CNS Spectrums

www.cambridge.org/cns

Assessment of cognitive and psychiatric disturbances in people with post-COVID-19 condition: a cross-sectional observational study

Federico Masserini[1], Simone Pomati[2], Valentina Cucumo[2], Alessia Nicotra[1], Giorgia Maestri[1], Matteo Cerioli[1], Luca Giacovelli[1], Carolina Scarpa[1], Luca Larini[1], Giovanna Cirnigliaro[1], Bernardo dell'Osso[1,3,4] and Leonardo Pantoni[1]

[1]Neuroscience Research Center, Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy; [2]Center for the Diagnosis and Treatment of Cognitive Disorders, Neurology Unit, Ospedale Luigi Sacco, Milan, Italy; [3]Department of Psychiatry and Behavioral Sciences, Bipolar Disorders Clinic, Stanford Medical School, Stanford University, Stanford, CA, USA. and [4]CRC "Aldo Ravelli" for Neurotechnology & Experimental Brain Therapeutics, University of Milan, Milan, Italy.

Original Research

Cite this article: Masserini F, Pomati S, Cucumo V, Nicotra A, Maestri G, Cerioli M, Giacovelli L, Scarpa C, Larini L, Cirnigliaro G, dell'Osso B, and Pantoni L (2024). Assessment of cognitive and psychiatric disturbances in people with post-COVID-19 condition: a cross-sectional observational study. *CNS Spectrums* **29**(6), 640–651.
https://doi.org/10.1017/S1092852924002153

Received: 05 March 2024
Accepted: 10 September 2024

Keywords:
post-COVID-19 condition; COVID-19; cognition; psychiatric symptoms; multidimensional assessment

Corresponding author:
Leonardo Pantoni;
Email: leonardo.pantoni@unimi.it

Abstract

Objective. Cognitive and psychiatric symptoms have been increasingly reported after severe acute respiratory syndrome coronavirus 2 infection, developing soon after infection and possibly persisting for several months. We aimed to study this syndrome and start implementing strategies for its assessment.

Methods. Consecutive patients, referred by the infectious disease specialist because of cognitive complaints after COVID-19, were neurologically evaluated. Neurological evaluation included a cognitive screening test (Montreal Cognitive Assessment, MoCA). Moreover, patients were invited to fill out a general symptom questionnaire and a self-administered multidimensional assessment of psychiatric symptoms, followed by a full psychiatric assessment if scores were above validated cutoffs.

Results. Of 144 referred patients, 101 (mean age 55.2±13.1, 63.4% females) completed the cognitive screening and the self-administered psychiatric questionnaire. Acute infection severity was low for most patients and the most common persisting symptoms were fatigue (92%), sleep problems (69.5%), and headache (52.4%). MoCA outlined cognitive deficits in ≥1 cognitive domain in 34% of patients, mainly in memory and attention. About 60% of patients presented depressive, anxiety, or stress-related symptoms. Psychiatric scale scores significantly correlated with overall symptom burden and MoCA score. No significant correlation was found between MoCA scores and overall symptom burden.

Conclusion. We hypothesize that persistent cognitive complaints after COVID-19 might reflect a concomitant or reactive psychopathological condition, possibly coupled with an infection-related impact on cognitive functions. The application of a combined neurological and psychiatric assessment seems crucial to appraise the nature of post-COVID-19 condition.

Introduction

The COVID-19 pandemic has affected hundreds of million people worldwide since its beginning in 2020.[1] As the pandemic unfolded, reports of neurological manifestations during the acute phase of COVID-19 have steadily increased, together with a significant proportion of patients experiencing symptoms that persisted after resolution of primary infection.

Neurological manifestations related to COVID-19 can be broadly divided into two categories: manifestations that occur during, and are limited to, the acute phase (e.g., encephalopathy, central hypoventilation, delirium, mechanical-ventilation-related complications, and others) and manifestations and/or conditions that may persist (or begin) after primary infection resolution (e.g., brainstem encephalitis, myelitis, Guillain-Barré syndrome, long-COVID, and related syndromes).[2]

The diverse, often fluctuating, or relapsing symptoms persisting after COVID-19 were initially labeled "long-COVID" by patients themselves, conceptually tapping into the possibility of prolonged manifestations of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Nonetheless, an agreed-upon description and definition of post-COVID persisting symptoms—or even a widespread name to identify this syndrome—is still lacking, as shown by recent reviews on the matter.[3,4] In the attempt to better define this condition (and also to lay a common ground that could favor enrollment into observational studies), both the National Institute for Health Excellence (NICE) and World Health Organization (WHO) tried to provide an operative definition.[5,6] Both definitions, however, require only a fixed timeframe

onto which evaluate post-COVID symptoms, without providing any reference to which symptoms should be included in a hypothetical post-COVID case definition: NICE defines post-COVID-19 condition (PCC) as any symptom beginning within 12 weeks and persisting at least 12 weeks after acute COVID-19, while WHO defines PCC as any symptom beginning within 3 months from acute infection and lasting for at least two months. The absence of a precise case definition has led the number of manifestations attributed to the aftermath of COVID-19 to grow disproportionately (up to the recent figure of >200 different symptoms).[7] In addition, the term "long-COVID", often used to name this syndrome also in the literature, has a somewhat fluid meaning: for example, according to NICE guidelines, it refers to both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or longer), generating even more confusion since these terms are often used interchangeably[3] and since the real need for such temporal discrimination is somewhat disputable. For this reason, the WHO definition adopted the term "post-COVID-19 condition/syndrome (PCC/PCS)" over the term "long-COVID," with explicit reference to a unique time window for symptom onset and persistence, which reduces vagueness and ambiguity. For the same reasons, throughout this work, the term PCC (*as intended by the WHO*) will be used to refer to this post-COVID-19 syndrome. This is first and foremost a "terminological" choice: employing an unambiguously defined term improves the chances to agree on a unique case definition, fosters the creation of comparable studies to disentangle the complex features that belong to PCC, helps in correctly estimating the epidemiological dimension of the phenomenon (eg, invaluable to direct health resources appropriately), and reduces patients' uncertainness about his/her condition.

Finally, and partially overlapping with the other definitions, a third entity, by the name of "NEUROCOVID," was conceived at the beginning of the pandemic, and overlapped partially in its scope with the "temporal" classifications mentioned above.[8,9] NEUROCOVID refers to a heterogeneous ill-defined array of manifestations broadly related to the neurological domain, starting either during acute infection or in the postinfectious period[10,11] and adds further elements of complexity to an already hazy picture.

A growing body of literature suggests that some symptoms—that is, cognitive complaints such as memory and attention difficulties, psychiatric symptoms (anxiety and depression), and fatigue—are reported very frequently. These symptoms may be seen as reliable "cores" that might provide a basis for a definition of PCC, as summarized in a recent systematic review on the matter.[3] Moreover, a thorough description of symptom initiation and characteristics together with sociodemographic characterization of subjects presenting with post-COVID-19 condition has been scarcely reported.[12] Likewise, confirmation of cognitive and psychiatric symptoms with formal cognitive and psychiatric testing and a longitudinal assessment of symptoms evolution over time have not been previously performed. The consequence of falling short in recognizing the full breadth of this syndrome is that the need for medical attention of these patients goes largely unanswered.

In this study, we aimed to better describe and characterize cognitive and psychiatric manifestations developed after COVID-19 by implementing a structured outpatient protocol. The final output of such protocol application would be the development of strategies to manage, and possibly treat, manifestations of post-COVID-19 condition. A unified treatment strategy for PCC is indeed currently lacking and most treatment approaches tried insofar are limited to tackling single symptoms, borrowing from the experience of other conditions with similar manifestations.[13]

In this first article, we describe the general structure of our study, the neurological findings, and the psychiatric symptoms screening; in a second, twin, article,[14] we describe the results of the psychiatric assessment, as well as the treatment strategy employed to tackle patients' manifestations.

