Sleep Medicine:X 9 (2025) 100135

Contents lists available at ScienceDirect

Sleep Medicine: X

journal homepage: www.sciencedirect.com/journal/sleep-medicine-x

Insomnia, cardiorespiratory function and quality of life in individuals with post-COVID-19 fatigue

Nathalea Spode de Arruda [a,b], Alessandra Hofstadler Deiques Fleig [c], Charles Rech [b], Carine Cristina Callegaro [a,b,d,*]

[a] Postgraduate Program in Human Communication Disorders, Federal University of Santa Maria-UFSM, Santa Maria, RS, Brazil
[b] Physiology and Rehabilitation Laboratory, Federal University of Santa Maria-UFSM, Santa Maria, RS, Brazil
[c] Department of Clinical Medicine, Federal University of Santa Maria-UFSM, Santa Maria, RS, Brazil
[d] Physiotherapy and Rehabilitation Department, Federal University of Santa Maria-UFSM, Santa Maria, RS, Brazil

ARTICLE INFO

Keywords:
Covid-19
Sleep
Fatigue

ABSTRACT

Objective: This study aimed to compare the prevalence of insomnia, lung function, inspiratory muscle function, functional capacity, and quality of life in individuals with and without post-COVID-19 fatigue.
Methods: Thirty-four post-COVID-19 individuals participated in the study, 20 with fatigue (32 ± 12 years old, 15% male) and 14 without fatigue (31 ± 12 years old, 42.9% male). The Chalder Fatigue Scale (CFS) was employed to categorize the volunteers into two groups: those with fatigue (score ≥4) and those without fatigue (score <4). The Insomnia Severity Index (ISI) and the Epworth Sleepiness Scale (ESS) were used to assess insomnia and excessive daytime sleepiness, respectively. Pulmonary function was evaluated by spirometry, inspiratory muscle strength was assessed by the maximum inspiratory pressure (MIP), and inspiratory endurance was evaluated by maintaining an inspiratory load of 60% of MIP until fatigue. The 6-min walk test (6MWT) was used to evaluated functional capacity, while the WHOQOL-BREF questionnaire assessed quality of life.
Results: Individuals with post-COVID-19 fatigue demonstrated a higher prevalence of insomnia (80% vs. 49%) and excessive daytime sleepiness (45% vs. 7%), as well as lower MIP, shorter distance covered in the 6MWT, and lower FEV_1/FVC (forced expired volume in the first second divided by forced vital capacity), and FEV_1/FVC% of predicted. Additionally, they exhibited poorer quality of life in the physical and environmental domains. CFS demonstrated a direct correlation with ISI (r=0.436, p=0.01) and ESS (r=0.593, p=0.001), as well as an inverse correlation with the distance covered in the 6MWT (r=-0.398, p=0.022) and FEV_1 (r=-0.412, p=0.01). ISI was an independent predictor of CFS, with 62% of CFS variance explained by ISI variance.
Conclusion: Individuals with symptoms of post-COVID-19 fatigue may have a higher prevalence of insomnia, reduced inspiratory muscle strength, functional capacity, and Tiffeneau index, along with impaired quality of life. ISI is an independent predictor of post-COVID-19 fatigue.

1. Introduction

Individuals infected with COVID-19, even in a mild form, may have ongoing symptoms [1] such as fatigue, shortness of breath, muscle weakness, and poor sleep quality [2–4]. It has been found that 82% of patients still experience fatigue eight months after infection [5], which is linked to functional limitations [6] and reduced quality of life [5].

COVID-19 individuals also tend to have daytime sleepiness [7], and long COVID-19 cases have twice the risk of developing insomnia symptoms [8]. In the general population, fatigue is associated with insomnia [9] and obstructive sleep apnea (OSA) [7]. However, more research is needed to understand the sleep disturbances in individuals with persistent fatigue post-COVID-19, since fatigue might also be related to respiratory muscle dysfunction [10] and impaired lung function [1]. Reduced inspiratory muscle strength has been observed in both hospitalized and non-hospitalized individuals with COVID-19 [11], as well as in athletes [1], and this has been connected to exercise intolerance post-COVID-19 [11]. Additionally, restrictive lung function

* Corresponding author. Laboratório de Fisiologia e Reabilitação- LAFIR. Av. Roraima, n° 1000, Universidade Federal de Santa Maria, Centro de Ciências da Saúde, prédio 26, anexo B, sala 002, Bairro Camobi, Santa Maria, RS, CEP: 97105-900, Brazil.
E-mail address: carine.callegaro@ufsm.br (C.C. Callegaro).

https://doi.org/10.1016/j.sleepx.2024.100135
Received 30 July 2024; Received in revised form 16 November 2024; Accepted 25 November 2024
Available online 27 November 2024

patterns have been reported six months after discharge from the ICU [12].

Fatigue is the prevailing symptom following COVID-19 infection, significantly impacting individuals' quality of life. Nevertheless, whether fatigue results from sleep disturbances, muscular issues, or impaired lung function remains uncertain. The primary objective of this study is to conduct a comparative analysis of the frequency of insomnia and OSA, pulmonary function, inspiratory muscle strength and endurance, functional capacity, and quality of life among individuals experiencing post-COVID-19 fatigue and those without this condition. Additionally, the study seeks to identify the factors that contribute to the manifestation of fatigue symptoms.

2. Methods

2.1. Participants and procedure

A sample size of 26 was determined based on a difference of 95 m in the distance covered in the 6-min walk test by individuals post-COVID-19 (518 ± 90 m) compared to healthy individuals (423 ± 68 m) [13], with a statistical power of 85% and an alpha error of 0.05.

