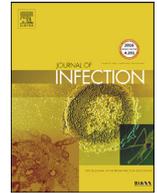




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Determinants of persistence of symptoms and impact on physical and mental wellbeing in Long COVID: A prospective cohort study

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SUMMARY

Background: Residual symptoms can be detected for several months after COVID-19. To better understand the predictors and impact of symptom persistence we analyzed a prospective cohort of COVID-19 patients.

Methods: Patients were followed for 9 months after COVID-19 onset. Duration and predictors of persistence of symptoms, physical health and psychological distress were assessed.

Results: 465 patients (54% males, 51% hospitalized) were included; 37% presented with at least 4 symptoms and 42% complained of symptom lasting more than 28 days. At month 9, 20% of patients were still symptomatic, showing mainly fatigue (11%) and breathlessness (8%). Hospitalization and ICU stay vs. non-hospitalized status increased the median duration of fatigue of 8 weeks. Age > 50 years (OR 2.50), ICU stay (OR 2.35), and presentation with 4 or more symptoms (OR 2.04) were independent predictors of persistence of symptoms at month 9. A total of 18% of patients did not return to optimal pre-COVID physical health, while 19% showed psychological distress at month 9. Hospital admission (OR 2.28) and persistence of symptoms at day 28 (OR 2.21) and month 9 (OR 5.16) were independent predictors of sub-optimal physical health, while female gender (OR 5.27) and persistence of symptoms at day 28 (OR 2.42) and month 9 (OR 2.48) were risk factors for psychological distress.

Conclusions: Patients with advanced age, ICU stay and multiple symptoms at onset were more likely to suffer from long-term symptoms, which had a negative impact on both physical and mental wellbeing. This study contributes to identify the target populations and Long COVID consequences for planning long-term recovery interventions.

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Introduction

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led to the collection of an impressive amount of clinical data focusing on the management of severe disease in acute care settings and substantial evidence on short-term outcomes of coronavirus disease 2019 (COVID-19) inpatients. The amount of follow-up data on the clinical course of patients who recovered from the acute phase of COVID-19 is rapidly

increasing, as the evidence from previous coronavirus outbreaks suggests that some degree of lung damage could persist for years.¹ However, the representativeness and the validity of the available evidence are still insufficient, due to the short duration of follow-up, mostly performed up to 3 months after discharge, or due to small sample sizes for longer term studies.^{2–9} Recently, the results of a follow-up study in Wuhan have shown that 76% of the 1733 participants still suffered at least one symptom 6 months after the onset of COVID-19.¹⁰ Fatigue or muscle weakness and sleep difficulties were the most common ones, occurring in 63% and 26% of the patients, respectively.¹⁰ Lingering anxiety or depression, radiological abnormalities and impaired pulmonary diffusion capacities were reported in a sizeable proportion of patients,¹⁰ supporting the need of longer follow-up studies on persistent symptoms.

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To better define easy-to-measure predictors and impact of symptom persistence among COVID-19 survivors and to identify specific clinical needs after the recovery from active SARS-CoV-2 infection, we prospectively collected data from a longitudinal cohort of 465 COVID-19 patients, including those managed as inpatients (hospitalized) and outpatients (non-hospitalized).

Methods

Study population

A registry of COVID-19 patients diagnosed at Verona University Hospital was generated in March 2020 (ClinicalTrials.gov NCT04497194). We consecutively screened for inclusion in the study all patients older than 18 years diagnosed with symptomatic and laboratory-confirmed SARS-CoV-2 infection at Verona University Hospital during the period February 29–May 2, 2020, as detailed in the Supplementary Methods. Persistence of symptoms reported at admission was investigated using structured phone interviews at 6 ± 2 weeks, 12 ± 4 weeks, and 9 ± 2 months after symptom onset. A total of 48 (10%) patients were lost during follow-up. Data from 6-week to 12-week follow-up including part of this cohort have been previously published.¹¹

Clinical management

Criteria for hospitalization included hypoxia and need for oxygen support with potential for clinical deterioration.^{4,5,11} Inpatient discharge was based on improvement of respiratory symptoms, irrespective of positivity of nasal swab. During the initial phases of the pandemic, the national standard of care for COVID-19 treatment consisted of hydroxychloroquine (HCQ) and/or lopinavir/ritonavir (LPV/r). Steroids were not routinely administered. Outpatients did not receive specific treatment. Since most inpatients received treatments that are no longer recommended and steroid administration was not consistent, treatment data were not included in the analyses.

