Neuropsychological functioning in post-ICU patients after severe COVID-19 infection: The role of cognitive reserve

Ana Costas-Carrera a,*, Marta Mónica Sánchez-Rodríguez a, Silvia Cañizares a, Antonio Ojeda b, Inés Martín-Villalba a, Mireia Primé-Tous a, Manuel Arturo Rodríguez-Rey a, Xavier Segúa a, Francisco Valdesiro-Pulido a, Roger Borras a, Josep Maria Peri a, Eduard Vieta a,c,d,e

a Neuroscience Institute, Hospital Clinic, Barcelona, Spain
b Anaesthesiology Reanimation and Pain Therapy, Hospital Clinic, Barcelona, Spain
c Institute of Biomedical Research Agustí Pi i Sunyer (IDIBAPS), Barcelona, Spain
d Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
e School of Medicine, University of Barcelona, Barcelona, Catalonia, Spain

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ABSTRACT

Background: Cognitive manifestations associated with Severe Acute Respiratory Syndrome by Coronavirus 2 (SARS-CoV-2) are yet to be described in the existing literature. The aim of this exploratory study is to analyze the impact of severe SARS-CoV-2 infection on neuropsychological performance 6 months following hospital discharge, and to identify which medical variables predict worse outcome. In this context, we study if cognitive reserve (CR) may play a protective role on cognitive impairment.

Methods: We enrolled a cohort of 102 severe SARS-CoV-2 survivors who had been admitted to the Intensive Care Unit (ICU) and were contacted 6-months post discharge. A total of 58 agreed to participate in this 6-month follow-up study. Patients with previously known cognitive impairment were excluded. Demographic, clinical and laboratory data were collected. Firstly, to test the magnitude of neurocognitive sequelae two standard deviations below normative group were considered. Secondly, to analyze the main effects of medical variables on cognition and the interaction with cognitive reserve, ANCOVA analyses were performed.

Results: 53.4% obtained a score below the cutoff point (<26) in the screening test MOCA. ICU variables including mechanical ventilation, days of sedation or high CRP days were related with cognition. Cognitive Reserve (CR) interacted with delirium (F = 6.8, p = 0.01) and sedation days (F = 9.40, p = 0.003) to predict verbal memory and interacted with high CRP to predict phonemic fluency (F = 6.47, p = 0.01). Finally, no differences in neuropsychological performance were found depending on subjective cognitive impairment (SCI). However, patients with SCI had a higher score in the HAD anxiety subscale (t = −2.2; p < 0.05).

Conclusions: In our cohort, cognitive dysfunction was related with ICU variables such as delirium, mechanical ventilation, and inflammation. CR modulated the impact of these variables on cognition. Cognitive complaints were related with anxiety but not with cognitive performance. Despite some limitations, including the need of replication of the findings with larger samples and control groups, our study suggests that high CR may be protective for severe COVID-19-related cognitive impairment.

1. Introduction

The disease resulting from the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), commonly known as COVID-19, has become a global pandemic causing a worldwide public health crisis. Symptoms of the disease include Acute Respiratory Distress Syndrome (ARDS), but also cardiac, renal, hematological, intestinal, and neurological problems (Wadman et al., 2020). Approximately 34% of patients with COVID-19 have presented neurological or psychiatric diagnosis in the following 6 months, and for those admitted to an ICU the estimated incidence of a diagnosis increased to 46% (Taquet et al., 2021). Hyperinflammatory response called “cytokine storm” has been related to neurological symptoms and to an increased risk for neurodegenerative diseases (Serrano-Castro et al., 2020).

* Corresponding author. Hospital Clínic de Barcelona. Neuroscience Institute. Clinical Health Psychology Section. C/ Rosselló, 140, 08036, Barcelona, Spain. E-mail address: anacostasca@gmail.com (A. Costas-Carrera).
Among the neurological alterations described are fatigue, dizziness, vertigo, anosmia, seizures, stroke, myopathies, encephahtis, and Guillain-Barre syndrome (Khatoon et al., 2020). Neuropsychiatric and neuropsychological symptoms have also been reported (Rogers et al., 2020; Llach and Vieta, 2021). In longitudinal studies, COVID-19 patients showed more cognitive decline than controls and this effect was higher in severe cases (Liu et al., 2021). Moreover, SARS-CoV-2 symptoms were associated with neuropsychological correlates (Ramani et al., 2020; Xu et al., 2020; Mattioli et al., 2021).

