



## ORIGINALS

### Post COVID-19 conditions: an analysis on fatigue and associated factors

Condiciones Post COVID-19: un análisis de la fatiga y factores asociados

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<https://doi.org/10.6018/eglobal.634421>

elocation-id: e634421

Received: 27/10/2024

Accepted: 14/02/2025

#### ABSTRACT:

**Objective:** To estimate the prevalence of post-covid-19 fatigue by self-report and analyze the associated factors among residents of the state of Paraíba, Brazil.

**Method:** This is a cross-sectional study, of the online survey type. Data collection was carried out between March 2023 and March 2024. Descriptive and inferential statistics were performed. Ethical precepts were respected.

**Results:** A total of 263 participants were included, predominantly female individuals, aged between 21 and 40 years old, who were diagnosed with Covid-19 only once, who classified the acute infection as mild, vaccinated against Covid-19, non-smokers and who consumed alcoholic drinks. The prevalence of self-reported post-covid-19 fatigue was 90.5%. It was found that individuals who reported persistence of symptoms for more than four weeks after infection (OR: 5.55;  $p=0.000$ ) and those who consumed alcoholic drinks (OR: 2.88,  $p=0.010$ ) had a higher chance of fatigue.

**Conclusions:** Fatigue is the most prevalent symptom of post-covid-19 conditions and was associated with persistent symptoms and alcohol consumption.

**Keywords:** Post-Acute COVID-19 Syndrome; COVID-19; Fatigue; Alcohol consumption.

#### RESUMEN:

**Objetivo:** Estimar la prevalencia de fatiga post-covid-19 por autorrelato y analizar los factores asociados entre residentes del estado de Paraíba, Brasil.

**Método:** Se trata de un estudio transversal, del tipo encuesta online. La recogida de datos se realizó entre marzo de 2023 y marzo de 2024. Se realizó estadística descriptiva e inferencial. Se respetaron los preceptos éticos.

**Resultados:** Se incluyeron 263 participantes, con predominio de individuos femeninos, en el grupo de edad de 21 a 40 años, que fueron diagnosticados con Covid-19 una sola vez, que clasificaron la infección aguda como leve, vacunados contra la Covid-19, no fuman y que hacían uso de bebidas alcohólicas. La prevalencia de fatiga post-covid-19 por autorrelato fue del 90,5%. Se comprobó que los individuos que informaron de persistencia de síntomas durante más de cuatro semanas después de la infección (OR: 5,55;  $p=0,000$ ) y aquellos que consumieron bebidas alcohólicas (OR: 2,88,  $p=0,010$ ) presentaron mayores probabilidades de presentar fatiga.

**Conclusiones:** La fatiga es el síntoma más prevalente de las condiciones post-covid-19 y estuvo asociada a la persistencia de síntomas y consumo de bebidas alcohólicas.

**Palabras clave:** Síndrome Post Agudo de COVID-19; COVID-19; Fatiga; Consumo de bebidas alcohólicas.

## INTRODUCTION

The Sars-Cov-2 infection presents persistence of symptoms after the acute phase, called post-Covid-19 conditions. These conditions are characterized as symptoms that persist for more than three months, lasting at least two months and that are not explained by another diagnosis<sup>(1)</sup>. Studies indicate that about 10-20% of infected individuals complain of long-lasting symptoms, regardless of the severity of the infection<sup>(2,3)</sup>.

The mechanism behind the post-covid-19 conditions is not yet fully clarified, however, it is observed that the cytokine release storm caused by the acute infection, as well as the ability of Sars-Cov-2 to spread through the nervous system, can cause prolonged symptoms in several organic systems<sup>(4)</sup>.

Among the most common conditions, fatigue and cognitive impairment stand out, since they significantly affect quality of life and daily activities<sup>(5)</sup>. In addition, individuals may present with myalgia, anosmia, headache, anxiety, depression, sleep disorders, among others<sup>(6)</sup>.

Those affected by post-covid-19 fatigue complain of difficulty in performing activities of self-care, mobility, work and participation in social and leisure meetings. The literature shows that this condition is present even at rest, negatively affecting the physical and mental functioning of the human body<sup>(7)</sup>.

Regarding the treatment, the therapeutic options for fatigue are very limited, requiring a holistic view of the multiprofessional team, because it is an unspecific and debilitating symptom. In this context, the management of comorbidities, mental health support and active participation in social services become important<sup>(8)</sup>.

Therefore, it is understood that conducting studies directed to the knowledge of post-covid-19 fatigue are of paramount importance, since it is a prevalent condition in the population and negatively affects the quality of life of individuals. Thus, the objective of this study was to estimate the prevalence of self-reported post-covid-19 fatigue and analyze the associated factors among residents of the state of Paraíba, Brazil.

