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Original Research

COVID-19-induced neuropsychiatric symptoms can persist long after acute infection: a 2-year prospective study of biobehavioral risk factors and psychometric outcomes

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Abstract

Objectives: To assess the prevalence of neuropsychiatric symptoms 2 years after the COVID-19 acute phase and to identify biobehavioral risk factors.

Methods: This 2-year prospective study assessed adult individuals with COVID-19 via face-to-face interview and laboratory testing at onset, and via telephone interview at 2-year follow-up. Data collected included COVID-19 severity and management at onset, as well as depression, anxiety, insomnia, cognitive failure, and fatigue at follow-up using standardized assessment tools.

Results: Out of 1,067 screened COVID-19 patients, 230 completed the 2-year follow-up (female, 53.5%; aged>40, 80.9%; native Italian, 94.9%; medical comorbidity, 53.5%; chronic medication, 46.3%; moderate to severe COVID-19, 24.9%; hospital admission, 28.7%; ICU, 5.2%). At follow-up, 9.1% had anxiety, 11.3% depression, 9.1% insomnia, 18.3% cognitive failure, and 39.1% fatigue, of clinical relevance. Headache (OR = 2.49, 95% CI = 1.01–6.16, $p = 0.048$), dyspnea (OR = 2.55, 95% CI = 1.03–6.31, $p = 0.043$), and number of symptoms (OR = 1.23, 95% CI = 1.01–1.51, $p = 0.047$) at onset were associated with anxiety at follow-up; dyspnea at onset was associated with depression at follow-up (OR = 2.80, 95% CI = 1.22–6.41, $p = 0.015$); number of comorbidities at onset was associated with insomnia at follow-up (OR = 1.48, 95% CI = 1.06–2.08, $p = 0.022$); female gender (OR = 2.39, 95% CI = 1.14–5.00, $p = 0.020$) and number of symptoms (OR = 1.20, 95% CI = 1.02–1.42, $p = 0.026$) at onset was associated with cognitive failure at follow-up; number of comorbidities (OR = 1.33, 95% CI = 1.03–1.73, $p = 0.029$) and symptoms (OR = 1.19, 95% CI = 1.04-1.37, $p = 0.013$) and raised interleukin 6 levels (OR = 4.02, 95% CI = 1.42–11.36, $p = 0.009$) at onset was associated with fatigue at follow-up.

Conclusions: COVID-19 survivors, especially if female, with preexisting health problems, and with a more severe acute phase, may present with long-lasting neuropsychiatric sequalae, urging interventions to sustain recovery particularly in these higher risk individuals.

Keywords: Long COVID; Post-COVID syndrome; Psychological well-being; Quality of life

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Introduction

As it became clear that that *COronaVIrus Disease* 19 (COVID-19) pandemic could put a burden on people's mental health, many studies investigated the potentially long-lasting psychological consequences (Dettmann et al. 2022; Panchal et al. 2021; Prati & Mancini 2021) of what may be considered as a collective traumatic experience (Stanley et al. 2021). Independent of such indirect effects of the pandemic, common neuropsychiatric symptoms such as anxiety, depression, and insomnia, with onset in the post-acute phase or persisting from the acute phase of the disease, have been reported among COVID-19 survivors (Colizzi et al. 2023a; Peghin et al. 2021a; Peghin et al. 2022). Such symptoms have been observed in the context of a broader symptomatic presentation, involving fatigue and cognitive impairments, as well as other physical symptoms such as sensory processing issues that reduce patients' quality of life (Alnefeesi et al. 2020; Ceban et al. 2022; Hao et al. 2020; Renaud-Charest et al. 2021). Symptoms that have developed during or after COVID-19 and that are not explained by an alternative diagnosis have been gathered under the umbrella

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definition of "long COVID" or "post-COVID syndrome" (Raveendran et al. 2021; Sivan & Taylor 2020). Research evidence has attributed the persistence of multiple symptoms beyond the initial COVID-19 infection to the direct biological effects of the virus involving brain infection through the olfactory epithelium (Butowt & von Bartheld 2021), systemic inflammation, astrogliosis and microglia activation (Steardo et al. 2020), and glutamate system disruption (Boldrini et al. 2021).

