Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Post-infection depressive, anxiety and post-traumatic stress symptoms: A prospective cohort study in patients with mild COVID-19

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ABSTRACT

Background: It remains unclear whether COVID-19 is associated with psychiatric symptoms during or after the acute illness phase. Being affected by the disease exposes the individual to an uncertain prognosis and a state of quarantine. These factors can predispose individuals to the development of mental symptoms during or after the acute phase of the disease. There is a need for prospective studies assessing psychiatric symptoms in COVID-19 patients in the post-infection period.

Methods: In this prospective cohort study, nasopharyngeal swabs for COVID-19 tests were collected at patients' homes under the supervision of trained healthcare personnel. Patients who tested positive for COVID-19 and were classified as mild cases (N = 895) at treatment intake were further assessed for the presence of psychiatric symptoms (on average, 56.6 days after the intake). We investigated the association between the number of COVID-19 symptoms at intake and depressive, anxiety and post-traumatic symptoms approximately two months later, adjusting for previous mental health status, time between baseline and outcome, and other confounders. Multivariate logistic regression and generalized linear models were employed for categorical and continuous outcomes, respectively.

Results: A clinically significant level of depressive, anxiety and post-traumatic stress symptoms were reported by 26.2% (N = 235), 22.4% (N = 201), and 17.3% (N = 155) of the sample. Reporting an increased number of COVID-related symptoms was associated with the presence of clinically significant levels of depressive (aOR = 1.059;95%CI = 1.002–1.119), anxiety (aOR = 1.072;95%CI = 1.012–1.134), and post-traumatic stress (aOR = 1.092;95%CI = 1.024–1.166) symptoms. Sensitivity analyses supported findings for both continuous and categorical measures.

Conclusion: Exposure to an increased number of COVID-19 symptoms may be associated with depressive, anxiety and post-traumatic symptoms after the acute phase of the disease. These patients should be monitored for the development of psychiatric symptoms after COVID-19 treatment discharge. Early interventions, such as brief interventions of psychoeducation on coping strategies, could benefit these individuals.

1. Introduction

The COVID-19 pandemic has affected a significant amount of individuals worldwide (Kim et al., 2020). Despite the efforts to limit viral spread, cases are increasing worldwide and deaths are continually occurring (Aljabali et al., 2020). This pandemic is generating further

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mental issues such as insomnia, anxiety, depression, stress, anger, and fear (Castaldelli-Maia et al., 2021; Torales et al., 2020). Those directly or indirectly affected by the virus could be more disturbed by these symptoms (Torales et al., 2020; Vindegaard and Benros, 2020; Castaldelli-Maia et al., 2021). Word cloud studies indicate that uncertainties about lack of COVID-19 tests and medical supplies are common (Lwin et al., 2020).

There is still much uncertainty about the best treatment to be administered to individuals affected by the disease (Lwin et al., 2020). Though highly transmissible, most cases present with mild symptoms (Aljabali et al., 2020). However, having been affected by the disease exposes the individual to an uncertain prognosis and a need to quarantine to mitigate viral spread (Fernández et al., 2020). These factors can predispose individuals to the development of mental symptoms during or after the acute phase of the disease. It is unclear whether COVID-19 can produce psychiatric symptoms during or after the acute illness phase (Fernández et al., 2020; Sinanović et al., 2020).

In general, survivors of critical illnesses have a high level of mental symptoms after the condition improves. Depression, anxiety and post-traumatic stress disorder (PTSD) are among the most reported events in patients with these conditions (Sparks, 2018). Patients infected with SARS-CoV-1 had a high rate of depressive symptoms during follow-up after the acute phase of the disease (Cheng et al., 2004; Wu et al., 2005; Lee et al., 2007). These symptoms lasted for an extended period, being reported up to a year after the improvement in SARS-CoV-1 symptoms (Lee et al., 2007). Anxiety symptoms were also reported during the post-SARS-CoV-1 follow-up (Cheng et al., 2004; Wu et al., 2005).

