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Post-COVID condition: a focus on psychiatric symptoms and diagnoses in patients with cognitive complaints

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Abstract

Objective. Cognitive and psychiatric symptoms are frequently reported after SARS-CoV-2 infection, but their interplay has been only partially explored. We investigated frequency and severity of psychiatric symptoms in patients with persistent cognitive complaints after COVID-19.

Methods. We conducted a cross-sectional study. Neurologists assessed 101 patients reporting cognitive symptoms after COVID-19. Patients were invited to fill a screening battery with self-reported psychometric scales (Depression Anxiety Stress Scales-21, Impact of Event Scale-Revised, Insomnia Severity Index). Patients scoring above validated cut-offs in ≥1 scale were referred to psychiatrists who administered the Mini-International Neuropsychiatric Interview (M.I.N.I.), Hamilton Anxiety (HAM-A), and Hamilton Depression (HAM-D) rating scales and asked to complete the Personality Inventory for DSM-5-Brief Form (PID-5-BF).

Results. Out of the 57 referred patients, 38 (64.4%) accepted to undergo the psychiatric examination. Among these, 18 (47.4%) were diagnosed with adjustment disorder (23.7%), anxiety disorder (10.5%), major depressive disorder (7.9%), and post-traumatic stress disorder (2.6%). Pharmacologic treatment before post-COVID condition (present in 12 patients, 31.6%) was associated with a score above cut-off on the HAM-A and HAM-D scales. A longer duration of untreated psychiatric illness after COVID-19 was associated with worse scores on the same scales. Patients with a higher PID-5-BF total score had a higher probability of receiving a psychiatric diagnosis.

Conclusion. Almost half of patients with post-COVID-19 conditions reporting cognitive symptoms were found to suffer from a psychiatric condition after psychiatric evaluation. The application of a psychiatric screening in a population suffering from long-term effects of COVID-19 can lead to early diagnosis and timely treatment.

Introduction

Post-COVID condition (PCC) is defined by the continuation or development of new symptoms within 3 months after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, from now on appointed as COVID-19, with these symptoms lasting for at least 2 months with no other explanation.[1-3]

This condition frequently includes fatigue, dyspnea, cognitive dysfunction, and mental health disturbances, notably affecting the patient's daily functioning. It may occur after recovery from acute COVID-19, or it may persist after the initial illness.[4] Post-COVID condition prevalence is reported to be around 43% among post-COVID patients, and the risk is higher for those patients who underwent hospitalization during the acute illness.[5] Presumably, the true prevalence is much higher, considering that patients with post-COVID condition are often reluctant to ask for help or do not know where to seek treatment.[6]

Neurological and psychiatric sequelae appear to be highly prevalent in post-COVID condition. Specifically, the variety of possible neurological symptoms after COVID-19, initially termed "Neuro-COVID" to encompass both acute/subacute manifestations as well as chronic symptoms developing after infection, ranges in severity from mild symptoms (eg, headache, dizziness, anosmia and ageusia) to more disabling conditions (eg, cognitive dysfunction, peripheral neuropathy, myopathy, seizures, intracranial hemorrhage, stroke, or

encephalopathy).[7] Even if, in the early pandemic days, a direct correlation between acute infection and cognitive manifestations was hypothesized, and indeed manifestations of acute infection, such as delirium, and chronic lingering post-COVID manifestations were grouped,[8] post-COVID-condition has since been increasingly recognized as a separate nosological entity.[2] Among its symptoms, memory problems represent the most frequently reported after fatigue, according to a meta-analysis including 41 studies on the post-COVID condition.[5] On the other hand, impaired concentration, frequently reported by post-COVID patients, can lead to memory problems, but it is also one of the core symptoms of psychiatric disorders frequently reported by post-COVID patients. Overall, this syndrome has a high impact on patient quality of life, even though the impact attributable to each manifestation may greatly vary.[9]

Actually, depression, anxiety, and post-traumatic stress disorder have high prevalence after COVID-19 (20%, 16-23%, 18-31% respectively).[10] Although a growing amount of data has been reported, most of the studies investigating post-COVID psychiatric symptoms rely only on self-administered psychometric scales, without a clinical assessment, with an intrinsic under- or over-diagnosis risk.[11] Moreover, psychiatric concerns can be misdiagnosed as their clinical presentation often overlaps with a somatic illness. For instance, the somatic symptoms of a panic attack may mimic those of an acute medical condition, leading to an 85% rate of misdiagnosis.[12] Eventually, the high rates of comorbidity between neurological and psychiatric disorders further complicate the diagnostic process.[13] Therefore, an accurate psychiatric assessment appears essential to properly and timely diagnose such disorders in the post-COVID scenario. In fact, the longer the duration of untreated illness (DUI), the worse the outcome, including more severe symptoms, poorer response to medication, higher comorbidity rates, lower remission rates, and higher suicide risk.[14]