Most research evidence regarding post-COVID neuropsychiatric symptoms comes from studies with a short-term follow-up of 3 months, the minimum observation period needed to satisfy the criteria for a post-COVID condition as per international consensus (Soriano et al. 2021). A lower number of studies are available focusing on follow-ups of 6 months or longer. A meta-analysis of 51 studies, including total of 18,917 patients followed for a maximum of approximately 6 months, found a large proportion of COVID-19 survivors presenting with neuropsychiatric symptoms, with insomnia being the most frequent symptom (27.4%), followed by fatigue (24.4%), objective cognitive impairment (20.2%), anxiety (19.1%), and post-traumatic stress (15.7%) (Badenoch et al. 2022). A subsequent meta-analysis of 18 studies encompassing a total of 10,530 patients expanded the data extraction to studies conducted up to approximately 18 months after the beginning of the pandemic, revealing an even higher prevalence of neuropsychiatric symptoms due to a substantial increase among patients followed-up for more than 6 months as compared to those followed-up for 3 to 6 months (Premraj et al. 2022). Such findings would suggest that neuropsychiatric symptoms are more likely to develop post-infection rather than just persist as a residual component of the acute phase (Colizzi et al. 2023a). Interestingly, while most long-term sequelae or persistent symptoms at 12 months after any hospital discharge have been suggested not to differ due to the cause of hospital admission, neuropsychiatric symptoms have been found to be more associated with COVID-19 (Rivera-Izquierdo et al. 2022), with a higher overall risk of new-onset mental disorders among hospitalized COVID-19 survivors compared with the general population (Nersesjan et al. 2023). Such evidence highlights the need for follow-up studies of post-COVID syndrome to focus on mental health-related domains (Rivera-Izquierdo et al. 2022).

However, the existing evidence is difficult to interpret. Although neuropsychiatric symptoms among COVID-19 survivors have been linked to the development of a post-COVID syndrome and thus to the direct effects of the infection, methodological caveats hinder drawing solid conclusions. Most evidence is based on cross-sectional, case–control, or retrospective studies, which are susceptible to recall bias (Premraj et al. 2022). In fact, prospective evidence that COVID-19 acute phase preceded and was in reasonable temporal proximity to the onset of neuropsychiatric symptoms is needed to support the suggestion that COVID-19 had a precipitating role in their manifestations. That would also limit interpreting the confounding effect of the pandemic at a social level, for which detrimental consequences have been reported independently of being infected with the virus (Colizzi et al. 2020; Pigaiani et al. 2020). Also, where present, follow-up durations are generally short, covering the first few months following the acute phase (Badenoch et al. 2022; Premraj et al. 2022), even though later phases seem to be more relevant for the manifestation of mental distress (Colizzi et al. 2023a). Furthermore, available evidence generally focuses on post-COVID prevalence, while being scant in terms of investigating risk factors, thus making it difficult to identify who is the most susceptible to post-COVID neuropsychiatric symptoms (Badenoch et al. 2022; Premraj et al. 2022). Where investigated, neuropsychiatric symptoms are often based on patient self-reported complaints (Mandal et al. 2021), which may lack standardization when compared with objective assessments (Aiyegbusi & Calvert 2020; Needham et al. 2012; Rossi et al. 2020).

We have addressed some of these limitations in previous analyses, finding that at both 12 and 24 months after the acute COVID-19 phase, patients are more likely to complain about neuropsychiatric symptoms than any other disturbances, with neuropsychiatric symptoms being higher than at the onset, while other disturbances generally reduce over time (Colizzi et al. 2023a; Colizzi et al. 2023b). However, it remains to be determined whether the elevated prevalence of post-COVID psychiatric syndrome in the longer-term stands up to scrutiny by using reliable instruments for detecting mental health conditions and rating their severity in the setting of a hospital medical outpatient clinic. Therefore, the aim of this study was twofold: (i) to assess the prevalence of neuropsychiatric symptoms in COVID-19 survivors 24 months following the acute phase of the disease, by using standardized assessment tools and (ii) to identify sociodemographic and clinical characteristics associated with post-COVID neuropsychiatric symptom occurrence 24 months following the acute phase of the disease.