Some studies in Asia investigated depression and/or anxiety in patients admitted in hospitals due to COVID-19 (Guo et al., 2020; Hu et al., 2020; Nguyen et al., 2020; Zhang et al., 2020). In a case-control design, Guo et al. (2020) investigated the mental status and inflammatory markers of 103 COVID-19 hospitalized mild patients, matching them with controls that were COVID-19 negative. Hu et al. (2020) carried out a cross-sectional survey with COVID-19 inpatients in two isolation wards of a COVID-19 designated hospital. Zhang et al. (2020) evaluated the prevalence and severity of depression and anxiety within patients recently recovered from COVID-19 infection, who were under quarantine. In Vietnam, Nguyen et al. (2020) carried out a cross-sectional study with individuals infected by COVID-19 attending outpatient departments of nine hospitals and health centers across the country. All these studies found increased levels of both anxiety and depression (6.8–21.0% and 7.4–31.5%, respectively). There was no follow-up study to investigate prospective symptoms of depression and anxiety in COVID-19 patients.

The ongoing COVID-19 pandemic has disrupted the lives of many across the globe, resulting in an increased burden of physical and mental health consequences. Brazil was one of the most affected countries, reaching around 250,000 deaths by mid-February 2021 (IHME, 2021). During the period of the present study (April 2020 to August 2020), the number of COVID-19 deaths reached more than 1000 per day. In the São Paulo state, several mitigation policies took place (e.g., closing of universities and schools, cancellation of public events, closing of all non-essential business, and limitation of public transport) (Siciliano et al., 2020), and mobility was decreased by 30–60% during the same period (IHME, 2021). Through this analysis, we investigated the association between COVID-19 symptoms and post-infection depressive, anxiety and post-traumatic symptoms among a sample of patients diagnosed with mild COVID-19 in Brazil. There is a need for prospective studies assessing psychiatric symptoms in COVID-19 patients, evaluating the post-infection period in other regions of the world. COVID-19 pandemic has affected countries in distinct ways. There were differences in how the countries reacted to the pandemic in terms of mitigation strategies, health risk perception, hospital resources availability (Bruinen de Bruin et al., 2020). These policies could have influenced the incidence of psychiatric symptoms.

2. Methods

2.1. Ethical approval

The present study was approved by the local ethics committee (*Comissão de Ética para Análise de Projeto de Pesquisa* - CAPPesq, protocol No. 32293020.9.0000.5510, approved on July 13th, 2020).

2.2. Study design

This was a prospective cohort study, which took place in São Caetano do Sul, a Brazilian city in the São Paulo state with around 160,000 inhabitants. All people who tested positive for COVID-19 and classified as mild cases at treatment intake (baseline: April 6th to July 15th) in the public health system of this city were given self-assessment questionnaires for the presence of psychiatric symptoms in a follow-up online assessment (outcome: July 20th to August 7th). We investigated the association between the number of COVID-19 symptoms at intake and clinically significant levels of depressive, anxiety and post-traumatic stress symptoms in the follow-up assessment, adjusting for previous mental health status, and the time between the baseline and outcome, among other possible confounders.

2.3. Sample

Residents of the municipality ≥18 years of age with suspected COVID-19 symptoms were encouraged to contact a specific website/phone platform for assessing COVID-19 (access at https://coronasaocaetano.org/) (baseline: April 6th to July 15th). They were invited to complete an initial screening questionnaire that included socio-demographic data; information on symptoms type, onset and duration; and recent contacts. People meeting the suspected COVID-19 case definition (i.e., having at least two of the following symptoms: fever, cough, sore throat, coryza, or change in/loss of smell (anosmia); or one of these symptoms plus at least two other symptoms consistent with COVID-19) were further evaluated (i.e., risk assessment and PCR testing) (Leal et al., 2020).

2.3.1. Inclusion criteria

COVID-19 PCR testing were performed through a home visit for self-collection of a nasopharyngeal swab (NPS – both nostrils and throat), which were collected at the patients' homes under the supervision of trained healthcare personnel. More details can be found in Leal et al. (2020). Due to shortages of some reagents, two RT-PCR platforms were used at different times during the study: ALTONA RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Hamburg, Germany) and the Mico BioMed RT-qPCR kit (Seongnam, South Korea). For serology, we tested 10 μL of serum or plasma (equivalent in performance) using a qualitative rapid chromatographic immunoassay (Wondfo Biotech Co., Guangzhou, China), that jointly detects anti-SARS172 CoV-2 IgG/IgM. The assay has been found to have a sensitivity of 81.5% and specificity of 99.1% in a U.S. study (Leal et al., 2020). In our local validation, after two weeks of symptoms, the sensitivity in RT-PCR confirmed cases (N = 59) was 94.9%, and specificity in biobank samples (N = 106) from 2019 was 100% (Leal et al., 2020). Patients testing RT-PCR negative were followed up by the primary health care program of their residential area. They were advised to contact the platform for additional consultation if they developed new symptoms.

