

## A Prospective Study of Patients with Persistent Symptoms After SARS-CoV-2 Infection Referred to Physical Medicine and Rehabilitation

### Um Estudo Prospetivo de Doentes com Sintomas Persistentes Após Infecção por SARS-CoV-2 Referenciados à Medicina Física e Reabilitação

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#### ABSTRACT

**Introduction:** New evidence and extrapolated data from other coronaviruses suggest that symptoms and consequences of COVID-19 may persist beyond the cure. The aims of this study were to evaluate persistent symptoms after SARS-CoV-2 infection and its impact on physical condition, activities of daily living, and quality-of-life; establish whether symptom persistence is associated with higher disability; and document the evolution of the multiple domains after a home exercise program.

**Methods:** Prospective study with patients referred to a Physical and Rehabilitation Medicine clinic, after SARS-CoV-2 infection. Patient evaluations, including a symptom questionnaire, the 1-Min Sit-to-stand test (1-MSTS), the EQ-5D questionnaire and the London Chest Activity Daily Living (LCA-DL) questionnaire, were performed before and after a home exercise program.

**Results:** Seventy-four patients were included. The majority (n = 71) had been hospitalized (mean stay 19.66 ± 13.35 days), 51% required intensive care. At first evaluation, 54 days after symptom onset, a mean of 18.6 repetitions in the 1-MSTS were performed. The percentage of LCA-DL was above 28% in 23% of the patients. Impairments on EQ-5D were present in 44% for mobility and 44% for anxiety/depression. Mean EQ-5D VAS was 66.5 out of 100. Fifty-one (70%) had at least one persistent symptom (Symptomatic Group), while 22 (30%) were asymptomatic (Asymptomatic Group). The Symptomatic Group had statistically significantly worse mean results on 1-MSTS (16.8 vs 22.9; p < 0.001), % LCA-DL score, EQ-D5 (7.8 vs 5.7; p < 0.001) and EQ-D5-VAS. No patient characteristic, clinical background, comorbidity, or hospitalization characteristics was significantly different between groups. Every patient was given a home exercise program; 47 patients joined an additional rehabilitation program or were clinically discharged and were therefore excluded from the second evaluation. Twenty-seven patients participated in a second evaluation. In the matched analysis, mean 1-MSTS improved by 3.4 repetitions. Mean LCA-DL, mean EQ-5D score (7.1 to 6.6) and EQ-VAS score changed favourably and significantly.

**Conclusion:** Two months after infection by SARS-CoV-2, persistent symptoms were frequent in patients referred to a Physical Medicine and Rehabilitation clinic. Additionally, the SARS-CoV-2 infection, as well as the persistence of symptoms, had a negative impact in the physical condition and functionality in ADL and quality-of-life. With a home exercise program in place, a statistically significant improvement was observed. Referral of patients with persistent symptoms to Physical and Rehabilitation Medicine may be warranted.

**Keywords:** Activities of Daily Living; Physical and Rehabilitation Medicine; Portugal; Post-Acute COVID-19 Syndrome; Quality of Life

#### RESUMO

**Introdução:** Nova evidência e dados extrapolados de outros coronavírus sugerem que os sintomas e consequências da COVID-19 podem persistir para além da cura. Os objetivos deste estudo foram: avaliar a persistência de sintomas após infecção por SARS-CoV-2 e o seu impacto no condicionamento ao esforço, atividades da vida diária e qualidade-de-vida; estabelecer se a persistência de sintomas condiciona maior incapacidade; e documentar evolução dos vários domínios, após um programa de exercícios domiciliário.

**Métodos:** Estudo prospetivo, de doentes referenciados à consulta de Medicina Física e de Reabilitação, após infecção por SARS-CoV-2. Foram realizadas avaliações clínicas com questionário de sintomas, o teste 1-Minuto Sentar-e-Levantar (1-MSTS), o questionário EQ-5D e o questionário *London Chest Activity Daily Living* (LCA-DL), antes e após um programa de exercício domiciliário.