Material and methods

Study design and participants

In this prospective cohort study (Peghin et al. 2021a; Peghin et al. 2021b) designed according to the STROBE guidelines (von Elm et al. 2007; Supplementary Table 1), we recruited COVID-19 patients presenting to the Infectious Disease Department of the University hospital of Udine, a tertiary referral hospital of about 1000 beds serving approximately 500,000 inhabitants, which has been appointed as a regional hub for COVID-19 patients. Between March 1, 2020 (the day when the first COVID-19 patient was identified), and May 30, 2020, all consecutive inpatients and outpatients aged 18 years or older experiencing COVID-19 were considered eligible for inclusion in the study. Participants were followed up for 2 years. After providing written informed consent, individuals with COVID-19 were assessed multiple times, at the onset of COVID-19 via a face-to-face interview and through laboratory testing, and then at 6-, 12-, and 24-month follow-ups via telephone interview. This report focuses on the 24-month follow-up.

Procedures

COVID-19 diagnosis was either confirmed, through a positive nucleic acid amplification test (NAAT) for SARS-CoV-2 in respiratory tract specimens, or suspected, through laboratory or imaging findings suggestive of infection and/or positive serology (Peghin et al. 2021a; Peghin et al. 2021b; Varghese et al. 2020). Cycle threshold (Ct) values (i.e., the number of cycles needed to detect the virus) of the first positive NAAT were collected. Based on the COVID-19 disease severity scale, patients were classified into increasing severity groups, from asymptomatic to critical disease (Bozio et al. 2021). Based on their disease management, patients were also classified as requiring Intensive Care Unit (ICU), hospital-ward, or outpatient-based treatment (Peghin et al. 2021a; Peghin et al. 2021b).

To obtain a comprehensive overview of mental health difficulties among COVID-19 survivors 24 months after the disease onset, in line with unstandardized investigations performed at either the 12- (Colizzi et al. 2023a) or the 24-month (Colizzi et al. 2023b) follow-ups, information was collected with reference to common psychiatric disorders (i.e., depression, anxiety, and insomnia), cognitive impairment (i.e., failures in perception, memory, and motor function), and somatic distress (i.e., fatigue) through standardized assessment tools. The Italian version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression. The questionnaire consists of 14 items, 7 for anxiety and 7 for depression, rated on a four-point Likert scale from 0 to 3. Scores range from 0 to 21 for each subscale, with scores between 11 and 21 indicating clinically relevant symptoms (Iani et al. 2014). The Insomnia Severity Index (ISI), which maintains good psychometric properties in its Italian version, was used to assess nature, severity, and impact of insomnia. The questionnaire consists of 7 items, rated on a five-point Likert scale from 0 to 4. Scores range from 0 to 28, with scores between 15 and 21 indicating clinically relevant insomnia of moderate severity and scores between 22 and 28 indicating severe insomnia (Castronovo et al. 2016). The Cognitive Failures Questionnaire (CFQ), a brief and reliable questionnaire that is useful in clinical practice, also in Italian populations, was used to assess deficits regarding attention, perception, memory, and motor functioning in everyday life. It consists of 25 items, rated on a five-point Likert scale from 0 to 4. Scores range from 0 to 100, with a score ≥43 suggestive of high cognitive failure (Stratta et al. 2006). Finally, the Italian version of the Fatigue Severity Scale (FSS), which has sound psychometric properties, was used to measure the severity of fatigue and its effect on the patient's activities and lifestyle. It consists of 9 items, rated on a seven-point Likert scale from 1 to 7. Scores range from 9 to 63, with a score ≥36 suggestive of clinically relevant fatigue (Siciliano et al. 2019).

Statistical analysis

Absolute values and percentages were calculated. COVID-19 survivors were dichotomized based on whether they presented with clinically relevant post-COVID neuropsychiatric symptoms on the HADS, ISI, CFQ, and FSS. A multivariable logistic regression was performed to explore whether any variables would be associated with a higher risk of suffering from such symptoms, estimating the odds ratios (ORs; 95% CI). Variables that were significant at $p < 0.05$ in univariable analysis were included, taking into account potential collinearities. Analyses were performed by STATA 18.