All the patients who tested positive and were classified as mild and completed a phone screening to COVID-19 symptoms during the acute phase of the disease (N = 1757) were included in the present study. They were invited to participate in the follow-up online assessment (outcome: July 20th to August 7th). We had a response rate of 50.9%. Table S1 presents differences a comparison between those that agreed to participate (N = 895) and those that did not (N = 862)."

2.3.2. Exclusion criteria

We excluded the following individuals from the present study:

- COVID-19 suspected cases who tested negative;
- COVID-19 positive patients who were classified as moderate and severe cases by a doctor;
- All pregnant women, and patients meeting pre-defined triage criteria for severe disease."

2.4. Measures

All the exposure measures were collected online via the dedicated Corona São Caetano web platform (access at https://coronasaocaetano.org/) or by phone. The outcomes were assessed online only.

2.4.1. Acute-phase COVID-19 symptoms

Patients testing positive for COVID-19 via RT-PCR were followed up to 14 days (a maximum of 7 phone calls) from completion of their initial questionnaire. They were contacted every 48 h by a medical student (supervised by a medical doctor) who completed another risk assessment and recorded any ongoing or new symptoms. Following the COVID-19 clinical assessment protocol of São Caetano do Sul (Leal et al., 2020), the following COVID-19 symptoms were assessed during these contacts: dyspnea; tachypnea; persistent fever (≥72 h); mental health disturbance (e.g., changes in consciousness, thought, perception); fever (at any timepoint); cough; sore throat; nasal congestion; coryza; headache; fatigue; asthenia; lack of appetite; myalgia; joint pain; diarrhea; nausea; vomit; anosmia; and dysgeusia. The total number of symptoms during the treatment was the primary exposure investigated in the present study.

2.4.2. Follow-up psychiatric symptoms

The GAD-7 scale is an instrument for assessing, diagnosing and monitoring anxiety symptoms. It was created by Spitzer et al. (2006). It was validated by Kroenke et al. (2007), according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV), for the assessment of signs and symptoms of anxiety disorder, and also to classify severity levels. This study uses the Brazilian Portuguese validated version (Moreno et al., 2016). GAD-7 consists of seven items, on a four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 21, assessing the frequency of signs and symptoms of anxiety over a two-week period. No missingness was observed in any of the question items. A cutoff ≥10 was used for defining a clinically significant level of anxiety symptoms (Muñoz-Navarro et al., 2017). In our sample, we found a Cronbach's alpha of 0.92 (Table S1).

The PHQ-9 scale is an adaptation of the PRIME-MD (Spitzer et al., 1994). It is a brief instrument for assessing, diagnosing and monitoring depressive symptoms. It was validated by Spitzer et al. (1999) and by Kroenke et al. (2001). The present study uses a version which has been translated and validated to Brazilian Portuguese (de Lima Osório et al., 2009). PHQ-9 was created based on the DSV-IV criteria for Major Depressive Disorder, for the assessment of its signs and symptoms, and also to classify severity levels. It consists of nine items, arranged on a frequency four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). Its score ranges from 0 to 21, assessing the frequency of signs and symptoms of anxiety over two weeks. No missingness was observed in any of the question items. A cutoff ≥10 was used for defining a clinically significant level of depressive symptoms (Levis et al., 2019). In our sample, we found a Cronbach's alpha of 0.90 (Table S1).

Weathers et al. (1993) developed the PCL-C scale, which was translated, adapted and validated to Brazilian Portuguese (Berger et al., 2004; Lima et al., 2012) to assess the consequences of different types of traumatic experiences. It is based on the DSM-III diagnostic criteria for PTSD. The patient must report the levels of last-month disturbance by 17 items, using a severity scale ranging from 1 (not at all), 2 (a little bit), 3 (moderately, 4 (quite a bit), and 5 (extremely). No missingness was observed in any of the question items. A cutoff ≥44 for defining a clinically significant level of post-traumatic stress symptoms (Archer et al., 2016). In our sample, we found a Cronbach's alpha of 0.94 (Table S1).