The cognitive manifestations of COVID-19 have been explained by different mechanisms, including the direct effect of the virus in the Central Nervous System (CNS) via the olfactory bulb (Guedj et al., 2021), neuroinflammation, systemic infection, and prolonged hypoxia (Steardo et al., 2020; Miskowiak et al., 2021). Patients with severe COVID-19 admitted to ICU are also at risk of developing post-intensive care syndrome (PICS), characterized by physical, cognitive, and psychological alterations (Inoue et al., 2019). PICS increases the risk of long-term cognitive impairment in roughly 6–51% of post-ICU patients (Collet et al., 2021). Moreover, delirium is one of the main factors related with cognitive impairment (Kotits et al., 2020) and was one of the most frequent behavioral manifestations of COVID-19 in up to 11% of all associated hospitalizations (Steardo et al., 2020).

Studies published thus far have demonstrated varying degrees of cognitive impairment in patients with severe SARS-CoV-2 manifestations (Kotits et al., 2020; Helms et al., 2020; Negrini et al., 2020). Sustained attention (Filatov et al., 2020; Zhou et al., 2020), processing speed, verbal memory (Almeria et al., 2020; Mazza et al., 2021), language (Beaud et al., 2020) and executive function (Beach et al., 2020; Zhou et al., 2020; Almeria et al., 2021) were the most affected. Regarding the clinical variables related to cognitive impairment; the number of days admitted to ICU (Negrini et al., 2020), presence of delirium (Beaud et al., 2020), oxygen therapy (Almeria et al., 2020), systemic inflammation at baseline (Mazza et al., 2021), neurological symptoms (like headache, anosmia or dysgeusia) (Almeria et al., 2020) or psychiatric symptoms (Filatov et al., 2020; Mazza et al., 2021; Mattioli et al., 2021) have been described as risk factors in COVID-19 patients.

Previous studies have focused on risk factors for cognitive impairment in post-COVID patients. However, the role of protective factors on cognition is understudied in this population. Cognitive Reserve (CR) is a construct which refers to the plasticity of the brain and is related to factors such as lifestyle, educational or intellectual level (Stern et al., 2012). CR is a protective factor for the risk of developing dementia (Valenzuela et al., 2006; Cheng et al., 2016), a predictor of better cognitive functioning in patients with psychiatric disorders (Amoretti et al., 2021; Forcada et al., 2015; Grande et al., 2016) and less risk of cognitive impairment after ICU discharge (Fernández-Gonzalo et al., 2020). Nevertheless, to our knowledge the possible protective effect of CR on patients who survived SARS-CoV-2 infection has not been studied yet.

As such the aim of this study is to address this gap in the literature in order to make more conclusive remarks regarding the role of CR in survivors of SARS-CoV-2. Based on previous clinical observations, we expect that patients who developed a serious form of SARS-CoV-2 infection and required ICU admission present some form of cognitive impairment 6 months after hospital discharge. A 6 month period was considered necessary in order to avoid the effect of other possible confounding factors which could interfere with cognition in the early post-ICU phase after hospital discharge. Moreover, we hypothesize that CR has a protective role on the negative effects of clinical severity variables on cognition.

Our main aims are:

1) To study the neuropsychological function in severe SARS-CoV-2 patients admitted to ICU services at 6-month after hospital discharge.

2) To analyze the relationship between cognitive performance and ICU severity variables that were described as potential risk factors for cognitive impairment.

3) To study the role of CR as a protective factor on the impact of SARS-CoV-2 on cognition.