Methods

Study design and patient enrollment

This is an observational, multidisciplinary, cross-sectional study conducted between September 1, 2021, and September 30, 2022, at the Luigi Sacco University Hospital, Milan, Italy. Patients with any cognitive symptoms (including but not limited to memory complaints, language complaints, brain fog, word-finding difficulties, attention and/or concentration problems, orientation difficulties, visuospatial manifestation) occurring during or after SARS-CoV-2 infection and persisting over time—and reported during clinical history taking at the infectious diseases outpatient post-COVID clinic—were referred to the neurology outpatient clinic. Approval was granted by the Ethics Committee of the Ospedale Luigi Sacco (Comitato Etico Milano Area 1), as part of a larger multicenter national study on the same population.[15]

Patient evaluation

After referral from the infectious disease clinic, we performed a standard neurological assessment (complete in-depth history taking and neurological examination) together with a cognitive screening test (Montreal Cognitive Assessment, MoCA). In addition, patients were offered to participate in an online questionnaire to explore further symptoms reported during and after acute SARS-CoV-2 infection and psychoactive drug use history. In the same questionnaire, patients were also invited to fill out a psychiatric screening battery composed of the following self-reported psychometric scales: Depression Anxiety Stress Scales (DASS-21), Impact of Event Scale-Revised (IES-R), Insomnia Severity Index (ISI), 5-level EuroQol 5-Dimensional Questionnaire (EQ-5D-5L), and Sheehan Disability Scale (SDS). MoCA total scores (MoCA-TS) were adjusted according to the most recent validation for Northern Italian population[16] and broken down into subdomains (MoCA-memory, MoCA-M; MoCA-executive function, MoCA-EF; MoCA-attention, MoCA-A; MoCA-orientation, MoCA-O; MoCA-visuospatial functions, MoCA-VS; and MoCA language, MoCA-L); memory index score (MIS) was also reported. We considered as pathological, unless otherwise stated, a score that corresponded to an equivalent score (ES) of zero.[17] We chose the MoCA as a measure of cognitive function because of its psychometric properties (i.e., a more sensitive rather than specific test to assess mild cognitive impairment), its more balanced assessment of different cognitive domains in respect of other screening tests, and the recently updated normative data,[16] which enabled us to break down the test results into single measures for each cognitive domain.

Patients who scored above validated cutoffs in at least one among DASS-21, IES-R, or ISI were then referred to the psychiatry unit outpatient clinic of the same hospital, where a specific assessment was performed. Figure 1 summarizes the entire enrollment process. A description of the assessment instruments, including psychometric scales with respective cutoffs, is available in the *Supplementary Materials.*

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

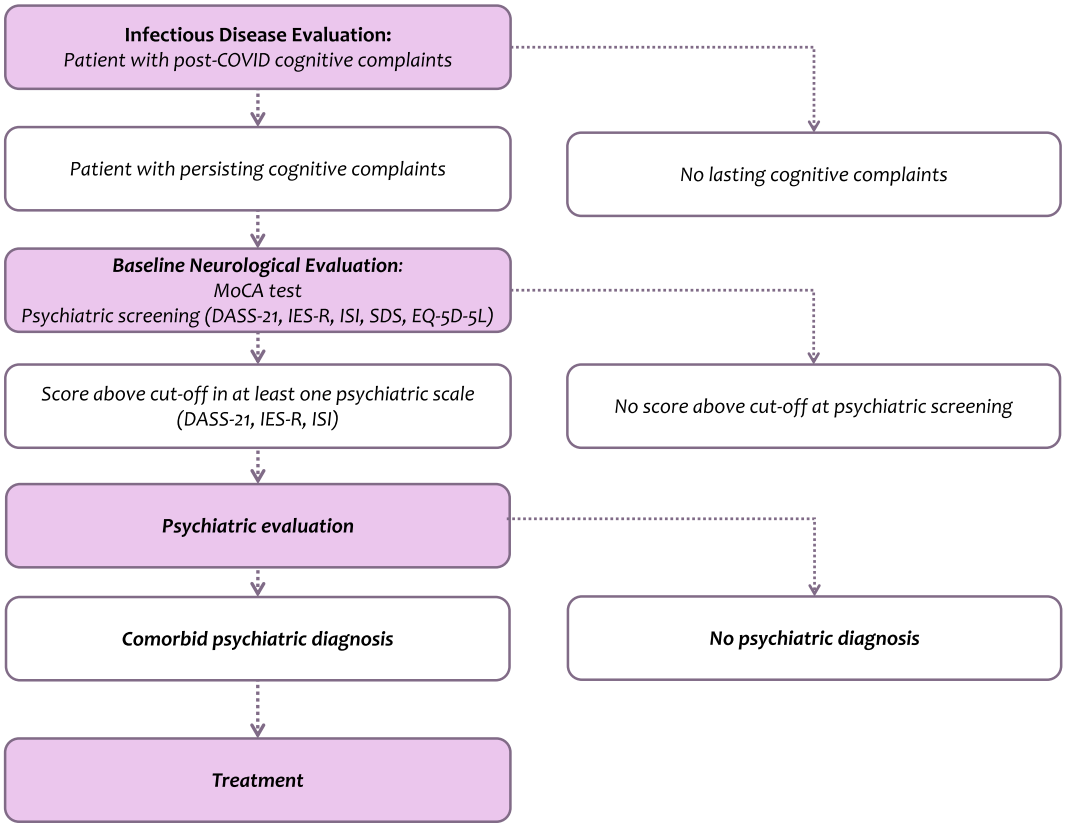

Figure 1. Patient's enrollment flowchart. Abbreviations: MoCA, Montreal Cognitive Assessment; DASS, Depression, Anxiety, Stress Scale; ISI, Insomnia Severity Index; IES-R: Impact of Event Scale revised; EQ-5D-5L, 5-level EuroQol 5-Dimensional Questionnaire; SDS, Sheehan Disability Scale.

Statistical analyses

Descriptive statistics were computed for sociodemographic variables and scores in cognitive and psychiatric scales for the whole group and for the subgroup of patients that filled the questionnaire. For this subgroup, each patient noncognitive symptom duration was aggregated to compute an index of symptom burden (which is expressed as the sum of the duration of any reported symptom divided by the time elapsed between the date of infection and the date of neurological referral, *further details about this computed metric are reported in the supplementary materials*). For numerical continuous variables, differences between groups were assessed through parametric tests (Student t-tests/ANOVA) for normally distributed variables and through nonparametric tests (Kruskal-Wallis or Mann-Whitney) for nonnormally distributed variables. For nominal (either dichotomic or multinomial) variables, chi-squared test of homogeneity was instead used to assess differences. Concordance between reported cognitive symptoms and cognitive deficits found at MoCA subtests was assessed by chi-squared test of homogeneity and computation of kappa statistics. Correlations between symptom burden, demographic variables, cognitive scores, and psychiatric scores were then assessed through Pearson's correlation coefficients. Correlation strength was interpreted according to the model described by Cohen (*summarized in the eMethods section of the supplementary materials*).[18] Binomial logistic or multiple regression analyses to assess predictors of overall symptom burden, cognitive scores, and psychiatric scores, were also performed according to the type of dependent variable used (multiple regression models for continuous dependent variables and binomial logistic regression models for dichotomic dependent variables).

The level of statistical significance was fixed at $p < 0.05$ (where indicated, Bonferroni correction for multiple comparisons was applied). Analyses were performed with IBM SPSS Statistic, v 28.0 and 29.0 (SPSS Inc., Chicago, USA), and GraphPad Prism (version 10.0 for Mac OS, GraphPad Software, Boston, Massachusetts USA).

Results

One-hundred forty-four consecutive patients complaining of cognitive symptoms after COVID-19 have been referred since September 2021, with a mean delay after acute SARS-CoV-2 infection of 13.16 months (standard deviation, SD, 5.81). One-hundred two (70.8%) completed the questionnaire. For one of these patients, the complete MoCA was not available and was thus excluded from the final analyses. Sociodemographic variables, symptoms developed after infection, and cognitive test scores (either adjusted or equivalent scores) were not different between patients who filled questionnaires compared with patients who did not (χ^2 statistics, $p>0.05$ for all comparisons, *data not shown*). Acute SARS-CoV-2 infection severity was on average mild: hospitalization was required in 42.6% of cases (35.6% requiring oxygen therapy), while intensive care treatment was required in 8.9% of cases. Complete sociodemographic characteristics, along with characterization of presenting cognitive symptoms, for both the original cohort and the subsample that completed the questionnaire, are reported in Table 1. The results that follow refer to the subsample completing the questionnaire (n = 101). The time between neurological evaluation and questionnaire filling was on average 16.7 days

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

Table 1. Sociodemographic, Acute Infection, and Cognitive Variables for the Whole Sample and for Subsample Completing the Questionnaire

	Whole sample	Subsample completing questionnaire
	n = 144	n = 101
Age	55.0 (SD 13.9, range 19–86)	55.2 (SD 13.1, range 22–85)
Education	13.9 (SD 3.5, range 3–19)	14.3 (SD 3.3, range 3–19)
Gender (F/M)	93/51 (65% females)	64/37 (63.4% females)
Oxygen therapy need	58 (40.2%)	36 (35.7%)
Ventilatory assistance need	26 (18.1%)	21 (20.8%)
Pandemic wave		
First wave	47 (32.6%)	37 (35.7%)
Second wave	56 (38.9%)	38 (37.6%)
Third wave	24 (16.7%)3	16 (15.8%)
Fourth wave and after	17 (11.8%)	10 (9.9%)
Referral delay	13.2 (SD 6.1)	13.1 (SD 5.8)
MoCA score adjusted	22.7 (SD 3.8, range 7–30)	22.8 (SD 3.7, range 7–29.1)
Any deficit at MoCA (ES 0/1)	50 (34.7%)	30 (29.7%)
Any deficit at MoCA (ES 1/2)	79 (54.9%)	54 (53.5%)

Abbreviations: SD, standard deviation; ES, equivalent scores; MoCA, montreal cognitive assessment; MoCA-TS, MoCA-total score.

