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MAJOR ARTICLE

Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study

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Background. As the coronavirus pandemic spreads, more and more people are infected with severe acute respiratory syndrome coronavirus 2. The short- and medium-term effects of the infection have been described, but the description of the long-term sequelae is lacking in the literature.

Methods. Patients healed from coronavirus disease 2019 (COVID-19) from February 2020 to May 2020 were considered for inclusion in this study, regardless of the severity of the disease during the acute phase. Eligible patients were consecutively contacted and a semistructured interview was administered between February and March 2021 by trained medical staff.

Results. Three hundred three patients were eligible and accepted to participate in the study and were enrolled. Of those surveyed, most patients (81%) reported at least 1 symptom, and the most prevalent symptoms were fatigue (52%), pain (48%), and sleep disorders (47%). Sensory alterations were present in 28% of surveyed patients, but in most of these cases (74% of those affected by sensory alterations or 20% of the overall sample) symptoms reported were either anosmia or dysgeusia. Higher prevalence was generally observed with increasing age, although the most relevant differences were observed when comparing young versus middle-aged adults.

Conclusions. At 12 months after acute infection, COVID-19 survivors were still suffering from symptoms identified at shorter follow-up, and the most frequent symptoms included fatigue, pain, and sleep disorders. A more severe impairment in the acute phase did not seem to predict more severe complications.

Keywords. COVID pandemic; COVID sequelae; COVID-19; long COVID.

During the second year of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continued to spread and affect more people worldwide. Although the development and approval of the first COVID-19 vaccines may provide a way to end the pandemic, as of March 2021 more than 120 million people have been diagnosed and certainly more have been infected [1]. The first evidence of long-term COVID-19 complications have recently surfaced, and, in the future, it may represent one of the most significant global disease burdens.

Huang et al [2] described the consequences of COVID-19 6 months after symptoms onset in patients who have been hospitalized during the acute phase of the disease. They show that most patients (76%) are symptomatic to some degree, with the most frequently reported symptoms being fatigue and muscle weakness (63%), sleep difficulties (26%), and anxiety (23%) [2]. Logue et al [3] also highlighted SARS-CoV-2 effects with a median follow-up of 169 days. They reported fatigue (14%), loss of smell and taste (14%), and brain fog (2%), defined as being slightly less wakeful or aware than normal, as the most frequent symptoms. In a 5-month follow-up study, Graham et al [4] examined long-term, COVID-related neurological manifestations, which included brain fog (81%), headache (68%), numbness and/or tingling (60%), dysgeusia (59%), anosmia (55%), and myalgia (55%). In addition, 85% of patients in the study also experienced fatigue.

Although the initial evidence centered around patients who were discharged from hospital, many diagnosed patients were

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never admitted into hospitals. During the first phase of the pandemic in Italy between February and May 2020, the epidemic mostly affected the urban areas of the north of the country [5]. These areas were unprepared for outbreak management; many patients required hospitalization, and, in a short time, hospitals reached full capacity, leading to early discharge of apparently stable patients and home surveillance of those who could not be admitted. For this reason, the Operations Center for Discharged Patients (Centrale Operativa Dimessi, COD19) was created as an active home surveillance system [6].

With the emerging evidence of long-term sequelae of COVID-19, COD19 started a 1-year follow-up of patients originally monitored during the first Italian phase of the pandemic. The purpose of this study is to report the clinical consequences in the population affected by COVID-19, both inpatients and outpatients, 12 months after the recovery from the acute illness.

METHODS

Study Design and Patient's Selection

This study was part of a large cohort study of COVID-positive patients at the COD19 operations center. Patients monitored from February 2020 to May 2020 were considered for inclusion in this study, regardless of the severity of the disease during the acute phase. We included all patients with a confirmed diagnosis of COVID-19, which was performed by molecular swab and polymerase chain reaction positive for viral ribonucleic acid. All patients were discharged by the monitoring service after reaching clinical stability and after performing 2 negative SARS-CoV-2 swabs within 24 hours of each other.

The following categories of patients were excluded: patients who died during the follow-up or after discharge; patients hospitalized at follow-up; patients under the age of 18; patients with psychiatric disorders; patients who refused to participate in the study; and patients who could not be contacted.