Results

Baseline sociodemographic and clinical characteristics

Out of 1,067 patients with a COVID-19 diagnosis screened during the study period, 599 COVID-19 patients completed the 6-month follow-up assessment (Peghin et al. 2021a) and 230 the 24-month follow-up assessment. At the 24-month follow-up, most patients were middle-aged (41–60 years, 43%), female (53.5%), and native Italian (94.9%). About one in two patients presented with a medical comorbidity (53.5%) and used chronic medication (46.3%) (Supplementary Table 2). Apart from a higher preponderance of native Italians and patients with liver disease among those who completed the 24-month follow-up assessment, no statistical differences in terms of sociodemographic and clinical characteristics were detected between participants who were and were not lost to follow-up 24 months after the acute phase (Supplementary Table 3). The study sample's chronic medications are reported in the Supplementary Table 4.

Table 1. Post-COVID neuropsychiatric symptom prevalence

	N = 230
HADS, Anxiety *n* (%)†	
0–7	176 (76.5)
8–10	33 (14.3)
11–21	21 (9.1)
HADS, Depression, *n* (%)†	
0–7	175 (76.1)
8–10	29 (12.6)
11–21	26 (11.3)
ISI, *n* (%)††	
0–7	128 (55.7)
8–14	81 (35.2)
15–21	21 (9.1)
22–28	0 (0)
CFQ, *n* (%)‡	
<43	188 (81.7)
≥43	42 (18.3)
FSS, *n* (%)¥	
<36	140 (60.9)
≥36	90 (39.1)

HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; CFQ, Cognitive Failures Questionnaire; FSS, Fatigue Severity Scale.
†, scores range from 0 to 21 for each subscale, with scores between 11 and 21 indicating clinically relevant symptoms.
††, scores range from 0 to 28, with scores between 15 and 21 indicating clinically relevant insomnia of moderate severity and scores between 22 and 28 indicating severe insomnia.
‡, scores range from 0 to 100, with a score ≥ 43 suggestive of high cognitive failure.
¥, scores range from 9 to 63, with a score ≥ 36 suggestive of clinically relevant fatigue.

Acute COVID-19 presentation

Almost all patients were symptomatic (92.6%), with the majority presenting with a mild disease (67.7%) rather than a moderate to critically severe disease (24.9%). Admission to hospital was required in almost one-third of the sample (28.7%), while ICU was deemed necessary in a relatively low proportion of subjects (5.2%). A median in-hospital stay of 7 days (IQR 4–10) was observed (Supplementary Table 2).

Post-COVID neuropsychiatric symptom prevalence

Information on post-COVID neuropsychiatric symptom prevalence 24 months after the acute phase of the disease is provided in Table 1. About one in ten patients were found to present with clinically relevant anxiety (9.1%) and depression (11.3%) as well as moderately severe insomnia (9.1%). Moreover, a higher proportion of COVID-19 survivors were found to present with high cognitive failure (18.3%) and clinically relevant fatigue (39.1%).

Variables associated with post-COVID anxiety and depression

Headache (OR = 2.49, 95% CI = 1.01–6.16, $p = 0.048$), dyspnea (OR = 2.55, 95% CI = 1.03–6.31, $p = 0.043$), and the number of overall symptoms (OR = 1.23, 95% CI = 1.01–1.51, $p = 0.047$) at onset were associated with a higher risk of presenting with