(SD 25.8 days, median 4 days, 25th-75th interquartile range, IQR 25-75, 6.2-27.2).

Symptom burden, cognitive symptom characterization, and cognitive scoring

The cognitive symptom reported most frequently at neurological evaluation, developed either during (54% of cases) or after acute infection (46% of cases, with a median delay of 80.5 days, IQR 25-75 40-140 days), was memory complaints (n = 66, 65.3%), followed by attention/concentration complaints (n = 47, 46.5%), and language difficulties (n = 40, 39.6%). As *per* enrollment protocol, cognitive symptoms lasted from the time of onset to the time of baseline neurological evaluation. The most frequently reported general symptoms were fatigue (n = 99, 98.0% of cases), followed by headache (n = 79, 78.2% of cases), sleep disturbances (n = 79, 78.2%), and dyspnea (n = 79, 78.2%). Fatigue persisted in many cases (n = 73, 73.7% of patients presenting it) until the evaluation. Cognitive and general symptom characterization are depicted in Figures 2 and 3. Patients had a mean cumulative symptom duration of 48.2 (SD 31.5) symptom-months, with a mean index of symptom burden of 3.13 (SD 1.60); a histogram of mean index of symptom burden is depicted in eFigure1.

Cognitive complaints were confirmed by an adjusted MoCA total score below cutoff (cutoff between ES 0/1) in 12.9% (n = 13) of cases; twenty-five (24.8%) patients considering a cutoff between ES 1/2 score. A MoCA subscore below the cutoff in ≥1 cognitive domain was found in 29.7% (n = 30) of cases (n = 54, 53.5% of cases considering also a score corresponding to an ES of 1), the most frequent being memory, followed by attention/executive functions (Figure 4).

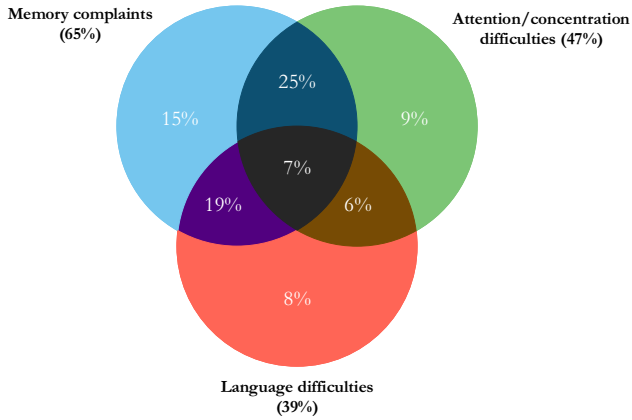

Figure 2. Venn diagram displaying the proportion of patients reporting the most frequently found cognitive symptom (attention complaints, memory complaints, and language difficulties), either alone or in combination (total *n* of subjects = 101).

We found no statistically significant association between cognitive complaint categories (i.e., memory, attention, and language) and deficits found at the corresponding MoCA subdomains (Pearson χ^2 p>0.05 for all comparisons, *contingency tables reported in the Supplementary materials*), nor between any reported cognitive complaint category and having a MoCA score (total or subscores) below cutoff (*data not shown*), or between any cognitive and most represented noncognitive symptoms (*contingency tables reported in the Supplementary materials*).

Psychiatric and psychoactive drug history

Forty-five (44.6%) patients reported a history of psychoactive drug use before psychiatric evaluation. The most frequent classes of psychoactive drugs were benzodiazepines (n = 30, 29.7% of cases) and antidepressants (n = 27, 26.7%); a significant proportion of these patients reported psychoactive drug use already before SARS-CoV-2 infection (51.6% of patients taking benzodiazepines and 66.7% of patients taking antidepressant medications).

Descriptive statistics for scores in each of the self-reported scales for psychiatric symptoms assessment (DASS-21, ISI, and IES-R) and overall impact on quality of life (EQ-5D-5L and SDS) are reported in Table 2. Overall, we found at least one score above the cutoff in 59 patients, with the most frequently altered scores being, respectively, DASS-stress (n = 42), DASS-anxiety (n = 41), and DASS-depression (n = 38); distribution of scores above the cutoff, as well as their overlap, are depicted in eFigure2. Patients who scored above validated cutoffs were then referred to the psychiatric department of our hospital for further evaluation and, if indicated, treatment.

Correlations between cognitive parameters, psychiatric scores, and overall symptom burden

A weak-moderate negative correlation was found between age and overall symptom burden (r = −0.382, p < 0.0001), and MoCA-A

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

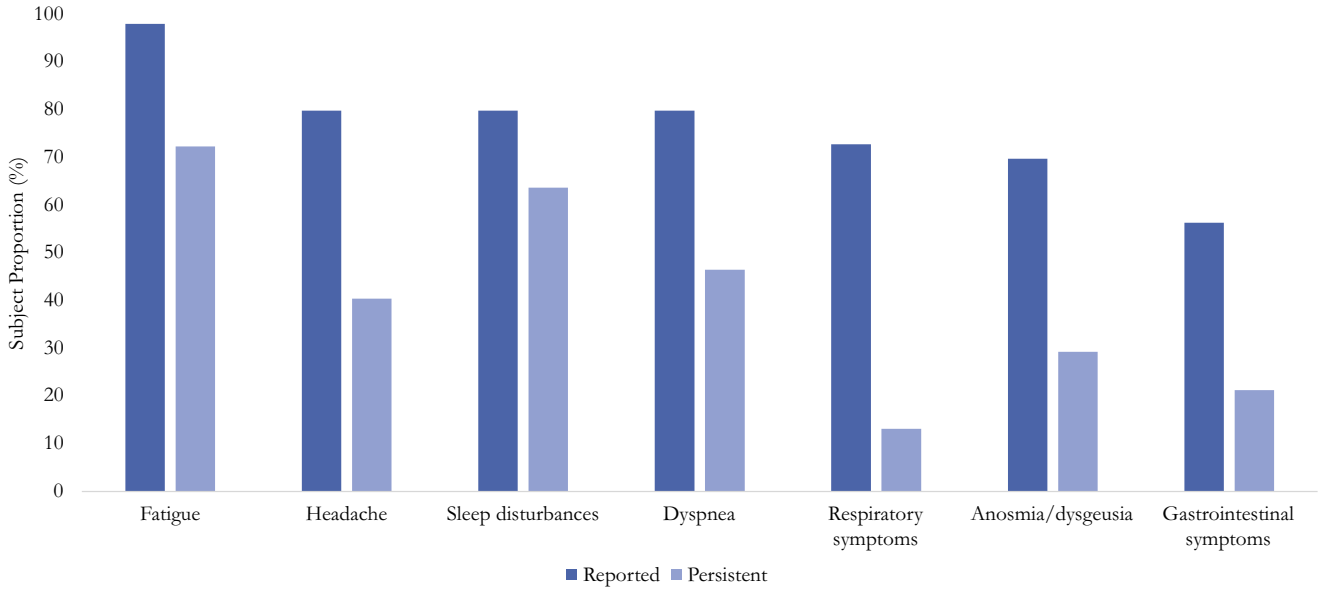

Figure 3. Bar chart representing noncognitive symptoms prevalence according to self-administered questionnaire answers. Blue bars identify occurrence at any point, while light blue bars identify persistence of the symptom at the time of questionnaire completion.