2. Material and methods

2.1. Study design and participants

This is a prospective cohort study developed in a tertiary university hospital. We included adult patients who were admitted to the Intensive Care Unit (ICU) for SARS-CoV-2 infection from April to December 2020. From an initial cohort of 102 COVID-19 survivors that were evaluated one-month follow-up after hospital discharge by the PAIN-COVID protocol (see Ojeda et al., 2021); 58 COVID-19 survivors agreed to participate in our study and were assessed 6 months after hospital discharge (see Flowchart 1).

Adult patients were enrolled if they had SARS-CoV-2 infection, confirmed with a respiratory tract sample using PCR-based tests and they fulfill at least one of the following inclusion criteria: 1) had an Acute Physiology and Chronic Health Evaluation (APACHE II) score over 14, 2) ICU stay over 10 days, 3) acquired weakness in ICU, 4) Delirium during ICU and acceptance to participate in the study by signing the informed consent form. The exclusion criteria were: 1) patients with non-confirmed SARS-CoV-2 infection according to WHO guidance, 2) previous diagnosis of cognitive impairment or Central Nervous System diseases, 3) terminal illness, 4) insufficient understanding of the Spanish language, 5) patients with whom it would be difficult to complete follow-up, 6) not willing to sign the informed consent form.

The local ethical committee approved the study protocol in accordance with the principles in the Declaration of Helsinki – approval number: HCB/2020/1194. Written informed consent was obtained from all participants.

2.2. Clinical and neuropsychological assessment

Demographic data were collected at Baseline Visit (4–6 weeks after hospital discharge); including age, gender, socio-cultural and socioeconomic status, work status and marital status. Barthel and Charlson indices and medical history were also recorded. The Barthel index (BI) is a measure of previous functional status and predicts healthcare outcomes, such as length of stay or in-hospital mortality (Ocagli et al., 2021). The Charlson comorbidity index (CCI) is a method of estimating the risk of death from comorbid disease and it is related with poor outcomes in COVID-19 patients (Kuswardhani et al., 2020).

The following data regarding ICU and hospital admission were also collected: Acute Physiology and Chronic Health disease Classification System (APACHE II) and Sequential Organ Failure Assessment Score (SOFA) severity scores, days under mechanical ventilation, presence of sepsis, days under sedation, delirium presence, maximum value of ferritin, d-dimer and C reactive protein, and ICU and hospital length of stay.

A validated self-report questionnaire, the Hospital Anxiety and Depression Scale (HADS), was used to assess psychopathology. Generally accepted standard cut-off scores were used to consider the presence of psychopathology in each subscale score (HADS ≥ 8).

To assess neurocognitive function, a set of subtests was selected to create a neuropsychological battery specific designed for this population. The battery included: The Montreal Cognitive Assessment (MOCA) screening test, Digit Span Forward (DSF) and Backward (DSB) and Vocabulary from Wechsler Adult Intelligence Scale– III (WAIS-III), The Stroop Test, The Free and Cued Selective Reminding Test (FCSRT), The Benton Judgment of Line Orientation (JLO), The Trail Making Test (TMT), The Controlled Oral Word Association Test (COWAT), The Animal Fluency Test (ANF) and The Boston Naming Test (BNT).
For each test, to normalize data correcting the effects of the subjects’ age, education, and providing a better compliance with the Normal Distribution.

All the assessments were performed 6 months from hospital discharge by trained clinical psychologists and explorations lasted approximately 60 min.

2.3. Statistical analysis

Descriptive statistics were calculated for each demographic, medical, clinical and neuropsychological variable. Continuous variables are presented as the mean ± standard deviation and as the median ± interquartile range when variables are not normally distributed. To compare these variables, we used the Student’s t-test or Mann-Whitney U test as appropriate. Categorical variables were expressed as total number (percentages) and compared between groups using Chi-square test.