This research received approval from the Human Research Ethics Committee of the Federal University of Santa Maria. All participants provided written informed consent. Volunteers were recruited by the researcher through social media postings, followed by a telephone screening to verify eligibility criteria. The assessments were conducted in two sessions within a maximum interval of 15 days. During the first session, a medical history interview was administered, which included anthropometric data and general characteristics such as income, most recent COVID-19 infection, number of infections, smoking status, previous illnesses, and current medications.

Subjects were included if they were between 18 and 59 years of age, clinically stable, had no pulmonary or neurological disease before COVID-19, and were not engaged in regular exercise. Individuals were excluded if they had self-reported uncorrectable vision or hearing problems, inability to walk, use of a walking aid, pulmonary hypertension, pulmonary or neuromuscular disease before COVID-19, unstable heart disease, unstable angina, hemodynamic instability, febrile state, uncontrolled seizure disorders, cognitive deficits, or balance deficits.

2.2. Measures

2.2.1. Chalder Fatigue Scale

The Chalder Fatigue Scale (CFS), translated and validated for the Brazilian population, was used to divide the participants into groups with and without fatigue. Scores were calculated using a bimodal score, where scores of zero and one were considered zero, and scores of two and three were considered one. Fatigue was considered when the final score was greater than or equal to four [14].

2.2.2. Short physical performance Battery

This test assesses balance impairments. The score used to determine eligibility for the study was an individual who could remain in orthostasis with their feet together for 10 s [15].

2.2.3. Post-COVID-19 functional status scale (PCFS)

This 5-item scale grades functional limitations. The score ranges from zero to four, with the highest score indicating the greatest severity of functional limitation. The questions pertain to post-COVID life, including topics such as survival, care, activities of daily living, instrumental activities of daily living, and participation in usual social roles. The instrument has been translated and validated for the Brazilian population [16].

2.2.4. Daytime sleepiness

The Epworth Sleepiness Scale (ESS) is a validated instrument for assessing the presence of excessive daytime sleepiness. It was translated into Portuguese and is available for use in Brazil [17]. The ESS consists of scoring the likelihood of falling asleep during eight everyday situations on a scale of 0–3. A score >10 points indicated excessive daytime sleepiness.

2.2.5. Insomnia Severity Index

The Insomnia Severity Index (ISI) is a self-report questionnaire comprising eight items designed to assess the severity of insomnia symptoms. The ISI has been translated and validated for the Brazilian population and is widely used in clinical and research settings [18].

2.2.6. Nocturnal oximetry

Nocturnal oximetry was assessed using a portable device (Biologix), which measures oxygen saturation at night. This device is also capable of assessing limb movements (actigraphy) and the presence or absence of snoring during use. Thus, data can be obtained to estimate wakefulness, sleep, and total sleep time [19]. An Oxygen Desaturation Index (ODI) of up to 5 events per hour is considered normal, up to 15 events per hour is mild, up to 30 events per hour is moderate, and above 30 events per hour indicates severe obstructive sleep apnea (OSA) [19].

2.2.7. Lung function

Spirometry was conducted according to the recommendations of the Brazilian Society of Pneumology and Tisiology [20] using a portable spirometer (Contec Sp80b). The volunteers were asked to take inspiration at the level of total lung capacity, followed by rapid and forced exhalation at the level of residual volume. To perform the bronchodilation test, four jets of 100 mcg of phenoterol were used, and the response was measured after 15–20 min of waiting. Data on expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the Tiffeneau index (FEV_1/FVC) were obtained. Lung disease was diagnosed based on the criteria set forth by the Brazilian Society of Pneumology and Tisiology [20].

2.2.8. Inspiratory muscle strength

Inspiratory muscle strength was determined using Maximum Inspiratory Pressure (MIP), obtained using a pressure sensor connected to LabChart 8 acquisition software (ADinstruments, Bella Vista, Australia). The participants were instructed to inhale deeply from the residual volume against an occluded circuit, but with a small air leak (2 mm), to assess MIP. The maneuvers were repeated up to 12 times to obtain three measurements with a variation of less than 10%. The highest value obtained is used as the MIP [21,22]. The equation of Neder et al. was used to calculate the predicted values according to sex and age [23]. A MIP below 70% of predicted was considered indicative of inspiratory muscle weakness [22].

2.2.9. Inspiratory endurance test

The MIP was measured using a pressure sensor, recorded, digitized, and stored digitally at 500 Hz using LabChart 8 acquisition software (ADinstruments, Bella Vista, Australia). MIP was determined, and the subjects were then placed in a sitting position for 15 min at rest. Subsequently, the subjects were fitted with a nose clip and instructed to inhale continuously through a mouthpiece connected to an inspiratory muscle training device designated as the POWER Breathe (Southam, UK). The device was adjusted to 60% of MIP. The subjects were required to maintain a respiratory rate (RR) of 15 breaths/min and inspiratory time/total breathing time ratio of 0.75. During each inspiratory effort, the subjects were instructed to: (1) Maintaining a constant inspiratory pressure during the inspiratory phase through visual feedback. (2) Diaphragmatic breathing was performed to avoid contraction of the non-respiratory muscles. Inability to perform the task (fatigue) was defined as a reduction in target MIP to less than 90% during three consecutive breaths, a criterion for stopping the test, or when the subject was unable to maintain breathing and remove the linear resistance

pressure equipment from the mouth. The duration of the test, in seconds, was used as a determinant of inspiratory resistance.

