JIM Research Letter

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Long-term neuropsychiatric outcomes in COVID-19 survivors: A 1-year longitudinal study

Dear Editor,

Among the main concerns provoked by the coronavirus disease 2019 (COVID-19) pandemic is the potential morbidity in survivors. These sequelae can lead to a post-COVID-19 syndrome, also known as long-COVID [1,2]. The systemic manifestations of long-COVID are heterogeneous including cognitive and psychiatric issues leading to poor quality of life (QoL) [3–5]. However, little is known about long-term neuropsychiatric outcomes. Thus, we aimed to assess neurocognitive, psychiatric and QoL outcomes in a cohort of hospitalised COVID-19 survivors 1 year after hospital discharge.

Methods

This is an observational longitudinal study in a large tertiary care hospital in Valencia (Spain) with laboratory confirmed SARS-CoV-2 infection hospitalised patients between 8 March and 25 April 2020. Exclusion criteria included patients aged ≥85 or <18 years, non-Spanish speaking subjects, nursing-home residents, pre-existing dementia, pre-existing or cognitive decline under evaluation, previous brain injury with cognitive sequelae, current alcohol/substance use disorder (except for nicotine) and previously lifetime history of major psychiatric disorders. The Biomedical Research Ethics Committee of La Fe University and Polytechnic Hospital reviewed and approved the study (2020-280-1). All recruited patients were contacted by telephone 2 (±1) and 12 (±1) months after the date of hospital discharge. A battery of standardised instruments validated in the Spanish general population was administered by telephone at 2 and 12 months including (i) immediate verbal memory and learning, delayed verbal memory, semantic verbal fluency and working memory (executive function) for the cognitive functioning; (ii) subjective cognitive complaints; (iii) anxiety, depression and post-traumatic stress disorder (PTSD) for the psychiatric morbidity and (iv) QoL. Neurocognitive dysfunction was pre-defined as impairment in any of the four neuropsychological tests after adjusting for age and education level. Psychiatric morbidity was pre-defined as a positive screening in any of the three questionnaires assessing psychiatric morbidity. Additional information on standardised instruments is provided in the Supplemental file.

Results

A total of 179 patients at 2 months and 171 (95.5% retention rate) at 12 months completed the assessments. The results obtained at 2 months have been previously published [6]. Table 1 describes the main baseline characteristics. Briefly, participants' age ranged from 23 to 82 years and 99 (57.9%) were male. Of them, 94 (55%) had at least one comorbidity. Additional information on education, clinical severity, analytical parameters, respiratory support, treatments and clinical outcomes are provided on Table 1.

At 12 months, 73.7% of the patients had at least one persistent symptom according to a standardised symptom questionnaire, listed as follows: fatigue (48.5%), memory complaints (32.2%), arthromyalgia (26.9%), dyspnoea (25.7%), headache (15.8%), chest pain (7.6%), paraesthesia (7%), sputum production (7%), cough (5.3%), anosmia (5.3%), ageusia/dysgeusia (2.3%), fever (1.2%) and tremors (1.2%).

Twenty-four per cent of patients self-reported having some degree of impaired cognition according to the cognitive complaints' questionnaire (11.7% impaired memory function and 12.3% moderate or severe memory impairment), whilst 53.8% and 22.2% of patients had normal and optimal memory function, respectively. Neurocognitive dysfunction and psychiatric morbidity were found in 80 (46.8%) and 77 (45%) patients, respectively. The most affected cognitive domain was semantic verbal fluency (32.7%) followed by immediate verbal memory/learning (20.5%), working memory/executive function (12.3%) and delayed verbal memory (7.6%). The most prevalent psychiatric

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Table 1. *Patients data: demographic, comorbidity, clinical severity, treatment, analytical parameters, respiratory support and clinical outcomes*

	Total ($N = 171$)
Demographics	
Age,[a] year, median [1st, 3rd quartile]	58 [50, 68]
Male sex, No. (%)	99 (57.9)
Education, year, median [1st, 3rd quartile]	11 [8, 16]
Level of education, No. (%)	
None	2 (1.2)
Primary	53 (31)
Secondary	60 (35.1)
University	56 (32.7)
Smoking, No. (%)	
Never	118 (69)
Former	43 (25.1)
Current	10 (5.8)
Coexisting conditions, No. (%)	
Any	94 (55)
Arterial hypertension	55 (32.2)
Diabetes	25 (14.6)
Dyslipidaemia	47 (27.5)
Chronic heart disease	8 (4.7)
Chronic renal disease[b]	3 (1.8)
Chronic liver disease	3 (1.8)
Chronic respiratory disease	21 (12.3)
Cancer	3 (1.8)
Previous medication use, No. (%)	
Antiplatelets	6 (3.5)
Statins	36 (21.1)
ACE inhibitor	13 (7.6)
Angiotensin II-receptor antagonist	27 (15.8)
SpO_2/FiO_2 at admission, median [1st, 3rd quartile]	452.4 [442.9, 461.9]
Radiological data at admission, No. (%)	
Lung infiltrates	169 (98.8)
Bilateral infiltrates	115 (67.3)
Analytical parameters	
Peak LDH, UI/L, median [1st, 3rd quartile]	321 [258, 435]
Peak C-reactive protein, mg/L, median [1st, 3rd quartile]	95 [43.9, 169.1]
Nadir lymphocyte count, cells/ml, median [1st, 3rd quartile]	900 [640, 1250]
Peak D-dimer, ng/ml, median [1st, 3rd quartile]	962 [498, 2102]
Treatment, No. (%)	
Hydroxychloroquine	160 (93.6)
Azithromycin	158 (92.4)
Lopinavir/ritonavir	71 (41.5)
Interferon β	24 (14)
Tocilizumab	40 (23.4)
Baricitinib	17 (9.9)

