Analysis of pulmonary function in post-Covid-19 patients at a university hospital

Análise da função pulmonar de pacientes com síndrome pós-covid-19 em um hospital universitário

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ABSTRACT

Objective: Evaluate the spirometry pattern of patients who persisted with respiratory symptoms after infection with SARS-Cov-2. **Methods**: Cross-sectional, observational, retrospective study in a single center, approved by the local Ethics Committee (registration number: 5,120,720). Patients who underwent spirometry due to Post-Covid Syndrome were evaluated to analyze the spirometric pattern presented. The following were collected: exam identification data, sex, age, symptom time, the need for mechanical ventilation, and quality of spirometry, in addition to the following exam parameters: FVC, FEV1, FEV1/FVC, FEV 25-75/FVC, and FEV 75, evaluating the Lower Limit of Normality, pre-bronchodilator and post-bronchodilator values. **Results**: Data from 72 patients were collected. Of these, 55.5% of patients had spirometry results within normal limits. The most frequent respiratory alteration was obstructive respiratory disorder, present in 29.2% of the patients. **Conclusions**: The presence of dyspnea in patients with normal spirometry may indicate further evaluation of lung function and other etiologies for dyspnea.

Keywords: Post-Covid-19 syndrome, Respiratory function tests, Spirometry, Dyspnea

RESUMO

Objetivo: Avaliar o padrão de espirometria de pacientes que persistiram com sintomas respiratórios após a infecção pelo SARS-CoV-2. **Métodos**: Estudo transversal, observacional e retrospectivo realizado em um único centro, aprovado pelo Comitê de Ética local (número do parecer: 5.120.720). Foram avaliados pacientes submetidos a espirometria devido à Síndrome Pós-Covid, a fim de analisar o padrão espirométrico apresentado. Os seguintes dados foram coletados: identificação do exame, sexo, idade, tempo de sintomas, necessidade de ventilação mecânica, qualidade da espirometria, além dos seguintes parâmetros do exame: CVF, VEF1, VEF1/CVF, VEF 25-75/CVF e VEF 75, avaliando o Limite Inferior da Normalidade, valores pré-broncodilatador e pós-broncodilatador. **Resultados**: Foram coletados dados de 72 pacientes. Destes, 55,5% apresentaram resultados espirométricos dentro dos limites normais. A alteração respiratória mais frequente foi o distúrbio ventilatório obstrutivo, presente em 29,2% dos pacientes. **Conclusões**: A presença de dispneia em pacientes com espirometria dentro da normalidade pode indicar uma avaliação adicional da função pulmonar, assim como outras etiologias para a dispneia.

Palavras-chave: Síndrome Pós-Covid-19 aguda, Testes de função respiratória, Espirometria, Dispneia

INTRODUCTION

Since its emergence, COVID-19 has been responsible for massive hospitalization and mortality rates. The virus can affect multiple organs, mainly the lung, and can lead, in the most severe cases, to acute respiratory failure. In the most severe cases, some patients have extensive damage to the alveolar epithelium and endothelium, which can lead to the proliferation of fibrous tissue and consequent interstitial fibrosing lung disease[1].

In this context, it has been observed that some of the patients remain with long-term symptoms after COVID-19. Among these, persistent dyspnea deserves to be highlighted, affecting about half of the patients previously infected with SARS-COV-2.[2] Another frequent symptom is fatigue, being cited in some studies as the most prevalent

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https://doi.org/10.11606/issn.2176-7262.rmrp.2023.206263

symptom after infection, often misinterpreted as dyspnea by patients[2-3]. Several other complaints have been reported after the infection, including headache, cognitive impairment, alteration in smell/taste, and arthralgia[4].

This set of symptoms that persist after infection is called Post-Covid Syndrome, responsible for a significant functional limitation. Regarding Post-Covid Syndrome, although there is no consensus on the definition, some studies also distinguish post-acute Covid, in which symptoms persist for more than three weeks from the onset of symptoms of infection, and long-term Covid-19, in which symptoms persist for more than three months from onset[4].

However, in the case of Post-Covid Syndrome, there are still few studies available describing its characteristics, evolution, duration, functional implications, or therapeutic options. In addition, there is often a dissociation between the patient's clinical severity and the radiological extension of the disease. While some patients with mild or absent clinical manifestations present chest computed tomography (CT) with exuberant alterations, others, despite presenting a significant limitation to efforts, have imaging exams with discrete or even absent parenchymal alterations[5]. When apparent, radiological manifestations most often suggest fibrosing interstitial lung disease.