**Resultados:** Setenta e quatro pacientes foram incluídos. A maioria (n = 71) foi hospitalizada (média de 19,7 ± 13,4 dias), 51% necessitaram de cuidados intensivos. Na primeira avaliação, realizada 54 dias após instalação de sintomas, a média de repetições no 1-MSL foi de 18,6. A percentagem de LCA-DL foi superior a 28% em 23% dos pacientes. Alterações no EQ-5D estavam presentes em 44% na mobilidade e 44% para ansiedade/depressão. O EQ-5D VAS médio foi de 66,5 de 100. Cinquenta e um (70%) tinham pelo menos um sintoma persistente (Grupo Sintomático), enquanto 22 (30%) eram assintomáticos (Grupo Assintomático). O Grupo Sintomático teve piores resultados médios no 1-MSL (16,8 vs 22,9; p < 0,001), % pontuação LCA-DL, EQ-D5 (7,8 vs 5,7; p < 0,001) e EQ-D5-VAS. Nenhuma das características de paciente, antecedente clínico, característica da doença ou da hospitalização foi significativamente diferente entre os grupos. Todos os pacientes receberam um programa de exercício domiciliário; 47 pacientes integraram um programa de reabilitação adicional ou tiveram alta clínica, pelo que foram excluídos da segunda avaliação. Vinte e sete pacientes foram submetidos a uma segunda avaliação. Na análise emparelhada, o 1-MSL melhorou em 3,4 repetições. O LCA-DL médio, a pontuação média no EQ-5D (7,1 para 6,6) e o EQ-VAS evoluíram favorável e significativamente.

**Conclusão:** Dois meses após a infecção por SARS-CoV-2, os sintomas persistentes foram frequentes em doentes referenciados para Medicina Física e de Reabilitação. Adicionalmente, a infecção por SARS-CoV-2, bem como a persistência de sintomas, tiveram impacto negativo na condição física e funcionalidade nas atividades da vida diária e qualidade de vida. Com um plano de exercícios domiciliários implementado, observou-se uma melhoria estatisticamente significativa. O seguimento em Medicina Física e de Reabilitação dos doentes com sintomatologia persistente poderá ser vantajoso.

**Palavras-chave:** Atividades da Vida Diária; Medicina Física e de Reabilitação; Portugal; Qualidade de Vida; Síndrome Pós COVID-19 Aguda

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## INTRODUCTION

The estimated time for COVID-19 recovery is two weeks for moderate disease and six weeks for severe cases.<sup>1</sup> However, new evidence and data from other coronaviruses suggest that symptoms and consequences of COVID-19 may persist beyond the cure.<sup>2,3</sup> The so called 'long COVID', or 'post COVID syndrome' includes a large spectrum of symptoms that linger for two months or more after acute infection, with impact to the patient's life, and that are not explained by an alternative diagnosis.<sup>4,5</sup>

The most consistently reported persisted symptoms are fatigue (35% - 72%) and dyspnoea (29% - 66%). Cough, arthralgia and myalgia are among the others in variable percentages.<sup>3,6-8</sup>

Advanced age, need for hospitalization or Intensive Care (ICU) stay and a high number of comorbidities are considered possible risk factors for slower recovery or symptom persistence.<sup>3,8-13</sup> Nevertheless, it is still undetermined who is at risk of long-term symptoms. Even patients with mild acute disease, with no need for hospitalization, frequently report symptom persistence.<sup>2,11,14</sup>

Like with acute manifestations of COVID-19, long term impact seems to be multisystemic, but the consequences of symptom persistence, or up to what point sequelae are debilitating, are not yet clear.<sup>15,16</sup>

Even in functionally independent patients, persistent symptoms may be limiting and inhibit physical activity, affecting activities of daily living (ADL) and even delaying return to work.<sup>6,8,9,12</sup> These aspects motivate referral to Physical and Rehabilitation Medicine (PRM).

The aim of this study was to evaluate what are the persistent symptoms after SARS-CoV-2 infection and the impact of SARS-CoV-2 in physical condition, ADL, and quality-of-life (QoL), in patients referred to the PRM clinic after SARS-CoV-2 infection.

