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Post-COVID-19 condition in patients with mild-moderate infection

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RESUMO

Introduction: Recognizing a post-COVID-19 condition's prevalence and severity is essential for patients follow-up decisions. However, few robust longitudinal data on long-lasting symptoms of COVID-19 are available, especially in mild-moderate disease.

Aims: This study aimed to identify the most frequent persistent and emerging symptoms of COVID-19, possible association with comorbidities, and the impact of COVID-19 infection on patients' health status, in a primary healthcare facility, up to one year of disease onset.

Methods: Telephone interviews were conducted six weeks, twelve weeks, and twelve months after COVID-19 infection to screen from acute phase clinical presentation up to one year after disease onset. Symptom persistence, patients' comorbidities and their impact on long-lasting effects of COVID-19 infection, and patients' self-perception of their health status were investigated.

Results: Long-lasting COVID-19 symptoms were predominantly asthenia, anosmia, dysgeusia, arthralgia, memory, and/or concentration problems. Health status after COVID-19 disease had worsened at post-acute disease (six and twelve weeks) and, after twelve months, some patients did not return to their usual health status. Susceptibility to prolonged symptoms could be associated with predictors, namely some symptoms present in the acute phase (myalgias, dyspnoea, asthenia, headache, anosmia, dysgeusia, diarrhoea, lumbar pain), presence of comorbidity, age over 40 and female sex.

Conclusions: The health consequences of COVID-19 extend far beyond acute infection. Prolonged COVID-19 symptoms were associated with specific patients' characteristics and acute disease presentation. Patients' health status deteriorated after COVID-19, and several patients did not recover one year later. For these reasons, attention should be guaranteed over time, independently of COVID-19 severity.

Keywords: COVID-19; Post-acute COVID-19 syndrome; Comorbidities.

INTRODUCTION

COVID-19 considered a threatening disease and an emergency in public medicine worldwide, is caused by a beta-coronavirus, SARS-CoV-2. Most COVID-19 patients have mild-moderate disease, although some patients have severe disease and require hospitalization. The acute phase of COVID-19 disease has been largely studied, however, there has been clear evidence that COVID-19 concerns go further than the initial symptomatic disease both in severe disease,[1-4] but also in mild-moderate disease.[5-8] The classification in severity of the acute disease had already been established.[9] However the full picture of the evolution and severity of long-term effects of COVID-19 is being resolved. It is generally believed that after COVID-19 recovery, prolonged disease may occur. COVID-19 disease may be divided, temporarily, into three different phases: acute, post-acute (after three-six weeks), and chronic COVID-19 (after twelve weeks) phases.[10-11] In this study, the long-term effects of COVID-19 were assessed at four time points, in these three phases, of mild-moderate COVID-19 disease.

Understanding the prevalence and severity of prolonged COVID-19 is important to inform decisions on patients'

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follow-up. We conducted an observational prospective study in patients with a Real-Time Reverse Transcription–Polymerase Chain Reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test in January 2021, overseen in a primary healthcare facility, in Portugal. This study aimed to identify the most frequent persistent or emerging symptoms of COVID-19, patients' auto-perception of COVID-19's impact on their health status, and possible predictors of long-term effects of the disease, up to one year since disease onset, namely patients' characteristics (risk factors, chronic conditions, and baseline health), comorbidities and symptoms present at the acute phase of COVID-19.

METHODS

Study design and patients

This prospective follow-up study was carried out in the centre of Portugal, at a primary health care facility. Inclusion criteria were patients with positive RT-PCR for SARS-CoV-2 in January 2021, followed up in the online platform Trace COVID-19 (https://tracecovid19.min-saude.pt). Exclusion criteria were death, institutionalization, and those who were lost because did not answer follow-up questionnaires. The primary healthcare facility oversaw all positive COVID-19 cases, which were in the community and those after discharge from a hospital stay. The patients were evaluated after six weeks, twelve weeks, and twelve months after symptoms onset and asked retrospectively about symptoms at the acute phase of the disease, using questionnaires developed for this purpose (Supplementary data). In acute, post-acute, and chronic COVID-19 phases, each symptom was considered only if it was not a condition that was present before the infection, to prevent bias. Telephone interviews were conducted to screen for COVID-19 symptoms persistence or emergence, demographic and initial clinical data, comorbidities, and patients' perception of their health status.

Data collection

Demographic data were collected from patients' electronic medical records in Trace COVID-19. The follow-up information regarding persistent or emerging symptoms, previous comorbidities, and personal health status was collected by telephone after six weeks, twelve weeks, and twelve months (Supplementary material S1). Informed consent was obtained from all individual participants included in the study.

Outcome

Patients were evaluated for persistent, recovered, or novel symptoms at three-time points after acute disease. Symptoms at six weeks, twelve weeks, and twelve months were defined as the presence of at least one of the following: cough (dry or with sputum), shortness of breath, fever (temperature >38 °C), headache, problems with taste and/or smell, asthenia, chest pain, sore throat, nasal congestion, gastrointestinal symptoms (appetite loss, diarrhoea, nausea and/or vomiting, abdominal pain), joint and/or muscle pain, lumbar pain, problems with sleeping and/or anxiety, memory and/or concentration problems.

