The Cognitive and Psychiatric Subacute Impairment in severe Covid-19.

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Research Article

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Abstract

**Background:** Neurologic impairment persisting months after acute severe SARS-CoV-2 infection has been described because of several pathogenic mechanisms, including persistent systemic inflammation. The objective of this study is to analyze the selective involvement of the different cognitive domains, it impacts on quality of life and the possible existence of related biomarkers.

**Methods:** Cross-sectional study of patients who survived severe infection with SARS-CoV-2 consecutively recruited from 13 neurology services in Spain between 90 and 120 days after hospital discharge. All patients underwent an exhaustive study of cognitive functions as well as plasma determination of pro-inflammatory factors (chemokines), and neurotrophic factors and light-chain neurofilaments. A Principal Component Analysis extracted the main independent characteristics of the syndrome.

**Results:** 152 patients were recruited. The results of our study show a pattern of cognitive impairment with preferential involvement of episodic and working memory, executive functions, and attention and relatively less affectation of information processing speed, denomination, verbal fluency, and other cortical functions. In addition, psychiatric affection such as anxiety and depression pictures are constant in our cohort. Several plasma chemokines concentrations were elevated compared with both, a non-SARS-Cov2 infected cohort of neurological outpatients or a control healthy general population, suggesting a pro-inflammatory chronic state derived of viral infection.

**Conclusion:** The neurologic Subacute Impairment in severe Covid-19 consist in an amnesic and dysexecutive syndrome with neuropsychiatric manifestations. We do not know if the deficits detected can persist in the long term and, in this case, if this can trigger or accelerate the onset of neurodegenerative diseases.

**Introduction**

In December 2019, a new coronavirus emerged as a pathogen in the Chinese city of Wuhan, causing severe acute respiratory syndrome (SARS) of high lethality\(^1\). SARS-CoV-2 spread rapidly throughout the world, and the WHO declared the disease caused by this global virus a pandemic in March 2020. At the time of writing this article, more than 195 million people worldwide had been infected with SARS-CoV-2, resulting in the death of more than 4,1 million individuals\(^2\).

Neurological impairment in this disease has been proven, both in the acute and subacute phases\(^3–7\). There are 4 mechanisms by which this neurological dysfunction can occurs: direct viral invasion, indirect effects of peripheral inflammation, peripheral organ dysfunction (lung, kidney, and liver) and cerebrovascular endothelial injury\(^8,9\).

Necropsic studies have proven some neuroinvasive capacity of SARS-CoV-2\(^7,10,11\). Furthermore, the relationship between viral neuroinvasive infections and neurodegenerative diseases (NDDs) has been described\(^12–16\), with preferent injury to the hippocampus and other regions of the temporal and frontal lobes related to cognition\(^17,18\).

Secondly, a loss of function of the blood brain barrier (BBB) can occur in situations of persistent systemic inflammation such as that occurring in SARS-Cov2 infection\(^19,20,21\). In addition, endothelial cells are key to the functional integrity of the BBB, and endothelial injury is a recognized element in the pathophysiology of SARS-CoV-2 infection\(^22\).

Finally, peripheral tissue injury typical of serious infections, such as severe COVID-19 can generate danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), enough for acting on CNS-specific
receptors, leading to microglial activation and, ultimately, pyroptosis or neuronal death of neuroinflammatory origin.

Cognitive and neuropsychiatric impairment persisting months after acute SARS-CoV-2 infection has been described. However, we lack detailed studies that analyze the selective involvement of the different cognitive domains using specifically designed tests, it impacts on quality of life and the possible existence of related biomarkers. This is the objective of our study on a hospital cohort of survivors of a severe SARS-Cov-2 infection.

Material And Methods

Design: Cross-sectional study of consecutive patients who survived severe infection with SARS-CoV-2; The clinical treatment of the patients was performed according to the routine clinical care based on the criteria of the attending physician of each patient.

Inclusion criteria:

- At least one positive PCR test (oropharyngeal swab) for SARS-CoV-2 infection.
- Respiratory failure with criteria for hospital admission; radiological criteria for lung disease (chest CT scan/X-ray with bilateral ground-glass opacities.
- More than 90 days and less than 120 days since hospital discharge.

Exclusion criteria:

- Cognitive impairment with a global deterioration scale (GDS) score of 4 or higher.
- Motor, sensorial, or intellectual disability or illiteracy that prevented performing neuropsychological tests.

