The Prevalence of COVID-19 Fog and the Impact on Quality of Life After SARS-CoV-2 Infection (QoL-COVID): A Cross Sectional Study

A Prevalência de COVID-19 Fog e Impacto na Qualidade de Vida da Infeção SARS-CoV-2 (QoL-COVID): Um Estudo Transversal

Inês REGO DE FIGUEIREDO✉[1], Joana BRANCO FERRÃO[2], Sara DIAS[3], Diogo DRUMMOND BORGES[3], Jorge FERNANDES[3], Vera BERNARDINO[3,4], Heidi GRUNER[3,4], António PANARRA[3,4]

ABSTRACT

Introduction: Coronavirus has an impact on both the physical and mental health of individuals. The literature regarding the patient's health status post-SARS-CoV-2 is still scarce with limited data on the prevalence of residual symptoms and quality of life (QoL) after the infection. The aim of this study was to understand the impact of SARS-CoV-2 on patient QoL, and remaining symptoms.

Methods: Single center cross-sectional study of patients who had been admitted to our COVID-19 ward between March 2020 and March 2021. By applying a QoL questionnaire (EQ-5D-5L) we assessed the overall sample, at three time points and in different groups of patients: those admitted to the intensive care unit (ICU) and the elderly.

Results: A total of 125 participants were included in our study. Most patients who were admitted had a severe course of disease (51%), with 22% of admissions to the ICU, with 8% requiring prone ventilation, 10% experiencing thrombotic complications and 18% of nosocomial infections throughout the admission. As for persistent symptoms related with COVID-19 fog, the most frequent were fatigue (57%), memory loss (52%) and insomnia (50%). Regarding QoL, the average decrease was 0.08 ± 0.2 in the index and 8.7 ± 19 in the Visual Analogue Scale (VAS). The QoL index decrease correlated with age, chronic obstructive pulmonary disease, asthma and heart failure, and all persistent symptoms, significantly. QoL VAS correlated significantly with fatigue, mood changes, difficulty concentrating and memory loss. The decrease in QoL and the persistent symptoms remained overall stable over the three time points. The ICU group showed no statistically significant difference in QoL, but the most frequently persistent symptoms were mood changes and attention disturbances. However, the elderly experienced a worsening in QoL expressed by index (0.69 ± 0.3 *vs* 0.8 ± 0.2, *p*-value = 0.01).

Conclusion: A decrease in QoL was observed following SARS-CoV-2 infection, correlating with both chronic conditions and persistent symptoms. The lack of difference through time points of both QoL and persistent symptoms suggests a long-standing effect.

Keywords: COVID-19; Mental Fatigue; Mental Status and Dementia Tests; Patient Reported Outcome Measures; Quality of Life; SARS-CoV-2

RESUMO

Introdução: O coronavírus tem um impacto negativo sobre os indivíduos afetados tanto a nível físico como mental. A literatura sobre o estado de saúde pós SARS-CoV-2 ainda é escassa, com poucos dados sobre a prevalência de sintomas residuais e a qualidade de vida (QoL) após a infeção. O objetivo deste estudo foi compreender o impacto da infeção SARS-CoV-2 na QoL dos doentes e em sintomas residuais.

Métodos: Estudo transversal observacional em doentes admitidos em enfermaria COVID-19 entre março 2020 e março de 2021. Aplicação de um questionário QoL (EQ-5D-5L) com avaliação de toda a amostra, em três pontos temporais e grupos de doentes: admitidos numa unidade de Cuidados Intensivos (UCI) e idosos.

Resultados: Foram incluídos 125 participantes. A maioria foi admitida por curso grave de doença (51%), tendo-se registado 22% admissões na UCI, 8% com necessidade de ventilação ventral, 10% com complicações trombóticas e 18% com infeções nosocomiais. Quanto aos sintomas persistentes associados ao COVID-19 *fog*, os mais frequentes foram fadiga (57%), perdas de memória (52%) e insónia (50%). Em relação à QoL, houve uma diminuição média de 0,08 ± 0,2 no índex e 8,7 ± 19 na *Visual Analogue Scale* (VAS). A diminuição do índice relacionou-se significativamente com a idade, doença pulmonar obstrutiva crónica, asma e insuficiência cardíaca, e todos os sintomas persistentes. O VAS correlacionou-se significativamente com fadiga, alterações do humor, dificuldades de concentração e perdas de memória. A diminuição da QoL e os sintomas persistentes permaneceram estáveis ao longo dos três pontos no tempo. Não se verificaram diferenças estatisticamente significativas na QoL do grupo de UCI, afetado sobretudo por sintomas persistentes relacionados com alterações do humor e perturbações da atenção. Os idosos apresentaram agravamento da QoL segundo o índice (0,69 ± 0,3 *vs* 0,8 ± 0,2, valor-*p* = 0,01).