A second aim was to compare, at the time of the first appointment, both symptomatic and asymptomatic patient groups, in order to perceive if the persistence of symptoms increases restrictions in the physical condition, ADL and QoL. Additionally, characteristics of the symptom-persistent population that may represent risk factors for 'long COVID' will be identified.

The last aim was to evaluate physical capacity, ADL and QoL, in a second appointment, after prescribing of a home-based exercise program, and compare results with the baseline evaluation.

## METHODS

### Study, design and participants

This prospective study included all COVID-19 patients referred to the Physical and Rehabilitation Medicine clinic, at Hospital Pedro Hispano, Porto, Portugal, with a first ap-

pointment between December 2020 and February 2021, after SARS-CoV-2 infection. All patients who were previously autonomous or with modified autonomy were included.

The study was approved by the Ethics Committee for Health of Unidade Local de Saúde de Matosinhos (N.º 12/ CES/JAS). All the participants were asked to carefully read and sign an informed consent form. Researchers ensured the confidentiality of study participants and the data collected. The study was conducted according to the criteria set by the Declaration of Helsinki, with pertinent National and International regulatory requirements.

### Data collection and clinical evaluation

Demographic data, clinically relevant background and disease related data were extracted from the hospital digital information system. All patients had laboratory confirmation of SARS-CoV-2 infection by real-time PCR methods.

The clinical evaluation included a symptom survey, the 1-Minute Sit-to-Stand test (1-MSTS), to evaluate response to effort, and the application of two clinical surveys – the EuroQoL five-dimension questionnaire (EQ-5D), related to QoL, and the London Chest Activity Daily Living questionnaire (LCA-DL), related to dyspnoea during ADL performance.

### Symptom survey

Our symptom survey included dyspnoea, cough, fatigue, perceived muscular weakness, myalgia, and arthralgia, among others. It alluded to the most commonly reported symptoms at the time.

### Physical condition

The 1-MSTS correlates with inferior limb strength and exercise capacity, and has been applied to different diseases [including chronic obstructive pulmonary disease (COPD)] mainly in the elderly. The exercise consists in getting up from a chair and sitting back, and performing repetitions as fast as possible, within one minute. Sitting and standing from a chair is also an important activity of daily living, and therefore the test also reflects functional status. Values of sit-to-stand capacity are normalized by age and geographic region. And an increase in 3 sit-to-stands represents a minimum clinically meaningful benefit after a rehabilitation program. The test is a validated measure of the functional outcome in COPD patients.<sup>17,18</sup>

### Activities of daily living

The London Chest Activity Daily Living questionnaire contains 15 ADL items divided into Personal Care (4 items), Domestic (6 items) Physical (2 items) and Leisure (3 items) sections. The patients report how dyspnoea interferes in

ADL, from 0 - 5, for each activity: 0 (I would not do it anyway), 1 (I have no shortness of breath doing this), 2 (I have a slight shortness of breath), 3 (I have a significant shortness of breath), 4 (I no longer do this) and, 5 (I need help in doing this or someone to do it for me). LCA-DL was recorded as a categorical variable, and the percent LCA-DL score was calculated (with the sum of the patient result divided by the total maximum LCA-DL). LCA-DL categories were considered affected if  $> 2$  points for Physical Activity and  $> 4$  for Personal Care. A score above 28% reflects patients with the worst functional condition.<sup>19</sup> The LCA-DL has a Portuguese validated version for CDOP, which was applied in this study.<sup>20</sup>

### Quality-of-life

Health-related quality-of-life was assessed using the EuroQol five-dimension questionnaire (EQ-5D). This is a self-evaluation of QoL based on five sections: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each section is rated from 0 - 3: 0 (no problems), 1 (slight problems), 2 (moderate problems), 3 (extreme problems/unable to perform). Changes in the EQ-5D were considered

if the score was  $> 1$ , representing a moderate-to-severe attainment. The visual analogue scale (EQ-VAS) is a quantitative measure that estimates the patient self-perception of general health, and the score ranges from 0 (the worst health you can imagine) to 100 points (the best health you can imagine). We applied the EQ-5D Portuguese validated version.<sup>21</sup>

### Home exercise program and follow-up

All patients received counselling and a home exercise program (Fig. 1). Patients without any other guided intervention (such as a hospital rehabilitation program) and without clinical criteria for discharge were reevaluated in a second appointment, with repetition of the previously described process.