Auto-perception of health status was asked in the three-time points of symptom analysis (after six and twelve weeks, twelve months of acute disease), and before disease onset, using a scale varying between 0 (worst imaginable health) and 10 (best imaginable health). This self-reported health status was recoded to poor (for a score ≤5), moderate (for a score between 6 and 8, included), and good (for a score ≥9).

Statistical analysis

In this study, some statistical approaches were applied in the data analysis using the software SPSS Statistics, v. 26. For categorical variables, frequency analysis was applied, and for quantitative variables, mean with standard deviation or median with interquartile range was used. Hypothesis tests were applied to make specific comparisons between some variables. To identify predictors of persistent symptoms after six weeks, twelve weeks, and twelve months after COVID-19 acute disease, logistic regression models were performed with a dependent variable of recovery (presence or absence of persistent symptoms), and odds ratios with their 95% confidence intervals were calculated.

Ethics

All patients were informed about the study and that they could refuse to participate at any time. This research was approved by Comissão de Ética da Administração Regional de Saúde do Centro – Governo de Portugal (Supplementary material S2).

RESULTS

Patients' characteristics

In January 2021, 298 patients with a positive RT-PCR

TABLE 1. Demographic data and comorbidities of patients

Characteristics	*n* (%)
Patients	240 (100)
Gender	
Female	135 (56.3)
Male	105 (43.7)
Age group (years)	
<18	31 (12.9)
[18; 65[	161 (67.1)
≥65	48 (20.0)
Number of comorbidities	
0	116 (48.3)
1 or 2	94 (39.2)
≥3	30 (12.5)
Comorbidities (prevalence ≥5%)	
Obesity (BMI ≥30kg/m^2)	46 (19.2)
Hypertension	45 (18.8)
Dyslipidaemia	24 (10.0)
Diabetes	18 (7.5)
Depressive syndrome	14 (5.8)
Autoimmune disease	14 (5.8)

Legend: BMI = Body mass index.

SARS-CoV-2 were overseen in our institution during the acute COVID-19 phase. After six weeks (post-acute COVID-19 phase), a questionnaire was applied by telephone to a sample of 240 patients who consented to participate in the study (57 did not answer the phone call and one refused to participate). Only 2.5% (6/240) of the patients in the study were hospitalized. Twelve weeks after the initial COVID-19 symptoms onset, from the 119 patients who were symptomatic after six weeks of acute infection, 98 patients answered a second questionnaire regarding persistent or emerging symptoms and self-perception of health status. To finalize the study, twelve months from COVID-19 disease, a last questionnaire was carried out and 41 answered the phone call from 54 patients who reported having persistent symptoms after twelve weeks.

Some demographic and clinical characteristics were analysed in the sample of 240 patients. The male/female ratio was 0.78 (56.3% female and 43.7% male). The age varied between six months and 88 years old with a mean of 43 years old and standard deviation of 21.2 years old. 12.9% were children (aged <18 years old) and 11.3% were adults aged ≥70 years old. Only 2.9% of the sample were adults aged ≥80 years old.

For the 209 adult patients (aged ≥18 years old), the mean ± standard deviation (mean±sd) for weight (in kilos) and height (in meters) were: 73.6±13.2 and 1.65±0.10, respectively. For the adult patients, the body mass index (BMI) varied between 18.29 and 42.97, with a mean of 27.05. Obesity was present in 19.2% of the patients (BMI ≥30 kg/m^2). There were no significant differences, in the average BMI between females and males (Levene's Test, p=0.022 and Independent Samples t-Test, p=0.516, α=5%).

Comorbidities that might be relevant for COVID-19 infection outcomes were also analysed. 48.3% of COVID-19-positive patient respondents did not have any comorbidity, but 39.2% had one or two comorbidities and 12.5% had three or more. The median number of comorbidities was one (interquartile range (IQR)=0-1.75) and the most prevalent comorbidities were metabolic (Table 1), highlighting obesity and hypertension as the most frequent.

Symptoms at the acute phase, post-acute, and chronic phases of COVID-19 disease

In the acute phase of COVID-19 infection, 13.8% of the respondents were asymptomatic, while 25.8% had one or two symptoms and 60.4% had three or more. Among the asymptomatic, three of them presented asthenia and two of them presented anxiety after six weeks. The median age of 240 respondents was 42 years (IQR=27.25-61), while the median age of 208 symptomatic was 43 years (IQR=30-62.75), including 18 of 31 children with at least one symptom. The median number of symptoms during the infection was three (IQR=2-4) and the five most frequent symptoms (anosmia, dysgeusia, headache, myalgia, asthenia) remained the most prevalent after six weeks. In the acute phase, females had more symptoms than males, with a significant statistical difference (Mann-Whitney Test, α=5%, p=0.030).

