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Presence of COVID-19 self-reported symptoms at 12 months in patients discharged from hospital in 2020–2021: a Spanish cross-sectional study

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The long-term effects of SARS-CoV-2 infection, and their determinants, are still unknown. This study aimed to assess symptoms one year after admission for COVID-19, according to the organ/system involved, and to identify factors. Cross-sectional study with retrospective data collection from March 2020 to February 2021. Inclusion criteria: aged ≥ 18 years and admitted for COVID-19. Exclusion criteria: death, not localized, refusal to participate, cognitive impairment or language barrier. A telephone survey was conducted on long COVID-related symptoms one year after hospital discharge. *n* = 486. The most frequent symptom groups were neurological (*n* = 225; 46.3%) and respiratory (*n* = 201; 41.4%). Multivariable analysis showed that a history of anxiety was significantly associated with psychiatric symptoms (ORa = 2.04, 95%CI = 1.02–4.06), fibromyalgia/chronic fatigue with general symptoms (ORa = 11.59, 95%CI = 1.47–9.34) and obesity with respiratory (ORa 1.90, 95%CI = 1.27–2.83) and musculoskeletal symptoms (ORa 1.96, 95%CI = 1.30–2.96). Male sex was associated with a significantly lower risk of neurological (ORa 0.64, 95%CI = 0.44–0.93), respiratory (ORa 0.45, 95%CI = 0.31–0.67), general (ORa 0.43, 95%CI = 0.29–0.63), psychiatric (ORa 0.34, 95%CI = 0.22–0.51), musculoskeletal (ORa 0.47, 95%CI = 0.32–0.70), dermatological (ORa 0.24, 95%CI = 0.14–0.42) and digestive (ORa 0.38, 95%CI = 0.20–0.73) symptoms. Advanced age (≥ 71 years) also had a protective effect against general (ORa 0.60, 95%CI = 0.39–0.95), psychiatric (ORa 0.39, 95%CI = 0.23–0.64), and dermatological (ORa 0.47, 95%CI = 0.24–0.92) symptoms. Patients admitted for SARS-CoV-2 infection frequently experience symptoms at one year, especially neurological and respiratory symptoms. Female sex, obesity, a history of anxiety and fibromyalgia/chronic fatigue were independent risk factors for presenting symptoms. Advanced age acted as a protective factor.

Keywords COVID-19, Long COVID, Post-acute COVID-19 syndrome, SARS-CoV-2, Fatigue

Abbreviations

OR	Odds ratio
WHO	World Health Organization
PASC	Post-acute sequelae of COVID-19
ME/CFS	Encephalomyelitis/chronic fatigue syndrome

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ARDS	Acute respiratory distress syndrome
ICU	Intensive unit care
FiO2	Inspiratory O_2 fraction
PaO2	Partial pressure of oxygen
RCP	C-reactive protein
IL-6	Interleukin-6
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure

Between the end of 2019, when the first case was reported, until 10 March 2023, SAR-CoV-2 caused nearly 700 million confirmed infections worldwide and almost 7 million deaths[1]. Although its pathophysiology and clinical manifestations in the acute phase are already well known[2], details on its long-term evolution, including the factors influencing it and its management, still need elucidation. This knowledge is of the utmost importance, since around 10–20% of infected patients still present symptoms or medical complications weeks or even months after infection[3]. In October 2021, the World Health Organization (WHO) defined long COVID as the presence of symptoms persisting for at least two months and at least three months after acute SARS-CoV-2 infection, which cannot be explained by an alternative diagnosis[4]. Long COVID, also called post-COVID condition or post-acute sequelae of COVID-19 (PASC), can affect any organ or system of the human body, including the central and peripheral nervous, cardiovascular, respiratory, and digestive systems[5–8]. In this line, a recent meta-analysis in 1.2 million patients who had suffered an acute symptomatic SARS-CoV-2 infection showed that about 6.2% still had symptoms compatible with long COVID three months after infection[9]. Its long-term association with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomia, especially with postural orthostatic tachycardia syndrome, is also important[10,11]. Moreover, evidence points to its significant impact on patients' quality of life, even a year after acute infection and regardless of the severity of the episode[12].

Therefore, our study aimed to assess the presence of symptoms one year after admission for SARS-CoV-2 infection, according to the organ/system involved, and to identify the factors influencing the appearance of each symptom group.

Materials and methods

Study design, setting and participants

This cross-sectional study with retrospective data collection took place in the city of Castellón (Spain), in a referral hospital serving about 283,000 inhabitants, from March 2020 to February 2021. Patients over 18 years of age admitted to the infectious diseases unit for SARS-CoV-2 infection, confirmed by RT-PCR or antigenic test, were included. Patients were excluded if they died during admission or subsequent follow-up up to one year after the hospital discharge, could not be located at the time of the telephone interview, refused to participate in the study, had a relevant cognitive impairment at the time of the interview, or could not comfortably communicate in a language known to the researchers. The patients finally included in the study underwent a telephone survey in which they were asked directly about the presence or absence of the main Long-COVID-related symptoms (grouped by organ and systems, as presented in Table 1). There was also an open question about any other symptoms they had experienced, apart from those mentioned in the interview.