The primary outcome was the magnitude of neurocognitive sequelae. The proportion of subjects with a score 2 SD under the population mean was calculated for each test score. Secondly, to examine the relationship between cognitive performance and measures of illness severity, negative affect, subjective cognitive impairment and demographic variables we performed correlation analyses. To test if clinical variables predicted the

| Table 1 |
| Demographical and clinical variables | Whole sample | Sex | t or U | p |
| Characteristics | (n = 56) | Male (n = 41) | Female (n = 17) | |
| Continuum variables | | | | |
| Age | 67 ± 9.1 | 64.80 ± 9.85 | 65.59 ± 8.14 | -0.28 | 0.774 |
| CRQ | 15 (10.75–18) | 14.73 ± 4.47 | 13 ± 4.56 | 272.5 | 0.193 |
| BMI | 27.93 ± 4.86 | 26 [24–30.4] | 29.38 ± 6.66 | -1.26 | 0.214 |
| Charlson Index | 3 [1–3] | 3 [1.5–4] | 2 [1–3] | 260.5 | 0.373 |
| Barthel Index | 100 (95–100) | 100 [95–100] | 95 [90–100] | 237.5 | 0.134 |
| APACHE II | 12.47 ± 4.74 | 12.73 ± 4.60 | 11.80 ± 5.19 | 0.64 | 0.525 |
| SOFA | 5 [4–7] | 4.5 [3.25–7] | 6.27 ± 2.37 | 380 | 0.126 |
| Ferritin | 1982.5 [1409–2902.25] | 2125 [1454–2983] | 2140.04 ± 1622.88 | 247 | 0.263 |
| D-Dimer | 6400 [3700–10000] | 7300 [3175–10000] | 6620 ± 3159.83 | 307.5 | 0.962 |
| Hospitalization days | 41.11 ± 17.93 | 39.85 ± 18.61 | 44.53 ± 16.03 | -0.86 | 0.392 |
| ICU days | 26.38 ± 14.21 | 25.17 ± 14.69 | 29.67 ± 12.33 | -1.01 | 0.299 |
| Mechanical ventilation days | 15 [8.5–20.5] | 14.35 ± 10.71 | 15 [12–21] | 205 | 0.277 |
| N° days of high CRP | 8 [5–17] | 8 [5–17] | 10.67 ± 7.25 | 292 | 0.774 |
| HAD anxiety | 4 [2–6] | 3.5 [1.25–6] | 5 [3–8] | 326.5 | 0.240 |
| HAD depression | 3 [1–4] | 3 [1–3.75] | 4 [2–5] | 305 | 0.464 |
| Categorical variables | | | | |
| Education level | | | | |
| - Primary level | 5 (8.6%) | 2 (4.9%) | 3 (17.6%) | 5.15 | 0.161 |
| - Secondary level | 12 (21%) | 9 (22%) | 3 (17.6%) | | |
| - Graduate/Postgraduate level | 40 (69%) | 30(73.2%) | 10 (58.8%) | | |
| - Unknown | 1 (1.4%) | | | |
| Employment status | | | | |
| - Employed | 10 (17.2%) | 8 (19.5%) | 2 (11.8%) | 6.04 | 0.196 |
| - Unemployed | 1 (1.7%) | 1 (5.9%) | | | |
| - Retired | 26 (44.8%) | 20 (48.8%) | 6 (35.3%) | | |
| - Sick leave | 20 (34.5%) | 13 (31.7%) | 7 (41.2%) | | |
| Civil Status | | | | |
| - Marriage | 39 (67.2%) | 33 (80.5%) | 6 (35.3%) | 12.93 | 0.005 |
| - Unmarried | 11 (19%) | 4 (9.8%) | 7 (41.2%) | | |
| - Widow | 7 (12.1%) | 4 (9.8%) | 3 (17.6%) | | |
| Tobacco consumption | | | | |
| - No | 36 (62.1%) | 22 (53.7%) | 14 (82.4%) | 5.60 | 0.061 |
| - Yes | 20 (34.5) | 18 (43.9%) | 2 (11.8%) | | |
| Psychiatric history | | | | |
| - Yes | 9 (15.5%) | 4 (9.8%) | 5 (29.4%) | 9.28 | 0.01 |
| - No | 47 (81%) | 37 (90.2%) | 10 (58.8%) | | |
| Sepsis | | | | |
| - Yes | 36 (62.1%) | 23 (56.1%) | 13 (76.5%) | 4.47 | 0.034 |
| - No | 20 (34.5%) | 18 (43.9%) | 2 (11.8%) | | |
| Delirium | | | | |
| - Yes | 22 (37.9%) | 16 (39%) | 6 (35.3%) | 0.004 | 0.947 |
| - No | 34 (58.6%) | 25 (61%) | 9 (52.9%) | | |
| Hypoxemia maintained >24 h | | | | |
| - Yes | 43 (74.1%) | 30 (73.2%) | 13 (76.5%) | 1.12 | 0.289 |
| - No | 13 (22.4%) | 11 (26.8%) | 2 (11.8%) | | |
| SCI after COVID-19 infection | | | | |
| - None | 32 (55.2%) | 27 (65.9%) | 5 (29.4%) | 7.47 | 0.024 |
| - Slightly | 22 (37.9%) | 11 (26.8%) | 11 (64.7%) | | 