Conclusão: Observou-se uma diminuição na QoL após a infeção por SARS-CoV-2, correlacionando-se com comorbilidades e sintomas persistentes. A ausência de variação da QoL e sintomas persistentes entre pontos temporais sugere efeito a longo prazo.

Palavras-chave: COVID-19; Fadiga Mental; Medidas de Resultados Relatados pelo Doente; Qualidade de Vida, SARS-CoV-2; Testes de Estado Mental e Demência

INTRODUCTION

The new beta coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in December 2019 in Wuhan, China. Most patients experience mild symptoms, but some could develop a more serious condition, such as pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ failure. The worldwide mortality rate in 2020 was estimated to be 4.1%.[1] In Portugal, on the 22nd July 2021, there had been 943 244 notified

cases, with 17 248 deaths and an estimated mortality rate of 1.8%.[2] Now that the COVID-19 pandemic has reached its third year, the focus is changing towards the long-term impact of the disease, in particular quality of life (QoL) and COVID-19 fog.[3]

The impact of COVID-19 on quality of life (QoL) has been assessed in a variety of settings. Firstly, in non-infected people that experienced higher levels of anxiety and lower QoL during quarantine, particularly women and the elderly.[4] Secondly, COVID-19 patients that did not require hospitalization also revealed a decrease in QoL compared to the general population, mainly in the domains of mobility and usual activities.[5] As for hospitalized COVID-19 patients, different populations have been evaluated, ranging from those who were clinically stable, to cardiovascular patients with severe complications or patients requiring intensive care unit (ICU) admission. They have all exhibited a lower quality of life,[6,7] that was frequently associated with persistent depression/anxiety.[3,8,9] This decline in QoL has also been reported in Portugal, where patients also exhibited physical and emotional disability.[10] In fact, a neurological condition, which consists of mood change, fatigue, headache, memory impairment, attention disturbances and sleep disorders, has been described as a consequence of COVID-19 disease, defined as COVID-19 fog.[3,7,11–13]

However, there are still some gaps in understanding the QoL deterioration following SARS-CoV-2 infection. For example, the duration or time frame, as most studies focus on up to three months and only in one time point. Also, in certain populations, such as the elderly, QoL has been mostly evaluated in relation to lockdown and quarantine, but not to infection requiring hospital admission.[14,15]

The aim of this study was to assess the prevalence of COVID-19 fog persistent symptoms as well as the impact of SARS-CoV-2 infection in the quality of life of patients admitted to a COVID-19 ward.

METHODS

We performed a cross sectional observational study of patients who had been admitted to our COVID-19 ward between March 2020 and March 2021.

We included patients with SARS-CoV-2 (positive PCR for SARS-CoV-2), within all the spectrum of disease severity, including asymptomatic patients admitted to hospital for other causes. Patients were included if they were admitted to our COVID-19 ward, coming directly from the emergency department, other wards (not dedicated to COVID-19), or ICU. Recruited patients had been admitted at our ward three (3M), six (6M) and 12 (12M) months before. Furthermore, we included all patients who were fluent in Portuguese, and with absence of diagnosed dementia.

We applied a health-related quality-of-life questionnaire (EQ-5D-5L,[16] both Index and Visual Analogue Scale-VAS), that had been translated, validated and with normative values for the Portuguese Population.[17] This QoL questionnaire used for cost-utility and estimation of quality-adjusted life years, assesses five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), at five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). We also evaluated COVID-19 fog using a questionnaire developed by us for assessing persistent symptoms previously described elsewhere (fatigue, mood changes, headaches, attention disturbances, insomnia, and memory impairment) (Fig. 1).[3,11,12]

Finalmente, gostaríamos de lhe perguntar se após a infeção COVID, mantém atualmente algum dos seguintes sintomas (coloque um círculo em redor da opção correta):

1. Fadiga
      Sim   Não

2. Alterações do humor
      Sim   Não

3. Dores de cabeça
      Sim   Não

4. Dificuldades de concentração
      Sim   Não

5. Dificuldades a dormir/insónias
      Sim   Não

6. Perdas de memória/esquecimentos
      Sim   Não

Muito obrigado pelo tempo dispensado a participar no nosso estudo.

