

Clinical characteristics of a group of patients who persist with respiratory symptoms after the acute phase of COVID-19

Authors: Gallego Claudio, Ortega Mayra, Méndez Ezcurra Luis, Poropat Alejandra, Lepek Gladys, García Fernández Alejandra, Agüero Silvia, Verdugo Silvina, Allegro Fabián, Salomone César

Hospital General de Agudos Parmenio P. Piñero, CABA, Argentina

Abstract

In convalescence from the SARS-CoV-2 infection, a high number of patients require medical consultation due to persisting symptoms.

Objective: To describe the clinical characteristics of patients who attend the Department of Respiratory Medicine due to persisting respiratory or thoracic symptoms after COVID-19 epidemiological discharge, and to assess their etiology by applying a follow-up protocol.

Materials and Methods: we included patients previously diagnosed with COVID-19 through PCR or with a combination of symptoms and epidemiological criteria who attended the Department of Respiratory Medicine spontaneously or referred by another health professional. Clinical examination, chest X-ray, spirometry, laboratory analysis, and the EQ-5D quality of life and PHQ-9 depression questionnaires were performed. According to the findings, the evaluation was complemented with D-dimer, six-minute walk test (6MWT), computed tomography (CT) and cardiac evaluation, following a predetermined algorithm. Mental health consultation was offered to patients with a result ≥ 10 in the PHQ-9 questionnaire.

Results: 95 patients were included: age 48 ± 11 years, BMI (Body Mass Index) = 28.4 ± 4.9 kg/m², 57 (60%) women and 64 (67.5%) Argentinians. Among foreigners: 19 (20%) were Bolivian, 8 (8.5%) Peruvian and 4 (4%) Paraguayan. 91 patients had a PCR-confirmed diagnosis; and from the remaining patients, two had positive serology and two clinical and epidemiological criteria. The most frequent comorbidities were: smoking (34%), arterial hypertension (21%), diabetes (16%), asthma (11%) and tuberculosis (5%); 38% did not refer any. 45 patients had been hospitalized, and 8 of them required treatment in the intensive care unit (ICU). The consultation time from epidemiological discharge was 46 ± 34 days (median = 38 days), and the most frequent symptoms were dyspnea (60%), cough (32%), chest pain (26%), low back pain (22%) and asthenia (10.5%); 50 patients required non-steroidal anti-inflammatory drugs (NSAIDs) for pain management. Regarding the depression questionnaire: 79% presented PHQ-9 > 4 (mild depression) and 36% ≥ 10 (moderate and severe depression); in the latter group we found higher prevalence in women: 44 vs. 24%, $p = 0.03$. We didn't find a relationship between depression assessed with PHQ-9 and age, nationality or isolation location; 13 patients agreed to consult with the Department of Mental Health (PHQ-9 14.9 ± 4 ; EQ-5D 39 ± 10).

In 6 patients, the spirometry showed values of forced expiratory volume in the first second (FEV₁) and/or forced vital capacity (FVC) $< 80\%$; they had history of pneumoconiosis ($n = 1$), asthma ($n = 1$) and obesity ($n = 1$), two presented an abnormal chest X-ray and the other one had been treated in the intensive care unit (ICU). Additional studies were performed in 24 patients (six-minute walk test [6MWT]: 3, CT: 6, echocardiogram: 2, D-dimer: 21). Persistence of ground-glass densities was found in 5 of the 6 tomographies. None of the patients required an additional medical approach during follow-up.

Conclusion: In post-COVID-19 patients, the most frequent symptoms for consultation were dyspnea, cough and chest or lumbar pain, as well as the finding of depression assessed by a questionnaire. The results favor the holistic approach in the evaluation and follow-up of these cases.

Key words: SARS-CoV-2; post-COVID-19 syndrome; post-acute COVID-19; post-COVID follow-up

In 2020 the world has suffered a pandemic caused by the SARS-CoV-2 which affected more than 80 million people –considering only confirmed cases– and resulting in more than 1.5 million deaths. At the beginning of January 2021 there were in Argentina more than 1.5 million cases and approximately 40,000 deaths. During the follow-up of those patients, it could be observed that around 10% of recovered individuals show prolonged symptoms after having the disease¹. These patients are described with the expression post-acute COVID-19 and generate a high demand of consultations with the health system, which is also under the pressure of receiving new cases.