Recruitment: Patients were consecutively recruited from 13 neurology services in Spain during the first wave of pandemic through a retrospective review of patients with hospital admission for severe Covid-19. For comparison purposes on circulating plasma chemokines and growth factors, plasma samples from two non-SARS-Cov-2 infected control groups were used. The first group was a cohort of neurological patients (n=46, mean age 71 y. o., SD 10.1, 17 males and 29 females) 60% affected with mild cognitive impairment (Mean MOCA score 18.5, SD 7.6). The second control group was a healthy general population from the National ADN biobank of Salamanca (n=40, mean age 52,2 y.o., SD 2.3, 20 males and 20 females). Both groups were recruited for a different project and its use was approved by the ethical committee of Regional University Hospital of Málaga (RUHM).

Study variables:

Retrospective Data collected during admission period:

- Clinical: Age, sex, length of hospital stays, comorbidities, symptoms related to SARS, neurological symptoms during admission and anti-COVID drug treatment.
- Analytical: Complete blood count, serum electrolytes, total protein, C-reactive protein, D-dimer, creatine kinase (CK), lactate dehydrogenase (LDH), transaminases, blood urea nitrogen (BUN), creatinine and ferritin.

Data collected during the visit (90-120 days after hospital discharge):

- Neuropsychological study protocol:
Global Cognition was studied through the Montreal Cognitive Assessment (MoCA) for dementia.

Memory was evaluated using the Spanish version of the California Verbal Learning Test (CVLT) also named Test de Aprendizaje Verbal España-Complutense (TAVEC) and Free and Cued Selective Reminding Test (FCSRT) for verbal episodic memory, Boston Naming Test (BNT) for denomination capacity, Rey Complex Figure Test (RCFT) for visuospatial episodic memory, and Digit Retention Test (DRT) of Wechsler Adult Intelligence Scale (WAIS) for working memory and memory reserve.

Executive function (RCFT, Trail Making Test Time B (TMT-B) and the Verbal Fluency Test (FAS)) and attention (TMT-A), were also evaluated.

Psychiatric impairment was evaluated using the State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory II (BDI-II) tests.

All tests have been previously standardized for age, sex and educational level for the Spanish population. Specifically, FCSRT, BNT, RCFT, FAS, DRT (verbal span) and TMT-A, and B were standardized within the framework of the NEURONORMA project. The rest of the tests have been standardized for age, sex and education level when possible according with their respective published normative values: TAVEC, MoCA, STAI and BDI.

An estimate of quality of life was made with the EuroQol 5D test (EQ-5D), also validated for Spanish population.

- **Analytical Study Protocol:**

  - **Basic screening:** The same as that collected during admission.

  - **Plasma chemokines and growth factors:** MIP-1alpha/CCL3 (Macrophage inflammatory proteine-1-alpha), SDF-1 (Stromal cell-derived factor 1), Fractalkine/CX3CL1, Eotaxin 1, BDNF (Brain derived neurotrophic factor), VEGF (Vascular Endothelial Growth Factor) and MCP-1/CCL2 (Monocyte Chemotactic Protein-1) levels were determined using the Luminex™ xMAP technology platform. All samples, control groups and COVID patients were measured in the same plates for avoiding interassay variability.

  - **Serum neurofilaments:** Light Chain Neurofilament (NFL) levels were determined using a digital enzyme immunoassay and the SIMOA HD1 Analyser platform.

- **Interpretation of the tests:** To reduce the impact of the absence of a cognitive function study prior to infection on the correct interpretation of our results, we have used tests with normative values for the Spanish population. To categorize each patient individual result in normal or abnormal values we used cut-off points stratified by age, sex and educative level. Abnormal values were defined by ±1 SD (±1Z) of the mean for the reference group of age, sex and educational level. This criterion was chosen instead of others, such as ±1.5 SD, to increase the sensitivity of the deviation from the mean when categorizing the test results; we did not intend to categorize the results as “healthy” or “pathological” but simply detect deviations from normal state.

See the supplementary material for a list of the tests (Supplementary Table S1) and for an explanation of the protocol used for neuropsychological evaluations (Supplementary Box 1).