Figure 1 – COVID-19 fog persistent symptoms questionnaire

The questionnaires were sent by mail, for self-administration by patients, together with a presentation letter regarding the project, and informed consent form, as well as an envelope for return.

The EQ-5D-5L questionnaire was filled twice, firstly concerning the status before the SARS-CoV-2 infection (pre-test), and secondly regarding the patient's current status (post-test). We used the retrospective test or *thentest* method,[3] which has been shown to be as valid as a prospective method,[4] despite some bias, such as the *recall bias*.[5]

After receiving the patient questionnaires, we collected each patients' information from the medical records: demographics and relevant medical history according to the guidelines of the Directorate General of Health, Portugal's Public Health authority (chronic obstructive pulmonary disease, asthma, heart failure, type 2 diabetes mellitus, cirrhosis, renal failure, obesity, neoplasia, post-solid organ transplant status, and immunosuppression),[18] chronic medication, degree of autonomy for activities of daily living (ADL), according to the KATZ scale, symptoms, cause for hospital admission (COVID-19 disease or other), and severity of SARS-CoV-2 infection. Severity markers such as need for ventilation (both noninvasive and invasive), and prone ventilation, ICU admission, nosocomial infections, and thrombotic complications, need for renal replacement therapy (RRT) and length of stay (LOS) were also collected. Two different LOS were considered: total (from hospital admission to discharge) and SARS-CoV-2 (refers exclusively to time when SARS-CoV-2 infection was considered active). Severity was assessed at admission, according to the guidelines of the Directorate General of Health[18]: asymptomatic, slight, moderate (fever and dyspnea), severe (requiring oxygen) and critical (ARDS or hemodynamic instability).

The study was approved by the Hospital's Ethics Committee and all data was anonymized.

Data was analyzed comparing both the previous and current quality of life, but also according to its difference, both with index and VAS from EQ-5D-5L. We also performed subgroup analysis according to three different time points (three, six or 12 months after SARS-CoV-2 infection), ICU admission and elderly population (65 years old or older).

Continuous data were expressed as mean and standard deviation if they presented a normal distribution and median and interquartile range (IQR), if otherwise. The chi-square or the Fisher exact test were used in the comparison of categorical variables. The *t*-Student test was used for continuous parametric variables and the Wilcoxon test for non-parametric continuous variables. ANOVA was performed for parametric data, when more than two groups were assessed, and Spearman for correlations. We performed the Bonferroni correction if more than two groups were being compared. Logistic regression was performed to account for bias.

Statistical analysis was performed using STATA® (StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP). A *p*-value of < 0.05 was considered statistically significant.

RESULTS

A total of 400 patients fulfilled the criteria and were included in the study, out of 478 patients admitted during the study time frame. Letters were sent according to the time frame: 82 to the 3M, 187 to the 6M and 131 to the 12M group. Out of those 400, 125 patients responded: 31 at 3M, 58 at 6M and 36 at 12M post admission, yielding about a 30% response rate (Fig. 2).

Of the 125 participants, 51% were female (n = 64), about 93% were white (n = 116) and 82% (n = 102) were independent in their ADL. Average age was 70 ± 13 years old [Appendix 1, Table 1 (Appendix 1: https://www.acta-medicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Most patients were admitted due to COVID-19 disease (77%, n = 96), but 29 patients were admitted due to other clinical conditions and tested positive for SARS-CoV-2 infection at hospital admission or during their stay in other hospital wards [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

The most common comorbidities were diabetes mellitus (37%, n = 46), heart failure (22%, n = 27) and obesity (21%, n = 26). Most patients had a severe course of disease (51%, n = 64) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Regarding severity markers: 22% (n = 28) of patients were admitted in the ICU, and 8% (n = 10) required prone ventilation. We present two different lengths of stay: 18.8 ± 13 days total LOS and 14 ± 10 days SARS-CoV-2 LOS. During the admission 10% (n = 13) experienced thrombotic complications and 18% (n = 22) nosocomial infections [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

As for persistent symptoms related with COVID-19 fog, the most frequent were fatigue (57%, n = 71), memory impairment (53%, n = 65) and insomnia (50%, n = 62). Attention disturbances (38%, n = 48), mood changes (30%, n = 37) and headaches (29%, n = 36), although less frequently, were also prevalent (Table 1).