Given the reported prevalence of psychiatric symptoms in post-COVID condition and their correlation with neurological symptoms, in this observational study, we aimed at (1) screening psychiatric symptoms in post-COVID-19 patients complaining of cognitive disturbances; and (2) assessing the potential consistency of this screening procedure with psychiatric clinical diagnoses. In a twin, accompanying paper, we report the results of the neurological and cognitive screening together with the correlation with psychiatric symptoms in this post-COVID-19 population.[15]

Methods

Study design and patient enrollment

This is an observational, multidisciplinary, cross-sectional study conducted between September 2021 and January 2023 at Luigi Sacco University Hospital, Milan, Italy.

Patients reporting persisting cognitive complaints occurring during or after COVID-19 were referred from the infectious diseases outpatient post-COVID clinic to the neurologic outpatient clinic.

During neurological assessment, a cognitive screening test (Montreal Cognitive Assessment, MoCA)[16] was administered. MoCA total scores were adjusted according to the most recent validation for Northern Italian population.[17] Moreover, patients were offered to participate in an online survey aimed at exploring additional symptoms reported during and after acute COVID-19 and psychoactive pharmacological history. During the same visit, 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),[18] Impact of Event Scale-Revised (IES-R).[19] Insomnia Severity Index (ISI),[20] 5-level EuroQol 5-Dimensional Questionnaire (EQ-5D-5L)[21] and Sheehan Disability Scale (SDS).[22] Patients who scored above the validated cut-off in at least one scale among DASS-21, IES-R, or ISI, and who provided consent for follow-up contact, were then referred to the psychiatric outpatient clinic of the same hospital, where a more specific assessment was performed. Firstly, psychiatrists administered the following clinical psychometric scales to objectively detect psychiatric symptoms and finally formulate a diagnosis: Mini-International Neuropsychiatric Interview (M.I.N.I.),[23] Hamilton Anxiety Rating Scale (HAM-A),[24] Hamilton Depression Rating Scale (HAM-D),[25] Montgomery Asberg Depression Rating Scale (MADRS),[26] and Young Mania Rating Scale (YMRS).[27] If a psychiatric diagnosis was made, patients were offered psychopharmacological treatment and follow-up according to current international guidelines. Finally, during the psychiatric evaluation, patients were offered to fill out the following self-reported psychometric scales: Post-traumatic Growth Inventory-Short Form (PTGI-SF)[28] and Personality Inventory for DSM-5-Brief Form (PID-5-BF).[29] DUI was considered the time elapsed between the onset of post-COVID condition and the time of the psychiatric assessment. A description of the assessment instruments, including psychometric scales with respective cut-offs, is available in the supplementary materials (S1). Figure 1 summarizes the entire enrollment process.

Ethical approval was granted by the Ethics Committee of Ospedale Luigi Sacco (Comitato Etico Milano Area 1), as part of a multicenter national study on the same population.[30]

Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Science, version 28.0 (SPSS Inc.). Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were reported as total amounts and percentages. All tests were two-tailed, and a P value < .05 was considered statistically significant. Given the non-normal distribution of our sample, non-parametric tests (Spearman's correlation, Mann-Whitney test, Kruskal-Wallis test) were used when appropriate. A chi square test was used to compare the distribution of data between categorical variables.

Results

Among the 101 patients who underwent the neurologic assessment and completed the psychiatric screening with self-administered scales, 57 (57.6%) scored above the cut-off in at least one scale and consented to follow-up psychiatric referral. Thirty-eight subjects (38.4%) accepted and were finally evaluated. The mean time between the screening and the psychiatric evaluation was 5.8 ± 2.8 months.

Sociodemographic characteristics and scores obtained in self-administered scales of the whole sample, of patients accepting psychiatric evaluation, and of patients who refused it, are displayed in Table 1.

