment.

The current literature on long COVID and its mental sequelae has relied on self-reported symptoms through questionnaires administered either in-person or through telephone interviews to comply with public health guidelines. However, the correlation between these self-reported symptoms needs to be clarified. There is an obvious need to accurately characterize the mental sequelae of COVID-19 and the risk factors associated with these outcomes.

This study aims to quantify the degree of physical and psychological fatigue in patients post COVID-19 and assess the correlation of fatigue with other mental sequelae—particularly depression, anxiety, and PTSD. Furthermore, we aim to explore its impact on HRQoL.

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Conclusions: This study may underscore the need for integrated care addressing physical and mental health in patients post COVID-19. The observed connections emphasize the importance of considering mental well-being for long-term health outcomes. Despite study limitations, our findings contribute valuable insights for future treatment strategies and highlight the necessity for comprehensive mental health support in post–COVID-19 care. This research provides valuable insights into the mental health implications of COVID-19 and its impact on post–COVID-19 fatigue and the overall well-being of affected individuals.

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This study aims to quantify the degree of physical and psychological fatigue in patients post COVID-19 and assess the correlation of fatigue with other mental sequelae—particularly depression, anxiety, and PTSD. Furthermore, we aim to explore its impact on HRQoL.

Our research questions for this study are outlined in Textbox 1.

Textbox 1. Research questions of the study.

Research Question 1 (primary outcome):

- Do patients with long COVID who experience depression and/or anxiety symptoms have a higher prevalence of fatigue?

Research questions 2 to 4 (secondary outcomes):

- Is there a correlation between the type of fatigue and depression and/or anxiety symptoms among patients post COVID-19?
- Is there a correlation between fatigue and the presence of PTSD symptoms in patients post COVID-19?
- Do patients with fatigue associated with mental health disorders have a lower health-related quality of life (HRQoL) after COVID-19?

Methods

Overview

This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [25]. This research is designed as an observational prospective cohort study.

Recruitment

Our study will be conducted in 1 private and 4 public Portuguese hospitals that have established follow-up post–COVID-19 medical consultations. Patients who meet the eligibility criteria will be invited to participate in the study at the end of their appointments in the follow-up clinics. This study will be conducted using a consecutive, nonrandom sampling technique.

Inclusion Criteria

Patients who cumulatively meet the following criteria will be eligible for inclusion: (1) ≥18 years; (2) previous case of COVID-19 at least 6 months after the diagnosis that is duly documented in the clinical record; (3) persistent symptoms after COVID-19 recovery, as defined by the WHO [9]; and (4) SARS-CoV-2 RNA confirmed by a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab or SARS-CoV-2 antigen confirmed with a nasopharyngeal swab by a health care professional within 7 days of initial symptoms.

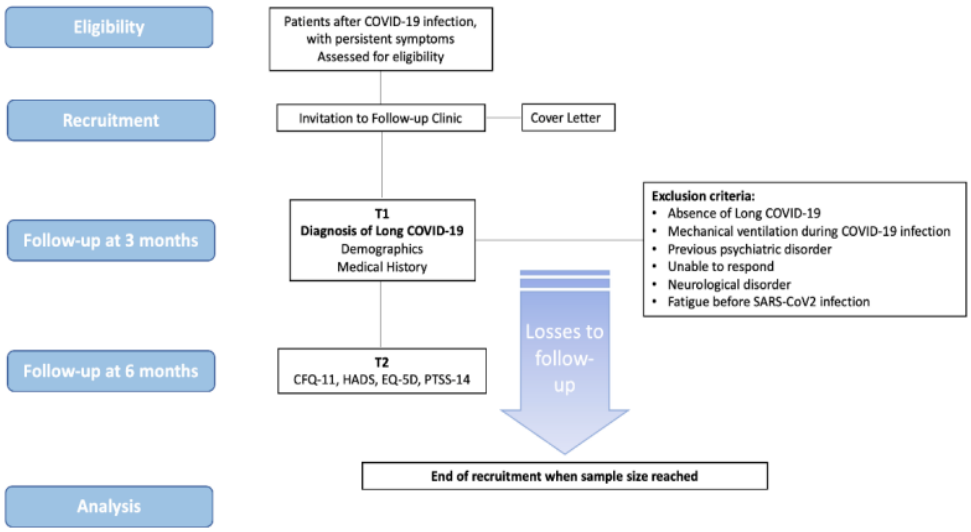
We will implement multiple measures to exclude the possibility of second infections and ensure that the individuals included have persistent symptoms following their initial COVID-19 recovery. Our inclusion criteria stipulate that individuals must have a positive test result for SARS-CoV-2 RNA or antigen within 7 days after their initial infection. Additionally, we will conduct thorough reviews of medical records and clinical assessments to assess symptom presentation and timing, differentiating between persistent cases and new infections. In cases of uncertainty or potential overlap with new infections, we are prepared to conduct repeat testing, which may include RT-PCR and genomic sequencing for accurate classification.

Exclusion Criteria

Patients who meet the following criteria will be excluded from participation: (1) preexisting psychiatric disorders diagnosed by a psychiatrist before contracting COVID-19; (2) inability to respond to the questionnaire; (3) concurrent neurological disorders, such as stroke with sequelae, Alzheimer disease, and Parkinson disease; (4) individuals subjected to invasive mechanical ventilation during their COVID-19 infection; or (5) those experiencing persistent fatigue symptoms within the 6 months before SARS-CoV 2 infection.

The study design and inclusion criteria will be reviewed regularly to ensure they align with current best practices and the latest understanding of COVID-19. A patient enrollment flowchart is presented in Figure 1.

Figure 1. Study flowchart. CFQ-11: Chalder Fatigue Scale; HADS: Hospital Anxiety and Depression Scale; PTSS-14: 14-item Posttraumatic Stress Scale.



Data Collection

Data collection will take place during appointments at the long COVID follow-up clinics in all participating hospitals. Qualified clinical study staff will gather the data using a clinical research form (CRF) (Multimedia Appendix 1). These individuals comprise health care professionals, such as nurses, clinical research coordinators, and health care experts who have received appropriate training and have the necessary expertise to conduct data collection and assessments in a clinical research setting. Their training ensures adherence to research protocols and ethical guidelines, guaranteeing accurate and consistent data gathering during clinical appointments. Two months after hospital discharge, we will mail all patients a letter offering a follow-up consultation in the outpatient clinic. Patients who agree to attend will be offered 2 appointments, consisting of an anamnesis and a physical examination, and given several self-administered tests in the waiting room. We will allocate 15 minutes for the questionnaire completion in the waiting room. In the first visit (T1, 3 months), the following data will be additionally collected: demographic characteristics like age, sex, and BMI (kg/m^2); each participant's medical history, such as the date of the first positive COVID-19 test (PCR or antigen) and smoking, alcohol, and drug consumption status; comorbidities and usual medication intake; and screening of symptoms and severity of the acute disease. Data collection in the second visit (T2, 6 months) will include post–COVID-19 symptoms, the Chalder Fatigue Scale [26] (CFQ-11), the Hospital Anxiety and Depression Scale (HADS) [27], the 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID-19, and the EQ-5D [28] questionnaire.

Ethical Considerations

This study involves human participants and has adhered to all applicable ethical standards and procedures. The Algarve University Hospital Centre Ethical Committee approved this study (141/21; Multimedia Appendix 2). The patients' race will not be included in the study because the ethics committee did not approve this differentiation. A paper-based consent form was previously approved by the ethics committee. This consent form has 2 components: information for the participant (regarding the project) and declaration of informed consent (to date and sign, in case of acceptance). The informed consent procedure, mailed to potential participants, will provide them with detailed information about the study's objectives, risks and benefits of participation, and data management practices (Multimedia Appendix 3). The study will follow ethical guidelines and regulations related to informed consent, and participants will have the opportunity to ask questions and provide voluntary consent before enrolling. Participants will be given a month for reflection before written informed consent. As for data management, the study will implement a secure and confidential system that uses data encryption and secure storage procedures to protect participant confidentiality and comply with data protection laws and regulations. Only authorized individuals who have a legitimate need to access the data will be permitted to do so, and any data sharing will be done in compliance with the relevant ethical and legal requirements. As applicable, all procedures from this investigation followed the Declaration of Helsinki. All researchers will comply with the Data Protection Acts of their respective academic institutions.

Primary Outcome

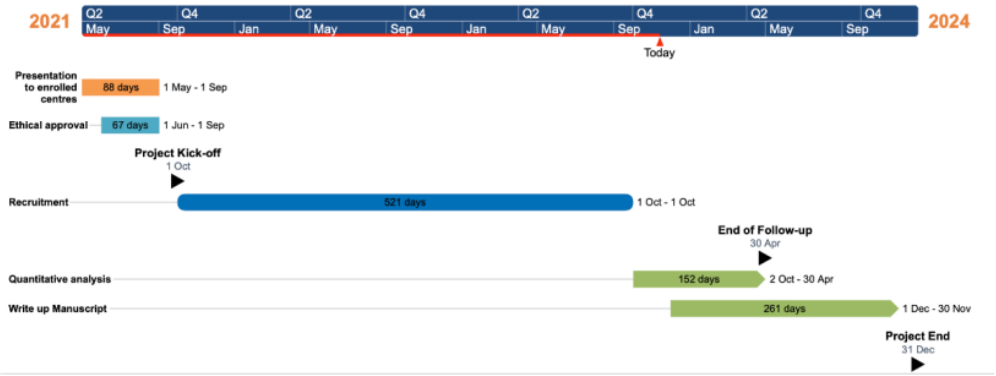
Fatigue

A validated fatigue assessment tool will be used at the follow-up visit to capture a broader range of participants. This will provide a more comprehensive understanding of the relationship between fatigue and mental symptoms in individuals with long COVID. Fatigue will be measured using the CFQ-11 [26]. This is an

in June 2022 at Faro Hospital and São Sebastião Hospital, and in October 2022 at Fernando Fonseca Hospital. The deadline for the end of the recruitment period in all centers was December 2023. The preliminary study results will be published in a peer-reviewed international medical journal after October 2023.

The study timeline is shown in Figure 2. This study is included as part of the first author's (LP) PhD thesis. The initial study results were presented at the PhD interview in November 2023. We aim to publish the study in an indexed scientific journal and present the results at national and international congresses.

Figure 2. Study timeline.



We plan to enroll 250 participants, including 100 with adverse mental health symptoms and 100 without, to explore the intricate relationship between adverse mental health symptoms and both physical and psychological fatigue in individuals recovering from long COVID. Preliminary analyses indicate a compelling connection, wherein patients who report heightened levels of depression and anxiety also tend to experience increased fatigue. These findings underscore the importance of considering mental health as a pivotal factor in understanding the enduring impact of COVID-19 beyond the acute phase. In addition to depression and anxiety, our study explores the persistence of PTSD symptoms in a subset of participants. Initial results suggest that, even after recovery from the acute phase of the infection, a proportion of individuals continue to grapple with the psychological repercussions of the virus. This observation aligns with emerging evidence suggesting a prolonged psychological impact of COVID-19, emphasizing the need for comprehensive mental health support for patients after contracting COVID-19. The identified links between mental health symptoms and fatigue have broad implications for the holistic care of this patient population. Understanding these connections can guide targeted interventions, emphasizing the importance of addressing mental well-being alongside physical recovery. As we delve deeper into the data and conduct further analyses, a more nuanced understanding of these relationships will emerge, informing future health care strategies and interventions.

Discussion

Expected Findings

As the COVID-19 pandemic ceases, more patients enter the chronic phase of the disease. Identifying groups at high risk of cognitive and psychiatric dysfunction may allow for targeted intervention to effectively meet their physical, neurological, and psychological health care needs. Our study, conducted in the aftermath of the COVID-19 pandemic, provides a unique opportunity to investigate the persisting health effects of the virus on those who have recovered from the acute phase of the disease. We specifically aim to explore post–COVID-19 fatigue and mental health disorders using specific tools to separate physical and psychological fatigue symptoms. We also use a prospective cohort multicenter study design, which is less prone to bias, and we aim to include both hospitalized and nonhospitalized patients, covering all degrees of acute COVID-19 severity. We anticipate that our research will reveal a significant association between the presence and severity of mental health symptoms, including depression, anxiety, and PTSD, and the degree of physical and psychological fatigue in patients following COVID-19. We expect to observe that patients experiencing more pronounced mental symptoms will report higher levels of physical and psychological fatigue.

The potential links between mental symptoms and fatigue suggest a connection between the mental well-being of patients post COVID-19 and their experience of fatigue, encompassing both physical and psychological dimensions. The existing research has indicated a high prevalence of anxiety and depression symptoms among patients hospitalized with COVID-19 infection, with a quarter of patients experiencing at least mild symptoms of acute stress disorder [42]. Moreover, a study conducted in Iran after the outbreak of COVID-19 found a correlation between the prevalence of chronic fatigue syndrome and PTSD [45]. The study reported that 5.8% of subjects experienced PTSD symptoms 6 months after the onset of SARS-CoV-2 infection. Interestingly, the study also noted that female sex was associated with a higher risk of fatigue. At the same time, variables such as oxygen saturation at admission, primary symptoms, ICU admission, and laboratory test parameters did not show a significant association with fatigue occurrence.

Based on these findings, we anticipate that patients post COVID-19 may exhibit more pronounced symptoms of

Textbox 2. The 5 phases of the statistical analyses carried out in this study.

- Phase 1: Characterization of the patient sample
  - 1.1. Sociodemographic analysis of the variables collected at T1 and the variables from the surveyed instruments at T2. This involves descriptive analysis, both univariate and bivariate, which will be differentiated by:
    - 1.1.1. Quantitative variables: mean and SD, coefficient of variation, and median and IQR
    - 1.1.2. Qualitative variables (nominal and ordinal categorical): analysis of distributions through absolute and relative frequencies, including absolute and relative accumulated frequencies
    - 1.1.3. Quantitative variables will be reported alongside appropriate tests for normal distribution to ensure the accuracy and validity of our statistical analyses.
  - 1.2. Bivariate and descriptive analysis using 2D tables will be calculated for all qualitative variables belonging to T1 with all instrument scores collected at T2: Chalder Fatigue Scale (CFQ-11), Hospital Anxiety and Depression Scale (HADS), 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID -19, and EQ- 5D plus recorded COVID-19 symptoms. The previous points will be reiterated in this bivariate context, utilizing the computational aid of split->file categorical variables in situations where one variable is metric and the other is categorical.
  - 1.3. Internal consistency and reliability analysis of the T2 instruments: calculation of the Cronbach alpha (general and partial) for all ordinal items and item subgroups differentiated by the subscales defined by the respective authors
- Phase 2: Determination of fatigue incidence caused by long COVID and its relationship with T1 and T2 variables
  - 2.1. Procedures for determining fatigue cutoff points in this cohort of patients:
    - 2.1.1. Bivariate analysis using optimal binning procedures for categorical variables (age class, sex, and BMI) with the total fatigue score, as well as partial scores of physical and psychological fatigue
    - 2.1.2. Multivariate analysis by constructing models in the format of decision trees via the CHAID (chi-square automatic interaction detection) algorithm [41], with total and partial fatigue scores as dependent variables
  - 2.2. Inferential analysis based on variables resulting from 2.1.1 and/or 2.1.2, considering the complexity of variables in T1 and T2:
    - 2.2.1. (1) Chi-Square tests to capture the association of categorical variables; (2) Shapiro-Wilk tests to verify the distribution of quantitative variables; (3) tests for comparing 2 or more population means: parametric analysis of variance (ANOVA) test and nonparametric (Kruskal-Wallis) test; and (4) correlation tests (Spearman or Pearson) to verify the degree of association between T2 instrument scales
- Phase 3: Determination of patient groups based on fatigue differentiation
  - 3.1. Conducting classification analysis using clustering techniques, specifically the 2-step cluster analysis, to explore variables with greater power in differentiating groups of patients
- Phase 4: Exploration of the best combination of T1 and T2 variables capable of discriminating patient fatigue levels through a discriminant multivariate analysis
- Phase 5: Investigation of the association between phase 3 groups and all T2 instrument scales using chi-square association tests

Power and Sample Size

We plan to conduct a prospective multicentric observational study to investigate the prevalence and severity of mental illness symptoms and fatigue in individuals with long COVID. Based on previous studies and expert opinion, we expect the prevalence of fatigue and mental symptoms in this population to be around 50% [42,43]. We aim to detect a minimum effect size of 0.2 with a power of 80% and a significance level of P=.05.