Considering quality of life, the index varied significantly from 0.81 ± 0.26 to 0.73 ± 0.26 (*p*-value < 0.001), as well
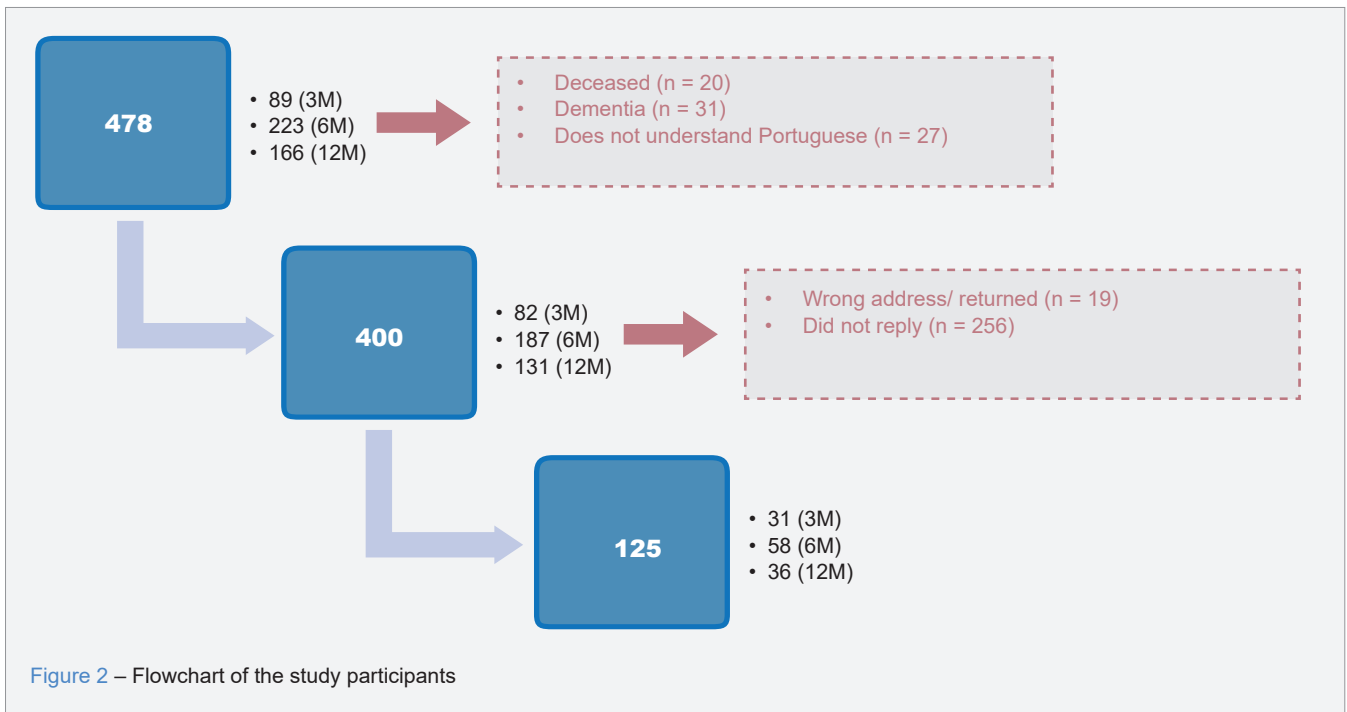
Figure 2 – Flowchart of the study participants

as the VAS from 72 ± 20 to 64 ± 22 (*p*-value < 0.001). The average decrease in QoL was 0.08 ± 0.2 in the index and 8.7 ± 19 in the VAS (Table 2). QoL index decrease correlated significantly with age (r = -0.18, *p*-value < 0.05), COPD (r = -0.24, *p*-value < 0.05), asthma (r = -0.19, *p*-value < 0.05) and heart failure (r = -0.23, *p*-value < 0.05), and all the evaluated persistent symptoms (fatigue: r = -0.33, *p*-value < 0.01; mood changes: r = -0.31, *p*-value < 0.01; headaches: r = -0.2, *p*-value < 0.05; attention disturbances: r = -0.31, *p*-value < 0.01; insomnia: r = -0.24, *p*-value < 0.05; and memory impairment: r = -0.29, *p*-value < 0.01). QoL VAS correlated with fatigue (r = -0.4, *p*-value < 0.01), mood changes (r = -0.24, *p*-value < 0.05), attention disturbances (r = -0.31, *p*-value < 0.01) and memory impairment (r = -0.32, *p*-value < 0.01), but not with age, LOS, comorbidities, or severity markers.

