ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Predictors of Long-COVID-19 and its Impact on Quality of Life: Longitudinal Analysis at 3, 6 and 9 Months After Discharge from a Portuguese Centre

Preditores da COVID-19 Longa e o seu Impacto na Qualidade de Vida: Análise Longitudinal aos 3, 6 e 9 Meses Após a Alta de um Centro Português

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Acta Med Port 2023 Oct;36(10):647-660 ▪ https://doi.org/10.20344/amp.19047

ABSTRACT

Introduction: Long-COVID-19 impacts health-related quality of life (HR-QoL) but data is scarce. The aim of this study was to describe and prospectively assess the prevalence and risk factors for long-COVID-19 after hospital discharge, and to evaluate its impact on patient HR-QoL.

Methods: Single-centre longitudinal study including all COVID-19 patients discharged between December 2020 and February 2021. Patients were contacted remotely at three, six and nine months. Data were collected as follows: 1) Long-COVID-19 symptoms were self-reported; 2) HR-QoL were assessed using the 3-level EuroQoL-5D (EQ-5D-3L) questionnaire. Pregnant women, demented, bedridden, and non-Portuguese-speaking patients were excluded.

Results: The three-, six- and nine-month assessments were completed by 152, 117 and 110 patients (median age: 61 years; male sex: 56.6%). Long-COVID-19 (≥ 1 symptom) was reported by 66.5%, 62.4% and 53.6% of patients and HR-QoL assessment showed impairment of at least some domain in 65.8%, 69.2% and 55.4% of patients at three, six and nine months, respectively. Fatigue was the most common long-COVID-19 symptom. Anxiety/depression domain was the most frequently affected in all three time-points, peaking at six months (39%), followed by pain/discomfort and mobility domains. Long-COVID-19 was associated with the impairment of all EQ-5D-3L domains except for self-care domain at each time-point. Neither intensive care unit admission nor disease severity were associated with long-COVID-19 nor with impairment of any EQ-5D-3L domain. After adjusting for sex, age, frailty status, and comorbid conditions, long-COVID-19 remained significantly associated with HR-QoL impairment at three (OR 4.27, 95% CI 1.92 – 9.52, $p < 0.001$), six (OR 3.46, 95% CI 1.40 – 8.57, $p = 0.007$) and nine months (OR 4.13, 95% CI 1.62 – 10.55, $p = 0.003$) after hospital discharge. In a longitudinal analysis, patients reporting long-COVID-19 at three months had an EQ-5D-3L index value decreased by 0.14 per visit ($p < 0.001$) compared to those without long-COVID-19 and both groups had a non-significant change in mean EQ-5D-3L index over the nine-month period (time-point assessment, Z = 0.91, $p = 0.364$).

Conclusion: Clinical sequelae associated with long-COVID-19 can persist for at least nine months after hospital discharge in most patients and can impair long-term HR-QoL in more than half of patients regardless of disease severity, and clinicodemographic characteristics.

Keywords: COVID-19; Portugal; Post-Acute COVID-19 Syndrome; Quality of Life

RESUMO

Introdução: Os dados referentes ao efeito da COVID-19 longa na qualidade de vida relacionada com a saúde (QV-RS) são escassos. O objetivo deste estudo foi descrever prospectivamente a prevalência e os fatores de risco associados à COVID-19 longa após a alta hospitalar e avaliar o seu impacto na QV-RS.

Métodos: Estudo longitudinal unicêntrico incluindo todos os doentes com COVID-19 com alta hospitalar entre dezembro de 2020 e fevereiro de 2021. Os doentes foram contactados telefonicamente aos três, seis e nove meses. Os dados foram colhidos da seguinte forma: 1) autorrelato dos sintomas associados à COVID-19 longa; 2) avaliação da QV-RS através do questionário de três níveis EuroQoL-5D (EQ-5D-3L). Excluímos grávidas, doentes dementes, acamados e não-falantes de português.

Resultados: Cento e cinquenta e dois, 117 e 110 doentes foram avaliados aos três, seis e nove meses (idade mediana: 61 anos; homens: 56,6%). A COVID-19 longa (≥ 1 sintoma) estava presente em 66,5%, 62,4% e 53,6% dos doentes, e 65,8%, 69,2% e 55,4% descreveram compromisso da QV-RS (≥ 1 domínio) aos três, seis e nove meses, respetivamente. O sintoma persistente mais comum foi a fadiga. O domínio ansiedade/depressão foi o mais afetado nos três momentos, com pico aos seis meses (39%), seguido pelos domínios dor/desconforto e mobilidade. A COVID-19 longa associou-se ao compromisso de todos os domínios da EQ-5D-3L, exceto ao do autocuidado. Nem a admissão nos cuidados intensivos nem a gravidade da doença se associou à COVID-19 longa nem ao compromisso de qualquer domínio da EQ-5D-3L. A COVID-19 longa permaneceu significativamente associado à diminuição da QV-RS aos três (OR 4,27, IC 95% 1,92 – 9,52, $p < 0,001$), seis (OR 3,46, IC 95% 1,40 – 8,57, $p = 0,007$) e nove meses (OR 4,13, IC 95% 1,62 – 10,55, $p = 0,003$) após ajuste para o sexo, idade, grau de autonomia e comorbilidades. Na análise longitudinal, o índice EQ-5D-3L estava diminuído em 0,14/visita ($p < 0,001$) nos doentes com COVID-19 longa aos três meses em comparação com os assintomáticos, e ambos os grupos mostraram uma variação não significativa do índice EQ-5D-3L durante os nove meses do estudo (Z = 0,91, $p = 0,364$).

Conclusão: As sequelas clínicas associadas à COVID-19 longa podem persistir por pelo menos nove meses após a alta hospitalar e podem comprometer a QV-RS a longo prazo em mais da metade dos doentes, independentemente da gravidade da doença e das características clinicodemográficas.

Palavras-chave: COVID-19; Portugal; Qualidade de Vida; Síndrome Pós-COVID-19

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Recebido/*Received*: 07/09/2022 - **Aceite/*Accepted*:** 10/01/2023 - **Publicado *Online*/*Published Online*:** 24/02/2023 - **Publicado/*Published*:** 02/10/2023

INTRODUCTION

The COVID-19 pandemic remains a public health concern with an unparalleled health and socioeconomic burden. The short-term outcomes of COVID-19 are still an area of active research and many studies have investigated the clinical characteristics, risk factors, and potential new treatments.[1] Another less studied, albeit equally worrying, aspect of the disease are the long-term consequences following the acute infection, also known as long-COVID-19. The Portuguese Directorate General of Health defines long-COVID-19 as the presence of persistent signs and/or symptoms occurring three months after the acute SARS-CoV-2 infection, lasting for at least two months, and not otherwise explained by alternative causes.[2]

The number of people affected by long-COVID-19 remains uncertain as data regarding its prevalence varies greatly between studies. A recent meta-analysis estimates that the global prevalence of long-COVID-19 is 43%, with regional differences (Asia, 51%; Europe, 44%; and North-America, 31%).[3] There is no published data on the prevalence of long-COVID-19 in Portugal.

The growing body of evidence suggests that long-COVID-19 is a multisystemic condition: prolonged fatigue, dyspnea, cognitive impairment, sleep disturbances, and chronic pain reflect multiorgan involvement.[4] It is well recognized that survivors of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome suffer from long-term physical and psychological consequences leading to decreased health-related quality of life (HR-QoL).[5–9] The effect of COVID-19 on the general health, physical function, and productivity of patients is starting to be clarified and, very recently, a group of investigators from China reported that COVID-19 survivors had not returned to the same health status two years after the acute infection.[10] Nevertheless, little is known about its pathophysiology and the specific impact of persisting COVID-19 symptoms on HR-QoL after the acute infection.