2.2.10. Six-minute walk test

The functional capacity of the subjects was assessed by measuring the distance covered in the 6-min walk test (6MWT), by the guidelines of the American Thoracic Society [19]. The 6MWT prediction equation proposed by Britto et al. [24], was employed, which takes into account the age, height, and sex.

2.2.11. Quality of life

The World Health Organization's Quality of Life Assessment Tool (WHOQOL-BREF) is a 26-item instrument that assesses quality of life. It comprises two general quality-of-life items and 24 items that represent the 24 facets of the original WHOQOL-100 instrument. Responses were provided on a Likert scale (1–5, with higher scores indicating a better quality of life). The four domains were physical, psychological, social relationships, and environment [25]. The results are expressed as a percentage from 0 to 100, with a closer proximity of100 % indicating a superior quality of life.

2.3. Statistical analysis

The data were analyzed using SPSS v.17 software. Descriptive statistics are expressed as mean and standard deviation, median and interquartile range, or frequency and percentage. The Shapiro-Wilk test was used to test the normality of the data. For normally distributed data, the Student's t-test was used. When the data did not show a normal distribution, the Mann-Whitney *U* test was used. For frequency data, the chi-squared test was used. Pearson's correlation coefficient was used for correlations when the data exhibited a normal distribution, whereas Spearman's correlation coefficient was employed for data with a non-normal distribution. The predictors of fatigue, as assessed by CFS, were determined using stepwise linear regression. Differences were considered statistically significant at p-values greater than 0.05.

3. Results

3.1. Sample characteristics

A total of 56 participants were screened between July and December 2023. Nine were excluded due to lack of time for the assessments, four for being over 59 years old, three for having comorbidities, and six for exercising. 34 participants were included in the study.

Table 1 presents the sample characteristics. The majority of the participants in the fatigue group (60%) exhibited mild functional limitations (p=0.002), whereas the majority of the volunteers in the non-fatigue group (76%) demonstrated no functional limitations (p=0.001). Additionally, a significant difference was observed between the groups in terms of CFS scores (p=0.001). Regarding quality of life, the fatigue group exhibited poorer results in the physical (p=0.001) and environmental domains (p=0.02), as shown in Fig. 1a.

3.2. Sleep disorders

Table 2 presents data related to sleep. Participants with fatigue exhibited higher scores on the ESS, indicating greater excessive daytime sleepiness (Fig. 1b). They also exhibited higher insomnia scores and a higher prevalence of insomnia (Fig. 1c). The nocturnal oximetry data demonstrated no differences between the groups.

3.3. Functional capacity

Table 3 presents the functional capacity data. Individuals with fatigue exhibited a shorter distance walked and a lower percentage of the predicted 6MWT (Fig. 2a). One participant was unable to complete the assessment due to hypertension at the time of the evaluation.

Table 1
Sample characteristics.

	All (n = 34)	Without fatigue (n = 14)	With fatigue (n = 20)	P
Sex, male % (n)[c]	26.5 (9)	42.9 (6)	15.0 (3)	0.07
Age, years[b]	26 (23–44)	26 (22–44)	25 (23–44)	1.00
Weight, kg[a]	75.0 ± 15	72.4 ± 10	76.3 ± 18	0.80
Height, m[a]	1.69 ± 0.09	1.72 ± 0.10	1.67 ± 0.08	0.12
BMI[b]	24 (22–28)	23 (22–25)	25 (23–29)	0.07
Time of Covid-19 infection (months)[a]	21 ± 11	21 ± 14	21 ± 10	0.97
Covid-19 infection[c]				
1 infection event, % (n)	64.7 (22)	71.0 (10)	60.0 (12)	0.49
2 infection events, % (n)	23.5 (8)	21.4 (3)	25.0 (5)	0.80
3 infection events, % (n)	8.8 (3)	7.1 (1)	10.0 (2)	0.77
4 infection events, % (n)	2.9 (1)	0.0	5.0 (1)	0.39
Self-reported anxiety, % (n)[c]	29.0 (10)	21.4 (3)	35.0 (7)	0.39
Self-reported depression, % (n)[c]	5.9 (2)	14.0 (2)	0.0	0.08
Sleeping sedatives, % (n)[c]	2.9 (1)	0.0	5.0 (1)	0.39
COVID-19 hospitalization % (n)[c]	6 (2)	0	10 (2)	0.23
Education[c]				
High School, % (n)	17.6 (6)	35.7 (5)	5.0 (1)	0.02*
Incomplete Higher Education, % (n)	29.4 (10)	14.3 (2)	40.0 (8)	0.10
Bachelor's Degree, % (n)	26.5 (9)	21.4 (3)	30.0 (6)	0.57
Postgraduate Degree, % (n)	26.5 (9)	28.6 (4)	25.0 (5)	0.81
Smoking[c]				
Active, % (n)	5.9 (2)	7.1 (1)	5.0 (1)	0.79
Passive smoking, % (n)	5.9 (2)	0.0	10.0 (2)	0.22
Income[c]				
Up to 2 thousand	35.3 (12)	21.4 (3)	45.0 (9)	0.15
Up to 4 thousand	26.5 (9)	21.4 (3)	30.0 (6)	0.57
Up to 10 thousand	20.6 (7)	28.6 (4)	15.0 (3)	0.33
More than 10 thousand	17.6 (6)	28.6 (4)	10.0 (2)	0.16
PCFS, % (n)[c]				
Grade 0	38.2 (13)	78.6 (11)	10.0 (2)	0.001*
Grade 1	5.9 (2)	0.0	10.0 (2)	0.22
Grade 2	38.2 (13)	7.1 (1)	60.0 (12)	0.002*
Grade 3	17.6 (6)	14.3 (2)	20.0 (4)	0.66
CFS (score)[a]	5.0 ± 3[a]	1.7 ± 0.9	7 ± 1.6	0.001*

Data expressed as mean ± standard deviation. BMI: Body Mass Index; PCFS: Post Covid Functional Scale- Grade 0: No functional limitations; Grade 1: Insignificant functional limitation; Grade 2: Mild functional limitation; Grade 3: Moderate functional limitation; Grade 4: Severe functional limitation. CFS: Chalder Fatigue Scale.
*p < 0.05.
[a] Student t-test.
[b] Mann Witney *U* test.
[c] Chi-square.