Data collection and measurements

As previously described,^{10–12} disease severity was measured according to the following levels: 1, not admitted to hospital with resumption of normal activities; 2, not admitted to hospital, but unable to resume normal activities; 3, admitted to hospital but not requiring supplemental oxygen; 4, admitted to hospital but requiring supplemental oxygen; 5, admitted to hospital requiring high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV), or both; 6, admitted to hospital requiring extracorporeal membrane oxygenation, invasive mechanical ventilation (IMV), or both.

For the symptom questionnaire, participants were asked to report persistent symptoms or any symptoms that became worse than before COVID-19 development. The onset of disease was defined as the first day of reporting at least one symptom for more than one day.

Symptoms included in the analysis were reported by at least 5% of patients at admission and included cough, diarrhoea, fatigue, breathlessness, myalgia, anosmia, and dysgeusia. Breathlessness was defined according to the modified British Medical Research Council (mMRC) dyspnoea scale, and presence of breathlessness was considered for mMRC scores ≥ 1 .¹³ Other symptoms reported by less than 5% of patients, such as headache, tachycardia, and insomnia were excluded from the analysis.

Physical health was measured through the self-rated health single-item questionnaire that uses a 5-point scale (1 = excellent; 5 = poor) to rate patients' global health. Patients were asked to

rate their physical health also before COVID-19 onset based on their own recollection.^{14–16}

Psychological distress was measured using the Kessler Psychological Distress Scale (K10), a 10-item questionnaire including questions about anxiety and depressive symptoms aiming to obtain a global measure of distress. Scores can range from 10 to 50 and may indicate no distress (10–19), mild mental disorder (20–24), moderate mental disorder (25–29), and severe mental disorder (30–50).¹⁷

Baseline data included age, gender, ethnicity, presence of absence of comorbidities (e.g., hypertension, cardiovascular disease, respiratory disease, diabetes, concomitant malignancy, and renal impairment), hospital admission at diagnosis, and need for ICU admission. Length of stay was recorded but not included in the analyses as the duration of hospitalization may not correctly reflect severity and could be affected by hospital policies, phase of the pandemic, or delays in discharge (e.g., for patients who cannot self-isolate or receive appropriate care). Similarly, ICU admission was used rather than ICU stay as the length of hospitalization in ICU may be associated with complications not directly related with COVID-19. Occurrence of new admissions to hospital (for outpatients) or readmission (for hospitalized patients) was also recorded during follow-up.

Statistical analysis

Descriptive statistics was used according to the measurement level: mean and standard deviation or median and IQR for continuous variables, count and percentages for nominal variables. All outcome variables estimates were reported with 95% Confidence Interval (95% CI). Wilcoxon–Mann–Whitney test was used for comparing independent groups. The association between categorical variables was assessed using Fisher's test. Patients were classified as non-hospitalized (severity scale level 1,2) and hospitalized (level 2–6, that also included the ICU group - level 5 and 6 - due to the limited number of severely ill patients). Logistic regression and ordered logistic regression were used to analyse dichotomous dependent variables for physical health (excellent vs. non excellent status) and psychological distress (no psychological distress vs. any level of psychological distress) and ordinal dependent variables, respectively.