Using these assumptions, we performed a sample size power analysis using a 2-sample t test. We found that a total sample size of 200 participants (100 with adverse mental health symptoms and 100 without) would be required to detect the minimum effect size of 0.2 with 80% power and a significance level of P=.05. The required sample size was calculated using an a priori power analysis with an online calculator [44]. To compensate for a projected 25% loss to follow-up, we aimed for 250 participants.

We plan to recruit participants from multiple hospitals and primary care centers across Portugal, focusing on individuals who have been diagnosed with long COVID and are experiencing mental illness symptoms and/or fatigue. Recruitment will be closely monitored throughout the study to assess the pace at which participants are enrolled. The need for sample size adjustment will be determined based on the observed recruitment rates and the accumulating data. We plan to conduct an interim analysis after the recruitment of the first 100 patients.

Results

This study received no specific grant from any funding agency in public, commercial, or not-for-profit sectors. Recruitment began in October 2021 at Portimão Hospital and Alvor Hospital,

depression and anxiety and heightened levels of physical and psychological fatigue. This insight emphasizes the importance of considering mental health as a crucial factor in understanding the long-term effects of COVID-19. It underscores that the impact of the virus extends beyond the acute illness phase and can manifest in persistent mental symptoms that influence patients' overall well-being. Moreover, it can imply that addressing anxiety symptoms in post–COVID-19 care may have a positive impact on reducing fatigue and improving patients' quality of life. We also aim to explore the prevalence and severity of PTSD symptoms in a subset of patients following COVID-19. While this is not the primary focus of our research, assessing the presence of PTSD symptoms in this study population allows for a better characterization of the patient group. Some participants continue to experience PTSD symptoms following COVID-19 infection, suggesting that the psychological impact of the virus can be long-lasting. These findings may shed light on the need for comprehensive mental health support for patients post COVID-19.

The implications of our potential findings are widespread. They underscore the importance of integrated care for patients post COVID-19 that addresses both physical and mental health aspects. Clinicians and health care providers will then be aware of the potential for persistent mental symptoms and their impact on patients' fatigue levels and overall HRQoL.

Limitations

Our study's limitations include the possibility of sampling bias, as individuals with more severe symptoms of fatigue or other mental health symptoms may be less likely to participate. This possibility could result in underrepresentation and bias within the study's findings. To minimize this, we will use diverse recruitment methods across multiple sites and collect data on participants' reasons for declining participation. We will also provide detailed information about the study and its potential benefits to participants while ensuring an ethical and respectful recruitment process sensitive to participants' health concerns and symptoms.

We also acknowledge the limitations related to our exclusion criteria and use of the CFQ-11, which has yet to undergo specific validation for patients with COVID-19. This recognition underscores the importance of future research endeavors to validate the applicability of the CFQ-11 within this patient population, despite its utilization in prior studies [46-48].

While there are valid concerns regarding the exclusion criteria and assessment of psychiatric disorders in our study—including the fact that assessing preexisting fatigue may be difficult—we have devised a plan to mitigate these concerns. We intend to meticulously collect detailed medical histories and review the medical records of all enrolled patients to ensure the precise application of the exclusion criteria. However, a notable limitation of our study arises from the absence of a baseline assessment conducted before the onset of COVID-19 infection. This absence impedes our ability to comprehensively evaluate the influence of COVID-19 on various health parameters, such as fatigue and mental health. The absence of a baseline assessment may also limit our capacity to distinguish between preexisting conditions and post–COVID-19 effects, which is a key consideration in understanding the full spectrum of the virus's impact on individuals. Additionally, while we acknowledge that the measurements used in the study are based on self-report—and therefore subjective—we emphasize that self-reported questionnaires are commonly used in scientific studies. These questionnaires hold significance in assessing the extent of physical and psychological fatigue in patients following COVID-19. Despite these limitations, our study is poised to make a significant contribution to the existing literature by shedding light on the impact of COVID-19 on mental health. This research has the potential to guide future treatment and management strategies, serving as a valuable resource for the health care community.

Conclusion

This study protocol outlines a critical investigation into the lingering physical and psychological effects of long COVID. It emphasizes the importance of understanding the ongoing health challenges individuals face even after recovering from the acute phase of the virus. This study's research questions focus on assessing the potential correlations of mental illness symptoms (ie, physical and psychological fatigue) among patients post COVID-19.

In the aftermath of a global pandemic, this research is timely and crucial. It has the potential to inform health care strategies and interventions that provide targeted and holistic care to individuals grappling with long COVID. Ultimately, this study aims to improve patient outcomes, enhance the quality of life for those affected, and contribute to broader efforts to address the multifaceted health implications of this unprecedented global crisis.

Authors' Contributions

LP conceptualized the study, wrote the first draft of the protocol, and planned the study. CR and RF helped write the first draft of the protocol. AB gave critical input throughout the study.
JB-E wrote the first draft of the protocol and gave critical input throughout the study. AM was responsible for the statistical planning and methodology. MD planned the study. All authors contributed to the manuscript and approved the submitted version. No generative artificial intelligence (AI) was used in any portion of the manuscript writing.

Conflicts of Interest

JB-E is an associate editor for BioMed Central (BMC) Medical Education and has received travel expenses from Medtronic for the "Save the Brain Initiative" training. The remaining authors have no conflicts of interest to disclose.

Multimedia Appendix 1

Study clinical research form (CRF).
[PDF File (Adobe PDF File), 1865 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Ethical approval.
[PDF File (Adobe PDF File), 126 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Informed consent form.
[PDF File (Adobe PDF File), 119 KB-Multimedia Appendix 3]

Multimedia Appendix 4

SPIRIT checklist.
[PDF File (Adobe PDF File), 75 KB-Multimedia Appendix 4]

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Abbreviations

CFQ-11: Chalder Fatigue Scale
CRF: clinical research form
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EQ-VAS: EuroQol Visual Analog Scale
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
ICU: intensive care unit
MERS: Middle East respiratory syndrome
PTSD: posttraumatic stress disorder
PTSS-14: 14-item Posttraumatic Stress Scale
RT-PCR: reverse-transcription polymerase chain reaction
SARS: severe acute respiratory syndrome
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Aim 2: To quantify the prevalence and severity of physical and psychological fatigue in long COVID and examine their correlation with mental health disorders, including depression, anxiety, and PTSD

Aim 3: To explore the association between fatigue subtypes, neuropsychiatric symptoms, and health-related quality of life (HRQoL) in individuals with post-COVID-19 condition, stratified by acute disease

9.

Association of Acute COVID-19 severity and Long COVID Fatigue and Quality of Life: Prospective Cohort Multicenter Observational Study

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2025

This paper presents a multicentre, prospective cohort study investigating the interrelationship between fatigue, depression, anxiety, and health-related quality of life (HRQoL) in patients suffering from long COVID. The research focuses on individuals who have continued to experience persistent symptoms for at least six months after their initial COVID-19 diagnosis, examining both the prevalence and associations of these symptoms, as well as how the severity of the original infection influences them.

9.1 Advances in Understanding Long COVID ‘s Complex Sequelae

This paper offers a comprehensive analysis of the interplay between fatigue, depression, anxiety, and quality of life in patients suffering from long COVID. It clarifies that long COVID is not a uniform condition, but one characterized by significant individual variability in symptoms and their persistence. Fatigue emerges as one of the most prevalent and debilitating manifestations, often accompanied by neuropsychiatric symptoms. The finding that fatigue and mental health disturbances are strongly related provides critical insight into the multifactorial

and interconnected nature of long COVID, advancing the field's understanding of the syndrome as more than just a collection of physical complaints.

9.2 Disease Severity Existing Assumptions Challenges

A particularly important contribution is the unexpected observation that patients who had mild or moderate acute COVID-19 can face more pronounced long-term fatigue and mental health burdens than those who experienced severe acute disease. This challenges the conventional wisdom that more severe initial illness predicts worse long-term outcomes. It suggests the need for vigilance and support for all COVID-19 survivors—not just those with severe acute illness—thereby reshaping strategies for post-acute follow-up and resource allocation.

9.3 Illuminates Pathways and Associations for Symptom Development

The study provides robust evidence that physical fatigue is more strongly associated with depression and anxiety than mental fatigue, and that anxiety and depression are directly linked to decreases in health-related quality of life. It also highlights possible cyclical relationships: for example, worsening fatigue may aggravate depression, which in turn can further fuel fatigue, creating a self-perpetuating cycle. By distinguishing between physical and mental fatigue, the paper contributes greater granularity and nuance to clinical and research discussions, paving the way for more tailored therapeutic interventions.

9.4 Impacts Clinical Practice and Follow-Up Care

Clinicians gain actionable evidence that long-term impairment and poor quality of life post-COVID are not exclusive to those with severe acute illness, and that comprehensive assessment - including mental health screening - is warranted in all patients presenting with prolonged symptoms. The suggested links between persistent physical symptoms and psychological sequelae advocate for multidisciplinary management addressing both physical and mental health in long COVID patients.

9.5 Informs Future Research and Health Policy

The paper identifies important directions for future investigation, such as clarifying the causal relationships between physical and mental health outcomes, evaluating the effect of early intervention, and better defining heterogeneous symptom trajectories. By conducting a multicentre study in both public and private hospitals and using validated tools, this research establishes a robust methodological standard and underscores the importance of population diversity in long COVID studies. It also highlights the need for improved measurement tools and the inclusion of objective clinical markers in future research.

9.6 Summary

In essence, the significance of this paper lies in its multidimensional characterization of long COVID, its challenge to preexisting clinical assumptions, its demonstration of the intertwined nature of fatigue and neuropsychiatric sequelae, and it's clear implications for follow-up care. It represents a significant step toward more effective, personalized, and inclusive post-COVID patient management, shaping the research agenda for understanding and addressing the lasting impact of COVID-19.

Observational Study

Medicine

OPEN

Association of acute COVID-19 severity and long COVID fatigue and quality of life

Prospective cohort multicenter observational study

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Abstract

Long COVID, or post-COVID-19 condition, is characterized by symptoms persisting beyond 12 weeks after severe acute respiratory syndrome coronavirus 2 infection, affecting individuals regardless of acute disease severity. Fatigue – often linked with depression and anxiety – is among its most debilitating manifestations. However, the associations between fatigue subtypes (physical vs mental), mental health symptoms, and acute disease severity on long-term health-related quality of life (HRQoL) remain unclear. This study examines the relationships between long COVID fatigue, depression, anxiety, acute disease severity, and HRQoL in a post-COVID-19 cohort. This prospective observational cohort study was conducted across 5 Portuguese hospitals between November 2020 and June 2022. Adults (≥18 years) with confirmed severe acute respiratory syndrome coronavirus 2 infection ≥6 months prior and fulfilling World Health Organization criteria for long COVID were included. Acute Coronavirus disease 2019 (COVID-19) severity was classified per World Health Organization definitions. The sampling strategy included patients across the severity spectrum. At 3 months postinfection (T1), patients received physician-led clinical assessments. At 6 months (T2), they attended in-person follow-up visits, completing standardized forms and validated questionnaires assessing post-acute sequelae. Fatigue was reported both binarily (yes/no) and via the chalder fatigue scale (11-item version). Anxiety and depression were assessed using the hospital anxiety and depression scale; post-traumatic stress disorder symptoms with the 14-item post-traumatic stress scale; and HRQoL with the EuroQol-5 dimensions. Descriptive statistics, analysis of variance, chi-square, and correlation analyses (Pearson's or Spearman's) were used to evaluate associations. Analyses were performed using SPSS (v27; IBM Corp., Amonk). Among 208 patients, fatigue was significantly associated with anxiety and depression ($P < .001$). Physical fatigue correlated more strongly with depression ($r = 0.65$, $P < .001$) and anxiety ($r = 0.58$, $P < .001$) than mental fatigue ($r = 0.50$ and $R = 0.48$, respectively; $P < .001$). Surprisingly, severe acute COVID-19 cases reported lower fatigue (CFQ: 13.3 ± 8.4) than mild (17.7 ± 7.2) or moderate (17.4 ± 8.0) cases ($P < .005$), and higher HRQoL (EuroQol visual analog scale: 74.3 ± 20.3, $P = .002$). Anxiety symptoms were more common in mild cases ($P < .001$); post-traumatic stress disorder symptoms did not differ by severity. Long COVID fatigue – especially physical – is strongly linked to depression and anxiety. Mild/moderate acute COVID-19 cases show greater fatigue and lower HRQoL than severe cases, highlighting the need for tailored long-term care regardless of initial severity.

Abbreviations: CFQ-11 = chalder fatigue scale (11-item version), COVID-19 = Coronavirus disease 2019, EQ-5D = EuroQol-5 dimensions, HADS = hospital anxiety and depression scale, HRQoL = health-related quality of life, ICU = intensive care unit, PTSD = post-traumatic stress disorder, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SD = standard deviation, WHO = World Health Organization.

Keywords: anxiety, depression, fatigue, long COVID-19, post-traumatic stress, quality of life

JBE is a member of the Board of Directors of the European Society of Anaesthesiology and Intensive Care (ESAIC) and has received speaker's fees from Medtronic. The remaining authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study adhered strictly to the guidelines of the Declaration of Helsinki, receiving ethical approval (Ethical Committee No. 141/21) from the Ethical Committee of Algarve University Hospital Centre, Faro, Portugal, on the 6th of September 2021. Signed informed consent was obtained from all participants. Additionally, the study followed the STROBE guidelines for observational studies.[23]

Trial Registration: ClinicalTrials.gov NCT05323318.

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifests with a broad spectrum of clinical presentations, ranging from asymptomatic or mild illness to severe, life-threatening conditions.[1–3] The acute phase of the disease typically lasts up to 4 weeks following diagnosis, with symptom resolution varying among individuals.[4] While many patients recover fully within 12 weeks, a subset continues to experience persistent or new symptoms beyond this period, a condition now recognized as long COVID or post-COVID-19 Condition.[3,5]

The World Health Organization (WHO) defines long COVID as the persistence or emergence of new symptoms within 3 months of the initial COVID-19 infection, lasting for at least 2 months, and not attributable to an alternative diagnosis.[6–8] This condition can affect individuals regardless of the severity of their acute illness.[3,8] Research indicates that a significant portion of adults who contract SARS-CoV-2 may experience long COVID, with prevalence estimates ranging from 10% to 26%.[9] A study conducted in Scotland investigated the true prevalence of long COVID at 6, 12, and 18 months, revealing crude prevalence rates of 13.8%, 12.8%, and 16.3%, respectively, along with adjusted figures of 6.6%, 6.5%, and 10.4%.[10,11] Consequently, despite the official cessation of the pandemic, our clinical practices remain dedicated to the ongoing assessment and management of patients suffering from long COVID.

Long COVID is highly heterogeneous, often presenting with neuropsychiatric symptoms such as fatigue, depression, anxiety, and cognitive dysfunction.[3–5,9,12–14] Other frequently reported symptoms include dyspnea, palpitations, anorexia, myalgia, and arthralgia.[12–14] Studies indicate that neuropsychiatric symptoms may persist in up to 90% of hospitalized patients and 25% of nonhospitalized individuals 6 months postinfection.[13] Potential mechanisms underlying these manifestations include brain injury, neuronal degeneration, chronic inflammation, viral persistence, and immune dysregulation.[14,15] Additionally, psychological stressors such as disease-related fears, stigma, and social isolation may contribute to the development and persistence of these symptoms.[16,17]

Among the most debilitating features of long COVID is fatigue, which can significantly impair daily functioning.[12] Fatigue in this context is defined as a "decline in physical or mental performance due to physiological, psychological, or peripheral factors linked to COVID-19."[18,19] Studies suggest that fatigue often coexists with depression and anxiety, yet the precise relationship between these symptoms remains unclear.[20,21] Given the profound personal, social, and economic consequences of neuropsychiatric sequelae in long COVID, a deeper understanding of their interconnections is essential.[19,22]

This study aims to examine the association between fatigue presented by patients with long COVID and symptoms of depression and anxiety, as well as its impact on quality of life. Our primary hypothesis is that patients with long COVID who report symptoms of depression and/or anxiety will exhibit a higher prevalence and severity of fatigue compared to those without these neuropsychiatric symptoms. Additionally, we assume that higher levels of fatigue, depression, and anxiety will be negatively associated with daily functioning, pain perception, and overall health-related quality of life (HRQoL) among long COVID patients

Our Secondary hypothesis is that there will be differences in long-term levels of fatigue, neuropsychiatric sequelae, and HRQoL between individuals who have experienced mild acute COVID-19 and severe acute COVID-19.