A diagnostic tool that becomes indispensable in these patients' assessment is the Pulmonary Function Test (CFT), including spirometry, plethysmography, carbon monoxide diffusing capacity, cardiopulmonary exercise test, and 6-minute walk test. These tests allow the identification of possible obstructive, restrictive, or mixed ventilatory disorders and the evaluation of cardiorespiratory capacity after infection.[3] Among the tests available, spirometry deserves to be highlighted. Due to its easy access and excellent cost-benefit ratio, it plays a fundamental role in the initial assessment and follow-up of these patients.

The aim of this observational, retrospective, cross-sectional study was to assess the lung function of patients with respiratory symptoms after COVID-19 infection.

METHODS

This is a retrospective, observational, cross-sectional study carried out with patients at the Hospital Universitário Alcides Carneiro (HUAC) of the Federal University of Campina Grande (UFCG), receiving approval from the Ethics Committee of the aforementioned institution (registration number: 5,120,720). Data were collected from questionnaires applied in patients referred to HUAC to perform pulmonary function (spirometry) after SARS-CoV-2 infection between September 2020 and December 2021. Spirometry was evaluated by a pulmonologist at the same hospital.

Patients older than 18 years with a long-term history of previous SARS-CoV-2 infection confirmed by serology (before vaccination); a rapid test collected by nasal swab for antigen assessment or nasal and oropharynx swab for RT-PCR assessment were eligible. Individuals who presented respiratory symptoms after the viral condition and who underwent the spirometry test at the service in question were included. Pediatric patients, those who were unable to perform the examination properly, or those diagnosed with previously known interstitial disease were excluded.

The exam identification data was collected, including sex, age, respiratory symptoms, time between the diagnosis of COVID-19 and the performance of spirometry, past of mechanical ventilation, and cardiovascular, respiratory, or locomotor system system comorbidities.

Then, the following parameters of the spirometry test were collected: Forced Vital Capacity (FVC), Forced Expiratory Volume in the First Second (FEV1), Tiffeneau index (FEV1/FVC), Forced Expiratory Flow 25-75% (FEV 25-75), and FEV 25-75%-CVF ratio (FEV 25-75/FVC), recording the Lower Limit of Normality (LIN) and assessing pre-bronchodilator (Pre-Bd) and post-bronchodilator (Post-Bd) measurements.

The information was collected via an individual online form using Google Forms, organized and revised in Microsoft Excel, and then analyzed with IBM SPSS for Mac version 23. Categorical variables were described through their absolute and relative frequencies, while numerical variables underwent the Kolmogorov-Smirnov test to assess their normality and homogeneity, then described in mean and standard deviation if normal; otherwise, they were reported with median and interquartile interval range. Associations were assessed through odds ratio calculation and significance was

evaluated by Chi-square or Fisher's exact test. The significance level was assumed to be 5%.

RESULTS

The 72 patients were included, with a mean age of 54.04 + 1.62 years, of which 43 (59.7%) were women. Among the symptoms mentioned, we found 20 (27.8%) patients with productive cough; 34 (47.2%) had a cough in the morning; 27 (37.5%) had a history of wheezing, and 68 (94.4%) had dyspnea.

Regarding previous diseases, five (6.9%) had already been diagnosed with Chronic Obstructive Pulmonary Disease (COPD), four (5.6%) had a history of previous tuberculosis, 12 (16.7%) had disease of the musculoskeletal system, 11 (15.3%) had a previous need for mechanical ventilation, 41 (56.9%) had cardiovascular disease, and 27 (37.5%) had a previous diagnosis of asthma. Smoking history was reported by 29 (40.3%) patients and, among them, 25 (34.7%) were current smokers. The median smoking load was 22.5 (IQR = 52.0) packs per year.

The diagnostic tests used for the diagnosis of each patient were the rapid serological test (51.4%), the RT-PCR of the pharyngeal swab sample (36.1%), the serology of IgM and IgG antibodies (11.1%), and the rapid swab antigen test (1.4%).

In the spirometric reports (Table 1), 21 (29.2%) had the obstructive respiratory disorder, two (2.8%) had the restrictive respiratory disorder, seven (9.4%) had a proportional reduction in FEV1/FVC, one (1.4%) isolated reduction in FVC, one (1.4%) isolated reduction in FEV1, and 40 (55.5%) had spirometry within normal limits. The fourth column ("Altered tests") reports the absolute and relative frequencies of patients presenting pre-BD results below the lower limit of normality.