The aim of this study was to describe and prospectively assess the prevalence and risk factors for long-COVID-19 up to nine months after hospital discharge, and to evaluate its impact on patients' HR-QoL.

METHODS

Study design and participants

This longitudinal study was conducted in two phases and included all COVID-19 patients (aged over 18 years old) admitted to a COVID-19 dedicated ward at Hospital Santa Maria, Centro Hospitalar Universitário Lisboa Norte, between December 1st, 2020, and February 28th, 2021. All patients had a positive nasopharyngeal swab test for SARS-CoV-2 by reverse-transcriptase polymerase chain reaction. Asymptomatic SARS-CoV-2 positive patients who had been hospitalized for other reasons and pregnant women were not included. As we aimed to explore the persistence of COVID-19 symptoms and its impact on HR-QoL through a questionnaire (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15050), we did not include those unable to answer independently, non-Portuguese speaking as well as bedridden, demented and mentally impaired patients. There was no readmission during the recruitment period and all patients were unvaccinated against SARS-CoV-2.

The study was approved by the Hospital Santa Maria's ethics committee (Nº132/21) in accordance with the Helsinki Declaration statements. The requirement for written informed consent was waived due to sanitary reasons, but all patients agreed to participate in the study in a verbal, explicit and informed way.

Phase 1: Clinical characterization

Demographics, comorbidities, and clinical data were assessed retrospectively during March 2021. As all authors were actively involved in the medical care of patients, all data were either self-reported by patients and/or extracted from existing clinical records. Data were stored according to the applicable legislation and the anonymity of patients was warranted.

Phase 2: Persisting symptoms and quality of life assessment

We created a telephone questionnaire to collect the post-discharge data regarding the symptoms' persistence and to assess the HR-QoL (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15050). Patients were contacted by trained physicians at three, six and nine months (+/- 2 weeks) after hospital discharge.

Initially, patients were asked if they had been experiencing symptoms attributable to COVID-19 and if so, to shortly describe them. Then, we asked the patients whether they had returned to their previous functional status. HR-QoL was assessed using the Portuguese version of the 3-level EuroQoL-5D (EQ-5D-3L) questionnaire and EuroQoL-Visual Analogue Scale (EQ-VAS).[11] In the EQ-5D-3L, patients had to rate their health state from 1 ("no problem") to 3 ("severe impairment/unable") in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-index was calculated for each patient using the Portuguese EQ-5D-3L value set.[11] As for the EQ-VAS, patients were asked to rate their overall health from 0 ("the worst possible health") to 100 ("the best possible health") at that moment. Patients were asked the same questions in each time-point regardless of their previous

answer and no answer was changed in respect to the previous or a later response.

Definitions

COVID-19 severity was classified using the World Health Organization clinical progression scale.[12] We also classified as severe disease the composite score of intensive care unit (ICU) admission and/or any type of ventilatory support (invasive or non-invasive). The terms "persisting COVID-19 symptoms" and "long-COVID-19" will be used interchangeably. See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for a detailed description of comorbid conditions and other definitions.

Statistical approach

We used STATA® (version 16) for statistical analysis. Continuous and categorical variables are presented as median [interquartile range (IQR)] and number (%), respectively. Continuous variables were compared using the Student's *t*-test or Mann-Whitney U test after checking for normality, and categorical variables using the chi-square (χ^2) test or the Fisher's exact test when appropriate. We used univariable logistic regression models to explore risk factors associated with long-COVID-19 and with HR-QoL impairment. To investigate the association between long-COVID-19 and HR-QoL, we performed multivariable logistic regression adjusting for demographic characteristics, comorbidities, and severity outcomes. Variables were eligible for multivariable analysis considering their clinical/biologic significance and/or their statistically significant between-group differences and were selected using a stepwise method. Only comorbidities that were present in at least 10% of the cohort were included in the model, hence enhancing the robustness of the effect estimates. A longitudinal analysis was performed to address the changes in the EQ-5D-3L index between patients with and without long-COVID-19 at the first assessment. Patients were censored if they were lost to follow-up. Significance was set as a two-sided α of less than 0.05.

RESULTS

During the study period, 546 patients were admitted to our unit. Of those, 169 (30.9%) died during hospitalization or in the following three months. After excluding demented/bedridden (n = 86), unreachable (n = 108), non-Portuguese speaking patients (n = 4) and those declining to participate (n = 27), 152 patients answered the first telephone questionnaire. During the following three months, 35 patients were lost to follow-up, and later another seven more patients [Appendix 3, Fig 1 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. At the end of the study, 110 patients completed the three time-point questionnaires.

Patient characteristics

The demographic, clinical and laboratory characteristics of all participants are shown in the Appendix 3, Table 1 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052). The median age was 61 (IQR 73 – 52) years, and the majority were men (n = 86, 56.6%). The most common comorbidity was high blood pressure (n = 88, 57.9%), followed by dyslipidaemia (n = 70, 46.1%), obesity (n = 57, 37.8%), and diabetes *mellitus* (n = 50, 32.9%). Depression and/or anxiety was present in 19.7% of patients. The median duration of hospital stay was 12 (IQR 18.5 – 8) days. Fever (75.3%), cough (70.3%), dyspnea (62.4%) and fatigue (52.5%) were the most common presenting symptoms. Only 17 patients (11.2%) did not receive any type of oxygen therapy. Of the remaining, 55 patients (n = 55/135, 40.7%; 36.2% of all patients) required at least one type of ventilatory support, the most frequent being high flow nasal cannula (n = 41, 26.9%). Thirty-six patients (23.7%) were admitted to the ICU with a median stay of 8.5 (IQR 13 – 5.5) days. Most patients (84.9%) were in a good health status before hospitalization [clinical frailty scale (CFS) ≤ 3]. After hospital discharge, the proportion of patients returning to their prior health status increased over time (three months, 69.1%; six months, 72.7%, nine months, 77.3%).

Persisting symptoms

At least one persisting symptom was reported by 66.5%, 62.4% and 53.6% of patients at three, six and nine months after hospital discharge (Fig. 1A).

At three months, the most common persisting symptoms were fatigue (59.2%) and cough/dyspnea (13.8%), both with decreasing prevalence over the follow-up period. The prevalence of pain/discomfort and cognitive disturbances peaked at six months (both 13.7%) but only the latter showed a significant increase from its previous value ($p = 0.008$). At the end of follow-up, more than half of patients still reported at least one symptom, the most frequent being fatigue (42.7%).