- **Statistical study:** All clinical data, laboratory variables and diagnostic tests were entered into a database for analysis using statistical software IBM SPSS version 21.0. For numerical data, the normality of the distribution of the data was determined by the Kolmogorov-Smirnov test. Data calculated as percentages were analysed using the chi-squared test. For the data expressed as the mean ± standard deviation, Student's T test or the Mann-Whitney/Kruskal Wallis test were used depending on the normality of the sample.
To determine the main components of our database, principal components analysis (PCA) was used; the analysis included related quantitative variables as well as age, length of hospital stay, and the analytical parameters found to be pathological during hospital admission. The Bartlett sphericity test and the Kayser-Meyer-Olkin (KMO) sample adequacy test were applied to demonstrate the adequacy of this type of analysis for our sample.

Correlations of the isolated components were analysed using Pearson's R for continuous and normally distributed data and using Spearman's rho for nonnormally distributed data.

Last, linear regression analysis of isolated components was performed using the score on the EQ5 quality of life scale as the dependent variable.

The missing data were excluded from statistical analysis except in the PCA, in which they were replaced by the mean.

**Ethical considerations**: This study was approved by the Ethics and Clinical Research Committee of the RUHM. Each participant or legal representative signed an informed consent form after receiving a complete description of the study and being given the opportunity to ask any questions. The process of obtaining informed consent adhered to the principles of the Declaration of Helsinki of the World Medical Association.

**Results**

A total of 152 patients infected with SARS-CoV-2 who met all inclusion criteria and none of the exclusion criteria were recruited. The group was composed of 46 patients with long-term depressive symptoms, 25 with a history of stroke (16 territorial and 9 lacunar), 11 with chronic anxiety symptoms, 6 with Parkinson's disease, 6 with subjective memory failure (with GDS <4), 3 with Multiple Sclerosis, 3 with non-lesional focal epilepsy, 1 with Guillain-Barré syndrome and 11 with another chronic neurologic conditions without dementia. In this sense, we must consider that our cohort is composed mainly of patients with neurological or psychiatric vulnerability but without cognitive impairment, as required by the inclusion criteria.

The epidemiological data, symptoms during admission and specific treatments received during admission are provided in Table 1.

The means for the analytical variables assessed during admission were within the normal range of our laboratory, except the following:

- D-dimer: mean value, 1266.02 ng/ml (SD: 1969);
- Ferritin: mean value, 703.53 mcg/l (SD: 662.22); and
- C-reactive protein (CRP): mean value, 94.49 mg/l (SD: 85.45).

Compared with the values obtained during the study visit (90-120 days after hospital discharge), the ferritin values were found in the normal range for our laboratory, while the D-dimer (586.36 ng/ml; SD = 683.75) and CRP (6.47 mg/ml; SD = 16.15) values remained slightly elevated, although their values had decreased substantially.

All analytical test results are available as supplementary material to this article (Supplementary Table S2).

Table 2 provides the psychopathological evaluation data for the sample.

Table 3 provides the total MoCA test score as well as the scores for the 7 subdomains.

Table 4 provides the results of the cognitive exhaustive evaluation test used for the sample.
Figure 1 provides the data for chemokines and growth factors in general population, mild cognitive impairment control group and COVID patients.

Supplementary table S3 provides the numerical data for chemokines, growth factors and NFL.

For a graphical representation of the cognitive deficits detected in our sample the results are presented as a function of the percentage of the maximum score obtained on each test and as the total score (Figure 2).

**Principal components analysis:**

To reduce the number of variables, we performed PCA, in which we included the following quantitative variables: age, length of stay, pathological analytical variables during admission (ferritin and D-dimer) and numerical variables corresponding to the cognitive and neuropsychiatric test results. Six components capable of explaining 55.34% of the variance were identified. The KMO value was 0.854, and the Bartlett sphericity test indicated a significance of <0.0001, confirming the power and adequacy of the analysis.

The rotated components matrix and the explained variance table are provided as supplementary material (Supplementary Tables S4 and S5, respectively).

**Correlation with quality of life:**

A regression analysis of the identified components was performed using quality of life as the dependent variable; the results are provided in Supplementary Tables S6, S7 and S8). A Durbin-Watson test value less than 2 ensures that the factors are not autocorrelated. The result of the analysis showed that components 2 (global cognition/executive functions) and 6 (impairment of the neuropsychiatric area) explained the variable quality of life with high significance.

