

Research Article

Persistent COVID, After Two Years of Overcoming the Acute Infection by SARS-Cov-2, Havana, Cuba, 2022

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Summary

Introduction: Persistent COVID is considered the lack of return to a usual state of health after an acute illness due to COVID-19. Objective: To describe the presence of symptoms of Persistent COVID in affected patients two years after the infection was overcome.

Methods: A prospective cohort study was carried out in 138 patients residing in Havana and Artemisa, who suffered from COVID-19 (44 mild, 87 moderate, 5 severe, 2 critical) in the period from March to June 2020, first Pandemic outbreak in Cuba. From July 2020 to July 2022, five interviews were conducted with the participants (3, 7, 12, 18, and 24 months) to determine the presence of reported symptoms of Persistent COVID.

Results: 62% of the patients suffered Persistent COVID four weeks after their clinical discharge. The most reported persistent symptoms were: respiratory distress (82.6%), muscle weakness (78.2%), headache (73.9%), fatigue (65.2%), and anosmia (52.2%). One year later, only 23.2% of the cases maintained persistent COVID. At 18 months, this persistence in 8% of the cases was the majority among severe and critical. Two years after suffering from the disease, the percentage of those affected remained the same as at 18 months, with a slight improvement in some patients. Persistent COVID was more frequent in people with comorbidities and over 40 years of age.

Conclusions: The presence of Persistent COVID is not exclusive to symptomatic patients for acute infection. The severity of persistent symptoms and their duration show a proportional relationship with severity, which points to a more severe and prolonged Persistent COVID the more severe the acute phase of the disease was suffered.

Keywords: COVID-19; Coronavirus; Symptoms; Sequelae; Convalescence

Introduction

More than two years after the notification of the first cases of COVID-19 (joint report by the WHO and the Government of China in February 2020), [1] it is considered that more than 8 million people have died and more than 90% of those infected have passed the acute phase of the infection. The latter may suffer from post-COVID-19 conditions made up of a wide range of health problems, which comprise a multi-organ symptom complex that affects patients who have suffered from COVID-19 and who remain symptomatic after the acute phase of the disease [2]. This entity, called post-acute COVID, long-term COVID, persistent COVID, or chronic COVID, is failure to return to a usual state of health after an acute illness from COVID-19, which may include the development of new, recurrent symptoms or ongoing, four to eight weeks after first being infected with the SarsCov-2 virus [3]. The maintenance of fluctuating symptoms of the disease for months could have a significant physical, occupational and emotional repercussion [4].

Three theories have been formulated to explain the pathogenesis of persistent COVID manifestations: the permanence of the virus in immunologically privileged sites such as the central nervous system, the aberrant immune response, and autoimmune phenomena secondary to infection [5]. Respiratory difficulty, cardiovascular, neurological, muscular, gastrointestinal and renal affections are reported as the main persistent symptoms [5-8]. Today, knowledge in this regard is limited. It is unfortunate that this persistent COVID issue does not receive enough media coverage. In most research scenarios, the health conditions of people after having suffered the disease are ignored. This fact confers special interest to the present investigation, which aims to describe the presence of persistent COVID symptoms in affected patients two years after the acute phase of the disease has passed.

Methods

As part of the research project *Genetic risk factors associated with the clinical severity of COVID 19 in Cuban patients*, from the National Center for Medical Genetics, an observational, longitudinal, prospective, cohort study was carried out in July 2020 to July 2022, in six municipalities of Havana and in the Province of Artemisa, Cuba. The selection of the study areas was in correspondence with the possibility of the researchers to follow up the participants over time, in the midst of a complex epidemiological situation, with movement restrictions and social isolation measures. Of the 439 Cuban patients who tested positive for the SARS-CoV-2 virus by PCR, between March 11 and June 11, 2020, in the municipalities of La Lisa, Marianao, Habana Vieja, Cotorro, Regla and San Miguel del Padrón in Havana, together with those affected from the Artemisa Province, those people over 18 years of age, with a clinical discharge date prior to June 11, 2020, were intentionally selected, not probabilistically. Those who were not fit, either physically or mentally, to give their testimony about the symptoms they exhibited at the time of the investigation. The study sample was made up of 138 patients.