Patients were categorized into two groups according to whether they had persistent symptoms or not. Risk factors for long-COVID-19 for each time-point were assessed (Table 1). Neither sex, age, nor CFS were associated with the presence of persisting symptoms. Patients who returned to their pre-hospitalization functional status were consistently less symptomatic at the third [odds ratio (OR) 0.24, 95% confidence interval (CI) 0.10 – 0.59, $p = 0.002$], sixth (OR 0.29, 95% CI 0.11 – 0.76, $p = 0.013$) and ninth (OR 0.21, 95% CI 0.07 – 0.62, $p = 0.004$) month of follow-up. Except for chronic kidney disease (CKD), which was associated

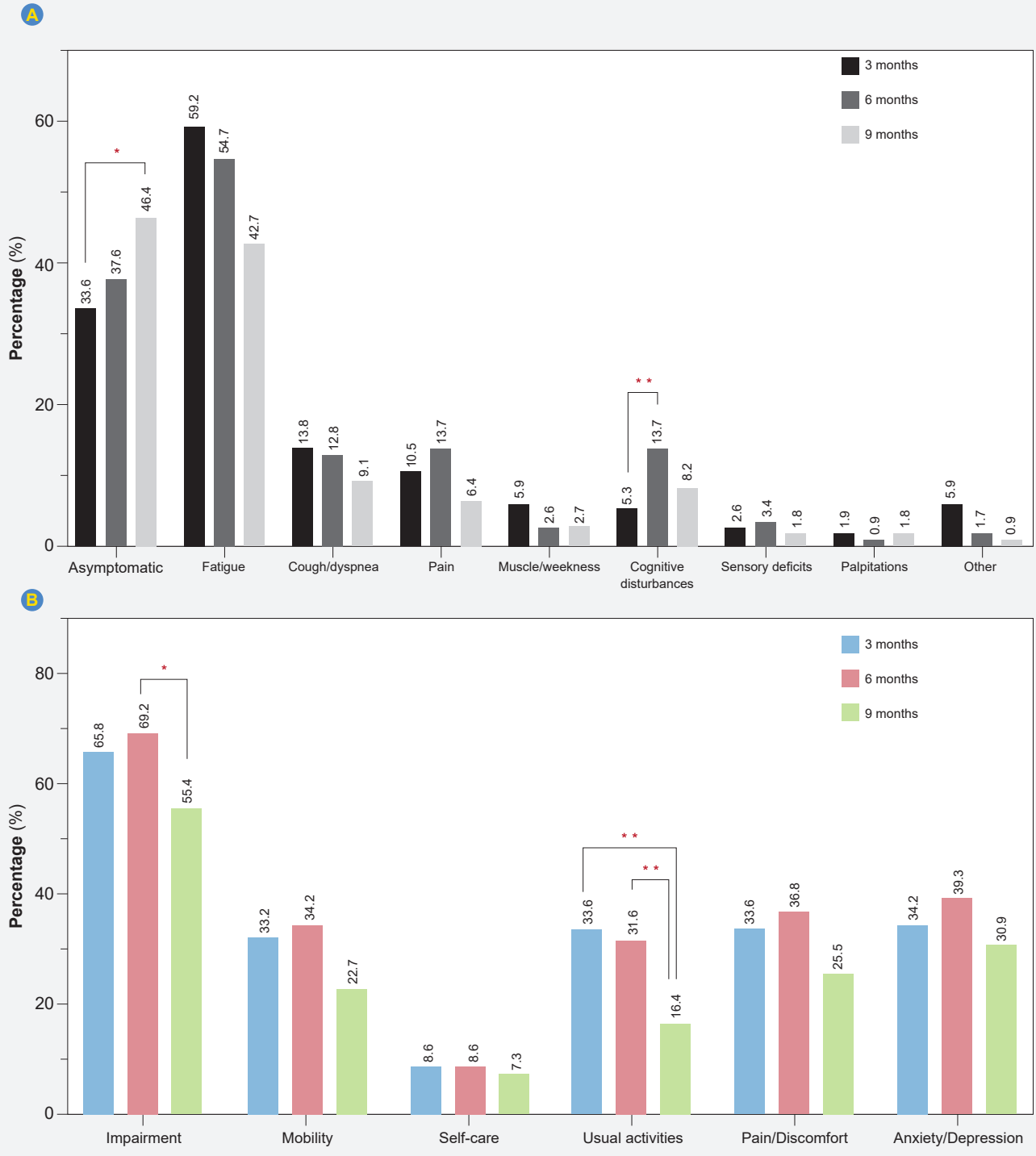

Figure 1 – Proportion of patients reporting (A) persisting symptoms and its specification at three, six and nine months after hospital discharge. Cognitive impairment included foggy brain, memory lapses, concentration difficulty. Sensory deficits included both taste and/or smell disturbances. Other symptoms included all the following: dizziness, postural imbalance, cold extremities/limb paresthesia, wheezing, hair loss; and (B) some degree of impairment in the EQ-5D-3L questionnaire at three, six and nine months after hospital discharge.

*$p < 0.05$; **$p < 0.010$

with a decreased probability of having persisting symptoms, none of the remaining pre-existing comorbidities were associated with long-COVID-19 at the three time-points. Neither the ICU nor in-hospital length of stay was associated with long-COVID-19. Severe disease was not associated with long-COVID-19 throughout the study. This is echoed by the WHO clinical progression scale, whose median value (5, IQR 5 – 5) did not differ between symptomatic and asymptomatic patients at the three time-points. See Appendix 3, Table 2 (Appendix 3: https://www.actamedicaportuguesa.

Table 1 – Univariate logistic regression for persisting symptoms at three, six and nine months after hospital discharge (section 1 of 2)

	Three months		Six months		Nine months	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographics						
Male sex	0.53 (0.26 – 1.07)	0.076	0.53 (0.24 – 1.13)	0.101	0.50 (0.23 – 1.08)	0.076
Age[a]	0.99 (0.97 – 1.02)	0.718	1.00 (0.97 – 1.02)	0.971	1.00 (0.97 – 1.03)	0.883
CFS[a]	0.89 (0.62 – 1.28)	0.518	0.87 (0.58 – 1.31)	0.505	0.83 (0.55 – 1.26)	0.390
Return do previous CFS	0.24 (0.10 – 0.59)	**0.002**	0.29 (0.11 – 0.76)	**0.013**	0.21 (0.07 – 0.62)	**0.004**
Comorbid conditions						
Cardiovascular disease	1.26 (0.63 – 2.49)	0.512	0.90 (0.42 – 1.94)	0.793	0.75 (0.35 – 1.62)	0.469
High blood pressure	1.07 (0.54 – 2.11)	0.855	0.81 (0.38 – 1.73)	0.581	0.76 (0.36 – 1.64)	0.489
Heart failure	0.51 (0.19 – 1.36)	0.178	0.33 (0.10 – 1.09)	0.068	0.14 (0.03 – 0.69)	**0.016**
Ischaemic heart disease	1.01 (0.33 – 3.12)	0.985	0.74 (0.19 – 2.89)	0.660	0.67 (0.17 – 2.64)	0.566
Dyslipidemia	0.94 (0.48 – 1.85)	0.860	1.15 (0.54 – 2.44)	0.721	0.89 (0.42 – 1.88)	0.753
Cerebrovascular disease	0.74 (0.20 – 2.76)	0.656	1.54 (0.29 – 8.32)	0.613	1.16 (0.25 – 5.46)	0.848
Obesity	1.03 (0.51 – 2.07)	0.929	0.78 (0.37 – 1.66)	0.524	0.99 (0.47 – 2.13)	0.997
Diabetes mellitus	0.65 (0.32 – 1.33)	0.240	0.58 (0.27 – 1.28)	0.179	0.68 (0.31 – 1.50)	0.339
Lung disease	1.46 (0.66 – 3.24)	0.346	1.47 (0.62 – 3.48)	0.385	1.86 (0.79 – 4.40)	0.154
Depression /anxiety	1.23 (0.52 – 2.92)	0.646	0.88 (0.36 – 2.17)	0.781	0.83 (0.33 – 2.12)	0.702
Chronic kidney disease	0.39 (0.16 – 0.94)	**0.036**	0.22 (0.07 – 0.67)	**0.009**	0.26 (0.08 – 0.89)	**0.032**
Osteoarthritis	1.63 (0.60 – 4.39)	0.337	1.25 (0.43 – 3.60)	0.684	1.88 (0.60 – 5.91)	0.281
Hypothyroidism	5.49 (0.68 – 44.17)	0.109	2.58 (0.52 – 12.77)	0.244	7.84 (0.95 – 65.03)	0.056
Chronic liver disease	1.82 (0.37 – 9.12)	0.464	4.56 (0.54 – 38.38)	0.163	1.48 (0.34 – 6.53)	0.603
Autoimmune disease	3.72 (0.45 – 31.12)	0.225	3.16 (0.36 – 27.99)	0.301	4.63 (0.52 – 41.0)	0.169
Active solid cancer	0.36 (0.08 – 1.67)	0.192	0.59 (0.08 – 4.36)	0.606	1.75 (0.15 – 19.93)	0.650
Active hematologic cancer	1.28 (0.24 – 6.82)	0.776	1.54 (0.29 – 8.32)	0.613	2.27 (0.42 – 12.23)	0.341