Abbreviations: CRC, Cognitive Reserve Questionnaire; BMI, Body Mass Index; AHT, Arterial Hypertension; APACHE-II, Acute Physiology and Chronic Health disease Classification System II; SOFA, Sepsis related Organ Failure Assessment; ICU, Intensive Care Unit; CRP, C-Reactive Protein; HAD, Hospital Anxiety and Depression Scale; SCI, Subjective Cognitive Impairment.
neuropsychological function regression analyses were conducted. We selected those cognitive variables expected to be more impaired according to previous studies.

Finally, ANCOVA analyses were used to test the effect of interaction between medical variables and cognitive reserve on neurocognitive performance. In all analyses we controlled the effect of age, sex and previous health status (Charlson Index). Scores of CR were classified in two groups (High CR ≥ 10 or Low CR < 10).

Statistical analyses were performed using R version 4.1.1. CRAN. Oficina de software libre (CIXUG). Spanish National Research Network. http://cran.es.r-project.org/

3. Results

3.1. Demographic and clinical variables

A total of fifty-eight patients were included in the study (29% women, mean age 65 ± 9.32; range age from 37 to 81). The six-month follow-up cohort did not differ from the drop-out group in terms of sociodemographic characteristics and clinical severity. Their demographic and clinical characteristics are described in Table 1.

Most patients had higher education (69%), were retired (45%) and were married (67%). They were mostly functionally independent before the admission in ICU services (BI mean: 95.62 ± 8.26), had low comorbidity (CCI mean 2.55 ± 1.6), were overweight (mean 27.93 ± 4.8), AHT (46%) and didn’t smoke (62%). The mean of ICU stay days was 26.38 ± 14.10 and mean hospitalization days 41.11 ± 17.93. Most of them developed sepsis (62%), sustained hypoxia (74%) and required mechanical ventilation (74%), while 38% presented delirium during ICU admission.

Laboratory findings didn’t find gender differences in ferritin or D-Dimer, but said differences were observed in sepsis ($\chi^2 = 4.47, p = 0.034$), with high prevalence for women (76.5% vs. 56.1% in men).

When patients were asked about cognitive complaints after hospital discharge, 84% denied cognitive complaints before COVID-19 infection, whereas almost 50% referred some type of cognitive complaint after the hospitalization. Women tended to report more cognitive complaints (70.6% vs 34.1% in men) and to have more psychiatric comorbidity (29.4% vs. 9.8% in men).

3.2. Neuropsychological functioning in post-ICU patients after COVID-19

More than half of sample (53.4%) obtained a score below the cutoff point (<26) for normal performance in the screening test MOCA and 19% below of the cutoff for mild cognitive impairment (see Table 2).

When the battery tests were analyzed with normative data ($Z$ scores), pathological scores ($Z < -2$) were seen in Stroop Word ($7.12.7$%), Stroop Color ($9.16.7$%), Stroop Interference ($1.19$%), TMT-A ($1.17$%), TMT-B ($1.17$%), Phonemic fluency ($3.5.2$%), FCSRT FR1 ($1.18$%), FCSRT FR total ($1.18$%), FCSRT Total ($2.3.6$%), FCSRT FR delay ($2.3.6$), FCSRT Total delay ($3.5.4$%), JLO ($2.3.5$%).