In the group of those who accepted to undergo the psychiatric examination, females were more prevalent (63%), while in the group of those who refused the examination, female/male distribution was balanced. The 19 patients who refused to undergo the

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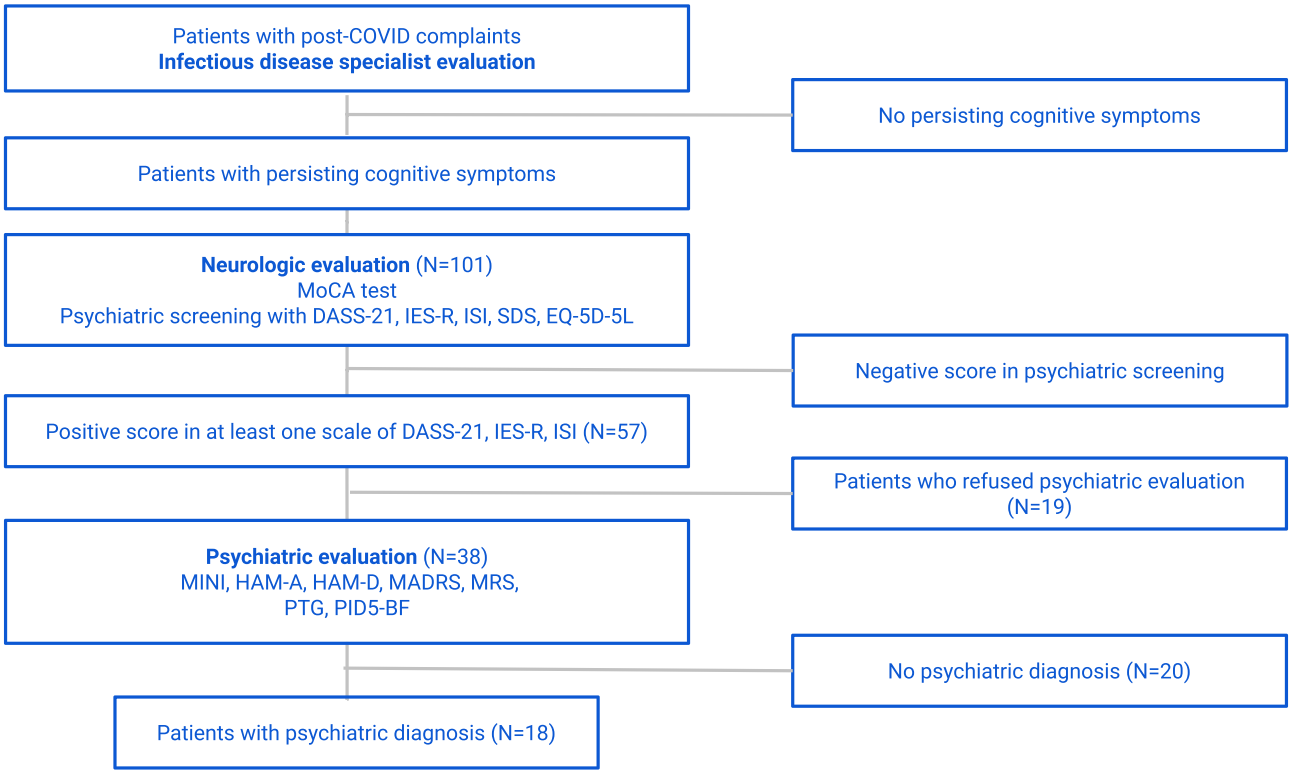

Figure 1. Enrollment flowchart.

psychiatric evaluation were on average younger (49.78 ± 11.79 years versus 59.2 ± 11.20) and had slightly higher MoCA score (24.83 ± 2.9 versus 24.21 ± 4.58), higher DASS-Anxiety (15.56 ± 8.91 versus 13.00 ± 8.9) and DASS-Depression (16.67 ± 9.23 versus 15.81 ± 9.9) scores compared to the means in our sample. The proportion of patients scoring above cut-off on the last two scales was higher in the group who refused the psychiatric examination than in the group who accepted it (77.8% and 83.3% versus 68.4% and 68.4%). However, by comparing these two groups, we did not find any statistically significant differences, confirming comparability between these two populations.

Out of the 38 patients evaluated, 18 (47.4%) were diagnosed with a psychiatric disorder. The diagnostic categories were the following: adjustment disorder (23.7%), anxiety disorder (10.5%), major depressive disorder (MDD) (7.9%), post-traumatic stress disorder (2.6%), and bipolar disorder (2.6%).

