Health-Related Quality of Life in Survivors of Severe COVID-19 of a University Hospital in Northern Portugal

Qualidade de Vida dos Sobreviventes da COVID-19 Grave de um Hospital Universitário no Norte de Portugal

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ABSTRACT

Introduction: Long-term health impairments are often experienced among survivors of critical illness, which may have a negative impact on their quality of life. The aim of this study was to characterize COVID-19 survivors of critical illness and to evaluate health-related quality of life and disability following hospital discharge.

Material and Methods: This is a retrospective case-series study that included COVID-19 survivors admitted to the Intensive Care Medicine Department of a University Hospital. Follow-up evaluation was performed between the 30th and the 90th day after discharge. Quality of life was explored using the five-level version of the EQ-5D instrument (EQ-5D-5L) and functionality using the 12-question World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).

Results: Forty-five survivors were enrolled, 28 (62.2%) men, median age 63.0 years. The EQ-5D-5L questionnaire showed moderate to extreme problems in some dimension in 29 patients (64.4%): mobility in six (13.3%), self-care in seven (13.3%), usual activities in 23 (51.1%), pain/discomfort in 14 (31.1%) and anxiety/depression in 17 (37.8%). When using the 12-question WHODAS 2.0 questionnaire, moderate to extreme disability was reported in some question in 37 patients (82.2%): 19 (42.2%) in standing for long periods, 18 (40.0%) in long-distance walking; 14 (31.1%) on taking care of household responsibilities and 17 (37.8%) in their day-to-day work; 23 (51.1%) felt emotionally affected by their health problems.

Discussion: Based on COVID-19 survivors-reported outcomes after critical illness, mobility, pain/discomfort, and anxiety/depression were the main problems that persisted one to three months after hospital discharge.

Conclusion: An organized follow-up structure is crucial to improve health-related quality of life in critical COVID-19 survivors.

Keywords: COVID-19; Critical Care; Follow-up Studies; Portugal; Quality of Life; Survivors

RESUMO

Introdução: Os sobreviventes de doença crítica apresentam frequentemente sequelas a longo prazo. O objetivo deste estudo foi caracterizar os sobreviventes da COVID-19 grave e avaliar a qualidade de vida após a alta hospitalar.

Material e Métodos: Série de casos que inclui sobreviventes COVID-19 admitidos no Serviço de Medicina Intensiva de um Hospital Universitário. A consulta de seguimento foi realizada entre o 30º e o 90º dia após alta hospitalar. A qualidade de vida foi avaliada através do questionário EQ-5D com cinco níveis (EQ-5D-5L) e a funcionalidade através do instrumento *World Health Organization Disability Assessment Schedule* 2.0 (WHODAS 2.0) de 12 questões.

Resultados: Foram incluídos 45 sobreviventes, 28 homens (62,2%), idade mediana de 63,0 anos. No questionário EQ-5D-5L 29 sobreviventes (64,4%) mostraram problemas moderados a extremos em alguma dimensão: seis (13,3%) na mobilidade, sete (13,3%) nos cuidados pessoais, 23 (51,1%) nas atividades habituais, 14 (31,1%) na dor/desconforto e 17 (37,8%) na ansiedade/depressão. No WHODAS 2.0 37 sobreviventes (82,2%) revelaram alterações funcionais moderadas a extremas em alguma questão: 19 (42,2%) em permanecer de pé por longos períodos, 18 (40,0%) em percorrer longas distâncias, 14 (31,1%) em cuidar das responsabilidades domésticas e 17 (37,8%) no dia-a-dia no trabalho; 23 (51,1%) mostraram-se emocionalmente afetados pelos seus problemas de saúde.

Discussão: A avaliação dos sobreviventes COVID-19 após a doença crítica demonstra que a mobilidade, a dor/desconforto e a ansiedade/depressão são os principais problemas que persistem um a três meses após a alta hospitalar.

Conclusão: O acompanhamento estruturado após alta poderá ter impacto significativo na qualidade de vida destes doentes.