This situation repeated itself in different parts of the world and resulted in the development of local guides with algorithms for cost-effective management of these patients^{1, 2}, facilitating the isolation of those with respiratory or cardiac complications that require strict and specialized follow-up. Some of the severe manifestations of COVID-19 that stand out are: lung parenchymal involvement³, damage of the microvasculature with thrombosis-associated risk and myocardial involvement⁴. However, most patients who attend the consultation after the acute phase present prolonged nonspecific symptoms that will gradually improve within weeks or a few months without showing medium-term or probably long-term sequelae.

This work intends to describe the clinical characteristics of patients categorized as post-acute COVID-19 for persisting with respiratory symptoms after the epidemiological discharge, using an algorithm based on the previously mentioned guides.

Materials and Methods

The prospective descriptive cohort was developed in the Hospital General de Agudos Parmenio Piñero between October and December, 2020 and was approved by the Independent Ethics Committee of the Hospital General de Agudos Dr. Teodoro Álvarez (CR 3766).

All the patients who had attended the Department of Respiratory Medicine spontaneously or referred by another health professional with persistent respiratory or thoracic symptoms after the COVID-19 epidemiological discharge entered the study in a consecutive manner. All the patients had been previously diagnosed through polymerase chain reaction (PCR), but the study also admitted patients who fulfilled epidemiological criteria (person cohabiting with a confirmed case) with a history of clinical condition compatible with SARS-CoV-2 infection. We excluded patients previously diagnosed with respiratory or cardiovascular sequelae related to this disease. The patients underwent a clinical examination (questions about current symptoms, medical record and physical examination), chest X-ray, pulse oximetry, spirometry, laboratory analyses (hemogram, erythrocyte sedimentation, glycemia, ionogram, hepatogram, urea and creatinine) and answered the EQ-5D quality of life and PHQ-9 depression questionnaires.

On the basis of the results obtained in the initial evaluation we applied a follow-up algorithm that is shown in **Figure 1**. Patients with dyspnea or chest pain in whom it was considered necessary to dismiss the cardiovascular origin of the symptoms we included determination of D-dimer through laboratory tests. If the clinical examination or the result of the D-dimer test justified a cardiac evaluation, the study would be completed with the six-minute walk test (6MWT), an echocardiogram and an evaluation performed by a specialist.

If the origin of the chest pain was determined to be musculoskeletal, they would be prescribed NSAIDs. We randomly administered 75 mg of diclofenac by oral route (OR) every 12 hours or 10 mg of ketorolac by OR every 8 hours, as available.

Patients with cough or dyspnea of presumed respiratory origin or with alterations in the spirometry or chest X-ray completed their evaluation with the 6MWT and computed tomography (CT), depending on the findings. The use of antitussives in an individualized manner was considered.

The initial evaluation included two questionnaires:

1. EQ-5D health questionnaire (Spanish version)⁵: designed to be self-administered, this questionnaire evaluates the patient's health condition through 5 questions that refer to: mobility, self-care, daily activities, presence of pain or discomfort and anxiety or depression. It is complemented by a visual analog scale in which the patient makes a mark between zero (the worst imaginable health condi-