In order to consider the participants in this study discharged, the provisions of version 1.5 of the National Action Protocol for COVID-19 were taken into account, which establishes: once the patient was PCR negative and passed the acute phase of the disease, with the guarantee of its follow-up in the health area, a clinical discharge with surveillance for 14 days at home is decided [9].

Patients who consented to participate in research underwent five interviews as part of the follow-up designed to explore the persistence of reported symptoms of COVID-19. These interviews were planned in homogeneous periods for each participant according to the date on which the acute phase of the disease was overcome in correspondence with their clinical discharge: first interview between two and six weeks after clinical discharge, second interview seven months later, third interview one year later, the fourth interview at 18 months and the last interview two years after clinical discharge. It is important to clarify that even when no symptoms of persistent COVID were reported in a previous interview; all the participants were interviewed on all five occasions, taking into account the description in the literature of fluctuating symptoms.

The exit criteria were established: the recurrence of the positive PCR to Sars- CoV-2 in the study period, death, change of residence, leaving the country, or any other event that made it difficult to question the participants, as well as the presence of any other disease that could bias the self-assessment of the state of health, taking into account that the research is based on symptoms reported by the patients themselves.

The information obtained was tabulated and processed in an Excel spreadsheet, to carry out the corresponding statistical analysis through the use of summary measures (absolute frequency and relative frequency) of the descriptive statistics. The formula $\chi^2 C = \sum (Fo - Fe)^2 / Fe$ was used to calculate the Chi Square, and the Chi Square calculator for the calculation of p whose interpretation allows us to estimate the probability that two variables are dependent or not, for p values less than or greater than 0.05.

Sociodemographic variables such as age (according to age groups) and sex (Female and Male) were studied; variables of clinical interest that included Personal Pathological History (Diabetes mellitus, High blood pressure, Obesity, Heart disease, Asthma, Immunodeficiencies, Chronic Kidney Disease, Neuropsychiatric disorders, others), COVID-19 symptoms (dry cough, fever, diarrhea, fatigue, smell disturbances, taste disturbances, insomnia, irritability, anxiety, difficulty breathing, sore throat, headache, skin lesions, hair loss, complications (pneumonia, respiratory distress, cardiac arrhythmias, kidney failure, venous or arterial thrombosis, acute myocardial infarction, decompensation of a chronic disease suffered) and the duration of the symptoms from clinical discharge to the time of each interview.

During the first outbreak of COVID-19 in Cuba, all patients diagnosed with positive PCR were admitted to hospitals or isolation centers, which allowed grouping the participants according to the classification referred to in the medical history consulted according to the severity with which they suffered the disease in, mild (mild or asymptomatic symptoms), moderate (those who were treated in wards and did not present complications), severe (those who presented complications, were reported as serious and were in the Intensive Care Unit, ICU) and critical (those who were reported as critical and were in the ICU).

Follow-up for Persistent COVID performed on each participant was possible for two years, stopping once the convalescents received their first dose of the COVID-19 vaccine. Recent articles propose a possible relationship between autoimmunity, the presence of antibodies against SARS-CoV-2, and the expression of Persistent COVID-19, so vaccination could bias the results [3].

Ethical Aspects

The project to which this study belongs was approved by the MINSAP Innovation Committee. For its realization, the approval of the Research Ethics Committee and the Scientific Council of the National Center of Medical Genetics of Cuba was obtained. The principles of the Declaration of Helsinki on research involving human subjects were complied with [10].

Results

Of the 138 patients that made up the study sample, 44 suffered from the acute phase of COVID-19 with mild or asymptomatic symptoms, 87 moderate, 5 severe and 2 critical, distributed in the six municipalities studied in Havana and in the Artemisa Province (Table 1).

The most frequent symptoms reported during the acute stage of infection were: respiratory distress (91%), insomnia

Table 1: Distribution of the cases studied by areas of residence, according to severity of acute COVID-19.