For the longitudinal analysis, the product-limit method (Kaplan and Meier) with 95% CI was used to describe COVID-19-associated symptom duration. Baseline for survival analysis was considered as days from symptom onset, as reported at admission. Follow-up data were censored at 9 ± 2 months after enrolment, or at last determination for those lost at follow-up, or at death. Kaplan-Meier estimator and Cox proportional hazard model were used for the analysis and model building. Kaplan-Meier curves were plotted to illustrate the association between each binary predictor and symptom persistence, while for comparing survival functions the log rank test was used. We used a multivariable Cox proportional hazards model to estimate the independent effect of potential predictors for the persistence of each symptom at 9-month follow-up. For the multivariable model, we used numerical variables in their original scale. Factors that were significantly associated with presence of long-term symptoms at 9-month follow-up at bivariable Cox proportional hazards regression analysis were included in the multivariable Cox regression. Predictors of symptom duration that were significantly associated with time in multivariable Cox proportional hazards regression analysis (e.g., fatigue) were displayed separately. Age was included in the model as continuous predictor and the survival function was plotted setting age at the value of 50. The choice of the age cut-off of 50 years was based on the increased risk for severe COVID-19 reported in older adults.¹⁸

Table 1Baseline characteristics of included patients ($n = 465$).

Characteristic	Overall ($n = 465$)
Age, years (Q1; Q3)	56 (45; 66)
Male gender (%)	253 (54.41)
Caucasian ethnicity (%)	450 (96.78)
No reported comorbidities (%)	260 (55.91)
Comorbidities (%)	205 (44.09)
Hypertension	123 (26.45)
Cardiovascular disease	56 (12.04)
Diabetes	30 (6.45)
Respiratory disease	33 (7.10)
Concomitant malignancy	19 (4.09)
Renal impairment	11 (2.37)
Other	51 (10.97)
Hospital admission (%)	235 (50.54)
Duration of hospitalization, days (Q1; Q3)	10 (6; 17)
ICU admission (%)	47 (10.11)
ICU length of stay, days (Q1; Q3)	12 (6;13)

Data are n (%) or median (Q1; Q3); ICU = intensive care unit.

Stata® Version 16.1 (College Station, TX: StataCorp LP) with a two-tailed α error of 0.05 was used in all analyses.

Results

A total of 465 patients were included in the study between February 29 and May 2, 2020. Baseline characteristics of enrolled participants are shown in Table 1. Mean age was 56 years (IQR, 45 - 66). A total of 230 (49%) were managed as outpatients, while 235 (51%) patients required hospitalization. According to disease severity, 37% of the outpatients were at severity scale level 1 and 12% at level 2; among those hospitalized, 9% were at level 3 and 32% at level 4, while 10% required ICU admission (level 5,6). Inpatients were more likely to be older ($p < 0.001$), of male gender ($p < 0.001$) and have comorbidities ($p < 0.001$) compared to outpatients (Appendix Table 1).

During the follow-up there were 36 cases of new hospital admissions or readmissions that were mainly due to post-COVID rehabilitation or complications of pre-existing diseases (Appendix Table 2). Three hospitalized patients aged 85, 87, and 89 years died at month 3, 4, and 7 after COVID-19 symptom onset due to concomitant diseases (leukaemia, colon cancer, and end-stage heart failure, respectively). A total of 48 (10%) patients could not be reached over the phone to perform interviews and were lost at 9-month follow-up.

At presentation, 37% of patients reported 4 or more symptoms. Persistence of at least one symptom was reported at day 28 by 42% of patients, at week 12 by 31%, and at month 9 by 20% (Table 2). Independent risk factors for the persistence of one or more symptoms at 9-month follow-up were age > 50 years, ICU stay, and presentation with more than 4 symptoms (Table 3). At 9-month follow-up, inpatients were more likely to complain

of fatigue ($p < 0.001$), breathlessness ($p = 0.014$), and myalgia ($p = 0.021$) compared to outpatients (Appendix Table 3). Fig. 1 summarizes the frequency of the most common symptoms associated with COVID-19 at clinical presentation and at follow-up. At month 9, anosmia and diarrhoea resolved and only 1% of patients complained of cough and 4% of dysgeusia. Conversely, long-term symptoms included myalgia, breathlessness, and fatigue that were still present in 7%, 8%, and 11% of patients, respectively.