3.4. Lung function

The pulmonary function data are presented in Table 4. Participants with post-COVID-19 fatigue exhibited lower pre-bronchodilator FEV_1, lower FEV_1/FVC, and a lower percentage of predicted FEV_1/FVC. However, the predicted FEV_1 percentage did not differ between groups. Following the administration of bronchodilators, FEV_1 and FEV_1/FVC

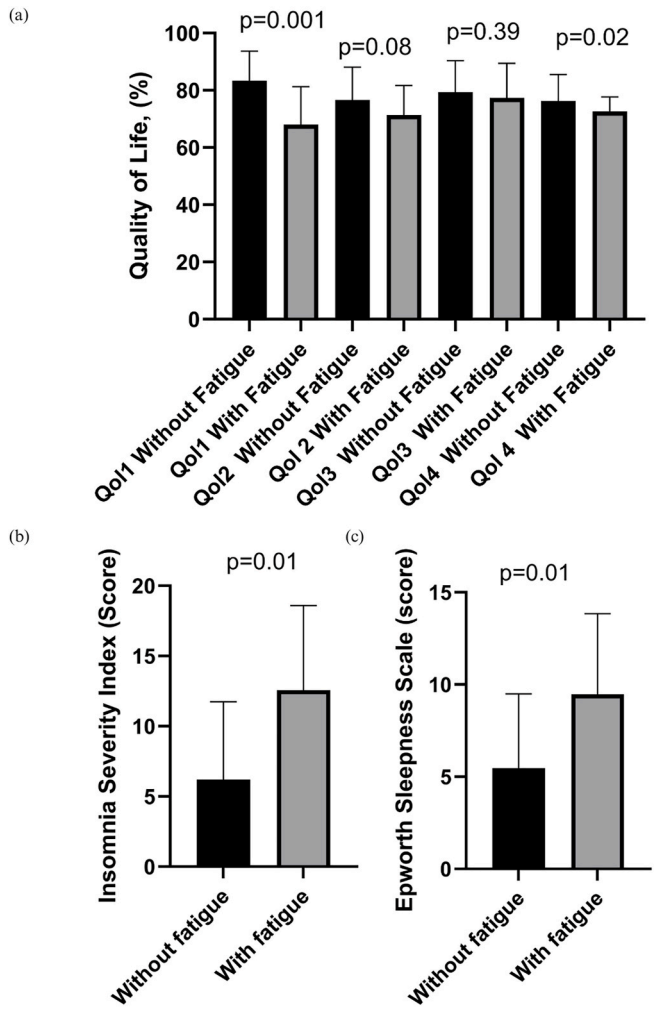

Fig. 1. Data expressed as mean ± standard deviation. a) Qol1:Quality of Life Physical Domain; Qol2:Quality of Life Psychological Domain; Qol3: Quality of Life Social Relations; Qol4: Quality of Life Environment. Student t-test.

Table 2
Daytime sleepiness, insomnia, nocturnal oximetry.

	All (n = 34)	Without fatigue (n = 14)	With fatigue (n = 20)	P
ESS, points[a]	7.7 ± 4.6	4.8 ± 3.4	10.0 ± 4	0.01*
Excessive daytime sleepiness, % (n)[c]	29.4 (10)	7.0 (1)	45.0 (9)	0.01*
ISI, points[a]	9.7 ± 6	6.0 ± 6	12.0 ± 6	0.01*
Severity of insomnia, % (n)[c]				
Absence	35.3 (12)	57.0 (8)	20.0 (4)	0.02*
Presence	64.7 (22)	43.0 (6)	80.0 (16)	0.02*
Sleep duration (h)[a]	7 ± 1.4	7.3 ± 1.2	6.8 ± 1.6	0.32
Desaturations (events)[b]	6 (2.5–24)	7 (5–16)	5 (2–28)	0.94
ODI (events/hour)[b]	0.9 (0.4–3)	1.2 (0.6–2)	0.8 (0.2–3)	0.92
Mild OSA, % (n)[c]	11.8 (4)	14.3 (2)	10.0 (2)	0.70
Moderate OSA, % (n)[c]	5.9 (2)	0.0	10.0 (2)	0.24

Data expressed as mean ± standard deviation. ESS: Epworth Sleepiness Scale. ISI: Insomnia Severity Index. ODI: Oxygen Desaturation Index; OSA: Obstructive Sleep Apnea.
*p < 0.05.
[a] Student's t-test.
[b] Mann Witney *U* test.
[c] Chi-square.

Table 3
Functional capacity.