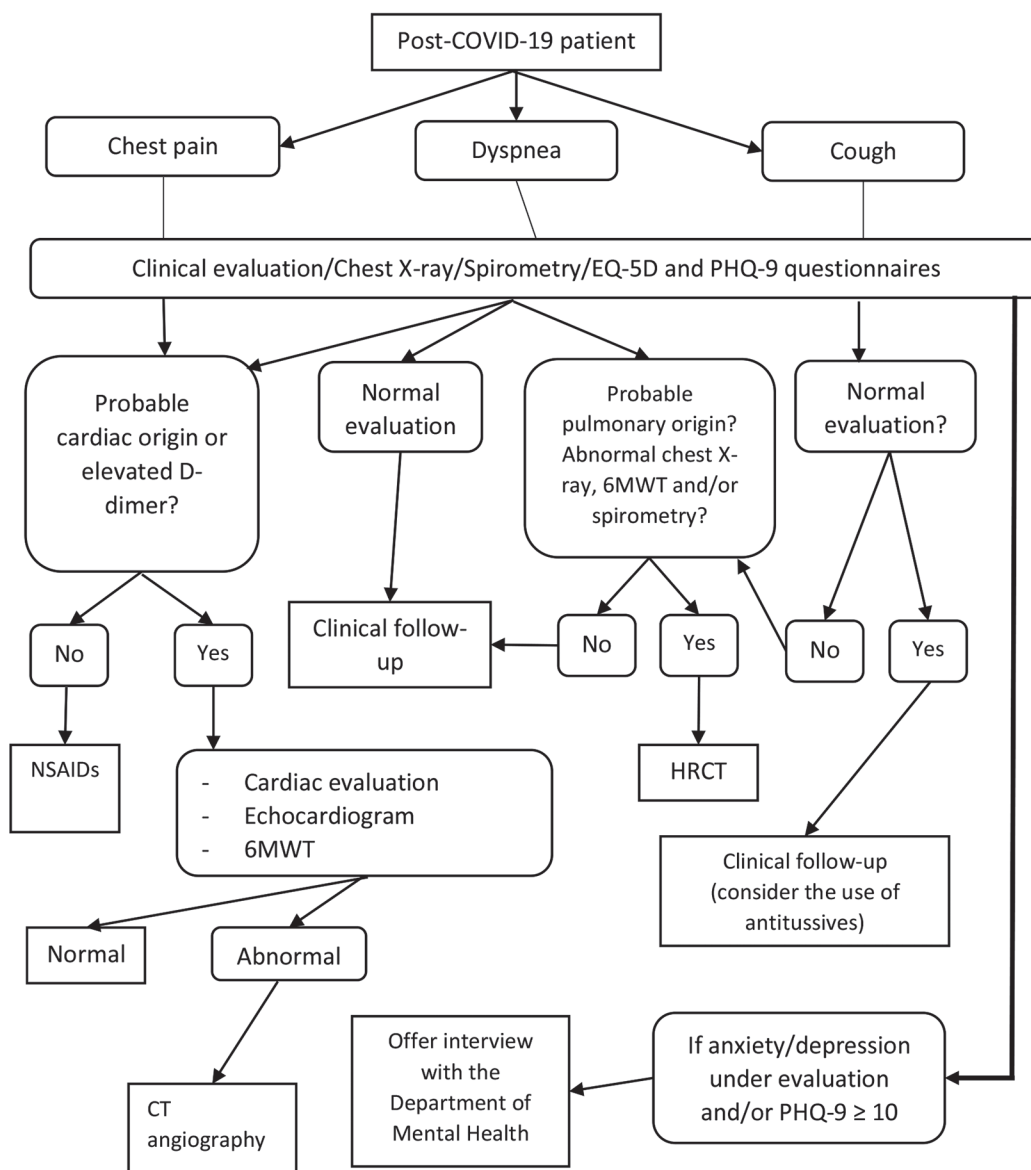


Figure 1. Algorithm that shows the diagnostic and follow-up approach of patients.

tion) and 100 (the best) in order to indicate the situation he/she is going through at the moment of the consultation.

- PHQ-9 depression questionnaire^{6, 7}: includes 9 items that evaluate the presence of symptoms of depression (that correspond to the DSM-IV criteria) in the last two weeks. The patient classifies the answer to each item according to its severity, for example: 0 = “never”, 1 = “some days”, 2 = “more than half the time” and 3 = “almost every day”. Those values are summed up and a score is obtained which categorizes the degree of depression: 0-4 without evidence, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe. All patients with values ≥ 10 (compatible with moderate or severe depression) or with values < 10 but whose clinical evaluation suggests significant alterations in the emotional sphere were offered an evaluation with the hospital’s Department of Mental Health.