### Statistical analysis

Statistical analysis of the collected data was done through the IBM SPSS statistics software version 26.0. Continuous variables were presented as mean (standard deviation) and categorical variables as frequency rates (percentages). A descriptive and comparative statistical


## Exercícios propostos:

### 1 | Calistênicos


**Inicie com 10 repetições;** Progrida gradualmente, mediante a sua capacidade, tentando aumentar para mais 2 repetições (R) semanalmente.  
Semana 1: 10R | Semana 2: 12R | Semana 3: 14R | Semana 4: 16R | Semana 5: 18R | Semana 6: 20R




**1.1**  
Respire calma e lentamente;




**1.2**  
Sentado, estique o joelho completamente, expirando. Baixe de forma controlada, inspirando;



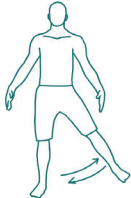
**1.3**  
Levante os braços e baixe lentamente; Deve inspirar num movimento e expirar no outro;




**1.4**  
Em pé, dobre os joelhos, como se fosse sentar numa cadeira, expirando;



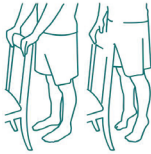
**1.5**  
Levante o joelho até à barriga, expirando. Volte à posição inicial, inspirando;



**1.6**  
Afaste a perna para o lado, expirando. Volte à posição inicial inspirando;



**1.7**  
Dobre o joelho para trás expirando. Volte à posição inicial inspirando;



**1.8**  
Em pé, se necessário apoiado numa cadeira para manter o equilíbrio, levante os calcanhares do chão, expirando. Volte à posição inicial inspirando;

**ESCALA DE BORG**

- 6.
7. Muito, muito leve
- 8.
9. Muito leve
- 10.
11. **Algo leve**
12. **Moderado**
13. **Algo forte**
- 14.
15. Forte
- 16.
17. Muito forte
- 18.
19. Muito, muito forte
- 20.

### 2 | Marcha / Caminhada

A marcha/caminhada é das formas mais acessíveis e fáceis de ganhar força muscular e resistência. Comece por iniciar a marcha no domicílio ou no exterior\* segundo o exemplo:  
Semana 1: 5 a 10min | Semana 2: 10 a 15min | Semana 3: 15 a 20min | Semana 4: 20 a 25min | Semana 5: 25 a 30min | Semana 6: 30min;  
A partir daqui tente evoluir aumentando a velocidade/distância percorrida durante os 30 minutos.

\*Caso tenha possibilidade para caminhar no exterior, opte sempre que possível, por piso plano e com superfície regular. Verifique se existem bancos ou locais onde se possa sentar para descansar se tiver essa necessidade.

Figure 1 – Home exercise program: “Re-education to effort/Rehabilitation after COVID-19”

analysis was established, between symptomatic and asymptomatic patients, during the first appointment, using the Mann-Whitney-U test for discrete variables, and the chi-square test for categorical variables. Results were also compared between the first and the second appointment by means of the Wilcoxon test, for matched in-patient analysis. *p*-values < 0.05 were considered statistically significant.

## RESULTS

### First evaluation

Seventy-four patients were included in the study, 66% males, averaging  $61.5 \pm 13.8$  years of age, where 46% were obese. The majority ( $n = 71$ ) had been hospitalized for a mean duration of  $19.7 \pm 13.4$  days, with 51% need-

ing Intensive Care and 32% requiring invasive mechanical ventilation (IMV) (for an average of  $12.0 \pm 8.9$  days); 42% of patients underwent physiotherapy during the hospitalization period (Table 1).