## METHOD

This is a cross-sectional, analytical, online survey, constructed according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology for RDS Studies (STROBE-RDS) Guide and guided by the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

The study population was composed of individuals living in the state of Paraíba, who had a confirmed diagnosis of Covid-19 (by serology, rapid test or RT-PCR).

The study sample was constituted by stratified sampling. The stratum was performed according to optimal allocation method, considering as auxiliary variable the number of beds (clinical/adult) for Covid-19 in each of the strata and considering fixed selection cost for all elements of the target population, as described in a study previously conducted<sup>(9)</sup>.

The calculation of the sample size includes the survey in each region of the country, taking into account the information that the percentage of persistence of COVID-19 symptoms in the resident population is 8.12%. This percentage was obtained considering that the cases of Covid-19 in each region related to people who present persistence of symptoms after the acute phase are 329770 people (which would represent 50.2% of the approximate cases), from the reference of Miranda and collaborators<sup>(10)</sup>. Thus, by means of estimates of the resident population in 2021 for all states, considering estimates for the TCU – Brazil, obtained from <https://datasus.saude.gov.br/populacao-resident>, it was possible to present approximation of estimates of the proportion of cases of persistence of Covid-19 symptoms in the state of Paraíba (Table 1).

**Table 1:** Population information of interest. Paraíba, Brazil, 2024.

| State   | Approximate cases of Covid-19 (excluding children) | Estimated number of persistent Covid-19 cases (considering 50.2% for each region) | Resident population (2021 estimate – DATASUS) | Estimated percentage of persistent Covid-19 symptoms in the resident population |
|---------|--|---|---|---|
| Paraíba | 656,912  | 329,770   | 4,059,905                                     | 8.12%   |

It is possible to observe then that the sample calculation was possible to be carried out with these indicators. Thus, the formula considered was the following<sup>(9,11)</sup>:

$$n = \frac{N \times z^2 \times p \times (1 - p)}{p \times (1 - p) \times z^2 \times + (N - 1) \times e}$$

Considering:

N: Size of the resident population.

z: Quantile of the normal distribution considering the confidence level. For this study, we consider the 95% confidence level, which implies that  $z = 1.96$ .

p: Reference percentage for analysis (8.12% according to chart 1).

e: Margin of error. For accuracy purposes, it was decided to consider  $e = 3.3\%$

It is important to clarify that the population information provided in chart 1 is not provided for each region. However, due to the importance of obtaining estimates by region, a post-stratification procedure was also considered, in order to provide optimal estimates for each region. Thus, considering the data provided, the sample size resulted in 263 individuals.

The study included individuals of both sexes, aged 18 years or older, who had a confirmed diagnosis of Covid-19 and had access to the internet. Individuals who did not reside in the state of Paraíba before 2020 (beginning of the Covid-19 pandemic) were excluded.

Data collection took place between March 2023 and March 2024. For the collection operation, a team of previously trained employees was used. Participants were recruited through social networks. Data were collected through a questionnaire structured on the REDCap® platform, containing questions about sociodemographic and clinical characteristics.

The data were processed in the software Statistical Package for the Social Sciences (SPSS), version 26.0 for Windows. The analysis was developed through descriptive and inferential statistics. To investigate the factors associated with the presence of fatigue, bivariate analysis was performed using the chi-square and Fisher's exact tests.

Subsequently, in order to estimate the odds ratio (OR) for each variable, the binary logistic regression model was applied to the significant variables ( $p\text{-value} \leq 0.05$ ).

It is important to consider that all variables considered in the study were tested for modeling purposes from the variables that presented a  $p\text{-value}$  below 0.25. Thus, these variables were simultaneously included in the logistic regression model by stepwise method. In the final model, variables that presented a statistically significant association with  $p < 0.05$  were considered.

In general, the stepwise method is an interactive approach used in statistical analysis to select predictors that have a significant impact on the variable of interest. In this case, the probability of fatigue was analyzed and the results were evaluated through odds ratios considering the variables.

The present study followed the ethical precepts laid down in Resolution 466 of the National Health Council (CNS/MS/BRAZIL) on research involving human beings. For this, the project was approved by the Research Ethics Committee under opinion n. 5.542.659. It is noteworthy that the participants of the research were invited to carry out the reading of the Informed Consent Form (ICF), whose participation began only after choosing the option "I agree to participate in this research".

## RESULTS

There were 263 participants, mostly female (79.8%), aged between 21 and 40 years (41.0%), brown (46.8%), married/stable union (52.5%), with a postgraduate degree (30.8%), monthly income between one and two minimum wages (39.2%) and employed during the study (58.9%).

