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Persistence of symptoms in long-COVID: follow-up trajectories of 30 symptoms in 755 patients from a national multicenter study from Italy

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Abstract

Aim of the study was to define the patterns and determinants of symptom persistence in Long-COVID. The study population was represented by a multicenter cohort of patients with persisting symptoms after SARS-CoV-2 infection. Data collection included demographics, comorbidities, characteristics of acute infection, vaccination, reinfection, plus 30 different symptoms. The associations between covariates and persistence were assessed in multivariable logistic regression models. The study evaluated, at a mean interval of 453 days from acute SARS-CoV-2 infection, symptom persistence in 755 patients who had Long-COVID symptoms at a mean interval of 223 days from COVID-19. At second evaluation, 423 (56.0%) patients still presented one or more symptoms and 332 (44.0%) were symptom free. In those who remained symptomatic, the mean number of symptoms significantly reduced between the two evaluations. Compared to the first evaluation, the overall mean symptom regression rate was 72%, with lower regression rates observed for dyspnea (53%), anxiety (54%) and sleep disturbances (55%). The risk of persistence was increased for female sex, higher BMI, hospitalization and stronger ventilatory support during acute disease, higher number of initial symptoms and particular comorbidities (anxiety, chronic pulmonary disease, asthma), and decreased with the increase of age and time from acute SARS-CoV-2 infection. Neither SARS-CoV-2 vaccination nor reinfection showed significant associations with persistence. In this case series, roughly half of the patients that were symptomatic 7 months after acute SARS-CoV-2 infection remained symptomatic after an additional 7 months. The pattern and predictors of persistence draw attention to certain particular risk factors and manifestations that tend to persist longer than others.

Keywords COVID-19 · Long-COVID · Symptoms · Fatigue · Dyspnea

Introduction

Five years into the SARS-CoV-2 pandemic, both the scientific community and the national and international institutions have recognized Long-COVID as a distinct clinical condition that can follow acute SARS-CoV-2 infection, presenting with a variety of symptoms and manifestations [1–4]. Long-COVID may be severe and debilitating, with a significant impact on individual well-being, functional status and working capacity, and with relevant economic implications [5–8]. Although several studies have addressed the prevalence and identified risk factors for Long-COVID, many of them had a cross-sectional design, and few have addressed longitudinally in the same individuals the rate, timing and predictors of symptom persistence [9–12]. Available evidence indicates that in most of the cases, the symptoms may regress spontaneously with time, but a variable proportion of individuals show long-term and often disabling persistence after months or years after acute infection [13–18]. Assessing symptom trajectories and the determinants of persistence is therefore relevant both for the patients who were infected early in the pandemic and entered a chronic and symptomatic Long-COVID condition, and for those who were more recently diagnosed with Long-COVID and are uncertain about the possible duration of their manifestations. To contribute information on this issue, we used data from a multicenter national study of patients accessing care for Long-COVID in specialized centers, with the aim of assessing the rate, timing and determinants of symptom persistence.

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Materials and methods

Study overview

The present clinical study is part of the project"Analysis and strategies for responding to the long-term effects of the COVID-19 infection (Long-COVID)", funded by the National Centre for Disease Prevention and Control (CCM) of the Italian Ministry of Health, and aimed at monitoring the long-term effects of SARS-CoV2 infection, increasing knowledge about this condition and providing recommendations to standardize the approach nationwide [19]. The study, structured as an observational cohort, started in January 2023 and was completed in March 2024, with data extracted on April 2, 2024. The study included patients attending for the first time the clinics during the study and patients already followed, who returned after the study start for a planned follow-up visit after acute infection or for occurrence/persistence of potential Long-Covid symptoms. The assessment of symptoms had a mixed retrospective/prospective design. Symptom collection was retrospective, based on clinical records and patient interview, for patients who had two previous visits before the start of the study (January 2023), and prospective for patients with one or two visits after this date. Data on demographics, acute infection and comorbidities were taken from clinical records. Study data were entered by medical staff at the participating centers using an online dedicated platform. Two clinical evaluations were recommended, with the first conducted at least 4 weeks after acute infection (recommended: at least 3 months) and the second (follow up) after at least 3 months from the first visit (recommended: at least 6 months from acute infection).

Data collection

For data collection, a shortened version of the Post-COVID-19 Case Report Form (CRF) from the WHO Global Clinical Platform for COVID-19 was used [20], which included patient demographics, comorbidities, severity and timing of acute COVID, plus 30 different symptoms (fatigue, dyspnea, sleep disturbances, memory loss, joint pain or swelling, muscle pain, difficult concentration, cough, anxiety, taste reduction, smell reduction, palpitations/tachycardia, depressed mood, skin disorders/alopecia, thoracic pain, paresthesia, brain fog, headache, disorders of equilibrium or gait, visual disturbances, weight loss, diarrhea, hearing disturbances, pharyngodynia, loss of appetite, nausea or vomiting, fever, menstrual disorders, chilblains, delirium or hallucinations) [20]. Inclusion criteria for the present analysis were age at least 18, a recorded date of acute SARS-CoV-2 infection (defined by date of first positive swab), and two subsequent clinical evaluations, with the first characterized by the presence of symptoms persisting for at least 4 weeks after acute infection.