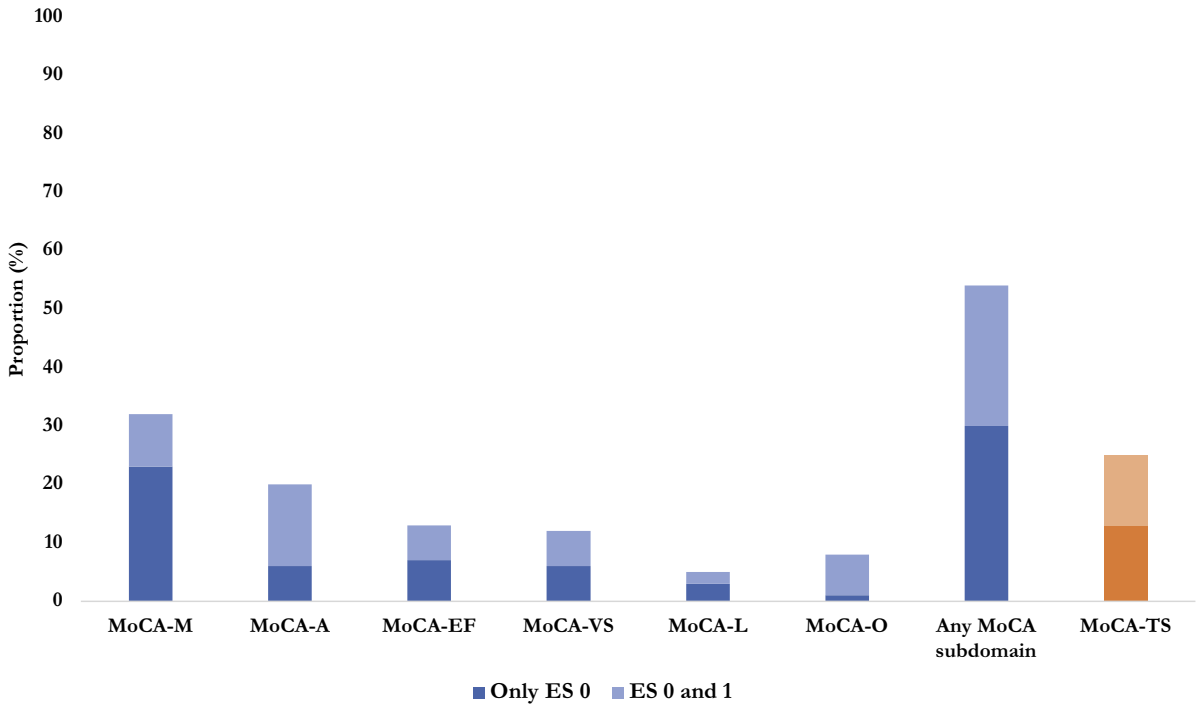

Figure 4. Bar chart representing the proportion of patients with a deficit at MoCA, either in subdomains or total score; dark colored bars depict the proportion of patients showing a deficit considering an equivalent score (ES) of 0 as pathological, while light colored bars depict the same proportion considering as pathological also an ES of 1. Abbreviations: MoCA, Montreal Cognitive Assessment; MoCA-M, MoCA-memory; MoCA-A, MoCA-attention; MoCA-EF, MoCA-executive functions; MoCA-VS, MoCA-visuospatial functions; MoCA-L, MoCA-language; MoCA-O, MoCA-orientation; MoCA-TS, MoCA-total score.

and MoCA-M scores; moderate-strong positive correlations were found between education and MoCA-TS and all MoCA subscores. No correlation between age and education and psychiatric variables was found except for a weak negative correlation with the SDS mean score (Pearson's $r = -0.269$, $p < 0.01$).

To filter out the possible effects of age and education, we adjusted for these covariates in a partial correlation model. A weak negative correlation was found between MoCA-M and acute infection duration ($r = -0.216$, $p < 0.05$); a moderate negative correlation was found between MoCA-TS and DASS-A ($r = -0.305$, $p < 0.01$) and IES-R ($r = -0.267$, $p < 0.01$); weaker significant correlations were also found between MoCA-TS and both DASS-S and EQ-5D-5L, no significant correlations were found between MoCA-TS and ISI, DASS-D, or SDS. Complete correlation matrices for both models (unadjusted and adjusted) depicted as heatmaps, together with heatmaps of their relative statistical significance are reported, respectively, in eFigure3 and Figure 5.

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

Table 2. Clinical History, Psychoactive Drug Intake, and Psychiatric Self-Administered Scales Descriptives of the Subsample of Subject Completing the Proposed Questionnaire

	Subsample completing questionnaire
	n = 101
Median time of questionnaire completion	4 days (IQR 21)
Acute infection duration	34.3 days (SD 22.5, median 28)
Acute infection severity	
Paucisymptomatic (no hospital)	58 (57.4%)
Hospitalized (no oxygen)	7 (6.9%)
Hospitalized (oxygen low)	14 (13.9%)
Hospitalized (oxygen high)	13 (12.9%)
Intensive care needed	9 (8.9%)
Psychoactive drug use	45 (44.6%)
Psychoactive drug use before COVID	26 (25.7%)
Overall symptom burden (index)	3.13 (SD 1.6, range 0.04 – 7.71)
DASS–21 depression	11.5 (SD 10.9, range 0–42)
DASS–21 anxiety	8.2 (SD 8.5, range 0–36)
DASS–21 stress	13.9 (SD 10.5, range 0–38)
ISI	8.71 (SD 5.6, range 0–28)
IES-r score	25.5 (SD 20.5, range 0–85)
EQ–5D–5L mean QoL score	64.7 (SD 19.2, range 20–100)
SDS mean	4.6 (SD 2.8, range 0–10)

Abbreviations: IQR, 25th-75th interquartile range; SD, standard deviation; DASS, Depression, Anxiety, Stress scale; ISI, Insomnia Severity Index; IES-R: Impact of Event Scale revised; EQ-5D-5L, 5-level EuroQol 5-Dimensional Questionnaire; SDS, Sheehan Disability Scale.

Weak correlations were detected between MoCA-A and DASS-A, MoCA-L and DASS-A, and MoCA-EF and DASS-D, DASS-A, DASS-S, ISI, and IES-R. Finally, a weak negative correlation was found between MIS and IES-R ($r = -0.233$, $p < 0.05$).

A moderately strong positive correlation was found between the index of symptom burden and scores at psychiatric self-administered scales ($r = 0.531$, $p < 0.0001$ for DASS-A and $r = 0.474$, $p < 0.0001$ for IES-R, $r = 0.546$, $p < 0.0001$, for ISI, $r = -0.501$, $p < 0.0001$ for EQ-5D-5L score, and $r = 0.502$, $p < 0.0001$ for SDS mean score). Overall symptom burden was also weakly positively correlated with infection duration ($r = 0.236$, $p < 0.05$). A weak positive correlation was found between IES-R and duration of acute infection ($r = 0.280$, $p < 0.01$). Finally, no correlation was found between measures of symptom burden and cognitive scores.

Predictors of cognitive impairment, comorbid psychiatric burden, and severity of noncognitive symptoms

A binomial logistic regression was performed to ascertain the effects on MoCA-TS (dichotomized for an ES threshold set at 0/1) of acute infection parameters (acute infection duration, infections severity, and pandemic wave), psychoactive drug history, continuous scores obtained at psychiatric scale, and overall symptom burden. The adjusted (controlled for age, sex, and education) logistic regression model was statistically significant, $\chi^2(13) = 38.732$ $p < 0.0001$. The model explained 62.2% (Nagelkerke R^2) of the variance in MoCA-TS and correctly classified 93.3% of cases. Of the predictor variables included, four were statistically significant: acute infection duration, IES-R, ISI, and DASS-S (Table 3a).

Similarly, a binomial logistic regression was performed to ascertain the effects of acute infection parameters, psychoactive drug history, cognitive scores, and overall symptom burden on having any psychiatric score above cutoff, after adjustment for age, sex, and education. The adjusted logistic regression model was statistically significant, $\chi^2(13) = 46.513$, $p < 0.0001$, explaining 54.4% (Nagelkerke R^2) of the variance and correctly classifying 76.7% of cases. Of the predictor variables included five were statistically significant: ventilatory support during acute infection, infection during the first two pandemic waves, history of psychoactive drug intake, overall symptom burden, and MoCA-TS (Table 3b). Finally, a multiple regression was run to predict overall symptom burden from acute infection duration, cognitive, and psychiatric variables. The multiple regression model significantly predicted overall symptom burden, $F(15, 74) = 5.836$, $p < 0.0001$, adj. $R^2 = 0.45$. Only DASS-A, DASS-S, ISI, and age added statistically significantly to the prediction ($p < 0.05$). Regression coefficients can be found in Table 3c.