The respiratory function exploration was performed according to the guidelines of the ATS/ERS (American Thoracic Society/European Respiratory Society)⁸ through a MIR Spirobank II spirometer. The 6MWT was done basing on the guidelines of the ATS⁹ with NONIN 8500M equipment.

Data obtained were analyzed with descriptive statistics tools. The Chi-Square Test was used for the qualitative variables (<https://www.socscistatistics.com>) and the Student t Test was used for the quantitative variables in the comparison between groups (Excel 2016), considering a value of $p < 0.05$ as significant.

Results

95 patients were included in the study, 91 of which had confirmed diagnosis of COVID-19 through PCR. Within the remaining patients, apart from having a compatible clinical condition, two had positive serology and two fulfilled epidemiological criteria.

Table 1 shows the demographic characteristics and isolation location throughout the course of the disease. It is worth mentioning that more than half of the patients came from their homes or a hotel adapted to fit the needs to care for isolated individuals; and among hospitalized patients ($n=45$): 39 (87%) required oxygen and 6 (13%) needed mechanical respiratory assistance.

The most frequent comorbidities were: smoking (34%), arterial hypertension (21%), diabetes (16%), asthma (11%) and tuberculosis (5%); 38% did not refer any (Table 2).

The time to make a consultation since epidemiological discharge was 46 ± 34 days (median = 38 days), or 63 ± 36 days (median = 55 days) if we take into account the time since the onset of COVID-19 symptoms. The most common symptoms which motivated the patients to make a post-COVID-19 consultation were: dyspnea (60%), cough (32%), chest pain, mostly described as oppressive and sporadic (26%), low back pain (22%) and asthenia (10.5%) (Table 3); 50 patients required NSAIDs for chest or lumbar pain of musculoskeletal origin.

Regarding the studies carried out in the initial consultation, in 6 patients the spirometry showed values of forced expiratory volume in the first second (FEV_1) and/or forced vital capacity (FVC) $< 80\%$; they had history of pneumoconiosis ($n = 1$), asthma ($n = 1$) and obesity ($BMI > 30 \text{ kg/m}^2$ ($n = 1$), two presented an abnormal chest X-ray and the other one had been treated in the intensive care unit (ICU). None of them required specific treatment related to COVID-19. Only 6 patients had $SpO_2 < 95\%$, with 92% as the lowest.

TABLE 1. Demographic characteristics and isolation location

Age	48 \pm 11 years
Sex	
Females	57 (60%)
BMI	28.4 \pm 4.9 kg/m ²
BMI > 30 kg/m ²	20 (21%)
Nationality	
Argentina	64 (67,5%)
Bolivia	19 (20%)
Peru	8 (8,5%)
Paraguay	4 (4%)
Isolation location	
Address	38 (40%)
Isolation at home	12 (12.5%)
Hospitalization (ward)	37 (39%)
Hospitalization (ICU)	8 (8.5%)

TABLE 2. Indicated comorbidities of 95 patients under evaluation

Comorbidity	n of patients (%)
None	36 (38)
Smoking	32 (34)
Arterial hypertension	20 (21)
Obesity (BMI \geq 30)	20 (21)
Diabetes	15 (16)
Asthma	10 (10,5)
Tuberculosis	5 (5)
Chagas' disease	3 (3)
Hypothyroidism	3 (3)
HIV positive	2 (2)
Dyslipidemia	2 (2)
COPD	1 (1)
Epilepsy	1 (1)
Heart failure	1 (1)
Rheumatoid arthritis	1 (1)
Pneumoconiosis	1 (1)
Fibromyalgia	1 (1)
Depression	1 (1)
Atopy	1 (1)

TABLE 3. Post-COVID-19 symptoms at the moment of the consultation

Symptom	% of patients
Dyspnea	57 (60)
Cough	30 (32)
Chest pain	25 (26)
Low back pain	21 (22)
Asthenia	10 (10.5)
Headache	5 (5)
Odynophagia	4 (4)
Myalgia/generalized pain	3 (3)
Anosmia	2 (2)
Diarrhea	2 (2)
Dysphonia	1 (1)
Dysgeusia	1 (1)

Additional individualized studies were done in 24 patients, basing on their clinical evaluation: 6MWT: 3, CT: 6, echocardiogram: 2, D-dimer: 21. Persistence of ground-glass densities was found in 5 of the 6 tomographies. They were considered as lesions in the process of resolution of pneumonia caused by SARS-CoV-2. D-dimer continued to be high in 4 patients (> 500) without active cardiac findings to justify it. None of the patients required an additional medical approach during follow-up.

