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Original Article

RISK FACTORS FOR CHRONIC FATIGUE IN POST COVID-19 PATIENTS AFTER 12 MONTHS: COHORT STUDY

FATORES DE RISCO PARA FADIGA CRÔNICA EM PACIENTES PÓS COVID-19 APÓS 12 MESES: ESTUDO DE COORTE

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RESUMO
Objetivo: Investigar a prevalência da fadiga em pacientes com COVID-19 após um mês e doze meses do diagnóstico e as variáveis preditoras. **Metodologia:** Estudo de coorte com pacientes diagnosticados com infecção por SARS-CoV-2 que preencheram questionário online um mês e um doze meses após o início dos sintomas da COVID-19, que consistia em dados sociodemográficos, manifestações sintomáticas causadas pela COVID-19, comorbidades, fadiga e funcionalidade. A análise multivariada foi realizada para estabelecer quais variáveis prediziam melhor o modelo proposto. **Resultados:** Após analisar um total de 299 indivíduos, observou-se que 159 (53,2%) e 140 (46,8%) apresentaram fadiga após 30 dias e um ano, respectivamente. Além disso, 85 (28,4%) indivíduos apresentaram dispneia após 30 dias, e 75 (25,1%) após um ano, com predominância do sexo feminino. As variáveis preditoras identificadas para a presença de fadiga após um ano foram: sedentarismo após 1 ano p=(0.06), limitação do estado funcional após 30 dias p=0.02 e dispneia após 1 ano p=0.01. **Conclusão:** Sedentarismo, limitação do estado funcional e dispneia são seus fatores de risco.
Palavras-chave: Fadiga. Dispneia. Pós-COVID-19. Sedentarismo. Funcionalidade.

ABSTRACT
Objective: To investigate the prevalence of fatigue in patients with COVID-19 one month and twelve months after diagnosis and the predictor variables. **Methodology:** Cohort study with patients diagnosed with SARS-CoV-2 infection who completed an online questionnaire one month and one twelve months after the onset of COVID-19 symptoms, which consisted of sociodemographic data, symptomatic manifestations caused by COVID-19, comorbidities, fatigue and functionality. Multivariate analysis was performed to establish which variables best predicted the proposed model. **Results:** After analyzing a total of 299 individuals, it was observed that 159 (53.2%) and 140 (46.8%) presented fatigue after 30 days and one year, respectively. Furthermore, 85 (28.4%) individuals presented dyspnea after 30 days, and 75 (25.1%) after one year, with a predominance of females. The predictor variables identified for the presence of fatigue after one year were: sedentary lifestyle after 1 year p=(0.06), limitation of functional status after 30 days p=0.02 and dyspnea after 1 year p=0.01. **Conclusion:** A sedentary lifestyle, limited functional status and dyspnea are its risk factors.
Keywords: Fatigue. Dyspnea. Post-COVID-19. Sedentary Life Style. Functionality.

Introduction

SARS-CoV-2 is part of a broad family of viruses that can cause illness in humans and animals. Since the first case was detected in China at the end of 2019, the virus has spread rapidly around the world. The World Health Organization (WHO) classified the disease caused by the virus, COVID-19, as an international health emergency and on March 11, 2020 it was declared a pandemic[1]. 670,597,192 cases of COVID-19 were confirmed worldwide in practically all countries and territories, with more than 6,832,607 deaths confirmed until February 1, 2023. In Brazil, 36,837,943 cases were confirmed until that date and 697,200 deaths[2].

COVID-19 disease can result in varied clinical manifestations. The main signs and symptoms are: fever (>37.8ºC), cough, dyspnea, myalgia, fatigue, upper respiratory symptoms and gastrointestinal symptoms[3]. The severity of the inflammatory response, the deficiency in the resolution of inflammation and the systemic involvement of SARS-CoV-2

could explain the persistence of COVID-19 symptoms[4,5]. The National Institute for Health and Care Excellence (NICE) guidelines define "post-acute COVID-19 syndrome" as the signs and symptoms (which persist between 4 and 12 weeks after the acute onset of the illness) and "post-COVID-19 syndrome" 19" or "Long COVID-19" as those that persist beyond 12 weeks[6].

The systemic and persistent sequelae of COVID-19 harm the pulmonary, cardiovascular, neuropsychological, endocrine, gastrointestinal and musculoskeletal systems. The phenotype is similar to the post-viral neurological syndrome of other respiratory syndromes, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[7,8]. The global estimate is that approximately 200 million individuals suffer long-term sequelae. Furthermore, even vaccinated patients are at risk of developing prolonged COVID-19.