**Plasma concentration of proinflammatory chemokines and growth factors (Figure 1):**

We selected five chemokines and two growth factors that have been related to neuroinflammation and cognitive impairment/neurodegeneration previously. Kruskal-Wallis analysis show that the chemokines SDF-1a (H=7.3. p<0.001), MCP-1 (H=14.1 p<0.01) and Eotaxin-1 (H=37.5. p<0.001) were elevated in post-Covid patients, as well as the trophic factor BDNF (H=28.7. p<0.001), when compared with both control groups. In addition, Fractalkine (H=14.0. p<0.01), and VEGF-A (H=11.1. p<0.01) were elevated when compared only with the MCI cohort. MIP1-A was equal among groups (H=4.9 p=0.1, nonsignificant). These results suggest a pro-inflammatory chronic stated derived of severe COVID-19 disease. Remarkably, the circulating pattern of chemokines and growth factors in postcovid patients was found to be the opposite of that of non-infected age-matched patients attending the neurology department because of subjective memory deficits complaints (MCI cohort).

**Correlation with plasma proinflammatory factors and NFL:**

To identify plasma markers that could potentially be related to the main components of this Syndrome, a bivariate correlation analysis was performed using components 1 and 4 and the values obtained for each given plasma factor. The results are shown in Table 5.

**Discussion**

The results of our study show a pattern of cognitive impairment with some peculiarities. Thus, there is preferential involvement of episodic memory, working memory, executive functions, attention, and relatively less affectation of information processing speed, denomination, verbal fluency, and other cortical functions such as visuo-constructive
ability (Table 4; Figure 2). In addition, the detection of psychiatric affection such as anxiety and depression pictures are constant in our cohort (Table 2). So, we could therefore refer to post-covid syndrome as an amnesic and dysexecutive syndrome with impaired attention and psychiatric comorbidity. This pattern can be typified as suggestive of fronto-subcortical involvement and can be found in other situations with a neuroinflammatory basis of viral ethiology (eg, HIV encephalopathy)\(^\text{17}\).

After PCA, the following 6 independent components were identified as the cognitive and psychopathological areas affected.

**Components 1 and 5**: These 2 components are grouped because they integrate **variables related to episodic memory**, that is, memory related to vital events. Component 1 includes some scores of the TAVEC test as well as the free memory score of the FCSRT test, which primarily evaluates episodic verbal memory. Furthermore, Component 5 includes the other scores for the FCSRT test (cued and delayed recall).

Impairment in **episodic verbal memory** was observed in 34.7% (for TAVEC short term free memory) to 38.5% (for TAVEC Recall with long-term keys) of our patients and constitutes a specific element of this syndrome. Additionally, **working memory** measured through the Digit Retention Test (DRT) (WAIS-IV), was affected in 26.4%-36.7% of the sample. Other types of memory such as **semantic memory**, explored through the BNT seem less affected.

Traditionally, this type of mnemonic impairment has been related to subcortical cognitive impairment and has been identified in other neuroinflammatory processes of viral origin, such as HIV-associated neurocognitive disorders (HANDs)\(^\text{39}\).

**Component 2**: **Variables related to global cognitive function and visuo-spatial abilities**: the overall MoCA score and subdomain scores, except for orientation and animal naming (which are integrated in component 4), and the FCSR direct copy and memory scores, which both measure visuospatial and executive function.

The mean overall MoCA score in our sample was 21.95 (±5.70) points. Deficits were identified by low scores in delayed recall and, to a lesser extent, in attention, abstraction and language.

In general, the scores of the tests included in this component was not very deficient. Our patients are preferably included in the spectrum of mild cognitive impairment (MCI) with relative respect for purely cortical functions such as visuospatial function.

**Component 3**: Component 3 includes variables related to **executive functions** and **verbal fluency**. The impairment of **executive functions** was substantial in our patients as shown by the scores of the FAS animals (43.7% abnormal), FAS vegetables (48.6% abnormal) and FAS kitchen (33.1% abnormal) tests, more related to executive functions. We attribute this result to a failure in executive functions reinforcing the idea that frontal lobe dysfunction is frequent in post-Covid19 syndrome.

These findings are consistent with published functional impairment data, especially in studies that evaluated brain positron emission tomography with fluorodeoxyglucose (FDG-PET) and demonstrated greater impairment in the amygdala, hippocampus, parahippocampal region and frontal lobes\(^\text{40–42}\), areas directly related to memory and executive functions.