Variables

Electronic health records (Orion Clinic-Conselleria de Sanitat Universal i Salut Publica, Comunidad Valenciana, Spain) were reviewed retrospectively one year after discharge from hospital to collect explanatory variables, including: demographic data (sex, age); disease history [comorbidities including obesity, defined by body mass index ≥ 30 kg/m^2, and age-adjusted Charlson comorbidity index (scale for assessing life expectancy at ten years, depending on the age at which it is assessed, and the subject's comorbidities)]; clinical course (hospital stay, evolution to acute respiratory distress syndrome [ARDS], need for admission to the intensive care unit [ICU], type of respiratory support, inspiratory O_2 fraction [FiO_2] and Pa/FiO_2 ratio on admission and extreme values during their stay); analytical parameters during hospital stay (values on admission and extreme values during admission of lymphocytes, C-reactive protein [CRP], ferritin, IL-6 [interleukin-6] and D-dimer); treatment (systemic corticotherapy during admission and total days of corticotherapy); and vaccination against SARS-CoV-2 after hospital admission (yes/no).

Participants who gave informed consent completed a telephone survey already described above, one year after admission, which constituted the primary outcome.

Statistical analysis

The statistical analysis was undertaken using SPSS software (version 23; IBM). First, a descriptive study of the sample was performed, expressing categorical variables as absolute or relative frequencies and quantitative variables as means (standard deviation, SD) or medians (interquartile range, IQR), depending on the normality of their distribution (only age showed a normal distribution). Next, the association between the different explanatory variables and outcomes was studied. Results were expressed by odds ratio (OR) and 95% confidence intervals (CI). Quantitative variables were dichotomized, using the 75th percentile as the cutoff value. The Bonferroni test was used to correct for multiple comparisons, so considering a statistical significance of $p < 0.05$ and the fact that 39 variables were included in the univariable analysis, only values of $p < 0.0012$ were considered

Neurological	Respiratory	General	Psychiatric	Musculoskeletal	Dermatological	Digestive	Otorhinolaryngological	Cardiovascular	Ophthalmological	Gynecological
Anosmia	Rhinorrhea	Fever	Anxiety	Arthromyalgia	Skin lesions	Odynophagia	Dysphonia	Palpitations/tachycardia	Vision loss	Amenorrhea
Ageusia	Cough	Headache	Depression	Arthritis	Urticaria	Dysphagia	Tinnitus	Vascular claudication	Xerostomia	
Paresthesia	Dyspnea	Asthenia	Insomnia		Alopecia	Diarrhea	Vertigo	Erectile dysfunction		
Deafness	Chest pain	Sweating					Otalgia			
Brain fog		Weakness								
Dizziness										
Tremor										
Instability										

Table 1. Self-reported symptoms in patients admitted for SARS-COV-2 infection at one year after discharge, grouped by organs or systems.

statistically significant. Finally, a multivariable analysis was completed, using binary logistic regression, including in the model the variables that had been shown to have a statistically significant influence on the presence or absence of the different symptom clusters. The analysis was also adjusted for sex and age.

Ethics

The research ethics committee of the Castellón General University Hospital approved the study, which complied with the guidelines of the Spanish Agency of Medicines and Health Products. All participants gave their verbal informed consent. Patient confidentiality and personal data were protected according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of data.

Results

Study sample

After excluding 334 patients, a total of 486 patients were included (Fig. 1): 292 (60.1%) were men, and the mean age was 61 years (SD 14). Nearly a quarter ($n=111$, 22.8%) were smokers or former smokers, 205 (44.2%) had a diagnosis of hypertension, and 153 (31.5%) were obese. The median age-adjusted Charslon comorbidity index score was 2 (IQR 1–3). With regard to the clinical characteristics of the index hospitalization, the median length of stay was 10 days (IQR 6–15), and 100 patients (20.6%) required ICU admission, with a median unit stay of 6 days (IQR 4–10). In addition, 193 patients (39.7%) presented ARDS; 93 (19.1%) required noninvasive mechanical ventilation, and 17 (3.5%) invasive. Regarding pharmacological treatment, 432 patients (88.9%) received systemic corticosteroids during admission (median duration 36 days, IQR 19–49). Following admission, 398 patients (81.9%) completed the SARS-CoV-2 vaccination regimen recommended at the time by the country's health authorities. None had received any dose of the SARS-CoV-2 vaccine prior to hospital admission. Patient characteristics, including analytical variables are described in full in Tables 2 and 3.

Self-reported symptoms at one-year follow-up

The most frequently self-reported symptoms at one year after admission for SARS-CoV-2 infection were mental fog ($n=177$; 36.4%), asthenia ($n=167$; 34.4%), dyspnea ($n=155$; 31.9%), arthromyalgia ($n=147$; 30.2%), and anxiety ($n=120$; 24.7%) (Fig. 2). In terms of symptom groups (Table 1), neurological symptoms were the most frequent ($n=225$, 46.3%), followed by respiratory ($n=201$, 41.4%), general ($n=185$, 38.1%), psychiatric ($n=168$, 34.6%), and musculoskeletal ($n=149$, 30.7%) symptoms. Only 144 patients (29.6%) reported having no symptoms at the time of the telephone interview (Fig. 3).

Association between explanatory variables and the presence of different symptom groups. Univariable analysis

A history of fibromyalgia/chronic fatigue was significantly associated with the presence of respiratory (OR = 8.19, 95%CI = 1.80-37.37), general (OR = 20.81, 95%CI = 2.68-161.41) and psychiatric (OR = 11.07, 95%CI = 2.42–50.55) symptoms. Obesity was the second most prominent risk factor, showing a statistical relationship with the presence of respiratory (OR = 2.00, 95%CI = 1.35–2.95) and musculoskeletal (OR = 2.01, 95%CI = 1.34–3.01) symptoms. Psychiatric symptoms were also associated with a history of anxiety (OR = 3.72, 95%CI = 2.09–6.64) and depression (OR = 3.47, 95%CI = 1.55–7.76).