Time point subgroup analysis

As previously mentioned, a total of 31, 58 and 36 patients participated in the 3M, 6M and 12M time points. Demographic data was well-adjusted, with the exception of gender, which showed predominance of the male gender at 3M and 12M (58%, n = 18 and 61%, n = 22), and females at 6M (64%, n = 37). The admission diagnosis and the comorbidity distribution throughout the time points followed the overall distribution. However, there was a difference in SARS-CoV-2 LOS which was higher in the 12M group (12 ± 13 *vs* 12 ± 6.7 *vs* 19 ± 12), *p*-value = 0.007). SARS-CoV-2 severity also varied by time point, with less prevalence of

severe disease in this last group (65% (n = 20) *vs* 57% (n = 33) *vs* 31% (n = 11), *p*-value = 0.006). In contrast, ICU admission was also higher at 12 months (19% *vs* 14% *vs* 39%, *p*-value = 0.016), along with mechanical ventilation (19% *vs* 9% *vs* 33%, *p*-value = 0.01) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

COVID-19 fog symptoms were similar throughout the three time points (Table 1). Regarding QoL, there was little difference between the three time points either in index or difference. However, current VAS QoL at 6M was significantly lower, even after Bonferroni *post-hoc* (69 ± 20 *vs* 58 ± 22 *vs* 67 ± 20, *p*-value = 0.039). (Table 2). A logistic regression was performed to adjust for gender and SARS-CoV-2 severity as potential confounders for COVID-19 fog symptoms and QoL as assessed by index and VAS, before, after and difference. As for COVID-19 fog symptoms, headache was affected by both gender and the severity of the infection (*p*-value = 0.003 and 0.008, respectively). Gender was also a confounding factor for VAS before and after the SARS-CoV-2 infection (*p*-value = 0.02 and 0.002, respectively). However, it had no influence on the VAS variation (*p*-value = 0.6).

ICU subgroup analysis

From the 125 patients, 28 (22%) were admitted to the ICU. There was a slight predominance in male gender admissions [64% (n = 18) *vs* 44% (n = 43)], but not statistically significant. There was also a difference in autonomy

Table 1 – COVID-19 fog persistent symptoms: total and by subgroup analysis

COVID-19 fog persistent symptoms	Total	3M	6M	12M	*p*-value	ICU	Ward	*p*-value	Elderly	Young	*p*-value
Fatigue	71 (57%)	15 (48%)	35 (60%)	21 (58%)	0.500	18 (64%)	53 (55%)	0.360	54 (63%)	17 (44%)	0.045
Mood changes	37 (30%)	6 (19%)	19 (33%)	12 (33%)	0.300	15 (54%)	22 (23%)	0.020	25 (29%)	12 (31%)	0.800
Headache	36 (29%)	9 (29%)	16 (28%)	11 (31%)	0.900	10 (36%)	26 (27%)	0.360	26 (30%)	10 (26%)	0.600
Attention disturbances	48 (38%)	11 (36%)	23 (40%)	14 (40%)	0.900	17 (61%)	31 (32%)	0.006	34 (40%)	14 (36%)	0.700
Insomnia	62 (50%)	15 (48%)	31 (53%)	16 (44%)	0.700	14 (50%)	48 (49%)	0.900	39 (45%)	23 (59%)	0.160
Memory impariment	65 (53%)	17 (55%)	29 (50%)	19 (53%)	0.900	17 (61%)	48 (49%)	0.300	45 (52%)	20 (51%)	0.900
n	125	32	58	36		28	97		86	39	

