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Post-COVID-19 psychiatric and cognitive morbidity: Preliminary findings from a Brazilian cohort study

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ABSTRACT

Objective: The present study aims to investigate the occurrence of psychiatric and cognitive impairments in a cohort of survivors of moderate or severe forms of COVID-19.
Method: 425 adults were assessed 6 to 9 months after hospital discharge with a structured psychiatric interview, psychometric tests and a cognitive battery. A large, multidisciplinary, set of clinical data depicting the acute phase of the disease, along with relevant psychosocial variables, were used to predict psychiatric and cognitive outcomes using the 'Least Absolute Shrinkage and Selection Operator' (LASSO) method.
Results: Diagnoses of 'depression', 'generalized anxiety disorder' and 'post-traumatic stress disorder' were established respectively in 8%, 15.5% and 13.6% of the sample. After pandemic onset (i.e., within the previous year), the prevalence of 'depression' and 'generalized anxiety disorder' were 2.56% and 8.14%, respectively. Memory decline was subjectively reported by 51.1% of the patients. Psychiatric or cognitive outcomes were not associated with any clinical variables related to the severity of acute-phase disease, nor by disease-related psychosocial stressors.
Conclusions: This is the first study to access rates of psychiatric and cognitive morbidity in the long-term outcome after moderate or severe forms of COVID-19 using standardized measures. As a key finding, there was no significant association between clinical severity in the acute-phase of SARS-CoV-2 infection and the neuropsychiatric impairment 6 to 9 months thereafter.

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1. Introduction

There is an urgent need for a better characterization of the profile of acute and chronic psychiatric and neuropsychological morbidity among COVID-19 victims and the role played by multiple pathophysiological components related to disease severity/staging and individuals' clinical characteristics. Cross-sectional studies addressing the incidence of psychiatric and cognitive abnormalities in the acute and severe cases of SARS-CoV-2 infection highlight the occurrence of delirium, encephalopathy, cognitive impairment, insomnia, psychosis and mood symptoms [1]. Regarding chronic symptoms, longitudinal studies conducted in post-COVID-19 cohorts have presented preliminary evidence of a high prevalence of psychiatric symptoms in the 'long phase' of the disease, namely anxiety, depression, fatigue, and post-traumatic stress disorder (PTSD) [2–6], though recent studies indicated that these symptoms tend to wane in the following months [7]. These large longitudinal studies are important but fail in differentiating infected from non-infected individuals as well as patients with asymptomatic, mild, moderate, and severe cases, who might present with different phenomenological characteristics [8,9].

Psychiatric and cognitive morbidity following SARS-CoV-2 infection may emerge from multiple factors as part of what is being referred to as post-acute COVID-19 syndrome (PACS) or "long COVID" [10]. Psychosocial stress represents an important mechanism that predisposes COVID-19 victims to emotional suffering, some of whom will ultimately present with signs and symptoms of major psychiatric disorders [11]. However, recent evidence indicates that neuropsychiatric outcomes may also represent features of systemic and central nervous system (CNS) involvement in the pathophysiology of COVID-19, resulting largely from indirect mechanisms mediated by inflammation, hypercoagulability, vascular, and immunological pathways, in addition to possible direct invasion of the brain by the coronavirus [4,12]. According to current knowledge, the interaction of multiple COVID-19-related pathophysiological mechanisms disrupts brain homeostasis, causing dysfunctions/injuries that will ultimately present as symptoms of mental and cognitive impairment ('neurocovid') [13]. A recent perspective piece suggested that, in vulnerable populations (particularly the elderly), SARS-CoV-2 infection may hasten underlying brain pathologies and increase the risk of late-life cognitive decline and progression to dementia [14].

The available knowledge on the so-called 'neurocovid' hypothesis was largely built from the clinical analysis of case series and uncontrolled studies conducted amidst the pandemic. In spite of the inherent methodological difficulties of carrying out research in this context, the current body of evidence about COVID-19-related neuropsychiatric morbidity does encourage the implementation of more refined symptom assessment protocols to address this matter in greater depth. Most studies so far have methodological limitations, such as cross-sectional design [15] and lack of standardized SARS-CoV-2 infection determination [16] and lack of severity markers [17]. Furthermore, the assessment of the mental state has been generally based on small arrays of neuropsychiatric symptoms [18], frequently assessed by self-report questionnaires [19], electronic databases [20], or by the attending physician's clinical impression [1], therefore restricted to dimensional or non-validated symptomatic scales [5,7,21]. Finally, most of the available literature was published in populations from Eastern and European countries, which may constrain the generalizability of findings [5].