Median duration of symptoms ranged from 7 days for diarrhoea (IQR, 5 - 8) to 21 days for fatigue (IQR, 7 - 87). As shown in Fig. 2, 75% of patients reported resolution of symptoms such as diarrhoea, myalgia and anosmia around 3 to 4 weeks after symptom onset, while dysgeusia, breathlessness, and fatigue persisted up to 6, 8, and 10 weeks, respectively. While no risk factors were significantly associated to the persistence of diarrhoea, cough, dysgeusia, anosmia, myalgia, or breathlessness (Supplementary Fig. 4), fatigue persistence was predicted at multivariable analysis by age, hospital admission, and ICU stay (Table 4). Specifically, patients who were hospitalized and those who required ICU admission complained more frequently of fatigue at 9-month follow-up compared to those who were not hospitalized or admitted to the ICU (log rank test, $p = 0.0001$ and $p = 0.0005$, respectively) (Fig. 3). Overall, we documented a slower resolution of fatigue among inpatients. At month 2 after symptom onset only 26% (95% CI 21 - 31%) of outpatients still complained of fatigue compared with 42% (95% CI 35 - 49%) of inpatients and 63% (95% CI 47 - 76%) of ICU patients. When modelled for patients aged 50 years, the estimated duration of fatigue was 9 months in approximately 20% of patients admitted to the ICU, while it decreased to 5-10% among those who were not hospitalized or did not require ICU admission (Appendix Fig.1).

The impact of baseline factors and persistence of COVID-19 symptoms on physical health was also investigated. A status of excellent physical health, reported by 90% of patients prior to COVID-19, declined to 24% at onset of disease and subsequently increased to 82% at 9-month follow-up (Appendix Table 5). Although a remarkable improvement was shown by patients over time, they did not achieve the optimal physical health levels reported before COVID-19 ($p = 0.001$, data not shown). A multivariable logistic regression model showed that hospitalization and symptom persistence at day 28 and month 9 after disease onset were independent predictors of not achieving excellent health status at follow-up (Table 5). The same results were obtained when ordinal predictors of physical health at 9-month follow-up were used (Appendix Table 6).

Finally, we investigated the presence of predictors on patients' mental health. Impaired mental health was reported by 75 (19%) patients at 9-month follow-up. Of these, 9% reported mild distress, 6% moderate, and 4% severe distress, respectively. Female gender and symptom persistence at day 28 and month 9 after disease onset were independent predictors of psychological distress (Table 6). The same results were obtained

Table 2

Frequency of symptoms at disease onset and at 9-month follow-up.

Timing Symptom	Disease onset ($n = 465$)		9 months ($n = 417$)*	
	N	% (95% CI)	N	% (95% CI)
Any one of the following symptoms	465	100.00	83	19.90 (16.34-24.03)
Cough	319	68.60 (64.23-72.67)	6	1.44 (0.65-3.17)
Breathlessness	269	57.85 (53.30-62.27)	35	8.39 (6.08-11.48)
Fatigue	352	75.70 (71.58-79.39)	47	11.27 (8.57-14.69)
Anosmia	148	31.83 (27.74-36.21)	0	0
Dysgeusia	202	43.44 (38.99-48.00)	16	3.84 (2.36-6.18)
Myalgia	119	25.59 (21.82-29.77)	13	6.71 (4.67-9.56)
Diarrhoea	93	20.00 (16.60-23.89)	0	0

Only symptomatic patients at baseline were enrolled in the study.

Most frequent symptoms (reported by $> 5\%$ of patients) are shown. *48 patients were lost at follow-up.

Table 3
Multivariable logistic regression model for persistence of symptoms at 9-month follow-up.

Variable	Bivariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Male gender	0.80	0.49–1.29	0.35	–	–	–
Hospitalization	2.65	1.58–4.43	<0.001	1.57	0.85–2.87	0.147
ICU stay	3.15	1.64–6.05	0.001	2.35	1.15–4.79	0.019
Age > 50 years	3.05	1.64–5.67	<0.001	2.50	1.28–4.88	0.007
≥ 4 symptoms	1.86	1.14–3.02	0.012	2.04	1.22–3.42	0.007
Comorbidity	1.81	1.11–2.94	0.017	1.00	0.50–2.01	0.996

ICU= intensive care unit.