2. Methods

2.1. Ethics

The study adhered strictly to the guidelines of the Declaration of Helsinki and received ethical approval (Ethical Committee No. 141/21) from the Ethical Committee of Algarve University Hospital Centre, Faro, Portugal, on September 6, 2021. Additionally, the study followed the STROBE guidelines for observational studies.[23]

2.2. Study design and setting

This study was designed as a prospective observational cohort study, conducted between November 2020 and June 2022, in 5 Portuguese hospitals, including 1 private and 4 public institutions. A full study protocol has been published elsewhere.[24] The study population consisted of symptomatic post-COVID-19 patients who attended specialized post-COVID-19 outpatient clinics for follow-up care. Patients were referred either by their primary healthcare providers or following hospitalization for COVID-19.

2.3. Study outcomes

2.3.1. Primary outcome. To determine whether patients with long COVID who experience symptoms of depression and/or anxiety have a higher prevalence of fatigue and report lower HRQoL, compared to those without these neuropsychiatric symptoms.

2.3.2. Secondary outcomes. To assess whether physical fatigue is more strongly associated with depression and anxiety compared to mental fatigue and evaluate whether patients experiencing both depression and anxiety have higher levels of both physical and mental fatigue than those with either condition alone.

To determine whether patients with mild or moderate acute COVID-19 experience higher levels of long-term fatigue than those with severe disease and explore whether the severity of the acute illness influences the persistence and type of fatigue (physical vs mental) in long COVID.

To examine whether individuals with mild acute COVID-19 have a higher prevalence of anxiety symptoms in the long COVID phase compared to those with moderate or severe disease and assess whether depression and post-traumatic stress disorder (PTSD) symptoms differ based on the severity of acute COVID-19.

To evaluate whether patients with mild or moderate acute COVID-19 report lower HRQoL scores in the long COVID phase than those with severe disease and investigate the extent to which fatigue, depression, and anxiety are associated with impairments in daily activities, pain perception, and emotional well-being.

2.4. Inclusion and exclusion criteria

Inclusion and exclusion criteria have been described in the study protocol.[24] In summary, Participants were eligible if they were 18 years or older, had a confirmed SARS-CoV-2 infection at least 6 months before enrollment, and experienced persistent symptoms meeting the WHO definition of post-COVID-19 disease. They also needed to have attended a post-COVID-19 follow-up consultation and provided written informed consent. COVID-19 diagnosis was confirmed through reverse transcription polymerase chain reaction or rapid antigen testing within 7 days of symptom onset. Exclusion criteria included preexisting psychiatric disorders, neurological conditions (e.g., stroke, Parkinson's, Alzheimer's, amyotrophic lateral sclerosis), and chronic fatigue predating COVID-19. Patients who had undergone invasive mechanical ventilation were excluded to avoid confounding from post-ICU syndrome. Additionally, individuals with cognitive or physical impairments that prevented questionnaire completion were not included.

2.5. Data collection

According to protocol,[24] data collection occurred at 2 time points. At T1 (three months postinfection), patients underwent

a comprehensive medical assessment conducted by physicians at the post-COVID-19 clinics. This assessment collected detailed demographic data, including educational background, preexisting medical conditions, body mass index, smoking habits, and information regarding acute COVID-19 severity, symptoms, and treatments received. Six months post-COVID-19 diagnosis (T2), patients attended a second in-person follow-up visit at the post-COVID-19 outpatient clinics. During this consultation, they completed standardized clinical research forms and validated questionnaires assessing post-acute sequelae of COVID-19, health status, fatigue, anxiety, depression, and PTSD. These assessments provided a structured evaluation of the long-term impact of COVID-19 on physical and mental health.

2.5.1. Assessment of COVID-19 severity. COVID-19 severity was categorized according to the WHO classification system.[25] Mild disease presented with symptoms but no radiographic pneumonia. Moderate disease included pneumonia on imaging without requiring supplemental oxygen. Severe cases involved pneumonia with respiratory distress, a respiratory rate >30 breaths/min, or oxygen saturation ≤93% on room air. Critical cases required intensive care, including mechanical ventilation, high-flow oxygen, or treatment for septic shock and multi-organ failure.

2.5.2. Assessment of fatigue. Fatigue was initially self-reported in a binary format (yes/no) during clinical evaluations using the post-acute sequelae of COVID-19 Checklist screening questionnaire.[26] We then used the chalder fatigue scale (11-item version) (CFQ-11)[27] to assess fatigue severity over the previous month. The CFQ-11 consists of 11 items rated on a 4-point Likert scale (0–3), with total scores ranging from 0 to 33, where higher scores indicate greater fatigue severity. It includes 2 subdomains: Physical fatigue (7 items; score range: 0–21) and Mental fatigue (4 items; score range: 0–12).

2.5.3. Assessment of depression and anxiety. Symptoms of depression and anxiety were assessed using the hospital anxiety and depression scale (HADS),[28] a validated tool for evaluating psychiatric symptoms in clinical, primary care, and general population settings. The HADS consists of 14 items, with 7 measuring anxiety and 7 measuring depression. Responses were categorized into the following severity ranges: 0 to 7: Normal; 8 to 10: Mild; 11 to 14: Moderate; 15 to 21: Severe. The HADS questionnaire has been validated for use in the Portuguese language, ensuring its applicability to the study population.[29]

2.5.4. Assessment of post-traumatic stress disorder (PTSD). PTSD symptoms were assessed using the post-traumatic stress scale, 14-item version questionnaire,[30] a validated patient-reported outcome measure based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, adapted for post-intensive care syndrome. Patients rated 10 PTSD-related symptoms on a 7-point Likert scale (1 = never to 7 = always), with total scores ranging from 10 to 70. A score above 35 indicated clinically relevant PTSD symptoms. The revised 14-item post-traumatic stress scale, 14-item version, based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, used a cutoff of 45 for probable PTSD.[31] For this study, the questionnaire was modified for post-COVID-19 patients by replacing "intensive care unit (ICU)" with "COVID-19," while maintaining the original diagnostic cutoffs.

2.5.5. Assessment of health-related quality of life (HRQoL). We used the EuroQol-5 dimensions (EQ-5D) questionnaire[32] to assess HRQoL. This instrument consists of 2 main components. The first is the EQ-5D-3L Questionnaire, which evaluates 5 key health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is rated on a 3-point scale, where 1 indicates no problems, 2 represents moderate problems, and 3 reflects severe problems. These responses calculate a health state index score, ranging from 0 (worst health state) to 1 (best health state).

The second component of the EQ-5D is the EuroQol visual analog scale. This scale allows patients to rate their overall health status from 0 to 100, with 0 representing the worst possible health state and 100 indicating the best possible health state. The EQ-5D has been validated for assessing HRQoL across various disease populations[33] and adapted for Portuguese-speaking populations.[34]

2.6. Sample size calculation

Fatigue is recognized as one of the most common and persistent symptoms of Long COVID, with previous studies reporting prevalence estimates ranging from 30% to 70% in post-COVID populations.[13,35–38] To ensure a representative sample and allow for meaningful subgroup analysis, we aimed to recruit enough participants across different severity levels of acute COVID-19. We assumed a moderate effect size (Cohen's $d = 0.5$) for group fatigue differences. Given a statistical power of 80% ($\beta = 0.20$) and a significance level of 5% ($\alpha = 0.05$), a minimum of approximately 200 participants was required to ensure adequate power for the primary analyses.

2.7. Statistical analysis

All statistical analyses were performed using SPSS software (version 27; IBM Corp. Amonk). Descriptive statistics were used to summarize the characteristics of the study population. Continuous variables were expressed as mean and standard deviation (SD) if they followed a normal distribution, whereas non-normally distributed variables were presented as median with interquartile range or range. Categorical variables were reported as absolute numbers (n) and percentages (%). To compare groups, we applied different statistical tests depending on the type and distribution of the data. The chi-square (χ^2) test was used to examine associations between categorical variables, such as the relationship between COVID-19 severity and fatigue or mental health symptoms. We conducted the Shapiro–Wilk test to determine whether continuous variables followed a normal distribution, which guided the choice of parametric or nonparametric tests for group comparisons. For comparisons of 2 or more independent groups, parametric tests were used when data were normally distributed, such as the analysis of variance, to assess differences in mean fatigue scores across COVID-19 severity groups. If data were non-normally distributed, we applied the Kruskal–Wallis test, a nonparametric alternative suitable for comparing multiple independent groups. To explore the relationship between fatigue and mental health outcomes, we performed linear association analyses using correlation coefficients, Pearson's or Spearman's, according to the variables normally distributed. When variables were not normally distributed, we applied Spearman's rank correlation, which assesses monotonic relationships. Fatigue was analyzed using the total fatigue score (range: 0–33), with subgroup analyses focusing on physical fatigue (range: 0–21) and mental fatigue (range: 0–12). This allowed us to investigate whether different fatigue components were more strongly associated with COVID-19 severity or neuropsychiatric symptoms such as depression, anxiety, and PTSD. A P-value < .05 was considered statistically significant for all analyses.

3. Results

3.1. Patient baseline characteristics

A total of 233 patients with long COVID-19 were initially enrolled in the study, of whom 208 met the inclusion criteria

and were analyzed during the study period (Fig. 1). The distribution of participants across study centers was as follows: Alvor Particular Hospital (18.3%, n = 38), Amadora Sintra Hospital (5.3%, n = 11), Faro Hospital (10.1%, n = 19), São Sebastião Hospital (2.4%, n = 5), and Portimão Hospital, which had the most significant proportion of patients (63.9%, n = 133). All 208 participants completed the T2 follow-up questionnaires at a mean of 6.9 months after their initial SARS-CoV-2 positive test.

The median age of the study population was 55.0 years [Q1: 43; Q3: 67.0]. Age distribution varied by disease severity, with mild cases having a median age of 52.0 years [40.0; 61.5], while severe cases had a higher median age of 60.5 years [48.0; 70.0]. Most of the sample was female (53.4%, n = 111), and a significant association was found between female gender and mild acute COVID-19 ($P < .001$). Regarding smoking status, 65.3% (n = 130) of patients were nonsmokers. Patient characteristics according to COVID-19 disease severity are depicted in Table 1.

During the acute phase of COVID-19, 46.2% (n = 96) of patients required hospitalization, while 27% (n = 13) required intensive care with oxygen support via high-flow nasal cannula. The presence of arterial hypertension as a preexisting comorbidity was significantly associated with severe COVID-19 ($P = .004$), with 54.1% (n = 40) of hypertensive patients experiencing severe disease. Similarly, diabetes mellitus was strongly associated with COVID-19 severity ($P < .001$), with 68.0% (n = 17) of diabetic patients experiencing severe COVID-19, whereas 51.6% (n = 94) of nondiabetic patients had a mild disease course. No statistically significant associations were observed between COVID-19 severity and the presence of heart disease, chronic kidney disease, preexisting respiratory disease, or immunosuppression.

3.1.1. Primary outcome: association of depression and anxiety in long COVID patients with a prevalence of fatigue. A statistically significant association was observed between fatigue symptoms in long COVID and the presence of neuropsychiatric symptoms, including anxiety, depression, or both ($P < .001$). Patients experiencing depression, anxiety, or both reported significantly higher fatigue levels compared to those without these neuropsychiatric symptoms.

3.1.2. Secondary outcome: correlation between the type of fatigue and depression and/or anxiety symptoms among patients post-COVID-19. The mean total fatigue score, assessed using the CFQ-11 Likert scale, was 15.9 ± 8.1. Notably, significant differences emerged based on the severity of the acute COVID-19 episode; patients who experienced severe acute COVID-19 reported lower fatigue levels (13.3 ± 8.4) compared to those with mild (17.7 ± 7.2) and moderate disease (17.4 ± 8.0), with a statistically significant difference ($P < .005$). Similar patterns were observed in the CFQ physical fatigue subscale, where the overall mean score was 10.4 ± 5.4. Severe COVID-19 patients reported significantly lower physical fatigue scores (8.6 ± 5.5) than patients with moderate (11.0 ± 5.2) or mild disease (11.7 ± 5.0) ($P = .005$). This trend was consistently seen also in the CFQ mental fatigue subscale; severe cases experienced less mental fatigue (4.8 ± 4.3) compared to moderate (6.4 ± 4.0) and mild (6.6 ± 3.2) cases, $P < .001$.

Correlation analysis confirmed a stronger relationship between physical fatigue and neuropsychiatric symptoms, with depression ($r = 0.65$, $P < .001$) and anxiety ($r = 0.58$, $P < .001$) showing higher associations than mental fatigue ($r = 0.50$ for depression, $r = 0.48$ for anxiety, both $P < .001$).

3.1.3. Secondary outcome: correlation between long-COVID fatigue and acute disease severity. Statistically significant differences in fatigue levels were observed among patients based on the severity of their acute COVID-19. Patients who had severe acute COVID-19 reported lower fatigue levels (total CFQ score: 13.3 ± 8.4) compared to those with mild (17.7 ± 7.2) and moderate (17.4 ± 8.0) disease ($P < .005$).

This trend was also evident in the CFQ physical fatigue subscale, where the total sample had an average score of 10.4 ± 5.4. Patients with severe disease had the lowest physical fatigue scores (8.6 ± 5.5), while those with moderate (11.0 ± 5.2) and mild (11.7 ± 5.0) disease reported higher fatigue ($P = .005$).

Similarly, on the CFQ mental fatigue subscale, patients with severe disease reported the lowest scores (4.8 ± 4.3), whereas those with moderate (6.4 ± 4.0) and mild (6.6 ± 3.2) disease experienced higher mental fatigue ($P < .001$).

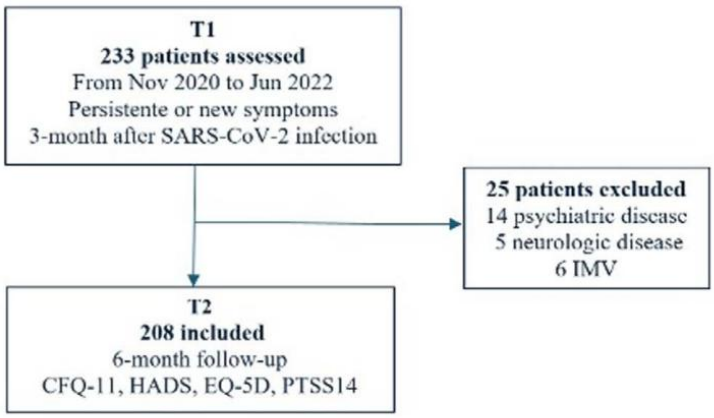

Figure 1. Study flow diagram. CFQ-11 = chalder fatigue scale (11-item version), EQ-5D = EuroQol-5 dimensions, HADS = hospital anxiety and depression scale, IMV = invasive mechanical ventilation, PTSS-14 = post-traumatic stress scale, 14-item version, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 1

Sociodemographic and clinical characteristics of the study population and COVID-19 severity.