3M: three months; 6M: six months; 12M: 12 months; ICU: Intensive Care unit

status for those admitted to the ICU, for which the majority was independent [96% (n = 27) *vs* 73% (n = 75), *p*-value = 0.02]. Comorbidities were similar between groups, with the exception of heart failure, which was more prevalent in the non-ICU group [7% (n = 2) *vs* 26% (n = 25), *p*-value = 0.03] [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Both admission diagnosis and SARS-CoV-2 severity were different between the two groups: all patients admitted in the ICU had COVID-19 disease [100% (n = 28) *vs* 70% (n = 68), *p*-value < 0.001] and critical condition was the most frequent in this group (82%, n = 23, *p*-value < 0.001). LOS (both total and SARS-CoV-2) was also higher in the ICU group (27 ± 18 *vs* 16 ± 16, *p*-value = 0.02; 21 ± 12 *vs* 12 ± 8, *p*-value < 0.001) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

From the 28 patients admitted to the ICU, 82% (n = 23) required IMV and five patients alone NIMV. A total of eight patients underwent non-invasive ventilation in the ICU compared to the COVID-19 ward [29% (n = 8) *vs* 3% (n = 3), *p*-value < 0.01]. There was a higher prevalence of nosocomial infections in the ICU group (32% *vs* 13%, *p*-value = 0.02) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Regarding COVID-19 fog symptoms, the results were similar between the two groups, with the exception of mood changes [54% (n = 15) *vs* 23% (n = 22), *p*-value = 0.02] and attention disturbances [61% (n = 17) *vs* 32% (n = 31), *p*-value = 0.006], which were higher in the ICU group (Table 1).

As for the QoL, it didn't seem affected by ICU admission, since the index, VAS and difference were similar in both groups (Table 2).

Considering the statistically significant difference in admission diagnosis between ICU and ward patients, a subanalysis was performed, including only patients admitted due to COVID-19 disease [Appendix 2, Tables 1 and 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15045)]. COVID-19 fog symptoms showed the same distribution, with a statistically significant higher prevalence of mood changes [54% (n = 15) *vs* 22% (n = 15), *p*-value = 0.002] and attention disturbances [61% (n = 17) *vs* 56% (n = 22), *p*-value = 0.01]. QoL remained unchanged with index, VAS and difference alike.

Elderly subgroup analysis

The elderly (over 65 years old) consisted of 69% (n = 86) of our sample. They were overall similar in relation to gender and ethnicity, but they were more dependent in ADL [27% (n = 23) *vs* 0%, *p*-value < 0.001]. Both the elderly and the young had a similar distribution of comorbidities, with the exception of heart failure, which was more frequent in the elderly [28% (n = 24) *vs* 8% (n = 3), *p*-value = 0.01], and post solid organ transplantation status which was less frequent in this group [2% (n = 2) *vs* 13% (n = 5), *p*-value = 0.02] [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Hospital admission for COVID-19 disease [81% (n = 70) *vs* 67% (n = 26), *p*-value = 0.007] was more prevalent in the elderly, but disease severity and severity markers were much the same between the two groups [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Table 2 – Quality of life (index, VAS and difference): total and by subgroup analysis

EQ-5D-5L	Total	p-value	3M	6M	12M	p-value	ICU	Ward	p-value	Elderly	Young	p-value
Index before SARS-CoV-2	0.81 ± 0.26		0.80 ± 0.20	0.78 ± 0.30	0.80 ± 0.24	0.700	0.85 ± 0.20	0.79 ± 0.26	0.380	0.78 ± 0.20	0.86 ± 0.23	0.100
Index after SARS-CoV-2	0.73 ± 0.30	< 0.001	0.70 ± 0.30	0.70 ± 0.30	0.75 ± 0.28	0.800	0.76 ± 0.20	0.72 ± 0.29	0.590	0.69 ± 0.30	0.80 ± 0.20	0.010
Index difference	-0.082 ± 0.20		-0.10 ± 0.10	-0.07 ± 0.20	-0.07 ± 0.2	0.770	-0.08 ± 0.16	-0.08±0.2	0.900	-0.10 ± 0.20	-0.03 ± 0.20	0.100
VAS before SARS-CoV-2	72 ± 20		76 ± 15	68 ± 21	76 ± 21	0.090	73 ± 20	72 ± 20	0.700	70 ± 19	76 ± 21	0.100
VAS after SARS-CoV-2	64 ± 22	< 0.001	69 ± 20	58 ± 22	67 ± 20	0.039	65 ± 22	64 ± 22	0.800	62 ± 20	68 ± 23	0.100
VAS difference	-8.74 ± 19.00		-6.00 ± 19.00	-10.00 ± 16.00	-8.00 ± 21.00	0.600	-8.90 ± 22.00	-8.70 ± 18.00	0.900	-10.00 ± 18.00	-5.60 ± 19.00	0.200
n	125		32	58	36		28	97		86	39	