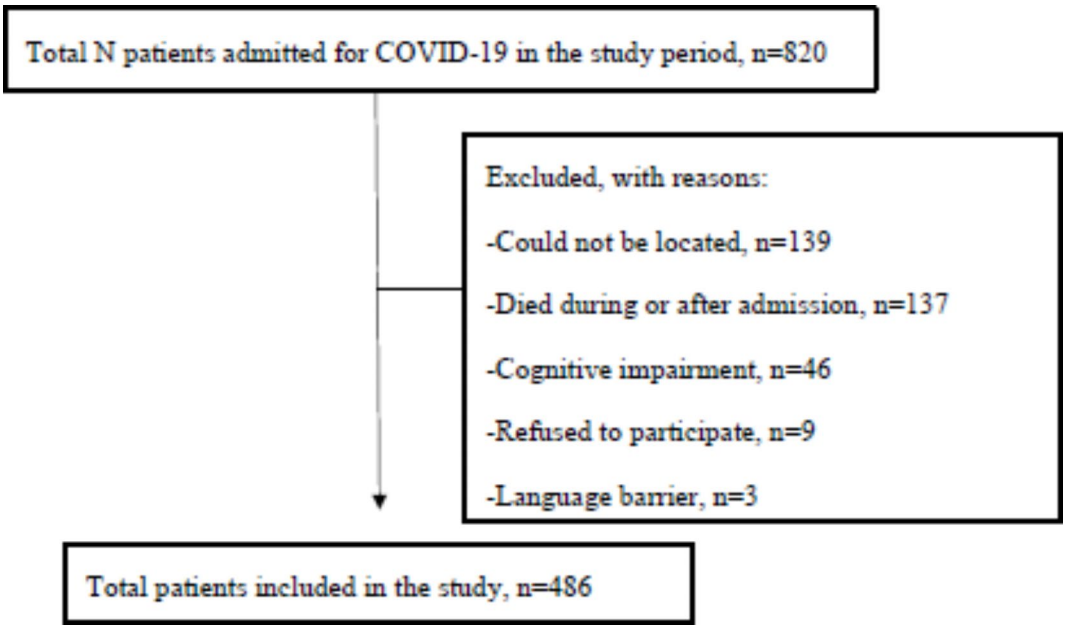

Fig. 1. Patient flow chart.

Variables	Symptom group																
		Neurological		Respiratory		General		Psychiatric		Musculoskeletal		Dermatological		Digestive		Otorhinolaryngological	
	n (%)	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Clinical characteristics																	
Male	292 (60.1)	0.66 (0.46–0.95)	0.024	0.42 (0.30–0.60)	**< 0.001**	0.40 (0.28–0.58)	**< 0.001**	0.31 (0.21–0.46)	**< 0.001**	0.46 (0.31–0.68)	**< 0.001**	0.26 (0.15–0.44)	**< 0.001**	0.39 (0.20–0.76)	0.004	1.79 (0.47–6.8)	0.390
Smoker/ex-smoker	111 (22.8)	0.64 (0.41–0.99)	0.042	0.61 (0.39–0.96)	0.030	0.99 (0.64–1.53)	0.960	0.75 (0.48–1.19)	0.220	1.53 (0.98–2.38)	0.062	0.40 (0.19–0.86)	0.016	0.95 (0.44–2.05)	0.890	0.75 (0.16–3.51)	0.710
Hypertension	205 (44.2)	1.00 (0.70–1.44)	0.990	1.16 (0.80–1.67)	0.430	0.87 (0.60–1.26)	0.450	0.69 (0.47–1.01)	0.057	1.09 (0.74–1.61)	0.670	0.65 (0.38–1.104)	0.108	0.87 (0.45–1.67)	0.670	1.15 (0.35–3.81)	0.820
Dyslipidemia	140 (28.8)	0.82 (0.55–1.22)	0.330	1.05 (0.70–1.56)	0.820	0.87 (0.58–1.31)	0.500	0.78 (0.52–1.19)	0.260	0.91 (0.59–1.40)	0.680	0.93 (0.53–1.64)	0.801	1.03 (0.51–2.07)	0.950	0.93 (0.24–3.54)	0.910
Anxiety	56 (11.5)	1.78 (1.01–3.13)	0.044	2.43 (1.38–4.31)	0.002	2.05 (1.17–3.59)	0.011	3.72 (2.09–6.64)	**< 0.001**	1.68 (0.95–2.98)	0.072	1.57 (0.77–3.21)	0.220	1.66 (0.70–3.96)	0.250	1.73 (0.37–8.23)	0.480
Depression	27 (5.6)	3.54 (1.47–8.54)	0.003	2.15 (0.98–4.75)	0.052	2.95 (1.32–6.58)	0.006	3.47 (1.55–7.76)	**0.001**	1.60 (0.72–3.54)	0.240	2.24 (0.91–5.52)	0.072	0.86 (0.20–3.77)	0.840	4.00 (0.82–19.50)	0.064
Fibromyalgia/ chronic fatigue	13 (2.7)	4.00 (1.09–14.72)	0.025	8.19 (1.80-37.37)	**0.001**	20.81 (2.68-161.41)	**< 0.001**	11.07 (2.42–50.55)	**< 0.001**	5.35 (1.62–17.67)	0.002	1.10 (0.24–5.08)	0.900	2.02 (0.43–9.46)	0.360	3.86 (0.46–32.60)	0.180
Obesity (BMI > 30 kg/m^2)	153 (31.5)	1.72 (1.17–2.54)	0.006	2.00 (1.35–2.95)	**< 0.001**	1.73 (1.17–2.56)	0.006	1.52 (1.02–2.26)	0.038	2.01 (1.34–3.01)	**0.001**	0.87 (0.50–1.53)	0.630	1.80 (0.94–3.44)	0.074	1.25 (0.36–4.34)	0.720
Cardiac insufficiency	17 (3.5)	1.03 (0.39–2.72)	0.950	1.27 (0.48–3.35)	0.630	0.21 (0.05–0.92)	0.023	0.78 (0.27–2.26)	0.649	0.94 (0.33–2.72)	0.910	0.37 (0.05–2.83)	0.320	0.67 (0.09–5.19)	0.700	2.87 (0.35–23.79)	0.310
COPD	5 (1)	1.75 (0.29–10.57)	0.540	0.35 (0.04–3.17)	0.330	0.40 (0.05–3.64)	0.400	0.47 (0.05–4.24)	0.490	0.56 (0.06–5.08)	0.600	1.52 (0.17–13.79)	0.710	0.92 (0.89–0.94)	0.500	0.98 (0.96–0.99)	0.730
Asthma	4 (0.8)	0.46 (0.42–0.51)	0.031	0.41 (0.37–0.46)	0.017	4.95 (0.51–47.90)	0.130	5.76 (0.60-55.84)	0.088	2.28 (0.32–16.33)	0.400	2.03 (0.21–19.79)	0.530	3.68 (0.37–36.23)	0.230	0.98 (0.96–0.99)	0.760
Chronic kidney disease	14 (2.9)	0.87 (0.30–2.54)	0.790	0.78 (0.26–2.37)	0.660	0.64 (0.20–2.08)	0.460	1.05 (0.35–3.19)	0.930	0.37 (0.08–1.67)	0.180	0.46 (0.06–3.55)	0.440	1.85 (0.40–8.57)	0.420	0.98 (0.96–0.99)	0.560
Diabetes	71 (14.6)	1.06 (0.66–1.71)	0.800	1.07 (0.66–1.73)	0.790	0.82 (0.50–1.34)	0.420	0.70 (0.41–1.18)	0.170	0.86 (0.51–1.46)	0.570	0.81 (0.40–1.66)	0.570	2.88 (1.43–5.76)	0.002	1.88 (0.49–7.24)	0.350
Clinical outcomes																	
ARDS	193 (39.7)	1.22 (0.84–1.75)	0.290	1.20 (0.83–1.74)	0.330	0.82 (0.56–1.19)	0.300	0.97 (0.66–1.43)	0.890	1.08 (0.73–1.60)	0.710	0.91 (0.54–1.53)	0.710	0.77 (0.39–1.51)	0.450	1.27 (0.38–4.23)	0.690
ICU admission	100 (20.6)	1.72 (1.10–2.68)	0.016	1.03 (0.66–1.62)	0.880	1.05 (0.67–1.65)	0.830	1.21 (0.77–1.90)	0.420	1.69 (1.07–2.68)	0.023	1.20 (0.65–2.20)	0.560	0.779 (0.34–1.81)	0.560	1.46 (0.38–5.61)	0.580