Fatigue is the primary and prevalent sequelae, even in asymptomatic COVID-19[8]. Approximately 63% of individuals with COVID-19 sequelae have difficulty performing daily tasks, self-care and mobility and have social and recreational impairment with difficulty returning to work[9]. This sequelae is emblematic because fatigue as a symptom is still not well understood. Unlike healthy individuals, where it occurs as a physiological response to intense and prolonged activities in a transient and predictable way[10].

Fatigue is a complex biological, psychosocial and behavioral phenomenon, and can be subdivided into two main types: muscular fatigue, which is caused due to excessive physical activity and chronic fatigue, generally caused by a huge load of stress in the routine, being mainly linked to the professional, romantic and family spheres. However, unlike muscular fatigue, chronic fatigue lasts for at least six months and is disabling, and the patient may not be able to carry out their usual activities normally, in addition to being prone to depression[11].

The present study aims to answer two research questions: (1) what is the prevalence of chronic fatigue in patients who had COVID-19 after one month and twelve months of diagnosis?; and (2) which variables may be associated as predictors of fatigue chronic post-COVID?

Methods

Study design and ethical aspects

This is a cohort study, part of the research project entitled “Functional clinical assessment and quality of life of patients after 1, 2, 6 and 12 months of diagnosis of SARS-CoV-2 infection in the city of Londrina” developed and conducted in partnership between the State University of Londrina (UEL) and the Municipal Health Department of Londrina – Paraná. The research was authorized by the Municipal Health Department and approved by the Research Ethics Committee involving Human Beings of UEL CAAE number 36782620.0.0000.5231. All participants received information about the research and answered the questionnaire only after agreeing to the Free and Informed Consent Form.

Participants

Participants were recruited through a survey carried out on the official platform of the South American state's state notification system called Notifica COVID-19, a single basis for compulsory notification of suspected and confirmed cases of COVID-19 by all municipalities. A self-report form is completed by healthcare professionals with all patients with all patients with COVID-19 syndrome, and contains identification data, clinical data (signs and symptoms), presence of comorbidities or risk factors, hospitalization, medications, imaging tests, laboratory data, notifier, notification classification (suspected, discarded or

confirmed) and classification criteria (laboratory or clinical/epidemiological). All individuals with a positive diagnosis by the PCR-RT molecular test for SARS-CoV-2, aged 18 years or over, not hospitalized (mild and moderate cases) who agreed to participate in the study were included in the study. Individuals without elucidation of the etiological agent, patients who required hospitalization, with reinfection of COVID-19, without the possibility of contact, people deprived of liberty, elderly people in long-term care institutions and people who had difficulty using digital technology or Internet access.

After completing the questionnaires, the participant received a booklet of guidelines and exercises based on material prepared by the WHO that provides support for self-managed rehabilitation after COVID-19[12]. The booklet contains information on: dyspnea management, physical exercises, guidance on voice problems, difficulties with activities of daily living, cognitive changes, mood changes and stress, and emergency contacts.

Data collect

Data were collected from October 12, 2020 to May 1, 2022. Participants received the questionnaire (Google Forms) through a chat application (WhatsApp) four weeks and one year after being diagnosed with COVID-19 which consisted of sociodemographic data (sex, age), 25 symptomatic manifestations caused by COVID-19 in adults 30 days and one year after diagnosis[13].

The Fatigue Severity Scale (FSS) was used, which is a questionnaire with nine statements where the patient chooses a number from one to seven that best describes the degree of agreement with each statement. The number one means that you completely disagree, the number seven that you completely agree, with the number four indicating that the patient neither agrees nor disagrees with statement[14]. The total number of points may vary from nine to 63, establishing that values equal or greater than 28 are indicative of the presence of fatigue[15].

To assess dyspnea, the Modified Borg Scale was used, an instrument that allows the assessment of dyspnea both at rest and in relation to exercise intensity, in order to determine subjective indices, according to the individual's perception, directly providing an individualized measure of dyspnea. perception of dyspnea. The scale was modified from the original in 1982 and is now scored from 0 to 10 points, with verbal expressions in which each number corresponds to an intensity of shortness of breath, from “none” to “maximum”. It is reproducible and valid in the assessment of dyspnea[16]. Individuals were instructed to answer the questionnaire at rest.