Regarding clinical characteristics, almost all reported fatigue as a persistent condition after the acute phase of Covid-19 (90.5%), mostly diagnosed only once (51.7%), vaccinated against Covid-19 (100.0%) and reported having been affected by the disease before vaccination (59.7%).

Concerning the severity of the infection, most who reported fatigue considered it mild (80.3%) and remained with debilitating physical and/or mental conditions for more than four weeks (78.2%). Those who reported having used alcoholic drinks during the period of infection were prevalent (58.6%).

In the bivariate analysis, there was a statistically significant association between persistence of symptoms for four weeks or more and presence of fatigue ( $p=0.017$ ) (Table 2).

**Table 2:** Analysis of the sample profile diagnosed with covid-19 associated with fatigue. Paraíba, Brazil, 2024 (n = 263).

| VARIABLES   | Fatigue             |                      | p-value       |
|---|---------------------|----------------------|---------------|
|   | No (n= 25)<br>n (%) | Yes (n=238)<br>n (%) |               |
| <b>How often were you diagnosed with Covid-19?</b>  |                     |                      | 0.199         |
| 1   | 16 (64.0)           | 123 (51.7)           |               |
| 2   | 8 (32.0)            | 87 (36.5)            |               |
| 3   | 0 (0.0)             | 24 (10.1)            |               |
| 4 or more   | 1 (4.0)             | 4 (1.7)              |               |
| Total   | 25 (100.0)          | 238 (100.0)          |               |
| <b>Have you been vaccinated against Covid-19?</b>   |                     |                      | -             |
| No  | 0 (0.0)             | 0 (0.0)              |               |
| Yes   | 25 (100.0)          | 234 (100.0)          |               |
| Total   | 25 (100.0)          | 234 (100.0)          |               |
| <b>Have you been diagnosed with Covid-19 before vaccination?</b>                                  |                     |                      | 0.830         |
| No  | 9 (36.0)            | 94 (40.3)            |               |
| Yes   | 16 (64.0)           | 139 (59.7)           |               |
| Total   | 25 (100.0)          | 233 (100.0)          |               |
| <b>How would you classify your worst Covid-19 infection?</b>                                      |                     |                      | 0.067         |
| Mild  | 24 (96.0)           | 191 (80.3)           |               |
| Moderate  | 01 (4.0)            | 42 (17.6)            |               |
| Severe  | 0 (0.0)             | 05 (2.1)             |               |
| Total   | 25 (100.0)          | 238 (100.0)          |               |
| <b>Did any physical/mental symptom persist for 4 weeks or more in any episode after Covid-19?</b> |                     |                      | <b>0.017*</b> |
| No  | 11 (44.0)           | 52 (21.8)            |               |
| Yes   | 14 (56.0)           | 186 (78.2)           |               |
| Total   | 25 (100.0)          | 238 (100.0)          |               |
| <b>Use of Tabaco/cigarette?</b>   |                     |                      | 1.000         |
| No  | 21 (87.5)           | 203 (86.0)           |               |
| Yes   | 03 (12.5)           | 33 (14.0)            |               |
| Total   | 24 (100.0)          | 236 (100.0)          |               |

| VARIABLES                       | Fatigue             |                      | p-value |
|---------------------------------|---------------------|----------------------|---------|
|                                 | No (n= 25)<br>n (%) | Yes (n=238)<br>n (%) |         |
| <b>Use of Alcoholic Drinks?</b> |                     |                      | 0.656   |
| No                              | 07 (29.2)           | 84 (35.4)            |         |
| Yes                             | 17 (70.8)           | 153 (64.6)           |         |
| Total                           | 24 (100.0)          | 237 (100.0)          |         |

Source: research data, 2024. \* Statistically significant association,  $p < 0.05$ . Note: not all participants answered all questions, therefore, the number (n) is reported in each variable.

The logistic regression analysis showed that individuals who presented any symptoms of physical and/or mental health for four weeks or more after the acute phase of covid-19 and used alcohol had a higher chance of reporting persistent post-covid-19 fatigue (Table 3).

**Table 3:** Variables associated with the presence of self-reported fatigue in residents of Paraíba. Paraíba, Brazil, 2024 (n = 263).

| VARIABLES   | Odds Ratio (OR) | 95% CI*        | p-value |
|---|-----------------|----------------|---------|
| <b>Presence of any symptom for four weeks or more</b> |                 |                |         |
| Yes   | 5.55            | (2.88 – 10.70) | 0.000†  |
| No  | -               |                |         |
| <b>Use of Alcoholic Drinks</b>                        |                 |                |         |
| Yes   | 2.88            | (1.21-4.31)    | 0.010†  |
| No  | 1.00            | -              |         |

Source: research data, 2024. \*95%CI: 95% confidence interval. †Statistically significant association,  $p < 0.05$ .