Table 1.
Average measurements of the spirometric variables (n = 72)

Variables	pre-BD	% predicted (pre-BD)	No. of altered exams	post-BD	% predicted (post-BD)	p*
FVC (L)	3.295 + 0.108	92.33 + 2.21	18 (25.0%)	3.266 + 0.107	91.51 + 2.19	0.092
FEV1 (L)	2.457 + 0.098	85.22 + 2.77	25 (34.7%)	2.521 + 0.974	87.39 + 2.65	<0.001
FEV1/FVC	0.740 + 0.014	91.89 + 1.74	22 (30.6%)	0.767 + 0.013	95.25 + 1.68	<0.001
FEF25-75/FVC	0.676 + 0.038	85.92 + 4.86	19 (26.4%)	0.763 + 0.042	96.75 + 5.37	<0.001
FEF25-75 (L)	1.965 + 0.147	81.57 + 5.29	22 (30.6%)	2.511 + 0.160	90.32 + 5.68	<0.001

BD: bronchodilator. *Student t-test for paired samples.

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We found six (8.3%) patients with a significant response to BD and two (2.8%) with an isolated response. Regarding the response to the bronchodilator, 66 (91.7%) showed no significant variation, one (1.4%) had a response to BD in FEV1, two (2.8%) had an isolated variation in FEV1, and three (4.2%) showed significant and marked variation in FEV1 and variation in FVC. It is worth noting that in this last category, one of the patients was asthmatic, and the others were smokers with a significant smoking history.

Table 2.
Discrimination of Obstructive Lung Diseases (OLD) observed

Disease	Absolute frequency	Relative Frequency
OLD Severe	1	1.4%
OLD Severe with low FVC by air trapping	1	1.4%
OLD Moderate	1	1.4%
OLD Moderate with low FVC by air trapping	2	2.8%
OLD Moderate with disproportionately low FVC	2	2.8%
OLD Mild	12	16.7%
OLD Mild with low FVC by air trapping	1	1.4%
OLD Mild with disproportionately low FVC	1	1.4%
Total	21	29.2%

OLD: Obstructive Lung Disease

Concerning the clinical variables of patients and their possible correlations with ventilatory disorders, we observed significant findings, reported in Tables 3 and 4. Patients complaining about "Productive cough", "morning cough", or "wheezing" were more likely to have developed Obstructive Ventilatory Disorders (OVD).

Table 3.
Association between symptoms and development of OLD

Comorbidity	OLD vs. no-OLD	Odds Ratio	p-value
Dyspnea	100% vs. 92.2%	-	0.187
Productive cough	47.6% vs. 19.6%	3.727 (CI 95% 1.240-11.20)	0.016
Cough in the morning	71.4% vs. 37.3%	4.211 (CI 95% 1.396-12.70)	0.008
Wheezing	47.6% vs. 21.6%	3.306 (CI 95% 1.116-9.790)	0.027
Duration of symptoms	21.68 vs. 21.64 weeks	-	0.914

Table 4.
Association between comorbidities and development of OLD

Comorbidity	OLD vs. no-OLD	Odds Ratio	p-value
Female sex	57.1% vs. 60.8%	-	0.775
COPD	14.3% vs. 3.9%	4.083 (CI 95% 0.630-26.47)	0.114
Previous pulmonary TB	4.8% vs. 5.9%	0.800 (CI 95% 0.078-8.161)	0.850
Rheumatologic disease	19.0% vs. 15.7%	1.265 (CI 95% 0.336-4.758)	0.728
Previous MV	19.0% vs. 13.7%	1.479 (CI 95% 0.383-5.705)	0.404
Cardiovascular disease	61.9% vs. 54.9%	1.335 (CI 95% 0.472-3.773)	0.585
Smoking	47.6% vs. 33.3%	1.818 (CI 95% 0.646-5.121)	0.255
Asthma	42.9% vs. 35.3%	1.375 (CI 95% 0.487-3.881)	0.547
Smoking history	55.53 vs. 52.50 pack-years	-	0.149

COPD: Chronic obstructive pulmonary disease. TB: Tuberculosis. MV: Mechanical Ventilation.

In our group of patients, 11 (15.3% of the total) required mechanical ventilation with orotracheal intubation, of which seven (7) had spirometry within normal limits, and four (4) with OVD, two (2) of them with reduced FVC by entrapment (one with severe and one with moderate OVD), one (1) of them with disproportionately reduced FVC, and one (1) other with mild OVD.