Continued

Variables	Symptom group															
		Neurological		Respiratory		General		Psychiatric		Musculoskeletal		Dermatological		Digestive		Otorhinolaryngological	
	n (%)	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Helmet-CPAP	93 (19.1)	1.70 (1.08–2.69)	0.021	1.09 (0.69–1.72)	0.720	1.03 (0.65–1.65)	0.890	1.18 (0.74–1.89)	0.490	1.76 (1.10–2.80)	0.018	1.47 (0.80–2.68)	0.210	0.86 (0.37-2.00)	0.730	0.94 (0.20–4.41)	0.940
High-flow oxygen	26 (5.3)	1.17 (0.53–2.58)	0.700	0.74 (0.32–1.69)	0.470	0.47 (0.19–1.20)	0.110	1.00 (0.44–2.30)	1.000	1.21 (0.53–2.78)	0.650	0.49 (0.11–2.12)	0.330	0.90 (0.21–3.95	0.890	0.98 (0.96–0.99)	0.430
Mechanical ventilation	17 (3.5)	2.19 (0.80–6.01)	0.120	1.62 (0.62–4.28)	0.320	1.14 (0.43–3.06)	0.790	1.03 (0.38–2.85)	0.950	2.64 (1.00-6.99)	0.043	0.80 (0.18–3.58)	0.770	0.67 (0.09–5.19)	0.700	2.87 (0.35–23.79)	0.310
Systemic corticosteroids during admission	432 (88.9)	0.56 (0.31–0.99)	0.043	0.52 (0.30–0.93)	0.025	0.68 (0.39–1.21)	0.190	1.06 (0.58–1.94)	0.840	0.72 (0.40–1.31)	0.280	0.70 (0.33–1.46)	0.340	0.71 (0.28–1.76)	0.450	0.21 (0.06–0.73)	0.007
SARS-CoV-2 vaccination after admission	398 (81.9)	0.67 (0.42–1.06)	0.086	0.77 (0.48–1.23)	0.270	0.69 (0.43–1.10)	0.120	1.41 (0.85–2.35)	0.180	0.73 (0.45–1.18)	0.200	0.44 (0.25–0.78)	0.004	0.66 (0.31–1.40)	0.280	0.581 (0.15–2.24)	0.430

Table 2. Univariable analysis of associations between categorical variables and the presence of symptoms one year after admission for COVID-19 (grouped by organs or systems). *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CPAP* continuous positive airway pressure, *ICU* intensive care unit. Significant values are in bold.

In contrast, male sex showed a protective effect against respiratory (OR = 0.42, 95%CI = 0.29–0.60), general (OR = 0.40, 95%CI = 0.28–0.58), psychiatric (OR = 0.31, 95%CI = 0.21–0.46), musculoskeletal (OR = 0.46, 95%CI = 0.31–0.68) and dermatological (OR = 0.26, 95%CI = 0.15–0.44) symptoms (Table 2).