The first evaluation took place approximately 54 days after symptom onset. From the 74 patients, 52 (70%) had at least one persistent symptom (Symptomatic Group), while 22 (30%) were asymptomatic (Asymptomatic Group).

Fatigue was the most frequently reported symptom, being reported by 54% of patients, followed by cough in 30%, dyspnea in 22%, myalgia in 20% and perceived weakness, thoracalgia and arthralgia in lower percentages (1% to 8%). In the 1-MSTS, an average of 18.61 repetitions were performed, mean oxygen saturation level during physical

Table 1 – Demographic and clinical characteristics of patients referred to the PRM appointment after COVID-19

| Demographic and clinical characteristics                                | Total n = 74    |
|---|-----------------|
| Men, n (%)  | 49 (66%)        |
| Age (years), mean $\pm$ SD  | 61.5 $\pm$ 13.8 |
| <b>Relevant clinical background</b>                                     |                 |
| Obesity, n (%)  | 34 (46%)        |
| Diabetes mellitus, n (%)  | 19 (26%)        |
| Smoker/ex-smoker, n (%)   | 12 (18%)        |
| Previous pulmonary disease, n (%)                                       | 9 (12%)         |
| Previous cardiac disease, n (%)   | 10 (14%)        |
| Others  |                 |
| Autoimmune, n (%)   | 2 (3%)          |
| Neoplastic, n (%)   | 4 (5%)          |
| <b>Hospitalized patients n = 71</b>                                     |                 |
| Time from symptoms to hospitalization (days), mean $\pm$ SD             | 8.3 $\pm$ 5.2   |
| In-hospital stay duration (days), mean $\pm$ SD                         | 19.7 $\pm$ 13.4 |
| Intensive Care, n (%)   | 51 (72%)        |
| Days in ICU, mean $\pm$ SD  | 12.8 $\pm$ 11.9 |
| Mechanic ventilation, n (%)   | 23 (32%)        |
| Days of IMV, mean $\pm$ SD  | 12.0 $\pm$ 8.9  |
| Lung CT, n (%) (n = 67)   |                 |
| Typical COVID pattern, NE   | 6 (9%)          |
| [25, 50[%   | 21 (33%)        |
| [50, 75[%   | 27 (40%)        |
| $\geq$ 75%  | 12 (18%)        |
| Relevant complications, n (%)   |                 |
| Bacterial infection   | 17 (24%)        |
| Pulmonary embolism  | 3 (4%)          |
| Others  | 7 (10%)         |
| In-hospital physiotherapy (n = 69)                                      | 29 (42%)        |
| Time from discharge to 1 <sup>st</sup> evaluation (days), mean $\pm$ SD | 24.8 $\pm$ 15.4 |

Results were presented as n, (%) or mean  $\pm$  SD (standard deviation).

ICU: Intensive Care Unit; IMV: invasive mechanical ventilation; CT: computerized tomography.

activity was  $94.7 \pm 3.2$ , with a mean modified Borg score of 1.52 and a mean Borg score of 12.36. The average percentage of LCA-DL was  $24.9 \pm 7.4\%$ . The LCA-DL score was above 28% in 23% of patients. Nineteen patients (31%) reported changes in the LCA-DL Personal Care domain, and 34 (59%) in the Physical Activity domain. The average total score of the EQ-5D survey was  $7.14 \pm 2.09$ . Changes in the EQ-5D were present in 44% of patients for Mobility, 30% for Self-care, 41% for Usual Activities, 26% for Pain/Discomfort and 44% for Anxiety/Depression. The average EQ-5D VAS score was 66.5 out of 100.