3M: three months; 6M: six months; 12M: 12 months; ICU: Intensive Care unit; VAS: Visual Analogue Score

Considering the COVID-19 fog symptoms, their distribution was comparable between groups, except fatigue, which was higher in the elderly [63% (n = 54) *vs* 44% (n = 17), *p*-value = 0.0045] (Table 1).

Regarding QoL, the only statistically significant difference between the two groups was on the index following SARS-CoV-2 infection, which was lower in the elderly (0.69 ± 0.3 *vs* 0.8 ± 0.2, *p*-value = 0.01). QoL was also lower according to VAS and index and VAS difference, but not statistically significant (Table 2).

DISCUSSION

This study's sample included 125 participants, with a response rate of about 30%. Its demographics followed the admission in a ward for SARS-CoV-2 infection as shown in other studies. We reported two different LOS (total and SARS-CoV-2) due to the heterogeneity of patient reasons for admission (admitted due to COVID-19 disease and those who were admitted due to other clinical conditions and tested positive for SARS-Cov-2 at hospital admission, and those who contracted nosocomial SARS-CoV-2 infection) and destination following discharge (those who required physical therapy following infection but still needed isolation). LOS was higher in the latter. In fact, resolution of SARS-CoV-2 infection evolved faster than these other aforementioned- conditions and patients who were stable and able to ensure isolation at home were discharged earlier.

Concerning the COVID-19 fog persistent symptoms, the prevalence in our sample was similar to what is described in previous studies considering fatigue, but it was slightly higher for memory impairment, attention disturbances and insomnia.[3]

Also consistent with other studies, we found a reduction in QoL following SARS-CoV-2 infection, both in Index and VAS. While QoL index correlated both with patient characteristics (age, COPD, asthma, and heart failure) and persistent symptoms, VAS only correlated with some persistent symptoms (fatigue, mood changes, difficulty concentrating and memory loss). Even though worsening of QoL with age had already been suggested,[6] we did not find correlation with other factors described in our study, such as gender and severity markers.[7] Considering the comorbidities, which were correlated with a QoL worsening, we hypothesize that it might be related to a deterioration/decline in the baseline health status.

On the 3-time point subgroup analysis, we observed different SARS-CoV-2-related LOS, which relates to the different definitions of disease duration over the period of our study. Initially, patients required a double negative swab to be considered as cured, and more recently, patients with mild disease were considered cured at seven days, or 20

for severe disease or immunocompromised patients, according to the national guidelines.

We also found different levels of disease severity at admission over the three time points. This resulted from hospital admissions in the 12M group period that were made for monitoring patients with risk factors for severe disease, despite low severity at admission, and patients unable to quarantine. In contrast with an increase of disease severity at admission, severity markers, such as ICU admission and mechanical ventilation, decreased over time, which suggests a positive preventive effect of COVID-19 vaccination.

COVID-19 fog persistent symptoms were similar throughout the three time-points. Nevertheless, headache is confounded by both gender and the disease severity, and therefore those results are not reliable. Despite that, all other persistent symptoms show consistency

Regarding QoL, the results were consistently low through the time period of our analysis. However, there were no differences between the three time points, when considering the index value, even after adjusting for confounding factors (gender and disease severity), showing consistency through time. Even though VAS is affected by gender, which has been reported,[19] its variation is not, which suggests that the change in QoL assessed by VAS is stable over time.

These results suggest that the effects of the disease on QoL and on COVID-19 fog symptoms occur at an early stage and its effects last for up to 12 months.