The primary objective of the present study is to ascertain the mental and cognitive state of COVID-19 survivors after 6 to 9 months of the acute episode, with emphasis on the assessment of patients who recovered from moderate or severe forms of the disease requiring hospitalization, using a comprehensive protocol composed by objective and validated psychometric instruments. As a secondary and exploratory goal, we determined the extent to which these impairments were correlated with the severity of the acute disease, as well as with the occurrence of stressful events related to the COVID-19 pandemic, trying to predict potential variables associated with a worse neuropsychiatric morbidity.

2. Methods

2.1. Study design and setting

The study was conducted at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a tertiary, university-based medical facility that is responsible for providing care for moderate and severe cases of the COVID-19 in Brazil. The 'HCFMUSP post-COVID-19 cohort' was constituted to facilitate multidisciplinary studies addressing long-term medical, functional and neuropsychiatric outcomes among adults and elders who survived moderate or severe forms of COVID-19. Subjects were assessed 6–9 months after hospital discharge (mean interval of 207 days, SD 20.4) through structured interviews and assessment protocols pertaining to an interdisciplinary medical team. A full description of our methodology as well a flowchart can be seen at Busatto et al. [22]. In the present communication, we will report on the assessment of psychiatric and cognitive outcomes.

This research protocol has been approved by the Ethics Committee at HCFMUSP (CAPPesq-HC), and registered at the Brazilian Registry of Clinical Trials (ReBEC) under the registration number 4.270.242 (RBR-8z7v5wc) and will be reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. [23]

2.2. Participants

All patients hospitalized at HCFMUSP for at least 24 h due to moderate or severe forms of COVID-19 between March and September 2020 ($n = 3751$) were regarded as eligible for this 'post-COVID-19 cohort'. The requirement of hospital treatment was used to ascertain moderate forms of COVID-19, and the need of intensive care unit (ICU) treatment was used to define severe cases. We present herein a preliminary analysis of the first 2009 individuals who were invited to participate (compared with the total cohort sample described above and in Busatto Filho et al., 2021). From hospital registries, we ascertained all patients aged 18 years or older who were discharged from hospital in this time period, excluding the deceased ($n = 1803$). Diagnostic confirmation was based on clinical presentation combined with Polymerase Chain Reaction (PCR) tests to detect viral RNA or enzyme-linked immunosorbent assays to detect the presence of anti-SARS-CoV-2 serum antibodies (in subjects for whom a RT-PCR test collected up to the 10th day of symptom onset was not available). We also included 6 patients with highly suspected COVID-19 (based on clinical and chest-CT findings) without PCR confirmation. These patients were contacted by telephone and enrolled in this follow-up study. In case of acceptance, an appointment was made at an outpatient clinic dedicated to the assessment of this cohort. From all contacted patients, a small number of patients declined participation, reporting being too impaired to visit the clinic ($n = 18$). Further exclusions were due to failed telephone contact ($n = 645$), refusal to participate in the study as expressed by the patient or his/her informant upon telephone contact ($n = 297$), inability to comply with the assessment protocol due to pre-existing dementia or severe intellectual deficiency ($n = 10$), or unknown reasons (i.e., subjects who did not show at the scheduled appointment) ($n = 408$). A total of 425 volunteers signed informed consent and completed neuropsychiatric assessments between October/2020 and January/2021. A flow-chart can be seen in Supplementary Fig. 1.

2.3. Assessment protocol

A set of data relative to the acute stage of the disease was retrieved from hospital charts and databases, providing baseline information on duration of hospital stay; requirement/duration of ICU care; requirement of orotracheal intubation, mechanical ventilation, or dialysis; and

any available information about previous diagnoses, comorbidities, and relevant clinical symptoms. There was no systematic capture of neuropsychiatric and/or cognitive symptoms at baseline, except for recorded information about incident delirium, seizures, or any signs suggestive of encephalopathy or cerebrovascular events during the acute phase of the disease.