Palavras-chave: COVID-19; Medicina Intensiva; Portugal; Qualidade de Vida; Seguimentos; Sobreviventes

INTRODUCTION

On the 2nd of March of 2020, the first case in Portugal of infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was diagnosed.[1] This challenging disease with a daily stunning speed of infection led to abrupt adjustments in hospital and healthcare teams, with profound consequences to the physical and mental health of all those involved: professionals, patients and families.[2,3] A recent meta-analysis reported that approximately 20% of COVID-19 hospitalized patients required admission to Intensive Care Medicine.[4]

Long-term impairment in physical, cognitive and mental health after critical illness are often experienced among survivors and their families, which is known as post-intensive care syndrome (PICS).[5] One year after critical illness, 60% of survivors have one or more PICS-related problems.[6] Moreover, moderate or severe disability six months after critical illness is present in 25% of survivors and it is associated with reduced health-related quality of life.[7] The pressing question remains understanding what the outcomes of COVID-19 patients are after discharge from Intensive Care and what are the implications of PICS.[8] The largest clinical follow-up study published about COVID-19 patients

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reported that the severity of illness was a risk factor for psychological symptoms, mobility problems, persistent pain/discomfort, and anxiety/depression in survivors.[9]

The aim of this study was to characterize survivors of COVID-19 critical illness and to evaluate health-related quality of life and disability following hospital discharge.

MATERIAL AND METHODS

Study design and participants

This retrospective case-series study included all COVID-19 survivors admitted to the Intensive Care Medicine Department of Centro Hospitalar Universitário São João in Porto, Portugal, with an effective hospital discharge until the 15th of July of 2020. The eligible adult survivors were those with an intensive care length of stay lasting longer than 24 hours.

In this Intensive Care Medicine Department there is a follow-up clinic dedicated to the assessment of patients after critical illness which includes intensivists and an intensive care trained nurse specifically dedicated to contacting survivors by telephone and to apply disability scales as a triage method before medical evaluation. The evaluation period of survivors includesthe period between the date of hospital discharge and the date of clinical telephone evaluation.

The study was approved by the Ethics Committee of Centro Hospitalar Universitário São João (CE 376/2020) and all the included patients gave verbal informed consent at the time of contact.

Data collection

Demographic, clinical, laboratory and treatment data were extracted from the hospital electronic information systems. All patients had laboratory confirmation of SARS-CoV-2 infection by real-time PCR methods.

Follow-up evaluation of survivors was performed over the telephone by the intensive care nurse of the Intensive Care follow-up team, between the 30th and the 90th day after hospital discharge, following the specific requirements of each scale evaluated in this study. Answers were provided by the patient, except in three cases in which the family did it.

Health-related quality of life

Health-related quality of life was assessed with the EuroQol five-dimension five-level questionnaire (EQ-5D-5L). This is a descriptive self-evaluation that assesses five dimensions: mobility, self-care (hygiene and dressing), usual activities (work, study, housework, family and leisure activities), pain/discomfort and anxiety/depression. Each dimension has five levels of disability: no problems, slight problems, moderate problems, severe problems and unable to or extreme problems, classified between 1 and 5.[10] The visual analogue scale (EQ-VAS) is a quantitative measure of health outcomes that reflects the self-rated health of patients, where the endpoints are labelled between “the worst health you can imagine” (zero points) and “the best health you can imagine” (100 points).[10] The results will be presented as disability degree for each dimension. We applied the validated EQ-5D-5L Portuguese version.[11]

Functionality and disability

In order to complement the evaluation of the impact of critical illness on global functionality and disability the 12-question World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) was applied. It covers six domains of functioning, each one based on two questions with the intention of recognizing functional impairments in the last 30 days: cognition (understanding and communication), mobility (moving and getting around), self-care (hygiene, dressing, eating and staying alone), getting along (interacting with other people), life activities (domestic responsibilities, leisure, work and school) and participation (joining community activities). Each question was scored from 1 (no difficulty) to 5 (extreme difficulty or cannot do) with the possibility of answering “not applicable” (N/A) if the person did not have the opportunity to complete the task in the last 30 days.[12] The results will be presented as disability degree in each question. We applied the validated Portuguese version of 12-question WHODAS 2.0.[13]

Statistical analysis

Statistical analysis was carried out using SPSS software (version 23.0). Continuous variables were presented as median (interquartile range) and categorical variables as frequency rates (percentages).

The answers to the EQ-5D-5L and WHODAS 2.0 questionnaires were dichotomized into no or mild problems/disability (score 1 or 2) and moderate to extreme problems/disability (score 3, 4 or 5). For the comparison of disability degree according to whether invasive mechanical ventilation (IMV) was used or not, and according to the period in which the follow-up assessment was performed (between day 30 and 44 or between day 45 and 90), we used the Mann-Whitney U test. *P*-values < 0.05 were considered significant.