Patients who received a psychiatric diagnosis had on average higher scores on PID-5-BF (Mann-Whitney's U = 225.500; $P = .015$).

The MoCA score correlated with a MDD diagnosis (Kruskal-Wallis test statistic 11.538; $P = .042$). Longer DUI correlated significantly with higher scores at the HAM-D (Spearman's rho 0.363; $P = .035$) and HAM-A (Spearman's rho 0.453; $P = .006$) scales. Table 2 reports the scores of scales obtained at the psychiatric evaluation.

Eight patients (21.1%) had a previous psychiatric diagnosis, 10 (26.3%) reported a positive psychiatric family history, while 12 (31.6%) were at least on one psychopharmacological drug before COVID-19. Additionally, 12 patients (31.6%) were on psychotherapy at the time of the psychiatric assessment. The patients who received a psychopharmacological treatment before COVID-19 had significantly worse total scores on the HAM-D (Mann-Whitney's $U = 190.000$; $P = .034$) and scored above the cut-off in a significantly higher proportion of cases (chi square test 6.756; $P = .009$). The same finding was observed for the HAM-A considering both the total score (Mann-Whitney's $U = 233.000$; $P = .002$) and the proportion scoring above the cut-off (chi square test 4.277; $P = .039$). Moreover, these patients presented higher scores at the MADRS (Mann-Whitney's $U = 223.500$; $P = .006$). Considering patients who were on psychotherapy treatment, we found that this was associated with better scores on the PTGI-SF (Mann-Whitney's $U = 214.500$; $P = .016$), notably in the Personal Strength (Mann-Whitney's $U = 214.000$; $P = .002$) and New Possibilities (Mann-Whitney's $U = 228.500$; $P = .001$) domains.

Discussion

In this study, we aimed to investigate psychiatric symptoms in post-COVID patients complaining of cognitive disturbances. The first major finding concerns the high rates of psychiatric comorbidity in this selected population. Furthermore, we identified several clinical factors associated with the development of such psychiatric disturbances.

These findings suggest that psychiatric screening in a population suffering from long-term cognitive effects of COVID-19 leads to the detection of patients who need psychiatric intervention and may benefit from timely treatment.

Almost half of the patients who accepted to undergo the psychiatric evaluation were diagnosed with a psychiatric disorder, and almost all of them received psychopharmacological treatment after the diagnosis. These results are in line with previous studies that reported a high incidence of psychiatric symptoms in post-COVID

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Table 1. Sociodemographic and Clinical Characteristics of the Total Sample

	Patients who scored above cut-off at self-administered scales (N = 57) n (%) or [mean ± SD]	Patients who did not undergo psychiatric evaluation (N = 19) n (%) [mean ± SD]	Patients who underwent psychiatric evaluation (N = 38) n (%) or [mean ± SD]
Age (yr)	[56.49 ± 12.29]	[51.16 ± 12.94]	[59.2 ± 11.20]
Sex			
Male	23 (40.35)	9 (47.37)	14 (36.80)
Female	34 (59.65)	10 (52.63)	24 (63.20)
Marital status			
Single	6 (10.53)	1 (5.26)	5 (13.20)
Engaged-married	39 (68.42)	15 (78.95)	24 (63.20)
Separated-divorced	8 (14.04)	1 (5.26)	7 (18.40)
Widowed	2 (3.51)	0 (0.00)	2 (5.30)
Other	2 (3.51)	2 (10.53)	0 (0)
Employment			
Full-time	41 (71.93)	15 (78.95)	26 (68.40)
Part-time	1 (1.75)	0 (0.00)	1 (2.60)
Unemployed	3 (5.26)	1 (5.26%)	2 (5.30)
Retired	12 (21.05)	3 (15.79)	9 (23.70)
Educational status			
Primary school	2 (3.51)	0 (0.00)	2 (5.30)
Secondary school	6 (10.53)	1 (5.26)	5 (13.20)
High school	27 (47.37)	12 (63.16)	15 (39.50)
Degree	22 (38.60)	6 (31.58)	16 (42.10)
Living status			
Alone	11 (19.30)	3 (15.79)	8 (21.10)
With elderly-fragile people	6 (10.53)	1 (5.26)	5 (13.51)
Previous psychiatric diagnosis	13 (22.81)	5 (26.32)	8 (21.10)
Previous psychopharmacological therapy	17 (29.82)	5 (26.32)	12 (31.60)
Organic comorbidities	27 (47.37)	5 (26.32)	22 (57.90)
Other therapies	41 (71.93)	13 (68.42)	28 (73.68)
Hospitalization	29 (50.88)	7 (36.84)	22 (57.90)
Oxygen-therapy	29 (50.88)	9 (47.37)	20 (52.60)
Invasive ventilation	12 (21.05)	5 (26.32)	7 (18.40)
DASS–21 depression (cut-off 10/42)	41 (71.93), [15.91 ± 9.64]	15 (78.95), [16.11 ± 9.3]	26 (70.27), [15.81 ± 9.94]
DASS–21 anxiety (cut-off 8/42)	41 (71.93), [13.84 ± 8.85]	15 (78.95), [15.47 ± 8.66]	26 (70.27), [13 ± 8.95]
DASS–21 stress (cut-off 15/42)	40 (70.18), [20.79 ± 9.25]	12 (63.16), [20.21 ± 9.54]	28 (75.68), [21.08 ± 9.22]
IES-R (cut-off 33/88)	29 (50.88), [35.84 ± 18.98]	9 (47.37), [36.47 ± 20.62]	21 (55.26), [35.55 ± 18.12]
SDS	[16.13 ± 8.51]	[16.74 ± 9.58]	[15.81 ± 7.89]
ISI (cut-off 8/28)	37 (64.91), [10.2 ± 6.29]	14 (73.68), [9.79 ± 4.69]	23 (62.16), [10.41 ± 7.02]
MoCA adjusted (positive if score under cut-off)[14]	4 (7.0), [23.5 ± 2.09]	0 (0), [22.85 ± 2.77]	4 (10.5), [24.69 ± 0.82]