Table 1 – Univariate logistic regression for persisting symptoms at three, six and nine months after hospital discharge (section 2 of 2)

	Three months		Six months		Nine months	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Clinical manifestations						
Fever	1.66 (0.80 – 3.44)	0.175	2.07 (0.92 – 4.68)	0.079	1.75 (0.76 – 4.02)	0.185
Cough	1.94 (0.97 – 3.90)	0.062	1.65 (0.76 – 3.58)	0.204	1.73 (0.78 – 3.82)	0.176
Dyspnea	1.47 (0.75 – 2.91)	0.265	1.09 (0.50 – 2.40)	0.816	1.59 (0.73 – 3.50)	0.245
Fatigue	1.46 (0.74 – 2.87)	0.278	1.23 (0.58 – 2.61)	0.584	0.80 (0.38 – 1.70)	0.566
Myalgia/arthralgia	1.90 (0.94 – 3.87)	0.075	1.53 (0.71 – 3.29)	0.281	1.13 (0.53 – 2.40)	0.760
Chest pain	1.30 (0.55 – 3.07)	0.551	0.67 (0.26 – 1.71)	0.401	1.07 (0.40 – 2.83)	0.892
Diarrhea	0.84 (0.37 – 1.94)	0.687	1.37 (0.51 – 3.67)	0.535	1.52 (0.57 – 4.02)	0.400
Headache	1.55 (0.61 – 3.96)	0.357	1.25 (0.46 – 3.40)	0.656	1.37 (0.51 – 3.68)	0.529
Nausea/vomiting	1.01 (0.36 – 2.87)	0.983	0.58 (0.14 – 2.45)	0.458	0.49 (0.11 – 2.17)	0.350
Dysgeusia	0.58 (0.17 – 2.00)	0.390	0.79 (0.17 – 3.72)	0.768	0.86 (0.16 – 4.45)	0.854
Anorexia	0.13 (0.03 – 0.64)	0.012	0.38 (0.06 – 2.40)	0.307	0.20 (0.02 – 1.87)	0.160
Anosmia	0.36 (0.08 – 1.67)	0.192	0.90 (0.14 – 5.61)	0.910	1.31 (0.21 – 8.18)	0.771
Odynophagia	1.01 (0.18 – 5.71)	0.991	1.21 0.11 – 13.76	0.877	1.75 (0.15 – 19.93)	0.650
Hospitalization and outcomes						
Time since disease onset and hospital admission (days)	1.11 (1.01 – 1.21)	**0.037**	1.09 (0.99 – 1.21)	0.087	1.09 (0.99 – 1.21)	0.079
Hospital length of stay (days)	1.01 (0.98 – 1.05)	0.518	1.03 (0.99 – 1.07)	0.212	1.01 (0.98 – 1.05)	0.509
ICU admission	1.42 (0.62 – 3.24)	0.402	1.70 (0.67 – 4.27)	0.261	1.66 (0.68 – 4.05)	0.266
ICU length of stay (days)	1.06 (0.93 – 1.20)	0.414	1.06 (0.92 – 1.23)	0.427	1.03 (0.90 – 1.17)	0.684
High flow nasal cannula	2.16 (0.94 – 4.98)	0.069	2.34 (0.95 – 5.80)	0.065	1.67 (0.72 – 3.87)	0.234
Non-invasive ventilation	1.12 (0.37 – 3.43)	0.837	1.24 (0.39 – 3.89)	0.715	2.40 (0.70 – 8.18)	0.162
Endotracheal intubation	1.89 (0.59 – 6.07)	0.284	2.17 (0.56 – 8.36)	0.260	1.84 (0.52 – 6.52)	0.343
Ventilatory support	1.81 (0.87 – 3.76)	0.114	2.08 (0.93 – 4.67)	0.076	2.03 (0.92 – 4.46)	0.080
Severe disease[b]	1.71 (0.83 – 5.51)	0.145	1.97 (0.89 – 4.36)	0.095	1.98 (0.90 – 4.32)	0.088
WHO ordinal scale	1.30 (0.83 – 2.04)	0.254	1.48 (0.85 – 2.59)	0.168	1.37 (0.83 – 2.24)	0.216

Data are shown as odds ratio (OR) and 95% confidence interval (CI).
[a] Per one-unite increase OR.
[b] Severe disease was defined as ICU admission rate and/or need for any kind of ventilatory support (invasive or non-invasive) during the in-hospital stay.
See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for further detail on comorbid conditions and outcomes' definitions.
CFS: clinical frailty scale; HIV: human immunodeficiency virus; ICU: intensive care unit; WHO: World Health Organization.

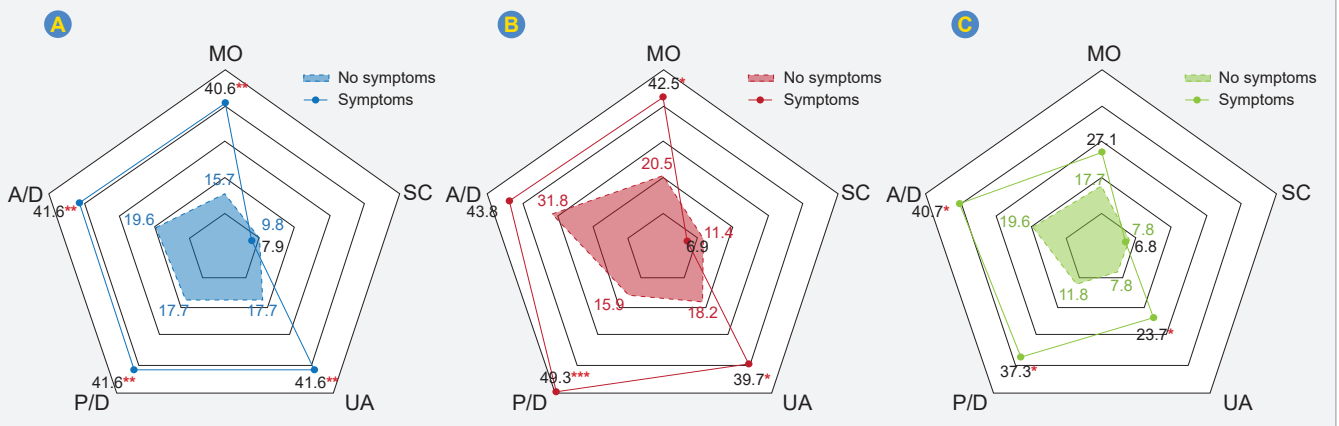

Figure 2 – Distribution and comparison of the proportion of patients reporting EQ-5D-3L domain impairment between patients who did and did not report persisting symptoms at three (A), six (B) and nine (C) months after hospital discharge.
A/D: anxiety/depression; MO: mobility; P/D: pain/discomfort; SC: self-care; UA: usual activities.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

com/revista/index.php/amp/article/view/19047/15052) for detailed comparison between the designated groups.