RESULTS

Population characterization

A total of 93 adult critically ill patients infected with SARS-CoV-2 were admitted to the Intensive Care Medicine Department of Centro Hospitalar Universitário São João from the 11th of March to the 10th June 2020. Among the 86 patients that stayed in the Intensive Care Medicine Department for more than 24 hours, 46 (53.5%) were already home by the 15th of July and were eligible for this study, 23 died during hospital stay (26.7%) and 17 (19.8%) were still hospitalized (Fig. 1). One patient of the 46 survivors refused to participate in this study.

Demographic and clinical characteristics of survivors are detailed in Table 1. All enrolled patients were admitted with the diagnosis of SARS-CoV-2 pneumonia. Forty-one (91.1%) were supported with some type of mechanical ventilation. High flow nasal cannula (HFNC) was used in 20

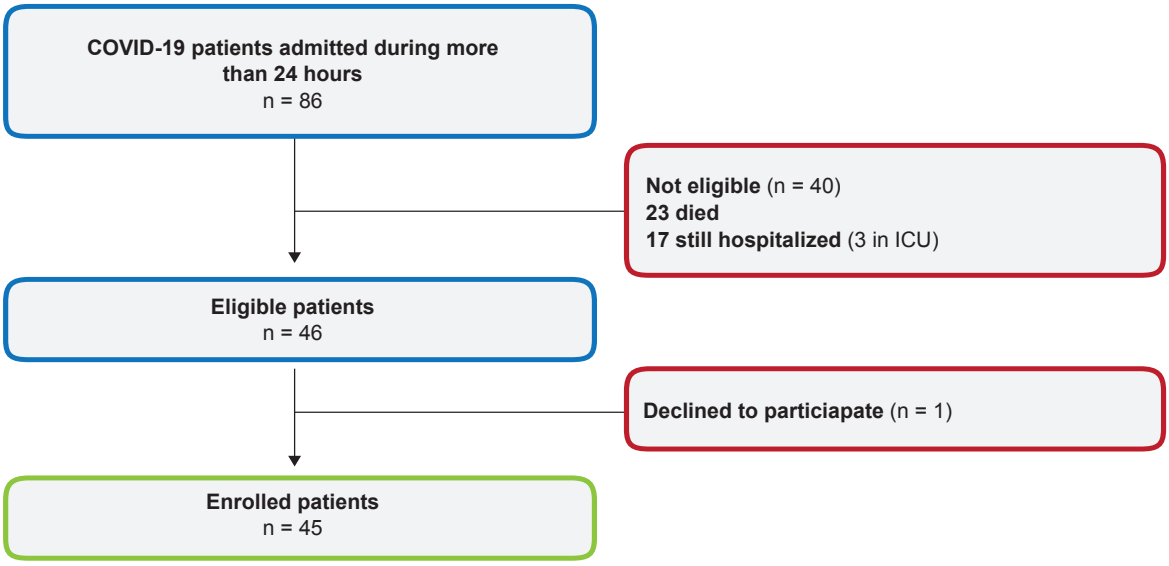

Figure 1 – Flow diagram of studied participants

Table 1 – Demographic and clinical characteristics of 45 COVID-19 survivors after critical illness

Demographic and clinical characteristics	All patients (n = 45)	IMV patients (n = 31)	No-IMV patients (n = 14)	*p* value
Age, years (IQR)	63 (55 - 73)	63 (49 - 73)	62 (59 - 74)	0.75
Male, n (%)	28 (62%)	20 (65%)	8 (57%)	0.64
First symptom to hospital admission, days (IQR)	6 (3 - 8)	6 (3 - 9)	4 (3 - 7)	0.48
Hypertension, n (%)	29 (64%)	22 (71%)	7 (50%)	0.19
Obesity, n (%)	18 (40%)	12 (39%)	6 (43%)	0.79
History of anxiety/depression, n (%)	16 (36%)	10 (32%)	6 (43%)	0.52
Known respiratory disease, n (%)	8 (18%)	5 (16%)	3 (21%)	0.69
Charlson Comorbidity Index, (IQR)	3 (0 - 4)	2 (0 - 4)	3 (2 - 4)	0.18
SAPS II Score (IQR)	36 (25 - 50)	36 (25 - 57)	30 (19 - 41)	0.14
APACHE II Score (IQR)	16 (12 - 22)	17 (13 - 23)	13 (10 - 17)	0.04
ICU length stay, days (IQR)	18 (6 - 25)	21 (15 - 33)	4 (3 - 6)	< 0.001
Hospital length of stay, days (IQR)	31 (15 - 38)	34 (23 - 42)	17 (15 - 27)	0.007
Mechanical ventilation, n (%) Invasive ventilation, n (%) High flow nasal cannula, n (%) Conventional non-invasive ventilation, n (%)	41 (91%) 31 (69%) 20 (44%) 14 (31%)	-	- - 7 (50%) 4 (29%)	-
ECMO, n (%)	6 (13%)	5 (16%)	1 (7%)	-
Continuous renal replacement therapy, n (%)	2 (4%)	2 (6%)	0	-