Eligible patients were consecutively contacted, and, after expressing consent to participate in the study, a semistructured interview was administered by phone interview between February and March 2021 by trained medical staff from the COD19 operations center.

For some categories of symptoms, such as the occurrence of neurological and cognitive impairments, second- and third-level investigations, including neurological and neurocognitive examination and neurophysiological and neuroradiological tests, were planned.

This study was approved by the Ethics Commission of the University of Milan, (Ethics Commission number: 126/20). Written informed consent was obtained from all participants.

Semistructured Interview

The most frequent symptoms reported in the literature were sought. A total of 37 items were surveyed and grouped into the following categories: respiratory disorders, fatigue and weakness, muscle and joint pain, movement impairments, neurological and cognitive impairments, sensory alterations, sleep disorders, and gastrointestinal symptoms.

We also explored whether complained symptoms were present before acute SARS-CoV-2 infection, and we coded a symptom as present only if it was not reported before acute SARS-CoV-2 infection.

All data regarding the acute phase of the disease were collected during monitoring by the COD19 operation center and either retrieved from electronic clinical records or by directly interviewing the patient when information was unavailable. Data included date of birth, sex, body mass index (BMI), smoking habits, symptoms at onset, admission to the hospital, type of hospitalization (in ward or in intensive care unit [ICU]), medications taken during hospitalization and after hospital discharge (corticosteroids, antivirals, antibiotics, anticoagulants), and comorbidities (hypertension, diabetes, cardiovascular diseases, malignant tumors, chronic obstructive pulmonary disease, and chronic kidney disease).

Disease severity during the acute phase was graded in 7 levels according to Huang et al [2]: (1) discharged from the emergency room, asymptomatic or with mild symptoms; (2) discharged from the emergency room, with symptoms; (3) hospitalized, not requiring supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, requiring high-flow nasal cannula, noninvasive mechanical ventilation (NIV), or both; (6) admitted to hospital requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; (7) death. Categories of BMI were defined as follows: underweight, BMI < 18.5 kg/m^2; normal weight, BMI 18.5–24.9 kg/m^2; overweight, BMI 25.0–29.9 kg/m^2; obese, BMI ≥30 kg/m^2.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR) (25th, 75th percentile), whereas categorical variables are reported as count (fraction).

Participants were categorized into 2 groups according to the Huang et al [2] scale: 1–2 categories (not hospitalized with or without symptoms) and 3–6 categories (hospitalized, requiring or not oxygen or admitted to ICU). Statistical analyses were performed using the Wilcoxon rank-sum test with continuity correction for continuous variables and with the Pearson's χ^2 test and Fisher's exact test where appropriate for categorical variables.

Multivariable logistic regression models were used to describe the relationship between symptoms at follow-up (dichotomous, present/not present) and age (continuous), sex (dichotomous, female/male), and acute phase severity (dichotomous, scale 1–2/scale 3–6). Linearity between outcomes and age was not assumed by using restricted cubic spline, with quantile-define knots at 5th, 35th, 65th, and 95th percentile [7].

To present the results, prevalences were computed for the overall sample and stratified for each predictor, presented with the corresponding adjusted odds ratios and 95% confidence intervals. Age groups were defined using nonboundary knots of the age spline. Statistical analyses were performed in R 4.0.4 [8].

Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Seven hundred seventeen patients were monitored between February 2020 and May 2020, and the follow-up study was conducted between February and March 2021. Of those, 303 were eligible and accepted to participate in the study and were enrolled (Figure 1). Patients with nonconfirmed diagnosis comprised those who were monitored for symptoms compatible with COVID-19 but who were never confirmed by a positive molecular swab.

For the 303 patients included in the study, median follow-up time was 12.2 (IQR, 11.5–12.6) months. Patients' characteristics are summarized in Table 1. Sexes were almost equally distributed in the overall sample (54% females), but different sex distribution was found in non-hospitalized vs. hospitalized patients, with hospitalized patients showing a higher fraction of male patients (males in non-hospitalized patients 35% vs. males in hospitalized patients 52%, $P = .05$). Median age was 53 (IQR, 42–63) years, but hospitalized patients were significantly older (median age, 57 vs 45 years; $P < .001$). Most patients had a normal weight, with a median BMI of 24.9 (IQR, 22.9–28.0), and BMI categories were similarly distributed in hospitalized and not hospitalized patients. Although most patients never smoked (63%), hospitalized patients had a higher prevalence of ex-smokers (29% vs 13%).