To verify physical inactivity, individuals were asked about their weekly physical activity time. Subjects who self-reported time spent practicing physical activity was less than recommended for the individual's health, being less than 150 minutes of aerobic physical activity of moderate or vigorous intensity per week) were considered insufficiently active and those who self-reported time greater than 150 minutes were considered physically active. of moderate or vigorous intensity aerobic physical activity per week.

Functional status was assessed using the post-COVID-19 Functional Status Scale (PCFS), an instrument designed to monitor direct recovery, assess functional sequelae and classify the ability to perform daily and work activities after infection. The scale is ordinal, contains six levels ranging from zero (no symptoms) to five (death), and comprises functional outcomes, focusing on limitations in tasks and activities of daily living, as well as lifestyle changes[17].

Statistical analysis

To estimate the number of participants in this study, the family z test from the *G*Power* program (3.1.9.7) was used for logistic regression, with binomial distribution and input effect size as two probabilities[12]. An alpha of 5%, power of 80%, and a probability of having persistent symptoms (Y=1) when someone is a woman (X=1) of 0.61 (Pr(Y=1 | X=1) H0) and not being a woman of 0.38 (H1). Furthermore, an R2 of 0.39 and parameter X π (proportion of cases) of 0.50 were stipulated. The estimated sample was calculated at 245 participants.

Numerical variables were tested for normality distribution using the Shapiro-Wilk test. When the assumption of normality was accepted, the variables were presented as mean (X) and standard deviation (SD), when not, the data were presented as median (Md) and quartiles (25 - 75%). For categorical variables, values were expressed as relative and absolute frequencies, while for numerical variables, data were presented as median and quartiles (25-75%). Bivariate analysis was used using chi-square cross tables (with Yates continuity correction when indicated) to establish an association between the presence/absence of fatigue (FSS score ≥ 28)[15] one year after the diagnosis of COVID-19 and the predictor variables (age, sex, high blood pressure, diabetes mellitus, obesity, sedentary lifestyle - less than 150 minutes of weekly physical activity, dyspnea, symptoms of anxiety and depression, limitation of functional status and number of persistent symptoms after 30 days of diagnosis). The values from these first analyzes were used in the stepwise logistic regression model (direct likelihood ratio) with the adjusted Odds ≤Ratio and a 95% confidence interval (CI) defined to express its magnitude[18].

To carry out the multivariate analysis, the following assumptions were followed: a) The chi-square omnibus of model coefficients was examined to verify whether the set of variables improves the prediction of log odds, b) the Nagelkerke R2 investigated whether these independent variables could explain a low sum of variance, and c) Hosmer and Lemeshow goodness-of-fit was used to understand whether the observed values were close to expected. The prediction accuracy of the model was carried out to verify the ability to accurately classify the presence or absence of fatigue into two categories one year after the diagnosis of COVID-19. For stepwise analysis, the probabilities of entering and removing variables from the model were set between 0.05 - 0.10[19]. Statistical significance was set at 5% and all analyzes were performed with MedCalc® Statistical Software version 20.014 (Ostend, Belgium) and IBM-SPSS® version 27 (Armonk, NY, USA). In the model presented, adjustment was made by sex.

Results

In the study, 299 patients who responded to the questionnaire were analyzed, there was a predominance of females, they were eutrophic, young, 38.3% had comorbidities and 43.1% had anxiety and depression. The sample characterization data are detailed in Table 1.

Table 1. Sample characterization

Variable	n=299 (100%)
Age (years) *Md 1q;3q	37
Sex	-
Feminine	200 (66,9%)
Race	-
White	209 (69,9%)

Comorbidity	-
Yes	116 (38,3%)
Systemic Arterial Hypertension	-
Yes	35(11,7%)
Diabetes Mellitus	-
Yes	19 (6,4%)
Obesity *(BMI ≥30)	
Yes	41 (13,7%)
Symptoms of Anxiety/Depression	
Yes	129 (43,1%)

Note: *Md (25-75%); Body Mass Index.
Source: authors

Fatigue was presented by more than half of the sample after 30 days and by almost half after one year. Information on fatigue and dyspnea 30 days and one year after diagnosis are presented in Table 2.

Table 2. Dyspnea and fatigue one month and twelve months after COVID-19 diagnosis.

Variable	One month	Twelve months	p-value
Dyspnea (Borg Scale)			
Yes	85 (28.4 %)	75 (25.1 %)	0.26
No	214 (71.6%)	224 (74.9%)	
Dyspnea (Borg Scale) *(Md)	0 [0- 0,5]	0 [0 – 0]	0.25
Fadigue			
Yes	159 (53.2%)	140 (46.8%)	0.04*
No	140 (46.8%)	159 (53.2%)	
Scale **FSS *(Md)	30 [15 – 46]	26 [13 – 42]	≤0.001*

Note: *Md (25-75%); **FSS: Fatigue Severity Scale; *p<0.05; * FSS≥28
Source: authors.