Hosmer–Lemeshow = 3.52; Prob > chi2 = 0.6201.

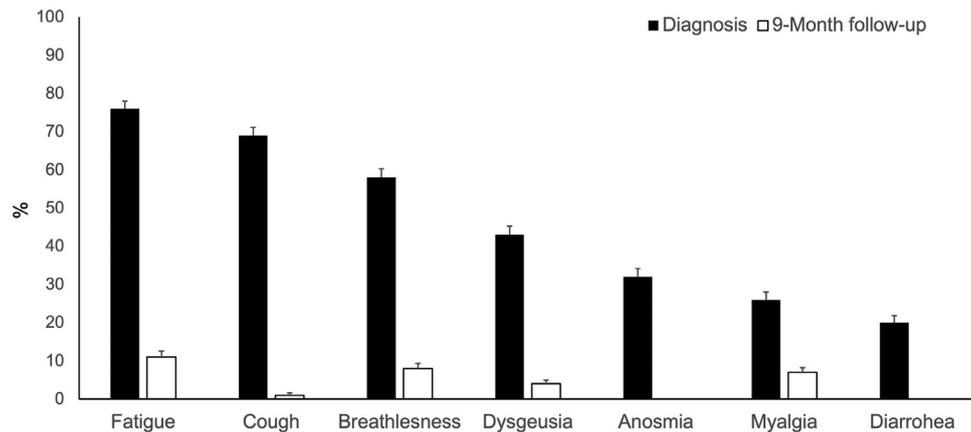


Fig. 1. Frequency of the most common SARS-CoV-2-related symptoms.

Table 4
Hazard ratios for variables included in a multivariable Cox proportional regression model for fatigue duration.

Variable	Bivariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Male gender	1.02	0.80–1.29	0.89	–	–	–
ICU stay	0.53	0.37–0.77	0.001	0.64	0.43–0.95	0.02
Comorbidity	0.73	0.58–0.93	0.01	1.28	0.93–1.77	0.13
Hospital admission	0.52	0.41–0.67	<0.001	0.68	0.49–0.94	0.02
Age	0.98	0.97–0.99	<0.001	0.99	0.98–1.00	0.005

HR = hazard ratio; ICU= intensive care unit. Significant values at bivariable analysis were used for multivariable analysis. Only fatigue among symptoms showed significant p values at multivariable analysis.

Table 5
Multivariable logistic regression model for physical health at 9-month follow-up.

Variable	Bivariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Male gender	1.03	0.63–1.70	0.893	–	–	–
9-month symptoms	8.71	5.045–15.03	<0.001	5.16	2.78–9.62	<0.001
Day 28 symptoms	5.71	3.22–10.12	<0.001	2.21	1.14–4.28	0.019
Hospitalization	6.24	3.31–11.74	<0.001	2.98	1.36–6.52	0.006
ICU stay	2.50	1.27–4.92	0.008	0.87	0.41–1.85	0.708
Age > 50 years	3.90	1.98–7.67	<0.001	2.02	0.92–4.43	0.081
≥ 4 symptoms	1.61	0.98–2.65	0.062	–	–	–
Comorbidity	2.74	1.64–4.60	<0.001	1.19	0.61–2.31	0.604

ICU= intensive care unit.

Hosmer–Lemeshow = 2.85; Prob > chi2 = 0.8983.

when ordinal predictors of psychological distress at 9-month follow-up were applied (Appendix Table 7).