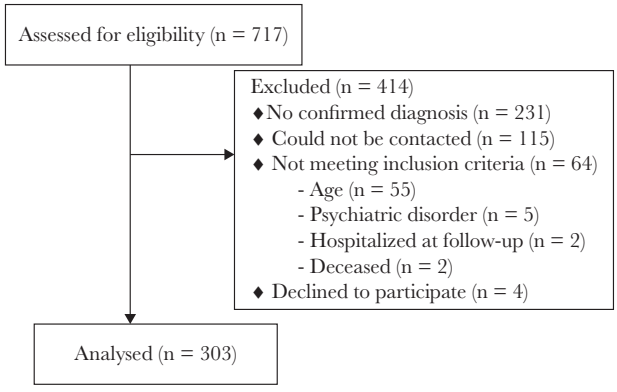

Figure 1. Flow chart of patients discharged from the COD19 service and participating in the study.

Table 1. Patient Characteristics During the Acute Phase

Characteristics	Overall, N = 303[a]	Acute Phase Severity: Scale 1–2: Not Hospitalized, N = 114[a]	Acute Phase Severity: Scale 3–6: Hospitalized, N = 189[a]	*P* Value[b]
Sex				**.005**
Female	165 (54%)	74 (65%)	91 (48%)	
Male	138 (46%)	40 (35%)	98 (52%)	
Age (years)	53 (42–63)	45 (38–54)	57 (47–68)	**<.001**
Body mass index (kg/m²)	24.9 (22.9–28.0)	24.5 (21.8–27.5)	25.2 (23.3–28.2)	**.033**
Body Mass Index Categories				.4
Underweight	9 (3.0%)	4 (3.5%)	5 (2.6%)	
Normal weight	154 (51%)	64 (56%)	90 (48%)	
Overweight	91 (30%)	31 (27%)	60 (32%)	
Obese	49 (16%)	15 (13%)	34 (18%)	
Smoking habits				**<.001**
Never smoked	192 (63%)	75 (66%)	117 (62%)	
Ex-smoker	70 (23%)	15 (13%)	55 (29%)	
Smoker	41 (14%)	24 (21%)	17 (9.0%)	
Comorbidities				
Hypertension	89 (29%)	15 (13%)	74 (39%)	**<.001**
Cardiovascular disease	32 (11%)	5 (4.4%)	27 (14%)	**.007**
Diabetes	28 (9.2%)	4 (3.5%)	24 (13%)	**.007**
Malignant tumors	18 (5.9%)	6 (5.3%)	12 (6.3%)	.7
Chronic obstructive pulmonary disease	17 (5.6%)	6 (5.3%)	11 (5.8%)	.8
Cerebrovascular disease	11 (3.6%)	0 (0%)	11 (5.8%)	**.008**
Chronic kidney disease	4 (1.3%)	0 (0%)	4 (2.1%)	.3
Acute Phase Severity				
Scale 1: Not hospitalized, asymptomatic	11 (3.6%)	11 (9.6%)	0 (0%)	**<.001**
Scale 2: Not hospitalized, symptomatic	103 (34%)	103 (90%)	0 (0%)	**<.001**
Scale 3: Hospitalized, not requiring oxygen	43 (14%)	0 (0%)	43 (23%)	**<.001**
Scale 4: Hospitalized, requiring oxygen (nasal cannula)	67 (22%)	0 (0%)	67 (35%)	**<.001**
Scale 5: Hospitalized, requiring oxygen (NIV)	71 (23%)	0 (0%)	71 (38%)	**<.001**
Scale 6: Hospitalized, ICU	8 (2.6%)	0 (0%)	8 (4.2%)	**.027**
Treatment During the Acute Phase				
Antivirals	187 (62%)	31 (27%)	156 (83%)	**<.001**
Antibiotics	134 (44%)	29 (25%)	105 (56%)	**<.001**
LMWH	94 (31%)	17 (15%)	77 (41%)	**<.001**
Steroids	14 (4.6%)	5 (4.4%)	9 (4.8%)	.9

Bold text indicates significant *P* value ($P < .05$).