As for quantitative variables, advanced age (≥ 71 years) showed a protective effect against the presence of psychiatric symptoms at one year (OR = 0.44, 95%CI = 0.27–0.70). No other statistically significant associations were observed (Table 3).

Association between explanatory variables and the presence of different symptom groups. Multivariable analysis

A history of anxiety was significantly and independently associated with the presence of psychiatric symptoms at one year (ORa = 2.04, 95%CI = 1.02–4.06). Fibromyalgia/chronic fatigue was associated with the persistence of general symptoms (ORa = 11.59, 95%CI = 1.47–9.34), and obesity with respiratory (ORa = 1.90, 95%CI = 1.27–2.83) and musculoskeletal symptoms (ORa = 1.96, 95%CI = 1.30–2.96).

In contrast, male sex was associated with a lower presence of neurological (ORa = 0.64, 95%CI = 0.44–0.93), respiratory (ORa = 0.45, 95%CI = 0.31–0.67), general (ORa = 0.43, 95%CI = 0.29–0.63), psychiatric (ORa = 0.34, 95%CI = 0.22–0.51), musculoskeletal (ORa = 0.47; 95%CI = 0.32–0.70), dermatological (ORa = 0.24, 95%CI = 0.14–0.42), and digestive (ORa = 0.38, 95%CI = 0.20–0.73) symptoms. Advanced age (≥ 71 years) also had a protective effect against presenting general (ORa = 0.60, 95%CI = 0.39–0.95), psychiatric (ORa = 0.39, 95%CI = 0.23–0.64), and dermatological (ORa = 0.47, 95%CI = 0.24–0.92) symptoms (Table 4).

Discussion

Our study followed up on cohort of adult patients, mainly made up of men with an average age of around 60 years of age and a modest burden of comorbidity, who had been admitted for SARS-CoV-2 and had not been vaccinated against at the time of acute infection. Just under half developed ARDS, and practically all of them were treated with systemic corticosteroids. A year after discharge, they frequently showed symptoms that they attributed to COVID-19. Only 29.6% were completely asymptomatic, a remarkable figure although still somewhat higher than reports from similar prospective studies with one-year follow-up in samples that included mild cases not requiring hospital admission[13,14]. Those results are particularly striking considering that the estimated incidence of long COVID in hospitalized patients is 50–70%, compared to 10–30% in community cases[15,16]. However, this could be explained by differences between the populations studied, for example due to selection biases in studies analyzing outpatients who needed follow-up care during their recovery from the acute infection and thus may have been more prone to long-term symptoms.

In keeping with other studies, our data show that both neurological and respiratory symptoms were particularly frequent[17,18], and generally and psychiatric symptoms somewhat less so, as described elsewhere[19]. Similarly, an international observational study of 3762 people from 56 different countries reported that, six months after infection, 65.2% of patients had at least one symptom[17]. Asthenia, weakness on exertion, and cognitive impairment were the most frequent[17].

Multiple theories exist about the pathophysiology of long COVID, involving endothelial damage, immune dysregulation and autoimmunity phenomena, thrombotic phenomena, inflammation, intestinal dysbiosis, and even viral persistence in certain reservoirs[20]. Less is known about which socio-epidemiological, clinical, or analytical factors influence its appearance, much less which of these parameters are at play in different symptom groups. According to our results, a history of anxiety, fibromyalgia/chronic fatigue, obesity, and above all female sex behave as clear independent risk factors for the presence of symptoms after SARS-CoV-2 infection. Other published cohorts have also demonstrated a clear association between female sex and long COVID as well as poorer long-term quality of life[21–23]. Indeed, Subramanian et al. included more than 480,000 patients, observing that female sex, obesity, and a history of fibromyalgia or anxiety were independent risk factors for developing long COVID[24]. The risk of long COVID attributable to female sex has its counterpoint in the fact that men are at higher risk of death from COVID-19[25]. Thus, among patients at high risk for an adverse outcome, data show that men are more likely to die, and women to experience persistent symptoms. Furthermore, as observed in our analysis and also in the study by Cai et al., the age range in which the probability of suffering symptoms would increase significantly is around 40–60 years[21].

Of note, the severity of the infection, as reflected by the degree of respiratory failure and type of respiratory support required, the inflammatory laboratory values, and the need for ICU admission, did not seem influence the appearance of any of the symptom groups at one year. Other authors have reported similar results, associating long COVID with a specific clinical profile (mainly female sex, obesity, and a history of fibromyalgia/chronic fatigue syndrome) rather than with the severity of the acute infection[12]. However, there are conflicting reports on this topic, with some studies finding that the severity of the acute infection was an independent determinant for long COVID[21].

Results should be interpreted in light of the study period and its implications. First of all, our sample comprises people admitted to hospital in the first year of the pandemic, which suggests that the vast majority were infected by the Delta variant of SARS-CoV-2. This variant is associated with a higher incidence of long COVID than Omicron, which became the dominant variant later on[21,26]. Secondly, none of our patients had been vaccinated before hospital admission, and prior immunization has been shown to reduce the subsequent incidence of long COVID[27–29]. This consideration is relevant when comparing our results with those of other cohorts, since most studies include a high percentage of previously vaccinated patients. However, we consider that these points constitute a strength of the study, since our (unvaccinated) sample was infected with the SARS-CoV-2 variant that probably generates the most persistent long-term symptoms, making a study of the risk factors that influence long COVID in this population particularly interesting. Furthermore, unlike other studies, we not only analyzed the presence of symptoms by symptom groups but also looked at the potential relationship