No differences in neuropsychological performance were found between patients expressing cognitive complaints after COVID-19 infection in comparison to patients who didn’t. However, there were differences between those groups in HADS anxiety subscale ($t = -2.2; p < 0.05$) but not in HADS depression subscale ($t = -0.8; p = 0.4$).

3.3. Relationship between neuropsychological and clinical variables

Results of regression analyses showed that most clinical variables had no significant direct effects on neuropsychological variables (see Table 3).

Days of mechanical ventilation were related with lower FCSRT total score ($\beta = -0.31, p = 0.02$) and Stroop interference score ($\beta = 0.3, p = 0.05$), days of sedation were related to lower FCSRT total score ($\beta = -0.40, p < 0.005$), lower FCSRT delayed score ($\beta = -0.29, p = 0.03$) and more Stroop interference score ($\beta = 0.31, p = 0.04$). On the other hand, ICU days and high PCR days were related with more Stroop interference score ($\beta = 0.4 p < 0.005; \beta = 0.33, p = 0.02$).

3.4. Role of cognitive reserve (CR)

The interaction effects between CR and ICU variables are described in Table 4.

CR interacted with delirium in FCSRT total ($F = 6.8, p = 0.01$) and FCSRT total delay ($F = 7.63, p = 0.01$) performance in a way that those with low CR who suffer delirium obtained the worst performance (see Fig. 1). A similar finding occurred with the interaction between CR and Stroop interference ($F = 6.87, p = 0.01$), in which those with low CR and delirium obtained the worst performance.

The number of sedation days also interacted with CR in FCSRT total delay ($F = 9.40, p = 0.003$), with a poorer performance in those with low CR and a high number of sedation days.

Finally, the number of days with high PCR interacted with CR in phonemic fluency ($F = 6.47, p = 0.01$) with worse performance in patients with low CR and more days with high PCR during ICU stay (see Fig. 2).

4. Discussion

This is the first study to prospectively investigate the neurocognitive sequelae in post-ICU COVID-19 survivors and the role of cognitive reserve as a protective factor.

We found the SARS-CoV-2 infection profile to be consistent with that described in general population. Contrary to other studies (Almeria et al., 2020), we didn’t find differences between sexes in levels of ferritin or D-dimer but sex differences were found in sepsis. Additionally, women had more psychiatric comorbidity and tended to refer more cognitive complaints.

According to the literature (Negrini et al., 2020), some type of cognitive sequelae is common, with 19% of the total sample performance below the cutoff for mild cognitive impairment in the screening test. Besides verbal memory, speed processing and executive function were the most affected domains, coinciding with findings from similar studies (Kotlis et al., 2020).

The number of days admitted to the ICU did not predict cognitive decline as demonstrated in the literature (Reaud et al., 2020), but mechanical ventilation predicted worse verbal memory function. This finding is similar to other studies that suggested oxygen therapy could be...
explained by the continuous hypoxia caused by pulmonary disease related COVID-19 infection (Almeria et al., 2020). Hypoxia is a potential risk factor for brain damage, especially in limbic regions like the hippocampus. The hippocampal CA3 neurons are particularly susceptible to hypoxic damage (Biswal et al., 2016) and this area is related with episodic memory (Zammit et al., 2017). While CA2, CA3 and dentate gyrus are involved in encoding, CA1 and subiculum are responsible for retrieval (Eldridge et al., 2021). Taking into account hypoxia and ARDS are core symptoms in COVID-19 infection, it seems plausible to consider them as risk factors for memory impairment in these patients.