Abbreviations: ICU, intensive care unit; LMWH, low molecular weight heparin; NIV, noninvasive mechanical ventilation.

[a]n (%); median (interquartile range).

[b]Pearson's χ^2 test; Wilcoxon rank-sum test; Fisher's exact test.

The most prevalent comorbidities were hypertension (29%), cardiovascular diseases (11%), and diabetes (9.2%), and their prevalence were significantly higher in hospitalized patients. In addition, cerebrovascular disease was present only in hospitalized patients (5.8% vs 0%; $P = .008$). Most of the nonhospitalized patients were still symptomatic, and most

hospitalized patients required oxygen, either through nasal cannula or NIV. Hospitalized patients received more frequent treatments, including antibiotics, antivirals, corticosteroids, and low molecular weight heparin, than nonhospitalized patients during the acute phase of the disease.

Figure 2 shows nonparametric regression (locally estimated scatterplot smoothing [LOESS]) estimates of the relationship between age at COVID-19 infection and the probability of presenting any symptoms at follow-up (Figure 2A), stratified by sex (Figure 2B), severity of the acute phase (Figure 2C), or both (Figure 2D). The probability increases with age, although females between 40 and 75 years of age seem to be at higher risk. Moreover, nonhospitalized patients seem to have a lower risk than hospitalized patients; however, in the combined groups (Figure 2D), this difference is mainly attributed to the male nonhospitalized patients.

Tables 2, 3 and 4 show the prevalence of symptoms at follow-up in the overall sample and stratified by age groups, sex, or acute phase severity, respectively. Of those surveyed, most patients (81%) reported at least 1 symptom, and the most prevalent symptoms were fatigue (52%), pain (48%), and sleep disorders (47%). Sensory alterations were present in 28% of surveyed patients; however, in most of these cases (74% of those affected by sensory alterations or 20% of the overall sample), patients reported symptoms of either anosmia or dysgeusia. Higher prevalence was generally observed with increasing age, although the most relevant differences were observed when comparing young versus middle-aged adults. For example, when comparing patients in the young age group (15–47 years) with the middle-aged group (47–58 years), significant differences included the proportion of patients who complained of the following: at least 1 symptom (92% vs 69%; $P < .001$); fatigue and weakness