Quality of life assessment

At three months, 65.8% had at least some impairment (level ≥ 1: moderate or severe impairment) in some EQ-5D-3L domain. This proportion slightly increased at six months (69.2%) but then suffered a significant reduction ($p = 0.032$) towards the end of the study (55.4%) (Fig. 1B).

Impairment on the anxiety/depression domain was the most frequently reported in all three time-points, peaking at six months (39.3%). We observed the same trend in the pain/discomfort and mobility domains. The impairment of all these domains showed a decreased frequency at the end of the follow-up, even though the difference was not statistically significant. Only the proportion of impairment of usual activities, reported by nearly one third (33.6%) of patients in the initial assessment, showed a significant decrease between successive time-point assessments.

Three months after hospital discharge (Fig. 2A), the proportion of patients reporting mobility, usual activities, pain/discomfort, and anxiety/depression impairment was significantly higher among patients with long-COVID-19 compared to asymptomatic patients (all $p < 0.010$). This pattern stayed approximately stable over time as the differences in the proportion of each EQ-5D-3L domain impairment (except for mobility) remained statistically significant between patients with and without long-COVID-19 (Fig. 2C), except for the anxiety/depression domain whose difference was lost at six months due to an increase in the proportion of impairment among asymptomatic patients. Self-care impairment was similarly reported between groups throughout the study.

In an univariable logistic regression model (Table 2) the presence of long-COVID-19 at each time-point was significantly associated with the impairment of all EQ-5D-3L domains throughout the study [OR (95% CI) ranging from 2.81 (1.18 – 6.67), $p = 0.019$ for anxiety/depression domain at nine months; and 5.14 (2.03 – 13.02), $p = 0.001$ for pain/discomfort domain at six months] except for the self-care domain. Being male was associated with lower odds of impairment of all EQ-5D-3L domains, but only reached statistical significance in the mobility domain at three months ($p = 0.047$), pain/discomfort at six months ($p = 0.002$) and anxiety/depression at three ($p = 0.011$) and six ($p = 0.004$) months. Increasing age was associated with compromised mobility at all three time-points and with pain/discomfort at six (per one-unit increase OR 1.03, 95% CI 1.00 – 1.06, $p = 0.041$) and nine months (per one-unit increase OR 1.06, 95% CI 1.02 – 1.10, $p = 0.002$), and it showed a non-significant positive correlation with all other domains throughout the follow-up period. Increasing CFS was associated with mobility impairment at all time-points and with self-care disability at six and nine months after discharge. Noteworthy, patients who returned to their previous health status had consistent and statistically significant decreased odds of impairment in all EQ-5D-3L domains at all time-points.

Regarding previous comorbidities, osteoarthritis and lung disease were the ones that most frequently showed statistically significant between group differences in all EQ-5D-3L domains [Appendix 3, Tables 3 to 7 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. The presence of osteoarthritis was associated with mobility, self-care and pain/discomfort domains, and lung disease with mobility, usual activities, and anxiety/depression domains impairment

Table 2 – Univariate logistic regression for all EQ-5D-3L domains impairment (moderate to severe) at three, six and nine months after hospital discharge

	M	Long-COVID-19[a]	Male sex	Age	CFS	Return to previous CFS
MO	3	3.67 (1.57 – 8.62)**	0.49 (0.25 – 0.99)*	1.05 (1.02 – 1.08)**	2.17 (1.44–3.29)***	0.15 (0.07 – 0.31)***
	6	2.87 (1.21 – 6.83)*	0.68 (0.32 – 1.46)	1.04 (1.01 – 1.08)**	2.00 (1.26 – 3.16)**	0.12 (0.05 – 0.30)***
	9	1.74 (0.69 – 4.36)	0.92 (0.38 – 2.24)	1.05 (1.01 – 1.09)*	2.26 (1.33 – 3.82)**	0.32 (0.12 – 0.85)*
SC	3	0.79 (0.25 – 2.55)	1.25 (0.39 – 4.02)	1.08 (1.02 – 1.14)**	1.53 (0.84 – 2.78)	0.11 (0.03 – 0.42)**
	6	0.57 (0.16 – 2.11)	0.84 (0.23 – 3.09)	1.03 (0.98 – 1.09)	2.60 (1.24 – 5.45)*	0.13 (0.03 – 0.54)**
	9	0.85 (0.20 – 3.61)	1.48 (0.34 – 6.53)	1.03 (0.98 – 1.09)	2.88 (1.27 – 6.52)*	0.15 (0.03 – 0.66)*
UA	3	3.32 (1.46 – 7.55)**	0.63 (0.32 – 1.24)	1.01 (0.96 – 1.04)	1.81 (1.22 – 2.67)**	0.22 (0.11 – 0.46)***
	6	2.97 (1.21 – 7.28)*	0.45 (0.21 – 1.01)	1.02 (0.99 – 1.05)	1.48 (0.96 – 2.28)	0.08 (0.03 – 0.20)***
	9	3.66 (1.12 – 11.94)*	0.84 (0.31 – 2.31)	1.01 (0.98 – 1.05)	1.42 (0.82 – 2.44)	0.11 (0.04 – 0.34)***
P/D	3	3.32 (1.46 – 7.55)**	0.56 (0.28 – 1.10)	1.02 (0.99 – 1.04)	1.17 (0.81 – 1.68)	0.43 (0.21 – 0.89)*
	6	5.14 (2.03 – 13.02)**	0.29 (0.13 – 0.64)**	1.03 (1.00 – 1.06)*	1.23 (0.82 – 1.87)	0.27 (0.12 – 0.63)**
	9	4.46 (1.64 – 12.15)**	0.46 (0.19 – 1.10)	1.06 (1.02 – 1.10)**	1.43 (0.89 – 2.28)	0.09 (0.03 – 0.26)***
A/D	3	2.92 (1.32 – 6.47)**	0.41 (0.21 – 0.82)*	1.00 (0.98 – 1.03)	0.96 (0.67 – 1.39)	0.30 (0.15 – 0.63)**
	6	1.67 (0.76 – 3.67)	0.32 (0.15 – 0.69)**	1.01 (0.98 – 1.04)	1.24 (0.83 – 1.88)	1.34 (0.57 – 3.12)
	9	2.81 (1.18 – 6.67)*	0.57 (0.25 – 1.29)	1.02 (0.99 – 1.05)	0.95 (0.61 – 1.49)	0.30 (0.12 – 0.77)*

Data are shown as odds ratio (OR) and 95% confidence interval (CI). Age and CFS was taken as continuous variables (per one-unit increase OR).
[a] Long-COVID-19 symptoms (at least one persisting symptom) at each time-point.
[b] Severe disease was defined as ICU admission rate and/or need for any kind of ventilatory support (invasive or non-invasive) during the in-hospital stay.
See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for further detail on comorbid conditions and definitions of outcomes .
A/D: anxiety/depression; CFS: clinical frailty scale; HIV: human immunodeficiency virus; ICU: intensive care unit; MO: mobility; M: months; P/D: pain/discomfort; SC: self-care; UA: usual activities; WHO: World Health Organization.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

(Table 2). The presence of pre-existing depression was only associated with anxiety/depression impairment later during follow-up (nine months, $p < 0.010$).