Discussion

Reports describing the long-term consequences in patients recovering from COVID-19, the so called “Long COVID”, have expo-

entially increased in the past months.^{10,19–23} While several studies assessed the persistence of symptoms lasting longer than 28 days, to date a limited number of studies have explored long-term (e.g., over 3 months) effects of COVID-19.^{3,4,6,10,19–25}

Moreover, although prolonged fatigue, muscle weakness, and breathlessness have been associated with abnormalities at chest

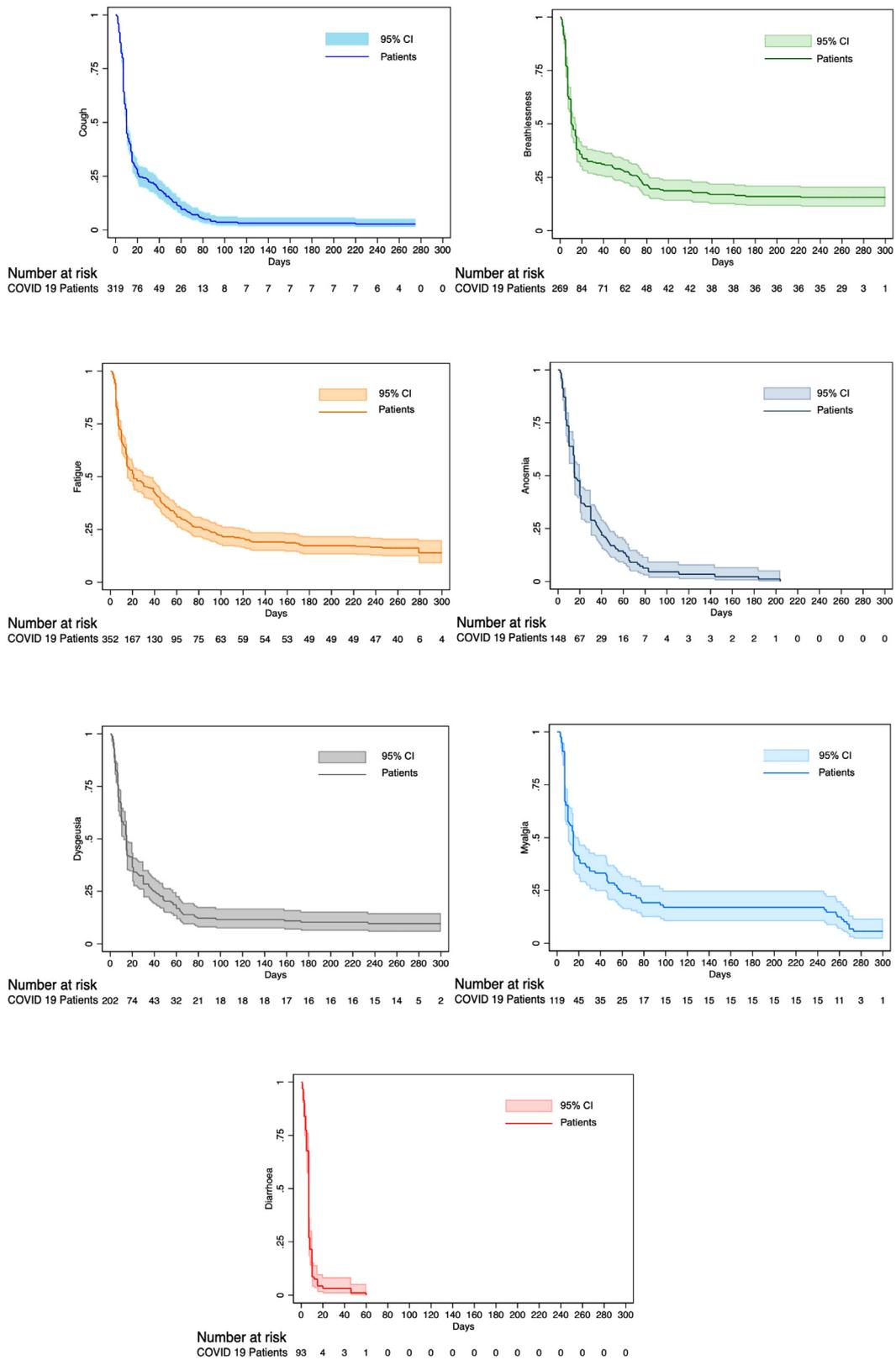


Fig. 2. Kaplan Maier curves reporting duration of symptoms among COVID-19 patients.

image, their predictors, evolution over time, and implications on the quality of life are still under investigation.¹⁰

In this study, we aimed at collecting longitudinal and long-term data to better define the factors associated with Long COVID in a prospective cohort through the analysis of easy-to-measure de-

terminants of physical and psychological wellbeing. The time kinetics of reduction of symptoms showed a slower improvement of the two main symptoms of Long COVID, breathlessness and fatigue, compared to others that are more typical of the acute phases of the disease such as cough or diarrhoea. Fatigue appeared to

Table 6
Multivariable logistic regression model for psychological distress at 9-month follow-up.