Discussion

Our study showed that our overall young and highly educated PCC patient sample is burdened with a significant number of cognitive and noncognitive symptoms, lasting for a considerably long time. Among cognitive complaints, memory problems were the most frequently reported, alone or in combination with attention/concentration and word-finding difficulties. We also found a very high proportion of comorbid psychiatric burden which was associated with a relevant level of perceived disability.

Among general complaints, fatigue was reported in most of our patients, followed by headache, and sleep difficulties. For these noncognitive symptoms, we developed a single variable that could reflect the overall burden in a simple way. Several other dedicated and more structured tools to investigate symptoms related to post-COVID have been published and validated, for example, the Symptom Burden Questionnaire for Long-COVID (SBQ-LC).[19] These instruments, however, were not available at the time we conceived our protocol.

Overall, these findings, as well as the case-profile of PCC that emerged from our data, are in agreement with the most recent studies on the topic, and with what we outlined in our recent review.[3] The timing of symptom onset and average duration, moreover, overlaps with (and possibly corroborates) the most recent guidelines and consensus recommendations on PCC proposed, respectively, by NICE and WHO.

Enrollment in our study took place in a time of the pandemic in which a few restrictive measures were still in place in Italy to control SARS-CoV-2 spread (mainly social distancing only in public places and vaccination/infection resolution certificate requirements to access recreational establishments, as bars or restaurants) and after the bulk of the vaccination campaign was already over.[20,21] During this period mortality and hospitalization rates were plunging, despite peaking infection rates during early winter 2021 in correspondence with the spread of the SARS-CoV-2 B.1.1.529 variant. Considering the pressure on the Italian health system and the high rate of vaccinated people (> 80%), the emergency state proclaimed

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

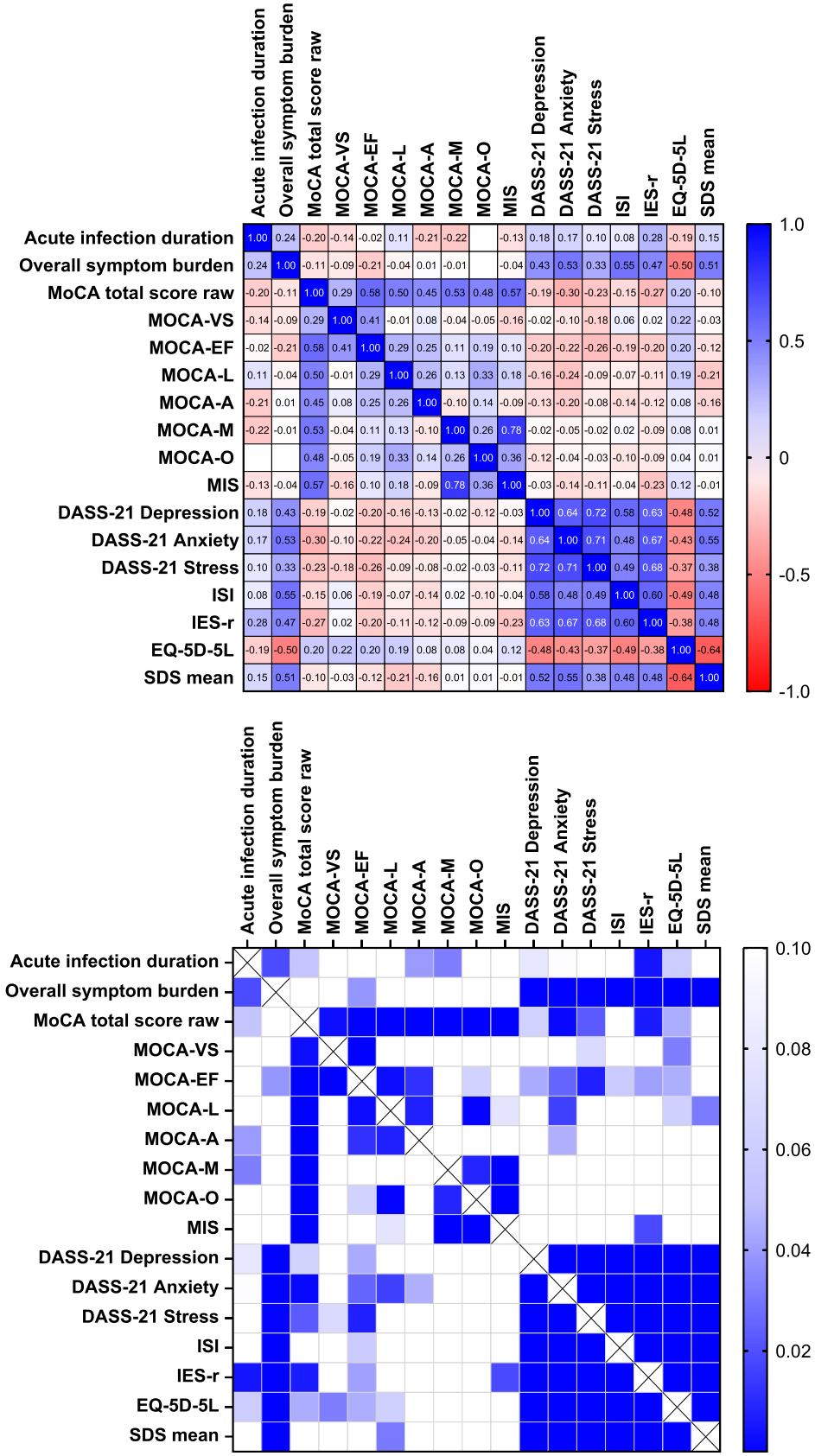

Figure 5. Pearson's correlation matrices, after adjustment for age and education (data represented as residuals after linear regression for the two aforementioned variables), represented as heatmaps. In the heatmap above Pearson's correlation coefficients are represented, while in the heatmap below, p values for the same correlations are depicted. Abbreviations: MoCA, Montreal Cognitive Assessment; MoCA-M, MoCA-memory; MoCA-A, MoCA-attention; MoCA-EF, MoCA-executive functions; MoCA-VS, MoCA-visuospatial functions; MoCA-L, MoCA-language; MoCA-O, MoCA-orientation; MIS, Memory Index Score; ISI, Insomnia Severity Index; IES-r, Impact of Event Scale revised; EQ-5D-5L, 5-level EuroQol 5-Dimensional Questionnaire; SDS, Sheehan Disability Scale.

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

Table 3a. Regression Coefficients Table for Binomial Logistic Regression Model (dependent variable: MoCA Total Score dichotomized according to an ES cutoff between 0 and 1)

	Model 1 (not adjusted)					Model 2 (adjusted)				
	B	Wald	p value	Exp(B)	95% C.I for Exp(B) [lower-upper]	B	Wald	p value	Exp(B)	95% C.I for Exp(B) [lower-upper]
Acute infection duration	−0.034	3.298	0.069	0.967	0.93–1.00	**−0.056**	**4.458**	**0.035**	**0.946**	**0.90–1.00**
Ventilatory support yes/no	**−2.462**	**6.149**	**0.013**	**0.085**	**0.01–0.60**	−2.399	3.212	0.073	0.091	0.01–1.25
First two pandemic waves	−1.495	1.723	0.189	0.224	0.02–2.09	−0.838	0.447	0.504	0.433	0.04–5.05
Any psychoactive drug reported	−0.607	0.542	0.461	0.545	0.11–2.74	0.443	0.150	0.698	1.558	0.17–14.65
Overall symptom burden	0.476	1.813	0.178	1.609	0.81–3.22	−0.001	0.000	0.999	0.999	0.41–2.44
DASS–21 depression subscore	0.063	0.911	0.340	1.065	0.94–1.21	0.200	3.022	0.082	1.221	0.97–1.53
DASS–21 anxiety subscore	−0.118	2.266	0.132	0.888	0.76–1.04	−0.191	2.623	0.105	0.826	0.66–1.04
DASS–21 stress subscore	−0.094	1.721	0.190	0.910	0.79–1.05	**−0.276**	**3.906**	**0.048**	**0.759**	**0.58–1.00**
Insomnia severity index	**−0.252**	**4.414**	**0.036**	**0.777**	**0.61–0.98**	**−0.441**	**5.468**	**0.019**	**0.644**	**0.44–0.93**
IES-R	**0.108**	**5.107**	**0.024**	**1.114**	**1.01–1.22**	**0.198**	**5.783**	**0.016**	**1.218**	**1.04–1.43**
Age						−0.023	0.180	0.671	0.977	0.88–1.09
Education						**0.626**	**7.258**	**0.007**	**1.870**	**1.19–2.95**
Gender						2.559	2.652	0.103	12.924	0.59–281.18
Constant	5.944	8.878	0.003	381.594		1.332	0.083	0.773	3.789	

Note: Statistically significant variables are reported in bold.