2.4.3. Possible confounders

Lifetime diagnosis of psychiatric disorder (yes vs. no), current psychiatric treatment (yes vs. no), age (continuous: 18–88 years), gender (male vs. female), education (up to high school vs. more than high school), civil status (married vs. single, which included previously married), income level (as defined by the Brazilian Institute of Geography and Statistics: up to three times the typical salary for a minimum wage job vs. more), current health treatment for any acute or chronic medical condition (yes vs. no) and time between the treatment intake and mental assessment (continuous: 6–116 days), were assessed as potential confounders.

2.5. Statistical analysis

STATA software version 16.2 was used to run the analysis. We carried out three different analyses: (1) analyzing the characteristics of the sample, including the difference between the sample respondents and non-respondents who did not participate in the follow-up survey (Tables 1–3); (2) analyzing the relationship between the COVID-19 symptoms and mental symptoms (Table 4, Figs. S1–S3); and (3) checking the robustness of the findings from the second analysis (Table 5).

We analyzed characteristics of respondents who completed the mental health follow-up (N = 895) and those who were lost to follow-up (N = 862) using logistic regression. This comparison was performed to identify any potential baseline difference between those included in the study and people who were lost to follow-up, which could generate bias. After excluding respondents who were not able to complete the mental health follow-up assessment, the final analytical sample included 895 participants. We subsequently conducted a descriptive analysis of sociodemographic measures, health profiles and the COVID-19 treatment

Table 1
Results of the logistic regression models for follow-up versus missing among classified as having mild COVID-19 patients at treatment intake, São Caetano do Sul, 2020.

Age	OR	z	95%CI		p
	0.98	−6.12	0.98	0.99	<0.001
Positive test day	1.00	0.72	1.00	1.00	0.474
Number of symptoms	1.02	1.41	0.99	1.06	0.158
Breathless*	0.52	−1.64	0.24	1.14	0.101
Tachypnea*	0.26	−2.09	0.07	0.92	0.037
Persistent fever*	0.47	−1.22	0.14	1.57	0.221
Mental health change*	0.47	−0.86	0.09	2.59	0.387
Fever**	0.87	−0.78	0.61	1.24	0.434
Cough**	1.05	0.48	0.86	1.27	0.634
Sore throat**	0.99	0.12	0.77	1.26	0.907
Nasal congestion**	1.03	0.30	0.84	1.27	0.763
Coryza**	1.09	0.76	0.87	1.37	0.449
Headache**	1.35	2.99	1.11	1.65	0.003
Fatigue**	1.13	1.24	0.93	1.38	0.215
Asthenia**	0.83	−1.63	0.66	1.04	0.104
Anorexa**	0.99	0.11	0.80	1.23	0.912
Myalgia**	0.96	−0.34	0.78	1.19	0.731
Joint pain**	0.68	−2.48	0.51	0.92	0.013
Diarrhea**	1.32	1.77	0.97	1.80	0.077
Nausea**	1.04	0.27	0.79	1.36	0.786
Vomit**	0.68	−1.33	0.39	1.20	0.183
Anosmia*	1.46	3.87	1.21	1.77	<0.001
Dysgeusia*	1.36	3.12	1.12	1.64	0.002

* Assessed by a healthcare professional.
** Self-reported.

Table 2
Descriptive analysis of 895 patients classified as having mild COVID-19 at treatment intake, São Caetano do Sul, 2020.

	Mean/n	SE/%
Sociodemographic		
Age	40.79	0.45
Female gender	541	60.44
Married	460	51.40
Education (up to high-school)	541	60.44
Monthly income (up to 3 minimum salaries)	536	59.89
Health profile		
Current health treatment	386	43.13
Lifetime psychiatric diagnosis	180	20.11
Current psychiatric treatment	95	10.53
COVID-19 profile		
Number of symptoms	4.19	0.10
Dyspnea*	11	1.25
Tachypnea*	3	0.74
Persistent fever*	4	0.56
Mental health change*	2	0.23
Fever**	65	7.40
Cough**	379	43.12
Sore throat**	159	18.09
Nasal congestion**	277	31.55
Coryza**	213	24.32
Headache**	363	41.39
Fatigue**	324	36.94
Asthenia**	179	20.41
Lack of appetite**	230	26.32
Myalgia**	259	29.57
Joint pain**	84	9.58
Diarrhea**	105	11.97
Nausea**	129	14.69
Vomit**	21	2.39
Anosmia*	456	51.94
Dysgeusia*	435	49.60

* Assessed by a healthcare professional.
** Self-reported.