Table 2. Predictors of post-COVID anxiety and depression

Anxiety			
	Univariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	1.46	0.58, 3.68	0.419
Age ≥50	0.94	0.36, 2.45	0.905
Ethnicity			
Native Italian	1		
European	0.98	0.12, 8.11	0.988
Comorbidities, number	0.80	0.51, 1.26	0.341
Chronic medication	0.43	0.16, 1.16	0.095
Overall symptoms, number	1.23	1.01, 1.51	**0.047**
Symptoms of psychiatric disorders (depression, anxiety, and insomnia)	1.06	0.05, 20.40	0.968
Lack of concentration and focus	0.63	0.03, 11.38	0.753
Fatigue	1.60	0.65, 3.96	0.309
Headache	2.49	1.01, 6.16	**0.048**
Neurological symptoms	1.47	0.31, 6.94	0.630
Anosmia/dysgeusia	2.42	0.85, 6.85	0.096
Rheumatological symptoms	1.48	0.38,5.73	0.572
Dyspnea	2.55	1.03, 6.31	**0.043**
URTI symptoms	0.74	0.16, 3.37	0.698
Cough	1.30	0.53, 3.20	0.567
Chest pain	0.63	0.03, 11.38	0.753
Cutaneous symptoms	5.39	0.93, 31.39	0.061
Gastrointestinal symptoms	1.34	0.54, 3.33	0.528
Management			
Outpatient	1		
Ward	1.64	0.64, 4.19	0.303
Intensive care unit	0.41	0.02, 7.38	0.549
IL-6 > 2	1.09	0.21, 5.73	0.914
Depression			
	Univariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	1.21	0.53, 2.77	0.648
Age ≥50	1.33	0.53, 3.31	0.544
Ethnicity			
Native Italian	1		
European	3.14	0.77, 12.70	0.109
Comorbidities, number	1.11	0.80, 1.55	0.531
Chronic medication	0.99	0.44, 2.26	0.991
Overall symptoms, number	1.12	0.92, 1.36	0.246
Symptoms of psychiatric disorders (depression, anxiety, and insomnia)	0.84	0.04, 16.06	0.908
Lack of concentration and focus	0.50	0.03,8.95	0.635
Fatigue	1.39	0.61, 3.16	0.428
Headache	1.34	0.57, 3.11	0.500
Neurological symptoms	1.13	0.24, 5.28	0.876
Anosmia/dysgeusia	1.38	0.58, 3.23	0.463
Rheumatological symptoms	0.77	0.21, 2.81	0.694
Dyspnea	2.80	1.22, 6.41	**0.015**
URTI symptoms	0.57	0.13, 2.56	0.463
Cough	1.46	0.64, 3.30	0.366
Chest pain	0.50	0.03, 8.95	0.635
Cutaneous symptoms	4.17	0.72, 23.96	0.110
Gastrointestinal symptoms	0.75	0.31, 1.80	0.519
Management			
Outpatient	1		
Ward	1.99	0.81, 4.84	0.131
Intensive care unit	1.99	0.40, 9.92	0.403
IL-6 > 2 pg/ml*	1.50	0.36, 6.26	0.578

IL-6, interleukin 6.
*Analysis was performed on a subsample of 96 patients with available data; clinically relevant anxiety and depression was based on Hospital Anxiety and Depression Scale (HADS) scores ≥11 at both subscales.

clinically relevant anxiety 24 months after the acute phase (Table 2). Out of all the variables screened in univariate analyses, dyspnea at onset was the only one increasing the risk of clinically relevant depression at the 24-month follow-up (OR = 2.80, 95% CI = 1.22–6.41, $p = 0.015$; Table 2).

Variables associated with post-COVID insomnia

The multivariate logistic model indicated that the number of comorbidities at onset increased the risk of presenting with insomnia at the 24-month follow-up (OR = 1.48, 95% CI = 1.06–2.08, $p = 0.022$). A weak association was also found for the number of overall symptoms at onset and the risk of insomnia at the 24-month follow-up (OR = 1.22, 95% CI = 0.99–1.50, $p = 0.054$; Table 3).

Variables associated with post-COVID cognitive failure

The multivariate logistic model indicated that the female gender (OR = 2.39, 95% CI = 1.14–5.00, $p = 0.020$) and the number of overall symptoms (OR = 1.20, 95% CI = 1.02–1.42, $p = 0.026$) at onset increased the risk of presenting with high cognitive failure at the 24-month follow-up (Table 4).

Variables associated with post-COVID fatigue

The multivariate logistic model indicated that the number of comorbidities (OR = 1.33, 95% CI = 1.03–1.73, $p = 0.029$) and overall symptoms (OR = 1.19, 95% CI = 1.04–1.37, $p = 0.013$) at onset increased the risk of presenting with fatigue at the 24-month follow-up. Further, patients whose interleukin 6 (IL-6) levels at onset were higher than the upper reference value (>2 pg/ml) were at higher risk of presenting with fatigue at the 24-month follow-up (OR = 4.02, 95% CI = 1.42–11.36, $p = 0.009$; Table 5).