COVID-19 symptoms at six weeks, twelve weeks, and twelve months after acute infection and initial symptoms during the acute phase are presented in Figure 1 and

Table 2. The most frequently reported symptom was asthenia, followed by anosmia and dysgeusia in all phases. Fever was present in 26.7% of the patients in the acute phase, however, it was absent in all other phases.

This study also included children (12.9%). In the acute phase, 58.1% of the children were symptomatic. A reduction in persistent symptoms was observed over time and twelve months after infection. At that time, inquired children did not have symptoms that could be related to COVID-19.

Health status

Analysing the health status auto-perception of 240 patients, it was found that 35.5% had worsened six weeks after the disease, in comparison to their basal health status (Table 3). Health status was evaluated in four-time points (before the acute phase, post-acute COVID-19, and two-time points of chronic COVID-19 disease) and showed a fluctuation in mean ± sd: 8.49±1.40; 7.05±1.87, 7.78±1.61 and 8.07±1.54, respectively. A significant difference in the patient's health status between the four phases is present (Friedman Test, α=1%, $p \approx 0$). Dispersion boxplots are illustrated in Figure 2.

Predictors of persistent symptoms of COVID-19

There is an association between the persistence of COVID-19 symptoms and some conditions in the acute phase. After six weeks, persistent symptoms were significantly associated with: the presence of certain symptoms in the acute phase (myalgias, dyspnoea, asthenia, headache, anosmia, dysgeusia, diarrhoea, lumbar pain), presence of three or more symptoms in the acute phase, presence of one comorbidity, having depression as a comorbidity, age classes ([40; 50[, [50; 60[and ≥65 years old. After twelve weeks, persistent symptoms were only significantly associated with sex (females were the most prevalent). Symptoms persisting after twelve months were significantly associated with sex (female), asthenia, and the presence of one comorbidity (Table 4).

DISCUSSION

The majority of COVID-19 patients have asymptomatic to mild-moderate COVID-19.[12] In the present study, 86.5% of COVID-19 patients were symptomatic in the acute phase, compared to 71.4% symptomatic patients observed in an Italian study performed in the primary care setting.[1] The mean patients' age in our study is similar to other studies considering patients with mild to moderate disease,[6] and are younger than patients with severe disease.[13]

WHO stated that the median time for COVID-19 recovery is two weeks for mild cases and three to six weeks for severe disease,[12] however, there is evidence that there are prolonged manifestations after initial recovery. Amenda *et al.* gave a picture of the progression of acute SARS-CoV-2 infection to post-acute COVID-19, but could not determine specific time points to describe the post-acute disease. A *BMJ* Practice Pointer was published in August 2020, when almost no peer-reviewed research or evidence-based guidance on the condition of long COVID-19 was available.[10] Greenhalgh characterized post-acute COVID-19 as extending beyond three weeks from the onset of first symptoms and chronic COVID-19 as extending beyond twelve weeks. In December 2022, WHO defined long COVID as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation. The main strength of our work is that we have followed up our patients in the three recognized phases of COVID-19 disease (acute, post-acute, and chronic phase) in patients with asymptomatic to mild to moderate disease. The most frequent acute symptoms in patients with mild to moderate COVID-19 were anosmia, ageusia, headache, myalgia, asthenia, cough, and fever. Asthenia was the most prevalent persistent symptom after six weeks (59.7%), representing a prevalence two-fold that of the acute phase). Although we can a decrease in frequency, it was still a relevant symptom after twelve weeks (31.6%) and after twelve months (24.4%). Similar results were observed in other long COVID studies.[1,5,13-17]

The persistence of this symptom led to investigations in some of the patients using primary care guidelines presented by Greenhangh in the BMJ journal.[10] Persistent olfactory dysfunction (anosmia) and taste dysfunction (ageusia) were the two most prevalent symptoms in an acute phase that persisted the most during prolonged COVID-19, after asthenia. In cases occurring during the first wave of pandemia, olfactory and gustation functions were underestimated symptoms, however, WHO recognized them as essential symptoms, especially in mild-moderate COVID-19. There have been diverse mechanisms proposed to explain COVID related anosmia. It appears that the upper airways are not only the main entry site for SARS-CoV-2 but may have an essential influence