Table 3
Depressive, anxiety and post-traumatic stress symptoms and disorders among 895 patients who had previously mild COVID-19, São Caetano do Sul, 2020.

	Mean	95%CI	Cutoff	n	%
Depressive Symptoms/ Depression (PHQ-9)	6.65	6.24–7.06	≧10	235	26.26
Anxiety symptoms/Anxiety Disorder (GAD-7)	5.97	5.61–6.33	≧10	201	22.46
Post-traumatic stress symptoms/PTSD (PCL-C)	31.58	30.72–32.45	≧44	155	17.32
Time of Mental Health Assessment (days after intake)	56.61	54.71–58.51	≧14	840	78.73
Severity (referred to in-person medical consultation)	N.A.	N.A.	N.A.	61	6.78

intake profile of participants. We additionally described the mean and prevalence of clinically significant levels of anxiety, depressive symptoms and post-traumatic stress symptoms in these patients. We then created scatterplot figures for continuous outcomes across time.

Multivariate logistic regression models for categorical outcomes (binarized scales) were carried out to explore the relationship between COVID-19 symptoms and mental health. These models were adjusted for all aforementioned confounders listed in Section 2.4.3. Clinically significant depressive, anxiety and post-traumatic symptoms, as described in Section 2.4.2., were included as separate independent variables in each model. Two distinct models were carried out for each type of psychiatric symptoms, one which included lifetime psychiatric diagnosis, and the other included current psychiatric treatment, due to significant correlation between these two variables determined via pairwise testing ($p < 0.05$).

We subsequently ran sensitivity analyses where we excluded: (i) individuals with a short time between baseline and outcome assessment, as individuals could be in the late active phase of the COVID-19 disease (≥14 days), (ii) those who progressed to a more severe COVID-19 case, and (iii) those with a previous psychiatric diagnosis. In a final sensitivity

Table 4
Results of the multivariate logistic regression models among 895 patients who had previously mild COVID-19, São Caetano do Sul, 2020.

Exposure: total number of COVID-19 symptoms					
Categorical outcomes	OR	z	95%CI		p
Entire sample					
Depression (PHQ-9)					
Model 1	1.059	2.04	1.002	1.119	0.042
Model 2	1.062	2.18	1.006	1.121	0.029
Anxiety disorder (GAD-7)					
Model 1	1.072	2.41	1.012	1.134	0.016
Model 2	1.072	2.46	1.014	1.134	0.014
PTSD (PCL-C)					
Model 1	1.092	2.66	1.024	1.166	0.008
Model 2	1.095	2.81	1.028	1.167	0.005

Model 1: Adjusted for lifetime diagnosis of psychiatric disorder, age, gender, education, civil status, income, current health treatment and time since the intake.
Model 2: Adjusted for current psychiatric treatment, age, gender, education, civil status, income, current health treatment and time since the intake.

Table 5
Results of the sensitivity analysis among 895 patients who had previously mild COVID-19, São Caetano do Sul, 2020.

Exposure: total number of COVID-19 symptoms					
Outcomes*	OR	z	95%CI		p
Those without any previous psychiatric diagnosis (n = 715)					
Depression (PHQ-9)					
Model 1	1.093	2.68	1.024	1.167	0.007
Model 2	1.094	2.69	1.025	1.168	0.007
Anxiety disorder (GAD-7)					
Model 1	1.118	3.25	1.045	1.196	0.001
Model 2	1.118	3.25	1.045	1.196	0.001
PTSD (PCL-C)					
Model 1	1.134	2.97	1.044	1.233	0.003
Model 2	1.131	2.90	1.041	1.230	0.004
Those with time between intake and follow-up assessment ≧ 14 days (n = 718)					
Depression (PHQ-9)					
Model 1	1.062	2.11	1.004	1.123	0.035
Model 2	1.064	2.24	1.007	1.125	0.025
Anxiety Disorder (GAD-7)					
Model 1	1.080	2.64	1.020	1.144	0.008
Model 2	1.080	2.68	1.021	1.143	0.007
PTSD (PCL-C)					
Model 1	1.089	2.54	1.019	1.163	0.011
Model 2	1.092	2.69	1.024	1.164	0.007
Those who were not referred to in-person consultation (n = 840)					
Depression (PHQ-9)					
Model 1	1.060	2.03	1.002	1.123	0.042
Model 2	1.066	2.22	1.007	1.126	0.026
Anxiety Disorder (GAD-7)					
Model 1	1.076	2.47	1.015	1.141	0.007
Model 2	1.078	2.57	1.018	1.142	0.010
PTSD (PCL-C)					
Model 1	1.090	2.50	1.019	1.167	0.013
Model 2	1.096	2.74	1.027	1.171	0.006