Table 3. Predictors of post-COVID insomnia

	Univariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	1.83	0.71, 4.73	0.209
Age ≥50	1.21	0.45, 3.24	0.711
Ethnicity			
Native Italian	1		
European	0.98	0.12, 8.11	0.988
Comorbidities, number	1.48	1.07, 2.06	**0.019**
Chronic medication	1.47	0.58, 3.70	0.414
Overall symptoms, number	1.23	1.01, 1.51	**0.047**
Symptoms of psychiatric disorders (depression, anxiety, and insomnia)	1.06	0.05, 20.40	0.968
Lack of concentration and focus	0.63	0.03, 11.38	0.753
Fatigue	1.99	0.79, 5.00	0.144
Headache	2.49	1.01, 6.16	**0.048**
Neurological symptoms	1.47	0.31, 6.94	0.630
Anosmia/dysgeusia	0.93	0.38, 2.31	0.880
Rheumatological symptoms	2	0.65, 6.11	0.224
Dyspnea	2.06	0.83, 5.09	0.118
URTI symptoms	0.34	0.04, 2.61	0.298
Cough	2.47	0.98, 6.21	0.055
Chest pain	25.24	1.42, 447.60	**0.028**
Cutaneous symptoms	5.39	0.93, 31.40	0.061
Gastrointestinal symptoms	1.08	0.43, 2.71	0.875
Management			
Outpatient	1		
Ward	1.73	0.65, 4.59	0.271
Intensive care unit	1.05	0.13, 8.83	0.960
IL-6 > 2 pg/ml*	1.74	0.41, 7.44	0.455
	Multivariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Comorbidities, number	1.48	1.06, 2.08	**0.022**
Overall symptoms, number	1.22	0.99, 1.50	0.054

IL-6, interleukin 6.
*Analysis was performed on a subsample of 96 patients with available data; clinically relevant insomnia was based on Insomnia Severity Index (ISI) score ≥15.

Table 4. Predictors of post-COVID cognitive failure

	Univariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	2.55	1.23, 5.29	**0.012**
Age ≥50	0.94	0.46, 1.01	0.859
Ethnicity			
Native Italian	1		
European	1.01	0.21, 4.89	0.985
Comorbidities, number	1.01	0.75, 1.35	0.956
Chronic medication	0.84	0.43, 1.66	0.625
Overall symptoms, number	1.22	1.04, 1.43	**0.014**
Symptoms of psychiatric disorders (depression, anxiety, and insomnia)	1.50	0.15, 14.83	0.727
Lack of concentration and focus	1.83	0.34, 9.77	0.480
Fatigue	1.50	0.76, 2.93	0.238
Headache	2.20	1.11, 4.35	**0.024**
Neurological symptoms	2.17	0.71, 6.63	0.172
Anosmia/dysgeusia	1.98	0.95, 4.09	0.067
Rheumatological symptoms	1.51	0.58, 3.91	0.397
Dyspnea	1.07	0.52, 2.17	0.859
URTI symptoms	1.59	0.63, 4.03	0.328
Cough	1.34	0.68, 2.62	0.394
Chest pain	1.83	0.34, 9.77	0.480
Cutaneous symptoms	4.74	0.92, 24.38	0.062
Gastrointestinal symptoms	1.23	0.62, 2.43	0.556
Management			
Outpatient	1		
Ward	0.72	0.31, 1.57	0.441
Intensive care unit	0.82	0.17, 3.95	0.810
IL-6 > 2 pg/ml*	0.80	0.24, 2.72	0.728
	Multivariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	2.39	1.14, 5.00	**0.020**
Overall symptoms, number	1.20	1.02, 1.42	**0.026**

IL-6, interleukin 6.
*Analysis was performed on a subsample of 96 patients with available data; clinically relevant insomnia was based on Cognitive Failures Questionnaire (CFQ) score ≥43.

Discussion

Available publications have suggested that neuropsychiatric symptoms are frequently encountered in the months after having suffered from COVID-19 (Badenoch et al. 2022; Premraj et al. 2022), possibly representing the most characteristic manifestation of the post-COVID syndrome (Rivera-Izquierdo et al. 2022), especially if the infection resulted in hospitalization to manage the disease (Nersesjan et al., 2023). However, evidence that COVID-induced neuropsychiatric symptoms would persist in the longer term is not unequivocal, as such evidence would need to integrate longitudinal information to track the trajectory of change in mental health-related domains by using direct measures of neuropsychiatric distress. Starting with a follow-up assessment performed 6 months after the acute infection (Peghin et al. 2021a) and then at either the 12- (Colizzi et al. 2023a) or 24-month (Colizzi et al. 2023b) follow-up, we tracked the evolution of mental health-related manifestations among COVID-19 survivors in previous reports. We also explored which sociodemographic and clinical characteristics at onset would predict post-COVID neuropsychiatric symptoms. Overall, we detected a progressive increase in neuropsychiatric symptoms over time, with a parallel decrease of any other complaint, and a potential plateau 24 months post-infection (Colizzi et al. 2023a; Colizzi et al. 2023b; Peghin et al. 2021a). More specifically, we found that between 9.6% and 25.2% of COVID-19 survivors had any mental-health-domain-related symptom at the 24-month follow-up, while patients with preexisting medical comorbidities and those suffering from severe COVID-19 in terms of dyspnea were at higher risk of post-COVID neuropsychiatric symptoms (Colizzi et al. 2023b).