		COVID-19 severity			
	Total N = 208	**Mild N = 97 (46.6%)**	**Moderate N = 29 (13.9%)**	**Severe N = 82 (39.4%)**	***P*-value**
Age, mean (SD)	55.0 (±14.8)	62.5 (±69.5)	69.1 (±72.8)	59.5 (±13.8)	**<.001**
Median [Q1; Q3]	55.0 [43.0; 68.0]	52.0 [40.0; 62.0]	58.0 [45.0; 70.5]	60.5 [48.0; 70.0]	
Female, N (%)	111 (53.4)	73 (65.8)	15 (13.5)	23 (20.7)	**<.001**
Smoking habits, N (%)					**.024**
Smoker	23 (11.6)	15 (65.2)	5 (21.7)	3 (13.0)	
Former smoker	46 (23.1)	15 (32.6)	7 (15.2)	24 (52.2)	
Nonsmoker	130 (65.3)	63 (48.5)	15 (11.5)	52 (40)	
UPY, mean (SD)	10.3 (± 21.8)	8.2 (± 17.6)	9.6 (±20.9)	12.9 (±26.1)	**<.001**
BMI mean (SD)	29.3 (±5.6)	29.7 (±6.1)	28.2 (±6.2)	29.2 (±5.0)	**.037**
Referral, N (%)		96 (46.4)	29 (14.0)	82 (39.6)	**<.001**
Health workers	25 (12.1)	20 (80.0)	5 (20.0)	0 (0.0)	
Hospital	105 (50.7)	7 (6.7)	18 (17.1)	80 (76.2)	
Primary care	77 (37.2)	69 (89.6)	6 (7.8)	2 (2.6)	
Hospital, N (%)		97 (46.6)	29 (13.9)	82 (39.4)	**<.001**
Alvor	38 (18.3)	31 (81.6)	5 (13.2)	2 (5.3)	
Amadora/Sintra	11 (5.3)	2 (18.2)	3 (27.3)	6 (54.5)	
Faro	21 (10.1)	4 (19.0)	3 (14.3)	14 (66.7)	
Feira	5 (2.4)	3 (60.0)	2 (40.0)	0 (0.0)	
Portimão	133 (63.9)	57 (42.9)	16 (12.0)	60 (45.1)	
Test type					
PCR	193 (92.8)				
TRAG	15 (7.2)				
Arterial hypertension	74 (36.1)	24 (32.4)	10 (13.5)	40 (54.1)	**.004**
Heart disease	21 (10.2)	9 (42.9)	4 (19.0)	8 (38.1)	.783
Diabetes mellitus	25 (12.1)	3 (12.0)	5 (20.0)	17 (68.0)	**<.001**
Chronic kidney disease	4 (1.9)	2 (50.0)	0 (0.0)	2 (50.0)	.704
Respiratory disease	22 (11.8)	10 (45.5)	4 (18.2)	8 (36.4)	.811
Type of respiratory disease					.483
Asthma	15 (71.4)	6 (40.0)	3 (20.0)	6 (40.0)	
COPD	4 (19.0)	2 (50.0)	0 (0.0)	2 (50.0)	
Other	2 (9.5)	2 (100)	0 (0.0)	0 (0.0)	
Immunosuppression	11 (5.3)	5 (45.5)	3 (27.3)	3 (27.3)	.390
Admitted to Hospital	96 (46.2)	2 (2.1)	14 (14.6)	80 (83.3)	**<.001**
Admitted to ICU	27 (13)	0 (0.0)	0 (0.0)	27 (100)	**<.001**
Home isolation, d, mean (SD)	10.2 (±6.8)	10.0 (±5.2)	12.4 (±8.1)	9.6 (±7.8)	**.009**

Bold indicates significant for $P < .05$.

AF = atrial fibrillation, BMI = body mass index, COPD = chronic obstructive pulmonary disease, COVID-19 = Coronavirus disease 2019, HF = heart failure, ICU = intensive care unit, N = number of cases, PCR = polymerase chain reaction, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, TRAG = rapid antigen testing, UPY = pack/year units.

A statistically significant negative correlation was found between long-COVID fatigue and acute disease severity, meaning that patients with more severe acute COVID-19 experienced lower fatigue levels in the long term. This trend was strongest for total fatigue, with mild and moderate cases showing higher long-term fatigue levels and severe cases exhibiting the strongest negative correlation ($r = -0.35$, $P < .001$). A similar pattern was observed for physical fatigue ($r = -0.33$, $P < .001$) and mental fatigue, though the latter had a slightly weaker correlation ($r = -0.31$, $P < .001$).

3.1.4. Secondary outcome: association between long-COVID mental disorders and acute disease severity. Anxiety symptoms, as assessed by the HADS subscale, were within the normal range across the total study population (mean: 7.8 ± 4.8) and among patients with severe acute COVID-19 (mean: 6.3 ± 4.5). However, a statistically significant difference was observed in patients with mild acute COVID-19, who had a mean anxiety score of 8.9 ± 4.6, reaching the threshold for mild anxiety symptoms ($P < .001$).

In contrast, symptoms of depression and post-traumatic stress (PTSS) remained within the normal range across all severity levels of acute COVID-19, with no significant differences observed ($P < .001$).

3.1.5. Secondary outcome: association of fatigue and mental health disorders with HRQoL after COVID-19. Patients who experienced severe COVID-19 reported a higher overall HRQoL, as measured by the EuroQol visual analog scale, with a mean score of 74.3 (±20.3) compared to 67.6 (±19.0) in mild cases and 64.3 (±19.8) in moderate cases ($P = .002$), Table 2.

Regarding specific HRQoL dimensions, a significant association was found between acute COVID-19 severity and difficulties in performing daily activities ($P = .013$), pain ($P = .026$), and anxiety ($P = .041$). However, no statistically significant differences were observed for mobility or self-care. Among individuals without reported activity limitations, 49.0% had experienced severe COVID-19, while 50.5% of those without anxiety symptoms and 51.3% of those without pain had also undergone severe disease. In contrast, most individuals who reported moderate difficulties in these domains had mild acute COVID-19 (46.3% for activity limitations, 52.4% for anxiety, and 52.8% for pain).

There were significant negative correlations between fatigue, mental health symptoms, and HRQoL in post-COVID-19 patients. Total fatigue exhibited the strongest negative correlation with HRQoL ($r = -0.55$, $P < .001$), indicating that higher fatigue levels were linked to a lower perceived quality of life. Both physical fatigue ($r = -0.52$, $P = .002$) and mental fatigue ($r = -0.50$, $P = .003$) also had significant negative associations with HRQoL.

Beyond fatigue, mental health symptoms had a notable impact on HRQoL. Anxiety ($r = -0.48$, $P = .004$) and depression

Table 2

Neuropsychiatric symptoms and COVID-19 severity.

		COVID-19 severity			
	Total N = 208	**Mild N = 97 (46.6%)**	**Moderate N = 29 (13.9%)**	**Severe N = 82 (39.4%)**	***P*-value**
CFQ total mean (SD)	15.9 (±8.1)	17.7 (±7.2)	17.4 (±8.0)	13.3 (±8.4)	**.005**
CFQ physical mean (SD)	10.4 (±5.4)	11.7 (±5.0)	11.0 (±5.2)	8.6 (±5.5)	**.004**
CFQ mental mean (SD)	5.6 (±3.8)	6.0 (±3.2)	6.4 (±4.0)	4.8 (±4.3)	**<.001**
HADS anxiety mean (SD)	7.8 (±4.8)	8.9 (±4.6)	8.4 (±5.5)	6.3 (±4.5)	**<.001**
HADS depression mean (SD)	5.7 (±4.0)	6.7 (±3.7)	5.7 (±4.4)	4.5 (±4.0)	**<.001**
PTSS 14 B mean (SD)	39.1 (±22.0)	43.0 (±19.9)	43.8 (±23.8)	33.0 (±22.5)	**<.001**
EQ-VAS mean (SD)	69.8 (± 19.9)	67.6 (±19.0)	64.3 (±19.8)	74.3 (±20.3)	**.002**
EQ mobility N (%)					.359
No problems	135 (70.7)	62 (45.9)	16 (11.9)	57 (42.2)	
Moderate problems	55 (28.8)	22 (40.0)	12 (21.8)	21 (38.2)	
Severe problems	1 (0.5)	1 (100)	0 (0.0)	0 (0.0)	
EQ self-care N (%)					.093
No problems	172 (90.1)	81 (47.1)	23 (13.4)	68 (39.5)	
Moderate problems	18 (9.4)	3 (16.7)	5 (27.8)	10 (55.6)	
Severe problems	1 (0.5)	1 (100)	0 (0.0)	0 (0.0)	
EQ activity N (%)					**.013**
No problems	104 (54.5)	45 (43.3)	8 (7.7)	51 (49.0)	
Moderate problems	82 (42.9)	38 (46.3)	18 (22.0)	26 (31.7)	
Severe problems	5 (2.6)	2 (40.0)	2 (40.0)	1 (20.0)	
EQ pain N (%)					**.026**
No problems	78 (40.8)	27 (34.6)	11 (14.1)	40 (51.3)	
Moderate problems	106 (55.5)	56 (52.8)	17 (16.0)	33 (31.1)	
Severe problems	7 (3.7)	2 (28.6)	0 (0.0)	5 (71.4)	
EQ anxiety N (%)					**.041**
No problems	91 (47.2)	33 (36.3)	12 (13.2)	46 (50.5)	
Moderate problems	82 (42.5)	43 (52.4)	15 (18.3)	24 (29.3)	
Severe problems	20 (10.4)	11 (55.0)	1 (5.0)	8 (40.0)	

CFQ 11 = chalder fatigue scale (11-item version), COVID-19 = Coronavirus disease 2019, EQ-5D = EuroQol 5 dimensions, EQ-VAS = EuroQol visual analog scale, HADS = hospital anxiety and depression scale, N = number of cases, PTSS-14 = post-traumatic stress scale, 14-item version, Q1 = first quartile, Q3 = third quartile, SD = standard deviation.

($r = -0.51$, $P = .002$) were both moderately correlated with poorer quality of life, highlighting their role in diminishing well-being. Post-traumatic stress symptoms ($r = -0.53$, $P < .001$) also showed a strong negative correlation with HRQoL, emphasizing the psychological burden of long COVID.

4. Discussion

This study explored the effects of long COVID-19 on fatigue, neuropsychiatric symptoms, and HRQoL in a cohort of 208 patients from multiple healthcare centers. Fatigue emerged as a predominant symptom, with a strong and statistically significant association with anxiety and depression. Patients who initially had a more severe acute COVID-19 infection experienced less long-term fatigue, both physically and mentally, compared to those whose initial COVID-19 illness was mild or moderate. Additionally, fatigue remained prevalent even among patients without neuropsychiatric symptoms, indicating additional contributing factors such as persistent inflammation and autonomic or mitochondrial dysfunctions.

Our findings align with previous studies,[35–38] which report that 20% to 47% of individuals with long COVID experience neuropsychiatric symptoms, consistent with the 28.8% observed in this study. A Spanish study using the HADS and EQ-5D scales found that over 80% of long COVID patients reported fatigue, with 23.5% experiencing depressive symptoms and 35.1% having anxiety.[37] Other exacerbating factors include stigma, negative illness perceptions, and uncertainty about diagnosis and treatment.[35,36]

Patients who experienced severe acute COVID-19 reported lower fatigue levels and better overall HRQoL compared to those with mild or moderate disease. This challenges the assumption that greater illness severity leads to more long-term impairment. Our data suggest a somewhat unexpected pattern: individuals who were less severely ill initially reported experiencing higher levels of persistent fatigue months after their infection. This challenges the common assumption that people who have more severe acute illness typically have worse long-term outcomes. Several reasons could explain this counterintuitive finding: on the 1 hand, severe cases might trigger stronger immune or therapeutic responses that could somehow reduce persistent symptoms like fatigue later on, and severely ill patients may have received more intensive medical interventions or rehabilitation support post-hospitalization, reducing fatigue in the long-term.

Additionally, while anxiety levels were lower in the severe COVID-19 group, symptoms of depression and PTSD remained within the normal range across all severity groups. These findings suggest that factors beyond initial disease severity influence post-recovery well-being. Understanding the mechanisms behind these differences could provide valuable insights into long COVID and help develop tailored rehabilitation strategies, particularly for those recovering from mild to moderate cases.

Physical fatigue was more strongly linked to anxiety, while both anxiety and depression were associated with mental fatigue.[37] Fatigue levels varied over time, with physical fatigue being more related to changes in activity patterns.[39] Surveys suggest that physical fatigue is more common than mental fatigue in long COVID,[9] pointing to distinct pathophysiological mechanisms separate from primary psychiatric disorders. A key question is whether fatigue precedes anxiety and depression or vice versa. Some studies suggest that post-viral depression may trigger PTSD symptoms, which, in turn, contribute to fatigue. This cyclical process could lead to a worsening of depression, further fueling fatigue in a self-perpetuating manner.[40] Our findings support the multifactorial nature of long COVID fatigue and highlight the need for a comprehensive treatment approach addressing physical and mental factors.

Further research should explore the timeline of symptom progression – whether fatigue leads to depression and anxiety, or vice versa. Additionally, studies should investigate whether early psychological interventions could prevent or mitigate fatigue in long COVID.

This study has several strengths. The multicenter design, involving 5 hospitals across both public and private sectors, ensures a diverse patient population, increasing the generalizability of the results. Additionally, with data collection at multiple time points (3- and 6-months postinfection), the prospective cohort study design strengthens causality assessment. It minimizes recall bias, providing a more accurate understanding of symptom progression in long COVID.

A key strength of this study is the comprehensive assessment of fatigue and neuropsychiatric symptoms using validated tools. This standardized approach allows for reliable symptom quantification, enabling a thorough evaluation of fatigue, anxiety, depression, and PTSD in long COVID patients. Additionally, the study included patients across all severity levels of acute COVID-19 (mild, moderate, and severe), allowing a comparative analysis of how initial disease severity influences long-term health outcomes. Another strength is the differentiation between physical and mental fatigue, which provides nuanced insights into the nature of post-COVID fatigue. This distinction is valuable for understanding whether different fatigue subtypes have unique underlying mechanisms or clinical implications. The study also highlights sex-based differences, showing a strong association between female gender and increased fatigue, anxiety, and depression, which aligns with emerging evidence on sex-related disparities in long COVID. Moreover, the findings challenge conventional assumptions by demonstrating that mild COVID-19 cases were associated with more significant long-term fatigue and mental health burden than severe cases. This paradox underscores the need for a more refined understanding of long COVID risk factors beyond initial disease severity. By integrating quality of life assessments, the study also provides clinically relevant insights into the broader impact of long COVID, reinforcing the need for targeted follow-up and support strategies.

However, it also has imitations. One major limitation is selection bias, as only patients seeking care at post-COVID-19 clinics were included. This may have led to an overrepresentation of more severe cases while underrepresenting individuals with mild long COVID. Additionally, the exclusion of mechanically ventilated patients limits the generalizability of the findings to the most severe cases. However, this decision was made to avoid including patients with post-ICU admission syndrome, which could introduce other causes of fatigue beyond long COVID. Furthermore, since the study was conducted in 5 Portuguese hospitals, the findings may not fully apply to different populations.

Another key limitation is the lack of a control group, which prevents determining whether the observed symptoms are specific to long COVID or part of a broader post-viral syndrome. The study relied on the CFQ-11 scale to assess fatigue, which is validated for chronic fatigue syndrome but not specifically for long COVID. While long COVID and chronic fatigue syndrome share overlapping clinical and pathophysiological mechanisms, using CFQ-11 alone may limit comparability with studies employing different fatigue assessment tools. This heterogeneity in fatigue measurement methods makes drawing direct comparisons across studies challenging.

Another limitation is the short follow-up period of 6 months, which does not provide insight into the long-term persistence or resolution of symptoms. Additionally, fatigue and neuropsychiatric symptoms can fluctuate over time, but they were only assessed at 2 time points. This limited temporal resolution may have missed essential symptom severity and progression variations.

The broader psychosocial context of the pandemic may have also influenced the results. Factors such as lockdowns, social isolation, and economic stressors could have contributed to the observed mental health symptoms, making it difficult to separate the direct effects of long COVID from pandemic-related distress. Finally, the study relied solely on self-reported questionnaires, introducing subjectivity and potential reporting bias. No objective clinical assessments, such as biomarkers or neurocognitive testing, were conducted to confirm the severity of symptoms. This limitation reduces the ability to validate findings against physiological or laboratory-based measures.

Finally, as this study used bivariate association and correlation analyses without multivariable adjustment for potential covariates, the findings should be interpreted as associations rather than causal relationships. The limited sample size, particularly in some subgroups, restricted our ability to conduct robust multivariable analyses.

In conclusion, this study examined the prevalence and association of fatigue, depression, anxiety, and PTSD in long COVID-19, as well as its impact on quality of life based on disease severity. Mild COVID-19 was more frequent in women and associated with greater fatigue, anxiety, and depression, whereas severe COVID-19 was linked to preexisting diabetes (diabetes mellitus) and hypertension (HTN). Patients with moderate acute illness experienced higher fatigue. However, acute disease severity did not impact PTSD symptoms. Patients with mild or moderate COVID-19 had a lower quality of life, particularly in activity, pain, and anxiety domains, compared to those with severe illness. The findings emphasize the need for ongoing follow-up and support for long COVID patients, even those with mild acute illness, due to its lasting impact on mental health and daily functioning. Future research should explore the role of pharmacological treatments, such as corticosteroids, in neuropsychiatric symptoms.