Model 1: Adjusted for lifetime diagnosis of psychiatric disorder, age, gender, education, civil status, income, current health treatment and time since the intake.
Model 2: Adjusted for current psychiatric treatment, age, gender, education, civil status, income, current health treatment and time since the intake.
* Multivariate logistic regression models.

analysis, we ran multivariate generalized linear models (GLM) for the continuous outcomes. Based on a previous study (Gustavsson et al., 2014), gamma-family GLM with log link were the models of choice, because of a log-normal distribution of the continuous outcomes of depression, anxiety and PTSD in our sample.

3. Results

3.1. Descriptive analysis

Table 1 presents the results of the logistic regression models quantifying any differences between those who participated in the mental health assessment compared to those who were lost to follow-up. The latter were more likely to be older and have greater odds of experiencing tachypnea and joint pain. Those included in our present study had greater odds of experiencing headaches, anosmia and dysgeusia. No significant difference was found for the total number of COVID-19 symptoms. Table 2 shows descriptive analysis of our sample (N = 895). The majority were female (60.4%), married (51.4%), had up to high-school education (60.4%) and three minimum salaries per month of income (58.9%). Around one in every five individuals have had a lifetime psychiatric disorder (20.1%), with only about half of these individuals undergoing psychiatric treatment (10.5%). Current health treatment was reported by 43.1% of the sample. Regarding the COVID-19 symptomatic profile, patients had a mean of 4.2 COVID-19-related symptoms. The most common symptoms were anosmia (51.9%), dysgeusia (49.6%), cough (43.1%), headache (41.3%), and fatigue (36.9%).

Table 3 presents depressive, anxiety and post-traumatic stress symptoms in the sample. Clinically significant levels of depressive, anxiety and post-traumatic stress symptoms were reported by 26.2% (N = 235), 22.4% (N = 201), and 17.3% (N = 155) of the sample, respectively. Among these patients, 39.2% (N = 92), 37.8% (N = 76), and 50.3% (N = 78), had a previous psychiatric diagnosis during lifetime. On average, we assessed patient mental health almost two months after the treatment intake (mean = 56.6 days, 95%CI = 54.7–58.5), with the majority being assessed after the acute phase of the disease (78.7%, N = 840). Few patients (6.7%, N = 61) were referred for in-person consultation.

Figs. S1, S2, and S3 present boxplots of continuous scores of depression, anxiety, and post-traumatic stress (y-axis) by the time of the mental health assessment (x-axis). There were wide ranges of scores for all the outcomes, more concentrated in the lower severity levels during the entire period (from 1 week to almost four months). For all the outcomes, a similar pattern of distribution was found through the time of the mental health assessment.

3.2. Relationship between COVID-19 and psychiatric symptoms

Table 4 presents the results of the logistic regression models of the exposure (previous total number of symptoms of COVID-19) for the categorical outcomes (clinically significant level of depressive, anxiety and post-traumatic stress symptoms). The exposure was significantly associated with all the outcomes, after adjustment for all confounders. With every one-symptom increase in previous COVID-19, the likelihood that a clinically significant level of depression, anxiety, or post-traumatic stress is present increases by approximately 6%, 7%, and 9%, respectively.

3.3. Sensitivity analysis

In the sensitivity analysis (Table 5), these results remained significant after the exclusion of (i) individuals with a short time between baseline and outcome assessment ($\geq$ 14 days), as individuals could be in the late active phase of the COVID-19 disease, (ii) those who progressed to a more severe COVID-19 case, and (iii) those with a previous psychiatric diagnosis. In the final sensitivity analysis (Table S2, GLM for continuous outcomes), we found a significant relationship between number of COVID-19 symptoms and all the outcomes, with the exception of post-traumatic stress symptoms when adjusting for lifetime psychiatric disorder (p = 0.053).