**Component 4**: The component includes **variables related to attention**, especially TMTs A, and **orientation and naming** (subtests of the MoCA). The scores obtained were abnormal for the 34.2% of the sample for the TMTs A. This finding
is commonly described in patients with inflammatory-based encephalopathies \cite{29,43}. The two MoCA subdomains included in this component that were less affected: Animal naming and Orientation.

**Component 6: Depression and Anxiety related variables.**

Over the course of the pandemic, the general population has been subjected to stressors derived from the social and economic impacts of the virus \cite{28,44}. It is, for this reason, difficult to separate the actual contribution of the biological factors highlighted in this article from other environmental factors. The BDI-II scores for our sample correspond to mild depression. Overall, 27.4\% of patients had a BDI score equal to or greater than 20 points, which indicates a clinical diagnosis of moderate or severe depression \cite{45}. A total of 35.56\% of the total sample had state STAI-State scores compatible with state anxiety. The results of our study show that regardless of its origin, neuropsychiatric impairment is another of the essential elements of the syndrome.

Cognitive impairment associated with depression is clearly seen in severe depression \cite{46}. However, the depression that we see in our patients is mild (mean score on the BDI-II = 14.95). For this reason, the non-existence of correlation with cognitive variables is not surprising.

Integrating all these results, we can state that the subacute neurological impairment in severe Covid-19 can be defined as a *global cerebral condition in the spectrum of MCI, characterized by a predominant deterioration of memory (especially, episodic and working memory), executive functions, attention, and neuropsychiatric impairment.*

Our results identify a pattern of subcortical deterioration with similarities to that described in cerebral small-vessel diseases with the predominant endothelial injury \cite{47,48}. There are also semiological parallels with neuroinflammation-based encephalopathies \cite{26,27,29}. Among the plasma factors studied herein, some, such as CRP and NFL, are correlated with endothelial injury \cite{49}.

Although our cohort is quite homogeneous, it could be hypothesized whether there could be different manifestations based on the previous existence of a situation of greater cognitive or psychiatric vulnerability. To test this possibility, we performed a post-hoc analysis dividing the sample into patients with a history of neurological or psychiatric disease versus those who did not. The results showed that there were no differences between these subgroups, thus highlighting the homogeneous nature of our results. We present these data as supplementary material (Tables S9-S12).

Quality of life was directly correlated with the main components that measure global cognitive function, and neuropsychiatric impairment; in the latter case, there was an inverse correlation with high trait anxiety and state anxiety scores and depression. We propose that impairment in these domains most determine the quality of life of our patients.

Interestingly, the analysis of circulating chemokines and growth factors suggest that 3 months after discharge, COVID-19 patients have a persistent neuroinflammatory state. This activation appears to be derived only of the infection by SARS-Cov-2, and not being associated to age-associated cognitive impairment, since patients with MCI not infected displayed a clearly different set of plasma chemokine concentrations.

The correlation analysis of the components with plasma chemokine proinflammatory factors found few significant correlations.

So, there was an inverse correlation between NFL levels and the Components related to the measurement of episodic memory (Rho=-0.310; p=0.018), global cognition (Rho=-0.297; p=0.024) and to Executive functions (Rho=-0.417;
NFL are markers of neuronal destruction whose correlation with global cognition has been described in the literature\textsuperscript{50}. Plasma NFL levels could be a robust biomarker of this syndrome.

Vascular Endothelial Growth Factor (VEGF) showed inverse correlation with the variables included in Component 4, mainly related to Attention. VEGF has been linked to endothelial dysfunction which, as already mentioned, appears to be an element present in SARS-Cov2 infection\textsuperscript{8} and more specifically, with cognitive decline present in some diseases with a large vascular component, such as DM\textsuperscript{51}. This finding reinforces our hypothesis that Post-Covid Neurologic Syndrome is intimately related to the typical vascular damage of Covid-19 disease.

In conclusion this Syndrome is a distinct condition that persists for at least 12 weeks after overcoming the acute phase of SARS-CoV-2 infection. The profile remains stable in different stratified populations based on cognitive vulnerability. Last, we identified biomarkers related to the main components of the syndrome. The possibility of any of them behaving as a prognostic biomarker and even as possible future therapeutic strategy development for Post-Covid Neurologic Syndrome should not be ruled out.

The main limitation of our study is the absence of an assessment of cognitive and neuropsychiatric function and of plasma markers prior to infection, preventing us from reliably measuring the impact of the infection. To minimize the impact of this fact on the interpretation of our results, we have used tests that have normalized values for the Spanish population, so that we can consider that the real control group in this study is the own general population stratified by age, sex and educational level.