When considering the variables chosen by stepwise method, from the complete model that considered all the explanatory variables candidate to be related to the study outcome, of the regression model, it was observed that the four variables with the highest weight of evidence were as follows: "How would you classify your worst Covid-19 infection?" (VI = 0.2797); "Persistence of symptoms after 4 weeks" (VI = 0.3267); "How often were you diagnosed with covid-19" (VI = 0.1169) and "Use of alcoholic drinks" (VI = 0.0996).

## DISCUSSION

There has been a growing trend in the potential long-term implications of Covid-19. Persistent symptoms are diverse and often reported among the population. In response to these considerations, and in response to the research question, the findings indicate a high prevalence of fatigue among Covid-19 survivors in Paraíba. This high prevalence is consistent with recent studies, which identify fatigue as one of the most common persistent symptoms after infection<sup>(12-14)</sup>.

In this context, a study conducted in Italy showed that two months after recovery 53% of patients had persistent fatigue, the most reported symptom during the recovery



phase<sup>(15)</sup>, reinforcing that fatigue is one of the main symptoms of post-Covid-19 infection, where the persistence of symptoms for more than four weeks post-infection was shown as a factor associated with fatigue in this study.

Research conducted in China reported that 63% of participants six months after leaving hospital for Covid-19 reported fatigue and muscle weakness<sup>(16)</sup>, suggesting that, although the virus is eliminated, its effects on the immune system and neuromuscular function may extend beyond the acute phase of the disease.

In the meantime, a study with 2,500 participants who had Covid-19 reported that 87% reported at least one persistent symptom, with fatigue being the most commonly reported sintology<sup>(17)</sup>. Based on studies on the pathogenicity<sup>(18-20)</sup> of Covid-19, these findings suggest that the persistence of fatigue may be related to continuous inflammatory processes, as well as mitochondrial dysfunction and oxidative stress induced by the virus.

Regardless of the severity of the initial infection, there is a persistence of post-Covid-19 fatigue, compromising the quality of life of the patient<sup>(21,22)</sup>. Equally, a meta-analysis also shows that the severity of initial infection is not a predictor for the development of fatigue<sup>(23)</sup>, which is confirmed by the data from this study, showing that even those who had mild infection can suffer with this symptom for long periods. Fatigue, in addition to compromising physical capacity, brings emotional sequelae, impairing the quality of life and daily functionality of the individual. Evidence points to the fact that disorders such as anxiety and depression are associated with persistent fatigue, a point that is widely discussed as a key condition for fatigue to be prolonged already<sup>(24)</sup>.

Although most of the participants in this survey were vaccinated against Covid-19, the prevalence of fatigue was still high. These results are comparable to recent reviews that show that fatigue may persist even after vaccination or with previous infections, and, although the vaccine may reduce the severity of the disease, it does hinder the possibility of persistent symptoms<sup>(25-27)</sup>.

The consumption of alcoholic drinks as a factor associated with fatigue was also verified in this study. This finding may be related to the immunosuppressive and inflammatory effects of alcohol, as some studies reported that alcohol consumption can increase the organism response to post-viral inflammation and higher risk of developing post-infection complications<sup>(28,29)</sup>.

This study, by focusing on the population of Paraíba, offers a significant contribution to understanding persistent fatigue in a distinct socioeconomic and epidemiological context. Most participants were women, with ages ranging between 21 and 40 years. These data reveal that fatigue does not appear to be closely linked to traditional demographic factors, such as age or gender. Instead, such findings suggest a stronger connection with clinical and lifestyle aspects, as studies that claim that the persistence of symptoms over the long term is often related to residual inflammatory load and underlying risk factors, rather than being influenced by sociodemographic variations<sup>(12,13)</sup>.

The limitations of this study relate to the transversal method, which does not allow for cause-and-effect analysis, which would require longitudinal studies. Moreover, since it is the reality of a single Brazilian state, it becomes important to perform in other

Brazilian states, aiming to analyze fatigue in different regional and socioeconomic contexts. Nevertheless, it is believed that the results presented are important for knowledge about post-covid-19 fatigue in the population, as well as the factors associated with such outcome. From this, it is possible to outline strategies for therapeutic conduction of this condition.

## CONCLUSION

The present research provides data about post-covid-19 fatigue in the population from Paraíba, Brazil, a reality that is still scarce in the scientific literature. Individuals who reported persistence of symptoms for four weeks or more and use alcohol had higher chances of presenting fatigue.

The results reinforce the need for development and improvement of rehabilitation strategies specific to post-covid-19 conditions, in order to reduce the negative impact of this symptom on daily life and quality of life. In addition, the continuous follow-up of these patients is crucial to understand the temporal course of these symptoms and to plan effective therapeutic interventions.

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ISSN 1695-6141

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