Table 5. Predictors of post-COVID fatigue

	Univariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Female gender	1.33	0.78, 2.27	0.295
Age ≥50	1.83	1.01, 3.30	**0.046**
Ethnicity			
Native Italian	1		
European	1.89	0.56, 6.40	0.306
Comorbidities, number	1.39	1.10, 1.76	**0.006**
Chronic medication	1.43	0.84, 2.45	0.188
Overall symptoms, number	1.19	1.04, 1.36	**0.010**
Symptoms of psychiatric disorders (depression, anxiety, and insomnia)	1.57	0.22, 11.34	0.656
Lack of concentration and focus	2.12	0.46, 9.72	0.332
Fatigue	2.28	1.33, 3.92	**0.003**
Headache	1.06	0.60, 1.85	0.851
Neurological symptoms	1.61	0.58, 4.45	0.359
Anosmia/dysgeusia	1.01	0.59, 1.73	0.962
Rheumatological symptoms	0.58	0.25, 1.34	0.203
Dyspnea	1.94	1.11, 3.41	**0.021**
URTI symptoms	0.85	0.37, 1.93	0.693
Cough	1.20	0.70, 2.05	0.505
Chest pain	25.24	1.42, 447.60	**0.028**
Cutaneous symptoms	8.18	0.94, 71.18	0.057
Gastrointestinal symptoms	1.89	1.09, 3.27	**0.023**
Management			
Outpatient	1		
Ward	1.32	0.71, 2.47	0.385
Intensive care unit	3.56	1.03, 12.32	**0.045**
IL-6 > 2 pg/ml*	4.02	1.42, 11.36	**0.009**
	Multivariable analysis		
Risk factors at onset	OR	95% CI	*p*-value
Age ≥50	1.37	0.71, 2.63	0.343
Comorbidities, number	1.33	1.03, 1.73	**0.029**
Overall symptoms, number	1.19	1.04, 1.37	**0.013**
Management			
Outpatient	1		
Ward	0.89	0.45, 1.77	0.740
Intensive care unit	2.90	0.81, 10.43	0.102

IL-6, interleukin 6.
*Analysis was performed on a subsample of 96 patients with available data; clinically relevant insomnia was based on Fatigue Severity Scale (FSS) score ≥36.

The present report expands on previous evidence, by assessing the occurrence of neuropsychiatric conditions in this sample of COVID-19 survivors followed-up for two years with psychometric tools routinely used in research and clinical practice. Prevalence of neuropsychiatric symptoms ranged between 9.1% and 35.2%, which substantially overlaps with the unstandardized investigations performed at the same timepoint (Colizzi et al. 2023b). Similar risk factors also emerged in the context of the psychometric assessment. In line with findings from the 12-month follow-up (Colizzi et al. 2023a), female COVID-19 survivors were at greater risk of presenting with high cognitive failure at the 24-month follow-up. Also, greater severity of acute disease and preexisting comorbidities were found to be consistently associated with post-COVID neuropsychiatric symptoms in both self-reported unstandardized investigations (Colizzi et al. 2023b) and in psychometric assessments performed at the 24-month follow-up. Furthermore, dyspnea at onset, which had emerged as a specific risk factor in those complaining of post-COVID neuropsychiatric symptoms 24 months after the acute phase (Colizzi et al. 2023b), was found to increase the risk of both anxiety and depression at the 24-month follow-up when assessed with a standardized tool. Further, a higher risk of fatigue was found among those COVID-19 survivors having an increase in the proinflammatory cytokine IL-6 during the acute phase, possibly indicating a link between COVID-19-induced neuropsychiatric distress and the underlying cytokine storm (Alpert et al. 2020).