The ICU group analysis had baseline differences, related to the different populations which were assessed (COVID-19 ward *versus* ICU), which resulted from patient selection for ICU admission regarding their age, comorbidities, and functional status. Furthermore, patients were heterogeneous regarding reason for hospital admission, and all patients admitted to the ICU had COVID-19 disease. Despite the previously described worsening of QoL in patients with ICU admission,[6] our cohort showed no differences between the COVID-19 ward and ICU group, both in index and VAS. Moreover, QoL worsened after hospital admission from SARS-CoV-2 in both groups. Therefore, besides our small subpopulation of ICU admitted patients, we hypothesize that ICU admission might not worsen the already existing deterioration of QoL from SARS-CoV-2, which was not assessed in previous studies, as they only focused on ICU patients. This is consistent with the findings of Garrigues *et al*, in which there was no difference in QoL between COVID-19 ward and ICU patients.[3] Of course, one must not exclude other factors, such as recall bias or the effect of intensive physical therapy and rehabilitation following ICU admission. Conversely, COVID-19 fog persistent symptoms of mood changes and attention disturbances were higher in ICU admitted patients, in contrast with the results of Gar-

rigues *et al*.[3]

Due to heterogeneity of reasons for hospital admission, which could impact our results, we performed a sub-analysis only with patients admitted for COVID-19 disease. Still, there was no change between ward and ICU patients in QoL as assessed by EQ-5D-5L index and VAS, contributing to the notion that ICU admission does not increase the QoL worsening from COVID-19. We still observed a higher frequency of COVID-19 fog persistence symptoms (mood changes and attention disturbances) in the ICU admitted patients.

Our elderly subgroup analysis was innovative, as there is lack of data regarding hospital admitted older patients with SARS-CoV-2, and also because there are no previously described correlations of decreasing QoL with age. Both older and young populations were comparable, with the exception of a higher degree of dependency in ADL and a higher prevalence of heart failure in the former. Out of the COVID-19 fog persistent symptoms, only fatigue was higher in the elderly.

Overall, QoL in the elderly was lower compared to the younger population, both in pre- SARS-CoV-2 and after-SARS-CoV-2 situations, but statistical significance was only found in the latter. The two groups differed in the decrease of QoL, both in index (-0.1 *vs* -0.03) and VAS (-10 *vs* -5.6), but it was not significant. The lack of significance can be due to the small size of our sample, but also to the lower QoL at baseline of the elderly group. These are comparable to the findings of Walle-Hansen *et al*, another study performed in the elderly, which showed a decrease in QoL, but no difference between the elderly and the young.[20]

This study has many issues. Firstly, our response rate was only of 30% which, even if expected, decreased our sample size, with particular impact in the subgroup analysis. Secondly, despite its validation, the retrospective method still raises some issues, namely the recall bias. However, this bias will always remain an issue, since its unlikely to have data of QoL of patients prior to their hospital admission. Thirdly, the self-administration component of the questionnaire may have led to missing data, and even some confusion in filling in. Filling in by phone or face-to-face interview could have overcome some of these issues. Fourthly, our sample included all patients with SARS-CoV-2 infection, including those with asymptomatic infection, admitted for other conditions. Although this heterogeneity reduces the strength of our conclusions, this was intentional, because we wanted to have a representative sample. Furthermore, we had issues specific to our sub-analysis. Primarily, our analysis by time-points, being a cross-sectional study, did not evaluate the same patients through time, but different patients at different times following SARS-CoV-2 infection. This could have been overcome if the different

samples had comparable baseline characteristics, which was not the case, with differences in the distribution of gender and disease severity. Therefore, confounder adjustment was performed through logistic regression, improving the robustness of our findings and conclusions. Finally, in the ICU group, the issue with the heterogeneity of the diagnosis (already addressed above) becomes more relevant, because only patients with COVID-19 were admitted. Hence, a sub-analysis was performed and included only patients admitted due to COVID-19 disease.

Nevertheless, we believe that our study has brought some light into some questions regarding long-term effects of SARS-CoV-2 in hospitalized patients, particularly in the elderly group.

CONCLUSION

SARS-CoV-2 infection has a significant impact in QoL, often associated with chronic conditions, and more severe in the elderly. The absence of variation throughout the different time points suggests a long-standing effect, which should be addressed in future studies. Similarly, the persistent symptoms associated with COVID-19 fog have high prevalence and can persist up to one year.

AUTHORS CONTRIBUTION

IF: Study design; data collection; data analysis; draft of the manuscript.

JBF, SD: Data collection; draft of the manuscript.
DDB, JF: Data collection.
VB, HG: Study design; critical review of the manuscript.
AP: 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.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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