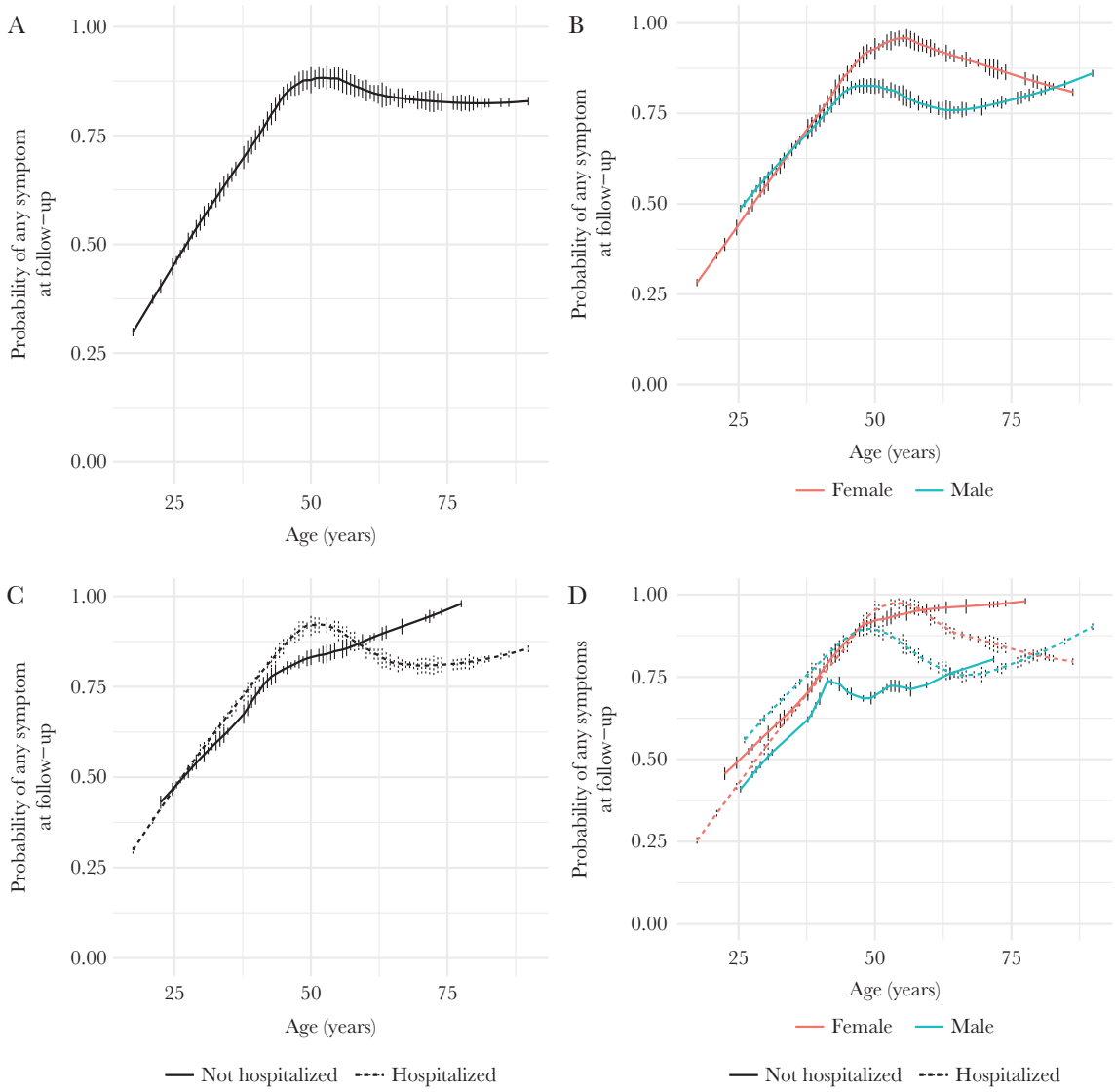

Figure 2. Relationship between age and probability of presenting any symptoms at follow-up (locally estimated scatterplot smoothing [LOESS]), with tick marks representing age distribution. (A) No strata. (B) Stratified by sex. (C) Stratified by severity of the acute phase. (D) Stratified by sex and severity of the acute phase.

Table 2. Symptoms at Follow-up Stratified by Age Groups

Outcome	Overall, N = 303	Age Group (Range in Years) 18–47, N = 106	47–58, N = 91	58–90, N = 106	Adjusted Log (Odds Ratio) (95% Confidence Interval) *P* Value 18–47 Years	47–58 Years	58–90 Years
Any one of the following symptoms	244 (81%)	73 (69%)	84 (92%)	87 (82%)	0.63 (−0.57 to 1.85) .302	3.85 (2.32–5.49) < **.001**	0.17 (−0.80 to 1.22) .737
Fatigue and weakness	158 (52%)	38 (36%)	56 (62%)	64 (60%)	1.52 (0.59–2.47) **.001**	3.30 (1.72–5.12) < **.001**	0.78 (0.02–1.55) **.044**
Muscle and joint pain	144 (48%)	35 (33%)	51 (56%)	58 (55%)	1.01 (0.08–1.95) **.033**	4.12 (2.31–6.28) < **.001**	0.74 (−0.02 to 1.52) .057
Sleep disorders	141 (47%)	35 (33%)	55 (60%)	51 (48%)	1.21 (0.28–2.15) **.011**	3.28 (1.60–5.23) < **.001**	0.19 (−0.58 to 0.96) .626
Respiratory disorders	110 (36%)	29 (27%)	41 (45%)	40 (38%)	0.39 (−0.56 to 1.34) .426	3.34 (1.50–5.53) **.001**	0.38 (−0.40 to 1.16) .341
Neurological and cognitive impairments	110 (36%)	31 (29%)	41 (45%)	38 (36%)	0.65 (−0.29 to 1.60) .179	2.41 (0.74–4.36) **.008**	0.15 (−0.64 to 0.93) .704
Sensory alterations	84 (28%)	31 (29%)	30 (33%)	23 (22%)	0.69 (−0.37 to 1.76) .205	0.04 (−1.55 to 1.76) .962	−1.35 (−2.56 to 0.33) **.016**
Movement impairments	54 (18%)	16 (15%)	18 (20%)	20 (19%)	0.46 (−0.73 to 1.66) .454	2.08 (−0.06 to 4.80) .087	−0.06 (−1.14 to 0.93) .907
Gastrointestinal symptoms	35 (12%)	10 (9.4%)	14 (15%)	11 (10%)	0.58 (−0.97 to 2.28) .477	5.11 (1.30–10.71) **.030**	0.10 (−1.32 to 1.49) .882

Bold text indicates significant *P* value (*P* < .05).