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Aim 4: To determine the prevalence of newly diagnosed OSA in adults with long COVID, evaluate its association with persistent symptoms (particularly fatigue) and COVID-19 acute severity, and investigate gender-specific clinical patterns

10.
Newly diagnosed Obstructive Sleep Apnea in long COVID-19 patients: a Prospective Cohort Multicentre Observational Study

Pires L, Moniri A, Marreiros A, Belchior I, Fatal T, Ribeiro AR, Chaves Ramos H, Cunha K, Ferreira J, Barroso AS, Méndez Gonzalez L, Guimarães MJ, Conde B, Dias C, Ferreira-da-Silva R, Berger-Estilita J, Drummond M

2026

This paper describes a multicentre prospective cohort study that holds significant value for multiple reasons, especially considering the context of the ongoing COVID-19 pandemic and the growing recognition of long COVID as a significant public health issue.

10.1 High Prevalence of OSA in Long COVID Patients

The most striking result of the study is the identification of a significantly higher prevalence of newly diagnosed obstructive sleep apnea (OSA) among patients with long COVID-19 compared to expected rates in the general population. Specifically, 66.3% of the post-COVID cohort met diagnostic criteria for OSA (AHI ≥5) at 6 months after infection, with 17% presenting with severe OSA (AHI ≥30). These figures far exceed previous national and international estimates for OSA in the general population, strongly suggesting that long COVID may be associated with a substantial increase in OSA risk or may unmask previously undetected OSA in vulnerable individuals.

10.2 Clinical Symptom Overlap and Diagnostic Implications

Another important contribution is the study's demonstration of significant overlap between persistent long COVID-19 symptoms (such as fatigue, brain fog, memory loss, and hypersomnolence) and the symptomatology of OSA. This overlap complicates clinical diagnosis and highlights the risk of underdiagnosing OSA in long COVID patients. Recognising OSA is crucial as it is a modifiable condition with effective treatments. Distinguishing OSA-related fatigue from post-viral fatigue could impact patient management, recovery trajectory, and overall quality of life.

10.3 Gender-Specific and Obesity-Related Findings

The study uncovers a unique gender-specific pattern in OSA prevalence following COVID-19: OSA increased with more severe acute COVID-19 in men, but in women, OSA prevalence increased in those who presented with mild disease. Additionally, while obesity was a risk factor for OSA in both sexes, after multivariate analysis, the link between OSA severity and SARS-CoV-2 infection, only was kept in women, not men. These findings indicate possible underlying biological, hormonal, or pathophysiological mechanisms that differ by sex, suggesting avenues for personalized care and further research.

10.4 Implications for Public Health and Clinical Practice

Given the potential for missed diagnoses of OSA in long COVID patients, the research underscores the urgent need for routine screening for OSA—particularly in those with persistent fatigue, cognitive symptoms, or at high risk (e.g., obese individuals, those with moderate/severe initial COVID-19). Early identification and treatment could have profound benefits by reducing symptom burden and lowering the risk of chronic complications.

10.5 Foundation for Future Research

This study lays the groundwork for future research into the long-term trajectory of OSA following COVID-19, the mechanisms linking SARS-CoV-2 infection to sleep-disordered

breathing, and the validation of specific tools to differentiate post-viral from OSA-related fatigue. It suggests that ongoing longitudinal and mechanistic studies—particularly those considering sex-based differences, baseline pre-infection sleep data, and inflammatory or neuromuscular sequelae—are critical for advancing the field.

10.6 Broader Impact

By drawing attention to the possibility that long COVID could be either causing or unmasking a significant burden of undiagnosed OSA, the study informs policymakers, healthcare providers, and researchers about an underappreciated aspect of the post-COVID syndrome. This knowledge could lead to improved patient outcomes, better healthcare resource planning, and potentially a reduction in the long-term healthcare burden associated with both OSA and long COVID.

10.7 Summary

This study is critical because it documents a high prevalence of newly diagnosed OSA in long COVID patients, establishes the complexity of distinguishing OSA from post-viral symptoms, reveals gender- and obesity-related variations in risk, and emphasizes the clinical need for targeted sleep disorder screening in post-COVID care. Its findings will directly inform clinical practice, future research, and public health strategies in the wake of the COVID-19 pandemic.

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Title: Newly diagnosed Obstructive Sleep Apnea in long COVID-19 patients: a Prospective Cohort Multicentre Observational Study

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1. INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive partial or complete airway blockages during sleep, leading to interruptions in breathing, blood oxygen, desaturation and arousals.[1,2] Its prevalence varies according to diagnostic criteria and population-specific characteristics, but can be as high as 23% in women and 49% in men and is dependent on the Apnea Hypopnea Index (AHI) cut-off used for the diagnosis and on the studied population features.[3-6] Previous OSA is a risk factor for COVID-19 severity due to nocturnal hypoxemia, exacerbating or causing endothelial dysfunction, low-grade systemic inflammation, oxidative stress, micro aspiration, and cardiac dysfunction.[7] Furthermore, OSA activates the renin-angiotensin-aldosterone system (RAAS) and angiotensin-converting enzyme-2 (ACE2), which is the SARS-CoV-2 entry receptor in the cells.[8] Recent studies have reported an increased incidence of OSA in post-COVID-19 patients.[9,10] There is no consensus on the definition of clinical manifestations after SARS-CoV-2 infection that remain weeks after diagnosis. The World Health Organization describes these manifestations, commonly known as long COVID-19 or post-COVID condition and defines it as the persistence or development of new symptoms, within 3 months of the first SARS-CoV-2 infection, with a symptomatic duration of at least 2 months. It can affect anyone exposed to SARS-CoV-2, regardless of disease severity, and approximately 10% of infected individuals are affected. [11-16] It should be noted that fatigue is a common symptom of both long COVID-19 and Obstructive Sleep Apnea Syndrome. Infiltration of inflammatory cells, cytokine production, and the production of oxygen-free radicals in the upper airway muscles can result in fatigue and muscle weakness.[17-20]

This study aims to determine the prevalence of newly diagnosed OSA in adult patients with long COVID-19. Secondary objectives include assessing the association between acute COVID-19 severity and new-onset OSA and evaluating the prevalence of OSA in long-term COVID-19 patients with fatigue, as well as its relationship with OSA severity.

2. METHODS

2.1 Study Design and Population

This is a multicenter prospective observational cohort study, tributary to the Protocol *"Long COVID-19 Fatigue and Obstructive Sleep Apnea (PostCoV2OSA)"(-ClinicalTrials.gov Identifier: NCT05290350-).* We enrolled post-COVID symptomatic patients who attended the outpatient long COVID clinics at seven Portuguese hospitals (two private and five public) from November 2020 to June 2022. Patients were referred by primary health care clinicians (40.4%; n =78), after hospital admissions (48.2%; n =93) and by occupational medicine (health care workers) (11.4%; n =22). Inclusion Criteria: (i) ≥18 years; (ii) patients who had a previous COVID-19 at least 6 months before the initial study protocol evaluation, confirmed by SARS-CoV-2 positive real-time reverse-transcription polymerase chain reaction or antigen test on a nasopharyngeal swab; (iii) patients with persistent symptoms after the cure criteria defined by WHO. Exclusion Criteria: (i) patients with concomitant neurological disorders that could increase OSA risk (such as stroke, Parkinson's disease); (ii) patients with persistent fatigue symptoms 6 months before SARS-CoV-2 infection; (iii) patients with severe COVID-19 complications (such as myocarditis, pulmonary fibrosis); (iv) OSA diagnosis before COVID-19.

Data was collected 3 months (T1) after acute infection (T0), by qualified clinical study staff, i.e., physicians conducting the long COVID-19 medical consultations. Demographic

characteristics include age, gender and body mass index (BMI, kg/m2). Medical histories of each participant, cigarette smoking, comorbidities, and drug intake (antihistamines, psychotropics, sedatives) were collected.[21] During this visit, a home sleep apnea test was scheduled. A second presential visit was done at 6 months post-COVID-19 (T2), where patient's completed the clinical research forms with standardized questionnaires on long COVID-19 symptoms.

2.2 Assessment of obstructive sleep apnea

The OSA diagnosis was performed using a portable monitoring device type III Embletta MPR® PSG Sleep Study, 6-7 months after COVID-19 diagnosis (T2). All sleep recordings were obtained in the patients' home environment and manually scored by the center's trained sleep technicians, who were blind to the results of the previous questionnaires. We used the American Academy of Sleep Medicine (AASM) 2012 criteria that focus on the Apnea-Hypopnea Index (AHI), defining mild (5-15 events/hr), moderate (15-30 events/hr), and severe (over 30 events/hr) OSA. Apneas were defined as a reduction in airflow ≥ 90% for more than 10 seconds, and hypopneas were a 30% reduction in airflow for at least 10 seconds, accompanied by a 3% oxygen desaturation or an arousal.[22-23]

2.3 Assessment of symptoms

In the clinical research form, all the possible acute (T0) and long COVID-19 symptoms were listed (T2), and the patients answered yes or no. Fatigue was assessed using the Chalder Fatigue Questionnaire (CFQ-11) and Likert scores**.** Participants rated the fatigue they experienced over the previous month as compared to their usual energy levels. The questionnaire contains 11 items, each scaled from 0 to 3. The total score ranges from 0 to 33;

33 denotes maximal symptoms; and the scale is divided into two subscales: physical fatigue (seven items, range 0 to 21) and mental fatigue (four items, range 0 to 12).[24-26]

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS). The ESS is a validated 8-item questionnaire that evaluates the likelihood of falling asleep in common sedentary situations using a 4-point Likert scale (0–3). Total scores range from 0 to 24, with scores of 0–10 considered within the normal range in healthy adults, 11–14 indicating mild sleepiness, 15–17 moderate sleepiness, and 18–24 severe sleepiness. In accordance with standard interpretation, ESS scores ≥10 were considered indicative of excessive daytime sleepiness and were used as the cut-off in the present analysis.[27,28]

Memory loss was assessed through patient self-report during the structured follow-up evaluation. Participants were asked about the presence of new or persistent cognitive symptoms following COVID-19 infection, including subjective memory difficulties. These symptoms were recorded as part of the standardized clinical questionnaire administered during follow-up.

2.4 COVID-19 acute disease severity

Previous COVID-19 severity was categorized as mild illness (mild symptoms without the radiographic appearance of pneumonia), moderate (having symptoms and the radiographic evidence of pneumonia, with no requirement for supplemental oxygen), severe (having pneumonia, including one of the following: respiratory rate > 30 breaths/minute; severe respiratory distress; or SpO2 ≤ 93% on room air at rest) and critical cases (e.g. respiratory failure requiring mechanical ventilation or nasal high flow oxygen, septic shock, organ failure or ICU admission).[29]

2.5 Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 30.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize participant characteristics, which are presented as the mean and standard deviation for normally distributed continuous variables, median with interquartile range or range for non-normally distributed variables and counts with corresponding percentages for categorical variables. The Kolmogorov-Smirnov test was applied to assess the normality of the distributions of all continuous variables. To compare differences between two or more groups, we used parametric analysis of variance (ANOVA) when assumptions of normality were met, and the Kruskal-Wallis test as the non-parametric alternative when they were not. Associations between categorical variables were evaluated using the Chi-square test. When comparing continuous and categorical variables, the Mann-Whitney U test was used when the data did not follow a normal distribution.

In addition to analyses of the full cohort (22–89 years), a predefined age-restricted subgroup (30–69 years) was analyzed to facilitate comparison with prior population-based studies on OSA, which commonly report prevalence within this age range.

To evaluate factors independently associated with newly diagnosed OSA, a multivariable logistic regression model was constructed using OSA defined as an apnea–hypopnea index (AHI) ≥5 events/hour as the dependent variable. Independent variables included age, body mass index (BMI), sex, COVID-19 acute disease severity, and fatigue severity measured by the Chalder Fatigue Questionnaire (total score). An interaction term between COVID-19 severity and sex was included to assess potential sex-specific effects. Age was adjusted for BMI and sex. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. A p-value of < 0.05 was considered statistically significant.

3. RESULTS

3.1 Patient baseline characteristics

A total of 249 patients attended the post-COVID-19 consultations, of whom 77.5% (n=193) completed the study (Figure 1). The study population was predominantly white, 98.4% (n=190), with 55.4% (n=107) women. More than half of the participants (55.0%; n=106) had not been hospitalized during their acute COVID-19 illness, and nearly half (49.2%; n=95) had experienced a mild form of the disease. The mean age was 53.6 years (±14.7), with 50.8% of the cohort falling within the 41–64 age range. The mean body mass index (BMI) indicated an overweight population. Obesity was present in 33.2% (n=51) of participants, and among these, 12.4% (n=21) were classified as morbidly obese (Table 1).

During the acute phase of infection (T0), the most frequently reported symptoms were fatigue (84.8%; n=162), cough (76.9%; n=147), fever (62.3%; n=119), myalgias (57.6%; n=110), and dyspnea (56.0%; n=107) (Figure 2). At six months post-COVID-19 (T2), fatigue remained the most common symptom (84.8%; n=162). Myalgias decreased in prevalence (34.9%; n=66), whereas other symptoms largely mirrored those observed during the acute phase**,** including memory loss (30.6%; n=58), brain fog (28.0%; n=53), anxiety (26.4%; n=51), and excessive daytime sleepiness (ESS ≥10) (25.3%; n=49). The T1 visit occurred at 3.5 (±2.0) months after acute disease (median 3.1 months; IQR 2.9), and T2 at 6.7 (±1.3) months (median 6.4 months; IQR 1.2).

3.2 Results of obstructive sleep apnea prevalence and fatigue

The sleep test was performed a mean of 6.1 (±2.3) months (median 6.2; IQR:1.8) after COVID-19 diagnosis. According to the 2012 AASM criteria, the severity of OSA in the study

population was classified as mild in 30.7% (n=56), moderate in 18.5% (n=35), and severe in 16.4% (n=33).

The prevalence of OSA among patients aged 22-89 years (n = 191) was 66.3% (n = 128) using an AHI cutoff of ≥5. When using higher thresholds, OSA prevalence decreased to 35.7% (n=69) for AHI ≥15 and 17.0% (n=33) for AHI ≥30. In the three categories, OSA was more common in men than in women (Table 2). The most significant gender difference was observed in the AHI ≥30 group, where 29.0% (n=25) of men had severe OSA compared to only 7.4% (n=8) of women ($p < 0.001$). A similar trend in OSA prevalence was observed in the subgroup of patients aged 30 to 69 years (n = 145), with little variation from the overall 22 to 89-year-old population at the AHI ≥5 level. However, for the AHI ≥30 cutoff, the prevalence of severe OSA in the former age group was slightly lower (13.7% versus 17.0%) than in the broader population.

Among patients reporting fatigue at six months post-COVID-19 (T2), the prevalence of OSA was even higher, reaching 77.9% (105 out of 162 patients). The mean score on the CFQ was 16.6 (±8.2), with significantly higher scores in women (19.3 ±7.3) than in men (13.3 ±8.1) ($p < 0.001$). This gender difference was also observed in the CFQ subscales: for physical fatigue, women scored an average of 12.3 compared to 8.9 in men; for mental fatigue, the scores were 7.0 in women and 4.4 in men (both $p < 0.001$).

No significant association was found between OSA severity and the CFQ (p=0.687). Interestingly, in men, obesity was consistently observed across all OSA severity categories, with no substantial variation in body weight between different AHI cutoffs. In contrast, women exhibited a clear pattern: as AHI increased, so did BMI, suggesting a link between obesity and OSA severity specifically in female patients.

3.3 Correlation between OSA diagnosis and COVID-19 acute disease severity

Regarding COVID-19 severity by gender, we observed a statistically significant increase in male prevalence of severe disease (males 28.2%; females 6.7%), p<0.001. The distribution of males and females was similar in mild and moderate COVID-19. The comparison between patients with and without OSA shows that the prevalence in women decreases with increasing COVID-19 severity, whereas the prevalence of OSA in men increases with increasing COVID-19 severity (p=0.002). In the severe OSA subgroup (AHI ≥ 30), we observed the same difference between males and females.

In mild COVID-19 versus severe COVID-19 patients, the prevalence of some acute disease symptoms was higher in the following: excessive daytime sleepiness (ESS ≥10) (55.2% versus 22.4%; p=0.005), fatigue (52.5% versus 32.7%: p=0.017), memory loss (42.2% versus 33.3%; p=0.05) and brain fog (44.9% versus 28.6%; p=0.008). At 6 months post-COVID, this pattern persisted in fatigue, but we observed a larger difference between mild and severe disease in the other three symptoms. Post-COVID-19 fatigue prevalence was higher in women with mild COVID-19 than with severe COVID-19 (52.5% versus 32.7%); in men, the opposite was observed, with a higher prevalence of fatigue in severe versus mild COVID-19 (32.1% versus 60.7%); p=0.017.