Evaluation of mental state and global cognitive function was done in face-to-face interviews by a dedicated team of psychiatrists, psychologists, neuropsychologists, and undergraduate medical students using the following instruments (details provided on Supplementary Table 1): Clinical Interview Schedule - Revised (CIS-R), Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV), Hospital Anxiety and Depression Scale (HAD), Ask Suicide-Screening Questions (ASQ), Post-Traumatic Stress Disorder Checklist (PCL-C), Alcohol Use Disorder Identification Test (AUDIT), Memory Complaint Scale (MCS), Temporal and Spatial Orientation (as obtained from the Mini-Mental State Examination), Trail Making Test (TMT) – A, Verbal Fluency Test (VFT), – Clinical Frailty Scale (CFS), International Physical Activity Questionnaire (IPAQ) – Short Version. All examiners attended the training sessions on the assessment protocol in order to standardize procedures and maximize the reliability of psychometric measures. Prior to examination, a score sheet was completed to gather information about the patient's mental health antecedents (personal and family history of psychiatric disorders) and occurrence of psychosocial/stressful events related to the COVID-19 pandemic (e.g., death of close family members; financial problems; and other relevant life-events or stressors). Questions regarding substance use and general health status (GHS) were also included. The latter variable was acquired upon completion of a questionnaire presented to the participants during clinical examination. This variable had five possible ratings in a Likert scale relative to the patient's perception of global health, yielding five categorical GHS ratings, i.e., very bad; bad; average; good; or very good. The assessment protocol required on average 90 min to be completed, comprising a structured interview with psychometric and cognitive screening tests, as described below.

2.4. Statistical analysis

For descriptive statistics, we calculated percentages, mean, median, standard deviation, and the upper and lower limits of the 95% confidence interval to the percentage. For inferential statistics we used linear regression for numeric variables, binary logistic regression for binary variables, and Poisson distribution for trail making and verbal fluency. For selecting predictive variables to include in our analysis we used the LASSO (Least Absolute Shrinkage and Selection Operator) method in order to reduce the number of selected variables predicting new data with small error [24]. LASSO is reputed as a very sensitive machine learning method for increasing the quality of prediction by shrinking regression coefficients [25]. Each LASSO was repeated at least ten times in order to reduce its instability and possible effect of confounding factors.

After LASSO, the following variables were included as possible predictors: age, education level, temporo-spatial orientation score in Mini Mental State Examination (MMSE), general health status (GHS) and pre−/post-COVID-19 frailty (CFS), persistent cough, duration of hospitalization during acute phase of infection, length of stay in ICU, requirement of hemodialysis or orotracheal intubation, and presence of medical/neurological comorbidities (such as systemic arterial hypertension, diabetes mellitus, cancer, hepatic steatosis or cirrhosis, chronic renal disease, gastric ulcer, bleeding ulcer, rheumatoid arthritis, rheumatological disease, stroke and dementia).

3. Results

Data from an interim sample of 425 patients were used in the present analysis. The mean age of participants was 55.7 years (median 56.4), and 51.5% were women. Overall educational level was low, with 55.5% of participants not having completed high school (less than 12 years of education) (Table 1). Table 2A displays the characteristics of the sample during the acute phase of COVID-19 (hospital treatment), with emphasis on variables that could potentially predict unfavourable neuropsychiatric outcomes. Supplementary Table 2 describes the clinical profile of patients during hospital stay, with emphasis on the diagnosis of medical comorbidities and the requirement of intensive-care treatment.

Table 1 also presents an estimate of their subjective memory complaints (MCS score). The characterization of symptoms according to psychometric scales (HADS, ASQ, AUDIT, MCS) and cognitive screening tests (MMSE-orientation, TMT-A and VFT) at 6-month follow-up after COVID-19 infection is summarized in Table 2B. Table 3 presents the diagnostic classification according to CIS-R, SCID-5-RV (for the assessment of psychotic symptoms) and changes in substance use behaviour. Notably, we found evidence of psychotic symptoms according to SCID-5-RV schedule, with 8.7% of participants reporting hallucinations and 12.5% reporting delusions of any kind lifetime. Furthermore, we calculated both chronic diagnosis (all time) and new diagnosis (symptoms starting within less than one year). Noteworthy, when looking only to new diagnosis, we found a prevalence of 2.56% of 'depression' (1.16% severe depression), 2.79% of 'specific phobia', 8.14% of 'generalized anxiety disorder' and 1.4% of 'obsessive-compulsive disorder'.

Table 4 displays linear regression analyses searching for predictors of the psychiatry outcomes 'anxiety' and 'depression' according to HAD, and Table 4B displays predictors of the CIS-R outcome 'common mental disorder' (please see a complete definition in Supplementary Table 1), six months after the acute phase of COVID-19. In all instances, only two variables were able to predict the occurrence of these psychiatric diagnoses, namely 'current frailty' (according to CFS) and 'general health status' (GHS scale). 'Common mental disorder' was positively associated with GHS across all levels, i.e., better general health associated with better psychiatric outcomes. As compared to those with 'very bad' general health, patients with 'regular' health were 86% less likely to be diagnosed with a 'common mental disorder' ($p = 0.016$), similar to those

Table 1
Sociodemographic, psychosocial variables and subjective memory complaints.