Variable	Bivariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Female gender	0.22	0.12–0.38	<0.001	5.27	2.92–9.50	<0.001
9-month symptoms	2.80	1.66–4.72	<0.001	2.48	1.27–4.83	0.008
Day 28 symptoms	2.80	1.66–4.72	<0.001	2.42	1.29–4.51	0.006
Hospitalization	1.51	0.91–2.51	0.112	–	–	–
ICU stay	1.505208	0.72–3.14	0.275	–	–	–
Age > 50 years	0.859	0.62–1.78	0.859	–	–	–
≥ 4 symptoms	1.66	1.00–2.76	0.050	–	–	–
Comorbidity	1.30	0.78–2.15	0.310	–	–	–

ICU= intensive care unit.

Hosmer–Lemeshow = 1.30; Prob > chi2 = 0.8608.

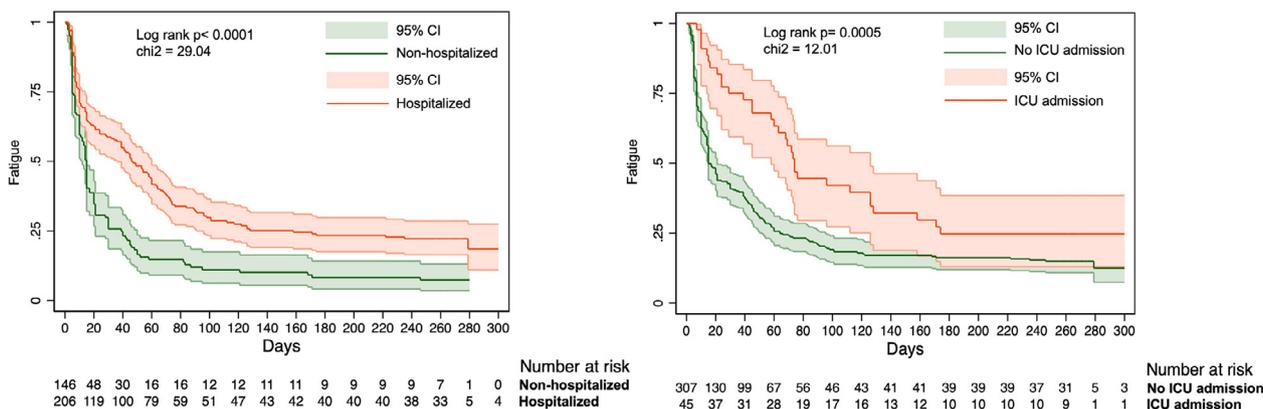


Fig. 3. Kaplan-Meier curves reporting the association between hospitalization and ICU admission with fatigue persistence at 9-month follow-up.

be the most common symptom at month 9 and was the only one showing independent predictors of persistence. Being hospitalized and, specifically, admitted to ICU, increased the median duration of fatigue of 4 and 8 weeks, respectively, compared to outpatients.