Study areas	Mild Cases	Moderate Cases	Serious Cases	Critical Cases	Total
(Municipalities or Province)	n=44 (31.9%)	n=87(63%)	n=5(3.6%)	n=2(1.5%)	N=138(100%)
La Lisa	8(5.8%)	13(9.4%)	1(0.7%)	-	22(15.90%)
Regla	3(2.2%)	10(7.2%)	-	-	13(9.4%)
Marianao	10(7.2%)	20(14.5%)	1(0.7%)	-	31(22.4%)
Habana Vieja	3(2.2%)	5(3.6%)	-	-	8(5.8%)
San Miguel del Padrón	7(5.1%)	14(10.1%)	2(1.5%)	1(0.7%)	24(17.4%)
Cotorro	9(6.5%)	10(7.2%)	1(0.7%)	1(0.7%)	21(15.2%)
Provincia Artemisa	4(2.9%)	15(11%)	-	-	19(13.9%)

n: number of individuals with the aforementioned characteristics.
N: Total number of individuals studied.

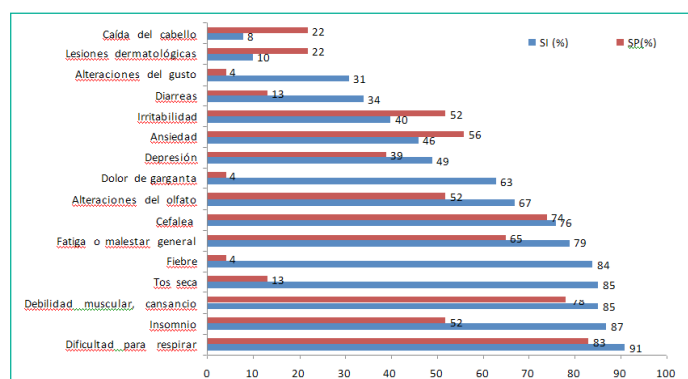


Figure 1: Relative frequencies of COVID-19 symptoms, during acute infection (SI) and in Persistent COVID (PS).

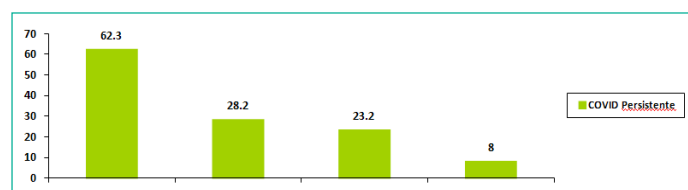


Figure 2: Percentage of patients with Persistent COVID, according to the time of the interview.

(86.6%), muscle weakness or tiredness (85.1%), dry cough (85.1%), fever (83.6%), fatigue or general malaise (79.1%), headache (76.1%), smell disorders (67.2%), sore throat (62.7%), among others. The persistent symptoms of COVID-19 that prevailed during the first interview, four weeks on average from clinical discharge were: respiratory distress (82.6%), muscle weakness or tiredness (78.2%), headache (73.9%), fatigue or general malaise (65.2%) and smell disorders (52.2%). Likewise, the participants reported the appearance of new symptoms after overcoming the infection, such as: anxiety (56.5%), insomnia (52.2%), irritability (52.2%), depressive episodes (39.1%), hair loss (21.7%), and skin lesions (21.7%) (Figure 1).

Among the less frequent clinical manifestations of Persistent COVID referred to at time of the first interview, the following were found: excessive body weight loss (8.7%), language impairment or dysarthria (8.7%), arrhythmias and/or occasional tachycardias (8.7%) and gait difficulty (4.3%). The patients described the onset of these events during SARS-CoV-2 infection, with no prior history.

The frequency of Persistent COVID, at an average time of four weeks after clinical discharge was 62.3% (86 of 138 patients reported more than one sustained symptom). In the second interview, 7 months after the infection was overcome, 28.2% of the participants (39 of 138) reported Persistent COVID. One year later, during the third interview, reported symptoms still persisted in 23.2% of the cases studied (32 of 138). Both, at 18 months and in the last interview, Prolonged COVID was evidenced in 11 people (8%) (Figure 2).

The symptoms of Persistent COVID reported during first and second interviews did not change, although the number of those affected was reduced by half, including mild, moderate, severe and critical cases. Symptoms such as respiratory distress, muscle weakness or tiredness, fatigue, neurological disorders, and decompensation of chronic diseases persisted after one year in 32 patients who suffered from the acute phase of the disease in a moderate, severe, or critical way (Figure 3).