3.4. Multivariable predictors of new-onset OSA

In multivariable logistic regression analysis, COVID-19 severity was independently associated with an increased likelihood of newly diagnosed OSA (OR 2.80, 95% CI 1.72–4.56, p < 0.001). A significant interaction between COVID-19 severity and sex was observed (p = 0.002), indicating sex-specific effects. Specifically, increasing COVID-19 severity was associated

with higher odds of OSA in males, whereas this association was markedly attenuated and no longer evident in females.

The combined effect of age, BMI, and sex was also independently associated with OSA (OR 1.001, 95% CI 1.001–1.002, p = 0.001), reflecting a cumulative risk in older individuals with higher BMI. Fatigue severity, as measured by the Chalder total score, was not independently associated with OSA in the adjusted model (OR 0.99, 95% CI 0.94–1.03, p = 0.664). Marginal predicted probability analyses further indicated that COVID-19 severity increased the probability of OSA among males, whereas no meaningful change was observed among females. The full statistical analysis is shown in the Supplementary Statistical Appendix.

4. DISCUSSION

This study revealed three key findings. First, there was a high prevalence of OSA among long COVID-19 patients, with 66.3% meeting the criteria for OSA (AHI ≥5) 6 months after infection. Notably, severe OSA (AHI ≥30) was present in 17.0% of participants and was significantly more common in men than in women. Second, fatigue remained a dominant and persistent symptom at 6 months post-COVID-19, reported by 84.8% of the cohort. Women experienced significantly higher fatigue than men, with higher scores across total fatigue and both physical and mental fatigue subdomains. Third, the study identified a gender-specific relationship between OSA prevalence and COVID-19 severity. Among men, the prevalence of OSA increased in severe acute COVID-19, while among women, OSA prevalence increased in mild acute disease. This inverse pattern suggests that there are gender-specific physiological or pathophysiological responses in the post-COVID period. Our findings support the hypothesis that patients with long COVID-19 have a higher prevalence of newly diagnosed

OSA. Additionally, persistent post-COVID-19 symptoms such as fatigue, memory loss, brain fog, and excessive daytime sleepiness may overlap with features of OSA syndrome, making the clinical presentation more complex and potentially contributing to underdiagnosis.[30]

In our cohort of both hospitalized and non-hospitalized patients assessed 6 months after acute COVID-19, 66.3% had OSA (AHI ≥5) and 35.7% had moderate-to-severe OSA (AHI ≥15). These rates are substantially higher than the estimated general OSA prevalence in Portugal. According to Benjafield et al[6], OSA prevalence in Portugal was estimated at 17.0% (AHI ≥5) and 12.5% (AHI ≥15), based on algorithmic projections using BMI, race, and geographic proximity to countries with OSA epidemiological studies, as there is a lack of direct data in our country. Duran et al. [31] reported an OSA prevalence of 26.7% in Spanish adults aged 30–70 years using older AASM 2007 scoring criteria. Tan et al[32] found a prevalence of moderate-to-severe OSA of 30.5% and 18.1% in a multiethnic Asian population using the AASM 2012 criteria, which is more sensitive than the previous ones.

Our results are consistent with Popovici et al[8], who reported a 57.9% prevalence of OSA (AHI ≥5) in Romanian patients at three months post-COVID. However, their study included only hospitalized patients, while our cohort included a broader population with a longer follow-up period. In addition, a population-based study by Lin et al[9] from Taiwan used ICD-10 coding and found a hazard ratio of 1.57 for new OSA diagnoses at 6-9 months post-COVID, further supporting our observations.

One likely contributor to this elevated OSA prevalence is obesity. In our study, 33.2% of participants were obese, a higher rate than the national estimate of 28.7% for Portuguese adults.[33] Obesity is a well-established risk factor for OSA, and in our cohort, we observed a clear relationship between obesity and OSA severity in women, but not in men. This is

consistent with previous literature: Mentsoudis et al[34] identified obesity as a predictor of poor COVID-19 outcomes, while the Coronado study[35] demonstrated that pre-existing OSA is independently associated with increased mortality from COVID-19.

Fatigue remained the most prevalent symptom 6 months post-infection, affecting 84.8% of patients overall and 77.9% of those with OSA (AHI ≥5). Scores on the CFQ were significantly higher in women across all subscales—total (19.3 vs. 13.3), physical (12.3 vs. 8.9), and mental (7.0 vs. 4.4)—with all comparisons reaching statistical significance ($p < 0.001$). These results align with those of Stavem et al[36], who reported similar CFQ scores in a Norwegian population four months post-COVID, with higher symptom burden in women.

An important finding of this study is that the association between COVID-19 severity and newly diagnosed OSA is sex-dependent. Across all AHI cutoffs, OSA was more prevalent in men, with the greatest disparity at the severe level (AHI ≥30: 29.0% in men vs. 7.4% in women, $p < 0.001$). Among men, OSA prevalence increased with more severe acute disease (severe COVID-19: 28.2% vs. 6.7% in women). In contrast, women showed a higher prevalence of OSA following milder COVID-19. This sex-specific pattern echoes prior findings on COVID-19 mortality.

After adjustment for age, BMI, and fatigue severity, increasing COVID-19 severity remained a strong independent predictor of OSA in males but not in females. This was confirmed by a statistically significant interaction between COVID-19 severity and sex, indicating that the effect of disease severity on OSA risk is markedly attenuated in women. These findings suggest that biological sex modifies the relationship between acute COVID-19 severity and subsequent development of OSA. Biological differences in ACE2 expression may contribute to these disparities. Estrogens have been shown to modulate the renin-angiotensin

system by downregulating ACE and upregulating ACE2, Angiotensin 2 receptor (AT2R), and Mas receptor (MasR), which may offer some protection to women.[37,38] Potential mechanisms may include sex-specific differences in inflammatory responses, fat distribution, upper airway anatomy, and regulation of the renin–angiotensin–aldosterone system. Estrogen-mediated modulation of ACE2 expression and inflammatory pathways may partially protect women from severity-related increases in OSA risk, whereas men may be more vulnerable to post-infectious neuromuscular and inflammatory airway changes.[39-43]

Importantly, fatigue severity was not an independent predictor of OSA after adjustment, underscoring that while fatigue is a prominent symptom of long COVID-19, it should not be assumed to reflect sleep-disordered breathing without objective evaluation. Together, these findings support the need for targeted OSA screening in long COVID-19 patients, particularly among males with a history of moderate to severe acute infection.

4.1 Limitations

While this prospective study provides important insights into the need for screening obstructive sleep disorders in patients with long COVID, several limitations must be acknowledged. Firstly, the observational design limits our ability to establish causal relationships; unmeasured confounding variables may influence the associations observed. Notably, we lacked pre-COVID-19 sleep data, and no baseline PSG was available to confirm whether OSA was a new post-infection diagnosis. There is also a potential for sampling bias, as individuals experiencing more severe or persistent symptoms may have been more motivated to participate, potentially leading to an overrepresentation of symptom burden in the study population. Secondly, while the CFQ-11 is widely used to assess fatigue, it has not been explicitly validated in long COVID-19 populations, which may limit the interpretability of

fatigue-related findings. Thirdly, our follow-up period was limited to 6–7 months, which constrains conclusions about the long-term trajectory of OSA following COVID-19. Fourthly, fatigue is common to both OSA and post-viral syndromes, making it difficult to distinguish between OSA-related and long–term COVID–related fatigue in this context. Changes in body weight between follow-up visits were not systematically recorded, and therefore their potential influence on symptom trajectories and obstructive sleep apnoea risk could not be evaluated. Lastly, although the study included a diverse cohort from seven hospitals across Portugal, which enhanced external validity, uneven recruitment across centres and potential overrepresentation of patients with more severe symptoms may have introduced bias.

Although participants were recruited prospectively, obstructive sleep apnea (OSA) was assessed at a single post-COVID follow-up approximately six months after the acute infection, which confers a cross-sectional design and limits causal inference regarding the temporal relationship between COVID-19 severity and OSA. In the absence of pre-COVID sleep studies, it is not possible to determine whether the OSA cases identified represent true de novo disease or previously undiagnosed pre-existing OSA. It is therefore plausible that COVID-19 infection may have unmasked or exacerbated underlying OSA, leading to its detection during follow-up. This consideration is particularly relevant when interpreting the sex-specific pattern observed in our cohort, with higher OSA prevalence among men with severe COVID-19 and among women with milder disease. Such findings may reflect differences in baseline OSA risk profiles, sex-related vulnerability, or differential post-infection recognition of previously unrecognized sleep-disordered breathing. Future longitudinal studies incorporating pre-infection sleep assessments will be necessary to clarify the temporal relationship between COVID-19 and OSA and to better understand the mechanisms underlying these observations.

5. FUTURE RESEARCH AND CONCLUSIONS

Given the high prevalence of newly diagnosed OSA in patients with long COVID-19 identified in this study, future research should aim to better understand the long-term trajectory of sleep-disordered breathing after SARS-CoV-2 infection. Specifically, longitudinal studies with extended follow-up are needed to determine whether OSA in this population is transient, progressive, or persistent. Including baseline pre-COVID-19 polysomnography or retrospective sleep data could also help clarify whether these cases represent truly new diagnoses or the unmasking of previously undiagnosed OSA. Further investigation is also warranted into the pathophysiological mechanisms underlying the link between COVID-19 and OSA. This includes exploring the role of inflammatory markers, upper airway remodelling, neuromuscular sequelae, and RAAS dysregulation following infection. In particular, the gender-specific patterns we observed - higher OSA prevalence in men with severe COVID-19 and women with milder disease - suggest potential biological and hormonal modulators that should be explored in mechanistic studies.

Additionally, distinguishing OSA-related fatigue from post-viral fatigue remains a diagnostic challenge. The development and validation of fatigue assessment tools specifically for the long COVID-19 population could improve symptom classification and guide targeted interventions. Finally, clinical practice should consider routine OSA screening in long COVID-19 patients, especially those presenting with persistent fatigue, excessive daytime sleepiness, or cognitive symptoms, and in high-risk groups such as those with obesity or a history of moderate to severe COVID-19. Early identification and treatment of OSA in this context could improve quality of life, reduce symptom burden, and prevent long-term complications.

In conclusion, this multicenter prospective study demonstrates a significantly increased prevalence of OSA among patients with long COVID-19, highlighting the overlap between OSA and post-COVID-19 symptoms and underscoring the importance of integrating sleep evaluations into post-COVID-19 care pathways. These findings contribute to the growing body of evidence on the long-term effects of COVID-19 and suggest new avenues for improving patient outcomes through multidisciplinary and personalized approaches to recovery.

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Ethical Approval: All procedures followed the ethical standards of the Helsinki Declaration of 1964 and its later amendments. Approval number 140/21 by the ethics committee of the Local Health Unit of Algarve.

Consent to participate: Written informed consent to participate in the study was obtained from all individuals enrolled.

Data availability: Data can be provided by the corresponding author upon reasonable request.

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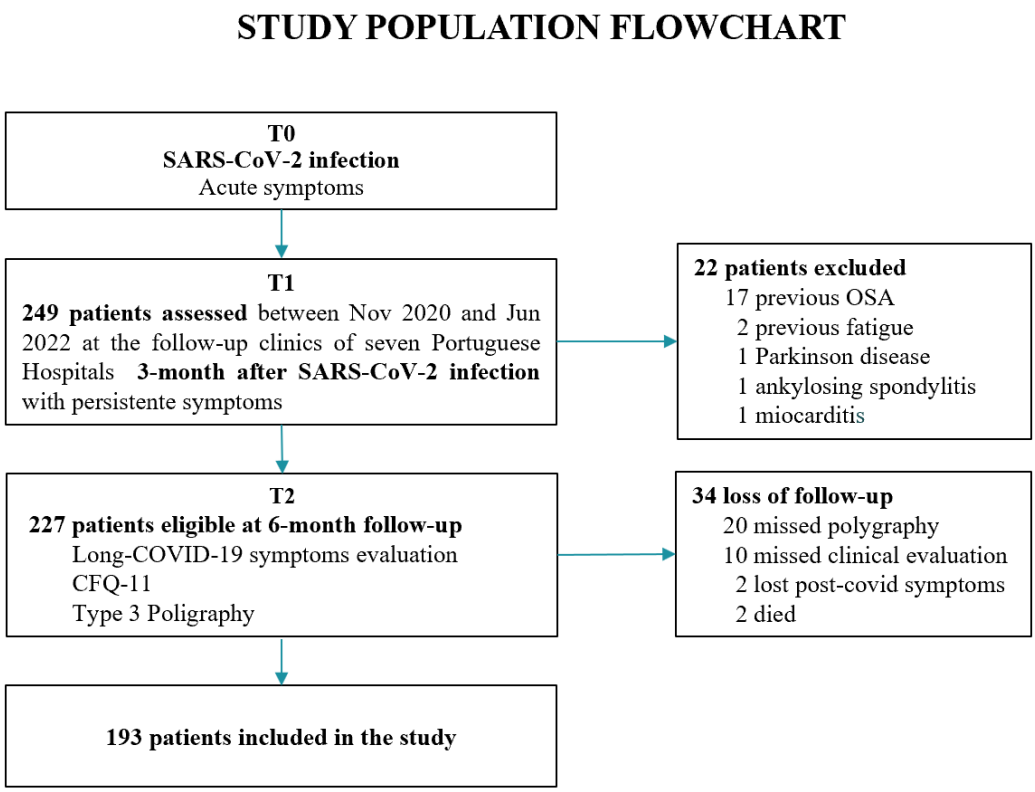

Figure 1. Study population flowchart

Table 1. General characteristics of study population

DEMOGRAPHIC AND CLINICAL VARIABLES	
Total n	193
Gender n (%)	
Females	107 (55,4%)
Males	86 (44,6%)
Age	
Mean (SD)[1]	53,6 (14,7±)
Age Categories n (%)	
18-40	41 (21,2%)
41-64	98 (50,8%)
65-79	47 (24,4%
≥80	7 (3,6%)
Body Mass Index[2]	
Mean (SD)[1]	28,5 (±5,5)
≥30 n (%)	51 (30,2%)
≥40 n (%)	21 (12,4%)
Comorbidities n (%)	
Hypertension	
Diabetes Mellitus	74 (38,5%)
Respiratory disease	25 (12,9%)
Heart Disease	22 (11,3%)
Psychiatric disease	18 (9,3%)
Immunosuppression	16 (8,2%)
Smoking Habits n (%)	10 (0,5%)
Smoker	
Former Smoker	23 (11,9%)
Non-Smoker	43 (22,3%)
Units Pack	127(65,8%)
Mean (SD)[1]	
Referencing Place n (%)	10,3(±21)
Hospital	
Primary care	93 (48,2%)
Occupational Medicine	78 (40,4%)
Hospital Admission n (%)	22 (11,4%)
Intensive Care n (%)	87 (45,0%)
	20 (10,3%)

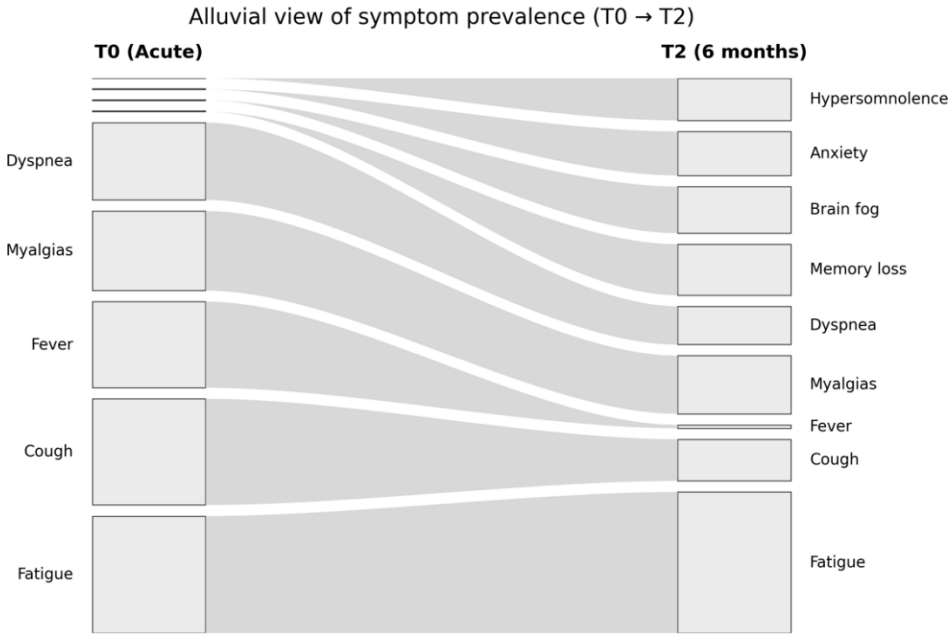

Figure 2. Alluvial diagram showing the evolution of symptom prevalence from the acute COVID-19 phase (T0) to six months post-COVID-19 (T2). The height of each symptom stratum and the width of the connecting flows are proportional to the relative prevalence at each time point, allowing visual comparison of persistence and change in symptom burden over time. *Percentages are based on symptom prevalence at each time point; symptoms not reported at T0 appear only at T2.*

Table 2. Comparison of the variables age, obstructive sleep apnea prevalence and fatigue by gender, aged 22-89 years.