4. Discussion

The present study aimed to examine the post-infection levels of psychiatric symptoms among individuals with mild COVID-19 disease. We aimed to investigate whether COVID-19 infection symptomatology could be associated with psychiatric symptoms. We found that an increased number of COVID-related symptoms were associated with a clinically significant level of depressive, anxiety, and post-traumatic stress symptoms. Sensitivity analyses supported those findings. More importantly, our findings adjusted for confounders that could increase the vulnerability of psychiatric symptoms. These results shed light on a significant subpopulation at risk for mental symptoms. To date, this study is the largest to concomitantly evaluate depressive, anxiety, and post-traumatic stress symptoms in patients who had mild COVID-19 disease. This is important because the vast majority of COVID-19 patients are classified as mild cases, facing long periods of at-home isolation.

Five studies in Asia investigated depressive and/or anxiety symptoms in COVID-19 patients using the same scales as in the present study (Guo et al., 2020; Hu et al., 2020; Nguyen et al., 2020; Zhang et al., 2020; Kang et al., 2021). Prevalence of depression and anxiety varied between 7.4 and 31.5%.and 6.8–21.0%, respectively (Guo et al., 2020; Hu et al., 2020; Nguyen et al., 2020; Zhang et al., 2020; Kang et al., 2021). All of these studies were conducted in Asia (three in China, one in Korea, and one in Vietnam). Just after treatment discharge of mild cases in Turkey, 18.4% and 18.8% were considered having 'probable' anxiety and depression (Poyraz et al., 2021).The prevalence of a clinically significant depressive symptoms in our study (26.2%) is within range of previous studies, but clinically significant anxiety symptoms were greater (22.4%) than previously reported values (6.8–21.0%). Our results were more similar to those found by Zhang et al. (2020), who sampled home-quarantined COVID-19 patients. The lowest depression and anxiety prevalences were found in the Guo et al. (2020) study, which included COVID-19 hospitalized patients.

A clinically significant level of post-traumatic stress symptoms, reported by 17.3% (N = 155) of respondents with mild COVID-19 in our study, has remained largely unassessed within the general population during the COVID-19 pandemic. A much lower level (5.6%) of PTSD was found by Kang et al. (2021) in mild patients during the acute phase of the disease. Such as in the present study, an increased level of clinically significant post-traumatic stress symptoms (25.4%) was found by Poyraz et al. (2021) just after the COVID-19 treatment discharge. Research regarding post-traumatic stress symptoms, using the PCL-C scale, has been predominantly carried out within specified populations; within China, 16.3% of nurses in the Hubei province (Wang et al., 2020), 2.9% of university students (Tang et al., 2020) and 14.4% of youth (Liang et al., 2020) reported post-traumatic stress symptoms. Among a sample in Spain, some of whom experienced COVID-19 symptoms, 15.8% reported post-traumatic stress symptoms (González-Sanguino et al., 2020): a similar prevalence to that observed within this sample. Further, research conducted regarding the SARS outbreak in 2003 has demonstrated that 13–21.7% of healthcare workers experienced post-traumatic stress symptoms (Lin et al., 2007). Previous estimates of post-traumatic stress levels within Brazil were 8.5% (de Castro Longo et al., 2020) demonstrating that the prevalence within individuals presenting with mild COVID-19 is increased in comparison to past estimates.

Our results support the hypothesis that the prevalence of clinically significant levels of depressive, anxiety and post-traumatic stress symptoms were elevated in people with increased number of COVID-19 symptoms at baseline. These findings echo warnings from the previous SARS outbreak, wherein survivors of SARS infections experienced

increased psychological distress, persisting one year or more subsequent to the outbreak (Lee et al., 2007). Similar findings were observed following the occurrence of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2015, indicating that survivors experienced mental health consequences following the outbreak (Park et al., 2020). Mental health supports should be strengthened, and healthcare systems must prepare for an influx of individuals experiencing psychological distress as a result of the COVID-19 pandemic. Following the PTSD model, these individuals should be referred to early interventions. Brief interventions of psychoeducation on coping strategies have been effective in promoting mental health among individuals who experienced traumatic life events (Oosterbaan et al., 2019). Internet-based psychological intervention for acute COVID-19 patients has also been described, and could be an interesting early-intervention tool for those who experience psychological distress during this phase (Wei et al., 2020).