Abbreviations: SD, standard deviation; DASS, Depression Anxiety and Stress Scale; IES-R, impact of event scale revised; SDS, Sheehan disability scale; ISI, insomnia severity index; MoCA, Montreal Cognitive Assessment.

patients. A meta-analysis demonstrated a prevalence of 47% and 45% for anxiety and depression, respectively.[31] Other studies estimate that up to 35% of COVID hospitalized patients display symptoms of anxiety and depression.[32,33] Previous studies also indicate that the risk of developing psychiatric sequelae seems higher among COVID survivors compared to the general population.[34-40] Moreover, recent studies suggest that neuropsychiatric symptoms seem less likely to recover without intervention at

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Table 2. Psychometric Evaluation Scores in Patients Who Underwent Psychiatric Evaluation (N = 38)

Psychometric scales	n° (%) [mean ± SD]
HAM-A	[9.86 ± 7.0]
Positive	6 (15.8)
Negative	31 (81.6)
HAM-D	[7.28 ± 6.7]
Positive	10 (26.3)
Negative	26 (68.4)
MADRS	[11.08 ± 8.4]
Positive	25 (65.8)
Negative	12 (31.6)
Y-MRS	[2.11 ± 2.17]
Positive	0 (0)
Negative	35 (92.1)
PTGI	[32.11 ± 22.7]
Positive	12 (31.6)
Negative	24 (63.2)

Note: Positive stands for above cut-off, negative for below cut-off.
Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale, MADRS, Montgomery Asberg Depression rating scale; YMRS, Young Mania Rating Scale, PTGI-SF, Post-traumatic Growth Inventory-Short Form.

6 months [41] and 1 year follow-up.[42] This is similar to what occurred during the 2002 to 2004 severe acute respiratory syndrome (SARS) epidemic, when many SARS survivors developed psychiatric morbidity that persisted at 4-year follow-up.[43]

Interestingly, among the group of patients who refused to undergo the psychiatric evaluation, screening scores on the DASS-Anxiety and DASS-Depression scales were even higher compared with scores of the patients we evaluated. This indicates that those are potential psychiatric patients that could be diagnosed and treated accordingly, further supporting the importance of psychiatric assessment for post-COVID patients. It is also noteworthy that this group of patients with cognitive complaints and subjective anxiety and depression symptoms detected at DASS-21, spontaneously attended the neurologist but, when invited, refused to go to the psychiatrist. This may have happened because the psychic symptoms can be perceived as less distressing than the cognitive symptoms. Also, in the time elapsed from the screening completion to the psychiatrist's visit proposal, the anxiety-depressive symptoms may have resolved spontaneously, as frequently occurs in adjustment disorder.[44] Finally, it could indicate the stigma that still affects mental disorders, for which patients perceiving psychic symptoms struggle to arrive at the psychiatrist's attention.[45]

As expected, we found that patients diagnosed with major depressive disorder scored worse on the MoCA. Cognitive complaints represent indeed a core symptom of many psychiatric conditions, including depressive disorders. Considering the high level of overlap between neurological and psychiatric symptomatology,[13] it is plausible that a significant part of patients complaining of cognitive symptoms referred to as the so-called "Neuro-COVID"[7] could indeed be affected by an underlying concomitant psychopathological condition. Our results indicate that psychiatric disorders represent a significant and possibly underestimated component of the post-COVID condition.