Results are expressed as n (%) or median (25th - 75th percentiles). IMV: invasive mechanical ventilation; SAPS Score: Simplified Acute Physiology Score II; APACHE II Score: Acute Physiology And Chronic Health Evaluation II; ICU: Intensive Care Unit; ECMO: extracorporeal membrane oxygenation.

patients (44.4%) for a median of 2.0 days (1.3-3.8) and 14 patients (31.1%) were supported with conventional non-invasive mechanical ventilation (NIV) for a median time of 1.0 days (1.0-2.0). Endotracheal intubation and IMV were performed in 31 (68.9%) and maintained for a median period of 18.0 days (11.0-26.0). These patients had a higher APACHE score and a longer ICU and hospital length of stay. Veno-venous Extracorporeal Membrane Oxygenation (ECMO) support was performed in 6 (13.3%), with a median duration of 15.0 days (11.0-18.3). Among 31 patients who underwent deep sedation, fentanyl perfusion (150 (100-200) mcg/h) was used in all of them for a median period of 14 days (8-22) and midazolam infusion (4 (2-6) mg/h) was used in 20 (44.4%) for a median period of eight (4-15) days. Dexmedetomidine was used in 27 patients (60.0%), mainly during the weaning process (96%), representing a sedative/anxiolysis strategy in 85% of patients with IMV, trying to avoid or control the expression of delirium in patients subjected to prolonged deep sedation. Delirium was described in eight patients (17.8%).

Quality of life and disability outcomes

Median time from discharge to follow-up assessment was 55.0 days (42.0-64.0).

Moderate to extreme problems (level ≥ 3) in some dimension of the EQ-5D-5L questionnaire were described in 29 patients (64.4%). The representation of moderate to extreme problems regarding the five dimensions was the following: mobility in six patients (13.3%), self-care in seven patients (13.3%), usual activities in 23 patients (51.1%), pain/discomfort in 14 patients (31.1%) and anxiety/depression in 17 (37.8%). The median EQ-VAS score was 75.0 (60.0 - 90.0).

In the 12-question WHODAS 2.0, 38 survivors (84.4%) reported moderate to extreme functionality impairments in at least one question. Moderate to extreme disability were mostly reported in the following questions: 19 (42.2%) in standing for long periods, 18 (40.0%) in walking a long distance, 17 (37.8%) in their day-to-day work/school responsibilities, 14 (31.1%) in taking care of their household responsibilities, 12 (26.7%) in joining community activities. Twenty-three (51.1%) assumed that they felt emotionally affected by their health problems and 12 of these 23 (52.2%) had no previous anxiety/depression disorders.

Moderate to extreme disability according to whether IMV was used or not, and according to the period in which the follow-up assessment was performed is represented in Table 2. Invasive mechanically ventilated patients reported significantly higher levels of disability in 3 questions of the WHODAS 2.0 questionnaire: standing for long periods (p = 0.04), walking a long distance (p = 0.02) and day-to-day work responsibilities (p = 0.02). There was no association between moderate to extreme disability and the period in which the follow-up assessment was performed.

Of the 19 survivors with an active professional life before hospital admission (42.2%), 15 (78.9%) were still on sick leave and only four (21.1%) had returned to their regular professional activities.

DISCUSSION

In the current case-series study of survivors of COVID-19 critical illness, performed one to three months after discharge, the incidence of moderate to extreme problems in health-related quality of life, assessed by the EQ-5D-5L instrument, was 64% and moderate to extreme disability, evaluated by the WHODAS 2.0 questionnaire, was observed in 84%.