*__Dependent variable__: MoCA-total score ES 0/1

Abbreviations: C.I., confidence interval; MoCA, Montreal Cognitive Assessment; ES, equivalent scores; DASS, Depression, Anxiety, Stress scale; IES-R, Impact of Event Scale revised.

at the beginning of the pandemic in March 2020 was eventually lifted at the end of March 2022.

Notwithstanding, most of our patients were infected in the first two pandemic waves, whereas burden of acute infection was overall low. Our population characteristics are substantially different from the ones in the study by Beretta et al., performed, however, in a substantially different setting (i.e., hospitalized patients developing neurological symptoms during or after COVID-19),[15] who were mostly males, significantly older (15 years older on average), and with a significant proportion of more severe infections. On the other hand, our population characteristics are consistent with what has been found in several other observational studies performed in post-COVID-19 subjects in the same outpatient setting.[22,23]

In our cohort, reported cognitive complaints have been confirmed by identification of relative cognitive impairment at MoCA in a minor, although significant, proportion of cases. However, we did not find any correspondence between specific cognitive symptoms reported by patients and gathered in clinical history and cognitive impairment identified by MoCA subscores (e.g., memory complaints with MoCA-M), also when moving the threshold to ES between 1 and 2. We might conclude that cognitive impairment is ill-recognized and ill-reported by these subjects. However, the lack of association between cognitive symptoms and impairment could also point to the possibility that these symptoms are not strictly related to the underlying cognitive impairment itself but could be associated with the comorbid psychiatric conditions. Finally, another alternative explanation may be that MoCA subscores simply lack of sensitivity, even when moving the thresholds toward higher levels of functioning, and this should be the object of further research.

In line with previous studies,[3] we chose MoCA as a measure of cognitive function because of its psychometric properties (i.e., a more sensitive rather than specific test to assess mild cognitive impairment), its more balanced assessment of different cognitive domains in respect of other screening tests, and the recently updated normative data.[16] Considering the limited resources for a more extensive neuropsychological assessment, this enabled us to break down the test results into single measures for each cognitive domain. Nonetheless, we are aware that this is a limitation.

We found an expected, although weak, association between cognitive scores and neuropsychiatric parameters, mainly anxiety, posttraumatic stress disorder symptoms, and depression. Notably, and differently from attention and executive measures, memory scores did not correlate with psychiatric scales nor with overall symptom burden, displaying a weak association only with acute infection duration. Neuropsychiatric parameters were associated quite strongly with the overall burden of general symptoms and showed a moderate inverse correlation also with age, while no association was found between overall symptom burden and cognitive scores. The inverse correlation of neuropsychiatric burden

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

Table 3b. Regression Coefficients Table for Binomial Logistic Regression Model (dependent variable: any psychiatric score above cutoff at DASS, ISI or IES-R)

	Model 1 (not adjusted)					Model 2 (adjusted)				
	B	Wald	p value	Exp (B)	95% C.I for Exp(B) [lower-upper]	B	Wald	p value	Exp (B)	95% C.I for Exp(B) [lower-upper]
Acute infection duration	−0.034	3.298	0.069	0.967	0.93–1.003	−0.014	0.480	0.488	0.987	0.95–1.03
Ventilatory support yes/no	−2.462	0.993	6.149	0.085	0.12–0.60	**2.272**	**4.190**	**0.041**	**9.697**	**1.10–85.38**
First two pandemic waves	−1.495	1.723	0.189	0.224	0.024–2.09	1.357	3.335	0.068	3.885	0.91–16.67
Any psychoactive drug reported	−0.607	0.542	0.461	0.545	0.11–2.74	**1.435**	**3.882**	**0.049**	**4.201**	**1.01–17.52**
Overall symptom burden	0.476	1.813	0.178	1.610	0.81–3.22	**0.831**	**9.111**	**0.003**	**2.296**	**1.34–3.94**
MoCA-total	**−0.289**	**3.833**	**0.050**	**0.749**	**0.56–1.00**	**−0.597**	**7.512**	**0.006**	**0.551**	**0.36–0.84**
MoCA-M	−2.077	2.160	0.142	0.125	0.01–2.00	−2.301	2.356	0.125	0.100	0.01–1.89
MIS (below cutoff)	1.986	2.368	0.124	7.284	0.58–91.36	2.275	2.770	0.096	9.728	0.67–141.77
MoCA A/EF (ES = 0)	−0.306	0.044	0.833	0.736	0.04–12.68	0.087	0.003	0.960	1.091	0.04–32.25
MoCA-L (ES = 0)	−2.915	2.108	0.147	0.054	0.00–2.77	−4.052	2.642	0.104	0	0.00–2.30
Age						0.030	1.079	0.299	1.030	0.97–1.09
Education						**0.476**	**10.560**	**0.001**	**1.609**	**1.21–2.14**
Gender						0.962	1.663	0.197	2.617	0.61–11.30
Constant	4.307	1.266	1.000	0.260	74.19–0.00	2.151	0.149	0.699	8.591	

Note: Statistically significant variables are reported in bold.

*__Dependent variable__: Any psychiatric score above cutoff (DASS-21, Insomnia Severity Scale, or IES-r)
Abbreviations: C.I., confidence interval; MoCA, Montreal cognitive assessment; ES, equivalent scores; MoCA-M, MoCA memory; MoCA A/EF, MoCA attention-executive function combined; MoCA-L, MoCA language; MIS, Memory Index Score (pathologic when below 7); DASS, depression, anxiety, stress scale; IES-R, impact of event scale revised.

and age during the COVID-19 pandemic has already been reported in other observational studies[24–26] and is in line with the overall prevalence of anxiety and depressive disorders in the population: that is, their prevalence in the different age classes is distributed following a U-shaped curve, with the highest prevalence in the 40–59 years age class, followed by progressive decrease at the extremes, and especially with older age.[27] Another possible explanation for this phenomenon may lie in the differential life attitudes and expectations that are typical of different age strata, which put the youngest at higher risk than the elderly to experience significant trauma during a global pandemic. If, on the one hand, the overall decreased social mobility of older people may make them less prone to be severely impacted by the restriction of a full pandemic lockdown, on the other hand, younger people are more often in a life state of personal and working development: in this context, the uncertainty perceived during a pandemic may impact the younger generations significantly more.[24,26]

Moreover, as shown by the regression models, acute infection duration, reactive symptoms (posttraumatic stress disorder and stress), and sleep problems were the only significant predictors of cognitive impairment, while overall symptom burden was predicted significantly by symptoms of anxiety, stress, and sleep disturbances, but not by COVID-19-related parameters. Finally, we found that acute infection severity, infection in the first two pandemic waves, history of psychoactive drug intake, overall symptom burden, and cognitive performance at MoCA significantly predicted comorbid psychiatric burden.

Trying to interpret our findings, we may hypothesize that cognitive impairment is associated with (and probably partly determined by) both acute SARS-CoV-2 infection and psychiatric comorbid conditions, possibly with differential impact on memory of the former and attention/executive functions and language of the latter. In turn, the comorbid psychiatric burden may be associated with the infection itself and possibly may be underpinned by the traumatic experience related both to acute infection treatment (as shown by the higher likelihood of developing psychiatric comorbidities associated with the need for ventilatory assistance) and public health restriction measures adopted in the early phase of the pandemic period. Finally, psychiatric burden could be the main underpinning of the noncognitive syndrome that affects these patients.