### Symptomatic versus asymptomatic at first evaluation

A comparison between the symptomatic and the asymptomatic groups was then performed on physical condition, ADL, and QoL (Table 2). The Symptomatic Group had the worst results in the 1-MSTS, with 16.8 repetitions, with 22.9 repetitions in the Asymptomatic Group ( $p < 0.001$ ). The score in the LCA-DL was also significantly higher in

the Symptomatic Group, 26.4% vs 20.9% ( $p = 0.034$ ). Similarly, results for the EQ-D5 and EQ-D5 VAS were substantially worse when persistent symptoms were present, with a score of 7.8 and 63.3 out of 100, respectively in the Symptomatic Group, against 5.7 and 85.1 out of 100 in the Asymptomatic Group ( $p < 0.001$ ).

Table 3 shows the comparison made between the two groups for the study of risk factors in persistent symptoms. The Symptomatic Group showed an average age of 62.3 years and the Asymptomatic Group 59.8 years, with no statistically significant differences. No differences were found in gender distribution. Regarding clinical background, in the Symptomatic Group a larger prevalence rate of obesity, diabetes mellitus, smokers/ex-smokers, previous lung disease and cardiac disease was observed, when compared with the Asymptomatic Group. Regarding hospitalization, 73% of the Symptomatic Group required ICU hospitalization, against 64% in the Asymptomatic Group. However, the differences between the groups were not found to be

Table 2 – Test results and comparison of the symptomatic and asymptomatic groups at 1<sup>st</sup> appointment

|                       | Symptomatic<br>(n = 51) | Asymptomatic<br>(n = 22) | p-value |
|-----------------------|-------------------------|--------------------------|---------|
| <b>1-MSTS</b>         | 16.8 ± 4.9              | 22.9 ± 5.6               | < 0.001 |
| <b>% LCA-DL score</b> | 26.4 ± 8.1              | 20.9 ± 1.5               | 0.034   |
| <b>EQ-D5</b>          | 7.8 ± 2.1               | 5.7 ± 1.3                | < 0.001 |
| <b>EQ-D5-VAS</b>      | 63.3 ± 16.2             | 85.1 ± 9.3               | < 0.001 |

Results were presented as mean ± SD (standard deviation); the Mann Whitney U test was applied. Note: one patient was excluded from analysis for lack of symptom information. 1-MSTS: 1Minute Sit-to-Stand; LCA-DL London Chest Activity Daily Living; EQ-D5 EuroQol Five-Dimension Questionnaire; EQ-D5-VAS EuroQol Five-Dimension Questionnaire Visual Analogue Scale.

Table 3 – Comparison between the symptomatic and asymptomatic groups for possible risk factors

|   | Symptomatic |        | Asymptomatic |        | p-value |
|---|-------------|--------|--------------|--------|---------|
|   | n = 51      | n (%)  | n = 22       | n (%)  |         |
| <b>Female</b>                                     | 19          | (37%)  | 5            | (23%)  | 0.225   |
| <b>Age (years), mean ± SD</b>                     | 62.3        | ± 14.1 | 59.8         | ± 13.5 | 0.340   |
| <b>Age &gt; 50</b>                                | 40          | (80%)  | 15           | (68%)  | 0.277   |
| <b>Obesity</b>                                    | 24          | (47%)  | 9            | (41%)  | 0.628   |
| <b>DM</b>   | 15          | (29%)  | 3            | (14%)  | 0.151   |
| <b>Smoker (active/ex)</b>                         | 10          | (20%)  | 3            | (14%)  | 0.541   |
| <b>Previous pulmonary disease</b>                 | 7           | (14%)  | 2            | (9%)   | 0.580   |
| <b>Previous cardiac disease</b>                   | 7           | (14%)  | 3            | (14%)  | 0.992   |
| <b>Hospitalization duration (days), mean ± SD</b> | 18.9        | ± 12.6 | 19.6         | ± 15.9 | 0.567   |
| <b>ICU</b>  | 37          | (73%)  | 14           | (64%)  | 0.446   |
| <b>ICU stay (days), mean ± SD</b>                 | 8.7         | ± 11.5 | 9.6          | ± 12.0 | 0.765   |
| <b>IMV</b>  | 18          | (35%)  | 5            | (23%)  | 0.289   |
| <b>IMV duration (days), mean ± SD</b>             | 3.9         | ± 7.6  | 3.6          | ± 7.4  | 0.507   |
| <b>Lung CT ≥ 50%</b>                              | 26          | (60%)  | 13           | (68%)  | 0.484   |
| <b>Hospitalization complications</b>              | 22          | (43%)  | 4            | (19%)  | 0.053   |