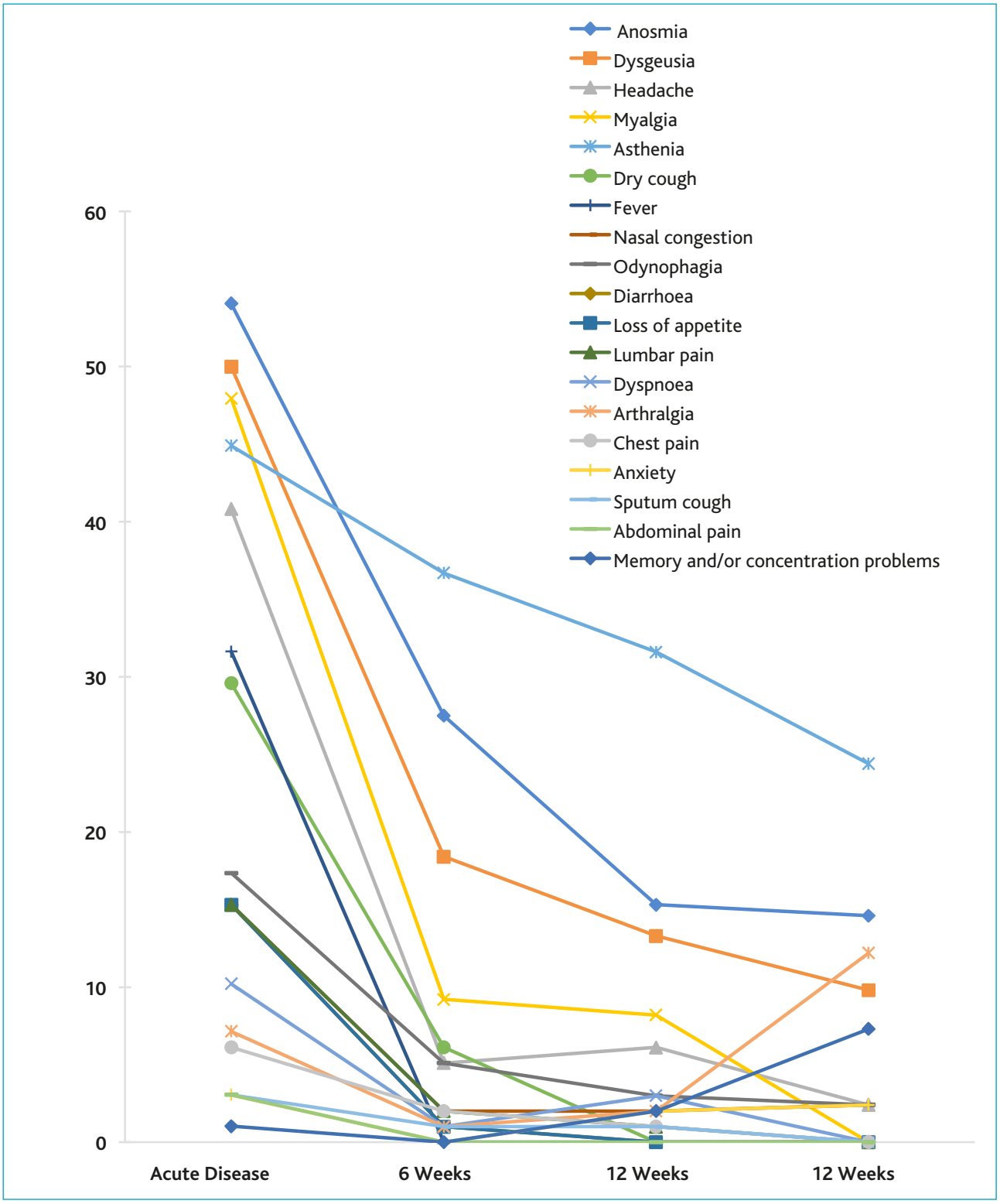

Figure 1. COVID-19 symptoms.

TABLE 2. Patients' characteristics and COVID-19 symptoms

Characteristics	Acute disease# *n* (%)	6 weeks# *n* (%)	12 weeks## *n* (%)	12 months### *n* (%)
Patients	240 (100)	119 (49.6)	98 (82.4)	41 (75.9)
Gender*				
Female	135 (56.3)	71 (59.7)	59 (60.2)	28 (68.3)
Male	105 (43.7)	48 (40.3)	39 (39.8)	13 (31.7)
Age group (years)				
<18	31 (12.9)	8 (6.7)	5 (5.1)	3 (7.3)
[18; 65[	161 (67.1)	85 (71.4)	71 (72.5)	29 (70.7)
≥65	48 (20.0)	26 (21.9)	22 (22.4)	9 (22.0)
Number of symptoms				
0	33 (13.8)	0 (0)	44 (44.9)	22 (53.7)
1 or 2	62 (25.8)	91 (76.5)	43 (43.9)	16 (39.0)
≥3	145 (60.4)	28 (23.5)	11 (11.2)	3 (7.3)
Symptoms				
Anosmia	95 (39.6)	31 (26.1)	15 (15.3)	6 (14.6)
Dysgeusia	90 (37.5)	23 (19.3)	13 (13.3)	4 (9.8)
Headache	79 (32.9)	13 (10.9)	6 (6.1)	1 (2.4)
Myalgia	78 (32.5)	14 (11.8)	8 (8.2)	0 (0)
Asthenia	68 (28.3)	71 (59.7)	31 (31.6)	10 (24.4)
Dry cough	67 (27.9)	6 (5.0)	0 (0)	0 (0)
Fever	64 (26.7)	0 (0)	0 (0)	0 (0)
Nasal congestion	33 (13.8)	3 (2.5)	2 (2.0)	1 (2.4)
Odynophagia	32 (13.3)	7 (5.9)	3 (3.0)	1 (2.4)
Diarrhoea	24 (10.0)	1 (0.8)	0 (0)	0 (0)
Loss of appetite	24 (10.0)	1 (0.8)	0 (0)	0 (0)
Lumbar pain	23 (9.6)	4 (3.4)	1 (1.0)	0 (0)
Dyspnoea	19 (7.9)	6 (5.0)	3 (3.0)	0 (0)
Arthralgia	8 (3.3)	3 (2.5)	2 (2.0)	5 (12.2)
Chest pain	7 (2.9)	2 (1.7)	1 (1.0)	0 (0)
Anxiety	7 (2.9)	15 (12.6)	5 (5.1)	1 (2.4)
Sputum cough	5 (2.1)	1 (0.8)	1 (1.0)	0 (0)
Abdominal pain	4 (1.7)	1 (0.8)	0 (0)	0 (0)
Memory and/or concentration problems	1 (0.4)	1 (0.8)	6 (6.1)	3 (7.3)