This partial disentanglement between psychiatric burden, cognitive impairment, and overall symptom burden in PCC has already been reported in previous observational studies.[12,22,23] Moreover, a recent work has demonstrated that perceived cognitive problems in these patients (as well as more general PCC symptoms) have an important intrinsic affective component:[28] this may lead to the conclusion that cognitive and noncognitive symptoms expressed as PCC may be underpinned by the interplay among premorbid and comorbid psychiatric burdens and acute infection itself (and likely the experience of infection as well). In turn, the development of psychiatric symptoms in PCC could have an impact on cognitive functions but would expectedly target primarily attention and executive functions, as expected,[29] and as shown in our study. The possible cause of cognitive impairment in post-

https://doi.org/10.1017/S1092852924002153 Published online by Cambridge University Press

Table 3c. Regression Coefficients Table for Multiple Logistic Regression Model (dependent variable: overall symptom burden)

	Model 1 (not adjusted)					Model 2 (adjusted)				
	Unstandardized coeff.	Standardized coeff.			95% C.I. for B [lower-upper]	Unstandardized coeff.	Standardized coeff.			95% C.I. for B [lower-upper]
	B	Beta	t	p value		B	Beta	t	p value	
Acute infection duration	0.004	0.058	0.594	0.555	−0.01–0.02	0.004	0.063	0.644	0.522	−0.01–0.02
Ventilatory support yes/no	**−0.715**	**−0.193**	**−2.070**	**0.042**	**−1.40–0.03**	−0.262	−0.071	−0.679	0.499	−1.03–0.51
First two pandemic waves	0.169	0.048	0.527	0.600	−0.47–0.81	0.271	0.076	0.864	0.391	−0.35–0.90
Any psychoactive drug reported	0.221	0.070	0.766	0.446	−0.35–0.80	0.332	0.105	1.164	0.248	−0.24–0.90
MoCA-total	**0.170**	**0.373**	**2.480**	**0.015**	**0.03–0.31**	0.077	0.168	0.995	0.323	−0.08–0.23
MoCA-M	0.977	0.263	1.612	0.111	−0.23–2.18	0.633	0.170	1.052	0.296	−0.57–1.83
MIS (below cutoff)	−0.253	−0.069	−0.453	0.652	−1.37–0.86	−0.221	−0.060	−0.408	0.685	−1.30–0.86
MoCA A/EF (ES = 0)	0.996	0.190	1.560	0.123	−0.28–2.27	0.984	0.188	1.566	0.122	−0.27–2.24
MoCA-L (ES = 0)	−0.273	−0.031	−0.271	0.787	−2.27–1.73	−0.969	−0.111	−0.950	0.345	−3.00–1.06
DASS–21 depression subscore	−0.011	−0.077	−0.562	0.576	−0.05–0.03	0.002	0.014	0.101	0.920	−0.04–0.04
DASS–21 anxiety subscore	**0.088**	**0.490**	**3.397**	**0.001**	**0.04–0.14**	**0.079**	**0.441**	**3.127**	**0.003**	**0.03–0.13**
DASS–21 stress subscore	−0.033	−0.220	−1.420	0.160	−0.08–0.01	−0.043	−0.286	−1.854	0.068	−0.09–0.00
Insomnia severity Index	**0.100**	**0.348**	**2.940**	**0.004**	**0.03–0.17**	**0.103**	**0.359**	**3.142**	**0.002**	**0.04–0.17**
IES-R	0.011	0.147	1.071	0.287	−0.01–0.03	0.006	0.082	0.601	0.550	−0.01–0.03
Age						**−0.033**	**−0.274**	**−2.795**	**0.007**	**−0.06–0.01**
Education						0.035	0.074	0.701	0.486	−0.06–0.13
Gender						0.066	0.020	0.216	0.829	−0.54–0.68
Constant	−2.855		−1.519	0.133	−6.60–0.89	0.751		0.336	0.738	−3.70–5.21

Note: Statistically significant variables are reported in bold.

*__Dependent variable__: overall symptom burden

Abbreviations: C.I., confidence interval; MoCA, Montreal Cognitive Assessment; ES, equivalent scores; MoCA-M, MoCA memory; MoCA A/EF, MoCA attention-executive function combined; MoCA-L, MoCA language; MIS, Memory Index Score (pathologic when below 7); DASS, Depression, Anxiety, Stress scale; IES-R, Impact of Event Scale revised.

COVID-19 is not yet clear: while direct central nervous system invasion by SARS-CoV-2 in causing brain pathological alterations has been ruled out in neuropathological studies,[30,31] indirect involvement, through the establishment of a neuroinflammatory *milieu* during acute infection that could alter brain physiology, has often been postulated and more recently shown in experiments performed in COVID-19 animal models.[32–34]

Overall, even though we can only postulate an association between SARS-CoV-2 infection, cognitive impairment, and psychiatric manifestations, our study seems to suggest that these dimensions almost invariably coexist in post-COVID-19 condition. It follows that, when evaluating patients suspected of being affected by this condition, a comprehensive evaluation, including cognitive performance and psychological/psychiatric symptom assessment, is crucial to avoid falling short in recognizing key manifestations of this neuropsychiatric syndrome and ultimately to prompt the patients toward possible treatment strategies. As global treatment strategies for PCC are not currently available,[13] we can only resort to manage specific symptoms and/or comorbid manifestations (e.g., depression), which for psychological symptom is often attempted and with some demonstrated success.[35] In the particular case of psychiatric disease and symptoms, management is crucial as these symptoms are associated with a particularly high toll on quality of life.[36,37] The psychiatric assessment of patients recruited in our study, as well as management strategies of confirmed psychiatric comorbid disorders, is the focus of a second, twin, article.[14]

Our study has several limitations. First and foremost, the lack of a control group (i.e., subjects with SARS-CoV-2 infection but without PCC). While this may limit the generalizability of our analyses, our study was conceived amid the initial pandemic with a primary clinical scope: to respond to the emerging clinical need of patients. We must also acknowledge that cognitive manifestations were required to be referred to our outpatient disease clinic: in this way, we may have missed patients presenting with no cognitive complaints and psychiatric/psychological complaints that were not referred to the neurological outpatient clinic. Second, the somewhat small sample may have underpowered our analyses, especially regression models, in detecting subtlest predictors of PCC. Third, we decided to use MoCA as a measure of cognitive impairment, both for global classification and for identifiable subdomains, even though, as discussed above, MoCA subdomains cannot be considered equivalent to a full neuropsychological evaluation. However, the ease of use of this brief cognitive screening test coupled with the large amount of information that can provide have been deemed as ideal for evaluation of the possibly broad number of patients in our clinical setting. Finally, no neuroimaging or biological data were available in our cohort, and this limited the possibility to further explore biological counterparts of PCC.

Conclusion

Despite the aforementioned limitations, our study is one of the few that features a detailed description of cognitive, psychiatric, and general symptoms, and compares reported symptoms with objective measures of cognitive impairment and neuropsychiatric burden. This allowed us to hypothesize new links between the main PCC clinical factors and COVID-19 and to establish a simple protocol that could be employed to screen for cognitive impairment and comorbid psychiatric conditions, and hence to direct patients toward further evaluation and treatment, when necessary. Overall, the assessment protocol we propose, together with the emerging case-definitions for PCC that are being progressively refined,[3] could provide a groundwork to employ in everyday clinical practice and for future enrollment in observational studies.

As the presented data are cross-sectional, further collection of longitudinal data is needed to ascertain natural history of both symptoms and cognitive impairment. As we wait for our longitudinal analyses, preliminary findings by other longitudinal studies suggest that both syndrome and cognitive impairment could be reversible.[38,39] Larger longitudinal studies, featuring a control group and a more extensive neuropsychological evaluation, are needed to further assess underpinnings of cognitive symptoms of PCC, as well as to confirm and corroborate our findings on the different interplay between infection, symptoms, cognitive impairment, and neuropsychiatric burden.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924002153.

Author contribution. Conceptualization: B.D., V.C., F.M., A.N., S.P.; Methodology: B.D., V.C., F.M., A.N., S.P.; Project administration: B.D., L.P.; Writing – review & editing: B.D., C.S., V.C., G.C., L.G., L.L., G.M., M.C., A.N., S.P., L.P.; Writing – original draft: C.S., F.M., G.C., L.G., L.L., M.C., L.P.; Investigation: V.C., F.M., A.N., S.P.; Data curation: F.M.; Formal analysis: F.M., S.P.; Supervision: S.P., L.P.; Resources: L.P.