Results were presented as n (%) or mean ± SD (standard deviation); the Mann Whitney U test or chi-square test were applied. Note: one patient was excluded from analysis for lack of symptom information. DM: diabetes mellitus; ICU: Intensive Care Unit; IMV: invasive mechanical ventilation; CT: computerized tomography

statistically significant. The duration of hospitalization, duration of stay in ICU and IMV period duration were also not statistically significant in the Symptomatic Group. Lastly, clinically significant complications during hospitalization, such as bacterial superinfection and pulmonary embolism, occurred in 43% of the Symptomatic Group, against 19% in the Asymptomatic Group ( $p = 0.053$ ).

### Re-evaluation

At the first evaluation, every patient was given a home exercise program that was adequate to their functional level, with instructions for exercise intensity progression. Twenty-three patients participated in an additional rehabilitation program and 24 were clinically discharged and were therefore excluded from the second evaluation.

Twenty-seven patients were re-evaluated in a second appointment, approximately one month later.

Sixty percent of patients remained symptomatic; once more, fatigue, cough and myalgias were the most frequently reported symptoms (43%, 21% and 18%, respectively). Considering the comparison between the first and the second appointment, the 1-MSTS average improved 3.4 repetitions ( $p < 0.001$ ). The LCA-DL score varied favorably with a 2.02 points ( $p = 0.002$ ) drop. The average result of the EQ-5D survey also had a drop of 0.5 points from 7.1 to 6.6 ( $p = 0.002$ ) and the EQ-D5 VAS improved 5.1 points ( $p = 0.001$ ; the average EQ-VAS score at the second appointment was 74.4). All these variations were considered statistically significant (Table 4).

### DISCUSSION

After infection by SARS-CoV-2 about 70% of patients referred to the PRM clinic showed symptom persistence, which is in line with the previously reported values of 60%

to 87% from the literature.<sup>2,3</sup>

This study also found a relevant impact that was not so discussed in previous papers, regarding the capacity for physical activity, dyspnea during ADL performance and QoL post SARS-CoV-2 infection. Considering the present population sample, an average of 18.6 repetitions/min was found in the 1-MSTS, when the average level for the elderly is 27 to 30 repetitions/min.<sup>17</sup> Regarding dyspnea's impact in ADL, close to one-quarter of the patients (23%) scored above 28% in the LCA-DL, a cutoff that differentiates patients with a worse functional condition.<sup>19</sup> In both the LCA-DL and the EQ-5D, about one third of patients reported an impact in the Personal Care domain, with an even higher percentage showing changes in Mobility and Physical Activity. Considering the previous literature, these are similar results to those already reported by Halpin *et al*,<sup>8</sup> and higher rates than those reported by Fernandes *et al*,<sup>22</sup> for the Portuguese post-COVID-19 population.

When comparing the Symptomatic and Asymptomatic groups, it was possible to confirm that the persistence of symptoms was associated with a worse physical condition, dyspnoea in ADL and QoL. No patient characteristics, clinical background, characteristic of the disease or the hospitalization analysed in this study help in the differentiation of symptomatic or asymptomatic patients. In contrast with what was previously reported, factors such as sex, old age, obesity or previous pulmonary disease were not risk factors for persistent disease in our population.<sup>11,23,24</sup> Comorbidities such as hypertension, asthma or psychiatric disease, previously highlighted as possible risk factors for long COVID, were not analysed, which is a limitation of this study.<sup>11,23,24</sup>

The relationship between severe COVID-19 and persistent symptoms is poorly established, even though it has been previously reported.<sup>9-13</sup> Other previously studied