		%	95%CI
Age (years)	< 60	58.49	53.74–63.09
mean: 55.7, SD 14.2	≥ 60	41.51	36.92–46.26
	Female	48.47	43.75–53.21
Sex	Male	51.53	46.79–56.25
	No formal education	4.47	2.84–6.92
	Incomplete Elementary School	33.41	29.09–38.03
	Elementary School	11.06	8.40–14.42
	Incomplete High School	6.59	4.57–9.39
	High School	27.76	23.72–32.21
	Incomplete Bachelor	4.71	3.03–7.20
	Bachelor	8.00	5.75–11.00
Education	Post-Graduation	4.00	2.47–6.36
	No	36.94	32.49–41.63
	Little	16.24	13.02–20.05
	Moderate	11.06	8.40–14.42
	A lot	24.47	20.62–28.78
Financial Problems[a]	Extreme	11.29	8.61–14.68
Death of Family	No	92.24	89.27–94.45
Member[a]	Yes	7.76	5.55–10.73
	Similar or better	48.93	44.17–53.7
	Slightly worse	35.80	31.36–40.5
MCS–1	Much worse	15.27	12.13–19.05
	Similar or better	53.06	43.25–62.64
	Slightly worse	35.71	26.92–45.59
MCS–2	Much worse	11.22	6.22–19.15

[a] Psychosocial stress due to or related to COVID-19. MCS, Memory Complaint Scale; MCS-1, self-assessment (patient); MCS-2, assessment provided by a family member.

Table 2
(A) Clinical variables that could potentially impact the incidence of neuropsychiatric symptoms. (B) Neuropsychiatric symptoms among patients with moderate or severe COVID-19 in assessment 1 post-discharge.

		N	Mean (SD)	Min.	1stQ	Median	3rdQ	Max.	95%CI
A	Duration of hospitalization (days)	424	16.53 (16.31)	1	7	11	21	142	15.12–18.25
	Duration of ICU stay (days)	210	13.62 (14.24)	0	6	9.5	15.75	126	11.99–15.93
	Length of orotracheal intubation (days)	128	10.77 (8.66)	0	6	8	13.25	52	9.46–12.49
	Length of hemodialysis (days)	45	14.38 (10.38)	0	5	13	21	36	11.54–17.55
	Frailty (CFS) prior to COVID-19	405	2.54 (1.13)	1	2	3	3	7	2.43–2.65
	Frailty (CFS) post-COVID-19	404	3.12 (1.24)	1	2	3	4	7	3.00–3.25
	Duration of cough (days)	126	112.80 (168.27)	1	15	61	191	1586	92.04–157.77
	Current O_2 saturation	418	96.30 (2.33)	81	96	97	98	100	96.05–96.50
	Current Body Mass Index (BMI)	419	31.90 (6.94)	17.68	27.47	30.55	35.09	61.57	31.26–32.59
	HADS Anxiety	425	6.18 (5.10)	0	2	5	10	21	5.71–6.68
	HADS Depression	425	4.81 (4.52)	0	1	4	8	19	4.39–5.25
	ASQ	425	0.60 (1.55)	0	0	0	0	11	0.47–0.77
	AUDIT	425	1.56 (3.65)	0	0	0	1	29	1.25–1.95
	MCS	425	5.29 (4.15)	0	2	5	8	14	4.90–5.69
	MMSE (orientation score, range 0–10)	425	9.33 (1.44)	0	9	10	10	10	9.18–9.45
	TMT-A (completion time, seconds)	422	69.10 (51.10)	0	37.08	53.58	84.75	350	64.60–74.39
	TMT-A (number of errors)	422	1.86 (20.98)	0	0	0	1	429	0.76–6.92
	VFT (number of words)	424	15.39 (5.30)	0	12	15	18	39	14.90–15.91
	VFT (number of errors)	417	0.04 (0.24)	0	0	0	0	2	0.02–0.07
B	VFT (number of perseverations)	421	0.76 (1.16)	0	0	0	1	8	0.66–0.88

ICU, Intensive Care Unit; CFS, Clinical Frailty Scale; HADS, Hospital Anxiety Depression Scale; ASQ, Ask Suicide-Screening Questions; AUDIT, Alcohol Use Disorder Identification Test; MCS, Memory Complaint Scale; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Test (animals).