Interviews between February 5, 2021 and March 19, 2021.

Interviews between March 29, 2021 and May 16, 2021.

Interviews between February 3, 2022 and February 11, 2022.

n = Number of symptomatic patients in the previous phase; % = Percentage of patients with persistent symptoms.

* At post-acute COVID-19 phase, there were no differences in the number of symptoms between females and males (Mann-Whitney Test, α=5%, p=0.115).

TABLE 3. Patients' health status (scores 0 to 10) at three different COVID-19 disease phases: before acute, post-acute (6 weeks) and chronic (12 weeks and 12 months)

		Before acute disease	6 Weeks	12 Weeks	12 Months
Patients *(n)*		240	240	98	41
Health status *n* (%)	**Poor (≤5)**	6 (2.5)	21 (8.8)	7 (7.1)	3 (7.3)
	Moderate (6 to 8)	75 (31.3)	95 (39.6)	58 (59.2)	20 (48.8)
	Good (≥9)	159 (66.2)	124 (51.6)	33 (33.7)	18 (43.9)
Mean±sd		**8.87±1.25***	**8.23±1.75***	**7.91±1.69**	**8.07±1.54**

*Considering the total patients infected with COVID-19 (n=240), the means of health status are significantly different between before and six weeks after the infection (Wilcoxon Test, α=1%, $p\approx0$). Furthermore, it was concluded that there was a significant decrease in the patient's self-perception regarding their health status before and after illness (One sample t-test for the difference of scores, α=1%, $p\approx0$).

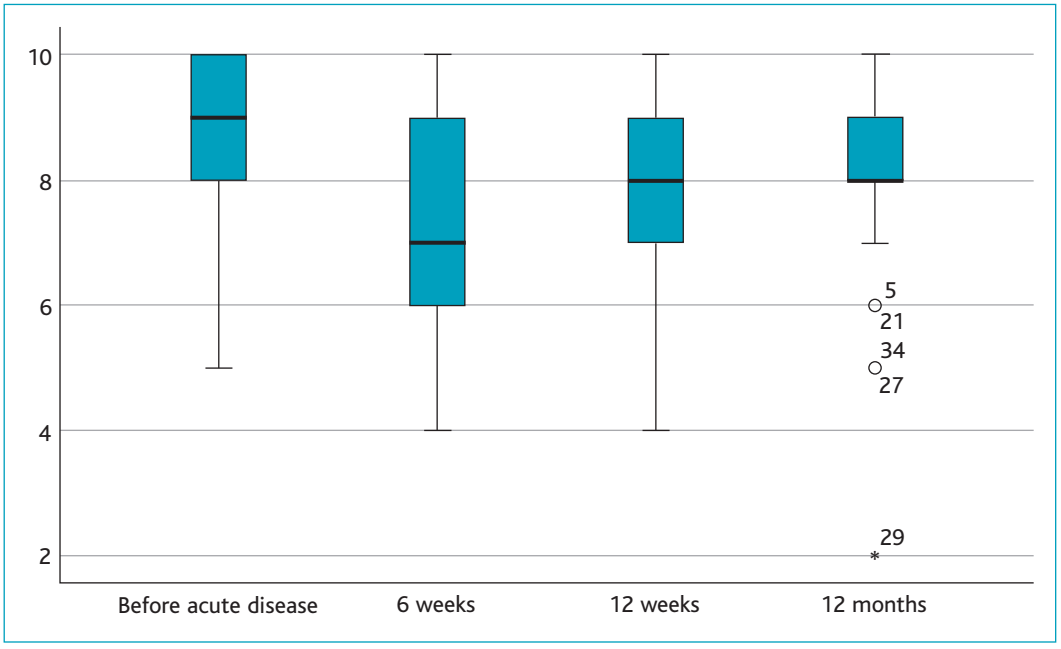

Figure 2. Patients' health status.

on the regulation of the systemic inflammatory response in prolonged disease.[18] It seems that these symptoms are more prevalent in European patients than Asian, due to higher angiotensin-converting enzyme-2 expression in nasal mucosa, which is used by coronavirus to invade the cells and cause infection.[19] Another mechanism that could explain anosmia is related to the immune-mediated damage to the supporting cells (non-neuronal cells) in the nasal olfactory mucosa.[20-21] Fever was only present in the acute phase and cough had a drastic reduction by the 6th week and was absent after twelve weeks.