Table 4 – Matched comparison of patients' tests results between first and second appointment

| n = 27                             | First appointment | Second appointment | p-value |
|------------------------------------|-------------------|--------------------|---------|
| <b>1-Minute Sit-to-Stand</b>       |                   |                    |         |
| Mean nr. of repetitions            | 18.6 ± 5.9        | 22.0 ± 6.9         | < 0.001 |
| Mean 1-MSTS change                 |                   | <b>&gt; 3.4</b>    |         |
| <b>LCA-DL</b>                      |                   |                    |         |
| Mean LCA-DL total score            | 14.3 ± 6.1        | 12.1 ± 3.7         | 0.002   |
| Mean LCA-DL change                 |                   | <b>&lt; 2.02</b>   |         |
| % total score LCA-DL (n = 16)      | 24.9 ± 7.37       | 23.2 ± 3.56        |         |
| <b>EQ-5D</b>                       |                   |                    |         |
| Mean EQ-5D total score             | 7.1 ± 2.1         | 6.6 ± 1.7          | 0.002   |
| Perceived health [EQ-5D VAS scale] | 69.3 ± 17.6       | 74.4 ± 15.6        | 0.001   |
| Mean EQ-5D VAS change              |                   | <b>&gt; 5.1</b>    |         |

Results were presented as mean ± SD (standard deviation); the Wilcoxon test was applied.

1-MSTS: 1-Minute Sit-to-Stand; LCA-DL London Chest Activity Daily Living; EQ-5D EuroQol Five-Dimension Questionnaire; EQ-D5-VAS EuroQol Five-Dimension Questionnaire Visual Analogue Scale.

factors included ICU admission or need for IMV, these being representative of the severity of the acute disease. In our study, these factors did not seem to influence symptom persistence in the studied population. Therefore, attention should be granted to the possibility of long COVID syndrome, even in the absence of indicators of acute severity in hospitalized patients.

With counselling and a home exercise plan, statistically significant improvements were ascertained in patients with long-term low-to-moderate attainment in every domain. A post-rehabilitation improvement of at least three repetitions in the 1-MSTS and a decrease of around 0.03 in the EQ-D5 score are outlined as minimum clinically meaningful differences.<sup>18,25</sup> As such, the average improvements in physical condition and quality-of-life presented here can be considered clinically relevant.

The main limitations of this study are the reduced size of the study sample, and a selection bias due to the selection channel – only patients referred to the PRM clinic were studied – possibly leading to an underestimation of asymptomatic patients and to a higher representation of hospitalized patients during the acute COVID phase. Moreover, the non-supervision or lack of adherence surveillance of the home exercise program limits the conclusions of the effect of physical activity in these patients. This might, however, reflect the reality of exercise practice after medical counselling. Another addition is the application of surveys commonly used in chronic obstructive pulmonary disease, but not developed specifically for COVID-19, given the lack of more appropriate tools, even though the 1-MSTS is already widely used in COVID studies.<sup>26</sup>

Predicting which patients could suffer from long-term symptoms remains a challenge. Clinicians should be aware of the possibility of long COVID following acute infection in all patients, regardless of comorbidities or severity of disease. Timely referral to a PRM clinic is pertinent, considering the positive patient evolution in the various domains after counselling with a home exercise program and given the role of the specialty in functionality optimization, exercise prescribing and physical reconditioning.

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## CONCLUSION

Two months after infection by SARS-CoV-2, persistent symptoms were frequent in patients referred to a Physical Medicine and Rehabilitation clinic. Additionally, the SARS-CoV-2 infection, as well as the persistence of symptoms, had a negative impact in the physical condition and functionality in ADL and quality-of-life.

## PREVIOUS PRESENTATIONS AND AWARDS

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## AUTHOR CONTRIBUTIONS

JR: Contribution to the design and draft of the work. Analysis and interpretation of data. Draft of the paper. Critical review and final approval of the version to be published.

DD, PA: Contribution to the design and draft of the work. Data collection. Critical review and final approval of the version to be published.

JA, PR: Analysis and interpretation of data. Draft of the paper. Critical review and final approval of the version to be published.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

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