As per our previous report (Colizzi et al. 2023a), we did not find clear-cut evidence that hospitalization status or management (e.g., ICU admission) modifies the risk of post-COVID neuropsychiatric symptoms at follow-up. Hospitalization has been shown to explain persistence of respiratory symptoms among COVID-19 survivors (Blomberg et al. 2021; Pérez-González et al. 2022) but not neuropsychiatric symptoms in some studies (Badenoch et al. 2022; Premraj et al., 2022), possibly suggesting that other parameters of severity are needed to predict vulnerability to post-COVID neuropsychiatric syndrome (Sudre et al. 2021).

Findings provided here are consistent, both in terms of prevalence and risk factors, with previous literature. In fact, meta-analytic evidence has suggested that a substantial proportion of COVID-19 survivors already present with neuropsychiatric symptoms 3 months following COVID-19 diagnosis (Badenoch et al. 2022; Ceban et al. 2022; Premraj et al. 2022). Also, a preponderance of females and people who have suffered a more severe acute illness and with underlying comorbidities have been observed among COVID-19 survivors presenting with neuropsychiatric symptoms, possibly due to a greater susceptibility of these populations to an elevation in proinflammatory markers (Ceban et al. 2022).

Collectively, incorporating a prospective design and implementing psychometric assessments, findings may contribute to initial evidence of a causal interpretation for the association between COVID-19 infection and neuropsychiatric symptoms. They are also consistent with experimental research into the effects of infection-induced depressive and sickness behavior symptoms (e.g., diurnal variation in mood, concentration difficulties, and fatigue) via inflammatory perturbation, both in human (Lasselin et al. 2020; Lasselin et al. 2021) and animal studies (Lasselin et al. 2020). Interestingly, previous research suggests that infection-induced levels of inflammatory markers have been shown to predict trajectories of individual symptoms of depression and sickness behavior for as long as 9 years (van Eeden et al. 2020), with women (Lasselin et al. 2018) and patients with chronic inflammatory and autoimmune diseases (Grygiel-Górniak et al. 2019) being more vulnerable to the detrimental neuropsychiatric effects of the infection-induced inflammation. It is thus entirely plausible that subpopulations of COVID-19 survivors, that is females and patients with either more severe acute COVID-19 or with preexisting comorbidities, may present with clinically relevant neuropsychiatric symptoms even years after the acute phase. It is worth mentioning that the Il-6 increase in particular has been found to be a core component of the cytokine storm syndrome in COVID-19, with medications that lower cytokine activity being

proposed to ameliorate neuropsychiatric symptoms, independently of the psychopharmacological treatment (Alpert et al. 2020).

This study has several limitations, including the lack of a control group of non-COVID-19 patients for a direct comparison in terms of mental distress, in order to disentangle the indirect effects of the pandemic related to routine disruptions, social isolation, and fear (Bortoletto et al. 2022; Colizzi et al. 2020; Pigaiani et al. 2020). Also, as recent evidence does not support a higher mental health burden among hospitalized COVID-19 survivors when compared to hospitalized patients with other infectious diseases (Nersesjan et al. 2023), future studies could enroll samples of patients with other medical conditions for a direct comparison in terms of neuropsychiatric symptom prevalence. Further, no brain assessments were carried out that would have offered greater insights into the neurobiological underpinnings of post-COVID symptoms (Alpert et al. 2020; Ho et al. 2021). Moreover, as the pandemic remains an unfolding phenomenon, formal psychometric assessments were only performed after two years, and report on the evidence of post-COVID neuropsychiatric distress, which did not allow for a pre-post comparison among the study sample. Finally, even though patients assessed at the 24-month follow-up were broadly similar from a sociodemographic and clinical perspective to those lost to follow-up, a selection bias cannot be fully ruled out.

The results presented here have important practice and policy implications. Findings indicate that COVID-19 survivors, especially if female, with preexisting health problems, and with a more severe acute phase as represented by both symptom and inflammatory levels, may present with mental health difficulties for at least two years, and possibly more, after the acute phase. The findings suggest the need to focus on the development of interventions at individual and health-service levels which may help mitigate the long-term harmful effects of COVID-19 infection on mental health.

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Ethical standard. The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Study ethical approval was obtained from the local Ethics Committee (CEUR-2020-OS-219, CEUR-2020-OS-205, CEUR-2021-OS-19).

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