Table 3
Prevalence of psychiatric diagnoses according to the CIS-R schedule, changes in substance use behaviour, and presence of psychotic symptoms according to the SCID-5 interview, among participants in the 'HCFMUSP post-COVID-19 cohort'.

Diagnosis	Onset at any time (%)	Onset less than 1-year (%)	Onset 1-year or more (%)
Mild Depression without somatic symptoms	1.65	0.70	0.95
Mild Depression with somatic symptoms	1.65	0.47	1.18
Moderate Depression without somatic symptoms	1.41	0.23	1.18
Moderate Depression with somatic symptoms	1.88	0.00	1.88
Severe Depression	1.41	1.16	0.25
Depression - Total	8.00	2.56	5.44
Panic Disorder	0.94		
Agoraphobia without Panic	0.71		
Agoraphobia with Panic	0.71		
Social Phobia	0.71		
Specific Phobia - Without COVID	2.82		
Specific Phobia - With COVID	3.76	2.79	0.97
Generalized Anxiety Disorder	14.12	8.14	5.98
Obsessive Compulsive Disorder	3.53	1.40	2.13
Mixed anxiety-depressive disorder	15.53		
Common Mental Disorder	32.24		
Post-Traumatic Stress Disorder	13.65		
Started or increased use of Alcohol post-COVID19	1.42		
Started or increased use of Tobacco post-COVID19	1.65		
Started or increased use of Cannabis post-COVID19	0.48		
Started or increased use of Sedative Drugs post-COVID19	6.27		
Started or increased use of Opioids post-COVID19	1.42		
Started or increased use of other drugs post-COVID19	2.38		
Delusions	12.47		
Hallucinations	8.71		

Table 4
(A) Linear regression analysis addressing the impact of general health status (GHS) subsequent to COVID-19 on the psychiatric outcome (anxiety or depression) after six months, as defined by the CIS-R interview. (B) Binary logistic regression for Common Mental Disorder (outcome variable) according to different categories of general health status (GHS) subsequent to COVID-19 (predicting variable).

A	Predicting variable	Coefficient	SE	95%CI	p-value
Anxiety	(Intercept)	9.15	1.72	5.77–12.52	<0.001
	GHS – Bad	−1.82	1.74	−5.24–1.60	0.296
	GHS – Average	−4.13	1.56	−7.20 to −1.06	0.008
	GHS – Good	−5.84	1.57	−8.93 to −2.75	<0.001
	GHS – Very Good	−6.81	1.72	−10.20 to −3.42	<0.001
	Current CFS score	0.58	0.21	0.16–0.99	0.006
Depression	(Intercept)	7.69	1.47	4.81–10.58	<0.001
	GHS – Bad	−1.63	1.48	−4.54–1.93	0.274
	GHS – Average	−4.56	1.33	−7.18 to −1.94	<0.001
	GHS – Good	−6.02	1.34	−8.66 to −3.38	<0.001
	GHS – Very Good	−6.38	1.47	−9.27–3.48	<0.001
	Current CFS score	0.67	0.18	0.32–1.02	<0.001

B	Predicting variable	OR	SE	95%CI	p-value
Common Mental Disorder	(Intercept)	1.39	2.41	0.28–10.35	0.71
	GHS - Bad	1.15	2.55	0.14–6.67	0.89
	GHS - Average	0.14	2.26	0.02–0.59	0.02
	GHS - Good	0.09	2.28	0.01–0.37	0.003
	GHS - Very Good	0.07	2.51	0.01–0.35	0.003
	Current CFS score	1.33	1.11	1.09–1.63	0.01

GHS, General Health Status; CIS-R, Clinical Interview Schedule – Revised; CFS, Clinical Frailty Scale.

with 'good' (91.5%, $p = 0.003$) and 'very good' general health (94.4%, p = 0.003). The same was true for frailty scores, where each additional point on the CFS increased the chance for having a 'common mental

disorder' in 32.5% ($p = 0.006$). The Area under the ROC curve of 0.72, indicating good quality of the model. Regarding 'depression' and 'anxiety', the occurrence of symptoms within these affective domains was associated with a worse estimate of general health (i.e., lower GHS) and frailty (i.e., higher CFS scores) (Table 4A). Psychiatric symptoms could not be associated with any clinical measure at the time of COVID-19 infection or psychosocial variables related to effect of COVID-19 pandemic.