The results of the univariate analysis between the presence of fatigue characterized by FSS greater than or equal to 28 questionnaire score after one year and associations with predictor variables (age, sex, arterial hypertension, diabetes mellitus, obesity, physical activity, dyspnea, symptoms of anxiety and depression, limitation of functional status and number of persistent symptoms after 30 days of COVID-19 diagnosis) are shown in Table 3.

Table 3. Association between the presence of fatigue after twelve months and sociodemographic variables, presence of comorbidity, dyspnea, physical activity, anxiety, functionality and presence of persistent symptoms after one month.

Variable	With fatigue (n=140)	No fatigue (n=159)	p-value
Sex	-	-	-
Feminine	99 (49.5%)	101 (50.5%)	0.18
Masculine	41 (41.4%)	58 (58.6%)	
Age	-	-	-
≤ 59 years	129 (46.7%)	147 (53.3%)	0.92
≥ 60 years	11 (47.8%)	12 (52.2%)	
Systemic Arterial Hypertension	-	-	-
Yes	130 (49.2%)	134 (50.8%)	0.03*
No	10 (28.6%)	25 (71.4%)	

Variable	With fatigue (n=140)	No fatigue (n=159)	p-value
Diabetes Mellitus	-	-	-
Yes	3 (15.8%)	16 (84.2%)	0.06
No	137 (48.9%)	143 (51.1 %)	
Obesity *(BMI ≥30)	-	-	-
Yes	21 (51.2%)	20 (48.8%)	0.54
No	119 (53.9%)	139 (53.9%)	
Physical activity	-	-	-
Yes	80 (55.6%)	64 (44.4)	0.004
No	58 (38.2%)	94 (61.8%)	
Dyspnea one month (Borg)	-	-	-
Yes	84 (39.1%)	131 (60.9%)	0.001
No	11 (73.3%)	4 (26.7 %)	
Symptoms of anxiety and depression (one month)	-	-	-
Yes	60 (46.5%)	69 (53.5%)	0.92
No	80 (47.1%)	90 (52.9%)	
Functionality change one month (PCFS)**	-	-	-
Yes	93 (60.4%)	61 (39.6%)	<0.001
No	47 (32.4%)	98 (67,6%)	
Presence of persistent symptom for one month	-	-	-
Yes	106 (54.9%)	87 (45.1%)	<0.001
No	34 (32.1%)	72 (67.9%)	

Note: *BMI: body mass index. **PCFS: Post Covid-19 Functional Status Scale
Source:authors.

For the multivariate analysis, six independent variables were entered into the logistic regression model (hypertension, physical activity, dyspnea, limitation of functional status and presence of persistent symptoms after 30 days of COVID-19 diagnosis). Details are found in Table 4.

Table 4. Multivariate analysis for fatigue after one year and predictor variables.

Variable	Odds Ratio [CI* 95%]	p- value
Systemic Arterial Hypertension	0,28 [0,12; 0,66]	0.05
Dyspnea	2,14 [1,18; 3,86]	0,01*
Physical activity	2,02 [1,22; 3,34]	0,006*
Functional status limitation 30 days	2,38 [1,39; 4,10]	0,002*
Symptoms persisting one month	1,40 [0,78; 2,53]	0,25

Note: *p<0.05 ** Binary logistic regression model.
Source: authors.

Discussion

In the present study, a high prevalence of fatigue was found to be a relevant persistent symptom in patients with COVID-19 after 30 days and one year of diagnosis. It was identified that 159 (53.2%) of patients experienced fatigue after 30 days of COVID-19 and 140 (46.8%) after one year. The population was young (median 34 years old), the majority were female (66.9%) and 53.2% had persistent symptoms after one year.

Seeble et al.[20] developed a study that sought to determine the prevalence of persistent symptoms post-COVID-19 where it was found that after one year only 22.9% of patients were completely free of symptoms and the most frequent symptoms were reduced functionality (56.3%), fatigue (53.1%), dyspnea (37.5%).

Similar study by Mikkelsen et al.[21] points out that fatigue has been the most common symptom experienced by patients affected by COVID-19, regardless of the need for hospitalization, with an estimated prevalence of 15 to 87%, which corroborates the present study, where it was 46.8 % prevalence of fatigue complaints after one year in non-hospitalized patients.