Our study showed that, especially in later phases of the prolonged disease, arthralgia and also psychological and neurological consequences of COVID-19 infection (including anxiety, concentration, and memory problems) occurred. Other studies in the literature, including a meta-analysis comprising 36 studies, have also shown that arthralgias and cognitive symptoms, anxiety, and

TABLE 4. Predictors of persistent COVID-19 symptoms

Characteristics	6 Weeks# OR (95% CI)	12 Weeks## OR (95% CI)	12 Months### OR (95% CI)
Gender			
Female	Referent	Referent	Referent
Male	0.76 (0.46-1.27)	0.38 (0.17-0.88)*	0.14 (0.03-0.77)*
Age group (years)			
<18	Referent	Referent	Referent
[18; 30[	1.56 (0.55-4.45)	0.56 (0.07-4.76)	NA
[30; 40[	2.16 (0.76-6.14)	1.33 (0.16-11.50)	NA
[40; 50[	3.31 (1.21-9.02)*	0.67 (0.09-4.99)	NA
[50; 65[	8.15 (2.88-23.03)**	0.76 (0.11-5.24)	NA
≥65	3.40 (1.27-9.10)*	0.96 (0.13-6.98)	NA
Number of symptoms in acute phase			
<3	Referent	Referent	Referent
≥3	6.13 (3.43-10.98)**	1.92 (0.70-5.29)	NA
Symptoms			
Fever	1.71 (0.96-3.06)	1.45 (0.61-3.45)	0.81 (0.22-2.96)
Dry cough	1.62 (0.92-2.86)	1.23 (0.51-2.95)	2.47 (0.64-9.54)
Sputum cough	1.54 (0.25-9.38)	NA	2.47 (0.21-29.63)
Odynophagia	1.58 (0.74-3.36)	1.62 (0.55-4.80)	2.08 (0.49-8.88)
Myalgias	3.66 (2.05-6.54)**	1.68 (0.75-3.75)	1.99 (0.57-6.90)
Dyspnoea	4.22 (1.36-13.11)*	2.04 (0.49-8.39)	NA
Asthenia	5.09 (2.69-9.65)**	1.89 (0.84-4.25)	3.67 (1.01-13.40)*
Headache	2.30 (1.32-4.00)**	0.84 (0.37-1.88)	2.38 (0.67-8.49)
Chest pain	2.61 (0.50-13.72)	NA	NA
Nasal congestion	1.26 (0.60-2.63)	2.56 (0.75-8.69)	3.69 (0.80-17.12)
Anosmia	3.38 (1.96-5.82)**	0.97 (0.44-2.15)	3.36 (0.90-12.60)
Dysgeusia	2.86 (1.66-4.92)**	0.85 (0.38-1.88)	1.65 (0.48-5.69)
Diarrhoea	5.91 (1.95-17.87)**	0.67 (0.22-2.02)	0.84 (0.16-4.36)
Nausea/vomiting	1.67 (0.53-5.27)	2.14 (0.40-11.62)	NA
Abdominal pain	NA	1.65 (0.15-18.87)	1.17 (0.07-20.02)
Arthralgia	NA	2.14 (0.40-11.62)	3.94 (0.37-41.49)
Loss of appetite	2.19 (0.90-5.34)	1.77 (0.56-5.64)	1.19 (0.21-6.72)
Lumbar pain	3.19 (1.21-8.41)*	0.49 (0.16-1.49)	3.94 (0.37-41.49)
Anxiety	2.61 (0.50-13.72)	1.65 (0.15-18.87)	NA

(continues)

TABLE 4. Predictors of persistent COVID-19 symptoms *(continued)*

Characteristics	6 Weeks# OR (95% CI)	12 Weeks## OR (95% CI)	12 Months### OR (95% CI)
Number of comorbidities			
0	Referent	Referent	Referent
1	1.89 (1.02-3.50)*	1.75 (0.67-4.59)	0.11 (0.02-0.59)*
2	2.20 (0.97-4.50)	1.17 (0.33-4.16)	0.68 (0.09-5.45)
≥3	2.20 (0.97-4.50)	1.00 (0.31-3.25)	0.30 (0.04-2.42)
Comorbidities			
Obesity (BMI ≥30)	1.58 (0.82-3.02)	1.00 (0.37-2.67)	0.91 (0.21-4.01)
Hypertension	1.50 (0.78-2.89)	0.76 (0.30-1.92)	0.31 (0.06-1.79)
Diabetes	1.30 (0.49-3.41)	1.09 (0.23-5.17)	NA
Asthma	1.28 (0.34-4.90)	NA	NA
CPOD	NA	1.65 (0.15-18.87)	1.17 (0.07-20.02)
Neurological disease	2.61 (0.50-13.72)	1.24 (0.20-7.74)	NA
Anxiety	2.46 (0.62-9.74)	1.68 (0.29-9.63)	0.56 (0.05-6.66)
Depression	4.01 (1.09-14.74)*	2.04 (0.49-8.39)	2.47 (0.21-29.63)
Osteoarticular diseases	2.46 (0.62-9.74)	1.24 (0.20-7.74)	2.47 (0.21-29.63)