Ten cases classified as mild and two asymptomatic in the acute phase of infection reported neurological disorders such as changes in mood, stress, depression, among others, during

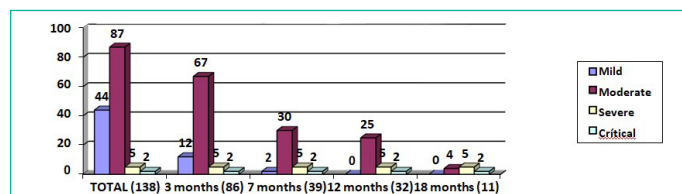


Figure 3: Distribution over time of patients with Persistent COVID according to severity of the acute phase of COVID-19.

Table 2: Distribution of people with or without Persistent COVID, according to age groups.

Age group (years)	Total estudios N (%)	With Persistent COVID n (%)	No Persistent COVID n (%)
19-39	51(37)	12(8.7)	39(28.3)
40-59	66(47.8)	55(39.8)	11(8)
60 a 79	17(12.3)	15(10.9)	2(1.4)
80 y más	4(2.9)	4(2.9)	-
Total	138(100)	86(62.3)	52(37.7)

n: number of individuals with the aforementioned characteristics.
Total number of individuals studied.

% were calculated based on the total cases studied and represent the percentage of people with or without Persistent COVID in each age group.

the first seven months of investigation. These patients did not manifest Persistent COVID either one year, 18 or 24 months after clinical discharge (Figure 3). Eighteen months after their clinical discharge, 92% of the participants did not report the persistence of symptoms. This was not the case for severe and critical cases that maintained, even after 24 months, respiratory distress, fatigue, exhaustion from routine activities, decompensation of chronic diseases and neurological disorders. These last alterations also persisted until the last interview in four cases that suffered from the acute phase of COVID-19 in a moderate way (Figure 3).

The distribution according to age groups of the participants showed that the percentage of patients with Persistent COVID was higher among older people. In the group between 19 and 39 years old, 8.7% of patients with persistent symptoms were found, however persistent COVID predominated among patients older than 40 years. Likewise, this condition was present in all the participants over 80 years of age in the investigation (Table 2).

The female sex represented 57.3% of the cases studied (79 of 138). Of the 86 people with Persistent COVID, 46 were women, for 53.5%, and 40 men, representing 46.5% of those affected. The Chi Square calculation $\chi^2C=1.31695$ (for one degree of freedom and a $p=0.251141$) confirmed that from a statistical point of view the probability of suffering Persistent COVID is independent of the sex of the individual. When the calculated Chi Square is less than the tabulated one ($\chi^2T=3.84$) with p greater than 0.05, the independence of the analyzed variables is demonstrated and the hypothesis that there are no differences between the observed and expected frequencies is fulfilled because the event occurred randomly.

52.1% (72 of 138) of the people suffered from at least one non-communicable chronic disease, the most frequent being hypertension (34.3%), followed by allergic disorders (25.4%), obesity (22.3%), asthma (19.4%), and diabetes mellitus (12.2%), among others less frequent such as cardiovascular disorders (4.3%), COPD (3.6%), immunosuppression (2.9%), hypercholesterolemia (2.9%), glaucoma (2.9%), thyroid disorders (2.9%), renal lithiasis (2.2%), gout (2.2%), renal failure (2.2%) and iron deficiency anemia (1.4%). In 94.2% (81 of 86) of patients with Persistent COVID, at least one of the referred chronic non-communicable diseases was reported, with frequencies similar to those found in total number of study participants. 33% (27 of 81) of the patients with Persistent COVID reported decompensated chronic diseases at three and seven months, 24.6% (20 of 81) at one year and 8.6% (7 of 81) at 18 and 24 months. Patients reported this decompensation more frequently for asthma (90% of asthmatics reported repeated asthma attacks in the study period after more than 10 years without presenting them), hypertension (51% with difficult blood pressure figures to stabilize), diabetes (48% with glycemia figures difficult to bring to normal parameters) and thyroid disorders (50% with alternating hyper and hypothyroidism). 71% of women of childbearing age reported menstrual cycle disorders after acute SARS-CoV-2 infection.

Discussion

There are very different data regarding the prevalence of Persistent COVID: some studies estimate that 20% of patients present symptoms at 4 weeks and

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