(*Continued*)

Table 1. *Continued*

Corticosteroids	61 (35.7)
Remdesivir	0 (0)
Respiratory support, No. (%)[c]	
Room air	86 (50.3)
O_2 nasal cannula	18 (11.5)
O_2 venturi mask	37 (21.6)
HFNC/CPAP/NIV	8 (4.7)
MV	21 (12.3)
Median length of MV, days [1st, 3rd quartile]	13 [10, 30]
ECMO	1 (0.6)
Outcomes and complications[d]	
Length of hospital stay, days, median [1st, 3rd quartile]	12 [9, 18]
ICU admission, No. (%)[e]	32 (18.7)
Length of ICU stay, days, median [1st, 3rd quartile]	16.5 [11, 24]
Delirium, No. (%)	8 (4.7)
Cerebrovascular event, No. (%)	0 (0)
VTE, No. (%)	17 (9.9)
Acute kidney injury, No. (%)[f]	9 (5.3)
Acute liver injury, No (%)[g]	56 (32.7)

Note: Data are summarised as No. (%) or median [1st, 3rd quartile], as appropriate.
Abbreviation: ACE, angiotensin-converting enzyme; ECMO, extracorporeal membrane oxygenation; HFNC/CPAP/NIV, high-flow nasal cannula/continuous positive airway pressure/non-invasive ventilation; ICU, intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen; VTE, venous thromboembolic event.
[a]Age at the time of battery administration 12 months after hospital discharge.
[b]Stage ≥2.
[c]Maximum respiratory support needed during hospital stay.
[d]Complications were considered until the date of the interview administration.
[e]Need for ICU admission at any time during hospitalisation.
[f]At least twofold increase of baseline serum creatinine or ≥50% decrease in baseline glomerular filtration rate.
[g]Elevation of alanine transaminase and/or aspartate transaminase enzymes > 2× the upper limit of normal.

morbidity was anxiety (35.1%) followed by depression (32.2%) and PTSD (24.6%). Poor QoL was found in 68 (39.8%) and 57 (33.3%) patients for the physical and mental component summary, respectively.

Discussion

This is the first longitudinal study to simultaneously evaluate cognitive, psychiatric and QoL domains and COVID-19 long-lasting attributable symptoms in survivors in the long term. Before the COVID-19 pandemic, mental and cognitive problems had been reported in intensive care unit survivors from different causes [7,8]. Nevertheless, these problems in non-critical care patients are underdiagnosed and their long-term prevalence in COVID-19 is unknown. We found 46.8% of patients with cognitive impairment and 45% with psychiatric morbidity at 1 year. Brain fog or long-COVID causes are to elucidate and might comprise inflammation, endothelial damage, autoimmunity, social stressors and others [9]. These results further support the long-lasting impact of COVID-19 on patients' QoL and health, specifically brain/mental health. Limitations of the study include the single-centre design, the lack of data on neuropsychiatric outcomes previous to COVID-19 and on functions other than cognitive or psychiatric comorbidity [10].

In summary, declined cognitive function, psychiatric morbidity and low QoL are prevalent in moderate to severe COVID-19 survivors 1 year

after hospital discharge. These data await confirmation by further prospective studies in other regions. Meanwhile, health policies should be designed to address these long-term problems. A multidisciplinary approach that includes neurocognitive rehabilitation and psychiatric evaluation and treatments should be offered to indicated patients.

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Conflict of interest

The authors declare no conflict of interest.

Ethics statement

This study was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe (2020-280-1).

Consent for publication

All authors have accepted the publication of the manuscript.

Author contributions

Conceptualisation and study design: R. Méndez, V. Balanzá-Martínez, S.C. Luperdi and Rosario Menéndez. Patient enrolment and database management: R. Méndez, P. González-Jiménez, Ana Latorre, Leyre Bouzas, Katheryn Yépez, Ana Ferrando and Soledad Reyes. Telephone interviews: I. Estrada. Drafting the manuscript: R. Méndez. Assistance in drafting the manuscript and critical review: V. Balanzá-Martínez, S.C. Luperdi and R. Menéndez. Revision of manuscript and approval of the final version: all authors. R. Méndez and R. Menéndez are the guarantors.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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