Some issues remain to be resolved. First, we do not know whether the deficits detected are transitory or persist long term. If long term, it is unknown whether the underlying neuroinflammatory phenomena can trigger NDDs in a manner analogous to what probably occurred during the 1918 “Spanish flu” pandemic\textsuperscript{16}.

**Declarations**

**Data Sharing and Data Accessibility:** All databases used during the preparation of this article are available to editor or reviewers if required and have been incorporated into the DRYAD repertoire (Dryad Home - Publish and Preserve your Data (datadryad.org)).

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**Competing interest:** The authors report no competing interests.

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**Appendix**

**Appendix 1:** Members of the Research group “Neurocovid”:

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- Reyes Garrido, V. Hospital Universitario Regional de Málaga.
- Rivero-Rodríguez M. Hospital Universitario Virgen de las Nieves, Granada.
| Epidemiological characteristics               |       |
|-----------------------------------------------|-------|
| Sex (V. %)                                    | 70/152 (46.1%) |
| Age in Years (±SD)                            | 69.09 (±11.37) |
| Duration of admission in days (±SD)           | 14.38 (±13.14) |
| Ethnicity                                     |       |
| Caucasian                                     | 150 (98.7%) |
| Latin                                         | 2 (1.3%)  |
| Level of study                                |       |
| Primary education                             | 73 (48.0%)  |
| Secondary education                           | 34 (22.3%)  |
| Higher education                              | 21 (13.8%)  |
| No studies                                    | 15 (9.8%)   |
| Unknown                                       | 9 (5.9%)    |
| Marital status                                |       |
| As a couple                                   | 99 (65.1%)  |
| Single                                        | 9 (5.9%)    |
| Widower                                       | 18 (11.8%)  |
| Separate                                      | 21 (13.8%)  |
| Previous GDS                                  |       |
| GDS1                                          | 108 (71.0%) |
| GDS2                                          | 35 (23.0%)  |
| GDS3                                          | 7 (4.6%)    |
| Comorbidities                                 |       |
| HT                                            | 95 (62.5%)  |
| DM                                            | 39 (25.6%)  |
| Previous cerebrovascular disease              | 47 (30.9%)  |
| Cancer disease                                | 8 (5.2%)    |
| Smoking                                       | 15 (9.8%)   |
| Regular alcohol consumption                   | 28 (18.4%)  |
| General symptoms during admission             |       |
| Fever (Temperature > 38°C)                    | 123 (80.9%) |
| Cough                                         | 107 (69%)   |
| Dyspnea                                       | 90 (58.1%)  |
| Anorexia                                      | 47 (30.3%)  |
| Diarrhea                                      | 55 (35.5%)  |
| Neurological symptoms during admission        |       |
| Headache                                      | 34 (21.9%)  |
| Loss of awareness                             | 11 (7.1%)   |
| Seizures                                      | 1 (0.6%)    |
| Stroke                                        | 2 (1.2%)    |
| PNS involvement                               | 6 (3.9%)    |
| Myalgias                                      | 17 (11%)    |
| Anti-Covid19 treatments                       |       |
| Hydroxychloroquine                            | 112 (72.3%) |
| Lopinavir/Ritonavir                           | 69 (44.5%)  |
| Others (Methylprednisolone. Anti-IL)          | 98 (64.4%)  |
Table 1. Epidemiological and clinical data during admission. DM: Diabetes mellitus. GDS: Gl 
\textit{d}eterioration Scale. HT: Hypertension. PNS: Peripheral Nervous System.

|                  | N  | Average Direct Score (±SD) | N (%) ≤1Z   |
|------------------|----|----------------------------|-------------|
| **BDI**          | 135| 14.95 (±10.73)             | 37 (27.40%) |
| **STAI State**   | 138| 23.79 (±10.98)             | 49 (35.56%) |
| **STAI Trait**   | 138| 24.18 (±11.18)             | 41 (29.49%) |

Table 2. Results of the psychopathological assessment of the cohort.