Neither ICU admission nor severe disease were associated with impairment of any EQ-5D-3L domain. While ICU length of stay was significantly higher among patients reporting mobility (12, IQR 19 – 7 days *vs* 6.5, IQR 9 – 4 days, $p = 0.025$) [Appendix 3, Table 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)] and impairment of usual activities (12, IQR 19 – 8 days *vs* 6.5, IQR 9 – 4 days, $p = 0.015$) [Appendix 3, Table 5 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)] at three months compared to those who did not, the total length

Cardiovascular disease	Lung disease	Osteoarthritis	Depression	ICU	Severe disease[b]
2.0 (0.97 – 4.19)	2.14 (1.01 – 4.52)*	3.02 (1.24 – 7.36)*	1.28 (0.55 – 2.95)	1.47 (0.68 – 3.21)	1.58 (0.79 – 3.17)
1.94 (0.86 – 4.38)	1.22 (0.52 – 2.85)	9.83 (2.97 – 32.56)***	1.71 (0.69 – 4.21)	1.09 (0.45 – 2.66)	1.04 (0.48 – 2.28)
3.56 (1.22 – 10.35)*	2.55 (1.00 – 6.51)*	3.74 (1.20 – 11.67)*	2.39 (0.86 – 6.60)	0.72 (0.24 – 2.14)	1.00 (0.40 – 2.48)
2.32 (0.61 – 8.79)	1.86 (0.57 – 6.05)	3.95 (1.17 – 13.34)*	0.32 (0.04 – 2.53)	0.56 (0.12 – 2.66)	0.72 (0.21 – 2.46)
2.90 (0.59 – 14.33)	1.88 (0.49 – 7.16)	4.43 (1.11 – 17.68)*	1.66 (0.40 – 6.93)	0.78 (0.16 – 3.90)	1.03 (0.27 – 3.88)
5.31 (0.63 – 44.76)	4.87 (1.09 – 21.81)*	8.27 (1.81 – 37.85)**	2.62 (0.56 – 11.93)	0.42 (0.05 – 3.56)	0.48 (0.09 – 2.47)
1.48 (0.73 – 2.99)	1.70 (0.80 – 3.57)	2.28 (0.94 – 5.53)	1.19 (0.52 – 2.73)	1.36 (0.63 – 2.95)	1.26 (0.63 – 2.52)
1.93 (0.84 – 4.44)	2.53 (1.08 – 5.89)*	3.33 (1.19 – 9.33)*	1.29 (0.51 – 3.26)	0.78 (0.16 – 3.90)	1.49 (0.68 – 3.30)
1.11 (0.39 – 3.11)	4.23 (1.48 – 12.07)**	3.15 (0.93 – 10.71)	1.17 (0.35 – 3.99)	0.42 (0.05 – 3.56)	1.24 (0.45 – 3.45)
1.93 (0.94 – 3.98)	0.94 (0.43 – 2.02)	2.28 (0.94 – 5.53)	0.67 (0.27 – 1.63)	0.84 (0.37 – 1.87)	1.26 (0.63 – 2.52)
2.76 (1.21 – 6.28)*	2.15 (0.94 – 4.93)	4.39 (1.51 – 12.77)**	2.24 (0.91 – 5.49)	1.70 (0.72 – 4.04)	1.01 (0.47 – 2.19)
1.65 (0.67 – 4.08)	1.03 (0.40 – 2.66)	4.29 (1.39 – 13.24)*	2.51 (0.93 – 6.77)	0.79 (0.28 – 2.22)	0.78 (0.32 – 1.91)
0.66 (0.33 – 1.30)	1.41 (0.67 – 2.97)	1.19 (0.48 – 2.93)	1.14 (0.50 – 2.63)	1.31 (0.60 – 2.83)	1.97 (0.99 – 3.91)
0.93 (0.43 – 1.97)	1.08 (0.47 – 2.47)	1.68 (0.61 – 4.60)	2.39 (0.97 – 5.86)	0.25 (0.09 – 0.73)*	0.73 (0.34 – 1.57)
1.17 (0.51 – 2.69)	2.43 (1.02 – 5.80)*	3.03 (0.99 – 9.20)	3.60 (1.37 – 9.48)**	0.73 (0.27 – 1.93)	1.52 (0.67 – 3.46)

of hospital stay did not differ between groups in all EQ-5D-3L domains throughout the study. See Appendix 3, Tables 3 to 7 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052) for full details on summary statistics regarding patient demographics, comorbid and clinical characteristics for each EQ-5D-3L domain.

We performed a multivariable logistic regression analysis to investigate the association between long-COVID-19 and HR-QoL compromise (impairment of at least one EQ-5D-3L domain) at each time-point (Table 3). After adjusting for sex, age, CFS and comorbidities, the presence of long-COVID-19 remained associated with HR-QoL deterioration at three (OR 4.27, 95% CI 1.92 – 9.52, $p < 0.001$), six (OR 3.46, 95% CI 1.40 – 8.57, $p = 0.007$ and nine months (OR 4.13, 95% CI 1.62 – 10.55, $p = 0.003$) after hospital discharge.

EQ-5D-3L index

Patients were categorized according to whether they had persisting COVID-19 symptoms at the first assessment aiming to describe changes in the EQ-5D-3L index over the nine months of follow-up and to determine whether the patterns of change differed between patients with and without