Still in this vein, a study by Azevedo et al.[22] evaluated the persistence of symptoms and return to work after hospitalization for COVID-19 and it was shown that two thirds of patients with pulmonary involvement reported persistence of symptoms six months after COVID-19 infection, such as memory loss (45.5%), myalgia (43.9%), fatigue (39.4%) and dyspnea (25.8%), and 50% returned slowly to work, with repercussions due to fatigue and/or loss of energy. Although fatigue resolves spontaneously after the acute episode, in most patients it can last three months or more[22].

The present study found that the variables predicting fatigue after one year were sedentary lifestyle, dyspnea and limitation of functional status after 30 years after the diagnosis of COVID-19. A sedentary lifestyle was shown to be a variable that is associated with the presence of fatigue one year after being diagnosed with COVID-19 (P=0.006), thus, physically inactive people have 2.02 (1.22 - 3.34) more chances of experiencing fatigue compared to people who practice physical activity. The data reinforces the need to make this habit common, especially in the period after the acute phase of the infection. In view of the damage caused by the SARS-CoV-2 virus, causing impairment of various organs and systems, physical activity is a habit that acts as a protective factor for the development of several chronic non-communicable diseases (NCDs), in addition to contributing to the better musculoskeletal and metabolic functioning and is recommended as a protective factor both for the worsening of the infection and for the post-acute phase of the infection [23-25].

In the current study, dyspnea at 30 days was shown to be a variable that is associated with the presence of fatigue one year after the diagnosis of COVID-19 (P=0.001), thus, people who have dyspnea at 30 days have 2.14 (1.18 – 3.86) more likely to experience fatigue compared to people who did not have dyspnea.

Dyspnea, like pain, is a subjectively experienced symptom, making measuring severity challenging. Pain and dyspnea are both processed in part by the limbic system[26]. These symptoms alert the body to threatening conditions and the potential loss of homeostasis, motivating the individual to seek help and engage in adaptive behaviors[27]. The behavioral consequences of lack of air have an impact on an individual's daily activities, affecting psychological well-being and social life. Avoiding exercise to reduce dyspnea initiates a vicious cycle, potentially leading to a deterioration in general performance status and dependence on care, as well as social isolation, reduced self-esteem and anxiety[27].

Furthermore, the limitation of functional status at 30 days was shown to be a variable that is associated with the presence of fatigue one year after the diagnosis of COVID-19 (P=0.002), thus, people who have limited functional status at 30 days have 2.38 (1.39 - 4.10) more chances of experiencing fatigue compared to people who did not have functional status limitations. Patients with post-acute sequelae of COVID-19 (PASC) develop significant limitations in activities of daily living (ADLs) such as walking, bathing or dressing with multifactorial causes of this functional decline, this physical weakness can be attributed to myopathy, neuropathy, cardiorespiratory deficiencies, cognitive impairment or a combination of these conditions according to the Brazilian Association of Cardiorespiratory Physiotherapy and Intensive Care Physiotherapy – Assobrafir[28].

One of the strengths of the present study is the prospective cohort model of one year after acute COVID-19 infection. Furthermore, this study included a large number of people who did not require hospitalization, as most studies address fatigue in hospitalized patients.

The limitations of this study are the following: despite forwarding the data collection instrument to all patients who had COVID-19 in the municipality during the data collection period, only those who had internet access and familiarity with digital technology responded. This study had a selection bias because it included data from younger people with higher education, the majority of whom were female, although adjustments were made for sex.

The lack of a control group made it difficult to infer whether self-reported symptoms were due to SARS-CoV-2 infection, preexisting comorbidities, or social effects related to the pandemic. Furthermore, the fatigue scale used had a subjective score that depended on the patient's perception of their functional status and the prolonged manifestations of COVID-19. Furthermore, the symptoms were self-reported by the participants, therefore, they were subjective according to the perception of each individual.

Conclusion

It was shown that COVID-19 causes fatigue in 53.2% of patients after 30 days of diagnosis and 46.8% even after one year of infection. Fatigue is the main symptom reported and can alter the physical and mental functionality of individuals. Furthermore, the predictive factors in the development of fatigue after one year were sedentary lifestyle, dyspnea and limitation of functional status after 30 days.

The results provide useful information for healthcare professionals caring for post-COVID-19 patients and clarifying the mechanisms underlying “post-COVID-19 fatigue syndrome” is essential for the development of preventive and early treatment methods.

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