|                                  | N  | Average Direct Score (±SD) | Maximum Score | Average Scaled Score | N (%) ≤1Z   |
|----------------------------------|----|----------------------------|---------------|----------------------|-------------|
| **Global MoCA score**            | 131| 21.95 (±5.70)              | 30            | 10.86 (±8.85)        | 33 (25.2%)  |
| **Visuo-spatial and executive function** | 129| 3.63 (±1.49)               | 5             |                      |             |
| **Animal naming**                | 129| 2.78 (±0.53)               | 3             |                      |             |
| **Attention**                    | 129| 4.23 (±1.66)               | 6             |                      |             |
| **Language**                     | 129| 2.07 (±1.10)               | 3             |                      |             |
| **Abstraction**                  | 129| 1.33 (±0.70)               | 2             |                      |             |
| **Delayed recall**               | 129| 1.94 (±1.69)               | 5             |                      |             |
| **Orientation**                  | 129| 5.62 (±0.92)               | 6             |                      |             |

3. MoCA test scores in the global sample. Abnormal values are considered if they are equal to or less t low the value corresponding to their standardized group by age, sex and educational level.
| N   | Average Direct Score (±SD) | Average Scaled Score (±SD) | Z (±SD) | ≤1Z | N (%) |
|-----|----------------------------|---------------------------|---------|-----|-------|
|     | **E C (Verbal Episodic Memory)** |                           |         |     |       |
|     | **E C Learning** 118 | **35.91 (±15.02)** | -0.87 (±1.54) | **49** | (41.5%) |
|     | **E C Short-term free ory** 118 | **8.01 (±5.55)** | -0.30 (±1.74) | **39** | (33.3%) |
|     | **E C Recall with short-keys** 118 | **8.77 (±3.7)** | -0.55 (±1.17) | **41** |       |
|     | **E C Long-term free ory** 117 | **7.53 (±4.2)** | -0.61 (±1.27) | **41** |       |
|     | **E C Recall with long-keys** 117 | **8.77 (±3.87)** | -0.59 (±1.27) | **45** |       |
|     | **E C Recognition** 117 | **13.36 (±3.2)** | -0.26 (±1.60) | **24** | (20.4%) |
|     | **Denomination** 141 | **12.30 (±3.13)** | 0.06 (±1.37) | **24** | (17.0%) |
|     | **E (Visuospatial Episodic Memory/ Executive Function)** |                           |         |     |       |
|     | **E Time Copy** 123 | **242.11 (±127.66)** | 11.67 (±4.72) | 0.56 (±1.57) | **19** | (17.4%) |
|     | **E Copy Direct Score** 109 | **28.73 (±9.42)** | 10.46 (±3.51) | 0.15 (±1.17) | **18** | (14.7%) |
|     | **E Memory Direct Score** 101 | **11.29 (±8.47)** | 8.26 (±3.69) | -0.58 (±1.23) | **40** | (39.6%) |
|     | **Attention / Executive Function** |                           |         |     |       |
|     | **Time A (Attention)** 114 | **94.96 (±80.83)** | 7.71 (±3.7) | -0.76 (±1.24) | **39** | (34.2%) |
|     | Errors A 108 | **0.46 (±1.23)** |                           |         |       |
|     | **Time B (Executive tion)** 91 | **182.25 (±141.33)** | 8.93 (±3.15) | -0.36 (±1.05) | **28** | (31.1%) |
|     | Errors B 87 | **1.87** |                           |         |       |
|     | **as Spanish version of FAS (Executive Function* and Verbal fluency**) |                           |         |     |       |
|     | **P** 142 | **10.00 (±5.27)** | 8.06 (±3.40) | -0.48 (±1.01) | **47** | (33.1%) |
|     | **M** 142 | **8.49 (±4.92)** | 8.56 (±3.53) | -0.28 (±1.07) | **38** | (26.8%) |
|     | **R** 142 | **8.43 (±4.73)** | 8.44 (±4.74) | -0.16 (±0.84) | **30** | (21.1%) |
|                | Count | Mean (±Standard Deviation) | Median (±IQR) | Percentile |%
|----------------|-------|---------------------------|---------------|------------|
| *Animals*      | 141   | 13.54 (±5.69)             | 7.30 (±3.12)  | -0.70 (±0.96) | 62 (43.7%) |
| *Vegetables*   | 142   | 14.00 (±5.27)             | 8.63 (±3.32)  | -0.80 (±1.08) | 69 (48.6%) |
| *Kitchens*     | 142   | 12.26 (±4.45)             | 9.99 (±3.61)  | -0.39 (±1.19) | 47 (33.1%) |