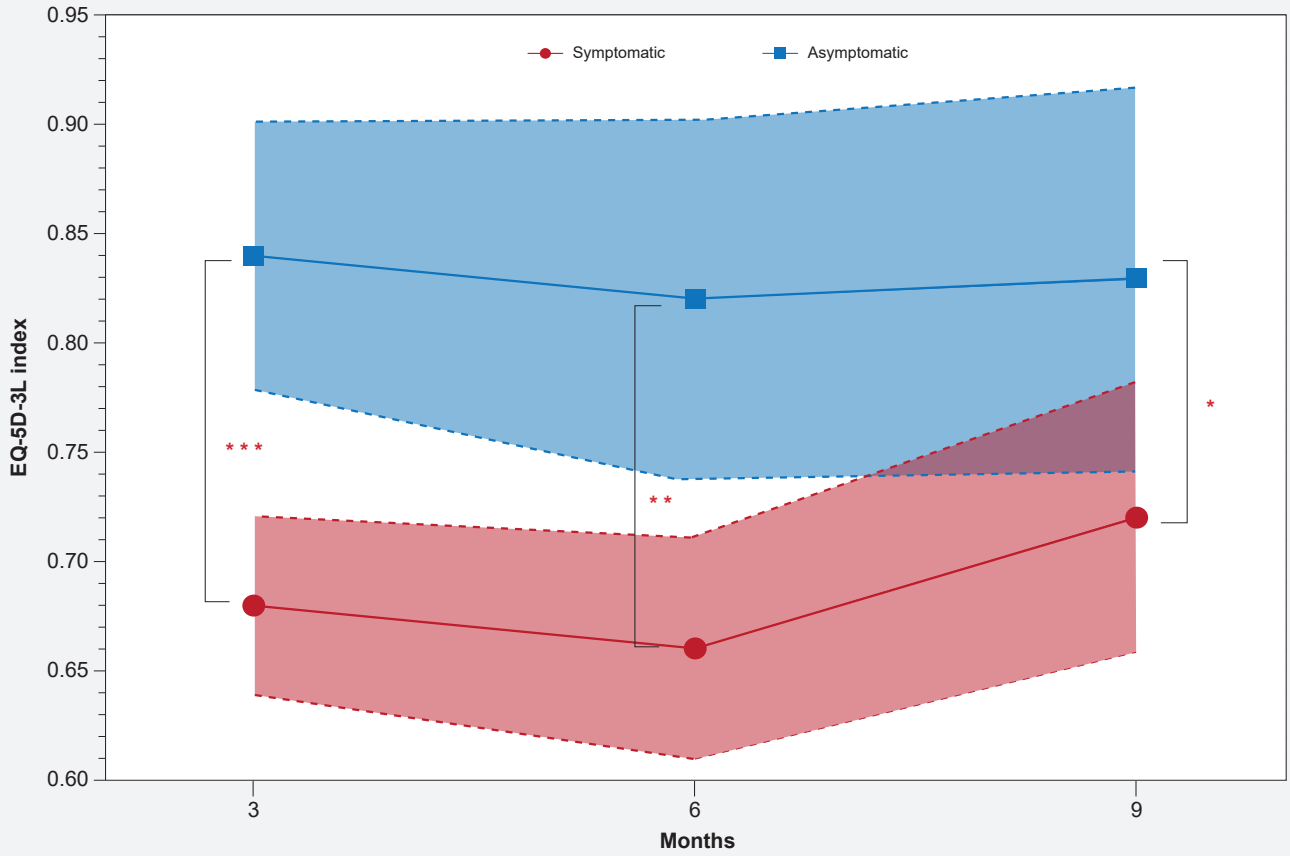

Figure 3 – Comparison of the EQ-5D-3L index (mean value and 95% confidence interval) at three, six and nine months after hospital discharge between patients with (red) and without (blue) long-COVID-19 symptoms at the first assessment.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

long-COVID-19 (Fig. 3).

Three months after hospital discharge, patients with long-COVID-19 had a decreased EQ-5D-3L index by approximately 0.14 per visit ($p < 0.001$) [Appendix 3, Table 8 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. Both groups had a non-significant change in the mean EQ-5D-3L index throughout the study (time-point assessment, Z = 0.91, $p = 0.364$). Therefore, although patients reporting long-COVID-19 at the first assessment had poorer HR-QoL, this disparity did not change significantly over the 9 months of follow-up, even though we observed an increasing trend over time in those with long-COVID-19 symptoms and even after adjusting for sex, age, CFS and comorbidities [multivariate estimated regression coefficients (95% CI): -0.10 (-0.15 – -0.05), $p < 0.001$]. [Appendix 3, Table 9 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)].

DISCUSSION

We carried out a longitudinal follow-up study of Portuguese COVID-19 patients who were systematically assessed at three, six and nine months after hospitalization for COVID-19. In this study, we reported a detailed characterization of the prevalence and risk factors associated with long-COVID-19 and found an unequivocal correlation between those symptoms and a sustained deterioration in HR-QoL over time.

Long-COVID-19 has been increasingly recognized and is now a matter of great interest as the sequelae of COVID-19 can persist for up to two years after acute infection. A Spanish multicentre study reported that more than one-third of hospitalized patients showed persisting symptoms 12 months after discharge.[13] Another single-centre longitudinal study from China, including 1192 hospital discharged patients, showed that 55% still have at least one sequelae symptom after two years of follow-up.[10]

Studies assessing patients prospectively and systematically at specific time-points after hospital discharge remain

scarce.[10,14–16] We show that more than 65% of patients report at least one symptom three months after discharge. Carvalho-Schneider *et al*[17] also found persisting symptoms in more than two-thirds of non-critical hospitalized COVID-19 patients assessed 60 days after discharge. Approximately three months after hospital admission, 74% of patients reported at least one ongoing symptom in a British study,[18] although a lower prevalence rate (50%) has been described.[19] With a median follow-up time after symptoms onset of 186 (IQR 175 – 199) days, a large Chinese cohort study including 1733 face-to-face interviews, found at least one persisting symptom in 76% of patients.[20] Nine months after disease onset, the prevalence of persistent symptoms may range from 20%[21] to more than 70%.[15] In our study, more than half of patients were still symptomatic nine months after hospital discharge regardless of demographic and clinical characteristics.

The high heterogeneity regarding the methodology of follow-up studies might justify the differences regarding the prevalence of long-COVID-19 and highlights the importance of using standardized tools to evaluate these patients in the future. Despite this, our results agree with the known decreasing tendency in the prevalence of long-COVID-19 symptoms over time. We observed that the proportion of COVID-19 survivors reporting at least one persistent symptom decreased significantly from 66.4% to 53.4% over a nine month period, and very similar results were reported by others.[16] The observed reduction of fatigue and dyspnea, the two most frequently reported long-COVID-19 symptoms, is in line with published data.[21]

Risk factors for symptom persistence have not been consistently reported. The female sex has been associated with a greater risk of long-COVID-19,[16,22,23] especially regarding mental health impairment,[13,16] while other authors describe no influence of sex.[10] We also did not find a higher risk of long-COVID-19 among women, even though we saw a non-significant trend toward a protective effect in male subjects throughout the study (Table 1). Advanced age is associated with a more severe COVID-19 phenotype and is one of the main prognostic determinants.[24,25] A frailer phenotype leads to a prolonged hospital stay and increased mortality during the COVID-19 acute phase.[24,26] Therefore, greater long-term persistence of symptoms would be expected in older and frailer patients.[16] One could also assume that severe disease, commonly associated with ICU admission, mechanical ventilation and longer hospital stay, would lead to lasting symptoms. Longer hospitalization is associated with physical and cognitive deconditioning, as well as longer recovery time after discharge.[27] In our study, neither age, frailty status, nor disease severity were risk factors for long-COVID-19. Although we report a similar median age compared to most published studies,[10,16,22] our results should be carefully interpreted since we have not included severely disabled, and hence frailer patients.

Consistent with others,[4,15,16,22] nearly 43% of our patients reported fatigue nine months after discharge. This is not surprising since some authors observed a higher prevalence of fatigue up to four years during the recovery phase of SARS[28] and recent data on COVID-19 already showed persisting fatigue up to two years.[10] Although the pathogenesis of long-lasting fatigue after COVID-19 is unclear, it probably arises from a combination of lung diffusion capacity impairment, cytokine disturbance, physical and psychological distress, as described after SARS pandemic.[28,29]

We were surprised to find that CKD was associated with a decreased odds of long-COVID-19 since it is a known risk factor for poor outcomes during the acute phase of the disease.[25,30] While most studies did not mention the effect of CKD on persisting COVID-19 symptoms, Xue-Zhang *et al*[22] reported that CKD was not associated with long-COVID-19. This unexpected finding deserves further investigation.