	All (n = 33)	Without fatigue (n = 14)	With fatigue (n = 19)	P
6MWT				
Distance walked[a]	542.5 ± 15	593.0 ± 74	516.0 ± 77	0.01*
Predicted distance[b]	578 (559–593)	581 (563–635)	578 (546–582)	0.17
Percentage of predicted distance[a]	94 ± 3	100 ± 9	85 ± 24	0.03*

Data expressed as mean ± standard deviation. 6MWT: Six-minute walk test.
*p < 0.05.
[a] Student's t-test.
[b] Mann Witney *U* test.

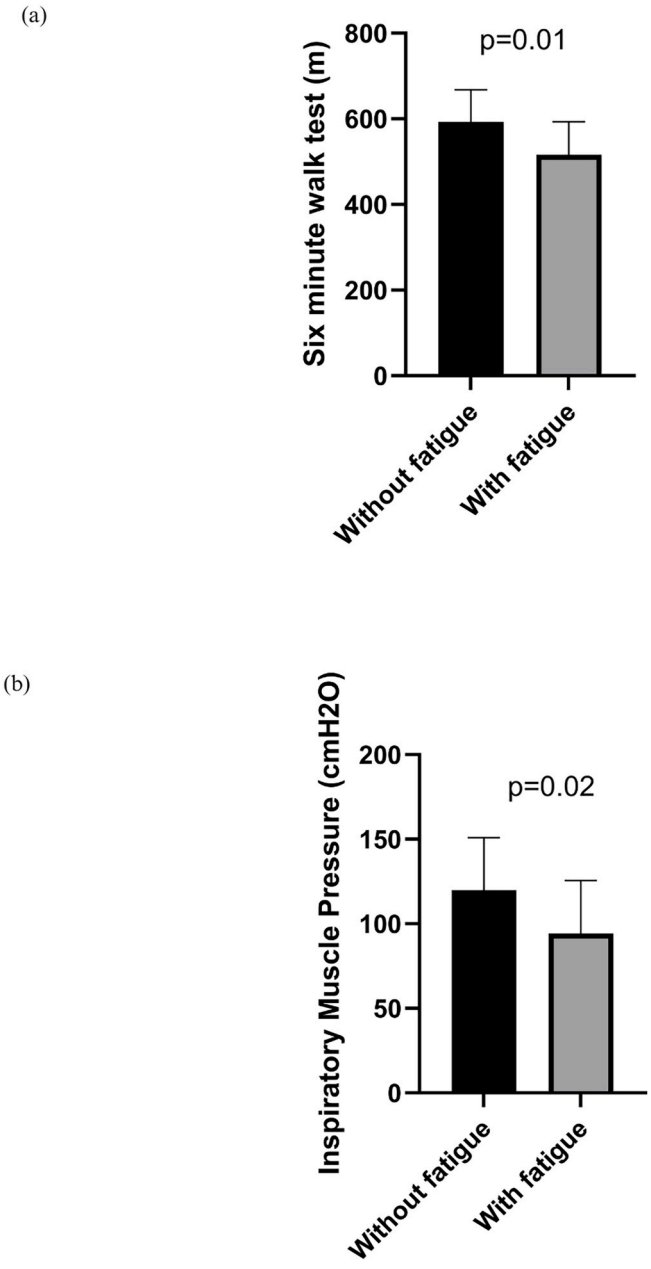

Fig. 2. Data expressed as mean ± standard deviation. Student t-test.

Table 4
Pulmonary function.

	All (n = 33)	Without fatigue (n = 13)	With fatigue (n = 20)	P
Pre-bronchodilator				
FVC (L)[a]	3.6 ± 1	3.7 ± 1	3.5 ± 0.6	0.47
Predicted FVC (L)[b]	3.6 (3.3–4.9)	3.7 (3.3–5)	3.4 (3.3–3.8)	0.22
FVC % of predicted (%)[a]	99 ± 18	102 ± 15	98 ± 20	0.60
FEV_1 (L)[a]	3.2 ± 0.8	3.6 ± 0.9	3.0 ± 0.5	0.02*
FEV_1 predicted (L)[b]	2.6 (2.2–3.6)	2.8 (2.3–3.8)	2.3 (2.2–2.8)	0.06
FEV_1 % of predicted (%)[a]	121 ± 33	121 ± 30	120 ± 35	0.89
FEV/FVC_1[a]	89 ± 6	92 ± 6	87 ± 5	0.04*
FEV_1/FVC predicted[b]	87 (82–88)	87 (82–88)	88 (82–89)	0.79
FEV_1/FVC % of predicted (%)[a]	104 ± 7	107 ± 6	102 ± 7	0.03*
Post-bronchodilator				
FVC (L)[a]	3,7 ± 0,8	4.0 ± 0,9	3,5 ± 0,6	0.07
Predicted FVC (L)[b]	3.6 (3.3–4.9)	3.8 (3.3–5)	3.4 (3.3–3.8)	0.13
FVC % of predicted (%)[a]	97 ± 18	97 ± 14	97 ± 20	0.92
FEV_1 (L)[a]	3,2 ± 0,8	3,6 ± 1	3.0 ± 0,6	0.02*
FEV_1 predicted[b]	2.6 (2.2–3.6)	2.8 (2.3–3.8)	2.3 (2.2–2.9)	0.41
FEV_1 % of predicted (%)[a]	120 ± 33	121 ± 30	119 ± 36	0.90
FEV/FVC_1[a]	89 ± 6	93 ± 5	88 ± 5	0.01*
FEV_1/FVC predicted[b]	87 (82–89)	87 (82–89)	88 (82–88)	0.81
FEV_1/FVC % of predicted (%)[a]	103 ± 6	106 ± 7	102 ± 6	0.07
OVD, % (n)	2.9 (1)	7.1 (1)	0.0	0.22
RVD, % (n)	17.6 (6)	14.3 (2)	20.0 (4)	0.66

Data expressed as mean ± standard deviation, % (n). FVC: Forced Vital Capacity; FEV_1: Forced expiratory volume in 1 s; OVD: Obstructive Ventilatory Disorder; RVD: Restrictive Ventilatory Disorder.
*$p < 0.05$.
[a] Student's t-test.
[b] Mann Witney *U* test;[c] chi-square.

remained lower in individuals with fatigue, and the predicted FEV_1 percentage did not differ between groups. Additionally, one participant was unable to perform the test maneuvers.