Table 5 summarizes data relative to linear regression analysis addressing the effect of socio-demographic and clinical variables on the prediction of cognitive outcomes, i.e., temporo-spatial orientation (MMSE), attention (TMT-A) and verbal fluency (VFT with semantic restriction). Previous history of stroke or pre-existing dementia at baseline assessment (i.e., prior to the acute phase of COVID-19) were associated with worse performance in the orientation task of the MMSE ($R^2 = 0.283$). Older age and disorientation (according to MMSE) were associated with a worse performance in the TMT-A ($R^2 = 0.114$). Finally, older age, higher frailty (CFS) scores prior to COVID-19 and temporo-spatial disorientation (MMSE) in the current assessment were associated with a worse performance in the VFT; as opposed to that, higher education was (as expected) associated with better performance in the VFT. Curiously, individuals who had been submitted to hemodialysis due to COVID-19 complications during hospitalization had a better performance in this cognitive task. The aforementioned models explained 28%, 11% and 24% of the variability in new diagnoses of cognitive impairment according to the MMSE, TMT-A and VFT, respectively.

Supplementary Table 3 compares the results from cognitive tests (TMT-A and VFT) obtained in the present sample with Brazilian norms. In our sample, patients performed worse in TMT-A across all ages (19–39: 34.37 vs 48.03 s; 40–59: 39.91 vs 60.8 s; 60–75: 43.62 vs 81.86 s). However, no apparent differences were found between our sample and Brazilian norms regarding VFT, unless a better performance of our sample in individuals under 65 years old (13.79 vs 16 words).

Finally, the comparison of baseline (in-hospital) clinical and socio-demographic variables of participants and non-participants showed striking similarities in mean age (55 years in both groups), gender distribution (53% and 51% of males, respectively), body mass index (32,5 and 30,8) and duration of symptoms upon hospital admission (8 days for both groups). Participants had in fact a higher number of medical comorbidities, longer hospital stay (14 vs. 9 days) and a higher proportion of them required ICU treatment (65% vs. 42%) or orotracheal intubation (43% vs. 29%), subsuming that the actual participants had experienced more severe forms of the acute disease as compared to non-participants (data not shown).

4. Discussion

The present study provides original data highlighting the high prevalence of neuropsychiatric impairment in the long-term outcome of moderate or severe forms of SARS-CoV-2 infection. To the best of our knowledge, the objective assessment of mental state with the aid of validated diagnostic instruments is a relevant and original contribution in the characterization of psychiatric and cognitive impairments among COVID-19 survivors; most of the previous studies dedicated to the assessment of long-term post-COVID-19 neuropsychiatric morbidity were based solely on unstructured questionnaires, self-report tests, telephone-based interviews or other forms of remote assessment, yielding at best a preliminary overview of complaints and symptoms. Moreover, studies that proposed to assess potential predictors of psychiatric and cognitive morbidity included only a few variables, most of them assessed retrospectively. The protocol that we used in the present study was built to provide diagnostic classification and to depict a more detailed symptomatic profile of post-COVID-19 psychiatric and cognitive morbidity. A comprehensive array of clinical and functional variables that had been previously tabulated during hospital treatment, along with a set of COVID-19 related psychosocial stressors, were used to evaluate the contribution of these acute-phase variables to the long-term psychiatric outcomes.

The CIS-R diagnoses of 'common mental disorder', 'anxiety' and 'PTSD' were highly prevalent. Also, we found that roughly one-third of the new diagnoses of 'depression' and 'obsessive-compulsive disorder', and the majority of diagnoses of 'generalized anxiety disorder' were established within the previous year in our sample of post-COVID-19 survivors. This is in line with previous studies that called attention to the high prevalence of mental health problems in the course of COVID-19 [26,27]. The prevalence of 'common mental disorder' in this post-COVID-19 cohort (32.2%) was higher than previously reported in the Brazilian general population (26.8%), as indicated by epidemiological studies using the CIS-R schedule' [28]. Regarding the CIS-R diagnosis of 'depression', prevalence in the present sample (8.0%) was higher than expected in epidemiological studies concerning high- and low-income countries (respectively 5.5% and 5.9%, 12-month prevalence), as well as in general Brazilian population using the same instrument (around 4 and 5%) [29]. The CIS-R diagnosis of 'generalized anxiety disorder' (GAD) in the present sample (14.1%) was considerably higher than the

Table 5
Linear regression analysis displaying statistically significant effects of variables predictive on cognitive outcome, according to the assessment of MMSE temporo-spatial orientation, attention (TMT-A) and verbal fluency (VFT).