Other ICU variables such as the presence of delirium or days of sedation also predicted worse memory performance. Although sedation was described as a potential risk factor for cognitive impairment after ICU discharge (Inoue et al., 2019); delirium at ICU seems to be the most important predictor variable for long-term cognitive impairment (Collet et al., 2013; Inoue et al., 2019), delirium in the ICU isocortex. The hippocampal CA3 neurons are particularly susceptible to risk factor for brain damage, especially in limbic regions like the hippocampus. The hippocampal CA3 neurons are particularly susceptible to hypoxic damage (Biswal et al., 2016) and this area is related with episodic memory (Zammit et al., 2017). While CA2, CA3 and dentate gyrus are involved in encoding, CA1 and subiculum are responsible for retrieval (Eldridge et al., 2021). Taking into account hypoxia and ARDS are core symptoms in COVID-19 infection, it seems plausible to consider them as risk factors for memory impairment in these patients.

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Table 4
Interaction effect between CR and ICU variables.

|                | CR1 Delirium | CR1 No Delirium | CR2 Delirium | CR2 No Delirium | Group | CR | GroupXCR |
|----------------|--------------|-----------------|--------------|-----------------|-------|----|----------|
|                | Mean (IC 95%) | Mean (IC 95%)   | Mean (IC 95%) | Mean (IC 95%)   | F    | p  |         |
| Verbal Memory  |              |                 |              |                 |       |    |         |
| FCSRT total    | 43.1 (40.8-45.4) | 44.6 (42.7-46.5) | 28.2 (23.5-32.9) | 38.2 (34.2-42.2) | 5.62 | 0.02 | <0.001 |
| FCSRT total delay | 14.78 (13.66-15.9) | 15.09 (14.16-16.5) | 7.52 (5.25-9.8) | 12.23 (10.29-14.2) | 3.09 | 0.08 | <0.001 |
| Processing Speed |              |                 |              |                 | 29.37 | 0.001 |         |
| SCWT W         | 107.9 (98.9-117) | 101 (93.5-108) | 89.4 (68.6-110) | 90.1 (73.1-110) | 1.45 | 0.23 | 0.29 |
| Language       |              |                 |              |                 |       |    |         |
| BNT            | 53.4 (50.8-56) | 54.9 (52.8-57) | 44.7 (39.5-49.9) | 48.2 (44.1-52.3) | 1.43 | 0.23 | 0.16 |
| Executive function |          |                 |              |                 |       |    |         |
| TMT-B          | 99.2 (48.1-150) | 122.1 (79.7-164) | 209 (105.6-312) | 247.5 (159.4-336) | 0.94 | 0.33 | 0.003 |
| Sepsis         | Mean (IC 95%) | No Sepsis       | Mean (IC 95%) | No Sepsis       | F    | p  |         |
|                |              |                 |              |                 |       |    |         |
| Verbal Memory  |              |                 |              |                 |       |    |         |
| FCSRT total    | 25.2 (23.7-27.3) | 26.2 (22.9-29.6) | 19 (14.24-1) | 17.2 (11.4-22.9) | 0.42 | 0.51 | 26.38 |
| FCSRT total delay | 9.84 (8.94-10.73) | 10.08 (8.71-11.44) | 6.41 (4.34-8.47) | 6.82 (4.46-9.17) | 0.16 | 0.68 | 23.78 |
| Processing Speed |              |                 |              |                 |       |    |         |
| SCWT P         | 103.4 (96.6-110.2) | 105.7 (95.2-116.2) | 79.4 (60.1-98.7) | 98.4 (80.3-116.5) | 1.46 | 0.15 | 0.72 |
| Language       |              |                 |              |                 |       |    |         |
| BNT            | 54.6 (52.6-56.6) | 53.2 (50.2-56.3) | 48.2 (43.6-52.8) | 45.5 (40.7-50.2) | 2.69 | 0.10 | 13.79 |
| Executive function |          |                 |              |                 |       |    |         |
| TMT-B          | 101 (62.2-140) | 147 (88.1-206) | 219 (130.1-308) | 252 (149.8-353) | 3.37 | 0.07 | 8.35 |
| Sepsis         | Mean (IC 95%) | No Sepsis       | Mean (IC 95%) | No Sepsis       | F    | p  |         |
|                |              |                 |              |                 |       |    |         |
| Days in ICU    | Mean (IC 95%) | Mean (IC 95%)   | Mean (IC 95%) | Mean (IC 95%)   | F    | p  |         |
| MV days        | Mean (IC 95%) | Mean (IC 95%)   | Mean (IC 95%) | Mean (IC 95%)   | F    | p  |         |
| Verbal Memory  |              |                 |              |                 |       |    |         |
| FCSRT total    | 43.8 (42.4-45.6) | 34.8 (31.3-38.4) | 8.29 | 0.006 | 20.38 | <0.001 | 0.03 |
| FCSRT total delay | 15 (14.1-15.9) | 10.7 (8.3-12.5) | 2.96 | 0.09 | 19.36 | <0.001 | 2.40 |
| Processing Speed |              |                 |              |                 |       |    |         |
| SCWT P         | 103.3 (96.9-110) | 88.4 (74.3-102) | 0.92 | 0.34 | 3.59 | 0.06 | 0.37 |
| Language       |              |                 |              |                 |       |    |         |
| BNT            | 54.3 (52.4-56.2) | 48.4 (44.7-52.2) | 0.28 | 0.59 | 8.46 | 0.005 | 1.64 |
| Executive function |          |                 |              |                 |       |    |         |
| TMT-B          | 113 (74.8-152) | 238 (160.9-315) | 0.45 | 0.50 | 8.31 | 0.006 | 0.99 |
| Phonic Fluency | 37.7 (33.85-41.6) | 16.3 (8.65-24) | 0.72 | 0.39 | 24.15 | <0.001 | 0.17 |
| SCWT interference | 2.50 (0.27-5.28) | 0.84 (6.99-5.23) | 3.71 | 0.06 | 0.97 | 0.32 | 0.05 |