3.5. Inspiratory muscle strength and endurance

Table 5 presents the data from the inspiratory muscle strength and endurance inspiratory resistance test. Participants with post-COVID-19 fatigue exhibited lower MIP (Fig. 2b). However, there were no statistically significant differences between the groups in terms of inspiratory muscle endurance.

The CFS demonstrated a direct correlation with the ISI (r=0.436, p=0.010) and the ESS (r=0.593, p=0.001). Additionally, there was an inverse correlation between the distance covered in the 6MWT and the CFS (r=-0.398, p=0.022), as well as between the CFS and both the physical (r=-0.617, p=0.001) and psychological (r=-0.387, p=0.020) domains of QoL.

CFS was not associated with MIP (r=-0.300, p=0.080) or percentage of predicted MIP (r=-0.149, p=0.401). There was also no significant association between CFS and pre-bronchodilator FVC or percentage of predicted FVC. There was no correlation between CFS and the percentage of predicted FEV_1 (r=-0.016, p=0.929), while the correlation between CFS and FEV_1/FVC was r=-0.308 (p=0.08). The correlation between CFS and percentage of predicted FEV_1/FVC was not significant (r=-0.289, p=0.103). However, a significant association was observed between CFS and pre-bronchodilator FEV_1 (r=-0.412, p=0.010).

Table 5
Inspiratory muscle function.

	All (n = 27)	Without fatigue (n = 10)	With fatigue (n = 17)	P
MIP (cmH_2O)[a]	105 ± 33	120 ± 31	94 ± 30	0.02*
Predicted MIP (cmH_2O)[b]	99 (94–100)	99 (95–114)	99 (90–99)	0.30
MIP % of predicted (%)[a]	104 ± 32	114 ± 27	96 ± 34	0.07
Inspiratory muscle weakness (%)[c]	20.6 (7)	7.1 (1)	30.0 (6)	0.10
Inspiratory resistance (s)[a]	126 ± 76	124 ± 97	128 ± 64	0.91
Work of Breathing (cmH_2O)[a]	22298 ± 20964	16976 ± 9726	16401 ± 7284	0.87
MIP during the endurance test (cmH_2O)[a]	56 ± 10	61 ± 9	55 ± 13	0.24

Data expressed as mean ± standard deviation. MIP: Maximum inspiratory pressure.
*$p < 0.05$.
[a] Student's t-test.
[b] Mann Witney *U* test. $p < 0.05$.

In the stepwise linear regression test, controlling for gender, 62% of the variance in CFS was explained by the variance in ISI. ISI was significantly correlated with the physical (r=-0.775, p=0.001), psychological (r=-0.366, p=0.030), and environmental domains of QoL (r=-0.392, p=0.020). The ESS demonstrated a significant association with the environmental domain of QoL (r=-0.388, p=0.020) and with the distance covered in the 6MWT (r=-0.345, p=0.050).

There was no significant correlation between the presence of fatigue and the duration of COVID-19 infection (r=-0.038, p=0.830) or the number of infection events (r=0.135, p=0.471).

4. Discussion

In this study, we conducted a comparison of insomnia, OSA, lung function, inspiratory muscle strength and endurance, functional capacity, and QoL between individuals with and without post-COVID-19 fatigue. We also investigated the factors contributing to fatigue symptoms. Our results show that insomnia, daytime sleepiness, functional capacity, and respiratory muscle function are all associated with post-COVID-19 fatigue. Additionally, we found that insomnia is an independent predictor of fatigue.

In the current investigation, individuals with post-COVID-19 fatigue exhibited elevated ESS and ISI scores, along with diminished QoL, functional capacity, Tiffeneau index, and lower MIP. The persistence of post-COVID-19 symptoms is also related to sleep disorders, with 62% of patients experiencing worse sleep quality after hospital discharge [2]. The prevalence of sleep disorders, including insomnia, OSA, and daytime sleepiness, in post-COVID-19 patients ranges between 6% and 70% [26]. The present study found that individuals with post-COVID-19 fatigue had a higher prevalence of daytime sleepiness and insomnia than those without fatigue. Furthermore, there was a significant association between the CFS score and both the ESS and the ISI. Additionally, the ISI was identified as an independent predictor of fatigue.

The global COVID-19 pandemic has significantly increased self-reported cases of daytime sleepiness and fatigue. Recovered COVID-19 individuals experience these symptoms at twice the rate of non-affected individuals [27]. Sleep disorders such as insomnia and OSA contribute to fatigue [7]. A study of 2311 participants from 16 countries found that pre-existing insomnia increases the risk of prolonged post-COVID-19 symptoms [28]. Another study reported a 35% prevalence of newly diagnosed OSA among patients experiencing post-COVID-19 fatigue and daytime sleepiness [29]. Severe cases of COVID-19 are associated with an increased likelihood of developing

OSA [30]. Given that the majority of participants in our study experienced mild COVID-19 and did not require hospitalization, there was a low prevalence of OSA, and no difference was observed between patients with and without post-COVID-19 fatigue. Additionally, the sample was neither obese nor older, which may explain the low prevalence of OSA.