It is unclear whether COVID-19 can produce psychiatric symptoms during or after the acute illness phase (Vindegaard and Benros, 2020). The virus can invade the brain. Arteriolosclerosis, neuronal loss, leptomeningeal inflammation, axon degeneration infarcts, swollen axons, neuronal satellitosis, myelin loss, gliosis, hydrocephalus, hypoxic-ischemic injury, edema, hemorrhage, atrophy, encephalitis, have all been discovered throughout postmortem brain research (Generoso et al., 2021). Neuropsychiatric issues, such as: headaches, paresthesia, myalgia, impaired consciousness, confusion or delirium, and cerebrovascular diseases have been reported among individuals with COVID-19 (Sinanović et al., 2020). However, the symptoms assessed in the present study (i.e., depressive, anxiety and post-traumatic stress) are substantially different from neuropsychiatric symptoms observed among these individuals in the acute phase of COVID-19. In addition, we found no differences in the level of psychiatric symptomatology depending on the time of assessment after the acute phase of the disease. Other recent studies also support findings regarding an increased likelihood of depressive, anxiety and post-traumatic stress symptoms among COVID-19 patients due to environmental factors (Generoso et al., 2021; Méndez et al., 2021). It is likely that the onset of psychiatric symptoms post-COVID-19 is resultant from the psychosocial context of the pandemic (Dubey et al., 2020) and a 'post-infection syndrome' (Sher, 2021). People who have been infected with COVID-19 have likely experienced long periods of quarantine, and some have reported fear of transmitting the virus to members of their social and familial networks (Iglesias-Sánchez et al., 2020). This, in combination with uncertainties surrounding treatment and clinical course (Guo et al., 2020), could be working synergistically to worsen psychiatric symptoms. In addition, after recovering from the acute illness, many COVID-19 survivors experience chronic physical symptoms such as pain, dyspnea, fatigue, and cough. Among those with 'post-COVID syndrome' (also called 'long COVID', 'long haulers' or 'post-acute COVID'), there is an increased chance of psychiatric symptoms including increase suicidal ideation and behavior, such as neurological and physical disorders, and inflammatory damage to the brain (Sher, 2021). Future studies should explore neurobiological effects of SARS-Coronavirus-2 and mental health impacts.

4.1. Strengths and limitations

Assessing people for depressive, anxiety, and post-traumatic stress symptoms at different timepoints should be noted as an important limitation of the present study. We also did not assess such symptoms at the baseline and in a control group. However, we adjusted all the logistic regression and GLM models to the time of assessment, self-reported previous psychiatric diagnosis and treatment, and also conducted sensitivity analyses, excluding those who could potentially be assessed during the acute phase of COVID-19. We were also not able to assess other important behavioral disorders (i.e., substance use and sleep disorders). However, we were able to assess the symptoms of the most prevalent disorders following traumatic experiences in almost a thousand COVID-19 patients through reliable measures both for exposure and outcomes, with an acceptable response rate. The patients included in the present study were slightly different from those who did not attend the invitation. Despite the latter being older, no significant difference was found for the total number of COVID-19 symptoms, which was our exposure measure. The main issue for generalization of our findings was the inclusion of individuals dependent on the public healthcare sector only.

4.2. Conclusion

Exposure to increased levels of COVID-19 symptomatology may be associated with clinically significant levels of depressive, anxiety and post-traumatic stress symptoms after the acute phase of the disease, independently of previous psychiatric diagnosis. These patients should be monitored for the development of psychiatric symptoms after COVID-19 treatment discharge. Early mental health intervention such as psychotherapy and supportive groups could play an important role in preventing incident mental health problems in these people. It is probable that the increased prevalence of psychiatric symptoms post-COVID-19 is due to the social and psychological context of the disease. However, further studies should investigate the possible neurobiological mechanisms linking COVID-19 and mental health conditions.

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Declaration of interest

None.

Contributors

Conceptualization: FI, JCSB, FEL, JT, AV, SSM and JMCMData curation: FI, JCBS, TB, BZ, and FELFormal analysis: TB, BZ, MEM, SSM, and JMCMFunding acquisition: FI, JCSB, and FELMethodology: FI, JCSB, FEL, SSM and JMCMSupervision: FI, SSM, and JMCMWriting - original draft: FI, JT, AV, MEM, SSM, and JMCMWriting - review & editing: All the authors.

Ethical statement for progress in neuro-psychopharmacology and biological psychiatry

Hereby, I (João Mauricio Castaldelli-Maia) consciously assure that for the manuscript "Post-infection depressive, anxiety and post-traumatic stress symptoms: a retrospective cohort study with mild COVID-19 patients" the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

I agree with the above statements and declare that this submission follows the policies of Progress in Neuro-Psychopharmacology and Biological Psychiatry as outlined in the Guide for Authors and in the Ethical Statement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110341.

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