Regarding the depression questionnaire: 79% presented PHQ-9 > 4 (mild depression) and 36% ≥ 10 (moderate and severe depression); in the latter group we found higher prevalence in women compared to men: 25 of 57 (44%) vs. 9 of 38 (24%), $p = 0.03$. We didn't find any relationship between depression assessed with the PHQ-9 questionnaire and age, nationality or isolation location. Patients with PHQ-9 ≥ 10 were offered an interview with the staff of the Department of Mental Health of the hospital. 13 patients (38%) agreed: PHQ-9 14.9 ± 4 and a quality-of-life value calculated by means of the EQ-5D scale of 39 ± 10 . When we compared both questionnaires (the EQ-5D was answered completely by 84 patients), we found a weak inverse correlation between the value obtained through the PHQ-9 and the visual analog scale of the EQ-5D ($r=0.37$). However, the answer to the question that identifies patients with self-perceived anxiety or depression, "I'm not anxious or depressed", of the EQ-5D divided the group that didn't show evidence of depression, either, through the PHQ-9: out of 26 patients without self-perceived anxiety/depression in the EQ-5D, 22 (85%) had PHQ-9 < 10 .

At the end of the study, we obtained feedback from the Department of Mental Health about the 12 patients who participated (one patient had accepted the invitation but didn't show up). The main findings were: fear of reinfection, asthenia, sleep disorders and mild depression (**Table 4**).

On the other hand, around one third (36 individuals) of the patients made the first visit and underwent initial studies only. These patients didn't show evidence of significant pathologic findings and didn't return to the final visit. Those who completed the follow-up visits and answered a PHQ-9 questionnaire during the final visit showed a significant decrease in the depression markers assessed by the PHQ-9 questionnaire: baseline 7.8 ± 6 vs. final 3.6 ± 4 ($p < 0.001$).

TABLE 4. Findings of the mental health assessment of 12 evaluated patients

	% of patients
Fear of reinfection	
Asthenia	80
Sleep disorders	80
Mild depression	70
Mild trauma indicators	60
Generalized anxiety disorders	50
Anxiety associated with the fact of being the main income earner	40
Grief over the pandemic	20
Irritability	20
Feeling guilty and with fear of infecting other members of the family	10

Discussion

The most common reasons for consultation of the group of patients who had attended the Department of Respiratory Medicine with persistent symptoms post-acute phase of COVID-19 were: dyspnea, cough, chest pain, low back pain and asthenia. The psychological burden associated with recovery from a disease was assessed by means of a depression questionnaire that showed significant alterations in the mental health sphere in more than one third of the patients. On the other hand, we didn't find any

significant organic changes that could explain the symptoms or psychological alterations. This agrees with the approach described in various guidelines^{1,2,13} that indicate the need to use a holistic approach in these patients.

Our study included a population with predominance of mild and moderate forms of acute COVID-19 over the severe ones, with a mean age slightly lower than other series^{10,11} and with greater representation of tuberculosis among the comorbidities¹². Symptoms such as dyspnea, cough, asthenia and pain (chest pain or generalized pain, such as myalgia or arthralgia) are described in all the reports. The presence of low back pain not related to the isolation location stands out in our series, but we can't describe it as a result of prolonged decubitus position and we can't establish a causal relationship with the infection, either.