PREVALENCE OF LONG COVID OSA AND FATIGUE BY GENDER

	Total n=193	**Females** n=107	**Males** n=86	*p value*
Age				
Mean (SD)[1]	53.6 (14.7±)	54.3 (±14.9)	54.0 (±14.6)	*p=0.141*[a]
Median [IQR][2]	53.5 [24.0]	55.3 [27.2]	51.5 [25.7]	
OSA Prevalence n (%)				
AHI≥5	66.3% (128)	62 (57.9%)	66 (76.7%)	*p=0,006*[b]
AHI≥15	35.7% (69)	17 (15.8%)	31 (36.0%)	*p=0.002*[b]
AHI≥30	17% (33)	8 (7.4%)	25 (29.0%)	*p<0.001*[b]
CFQ Total				
Mean (SD)[1]	16.6 (±8.2)	19.3 (±7.3)	13.3 (±8.1)	*p<0.001*[c]
Median [IQR][2]	18.0 [12.5]	18.0 [12.5]	14.0 [14.0]	
CFQ Physical				
Mean (SD)[1]	10.8 (±5.5)	12.3 (±5.1)	8.9 (±5.4)	*p<0.001*[c]
Median [IQR][2]	12.0 [9.0]	13.0 [10.5]	9.0 [9.0]	
CFQ Mental				
Mean (SD)[1]	5.8 (±3.6)	7.0 (±3.2)	4.4 (±3.6)	*p<0.001*[c]
Median [IQR]	7.0 [5.0]	8.0 [4.0]	7.0 [4.0]	

11.
Conclusions and recommendations

This thesis aggregates findings from one protocol and two multicentre prospective cohort studies investigating the relationship between post-COVID-19 fatigue, psychiatric disorders, and sleep pathology.

The first paper defined a protocol that quantifies both physical and psychological fatigue and proposes to explore its association with depression, anxiety, and posttraumatic stress disorder (PTSD) in Portuguese adults up to nine months post- SARS Cov2- infection. The study advocates for the integration of physical and mental health care to address the multi-dimensional needs of affected patients comprehensively. I intended to create this protocol as an accessible and replicable instrument for use in other populations. To this end, the study employs internationally validated, standardised tools whose translation and adaptation follow methodological guidelines to achieve semantic, idiomatic, experiential, and conceptual equivalence through structured processes of back-translation, committee review, and pre-testing. By providing a clear protocol with instruments that can be readily adapted cross-culturally, the aim is to encourage comparative studies in diverse settings and contribute to a broader understanding of the relationship between post-COVID-19 fatigue and mental health. This replicability will support the evolution of research in this area, enabling different teams to assess fatigue prevalence and its determinants, as well as the impact of integrated physical rehabilitation and psychological support interventions, thereby reinforcing the need to consider the integration of physical and mental care in supporting COVID-19 survivors.

The second study evaluated the effects of acute COVID-19 severity on long-term fatigue subtypes and health-related quality of life (HRQoL). Notably, individuals with mild or moderate acute disease report higher levels of both physical and mental fatigue and display

significantly reduced HRQoL compared to those who experienced severe illness, challenging previous assumptions linking greater acute severity to worse long-term impairment. Fatigue is found to be most strongly associated with depression and anxiety, and both physical and mental fatigue independently predict lower daily functioning and life satisfaction. The study highlights the critical need for personalized rehabilitation and ongoing support, even in those whose initial infection was mild, and cautions against relying solely on the severity of acute illness as a predictor of long-term outcomes.

The third paper established a remarkably high prevalence of newly diagnosed Obstructive Sleep Apnoea (OSA) in individuals with long COVID, identifying distinct gender- and disease-severity-specific patterns and highlighting the clinical overlap between OSA and persistent post-COVID fatigue, cognitive dysfunction, and hypersomnolence. The results underscore the need for routine sleep assessments and tailored interventions to mitigate long-term complications in this population.

The findings emphasised that post-COVID-19 treatment should shift decisively toward integrated, patient-centered care that addresses both persistent physical and mental health symptoms simultaneously. Such an approach is essential for improving recovery trajectories, promoting quality of life, and mitigating the long-term burden of COVID-19 on individuals and healthcare systems.

11.1 Key Implications for Integrated Care

Holistic Assessment and Management

a) Interconnectedness of Symptoms**:** The anticipated strong association between fatigue (both physical and psychological) and mental health symptoms (depression, anxiety, PTSD) indicates that symptoms do not exist in isolation. Effective post-COVID-19 care must therefore assess and manage these symptoms together, rather than focusing exclusively on one domain.

b) Simultaneous Evaluation**:** Implementing combined screening for mental health disorders alongside assessments for fatigue and quality of life can help identify individuals at risk and facilitate timely, coordinated interventions.

Personalised Interventions and Multidisciplinary Teams

a) Individualised Care**:** The observed variability in the expression and severity of mental health and fatigue symptoms underscores the need for tailored, patient-specific treatment plans. These plans should draw on expertise from multiple health disciplines, such as pulmonology, psychuiatry, psychology, rehabilitation, and primary care, to construct comprehensive support for each patient.

b) Team-Based Approach**:** Multidisciplinary collaboration can enhance both the recognition and management of overlapping physical and psychological symptoms, ensuring that underlying mental health issues are not overlooked while addressing physical complaints, such as fatigue.

Long-Term Monitoring and Support

a) Beyond the Acute Phase: Expected findings suggest that mental symptoms (depression, anxiety, PTSD) and fatigue can largely persist beyond recovery from the acute phase of COVID-19. Integrated care programs should, therefore, provide ongoing monitoring and long-term support, rather than just episodic or short-term interventions.

b) Potential for Chronicity: Recognising the risk of chronic symptoms requires sustainable models of care that can adapt to patients' changing needs during recovery.

Enhanced Quality of Life as a Primary Outcome

a) Prioritising Well-being: The link between mental health, fatigue, and health-related quality of life (HRQoL) highlights that successful recovery is not merely the absence of disease, but rather achieving optimal functioning and well-being. Integrated programs should include routine HRQoL assessments and target interventions towards overall life satisfaction and daily functioning.

Education, Training, and Resource Allocation

a) Awareness among Clinicians: The findings highlight the need to train healthcare providers about the complex, multi-systemic nature of long COVID, ensuring vigilance for persistent or emerging psychological symptoms even in physically recovered individuals.
b) Resource Planning: Healthcare systems may need to allocate more resources to mental health services within post-COVID-19 clinics and ensure seamless communication between mental health providers and other specialties.

11.2 Final considerations

There was a high level of participation these long-COVID studies among patients and health care professionals. Limitations of this thesis include a sub-optimal response rate in some included centres, which preclude the generalizability of the results.

I emphasize again the importance of suspecting and diagnosing OSAS in long covid, to better treat patients and their symptoms.

Multidisciplinary

protocols are crucial for the development of long-COVID studies, aiming to improve the reproducibility of results. Further research is needed to identify the phenotypes of this heterogeneous syndrome and evolve into endotypes that are at the root of this pathology.

12.
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13.

Appendices

Appendix A – Documentation of studies one and two

Ethics Committee Request Decision

Project registration on ClinicalTrials.gov

EuroQol Research Foundation authorization to use the EQ-5D

Clinical Research Form in English

REPÚBLICA PORTUGUESA
SAÚDE

SNS
SERVIÇO NACIONAL DE SAÚDE

Centro Hospitalar Universitário do Algarve

Comissão de Ética para a Saúde

tel. 41110 / 8596
e-mail comissão.etica@chalgarve.min-saude.pt

Exm.(a) Sr.(a)
Conselho de Administração
Centro Hospitalar Universitário do Algarve

s. ref. s. com. n. ref./data 141/21, 06.09.2021

Assunto: Estudo" Sequelas neuropsicológicas como fator de risco para fadiga pós - COVID 19"

De acordo com o emitido pelo Presidente da CES de dia 21-07-2021 o questionário exclui qualquer dado de identificação do paciente. O parecer é positivo.

A Comissão de Ética para a Saúde,

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: May 6, 2022

ClinicalTrials.gov ID: NCT05323318

Study Identification

Unique Protocol ID:	141/21
Brief Title:	Neuropsychological Sequelae and Long COVID-19 Fatigue (PostCoV2Psy)
Official Title:	Neuropsychological Sequelae as a Risk Factor for Long COVID-19 Fatigue
Secondary IDs:	

Study Status

Record Verification:	May 2022
Overall Status:	Recruiting
Study Start:	April 1, 2022 [Actual]
Primary Completion:	September 30, 2022 [Anticipated]
Study Completion:	October 31, 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	Centro Hospitalar Universitario do Algarve
Responsible Party:	Principal Investigator Investigator: Ligia Pires [lpires] Official Title: Principal Investigator Affiliation: Centro Hospitalar Universitario do Algarve
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Exempt
Data Monitoring:	Yes
FDA Regulated Intervention:	No

De: EuroQol - Registration
Enviado: 10 de abril de 2022 18:09
Para: alves1029@hotmail.com
Assunto: General conditions for the registration ID : 48217

Dear Dr. Ligia Pires Vicente ,

We have registered your agreement with our Terms of Use regarding your request with tracking number: 48217 .

A team member will contact you as soon as possible to deliver the requested versions.

Yours sincerely,

Best regards,

Bernhard Slaap
Executive Director
EuroQol Research Foundation

T *+31 882026890* | E www.euroqol.org | Marten Meesweg 107 | 3068 AV Rotterdam
The Netherlands

HOSPITAL _____ **DOCTOR NAME** _____

A. INCLUSION DATA

1. Patient code: _____
   (Assigned randomly and only to the knowledge of each principal investigator by Center)
2. Date of positive PCR/TRAG:____/_____/_____
3. Origin of referral for the post-COVID medical consultation:
   Primary care? ___ Hospital? ___ Occupational medicine for health care workers? ___

B. SOCIODEMOGRAPHIC DATA

1. Birth date: ____/_____/_____
2. Sex (Female/Male)
3. Weight: ____ Kg Heigt: __,___ m BMI: _____
4. Schooling: _____ Profession: _____
5. Did you lose your job during de pandemia? Yes/No
6. Household: _____cohabitants

C. BACKGROUND

1. Smoking habits (Never Smoker / Ex-Smoker_____ UPY / Smoker_____UPY)
2. Alcohol comsumption_____ Drugs Comsumption_____
3. Comorbidities(Yes/No):
   i. Arterial hypertension
   ii. Diabetes
   iii. Heart disease (Which?_____)
   iv. Asthma
   v. COPD
   vi. Immunossupression (Which?_____)
   vii. Psychiatric disease, diagnose by psychiatrist
   (Which? _____)
   viii. Neurological disease
   (Which?_____)
4. Medication
   i. Previous to COVID-19 _____
   ii. After COVID-19: Corticoids (Yes/No), name/dose? _____
   Other medications _____

T1 – LONG COVID (Persistent symptoms 3 months post-COVID-19)

A) SEVERITY OF ACUTE DISEASE

1. Mild disease: mild symptoms with no evidence of pneumonia or hypoxemia.
2. Moderate disease: pneumonia (fever, cough, dyspnea, tachypnea) but with peripheral O2 saturation ≥ 90% in room air, and without hemodynamic instability.
3. Severe disease: pneumonia and at least one of the following criteria: tachypnea >30 cycles per minute; dyspnoea; pulse oximetry O2 < 90% in ambient air; hemodynamic instability.

Hospital Admission? Y/N **Intensive Care? Y/N** **Invasive Mechanical Ventilation? Y/N**

B) SYMPTOMS

Cough ___ Fatigue ___ Difficulty breathing ___ Chest pain ___

Muscle tension and pain ____ (Where? _____)

Pain in the joints ____ (Were? _____)

Headaches ___ Fever ___ Loss of appetite ___ Loss of taste ___ Loss of smell ___

Conjunctivitis ___ Misty vision ___ Decreased visual acuity ___ Memory loss ___ Brain fog ___

Daytime hypersomnolence ___ Insomnia ___Anxiety ___ Depression ___ Aphasia ___ Hemiparesis ___

Skin lesions ___ (Which and where? _____)

Diarrhea ___ Vomiting ____ Other _____

C) MEDICATION DURING HOSPITALIZATION? Y / N

Metilprednisolone (Total dose_____mg) Dexametasone (Total dose_____mg)

Remdesivir (Total dose_____mg) Tocilizumab (Total dose _____mg) Others _____

D) SOCIAL ISOLATION

Number of days you have been isolated at home _____ Days (Alone or with family members?)

Number of days in hospital sanitary isolation_____ Days

Pós – COVID-19

t1 (8 months after PCR/TRAG positive test): _____/_____/_____

A) SYMPTOMS

Cough ___ Fatigue ___ Difficulty breathing ___ Chest pain ___

Muscle tension and pain ____ (Where? _____)

Pain in the joints ____ (Were? _____)

Headaches ___ Fever ___ Loss of appetite ___ Loss of taste ___ Loss of smell ___

Conjunctivitis ___ Misty vision ___ Decreased visual acuity ___ Memory loss ___ Brain fog ___

Daytime hypersomnolence ___ Insomnia ___Anxiety ___ Depression ___ Aphasia ___ Hemiparesis ___

Skin lesions ___ (Which and where? _____)

Diarrhea ___ Vomiting ____ Other _____

B) Fatigue Chalder Scale scoring

Depression subscale ____ points

Anxiety subscale ____ points

Total score ____ points

C) HADS scoring

Depression subscale ____ points

Anxiety subscale ____ points

D) PTSS 14 scoring

Total score ____ points

E) EQ-5D scoring

Health status EQ-VAS____ % EQ-5D-3L (attach only)

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

STUDY CODE _____Date: ___ / ___ / ___

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best..

A1. **I feel tense or 'wound up':**

3 ( ) Most of the time

2 ( ) A lot of the time

1 ( ) From time to time, occasionally

0 ( ) Not at all

D2. **I still enjoy the things I used to enjoy:**

0 ( ) Definitely as much

1 ( ) Not quite so much

2 ( ) Only a little

3 ( ) Hardly at all

A3. **I get a sort of frightened feeling as if something awful is about to happen:**

3 ( ) Very definitely and quite badly

2 ( ) Yes, but not too badly

1 ( ) A little, but it doesn't worry me

0 ( ) Not at all

D4. **I can laugh and see the funny side of things:**

0 ( ) As much as I always could

1 ( ) Not quite so much now

2 ( ) Definitely not so much now

3 ( ) Not at all

A5. **Worrying thoughts go through my mind:**

3 ( ) A great deal of the time

2 ( ) A lot of the time

1 ( ) From time to time, but not too often

0 ( ) As much as I ever did

1 ( ) Rather less than I used to

2 ( ) Definitely less than I used to

3 ( ) Hardly at all

A13. **I get sudden feelings of panic:**

3 ( ) Very often indeed

2 ( ) Quite often

1 ( ) Not very often

0 ( ) Not at all

D14. **I can enjoy a good book or radio or TV program:**

0 ( ) Often

1 ( ) Sometimes

2 ( ) Not often

3 ( ) Very seldom

*Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Zigmond, AS; Snaith, RP (1983). "The hospital anxiety and depression scale". Acta Psychiatrica Scandinavica. 67 (6): 361–370.