(WAIS) (Working memory / Memory Reserve)

|                     | Count | Mean (±Standard Deviation) | Median (±IQR) | Percentile |%
|---------------------|-------|---------------------------|---------------|------------|
| Direct Span         | 121   | 4.95 (±7.54)              | 8.11 (±3.64)  | -0.63 (±1.21) | 44 (36.7%) |
| Reverse Span        | 121   | 3.25 (±1.38)              | 11.32 (±17.26)| -0.05 (±1.15)| 32 (26.4%) |

(T Verbal Episodic Memory)

|                     | Count | Mean (±Standard Deviation) | Median (±IQR) | Percentile |%
|---------------------|-------|---------------------------|---------------|------------|
| Free memory         | 128   | 19.53 (±9.07)             | 9.23 (±3.54)  | -0.25 (±1.18) | 40 (31.25%) |
| Cued memory         | 127   | 17.11 (±7.16)             |               |            | 32 (26.3%) |
| Total               | 127   | 35.76 (±11.04)            | 10.17 (±4.19) | 0.06 (±1.39) | 32 (25.2%) |
| Delayed             | 127   | 6.74 (±3.95)              | 9.10 (±3.54)  | -0.30 (±1.28) | 39 (30.7%) |
| Total Delayed       | 127   | 11.10 (±4.77)             | 9.50 (±4.92)  | -0.16 (±1.64) | 42 (33.1%) |

Quality of life

|                     | Count | Mean (±Standard Deviation) |
|---------------------|-------|---------------------------|
| D                   | 141   | 62.94 (±21.84)            |

4. Complete cognitive evaluation of the cohort.
| Measured Factor | N  | Component 1 (Episodic memory) | Component 2 (Global Cognition) | Component 3 (Executive Functions) | Component 4 (Attention) | Component 5 (Episodic memory) | Component 6 (Depression and Anxiety disorder) |
|----------------|----|-----------------------------|-------------------------------|---------------------------------|------------------------|-----------------------------|-------------------------------------------|
| MIP-1 (CCL3)   | 106| 0.107 (0.276)               | 0.013 (0.892)                | 0.048 (0.64)                    | -0.061 (0.535)          | -0.060 (0.538)              | 0.002 (0.983)                            |
| SDF-1 (CXCL12) | 117| 0.028 (0.763)               | -0.053 (0.571)               | 0.106 (0.254)                   | -0.148 (0.112)          | -0.008 (0.931)              | 0.072 (0.440)                            |
| Fractalkine (CX3CL1) | 104| 0.008 (0.932)               | -0.016 (0.875)               | -0.157 (0.111)                  | -0.318 (0.001)          | -0.034 (0.735)              | -0.115 (0.247)                           |
| Eotaxine (CCL11) | 120| 0.032 (0.729)               | -0.032 (0.726)               | -0.226 (0.013)                  | -0.064 (0.486)          | -0.060 (0.516)              | 0.022 (0.814)                            |
| BDNF           | 105| 0.117 (0.233)               | 0.050 (0.611)                | -0.213 (0.029)                  | -0.024 (0.806)          | -0.157 (0.109)              | -0.149 (0.129)                           |
| VEGF           | 108| 0.050 (0.606)               | 0.011 (0.910)                | -0.241 (0.012)                  | -0.203 (0.035)          | -0.131 (0.178)              | -0.031 (0.754)                           |
| MCP-1 (CCL2)   | 116| -0.005 (0.960)              | -0.077 (0.412)               | -0.174 (0.062)                  | -0.102 (0.277)          | 0.017 (0.855)               | -0.128 (0.169)                           |
| NFL            | 58 | -0.310 (0.018)              | -0.297 (0.024)               | -0.417 (0.001)                  | 0.101 (0.452)           | -0.049 (0.717)              | -0.079 (0.554)                           |

Bivariate correlation between identified components and chemokine levels. In all cases we expressed $r$. 

**Figures**
Figure 1

Plasma values of several chemokines and growth factors in control subjects (n=45), mild cognitive impairment patients (MCI, n=41) and COVID-19 patients (COVID+, n=128) 3-4 months after hospital discharge. Kruskal-Wallis Analysis. * P<0.01 versus control group. # p<0.01 versus MCI group. Data in boxplots are means and 5-95 confidence intervals.
Figure 2

Graphical representation of the profile of the main test used in our study comparing the average vs maximum score.

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