Knowledge about the relationship between COVID-19 severity, development of long-COVID-19 and decreasing HR-QoL is scarce. Halpin *et al*[31] found that COVID-19 severity is associated with a worse HR-QoL, while another study found no differences between ICU and ward patients.[32] Moderate to extreme problems in at least one dimension of the five-level EQ-5D questionnaire were described in around 64% of COVID-19 patients with a median time of 55 days after ICU discharge in a tertiary centre in Northern Portugal.[33] In our study, more than two-thirds of patients had at least some impairment in QoL at three months, and more than 55% at nine months after discharge. Notably, we also did not observe any positive association between disease severity, whether as a composite score (ICU admission and/or any kind of ventilatory support) or as ICU admission alone, and impairment of each QoL domain individually throughout the study (Table 2).

As others have shown,[10,32–34] the self-care domain was the least affected in our sample. Considering that nearly 85% of our patients were in good health status prior to hospitalization (CFS ≤ 3), and that self-care impairment usually reflects a severe disability, our results were expected. On the other hand, usual activities, anxiety/depression, and pain/discomfort are among the most frequently impaired domains,[10,32,33] as shown in our study. Fluctuations and relapses of long-COVID-19 symptoms have been described, but the underlying mechanism remains unclear.[10] We saw that the prevalence of impairment in the pain/discomfort and anxiety/depression domains increased at six months, being reported by almost 40% of patients. Curiously, up to 30% of patients that recovered from acute COVID-19 may fulfill criteria for fibromyalgia,[35] which has a similar pattern of changes in HR-QoL as we see in long-COVID-19.[36] This

could also explain why we observe a simultaneous increase in the prevalence of cognitive symptoms at six months (Fig. 1A), as memory impairment, foggy brain and problems with attention, are recognized consequences of depressive and/or anxious states[37] and chronic pain.[38]

The impact of baseline characteristics, including age and CFS, and the persistence of long-COVID-19 on HR-QoL, was also investigated. Righi *et al*[21] reported that a status of excellent physical health, present in 90% of patients prior to SARS-CoV-2 infection declined to 24% at disease onset and then increased to 82% at nine-months of follow-up. In our study, we also saw this trend as patients progressively achieved their previous health status over the study period, and this was associated with a significant reduction in the odds of reporting impairment in all EQ-5D-3L domains throughout the study (Table 2). Despite observing a negative effect of older age and higher CFS on mobility and self-care domains, these variables do not influence the global HR-QoL (Table 3).

One of our main goals was to explore the impact of long-COVID-19 on HR-QoL. Post-COVID-19 syndrome has been associated with long-term HR-QoL impairment[4] and our results emphasize this: the presence of long-COVID-19 at each time-point remained associated with HR-QoL impairment throughout the study after multivariate adjustment. More importantly, regardless of sex, age, health status and previous comorbid conditions, we found that the QoL, measured by the mean ED-5D-3L index, was significantly and persistently decreased over the 9 months of follow-up in patients reporting at least one persisting COVID-19 symptom three months after hospital discharge compared to those who did not [Fig. 3; Appendix 3, Table 9 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. We found this of clinical value as the identification of predictors for prolonged impaired HR-QoL after hospital discharge could help clinicians to identify patients at risk and to minimize the disease burden at an early stage. To the best of our knowledge, this has never been shown before and future studies should validate our findings.

Different SARS-CoV-2 variants may induce different long-COVID phenotypes.[39,40] Moreover, a recent systematic review suggests, although with a low level of evidence, that vaccination before SARS-CoV-2 infection could be associated with a lower risk of subsequent long-COVID-19.[41] We should reinforce that all our patients were unvaccinated, and the recruitment period occurred when the Alpha variant was the predominant variant in Portugal.[42] Thus, our findings could differ from current reality and should be interpreted carefully.

Despite our small sample size, our results confirm that long-COVID-19 is a matter of public health concern among COVID-19 survivors in our country. National health services should prioritize follow-up guidelines and algorithms concerning the management of patients with persistent symptoms. The Directorate-General of Health in Portugal published a guideline with diagnostic criteria and clinical approach to long-COVID patients. It suggests that patients at higher risk should be reevaluated four to six weeks after the acute illness. The role of primary care is well defined as

Table 3 – Multivariate logistic regression aiming to investigate the association between long-COVID-19 and the impairment of at least one EQ-5D-3L domain

	Three months		Six months		Nine months	
	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
Long-COVID-19	4.27 (1.92 – 9.52)	**< 0.001**	3.46 (1.40 – 8.57)	**0.007**	4.13 (1.62 – 10.55)	**0.003**
Male sex	0.48 (0.22 – 1.05)	0.067	0.30 (0.12 – 0.78)	**0.013**	0.53 (0.22 – 1.30)	0.166
Age[a]	1.01 (0.97 – 1.04)	0.484	1.01 (0.97 – 1.04)	0.713	1.03 (0.99 – 1.07)	0.105
CFS[a]	1.28 (0.78 – 2.10)	0.332	1.21 (0.69 – 2.14)	0.506	1.03 (0.58 – 1.84)	0.919
Return to previous CFS	0.27 (0.09 – 0.77)	**0.014**	0.51 (0.16 – 1.66)	0.262	1.63 (0.54 – 4.90)	0.386
Lung disease	0.89 (0.37 – 2.14)	0.786	1.83 (0.63 – 5.29)	0.266	3.27 (1.13 – 9.48)	**0.029**
Osteoarthritis[b]	0.99 (0.30 – 3.35)	0.995	-	-	3.22 (0.65 – 15.99)	0.145

Data are shown as odds ratio (OR) and 95% confidence interval (CI).
[a] Per one-unit increase OR.
[b] All patients with osteoarthritis had impairment in at least one EQ-5D-3L domains at six months, and were therefore excluded from the analysis.
CFS: clinical frailty scale.

well as the criteria for hospital referral.[43] Identifying patients at higher risk of disease burden is essential to reduce the collateral impact in the activities of daily life, improve clinical outcomes and reduce health-related costs.

The strength of our study is the well-defined longitudinal design with a long follow-up period where patients were all assessed at specific time-points, making it easier to draw conclusions. Our study has several limitations. First, being a single centre study with a relatively small number of patients, generalizability is compromised. Second, persistent symptoms were self-reported, without any objective assessment, which could represent an information bias. Third, no control group was considered, which hampers the possibility to assess whether the observed symptoms were due to COVID-19. Fourth, we did not collect other variables that might impact QoL (e.g.: education level, marital and socioeconomic status). Lastly, we did not have a baseline QoL assessment (e.g.: at admission; at discharge) to which our results could be compared.

CONCLUSION

Long-COVID-19 persists for at least nine-months after hospital discharge in most hospitalized patients and is unequivocally associated with impaired HR-QoL in more than half of patients regardless of disease severity and demographics. Identifying patients at higher risk of disease burden is crucial to improve outcomes and health-related costs. Follow-up guidelines for discharged COVID-19 patients should be carefully drawn and taken as a priority in a post-pandemic world.

AWARDS AND PRESENTATIONS

Preliminary results of the current study were presented at the National Congress of Internal Medicine (2021) as oral communications ("Health-Related Quality of Life Of COVID-19 Patients Three Months After Hospital Discharge" and "Persistent Symptoms in Patients With COVID-19 After Hospitalization"). The final results were presented at the National Congress of Internal Medicine (2022) ("Prevalence and Risk Factors for Long-COVID-19: Longitudinal Analysis after Hospital Discharge") and was recognized as one of the five best oral presentations in the clinical research category.

AUTHOR CONTRIBUTIONS

PG, MD: Conception of the study, data acquisition, drafting, critical review and supervision of the manuscript.

IP, HDG, FP, VM, HAB, CC, LD: Data acquisition, critical review of the manuscript.

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.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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