(62% vs 36%; *P* < .001); muscular and joint pain (56% vs 33%; *P* < .001); sleep disorders (60% vs 33%; *P* < .001); respiratory disorders (45% vs 27%; *P* = .001); neurological and cognitive impairments (45% vs 36%; *P* = .008); and gastrointestinal symptoms (15% vs 9.4%; *P* = .03). Sensory alterations were the only symptoms with a significantly lower frequency in older adults (aged between 58 and 90 years) compared with younger adults (22% vs 29%; *P* = .01). Significant differences between males and females included a higher prevalence of the following: at least 1 symptom (84% vs 77%; *P* = .02); fatigue and weakness (57% vs 46%; *P* = .02); sleep disorders (51% vs 41%; *P* = .03); and sensory alterations (32% vs 22%; *P* = .04). Regarding the acute phase severity, all prevalences were higher in the more severe group, except for the sensory alterations, but not with a significant difference. Even adjustment for age and gender did not reveal any impact from disease severity on risk of symptoms.

DISCUSSION

To our knowledge, this is the first cohort study that assesses the health consequences of COVID-19 patients at 1-year follow-up in either hospitalized and nonhospitalized patients. Regardless of the severity of the acute phase, most patients (81%) presented at least 1 symptom with the most prevalent being fatigue and weakness (52%), muscle and joint pain (48%), sleep disorders (47%), neurological and cognitive impairment (36%), and respiratory disorders (36%).

We show that the likelihood of presenting symptoms generally increases with age, as reported by Huang et al [2]. It is interesting to note that males showed lower prevalence for some symptoms. These findings are not limited to COVID-19, because similar data have been reported for the 2002–2004 severe acute respiratory syndrome (SARS) outbreak virus. Even in the case of SARS, 1 year after the disease, there was an impairment of the general health status [9]. According to Lam et al [10], more than 40% of patients affected by SARS presented psychiatric illness and 40.3% reported chronic fatigue.

In our sample, we found that 52% of patients complain of fatigue 1 year after the disease. Male sex seemingly represents a protective factor against this symptom. Huang et al [2] report a prevalence of fatigue of 63% 6 months after acute illness.

Table 3. Symptoms at Follow-up Stratified by Sex

Outcome	Overall	Sex Female (Reference)	Male	Adjusted Log (Odds Ratio)	95% Confidence Interval	*P* Value
Any one of the following symptoms	244 (81%)	138 (84%)	106 (77%)	−0.76	−1.41 to −0.13	**.020**
Fatigue and weakness	158 (52%)	94 (57%)	64 (46%)	−0.57	−1.06 to −0.09	**.022**
Muscle and joint pain	144 (48%)	83 (50%)	61 (44%)	−0.40	−0.89 to 0.08	.101
Sleep disorders	141 (47%)	84 (51%)	57 (41%)	−0.52	−1.01 to −0.04	**.034**
Respiratory disorders	110 (36%)	63 (38%)	47 (34%)	−0.26	−0.75 to 0.23	.295
Neurological and cognitive impairments	110 (36%)	66 (40%)	44 (32%)	−0.46	−0.95 to 0.03	.069
Sensory alterations	84 (28%)	53 (32%)	31 (22%)	−0.55	−1.09 to −0.02	**.044**
Movement impairments	54 (18%)	33 (20%)	21 (15%)	−0.39	−1.01 to 0.22	.218
Gastrointestinal symptoms	35 (12%)	21 (13%)	14 (10%)	−0.34	−1.09 to 0.39	.363

Bold text indicates significant *P* value (*P* < .05).