Cognitive outcome	Predicting variable	Coefficient	SE	95%CI	p-value
MMSE (orientation)	(Intercept)	9.49	0.059	9.37–9.60	< 0.001
	Previous Stroke	−1.31	0.277	−1.85 to −0.76	< 0.001
	Previous Dementia	−6.44	0.486	−7.39 to −5.48	< 0.001
	(Intercept)	97.63	21.572	55.23–140.03	< 0.001
TMT-A	Age (years)	0.97	0.168	0.64–1.30	< 0.001
	MMSE (orientation score)	−8.77	1.813	−12.34 to −5.21	< 0.001
	(Intercept)	8.79	2.348	4.18–13.41	< 0.001
	Hemodialysis required	1.45	0.733	0.01–2.90	0.049
	Frailty pre-COVID	−0.60	0.222	−1.04 to −0.16	0.007
	Age (years)	−0.04	0.019	−0.08 to −0.004	0.030
	Education level:				
	Incomplete Elementary	0.80	1.15	−1.45–3.06	0.49
VFT	Elementary School	1.82	1.30	−0.74–4.37	0.16
	Incomplete High School	2.03	1.42	−0.76–4.83	0.15
	High School	2.58	1.23	0.16–5.00	0.04
	Incomplete Bachelor	4.72	1.59	1.60–7.84	0.00
	Bachelor's degree	4.56	1.40	1.81–7.31	0.00
	Post-Graduation	5.41	1.65	2.17–8.66	0.00
	MMSE (orientation score)	0.88	0.18	0.53–1.23	< 0.001

MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test (A); VFT, Verbal Fluency Test (semantic restriction: "Animals").

12-month prevalence in the European general population (0.2–4.3%) [30], in Brazilian general population (9.9%) and in Brazilian individuals with coronary heart disease (10.2%), both using the same instrument [31]. A recent study using the same structured interview (CIS-R) in representative sample of Brazilian general population during COVID-19 pandemic found lower rates than reported in this manuscript, with 21.1% of common mental disorders, 2.8% of depressive disorders and 8% of anxiety disorders, highlighting high prevalence in our sample [32].

Even though the cross-sectional nature of the psychiatric data acquisition precludes the assessment of incidence rates, we were able to determine the prevalence of new psychiatric diagnoses. Our data indicate a high prevalence of new diagnoses of 'depression', 'generalized anxiety disorder' and 'obsessive compulsive disorder', contrasting with the findings of a recent meta-analysis of longitudinal studies that found only a small increase on mental health issues among general population pre- and post-COVID-19 pandemic [33]. Noteworthy, our sample is older and represented by COVID-19 survivors, and therefore more prone to be clinically impaired. We understand that the high proportion of new psychiatric diagnoses in our sample can be related to the severity of COVID-19 morbidity, but may also contain an indirect effect of controversial policies in Brazil during the COVID-19 crisis [34], given that the appropriateness of public policies has been shown to moderate mental health burden in the general population during COVID-19 pandemic [35]. The impact of the actual COVID-19 infection on new psychiatric diagnoses was challenged by a recent meta-analysis, although not controlling for the severity of the acute disease [36].

We found high rates of lifetime delusions (8.7%) and hallucinations (12.5%) in the present sample. Even though there are some reports of psychotic symptoms following COVID-19 [37], there are several reports indicating high rates of lifetime psychotic symptoms in the general population, ranging from 7.2 to 12.5% [38,39], consistent with our findings. In our study, 'delusions of religious content' accounted for a substantial proportion of the latter classification (6.15%), and we perceived that, in many such cases, non-delusional religious beliefs (e.g., acknowledging any form of spiritual interference or guidance as key to surviving the disease) could have led to an overestimation of this item. Therefore, after withdrawing 'delusions of religious content' from the former estimate, the overall prevalence of delusions was downgraded to 6.35%.

Impairments in several cognitive domains were found in our sample, especially executive and attentional deficits. Likewise, previous studies in COVID-19 survivors have pointed out to impairments in several cognitive domains in acute forms of the disease [4,40], particularly logical memory and executive functions (attention and cognitive flexibility), which were interpreted as possibly related to the systemic inflammatory process [40]. Long-term studies following patients with severe acute illnesses and acute respiratory distress syndrome point to cognitive decline and executive dysfunction as well [41,42]. Contrary to what we expected, cognitive morbidity after six months of SARS-CoV-2 infection was unrelated to any of the multiple clinical parameters relative to the acute phase of the disease, nor to any of psychiatric diagnoses that were established after six months of hospital discharge. Disorientation was only associated with pre-existing dementia or stroke, presumably reflecting cognitive impairment prior to COVID-19. Older age and disorientation (according to MMSE) were associated with worse performance in attention and verbal fluency tasks, and lower scores in verbal fluency were associated with frailty. In a recent study, Jaywant et al. [43] evaluated cognitive impairment prior to hospital discharge in a cross-section of 57 inpatients recovering from severe COVID-19, and, similar to our findings, the authors found high rates of attention and executive dysfunction unrelated to clinical severity. Conversely, Taquet et al. [20] in a large retrospective cohort study, found a positive association between disease severity and neuropsychiatric symptomatology using a large electronic health record.