Competing interest. L Pantoni is member of the editorial boards of Neurology, European Stroke Journal, Cerebrovascular Diseases, and associate editor of Neurological Sciences. He has received consultation fees, not related to the work submitted for publication, from Amicus and PIAM. B Dell'Osso has received lecture honoraria, not related to the work submitted for publication, from Angelini, Janssen Pharmaceuticals, Lundbeck, Livanova, Arcapharma, and Neuraxpharm. G Cirnigliaro is supported by 'Fondazione Romeo ed Enrica Invernizzi' (Corso Venezia 32, 20122, Milano (MI)).

All the authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding. This work has been supported by Fondazione Cariplo, grant n° 2021-4490. A.N. and G.M. have been partially supported by a liberal donation from PIAM Pharmaceutics Italy to the Neuroscience Research Center, Department of Biomedical and Clinical Sciences, University of Milan.

References

1. Miskowiak KW, Fugledalen L, Jespersen AE, et al. Trajectory of cognitive impairments over 1 year after COVID-19 hospitalisation: Pattern, severity, and functional implications. *Eur Neuropsychopharmacol.* 2022;**59**:82–92. doi:10.1016/j.euroneuro.2022.04.004
2. Nath A. Neurologic manifestations of severe acute respiratory syndrome coronavirus 2 infection. *Continuum (Minneap Minn).* 2021;**27**(4): 1051–1065. doi:10.1212/con.0000000000000992
3. Nicotra A, Masserini F, Calcaterra F, et al. What do we mean by long COVID? A scoping review of the cognitive sequelae of SARS-CoV-2 infection. *Eur J Neurol.* 2023;**30**(12), 3968–3978. doi:10.1111/ene.16027
4. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ.* 2020;**370**:m3026. doi:10.1136/bmj.m3026
5. Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med.* 2021;**9** (2):129. doi:10.1016/S2213-2600(21)00031-X
6. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis.* 2022;**22**(4):e102–e107. doi:10.1016/S1473-3099(21)00703-9

7. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine.* 2021;**38**:101019. doi:10.1016/j.eclinm.2021.101019
8. Chen X, Laurent S, Onur OA, et al. A systematic review of neurological symptoms and complications of COVID-19. *J Neurol.* 2021;**268**(2): 392–402. doi:10.1007/s00415-020-10067-3
9. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). *J Neurol.* 2021; **268**(9):3059–3071. doi:10.1007/s00415-021-10406-y
10. Misra S, Kolappa K, Prasad M, et al. Frequency of neurologic manifestations in COVID-19: a systematic review and meta-analysis. *Neurology.* 2021;**97**(23):e2269–e2281. doi:10.1212/WNL.0000000000012930
11. Guedes BF. NeuroCOVID-19: a critical review. *Arq Neuropsiquiatr.* 2022; **80**(5 Suppl 1):281–289. doi:10.1590/0004-282X-ANP-2022-S136
12. Hartung TJ, Neumann C, Bahmer T, et al. Fatigue and cognitive impairment after COVID-19: a prospective multicentre study. *EClinicalMedicine.* 2022;**53**:101651. doi:10.1016/j.eclinm.2022.101651
13. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* 2023;**21**(3): 133–146. doi:10.1038/s41579-022-00846-2
14. Cerioli M, Giacovelli L, Nostro C, et al. Post-COVID condition: a focus on psychiatric symptoms and diagnoses in patients with cognitive complaints. *CNS Spectrums*. 2024. *In press*. doi: 10.1017/S1092852924000464.
15. Beretta S, Cristillo V, Camera G, et al. Incidence and long-term functional outcome of neurologic disorders in hospitalized patients with COVID-19 infected with pre-omicron variants. *Neurology.* 2023;**101**(9):e892–e903. doi:10.1212/WNL.0000000000207534
16. Aiello EN, Gramegna C, Esposito A, et al. The Montreal cognitive assessment (MoCA): updated norms and psychometric insights into adaptive testing from healthy individuals in Northern Italy. *Aging Clin Exp Res.* 2022;**34**(2):375–382. doi:10.1007/s40520-021-01943-7
17. Capitani E, Laiacona M. Composite neuropsychological batteries and demographic correction: standardization based on equivalent scores, with a review of published data. The Italian Group for the neuropsychological study of ageing. *J Clin Exp Neuropsychol.* 1997;**19**(6):795–809. doi: 10.1080/01688639708403761
18. Cohen J. *Statistical power analysis for the behavioral sciences*. London: Routledge; 2013.
19. Hughes SE, Haroon S, Subramanian A, et al. Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): rasch analysis. *BMJ* 2022;**377**:e070230. doi:10.1136/bmj-2022-070230
20. Misure Sanitarie per Fronteggiare l'emergenza coronavirus (Camera dei Deputati della Repubblica Italiana) (2022).
21. Sars-CoV-2 Dashboard. The COVID-19 Task force of the Department of Infectious Diseases and the Italian Service Istituto Superiore di Sanità. https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-dashboard
22. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med.* 2021;**18**(9):e1003773. doi:10.1371/journal.pmed.1003773
23. Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry.* 2022;**9** (10):815–827. doi:10.1016/S2215-0366(22)00260-7
24. Cameron-Maldonado S, Perez CM, Fernandez-Repollet E, Lopez-Cepero A. Age-related differences in anxiety and depression diagnosis among adults in Puerto Rico during the COVID-19 pandemic. *Int J Environ Res Public Health.* 2023;**20**(11):5922. doi:10.3390/ijerph20115922
25. Collaborators C-MD. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet.* 2021;**398**(10312):1700–1712. doi:10.1016/S0140-6736(21)02143-7
26. Nwachukwu I, Nkire N, Shalaby R, et al. COVID-19 pandemic: age-related differences in measures of stress, anxiety and depression in Canada. *Int J Environ Res Public Health.* 2020;**17**(17):6366. doi:10.3390/ijerph17176366
27. Vos, T. et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet.* 2020;**396**(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
28. Liu TC, Yoo SM, Sim MS, Motwani Y, Viswanathan N, Wenger NS. Perceived cognitive deficits in patients with symptomatic SARS-CoV-2 and their association with post-COVID-19 condition. *JAMA Netw Open.* 2023;**6**(5):e2311974. doi:10.1001/jamanetworkopen.2023.11974
29. Ahn S, Mathiason MA, Yu F. Longitudinal cognitive profiles by anxiety and depressive symptoms in American older adults with subjective cognitive decline. *J Nurs Scholarsh.* 2021;**53**(6):698–708. doi:10.1111/jnu.12692
30. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol.* 2020;**19**(11):919–929. doi:10.1016/S1474-4422(20)30308-2
31. Rau A, Schroeter N, Blazhenets G, et al. Widespread white matter oedema in subacute COVID-19 patients with neurological symptoms. *Brain.* 2022; **145**(9):3203–3213. doi:10.1093/brain/awac045
32. Frank MG, Nguyen KH, Ball JB, et al. SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: evidence of PAMP-like properties. *Brain Behav Immun.* 2022;**100**:267–277. doi:10.1016/j.bbi.2021.12.007
33. Fernández-Castañeda A, Lu P, Geraghty AC, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell.* 2022;**185** (14):2452–2468.e16. doi:10.1016/j.cell.2022.06.008
34. Soung AL, Vanderheiden A, Nordvig AS, et al. COVID-19 induces CNS cytokine expression and loss of hippocampal neurogenesis. *Brain.* 2022;**145** (12):4193–4201. doi:10.1093/brain/awac270
35. McIntyre RS, Phan L, Kwan ATH, et al. Vortioxetine for the treatment of post-COVID-19 condition: a randomized controlled trial. *Brain.* 2024;**147** (3):849–857. doi:10.1093/brain/awad377
36. Wang Y, Su B, Xie J, Garcia-Rizo C, Prieto-Alhambra D. Long-term risk of psychiatric disorder and psychotropic prescription after SARS-CoV-2 infection among UK general population. *Nature Human Behaviour.* 2024;doi:10.1038/s41562-024-01853-4
37. Houben-Wilke S, Goërtz YMJ, Delbressine JM, et al. The impact of long COVID-19 on mental health: observational 6-month follow-up study. *JMIR Mental Health.* 2022;**9**(2)doi:10.2196/33704
38. Martini AL, Carli G, Kiferle L, et al. Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients. *Eur J Nucl Med Mol Imaging.* 2022;**50**(1):90–102. doi:10.1007/s00259-022-05942-2
39. Steinmetz A, Gross S, Lehnert K, et al. Longitudinal clinical features of post-COVID-19 patients-symptoms, fatigue and physical function at 3- and 6-month follow-up. *J Clin Med.* 2023;**12**(12):3966. doi:10.3390/jcm12123966