Interviews between February 5, 2021 and March 19, 2021.
Interviews between March 29, 2021 and May 16, 2021.
Interviews between February 3, 2022 and February 11, 2022.
*p<0.05; **p<0.01; BMI = Body mass index; CI = Confidence interval; CPOD = Chronic pulmonary obstructive disease; NA = Not applicable; OR = Odds ratio.

depression, were long-lasting COVID-19 symptoms.[22-24]

Different pathophysiological mechanisms, involving organ damage (lung, digestive tract, heart, brain, liver), biological mechanisms (including viral persistence, inflammation, autoimmunity, neurological dysregulation, microbiota dysbiosis, endothelial dysfunction), whereas multiple risk factors (including age, sex, pre-existing comorbidities, smoking, BMI, and acute COVID-19 severity) influence the development of long COVID-19.[17] It is well known that long COVID is a multi-systemic illness, however, the precise mechanisms that explain COVID-19 long term symptoms are not yet totally clarified.

Health status after COVID-19 disease had worsened at the two-time points analysed in post-acute disease (six and twelve weeks after infection) in comparison to usual health status. After twelve months of the acute infection, we could perceive that patients' perception of health status was better than after twelve weeks, but patients' perception of health status stayed worse than before infection. Many studies indicated that people with a positive RT PCR for SARS--CoV2 who had prolonged COVID-19 symptoms did not return to their basal health status,[1,6,13] which is following our work. The known inflammatory response after COVID-19 infection and the psychological environment related to symptomatic COVID-19 may be responsible for persistent and emerging late manifestations of the disease.

Prolonged COVID-19 symptoms are more frequent in patients over 40 years old and in females after twelve weeks and twelve months of acute infection. These findings are under what is found in the literature, showing a higher susceptibility for persistent symptoms in the female sex and older patients.[6-8,13,17] The presence of previous comorbidity, depression, and the acute manifestation of the disease (disease severity, number, and specific symptoms) were associated with COVID-19 symptoms persistence. Other studies have shown prolonged

symptoms associated with similar patients' characteristics.[6-7,13,17]

The findings in this report are subject to at least three limitations. Firstly, the follow-up of asymptomatic to mild-moderate COVID-19 patients was performed mainly by phone call and relied in patients' perspectives concerning symptoms and well-being (the patient was only observed in person if needed). Secondly, data on the acute phase was collected retrospectively, which can contribute to bias. Thirdly, these patients had SARS-CoV-2 infection before COVID-19 immunization since vaccines were not available at that time.

The management of post-acute COVID-19 relies on holistic care, symptom control, and detection of treatable complications. Nonetheless, it is important to take preventive actions to avoid infection and vaccination has been shown to significantly suppress morbidity and decrease long COVID-related symptoms.[25]

Most of these patients may be supported by a general practitioner with a special interest in long COVID-19. A recent BMJ *Practice Pointer*[26] (published in September 2022) gives guidance on the management of prolonged symptoms following COVID-19 infection in a primary care setting. Portuguese guidelines related to the clinical management of post-COVID-19 conditions, aiming to preserve the quality of life and functional capacity of patients were also published in March 2022.[27]

CONCLUSION

The health consequences of COVID-19 extend far beyond acute infection. Patients with mild-moderate COVID-19 disease may have long-term effects, both persistent or emerging symptoms, including asthenia, anosmia, dysgeusia, arthralgia, memory and/or concentration problems, and worsening of their health status. Although there are studies on persistent symptoms of COVID-19, the overall understanding of the course of mild-moderate COVID-19 disease and the risk factors for disease progression are still unclear. Comprehensive long-term investigation is essential to understand the physiopathology of the disease and guide the medical community in the future, to prevent the occurrence of long-COVID symptoms, develop treatment strategies, and follow-up according to patients' characteristics.