In the scientific literature, one or more PICS related problems are described in 60% of critical illness survivors one year after intensive care admission.[6] Hodgson *et al* described moderate or severe disability six months after critical illness in 25% of survivors and its association with reduced health-related quality of life. They also found that prior history of anxiety/depression and a longer duration of mechanical ventilation were predictors of disability.[7]

The population of critical COVID-19 patients may be particularly prone to develop PICS. Firstly, because risk factors for developing PICS are part of the typical clinical profile of the COVID-19 critical patient.[8] In fact, out of 45 survivors, 62.2% were male, median age was 63.0 years and comorbidities were present in 86.7% of critical survivors, the most prevalent being hypertension (64.4%), followed by obesity (40.0%), anxiety/depression (35.6%) and previous pulmonary disorder (17.8%). Secondly, because median Intensive Care and hospital length of stay are usually long – respectively, 18.0 (6.0 - 25.0) and 31.0 days (14.5 - 37.5) in this population – and prolonged bed rest and extended hospital stay contribute to muscular weakness that is associated with substantial impairments in physical function and health-related quality of life that often persist beyond 24 months after critical illness.[14] Thirdly, because these patients often need prolonged deep sedation[15] and we also observed an unusually high sedation requirements in a large proportion of COVID-19 patients in our clinical practice, which could explain the significant use of midazolam perfusion (44.4%).

In the EQ-5D-5L questionnaire, applied 30 and 90 days after hospital discharge, the most affected dimension was usual activities (51.1% describing moderate to extreme problems), followed by anxiety/depression (37.8% with moderate to extreme problems) and pain/discomfort (31.1% with moderate to extreme problems). These findings are consistent with the results of a recent work from Belfast that highlighted a significant level of functional and psychological morbidity in COVID-19 patients post-intensive care admission where 61% had moderate to severe problems participating in previous activities, 45.2% had at least moderate impairment of mobility and 35.5% described at least moderate symptoms of anxiety/depression at the time of follow-up.[16]

Additionally, in the present study, the 12-question WHODAS 2.0 questionnaire showed that mobility, life activities and participation were the most affected domains: 42% with moderate to extreme difficulty in standing for long periods, 40% in walking a long distance, 37% in day-to-day work/school responsibilities, 31% in joining community activities and 51% emotionally affected by their health problems. The largest clinical follow-up study published with COVID-19 adult patients so far reported that 86% of patients supported with HFNC, NIV or IMV presented at least one symptom six months after symptom onset with an important impact of the critical disease in mobility and physical status: 81% presenting fatigue or muscle weakness and 29% with a distance walked in 6-min that was below the lower limit of the normal range.[9] In fact, we also found that IMV patients reported significantly higher levels of disability in the two questions of the WHODAS 2.0 questionnaire concerning mobility: standing for long periods (p = 0.04) and walking a long distance (p = 0.02).

Psychological impairments were also significant. This can be intrinsically associated with the impact of the pandemic on social isolation and less cognitive stimulation which may exacerbate symptoms of anxiety/depression.[17] An evaluation of self-reported clinical sequelae after hospital discharge of COVID-19 hospitalized patients from

Table 2 – Moderate to extreme disability in EQ-5D-5L and WHODAS 2.0

Parameter	Total (n = 45)	IMV (n = 31)	No IMV (n = 14)	*p* value	Follow-up between 30-44 days (n = 13)	Follow-up between 45-90 days (n = 32)	*p* value
EQ-5D-5L, moderate to extreme problems							
Mobility	6 (15.6%)	5 (16.1%)	1 (7.1%)	0.39	2 (15.4%)	4 (12.5%)	0.36
Self-care	6 (15.6%)	6 (19.4%)	0	0.11	3 (23.1%)	3 (9.4%)	0.62
Usual activities	23 (51.1%)	19 (61.3%)	4 (28.6%)	0.09	8 (61.5%)	15 (46.9%)	0.11
Pain and discomfort	14 (31.1%)	12 (38.7%)	2 (14.3%)	0.12	4 (30.8%)	10 (31.3%)	0.95
Anxiety and depression	17 (37.8%)	13 (41.9%)	4 (28.6%)	0.71	5 (38.5%)	12 (37.5%)	0.43
WHODAS 2.0, moderate to extreme difficulty							
Cognition							
Learning a new task	5 (11.1%)	3 (9.7%)	2 (14.3%)	0.43	1 (7.7%)	4 (12.5%)	0.36
Concentrating on doing something	4 (8.9%)	3 (9.7%)	1 (7.1%)	0.70	1 (7.7%)	3 (9.4%)	0.66
Mobility							
Standing for long periods	19 (42.2%)	15 (48.4%)	4 (28.6%)	0.04	6 (46.2%)	13 (40.6%)	0.39
Walking a long distance	18 (40.0%)	15 (48.4%)	3 (21.4%)	0.02	6 (46.2%)	12 (37.5%)	0.20
Self-care							
Washing their whole bod	6 (13.3%)	6 (19.4%)	0	0.13	3 (23.1%)	3 (9.4%)	0.20
Getting dressed	5 (11.1%)	5 (16.1%)	0	0.09	3 (23.1%)	2 (6.3%)	0.28
Getting along							
Dealing with people	5 (11.1%)	2 (6.5%)	3 (21.4%)	0.21	1 (7.7%)	4 (12.5%)	0.92
Maintaining a friendship	3 (6.7%)	1 (3.2%)	2 (14.3%)	0.61	0	3 (9.4%)	0.60
Life activities							
Taking care for responsibilities	14 (31.1%)	11 (35.5%)	3 (21.4%)	0.20	4 (30.8%)	10 (31.3%)	0.47
Day-to-day work responsibilities	17 (37.8%)	14 (45.2%)	3 (21.4%)	0.02	6 (46.2%)	11 (34.4%)	0.08
Participation							
Community activities	12 (26.7%)	10 (32.3%)	2 (14.3%)	0.06	4 (30.8%)	8 (25.0%)	0.65
Emotionally affected by health problems	23 (51.1%)	15 (48.4%)	8 (57.1%)	0.31	5 (38.5%)	18 (56.3%)	0.12