Variables (sample size)	Symptom group																	
	Median (IQR)	Neurological		Respiratory		General		Psychiatric		Musculoskeletal		Dermatological		Digestive		Otorhinolaryngological	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Medical history																		
Age ≥ 71 years (n = 486)	61 (SD 14)	0.76 (0.51–1.15)	0.200	1.05 (0.70–1.58)	0.820	0.64 (0.41–0.98)	0.039	0.44 (0.27–0.70)	**< 0.001**	1.15 (0.74–1.77)	0.540	0.55 (0.28–1.06)	0.069	0.66 (0.30–1.46)	0.300	1.05 (0.27–4.02)	0.940
Age-adjusted Charlson comorbidity index ≥ 3 (n = 486)	2 (1–3)	0.89 (0.62–1.28)	0.530	1.01 (0.70–1.46)	0.970	0.76 (0.52–1.11)	0.150	0.66 (0.45–0.98)	0.037	1.32 (0.89–1.94)	0.170	0.58 (0.33-1.00)	0.049	1.21 (0.63–2.30)	0.570	1.27 (0.38–4.23)	0.690
Clinical outcomes																		
Hospital stay ≥ 15 days (n = 486)	10 (6–15)	1.36 (0.92–2.02)	0.130	1.30 (0.87–1.94)	0.190	0.99 (0.66–1.49)	0.980	0.86 (0.56–1.31)	0.480	1.90 (1.25–2.88)	0.002	1.14 (0.65–1.98)	0.650	1.06 (0.52–2.14)	0.870	0.95 (0.25–3.65)	0.950
ICU admission ≥ 10 days (n = 100)	6 (4–10)	0.45 (0.18–1.11)	0.079	0.66 (0.26–1.67)	0.380	0.48 (0.18–1.29)	0.140	0.65 (0.25–1.69)	0.380	0.92 (0.37–2.29)	0.850	0.94 (0.27–3.22)	0.920	0.45 (0.05–3.96)	0.464	6.08 (0.53–70.10)	0.100
PaO_2/FiO_2 at admission ≤ 300 (n = 385)	333 (300–373)	1.39 (0.89–2.18)	0.150	1.27 (0.81-2.00)	0.290	0.84 (0.53–1.33)	0.460	0.89 (0.56–1.43)	0.640	1.49 (0.93–2.38)	0.098	0.87 (0.45–1.71)	0.690	0.88 (0.38–2.03)	0.760	0.89 (0.18–4.46)	0.884
FiO_2 at admission ≥ 21% (n = 486)	21 (21–21)	1.40 (0.90–2.18)	0.130	1.21 (0.77–1.88)	0.410	1.00 (0.63–1.57)	0.990	1.34 (0.85–2.11)	0.200	1.29 (0.81–2.05)	0.290	1.09 (0.58–2.02)	0.800	1.91 (0.95–3.84)	0.065	1.46 (0.38–5.61)	0.580
Min PaO_2/FiO_2 ≤ 145 (n = 381)	300 (145–357)	1.33 (0.84–2.13)	0.220	0.90 (0.56–1.44)	0.650	0.83 (0.51–1.34)	0.440	0.89 (0.55–1.45)	0.640	1.25 (0.77–2.05)	0.360	1.35 (0.70–2.56)	0.370	0.83 (0.35–1.99)	0.670	0.37 (0.05-3.00)	0.330
Max FiO_2 ≥ 60% (n = 486)	32 (21–60)	1.45 (0.97–2.19)	0.073	1.03 (0.68–1.56)	0.880	1.04 (0.68–1.58)	0.860	1.06 (0.69–1.62)	0.800	1.56 (1.01–2.39)	0.043	0.86 (0.47–1.58)	0.630	0.94 (0.45–1.97)	0.830	0.64 (0.14–3.02)	0.570
Analytical parameters																		
Lymphopenia at admission ≤ 712 /μL (n = 484)	990 (712–1320)	1.13 (0.75–1.71)	0.560	0.79 (0.52–1.20)	0.260	0.90 (0.59–1.38)	0.630	0.70 (0.45–1.10)	0.120	0.94 (0.60–1.47)	0.780	0.73 (0.39–1.37)	0.330	0.49 (0.20–1.19)	0.110	1.13 (0.29–4.32)	0.860
CRP at admission ≥ 116 mg/L (n = 486)	64 (30–116)	0.87 (0.58–1.31)	0.500	0.76 (0.50–1.15)	0.200	0.65 (0.42–1.01)	0.052	0.72 (0.46–1.12)	0.140	0.82 (0.52–1.29)	0.390	1.22 (0.69–2.16)	0.480	0.38 (0.15–0.99)	0.040	0.64 (0.14–3.01)	0.570
Ferritin at admission ≥ 886 μg/L (n = 443)	482 (258–886)	0.82 (0.53–1.27)	0.370	0.59 (0.37–0.92)	0.020	0.61 (0.39–0.97)	0.038	0.68 (0.43–1.08)	0.100	0.93 (0.58–1.48)	0.740	0.84 (0.45–1.59)	0.600	0.53 (0.22–1.30)	0.160	0.36 (0.05–2.94)	0.320
IL-6 at admission ≥ 60 ng/L (n = 285)	34 (16–60)	0.99 (0.58–1.69)	0.960	0.90 (0.52–1.56)	0.700	0.65 (0.37–1.16)	0.150	0.71 (0.40–1.26)	0.240	1.14 (0.64–2.02)	0.670	0.94 (0.44–2.03)	0.880	1.04 (0.40–2.76)	0.930	1.99 (0.33–12.16)	0.450
D-dimer at admission ≥ 1080 ng/mL (n = 431)	610 (380–1080)	1.15 (0.75–1.79)	0.520	0.88 (0.56–1.37)	0.560	0.87 (0.56–1.37)	0.550	0.93 (0.59–1.47)	0.760	1.17 (0.73–1.86)	0.520	0.92 (0.47–1.78)	0.790	1.87 (0.91–3.86)	0.090	0.85 (0.17–4.16)	0.840
Min lymphocytes during admission ≤ 520/μL (n = 484)	720 (520–1097)	1.30 (0.87–1.97)	0.200	1.32 (0.87–1.99)	0.190	1.20 (0.79–1.82)	0.390	0.68 (0.44–1.07)	0.092	1.31 (0.85–2.02)	0.220	1.04 (0.58–1.86)	0.890	0.72 (0.32–1.60)	0.410	1.10 (0.29–4.23)	0.890
Max CRP during admission ≥ 136 mg/L (n = 485)	83 (40–136)	1.13 (0.75–1.71)	0.560	0.82 (0.54–1.26)	0.370	0.83 (0.54–1.27)	0.390	0.78 (0.50–1.21)	0.270	0.90 (0.57–1.41)	0.650	1.17 (0.66–2.07)	0.600	0.39 (0.15–1.02)	0.050	1.74 (0.50–6.05)	0.380
Max ferritin during admission ≥ 1189 mcg/L (n = 447)	655 (354–1189)	0.87 (0.57–1.32)	0.510	0.64 (0.42–0.99)	0.044	0.71 (0.45–1.10)	0.120	0.63 (0.398–0.996)	0.047	1.03 (0.66–1.61)	0.900	0.85 (0.46–1.57)	0.600	0.64 (0.27–1.48)	0.290	1.13 (0.30–4.34)	0.860
Max IL-6 during admission ≥ 67 ng/L (n = 357)	38 (16–67)	0.95 (0.59–1.53)	0.830	1.04 (0.64–1.69)	0.880	0.88 (0.54–1.46)	0.630	0.81 (0.49–1.35)	0.420	1.10 (0.65–1.85)	0.720	0.80 (0.39–1.64)	0.550	0.55 (0.21–1.49)	0.240	0.42 (0.05–3.49)	0.410