This study revealed that individuals experiencing post-COVID-19 fatigue exhibited significantly reduced Tiffeneau index compared to those without fatigue. Notably, this effect was observed even in young and non-hospitalized volunteers within our study cohort. Previous studies have reported pulmonary consequences of COVID-19. Competitive athletes post-COVID-19 infection exhibited reduced FEV_1 compared to their non-infected counterparts [31]. Reduced lung function, particularly in FVC and FEV_1, was reported in healthy athletes shortly after COVID-19 infection, with FVC abnormalities persisting even after 52 days [1]. Furthermore, Chamley et al. [32] found reductions in FVC, FEV_1, total lung capacity, alveolar volume, and diffusion capacity in active military personnel post-COVID-19 infection. In the present study, individuals with post-COVID-19 fatigue exhibited lower FEV_1 and lower FEV_1/FVC in absolute values, but only the percentage of predicted FEV_1/FVC was significantly lower in post-COVID-19 fatigue.

In addition to Tiffeneau index, inspiratory muscle strength was lower in post-COVID-19 fatigue participants. One study demonstrated that even in young individuals diagnosed with COVID-19 six months prior, respiratory muscle strength is negatively affected, and fatigue persists [10]. This appears to be one of the reasons for the continuation of post-COVID-19 symptoms [33]. These findings are consistent with our results. Furthermore, Bostanci's study showed a reduction in MIP even 52 days after infection in athletes, with approximately 80% experiencing post-COVID-19 fatigue [1]. Additionally, MIP can remain impaired even six months after hospital discharge [34].

MIP is also related to the distance covered in the 6MWT, a primary method for assessing functional capacity [34]. Furthermore, the persistence of post-COVID-19 symptoms is associated with a reduction in 6MWT distance [35]. Our findings are consistent with this, demonstrating a decrease in the distance covered in the 6MWT by participants with post-COVID-19 fatigue, as well as a reduction in the percentage of the predicted distance for each individual. Additionally, there was a significant association between the 6MWT and the CFS ($r=-0.398$, $p=0.02$). The 6MWT was also significantly associated with the ESS ($r=-0.345$, $p=0.05$), as well as with the quality of life in the physical ($r=0.401$, $p=0.02$) and environmental ($r=0.471$, $p=0.006$) domains. Beyer's 2023 study also revealed that patients with severe fatigue exhibited a reduction in the 6MWT, accompanied by limitations in quality of life [36].

Our study revealed significant differences between the groups in the physical and environmental domains of quality of life. The physical domain, which includes questions about energy and fatigue, sleep, and activities of daily living, showed a strong correlation with the CFS ($r=-0.617$, $p=0.001$) and the ISI ($r=-0.775$, $p=0.001$). In the environmental domain, encompassing questions about financial resources, safety, transportation, and the environment, there was a negative association with ESS (r-0.388, $p=0.020$) and ISI ($r=-0.392$, $p=0.020$). Additionally, there was a positive association between the distance covered in the 6MWT and QoL ($r=0.471$, $p=0.006$), but not with income ($r=0.195$, $p=0.269$). Consequently, insomnia leads to symptoms of sleepiness, adversely affecting quality of life, and is also related to functional capacity. These findings are consistent with a review [37] which indicated that prolonged symptoms associated with COVID-19 negatively impact individuals' quality of life.

This study presents several limitations. The group without fatigue trended towards a higher proportion of men ($p=0.070$). Given that men generally exhibit lower inspiratory muscle endurance than women [38], this difference in sex distribution may have influenced the observed results. However, excluding male participants from the statistical analysis did not significantly alter the findings. Additionally, while each group included one participant who reported active smoking habits, only the participant in the group without fatigue exhibited obstructive ventilatory disorder during spirometry testing. Despite these confounding factors, the fatigue group still demonstrated significantly lower FEV_1/FVC ratios. Future research should explore the potential relationships between sleep latency, sleep quality, fatigue, and insomnia in individuals with persistent post-COVID-19 symptoms.

5. Conclusion

Individuals with post-COVID-19 fatigue experience a higher prevalence of insomnia, reduced inspiratory muscle strength, diminished functional capacity, and reduced Tiffeneau index, all of which contribute to a decreased quality of life. Notably, the ISI emerged as an independent predictor of post-COVID-19 fatigue.

Given the potential for insomnia to exacerbate fatigue, individuals with post-COVID-19 fatigue should undergo sleep evaluations to determine the most appropriate treatment interventions.

CRediT authorship contribution statement

Nathalea Spode de Arruda: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alessandra Hofstadler Deiques Fleig:** Writing – review & editing, Conceptualization. **Charles Rech:** Writing – review & editing, Software, Conceptualization. **Carine Cristina Callegaro:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Funding

The Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul supported this work [grant number 07/2021] awarded to the researcher Carine Cristina Callegaro.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Bostancı Ö, et al. Respiratory muscle strength and pulmonary function in unvaccinated athletes before and after COVID-19 infection: a prospective cohort study. Respir Physiol Neurobiol 2023;308:103983.
[2] Jackson C, et al. Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study. Lancet Respir Med 2023;11(8):673–84.
[3] Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(4):601–15.
[4] Soriano JB, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22(4):e102–7.
[5] Calabria M, et al. Post-COVID-19 fatigue: the contribution of cognitive and neuropsychiatric symptoms. J Neurol 2022;269(8):3990–9.
[6] Ceban F, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: a systematic review and meta-analysis. Brain Behav Immun 2022;101:93–135.
[7] Maisel P, Baum E, Donner-Banzhoff N. Fatigue as the chief complaint-epidemiology, causes, diagnosis, and treatment. Dtsch Arztebl Int 2021;118 (33–34):566–76.
[8] Chen Si-Jing, Morin Charles M, Ivers Hans, et al. The association of insomnia with long COVID: an international collaborative study (ICOSS-II). Sleep Med 2023;112: 216–22.
[9] Alqahtani JS, et al. Sleep quality, insomnia, anxiety, fatigue, stress, memory and active coping during the COVID-19 pandemic. Int J Environ Res Publ Health 2022; 19(9).
[10] Güneş M, Yana M, Güçlü MB. Physical activity levels respiratory and peripheral muscle strength and pulmonary function in young post-COVID-19 patients: a cross-sectional study. Wien Klin Wochenschr 2023;135(9–10):251–9.
[11] Hennigs JK, et al. Respiratory muscle dysfunction in long-COVID patients. Infection 2022;50(5):1391–7.

[12] Konsberg Y, Szaro P, Aneman A, Kjellberg S, Solidakis N, Svedlund S, Nellgård B, Dalla K. Radiological appearance and lung function six months after invasive ventilation in ICU for COVID-19 pneumonia: an observational follow-up study. PLoS One 2023 Sep 1;18(9):e0289603.
[13] Omar A, Ferreira AS, Hegazy FA, Alaparthi GK. Cardiorespiratory response to six-minute step test in post COVID-19 patients-A cross sectional study. Healthcare (Basel) 2023;11(10):1386. https://doi.org/10.3390/healthcare11101386. PMID: 37239672; PMCID: PMC10217944.
[14] Cho HJ, et al. Cross-cultural validation of the chalder fatigue questionnaire in Brazilian primary care. J Psychosom Res 2007;62(3):301–4.
[15] Nakano MM, et al. Physical performance, balance, mobility, and muscle strength decline at different rates in elderly people. J Phys Ther Sci 2014;26(4):583–6.
[16] de Facio CA, et al. Post-COVID-19 functional status scale: cross-cultural adaptation and measurement properties of the Brazilian Portuguese version. Braz J Phys Ther 2023;27(3):100503.
[17] Bertolazi AN, et al. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol 2009;35(9):877–83.
[18] Castro LdSB, Rita Azeredo Lia. Adaptation and validation of the Insomnia Severity Index (ISI): population characteristics, normative values, and associated factors. Dissertation. Master's) Federal University of São Paulo; 2011.
[19] Smith MT, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American academy of sleep medicine clinical practice guideline. J Clin Sleep Med 2018;14(7):1231–7.
[20] SBPT. Guidelines for pulmonary function tests of the Brazilian society of pulmonology and phthisiology. Journal of Pneumology 2022;28(3):1–238.
[21] ATS. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111–7.
[22] Callegaro CC, et al. Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness. Respir Physiol Neurobiol 2010;171(1):31–5.
[23] Neder JA, et al. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. Braz J Med Biol Res 1999;32(6):719–27.
[24] Britto RR, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Braz J Phys Ther 2013;17(6):556–63.
[25] Fleck MP, et al. Application of the Portuguese version of the instrument for the assessment of quality of life of the World Health Organization (WHOQOL-100). Rev Saude Publica 1999;33(2):198–205.
[26] Tedjasukmana R, et al. Sleep disturbance in post COVID-19 conditions: prevalence and quality of life. Front Neurol 2022;13:1095606.
[27] Sarkanen T, et al. Association between hypersomnolence and the COVID-19 pandemic: the international COVID-19 sleep study (ICOSS). Sleep Med 2023;107:108–15.
[28] Chen SJ, et al. The association of insomnia with long COVID: an international collaborative study (ICOSS-II). Sleep Med 2023;112:216–22.
[29] Menzler K, et al. Undiagnosed obstructive sleep apnea syndrome as a treatable cause of new-onset sleepiness in some post-COVID patients. Eur J Neurol 2023;31:e16159.
[30] Gao X, et al. Causal associations between obstructive sleep apnea and COVID-19: a bidirectional Mendelian randomization study. Sleep Med 2023;101:28–35.
[31] Komici K, et al. Clinical characteristics, exercise capacity and pulmonary function in post-COVID-19 competitive athletes. J Clin Med 2021;10(14).
[32] Chamley RR, et al. Exercise capacity following SARS-CoV-2 infection is related to changes in cardiovascular and lung function in military personnel. Int J Cardiol 2024;395:131594.
[33] Nagel C, et al. Impairment of inspiratory muscle function after COVID-19. Respiration 2022;101(11):981–9.
[34] Núñez-Seisdedos MN, et al. Inspiratory muscle strength and function in mechanically ventilated COVID-19 survivors 3 and 6 months after intensive care unit discharge. ERJ Open Res 2023;9(1).
[35] Cortés-Telles A, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. Respir Physiol Neurobiol 2021;288:103644.
[36] Beyer S, et al. Post-COVID-19 syndrome: physical capacity, fatigue and quality of life. PLoS One 2023;18(10):e0292928.
[37] Poudel AN, et al. Impact of Covid-19 on health-related quality of life of patients: a structured review. PLoS One 2021;16(10):e0259164.
[38] Geary CM, et al. Diaphragm fatigue and inspiratory muscle metaboreflex in men and women matched for absolute diaphragmatic work during pressure-threshold loading. J Physiol 2019;597(18):4797–808.