REFERENCES

1. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-5.
2. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. J Med Virol. 2021;93(3):1242-3.
3. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020;81(6):e4-e6.
4. D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith LJ, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Res. 2021;7(1):00655-2020.
5. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288(3):335-44.
6. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, 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 – United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69(30):993-8.
7. Goërtz YM, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FV, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020;6(4):00542-2020.
8. Petersen MS, Kristiansen MF, Hanusson KD, Danielsen ME, Steig BÁ, Gaini S, et al. Long COVID in the Faroe Islands: a longitudinal study among nonhospitalized patients. Clin Infect Dis. 2021;73(11):e4058-63.
9. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: an overview and approach to classification. Open Forum Infect Dis. 2020;7(12):ofaa509.
10. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026.
11. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining post-COVID symptoms (post-acute COVID, long COVID, persistent post-COVID): an integrative classification. Int J Environ Res Public Health. 2021;18(5):2621.
12. European Observatory on Health Systems and Policies, Rajan S, Khunti K, Alwan N, Steves C, et al. In the wake of the pandemic: preparing for long COVID [Internet]. Geneva: World Health Organization; 2021. Available from: https://iris.who.int/handle/10665/339629
13. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32. Retracted and republished in: Lancet. 2023;401(10393):2025.
14. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021;27(4):626-31.
15. Davido B, Seang S, Tubiana R, de Truchis P. Post-COVID-19 chronic symptoms: a postinfectious entity? Clin Microbiol Infect. 2020;26(11):1448-9.
16. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2021;27(2):258-63.
17. Nalbandian A, Desai AD, Wan EY. Post-COVID-19 condition. Annu Rev Med. 2023;74:55-64.
18. Gallo O, Locatello LG, Mazzoni A, Novelli L, Annunziato F. The central role of the nasal microenvironment in the transmission, modulation, and clinical progression of SARS-CoV-2 infection. Mucosal Immunol. 2021;14(2):305-16.
19. Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, et al. Diagnosis of the coro-

navirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020;126:108961.
20. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv. 2020;6(31):eabc5801.
21. Gori A, Leone F, Loffredo L, Cinicola BL, Brindisi G, De Castro G, et al. COVID--19-related anosmia: the olfactory pathway hypothesis and early intervention. Front Neurol. 2020;11:956.
22. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. J Infect Dis. 2022;226(9): 1593-607.
23. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38:101019.
24. Li J, Zhou Y, Ma J, Zhang Q, Shao J, Liang S, et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. Signal Transduct Target Ther. 2023;8(1):416.
25. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022;22(1):43-55.
26. Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long covid: an update for primary care. BMJ. 2022;378:e072117.
27. Direção-Geral da Saúde. COVID-19: condição pós-COVID-19: norma nº 002/2022, de 17/03/2022. Lisboa: DGS; 2022.

AUTHORS CONTRIBUTION

Conceptualization, MC, and FS; methodology, MC, FS, RSR, and FB; validation, MC, and FS; formal analysis, FS; investigation, MC, RSR, and FB; resources, MC, FS, RSR, and FB]; writing – original draft, MC, and FS; writing – review & editing, MC, FS, RSR, and FB; visualization, MC, and FS; supervision and project administration, MC.

DECLARATION OF INTEREST STATEMENT

The authors report that there are no competing interests to declare.

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ABSTRACT

CONDIÇÃO PÓS-COVID-19 EM DOENTES COM INFEÇÃO LEVE A MODERADA

Introdução: Reconhecer a existência da condição pós-COVID-19; a sua prevalência e severidade é importante para definir cuidados a prestar aos doentes a longo prazo; no entanto, há poucos estudos longitudinais, em especial na doença leve a moderada.
Objetivos: Identificar os sintomas persistentes ou que surgiram *de novo* após a infeção por COVID-19, a sua possível associação a comorbidades e conhecer o impacto da infeção por COVID-19 no estado de saúde dos doentes numa unidade de saúde de cuidados primários, ao longo de um ano.
Métodos: Após infeção aguda por COVID-19 foram realizadas entrevistas telefónicas ao fim de seis semanas, doze semanas e doze meses de forma a avaliar a situação clínica do doente. Foram investigados os sintomas existentes na fase aguda e pós--aguda, a existência de comorbidades ou outras características específicas dos doentes, assim como a autoperceção do seu estado de saúde.
Resultados: Os sintomas de COVID-19 a longo prazo são predominantemente astenia, anosmia, disgeusia, artralgia e problemas de memória e concentração. O estado de saúde após infeção por COVID-19 piorou na fase pós-aguda de doença (seis e doze semanas) e, após doze meses, alguns doentes não retomaram o seu estado de saúde habitual. Foi possível associar a maior suscetibilidade a sintomas prolongados de COVID-19 com alguns preditores, nomeadamente alguns sintomas em fase aguda (mialgias, dispneia, astenia, cefaleia, anosmia, disgeusia, diarreia e dor lombar), presença de comorbidade, idade superior a 40 anos e sexo feminino.
Conclusões: Os efeitos da infeção por COVID-19 manifestam-se muito além da infeção aguda. Foi possível identificar alguns preditores de sintomas prolongados de COVID-19. Verificou-se uma deterioração do estado de saúde dos doentes após infeção por COVID-19. Por estes motivos, deverá ser mantida vigilância ao longo do tempo, independentemente da severidade da infeção por COVID-19.

Palavras-passe: COVID-19; Síndroma pós-COVID-19 agudo; Comorbidades.