Continued

Variables (sample size)	Symptom group																	
	Median (IQR)	Neurological		Respiratory		General		Psychiatric		Musculoskeletal		Dermatological		Digestive		Otorhinolaryngological	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Max d-dimer during admission ≥ 2120 ng/mL ($n=480$)	940 (570–2120)	1.31 (0.87–1.98)	0.200	0.92 (0.60–1.40)	0.680	1.01 (0.66–1.54)	0.980	0.79 (0.50–1.22)	0.280	1.25 (0.81–1.94)	0.310	1.36 (0.78–2.38)	0.280	0.99 (0.47–2.09)	0.980	0.65 (0.14–3.07)	0.590
Total days of corticosteroid treatment ≥ 49 ($n=486$)	36 (19–49)	1.19 (0.79–1.80)	0.400	1.01 (0.66–1.52)	0.980	1.33 (0.87–2.01)	0.180	1.18 (0.77–1.81)	0.450	1.51 (0.98–2.30)	0.061	1.47 (0.84–2.55)	0.180	0.70 (0.31–1.55)	0.370	1.71 (0.49–5.94)	0.390

Table 3. Univariable analysis of associations between quantitative variables (dichotomized at the 75th percentile) and the presence of symptoms one year after admission for COVID-19 (grouped by organs or systems). *ICU* intensive care unit, *PaO2* partial pressure of oxygen, *FiO2* inspiratory fraction of oxygen, *CRP* C reactive protein, *IL-6* interleukin-6. Significant values are in bold.

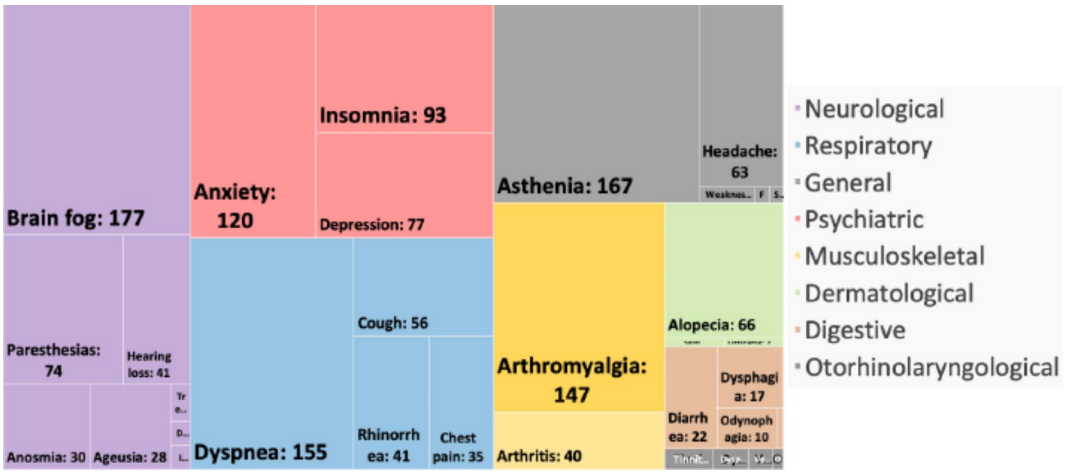

Fig. 2. Self-reported symptoms one year after hospital admission for SARS-CoV-2 infection, grouped by organs and systems.