The presence and severity of psychiatric manifestations were unrelated to two important psychosocial stressors (i.e., 'death of a close relative' or 'financial loss'), nor to any of the multiple clinical parameters relative to the acute phase of the disease. Psychosocial stressors [11] such as death of a close relative [44] or major financial loss [45] are reputed to be powerful triggers of psychiatric morbidity; however, these variables were not associated with a worse neuropsychiatric outcome in our sample. In the absence of any such associations between risk factors and observed outcomes, psychiatric and cognitive impairments observed in the long-term after moderate or severe COVID-19 could be viewed either as an expression of SARS-CoV-2 effects on brain homeostasis or a representation of non-specific psychiatric manifestations secondary to diminished general health status, given that these disorders are correlated with general health status regardless of the cause of diminished general health [46].

Surprisingly though, patients who had been submitted to hemodialysis during ICU treatment for COVID-19 performed better on the verbal fluency test. We do not have a prompt interpretation for this putative 'protective' effect of hemodialysis on this specific cognitive domain, although the beneficial effect of dialysis on the clearance of systemic toxins could be regarded as advantageous in relation to severely ill patients who remained at pre-dialytic states. Previous studies have shown that individuals discharged from ICU [47] (especially those with acute respiratory distress syndrome) may present with symptoms compatible with *post-intensive care syndrome* (PICS) [48], which consists in a combination of psychological, physical and cognitive impairments following conditions that did require critical care, and may persist for up to five years after ICU discharge [49].

We must also acknowledge the limitations of the present study. First, the assessment of psychiatric and cognitive impairment in this cohort was performed after 6–9 months of the acute episode, in the absence of a similar protocol implemented at baseline, and thus precludes the characterization of changes secondary to this viral disease. However, it is noteworthy that a myriad of detailed information regarding clinical, laboratory and supplementary tests were accessible at baseline. Second, selection bias might remove relevant cases from the study sample, given that patients with more severe consequences of the disease may be less prone to accept enrolment to the study and/or to comply with the procedures. Regarding psychiatric diagnoses, we acknowledge that the CIS-R interview focuses predominantly on mood and affective symptoms, without covering other relevant psychiatric domains. Because of that, we tried to buffer our assessment battery with other questionnaires and psychometric tests. In this regard, the assessment of psychotic symptoms based on the SCID-5-RV (Module B, Psychotic and Associated symptoms) may have been too specific to be implemented in a non-psychiatric sample. Even though all raters were trained for reliability, it is plausible that the lack of experience in the assessment of psychotic patients may have biased the completion of this questionnaire, particularly among less educated patients, to whom culture-bound and religious beliefs may have influenced their responses, causing the overrating of psychotic symptoms. Also, we did not include pre-existing psychiatric illness in our analysis due to lack of availability in the current dataset, though we plan to include this parameter in future analyses. Furthermore, comparison of these results to general population prevalence rather than to the prevalence of these conditions in other patients recovering from serious illness limits one's ability to assess the specificity of these findings. Furthermore, the category of 'new diagnosis' might be biased by memory recall bias. Finally, 6 patients with high clinical suspicion of COVID-19, but without laboratory confirmation by PCR, were included. These individuals had been admitted as inpatients within the first 6 weeks after the initial preparation of HCFMUSP as a COVID-only facility, and the decision to include them was based on the fact that the in-hospital RT-PCR testing setup was not yet fully operational at that time. Nonetheless, the clinical picture of these cases was highly compatible with COVID-19 and they were treated as such throughout hospitalization.

In summary, we found a high prevalence of psychiatric and cognitive

impairments following SARS-CoV-2 infection, specifically common mental disorders, depression, anxiety, PTSD, executive and attentional cognitive impairments. These deficits seem unrelated to psychosocial stressors or clinical risk factors documented in the acute-stage of COVID-19. The present findings should encourage longitudinal studies addressing changes in mental and cognitive state among COVID-19 survivors across distinct ranges of severity.

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Declaration of Competing Interest

Authors Declare no Conflict of Interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2022.01.002.

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