Table 4. Symptoms at Follow-up Stratified by Acute Phase Severity

Outcome	Overall	Acute Phase Severity		Adjusted 95%		*P* Value
		Scale 1–2: Not Hospitalized (Reference)	Scale 3–6: Hospitalized	Log (Odds Ratio)	Confidence Interval	
Any one of the following symptoms	244 (81%)	87 (76%)	157 (83%)	0.379	−0.30 to 1.06	.272
Fatigue and weakness	158 (52%)	57 (50%)	101 (53%)	−0.069	−0.61 to 0.46	.801
Muscle and joint pain	144 (48%)	48 (42%)	96 (51%)	0.178	−0.35 to 0.71	.510
Sleep disorders	141 (47%)	52 (46%)	89 (47%)	−0.016	−0.55 to 0.51	.953
Respiratory disorders	110 (36%)	40 (35%)	70 (37%)	−0.009	−0.55 to 0.53	.975
Neurological and cognitive impairments	110 (36%)	39 (34%)	71 (38%)	0.121	−0.41 to 0.66	.657
Sensory alterations	84 (28%)	35 (31%)	49 (26%)	−0.015	−0.57 to 0.55	.959
Movement impairments	54 (18%)	21 (18%)	33 (17%)	−0.047	−0.70 to 0.62	.887
Gastrointestinal symptoms	35 (12%)	13 (11%)	22 (12%)	0.034	−0.74 to 0.84	.932

Following the same time interval, Logue et al [3] report a prevalence of this symptom of 13.6%. To date, there is no pathophysiological explanation of the problem in literature, but some authors hypothesize that the causes are multifactorial [11]. One of the possible causes could be to the prolonged bed stay of patients, with consequent loss of muscle trophism and tone mostly followed by an incomplete recovery. However, our sample included inpatients and outpatients who are unlikely to have been bedridden for long periods of time, and who still reported a high prevalence of fatigue (50%).

Approximately half of the patients complained of arthromyalgia. Although Huang et al [2] reported a joint pain rate of 9% and myalgia of 2% 6 months after the acute phase of the disease. This complaint is not limited to COVID-19, because SARS-CoV-1 osteomuscular apparatus involvement has also been described [12]. A possible explanation lies in the presence of particular receptors on the muscular tissue that are used by the SARS-CoV-2 to enter into the cell, which include the angiotensin-converting enzyme 2 (ACE2) and the serine protease TMPRSS2 [13]. Quarantine, social distancing, and isolation can also partially explain the prevalence of arthromyalgia, because such measures inevitably led to reduction of physical activity with deconditioning possibly resulting in arthromyalgia. Severe acute respiratory syndrome coronavirus 2-induced polyneuropathy may also partially explain the phenomenon.

Several patients (47%) also complained of sleep disorders, and the prevalence was lower among males. Tansey et al [14] report a similar prevalence (44%) in survivors of SARS-CoV-1 infection 1 year after the acute event. This fraction is higher than the one detected in the general population; for example, Chen et al [15] report a prevalence of sleep disorders in the general population of 4.7%. A multifactorial origin for sleep disorders is plausible, and social isolation and decreased physical activity (in addition to the viral infection) are just some of the parameters that can be taken into consideration for the explanation of the phenomenon.

Another symptom reported by patients is neurocognitive impairment, which was reported by 36% of our patients. Mazza et al [16] hypothesize that it can be secondary to a cytokine storm, since a prolonged exposure to systemic inflammation can predispose patients to persistent neurocognitive dysfunction.

In our sample, 36% of patients complained of symptoms affecting the respiratory system. Dyspnea and increased respiratory rate are reported following light and moderate activity. Huang et al [2] reported that by increasing the critical level of the acute phase of the disease, the proportion of patients with lung diffusion impairment increased. This virus can damage the lungs in essentially 3 ways: acute respiratory distress syndrome with diffuse alveolar damage, diffuse thrombotic alveolar microvascular occlusion, and inflammatory mediator-associated airway inflammation [17]. Ngai et al [18] showed the pulmonary effects of SARS-CoV-1 with a 2-year follow-up, highlighting a marked worsening in DLCO, exercise capacity, resistance to exertion, and health status.

Approximately one third of patients reported sensory alterations. The most common symptoms were loss or alteration of taste and smell, reported by 20% of the sample. Male sex, from our sample, seems to be a protective factor. These symptoms are very characteristic of SARS-CoV-2 infection, and since the first phase of the pandemic they have been considered as symptoms highly associated with the disease. Some studies report a prevalence rate of olfactory and gustatory alterations during the acute phase of 85.6% and 88.0%, respectively [19]. Causes are still unknown and only partially explained. In 2006, Hwang [20] described a case of anosmia that persisted for 2 years after SARS-CoV-1 infection. Huang et al [2] report the prevalence of changes in smell of 11% and of taste changes of 7% at a follow-up of 6 months.