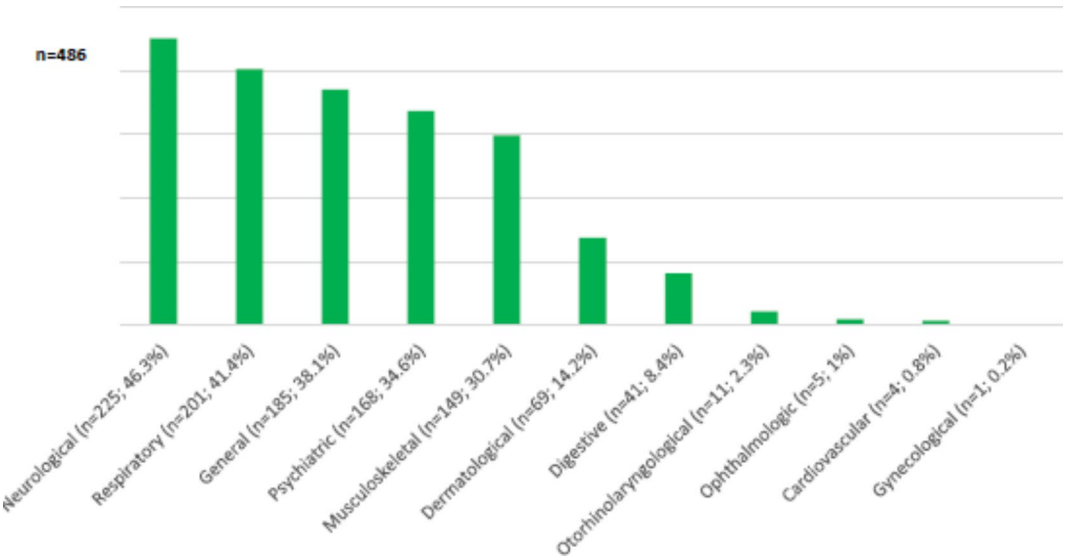

Fig. 3. Number of patients reporting at least one symptom of each of the following symptom types.

with poorly studied factors, such as analytical values during admission, the type of respiratory support used, and the medical treatment received.

That said, the study also has some limitations, beginning with its retrospective nature and the lack of a control group who did not require hospital admission or who were not infected with SARS-CoV-2. Another limitation, common to all the studies performed on this topic, is the lack of a baseline symptom survey prior to infection by SARS-CoV-2 with which to compare post-COVID symptoms, enabling a valid attribution of symptoms to long COVID. In addition, due to the considerable length of the questionnaire and the fact that all questions are answered with yes or no, some respondents may tend to answer yes or no to all questions [30]. Finally, as in most similar studies already published, the absence of a control group that has not been infected with SARS-CoV-2 is a notable limitation.

Conclusions

According to our results, patients admitted for SARS-CoV-2 infection during the first year of the pandemic reported **the presence of** symptoms related to the infection one year after hospitalization. Neurological and respiratory symptoms were the most frequent, with female sex, obesity, a history of anxiety and fibromyalgia/chronic fatigue standing out as independent risk factors. More studies are needed about the epidemiology, pathophysiology, and possible treatments for long COVID.

Variables	Neurological		Respiratory		General		Psychiatric		Musculoskeletal		Dermatological		Digestive		Otorhinolaryngological	
	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*p*	ORa (95% CI)	*P*
Male	0.64 (0.44–0.93)	**0.018**	0.45 (0.31–0.67)	**< 0.001**	0.43 (0.29–0.63)	**< 0.001**	0.34 (0.22–0.51)	**< 0.001**	0.47 (0.32–0.70)	**< 0.001**	0.24 (0.14–0.42)	**< 0.001**	0.38 (0.20–0.73)	**0.004**	1.81 (0.47–6.92)	0.390
Anxiety	–	–	–	–	–	–	2.04 (1.02–4.06)	**0.044**	–	–	–	–	–	–	–	–
Depression	–	–	–	–	–	–	1.77 (0.66–4.76)	0.256	–	–	–	–	–	–	–	–
Fibromyalgia/ chronic fatigue	–	–	4.34 (0.92–20.47)	0.064	11.59 (1.47–91.34)	**0.020**	4.26 (0.88–20.59)	0.072	–	–	–	–	–	–	–	–
Obesity (BMI > 30 kg/m^2)	–	–	1.90 (1.27–2.83)	**0.002**	–	–	–	–	1.96 (1.30–2.96)	**0.001**	–	–	–	–	–	–
Age ≥ 71 years	0.73 (0.49–1.11)	0.140	0.98 (0.64–1.50)	0.930	0.60 (0.39–0.95)	**0.027**	0.39 (0.23–0.64)	**< 0.001**	1.04 (0.67–1.63)	0.860	0.47 (0.24–0.92)	**0.028**	0.60 (0.27–1.35)	0.220	1.10 (0.29–4.23)	0.890

Table 4. Association between explanatory variables and the presence of symptoms one year after admission for COVID-19 (grouped by organs or systems). Multivariable analysis. *BMI* body mass index, *CI* confidence interval, *Ora* adjusted odds ratio. Significant values are in bold.

Data availability

Access to any other data is not facilitated since all relevant data is contained within the article.

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Author contributions

-IPC: conception and design of the study, writing of the manuscript, bibliographic search, data collection and analysis and interpretation of data.-CRM: conception and design of the study, writing of the manuscript, bibliographic search, data collection and analysis and interpretation of data.-SFE: data collection and bibliographic search.-ASF: data collection and bibliographic search.-MVV: data collection and bibliographic search.-SFJ: data collection and bibliographic search.-EDB: data collection and bibliographic search. -GHR: data collection and bibliographic search.-MJEG: data collection and bibliographic search.-DPS: data collection and bibliographic search.-ACA: data collection and bibliographic search.-MLMC: conception and design of the study, writing of the manuscript.-JUB: conception and design of the study, writing of the manuscript.-JMRR: conception and design of the study, writing of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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