(continued on next page)
admission, delirium, etc.). For this purpose, comparing severe COVID-19 patients admitted to ICU services with control groups admitted in ICU by other causes is necessary. Moreover, including a larger sample size would allow capturing the heterogeneity of CR in the population and improving understanding of how CR can be a protective factor of the effect of SARS-CoV-2 on cognition. Furthermore, psychological variables like anxiety and depression can be related with cognitive complaints in these patients and could explain some of the functional difficulties found in some cases. Therefore, to explore the psychological status of these patients is as important as exploring their cognitive or physical status.

Furthermore, a long-term follow-up of these patients is necessary to determine the extent of the deficits caused by the COVID-19 and whether this population could have an increased risk for neurodegenerative diseases as some researchers have suggested.

Finally, a future line of investigation could be the study of cognitive protector factors for severe COVID-19 patients and other severe patients who required ICU admission. Therefore, interventions to promote cognitive reserve in the community and cognitive stimulation respectively as primary and secondary prevention actions for severe COVID-19 patients could reduce the taxes of cognitive impairment in this population, as well as the long-term health and economic consequences of this illness.

5. Conclusions

In conclusion, patients with severe COVID-19 infection who required ICU admission could have some type of cognitive impairment in the long-term, especially in domains like processing speed, verbal memory, or executive function. Medical risk factors like delirium, sedation, inflammation, hypoxia and mechanical ventilation during hospitalization can be risk factors for worse cognitive performance in the long term in this population.

CR mediates the relationship between these medical risk factors and cognitive performance at the follow-up. Likewise, those patients with high CR at the baseline demonstrate less risk to develop cognitive impairment than those with low CR; especially in verbal memory or executive functioning.
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Our data suggest that there are not only risk factors for cognitive impairment in severe COVID-19 patients but also protective factors, and public health policies should invest in interventions that could reduce the long-term disease burden.

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Declaration of competing interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

Flowchart 1. Follow-up of patients admitted to ICU for COVID-19.

A total of 433 patients were admitted to the ICU for COVID-19 were recruited before 30 days since hospital discharge. 143 patients were admitted to participate in the study. 96 patients were assessed in the first interview (6-month hospital discharge). 102 patients accepted to participate. 38 patients accepted to enroll in the neuropsychological assessment (6-month hospital discharge). 8 patients did not attend the first visit. Remote domicile (N=1) Declined participate (N=10) Not localized (N=5) Not attend the second visit (N=1) Acknowledgements

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