Eighteen percent of the patients analyzed complained of an impairment in movement, which was not influenced by disease severity and gender. This fraction was higher than the one reported by Huang et al [2], which was 7%. This symptom can have different causes, including an impairment of peripheral nervous system, which can result in uncoordinated walking or can be due to fatigue and a lower respiratory threshold.

Fotuhi et al [21] described the neurobiology of SARS-CoV-2, hypothesizing that the damage to the peripheral nervous system has a multifactorial cause deriving from both a virus-specific neurotropism and a cytokine storm after the binding of SARS-CoV-2 to the receptor ACE2. Cases of Guillan-Barrè associated with COVID-19 are also reported in the literature. A review by

Trujillo Gittermann et al [22] shows a strong association between these 2 pathologies, without however confirming a cause-effect relationship.

Patients in our sample complained of gastrointestinal disorders in 12% of cases, including anorexia or diarrhea. Degeneration, necrosis, shedding of the gastrointestinal mucosa of varying degrees, and ACE2 were found histologically in one patient who died of severe COVID-19, suggesting that the damage to the intestinal mucosa results from the direct action of the virus [23]. Huang et al [2] showed a prevalence of anorexia, diarrhea, and vomiting in 13% of cases, which is very close to our results.

There are other, less frequent symptoms reported by patients that are more difficult to explain. A total of 5.6% of patients reported episodes of alopecia, which often regresses spontaneously but sometimes requires topical or systemic steroid therapy. Huang et al [2] reported a hair loss rate of 22% 6 months after the acute phase of the disease, whereas 67% of patients evaluated by Tansey et al [14] reported self-resolving alopecia, usually within 3 months from SARS-CoV-1 infection. Based on the recent literature, alopecia may be caused by either a greater androgenetic sensitivity or telogen effluvium [24, 25]. Visual impairment, which was present in 3.9% of patients, is difficult to explain from a pathophysiological point of view.

The variety of symptoms that involve different organs, the complexity of the presentation and the clinical course, and the unpredictability of the evolution lead to the definition of the long COVID syndrome. It is important to report that we did not find any association between the course of the disease in the acute phase and the symptom occurrence at 1-year follow-up; for this reason, close attention must be paid to the population affected by COVID-19, regardless of whether they have or have not been hospitalized. Particular care should be given to individuals who had COVID-19 infection in the ages ranging 47–58 years, and to women more than men, because they reported a higher prevalence of symptoms. The follow-up of COVID-19 patients needs to be managed using a multidisciplinary approach involving different specialties, because most patients seem to be affected by at least 1 symptom, which ranges from respiratory involvement to neurological complications.

There are several limitations of this study. The main limitation is the lack of a control group, which prevents a causal association between COVID-19 infection and symptoms at follow-up. Only 42.3% of patients originally monitored were included in this follow-up study. The main reasons for exclusion were an unclear diagnosis (32.2%) and the inability to reach these patients by phone (16%); however, very few patients refused to participate (0.6%), and reported deaths were low (0.3%). The study relied on a semistructured phone-interview that was administered by trained staff personnel 1 year after acute disease, which can cause recall bias. Second- and third-level investigations are ongoing, but we cannot exclude that some symptoms reported by patients have subjective rather than objective origin. We did not record whether a symptom that was present before the acute phase worsened after the infection, and, as such, our results may have underestimated COVID-19 health consequences. Moreover, variants of the virus have not been systematically assessed, and it is possible that the different variants may have been associated with a different set of long-term symptoms.

CONCLUSIONS

In conclusion, in a sample of confirmed COVID-19 diagnosis that included patients with a less severe acute phase, we highlight that clinical complications are still present at 1-year follow-up. Our main findings are that symptoms are still present at 12-month follow-up with a prevalence similar to shorter follow-up, and that they are present irrespective of COVID-19 severity. These data will be useful to promote health policy measures such as long-term surveillance programs and facilities dedicated to the management of patients affected by long COVID syndrome.

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