We set a follow-up protocol in order to identify which patients are at risk of having cardiac or respiratory sequelae with a clinical evaluation and low complexity tests (chest X-ray, spirometry, 6MWT and D-dimer), confirming such sequelae through tests with higher diagnostic specificity, as for example echocardiogram and CT. None of the patients assessed with this algorithm showed significant alterations. A high proportion of patients who obtained normal results didn't return for follow-up. We think the reason for this could be the spontaneous favorable evolution as well as reduced patient anxiety, but since they didn't make a subsequent follow-up phone call we can't confirm this idea, and this means there is a weakness in the design of the study in terms of follow-up.

In the patient's evaluation we included the EQ-5D quality of life questionnaire and also the one related to depression, the PHQ-9. There are some studies about psychological disorders in health workers who participated in COVID patients care¹⁴, but this evaluation was not commonly conducted with patients. It is true that physical manifestations associated with COVID may distort answers to this questionnaire¹³, but physicians not specialized in the diagnosis of mental health diseases could use it and so it turned out to be a practical way to identify patients with psychological alterations that could benefit from mental healthcare. The questionnaire showed elevated numbers that suggest depression in any of its degrees in most patients. 36% of the population under evaluation showed very elevated results compatible with moderate or severe depression. In that group there was higher prevalence of women, in accordance with the gender differences established in multiple research studies¹⁵. This group of patients were offered a consultation with the Department of Mental Health, and it was accepted by approximately one third. Whereas the EQ-5D question assessing anxiety/depression was useful to exclude individuals who didn't need a mental health care consultation, the PHQ-9 facilitated the identification of a subgroup defined as "patients at risk of suffering from significant depression", for whom such consultation was in fact necessary.

To conclude, in the group of post-COVID-19 patients who developed the disease mostly without requiring intensive care the most common symptoms for consultation were: dyspnea, cough and chest or lumbar pain, without an organic correlate requiring other actions beyond symptomatic treatment. Depression assessed through a questionnaire was also common. The results favor the holistic approach in the evaluation and follow-up of these patients.

References

1. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026. <https://doi.org/10.1136/bmj.m3026>
2. Sibila O, Molina-Molina M, Valenzuela C, et al. Documento de consenso de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) para el seguimiento clínico post-COVID-19. *Open Respiratory Archives*. <https://doi.org/10.1016/j.opresp.2020.09.002>
3. Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. *Mod Pathol* 2020; 33: 2156–68. <https://doi.org/10.1038/s41379-020-00661-1>
4. Lowenstein C, Solomon S. Severe COVID-19 is a Microvascular Disease. <https://doi.org/10.1161/CIRCULATIONAHA.120.050354>
5. Cabasés JM. El EQ-5D como medida de resultados en salud. *Gac Sanit* 2015; 29: 6. <http://dx.doi.org/10.1016/j.gaceta.2015.08.007>
6. Kroenke K, Spitzer R, Williams J. The PHQ-9 Validity of a Brief Depression Severity Measure. *J Gen Intern Med* 2001; 16: 606-13.

7. Baader T, Molina JL, Venezian S, et al. Validación y utilidad de la encuesta PHQ-9 (Patient Health Questionnaire) en el diagnóstico de depresión en pacientes usuarios de atención primaria en Chile. *REV CHIL NEURO-PSIQUIAT* 2012; 50: 10-22.
8. Graham BL, Steenbruggen I, Miller M, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med*. 2019; 200: e70.
9. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111-7
10. Tenforde M, Kim S, Lindsell C, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network. *MMWR* 2020; 69, July 24.
11. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 6. <http://dx.doi.org/10.1001/jama.2020.12603>
12. Richardson S, Hirsch J, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; 323(20): 2052-9. <http://dx.doi.org/10.1001/jama.2020.677>
13. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026. <http://dx.doi.org/10.1136/bmj.m3026>
14. Azoulay E, Cariou A, Bruneel F, et al. Symptoms of Anxiety, Depression, and Peritraumatic Dissociation in Critical Care Clinicians Managing Patients with COVID-19. *Am J Respir Crit Care Med* 2020; 20: 1388-98.
15. Vázquez Machado A. Depresión, diferencias de género. *Multimed* 2013; 17: 1-21.