EQ-5D-5L – EuroQol five-dimension five-level questionnaire. WHODAS 2.0 – World Health Organization Disability Assessment Schedule 2.0, 12-question questionnaire. IMV – invasive mechanical ventilation

Renmin Hospital of Wuhan University (Wuhan, China) showed that 23% had psychosocial symptoms and 18% sleep disorders.[18] Regarding critical COVID-19, Huang C *et al* reported that 41% had pain/discomfort problems and 32% anxiety/depression in the Eq-5D-5D questionnaire,[9] which was similar to our results.

The global self-perception of quality of life was positive with a median EQ-VAS score of 75.0 (60.0-90.0), which was also similar to the results of Huang C *et al*.[9] The EQ-5D-5L questionnaire reflects the perception of patientsthat was evaluated during a pandemic period where a significant part of the world's population was in isolation, having few social interactions and engaging mostly in controlled outdoor activities, which may have influenced the survivors' perception of disability. In contrast, the WHODAS 2.0 questions are more objective in evaluating the disability degree and that may explain why we found significant differences regarding mobility domain between IMV and no-IMV patients. On the other hand, almost one third of patients we studied did not need deep sedation and invasive ventilation which may influence favorable disability results. Dexmedetomidine was used in 60% of the patients for avoidance or early control of agitation and has been associated with a reduction in the duration of mechanical ventilation, delirium, intensive care length of stay and incidence of PICS.[19]

As recognized in the literature, survivors of critical illness often present a delayed return to work, with approximately two-thirds remaining on sick leave up to three months following hospital discharge, two-fifths up to 12 months and one-third up to 60 months.[20] Among the 19 previously employed survivors who participated in this study, 15 (78.9%) were still on sick leave and only four (21.1%) had returned to regular work.

We acknowledge several limitations to our study. First, this is a single center retrospective study with a small population of severe COVID-19. Second, the follow-up evaluation period was heterogeneous, having occurred between the 30th and 90th day after hospital discharge. Third, the applied scales reflect patients perception about the degree of their disability. Fourth, disability was evaluated during a pandemic period and the lockdown may have led to an over estimation of quality of life by the patients themselves. However, we believe this study reflects new data about the importance of clinical focus on functional outcomes in COVID-19 critically ill patients and the importance of an organized post-critical illness response to these survivors.

CONCLUSION

Health-related quality of life and disability assessment in COVID-19 survivors must be a priority. Activities associated with outdoor practices and interpersonal interaction were the most affected patient-reported outcomes with an important impact in anxiety disorders. The EQ-5D-5L questionnaire reported the highest incidence of moderate to extreme problems in usual activities, anxiety/depression and pain/discomfort. The disability assessment using the WHODAS 2.0 questionnaire showed that mobility, life activities and participation were the most affected domains. An organized follow-up structure in Intensive Care Medicine Departments and the recognition of the main impairments inherent to this kind of patients has the potential to improve functional and health-related outcomes in COVID-19 survivors and their families.

AUTHORS CONTRIBUTION

JF: 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.

LF, IC, JAP: Contribution to the design and draft of the work. Analysis and interpretation of data. Critical review and final approval of the version to be published.

PROTECTION OF HUMAN SUBJECTS

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 issued by 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 no conflicts of interest to declare.

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