As expected, a longer DUI correlates with worse scores on anxiety and depression scales. In fact, in the psychiatric setting, a longer DUI is associated with worse outcomes, including more severe symptoms and lower remission rates.[14] This evidence supports the value of psychiatric screening to provide a timely treatment that could improve the clinical outcome.

To date, this is among the few studies assessing personality traits with PID-5-BF and post-traumatic growth with PTGI-SF in patients with post-COVID conditions. We found that dysfunctional personality traits correlate with a psychiatric diagnosis. This is somehow expected, considering the high comorbidity rate between personality and psychiatric disorders.[46] Finally, we found that psychotherapy is associated with a positive post-traumatic response as measured by the PTGI-SF scale. Psychotherapy is generally associated with neurobiological functional improvement,[47] and a recent study suggests some benefits of cognitive-behavioral psychotherapy in post-COVID condition,[48] although the literature on the topic is still scarce. Future studies are needed to assess the possible role of psychotherapy interventions on the post-COVID condition.

Our study has some strengths. First, this is a multidisciplinary study that involves a combined psychiatric and neurological assessment and management. Secondly, we provide frequency data from clinical assessment, not only from self-administered psychiatric scales, which typically carry an under- or over-estimation bias.

Our study also presents several limitations, first of all its observational nature. Without an appropriate comparison group, it is not possible to completely differentiate between the direct and indirect effects of COVID-19 on mental health. Moreover, the self-administered psychometric scales used as screening tools were arbitrarily chosen and may be a source of selection bias. The recruitment process, the small sample size, and the high drop-out rate of patients who refused to undergo the psychiatric evaluation, despite scoring above the cut-off at screening scales, represent another important limitation and may reduce the external validity of the study.

Conclusions

Despite these limitations, our study may have important clinical implications. Even though the number of COVID-19 cases and hospitalizations has massively declined, post-COVID conditions continue to be a major public health issue. Psychiatrists and neurologists will have to face the neuropsychiatric consequences of COVID-19 for an indefinite period of time. Our study revealed that a combined neurological and psychiatric screening and assessment is highly recommended for patients who suffer from cognitive symptoms after COVID-19. We further hypothesize that the aforesaid protocol could be applied also for other similar infective or stressor events. Patients may not report mental health symptoms, possibly due to fear of the stigma or simply not appreciating that there are effective treatments available for these issues. A 1-year follow-up of our study has been scheduled to assess potential beneficial effects due to psychopharmacological treatment. In fact, treating the mental health effects of the post-COVID condition remains among the biggest challenges.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000464.

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N.C.; Investigation: B.D., C.S., C.N., F.M., G.C., L.G., L.L., M.C., M.C., N.C.; Methodology: B.D., C.S., C.N., F.M., G.C., L.G., L.L., M.C., M.C., N.C., S.P.; Writing – original draft: B.D., C.S., C.N., G.C., L.G., L.L., M.C., M.C., N.C., L.P.; Writing – review & editing: B.D., C.S., V.C., F.M., G.C., L.G., L.L., G.M., M.C., M.C., N.C., A.N., S.P., L.P.; Project administration: F.M., L.P.; Supervision: L.P.

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Competing interest. B Dell'Osso has received lecture honoraria, not related to the work sub-mitted for publication, from Angelini, Janssen Pharmaceuticals, Lundbeck, Livanova, Arcapharma, and Neuraxpharm. L Pantoni is a member of the editorial boards of Neurology, European Stroke Journal, Cerebrovascular Diseases, and an associate editor of Neurological Sciences. He has received consultation fees, not related to the work submitted for publication, from Amicus and PIAM. G Cirnigliaro is supported by "Fondazione Romeo ed Enrica Invernizzi" (Corso Venezia n°32, 20 122, Milano (MI)).

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