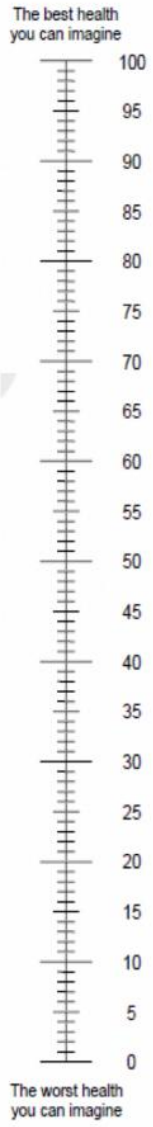
Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007 Mar;12(2):225-35;

EQ-VAS Questionnaire

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



Appendix B: Documentation of study three

Pulmonology Journal Timeline

Ethics Committee Request Decision

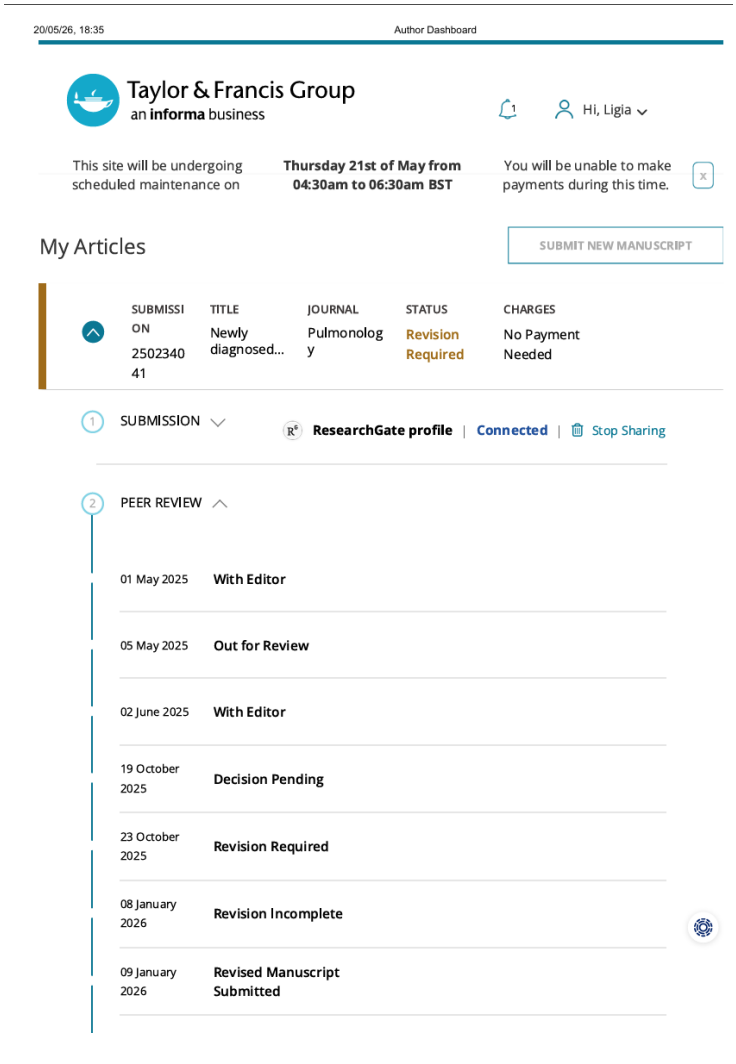
Study registration on ClinicalTrials.gov

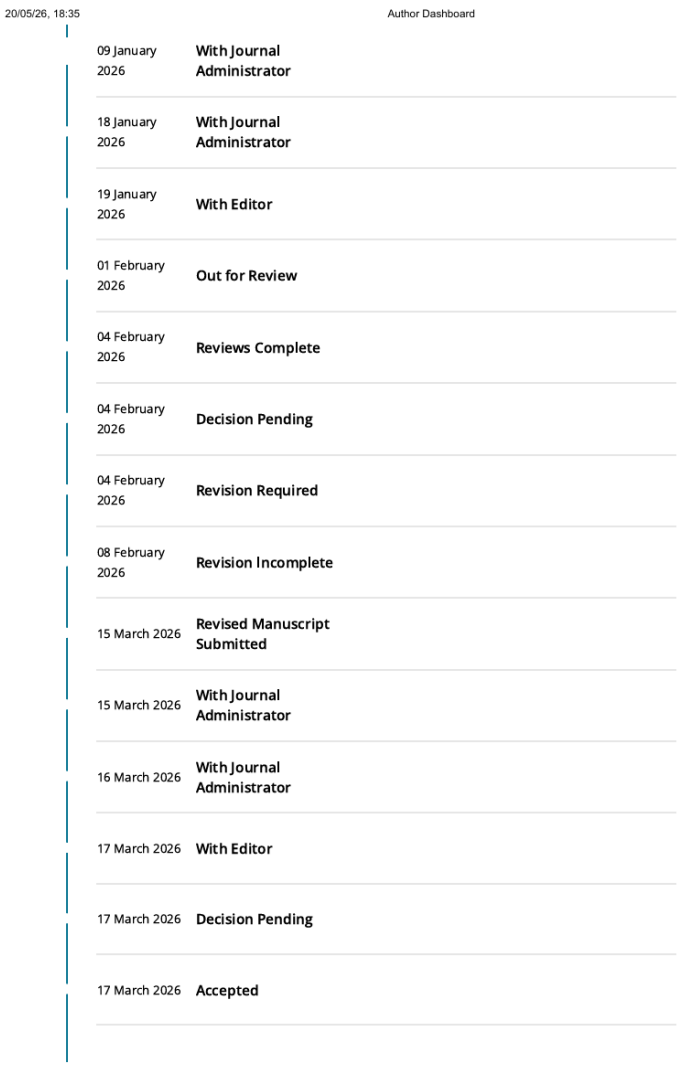
EuroQol Research Foundation authorization to use the EQ-5D

Research Grand of Portuguese Society of Pulmonology

Clinical Reseach Form in Portuguese

Pulmonology Journal Timeline





REPÚBLICA PORTUGUESA
SAÚDE

SNS
SERVIÇO NACIONAL DE SAÚDE

Centro Hospitalar Universitário do Algarve

Comissão de Ética para a Saúde

tel. 41110 / 8596
e-mail comissão.etica@chalgarve.min-saude.pt

Exm.(a) Sr.(a)
Conselho de Administração
Centro Hospitalar Universitário do Algarve

s. ref. s. com. n. ref./data 140/21, 06.09.2021

Assunto: Estudo "Apneia obstrutiva do sono em doentes com fadiga pós- COVID-19: estudo de coorte prospetivo multicêntrico"

De acordo com o emitido pelo Presidente da CES de dia 21-07-2021 o questionário exclui qualquer dado de identificação do paciente. O parecer é positivo.

A Comissão de Ética para a Saúde,

Protocol Registration Preview

This is a rough approximation of how the Protocol Registration will appear on the ClinicalTrials.gov public web site.

Long COVID-19 Fatigue and Obstructive Sleep Apnea (PostCoV2OSA)

Sponsor:

Centro Hospitalar Universitario do Algarve

Collaborators:

Sociedade Portuguesa de Pneumologia
Universidade do Algarve
Universidade do Porto
Center for Health Technology and Services Research
Linde Health Care

Information provided by (Responsible Party):

Ligia Pires, Centro Hospitalar Universitario do Algarve

De: EuroQol - Registration
Enviado: 8 de abril de 2022 17:38
Para: alves1029@hotmail.com
Assunto: General conditions for the registration ID : 48216

Dear Dr. Ligia Pires Vicente ,

We have registered your agreement with our Terms of Use regarding your request with tracking number: 48216 .

A team member will contact you as soon as possible to deliver the requested versions.

Yours sincerely,

Best regards,

Bernhard Slaap
Executive Director
EuroQol Research Foundation

T *+31 882026890* | E www.euroqol.org | Marten Meesweg 107 | 3068 AV Rotterdam
The Netherlands

SOCIEDADE PORTUGUESA
DE PNEUMOLOGIA

CERTIFICADO

BOLSA SPP PARA PROJETOS DE INVESTIGAÇÃO EM COVID-19

Certifica-se como vencedor em *ex-aequo*, o projeto de investigação, com o título:

"APNEIA OBSTRUTIVA DO SONO EM DOENTES COM FADIGA PÓS-COVID-19: ESTUDO DE COORTE PROSPETIVO MULTICÊNTRICO"

Da Autoria de: **Drª Lígia Pires**

Do **Centro Hospitalar Universitário do Algarve**

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

Professor Doutor António Morais
Presidente da Sociedade Portuguesa de Pneumologia

HOSPITAL _____ MÉDICO _____

A. Dados de Inclusão

1. Código do doente: _____
   (Atribuído aleatoriamente e apenas do conhecimento de cada investigador principal por Centro)
2. Data do consentimento informado: ____/_____/_____
3. Data de teste PCR positivo:_____/_____/_____

B. Dados Sociodemográficos

1. Raça: Caucasiana ____ Negra ____ Asiática ____ Outra ____
2. Peso: ____ Kg Altura: __,___ m IMC: _____
3. Escolaridade: _____ Profissão: _____
4. Esteve em lei off? Sim/Não
5. Perdeu o emprego? Sim/Não
6. Nº pessoas do agregado familiar ____ coabitantes infetados na mesma altura: ____

C. Antecedentes

1. Hábitos tabágicos (Nunca / Ex-Fumador / Fumador_____UMA)
2. Consumo de álcool e/ou abuso de drogas?_____
3. Comorbilidades (sim/não): **Não / Sim** (Se sim, indique quais)
   i. HTA
   ii. Diabetes
   iii. Patologia cardíaca (qual?_____)
   iv. Asma
   v. DPOC
   vi. Imunossupressão (qual?_____)
   vii. Síndrome de Apneia Obstrutiva do Sono (IAH prévio a COVID19_____)
   viii. Doença psiquiátrica, com diagnostico por psiquiatra _____
   ix. Doença neurológica (qual?_____)
4. Medicação
   i. Prévia a COVID-19 _____
   ii. Pós-COVID-19: Corticoides (Sim/Não), Quais e dose? _____
   Outros _____

1

COVID-19 DOENÇA AGUDA – t0

A) GRAVIDADE

a. **Doença ligeira:** sintomas ligeiros sem evidência de pneumonia ou hipoxemia;
b. **Doença moderada:** pneumonia (febre, tosse, dispneia, taquipneia) mas com saturação periférica de O2 ≥ 90% em ar ambiente, e sem instabilidade hemodinâmica;
c. **Doença grave:** pneumonia + pelo menos, um dos seguintes critérios: Taquipneia superior a 30 ciclos por minuto; dificuldade respiratória; SpO2 inferior a 90% em ar ambiente; instabilidade hemodinâmica;

Internamento? S / N **Cuidados Intensivos? S / N** **Ventilação Mecânica Invasiva? S / N**

C) SINTOMAS

Tosse seca ___ Fadiga ___ Dificuldade respiratória ___ Pressão ou dor no peito ___

Tensão e dores musculares ___ (localização _____)

Artralgias ___ (localização _____)

Dores de garganta ___ Rouquidão ____ Cefaleias ___ Febre ___

Perda de apetite ___ Perda de paladar ___ Perda de olfacto ___

Conjuntivite ___ Visão enevoada ___ Diminuição da acuidade visual ___

Perda de memória ___ Lentificação do pensamento ___ Hipersonolência diurna ___

Insónias ___Ansiedade ___ Depressão ___ Afasia ___ Hemiparésia ___

Alterações cutâneas ___ Náuseas ___ Vómitos ___ Diarreia ___ Outros _____

D) MEDICAÇÃO DURANTE O INTERNAMENTO

Corticoides: Dexametasona (Dose total_____mg) Outros _____
Antivirais: Remdesivir (dose total_____mg) Outros _____

E) ISOLAMENTO

1. Número de dias em que esteve isolado em casa _____ (Sozinho?/Com familiares?)
2. Número de dias que esteve internado no hospital _____

Pós – COVID-19

Data t1 (a partir dos 6 meses após teste de PCR): ____/_____/_____

A) SINTOMAS (persistentes ou "de novo", colocar cruzes nos sintomas presentes)

Tosse seca ___ Fadiga ___ Dificuldade respiratória ___ Pressão ou dor no peito ___

Tensão e dores musculares ___ (localização _____)

Artralgias ___ (localização _____)

Edemas dos membros inferiores ___

Dores de garganta ___ Rouquidão ____ Cefaleias ___ Febre ___

Perda de apetite ___ Perda de paladar ___ Perda de olfacto ___

Conjuntivite ___ Visão enevoada ___ Diminuição da acuidade visual ___

Perda de memória ___ Lentificação do pensamento ___ Hipersonolência diurna ___

Insónias ___Ansiedade ___ Depressão ___ Afasia ___ Hemiparésia ___

Alterações cutâneas ___ Náuseas ___ Vómitos ___ Diarreia ___

Diminuição da líbido ___ Disfunção erétil ___Outros _____

B) Pontuação da escala de fadiga de Chalder ____ pontos

C) Pontuação da escala de Sonolência de Epworth ____ pontos

D) Estudo do sono, IAH ____ hora

E) EQ-5D: Estado de saúde EQ-VAS____ % EQ-5D-3L

F) Provas respiratórias: Espirometria, mecânica ventilatória, capacidade de difusão CO

G) Análises: Hemograma, VS, Bioquímica (Creatinina, ureia, AST, ALT, D.Dímeros; pro-BNP)

ESCALA DE FADIGA DE CHALDER (t1)

Código do doente: _____ Data: ___ / ___ / ___

Em relação às duas últimas semanas marque com um x o que sentiu, de acordo com as opções ao lado.

FADIGA FÍSICA	**Nunca** 0	**Raramente** 1	**Às vezes** 2	**Sempre** 3
Cansei-me facilmente				
Precisei de descansar mais				
Estive sonolento				
Não consegui iniciar nada				
Estive com falta de ânimo				
Senti menos força nos músculos				
Senti-me fraco				
FADIGA MENTAL				
Tive problemas de concentração				
Tive dificuldade para pensar claramente				
Tive dificuldade para encontrar as palavras certas				
Tive problemas de memória				

PONTUAÇÃO

Fadiga física ____ pontos Fadiga mental _____ pontos Total ____ pontos

Versão Portuguesa 2001Centro de Estudos e Investigação em Saúde da Universidade de Coimbra (CEISUC).

QUESTIONÁRIO EQ-5D-3L (t1)

EQ-5D

AVALIAÇÃO DE GANHOS EM SAÚDE
QUESTIONÁRIO EQ-5D

Assinale com uma cruz (assim ☒), um quadrado de cada um dos seguintes grupos, indicando qual das afirmações melhor descreve o seu estado de saúde hoje.

▶ Mobilidade

- Não tenho problemas em andar ..... ❑1
- Tenho alguns problemas em andar ..... ❑2
- Tenho de estar na cama ..... ❑3

▶ Cuidados Pessoais

- Não tenho problemas com os meus cuidados pessoais ..... ❑1
- Tenho alguns problemas em lavar-me ou vestir-me..... ❑2
- Sou incapaz de me lavar ou vestir sozinho/a ..... ❑3

▶ Actividades Habituais *(ex. trabalho, estudos, actividades domésticas, actividades em família ou de lazer)*

- Não tenho problemas em desempenhar as minhas atividades habituais ..... ❑1
- Tenho alguns problemas em desempenhar as minhas atividades habituais ..... ❑2
- Sou incapaz de desempenhar as minhas atividades habituais ..... ❑3

▶ Dor / Mal-estar

- Não tenho dores ou mal-estar..... ❑1
- Tenho dores ou mal-estar moderados ..... ❑2
- Tenho dores ou mal-estar extremos ..... ❑3

▶ Ansiedade / Depressão

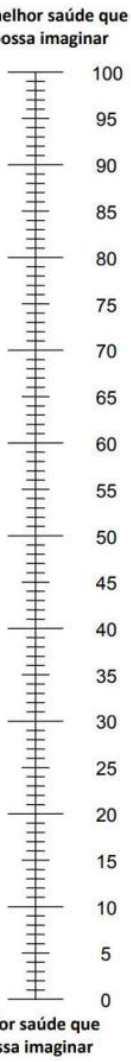
- Não estou ansioso/a ou deprimido/a ..... ❑1
- Estou moderadamente ansioso/a ou deprimido/a ..... ❑2
- Estou extremamente ansioso/a ou deprimido/a ..... ❑3

QUESTIONÁRIO EQ-VAS (t1)

► Gostaríamos de saber o quanto a sua saúde está boa ou má HOJE

- A escala está numerada de 0 a 100.
- 100 significa a melhor saúde que possa imaginar. O significa a pior saúde que possa imaginar.
- Coloque um X na escala de forma a demonstrar como a sua saúde se encontra HOJE.
- Agora, por favor, escreva o número que assinalou na escala no quadrado abaixo.

A SUA SAÚDE HOJE = ☐



Muito obrigado por ter preenchido este questionário.

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