The largest study available to date for 6-month follow-up of COVID-19 evidenced the persistence of fatigue or muscle weakness in 63% of patients.¹⁰ Similar to our findings, fatigue appeared more common among severely ill vs. non severely ill patients (OR 2.69) and associated with age.¹⁰ A smaller study including 150 outpatients recovering from COVID-19 and completing a single follow-up questionnaire reported persistence of symptoms in 27% of those aged 18 to 39 years compared to 43% of those aged 65 years and older. The most common long-term symptom was fatigue (14%), but few patients completed 9-month follow-up and no predictors for persistence of symptoms were studied.²⁵ A recent report including 96 patients (32% hospitalized) showed persistent fatigue at 12 months in 53% and a high component of neurocognitive symptoms (e.g., sleeping problems, problems finding words, etc.) associated with increased antinuclear antibodies (ANA) levels, hypothesising autoimmunity as a cofactor in Long COVID.⁹

Long-term fatigue pathophysiology and its impact on patients' daily life, however, are still under investigation. A study including 369 SARS survivors in 2009 showed that 40% of patients reported a problem of chronic fatigue for a mean period of 41.3 months after SARS.²⁶ No correlation with clinical severity was shown. Other studies have been exploring the relationships between COVID-19 and triggers of post viral fatigue syndrome, but they were limited by the low number of patients included or by a short follow-up.^{27,28}

The use of telephone questionnaires or Phone apps has also increased during COVID-19 pandemic along with the optimization of telemedicine.^{29–31} These tools are important as they allow for the

collection of a large number of patients and may ease the contacts with outpatients or during self-isolation.¹¹ In the COVID Symptom Study app, prospective data were collected by 4182 patients with COVID-19, showing symptoms lasting ≥ 28 days in 13%, ≥ 8 weeks in 5%, and ≥ 12 weeks in 2%.²⁹ Persistence of symptoms was associated with increased age and was mainly characterised by fatigue, breathlessness, and anosmia. Similar to our findings, the presence of multiple symptoms at disease onset was most predictive of Long COVID (OR 2.8).²⁹

Studies involving both outpatients and inpatients are still scarce. A study including 410 outpatients through standardized interviews (35% of these reporting missing data) at 7 to 9 months after COVID-19 diagnosis showed fatigue in 21% of cases followed by loss of taste or smell (17%), dyspnoea (12%), and headache (10%), highlighting the persistence of symptoms also in the outpatient setting.³² In our study, hospitalization impacted fatigue duration and global physical health, while no impact was shown on psychological distress. ICU stay was an independent predictor of persistence of symptoms at month 9.

Our study has some limitations, including the single-centre design and the absence of associated laboratory or imaging assessments. Nevertheless, to date this is one of the largest studies to our knowledge reporting a thorough analysis of COVID-19 long-term symptoms at 9 months after disease onset and including both inpatients and outpatients. We observed that fatigue is an important component of Long COVID and may persist up to 9 months after disease onset, and that being above 50 years of age, hospitalized, and admitted to ICU are independent predictors for long-term fatigue. Furthermore, prolonged symptoms appeared to have an impact on physical health recovery and on psychological distress.

Scientific communities are strongly encouraging the dissemination of data on persistent symptoms and disability reported in

COVID-19 survivors to unravel the additional burden of a disease that, so far, has mostly counted by its hospital admissions and deaths.¹⁹ These findings contribute to the recognition of high-risk groups for Long COVID, encourage post-discharge care of COVID-19 patients, and identify target populations for the implementation of prevention strategies and potential novel treatments.

Disclosures

The authors had no competing interests.

Compliance with ethics guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. All participants provided informed consent.

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Declaration of Competing Interest

The authors have no competing interests

CRediT authorship contribution statement

Elda Righi: Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Massimo Mirandola:** Visualization, Formal analysis, Writing – original draft, Writing – review & editing. **Fulvia Mazzaferri:** Writing – review & editing. **Giuditta Dossi:** Writing – review & editing. **Elisa Razzaboni:** Data curation, Writing – review & editing. **Amina Zaffagnini:** Data curation, Writing – review & editing. **Federico Ivaldi:** Data curation, Writing – review & editing. **Alessandro Visentin:** Data curation, Writing – review & editing. **Lorenza Lambertenghi:** Data curation, Writing – review & editing. **Cinzia Arena:** Writing – review & editing. **Claudio Micheletto:** Writing – review & editing. **Davide Gibellini:** Writing – review & editing. **Evelina Tacconelli:** Visualization, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jinf.2022.02.003](https://doi.org/10.1016/j.jinf.2022.02.003).

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