DISCUSSION

The main results of this study reflect spirometry findings in patients with a history of infection by Covid-19 in follow-up at a reference center for a population of about 1.2 million people in the state of Paraíba. It is important to emphasize the scarcity of studies on the sociodemographic pattern in question since it consists of a region in the interior of the Brazilian Northeast, but which has its epidemiological nuances.

Research participants were analyzed according to clinical criteria (gender, age, presence of comorbidities and previous symptoms, smoking or history of mechanical ventilation) and spirometry parameters after COVID-19.

It is important to point out that other diseases can lead to post-infectious syndromes, including fatigue. However, due to the high number of individuals who have been affected by SARS-Cov-2, Post-Covid Syndrome deserves individualized attention. This concern also applies to patients who had the disease without the need for hospitalization since most patients included in this study were not hospitalized but still presented long-term repercussions.[4]

Regarding the clinical parameters, the data showed a higher prevalence of females (59.7%), aged over 50 years (mean age: 54.05 +- 1.625). In addition, it is worth mentioning the high prevalence of dyspnea, reported by 94.4% of patients, a striking symptom in long Covid. Another important point is the history of mechanical ventilation in 15.3% of the patients, which may suggest some correlation between this factor and the cause of dyspnea - due to a possible dysfunction of the diaphragmatic muscles. In addition, there was a significant prevalence of variables such as Smoking (40.3%), Asthma (37.5%), and Cardiovascular Disease (56.9%), which may impose a relationship with more severe viral conditions and, consequently, greater post-Covid-19 clinical consequences.

Most individuals reported dyspnea, supporting its elevated prevalence in post-covid syndrome. However, most spirometries were normal (55.5%), suggesting this exam may not reflect all causes of dyspnea. Therefore, a complementary evaluation, including tests such as cardiopulmonary exercise tests and echocardiogram, may be useful.

Among the clinical variables evaluated, asthma was the most observed condition in patients with or without OVD, which may suggest the role of COVID-19 in worsening disease control in the patient's perception, whether due to inflammatory, structural, or psychological changes.

Furthermore, in a select group of patients, this discrepancy between the dyspnea complaint and the spirometric alterations may suggest an associated psychogenic component. After all, the severity of Covid-19 can be overrated when associated with trauma or anxiety disorders, which can lead doctors to overestimate respiratory complaints. Therefore, the importance of a multi-professional approach and follow-up has already been supported by the literature[6].

Given the particularities of COVID-19, the results of the present study corroborate the literature both concerning the time of persistence of symptoms after the acute phase and in correlation to the symptoms presented, as pioneered by Carfi et al.[2] and Augustin et al.[7]. However, the main point of disagreement is a higher frequency of dyspnea in despite of fatigue in our patients than in the cited studies. This phenomenon can be explained by the lower educational level of the population studied, which makes it difficult to understand what this symptom represents or even better cardiac-pulmonary capacity before the disease.

As a cross-sectional study, the present results are limited by the lack of a prospective follow-up of the patients for the systematic assessment of symptoms and spirometry. The scarcity of clinical data/medical assessments on lung function before SARS-Cov-2 infection limits information

on the patient's baseline status. It may lead to underestimating changes in lung function that, despite being significant and perceptible to the patient, still have results above the lower limit of normality, and overestimate changes in patients with previously unknown pulmonary conditions.

Conclusion

Therefore, dyspnea proved to be the most prevalent pulmonary symptom in our assessment of patients with post-Covid syndrome. However, the evaluation of pulmonary function by spirometry was not sufficient to elucidate this symptom since most patients had spirometry within normal limits. In that study, bronchodilators also did not improve lung function, which raises questions about their prescription for these patients. Regarding other symptoms, patients with cough and/or wheezing were more related to the presence of an obstructive ventilatory disorder, which may suggest bronchoreactivity in this group of patients, but this is a subgroup analysis.

Furthermore, while this represents a unique study, with several patients that are not yet significant, more studies should be encouraged in this still little-known post-COVID-19 phase. After all, doctors and researchers have focused on knowing the acute phase of the disease, not conceding the important consequences after this phase.

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Author contributions

Study design: PHBS; HAST. Data collection: PHBS; HAST; CMOC. Data analysis: FASLJ; TLFS; IGAB. Main Advisor: CMOC. Other advisors: TLFS; IGAB. All authors participated in some part of writing the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest

None declared. There was no funding or intervention from any pharmaceutical industry in this study.

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Editor:
Prof. Dr. Felipe Villela Gomes

Received: dec 27, 2022
Approved: mar 31, 2023