Definitions

Severity of acute SARS-CoV-2 disease was defined as mild (grade 1), moderate (grade 2), severe (grade 3) or critical (grade 4) according to the WHO grading [20]. Respiratory assistance was categorized as none, low or high flow oxygen, continuous positive airway pressure (CPAP), mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO). Phase of the pandemic was categorized as pre-Omicron or Omicron according to the occurrence of the date of acute infection before or after December 23, 2021 [21]. SARS-CoV-2 reinfection was defined by a new positive swab at least 3 months after a previous positive test. The comorbidities considered were neoplastic disease, ischemic heart disease, heart failure, renal failure, stroke, anxiety or depressive disorders, chronic liver disease, respiratory failure, chronic pulmonary disease, diabetes, hypertension, obesity, autoimmune diseases, asthma, obstructive sleep apnea syndrome (OSAS), plus a general category of other major conditions, reviewed by two of the authors. SARS-CoV-2 vaccination status was categorized in three groups according to the timing of the first dose administration (before SARS-CoV-2 infection, after SARS-CoV-2 infection, not vaccinated).

Data analysis

Data were summarized as proportions for categorical variables and as means with standard deviations for quantitative variables. Mean values were compared by Student's T test and proportions by the Chi-square test in contingency tables. Multivariable logistic regression models were used to assess the associations between clinical and demographic covariates and persistence of symptoms. The models included all covariates with a level of association <0.15 (p value) in univariate analyses, plus age and sex. Associations were expressed as adjusted odds ratios (AOR) with 95% confidence intervals (CI). The goodness of fit of the models was tested with the Hosmer–Lemeshow test and tests of collinearity among variables. No input was used to substitute missing data. All analyses were performed using the SPSS software, version 29.0 (IBM Corp, 2022, Armonk, NY, USA).

Results

Study population

The study population included 755 patients who had persisting symptoms at a mean interval of 223 days from acute infection (SD 216), reevaluated at 453 days (SD 288) from acute infection, with a mean interval of 229 days (SD 183) between the two assessments of symptoms. The general characteristics of the final sample by sex are reported in Table 1. Men were slightly older, more frequently affected by cardiovascular comorbidities (ischemic heart disease, heart failure, stroke and hypertension) and had suffered more severe acute SARS-CoV-2 disease, as consistently expressed by hospitalizations, admissions to intensive care unit, severity grading of acute disease and level of respiratory assistance. Women were more frequently vaccinated before infection and more commonly affected by anxiety, depression and autoimmune disorders (Table 1).

Symptoms

At re-evaluation, 423 (56.0%) patients presented at least one symptom and 332 (44.0%) were symptom free. In those who were still symptomatic, the mean number of symptoms per patient was significantly reduced compared to first evaluation, from 3.99 (SD 2.8) to 3.06 (SD 1.5) ($p < 0.001$).

The individual regression rates for each of the 30 symptoms evaluated is reported in Fig. 1. The mean symptom regression rate was 72%. Regression rates for the most common symptoms were 65% for fatigue, 53% for dyspnea, 55% for sleep disturbances, 61% for memory loss, 66% for muscular pain, 86% for difficult concentration, 59% for joint pain or swelling, 54% for anxiety, 64% for depressed mood, 77% for both taste and smell reduction, 69% for cough, 63% for paresthesias, 82% for skin disorders/alopecia, 73% for palpitations/tachycardia, 66% for brain fog, 73% for thoracic pain and 69% for headache (Fig. 1).

The prevalence of individual symptoms in the entire population at the first and second evaluation and the relative reduction in prevalence between these two time points are reported in Fig. 2. The prevalence of individual symptoms at the second evaluation included also occurrence of new symptoms: about one-quarter of the patients (178, 23.6%) reported at the second evaluation one or more symptoms (mean number 2.1, DS 1.7) that were not present at the first evaluation. Occurrence of individual new symptoms was however infrequent, and no new symptom occurred in more than 5% of the patients (Fig. 3). Most common symptoms of new onset were memory loss (in 5.4% of patients), dyspnea, fatigue and joint pain or swelling (in 4.4% of patients), sleep disturbances (3.7%), difficult concentration (3.2%), anxiety (3.0%), brain fog (2.6%), paresthesias (2.3%), muscular pain (2.1%) and depressed mood (2.0%). Considering both regression of symptoms and onset of new symptoms, the mean reduction in prevalence of individual symptoms between the first and second evaluation was 59%.

Determinants of persistence

Table 2 illustrates the covariates significantly associated with persistence of the most frequent symptoms in multivariable logistic regression models. In the table, asterisks denote the variables included in the models according to the predefined entry criteria (association at a p level <0.15 in the univariate analyses, plus sex and age), but not significantly associated with the persistence of symptoms in the multivariable analyses. The overall risk of persistence of at least one symptom at the second evaluation was increased for female sex, higher BMI, hospitalization for COVID-19, stronger ventilatory support during acute disease (CPAP, MV or ECMO), higher number of initial symptoms and particular comorbidities (anxiety, chronic pulmonary disease, asthma), and decreased with the increase of age and time after acute SARS-CoV-2 infection. Persisting fatigue was associated with female sex, higher BMI, hospitalization for COVID-19, number of initial symptoms, preexisting renal insufficiency and chronic pulmonary disease, and the risk of persistence decreased with the increase of time after acute SARS-CoV-2 infection. Persisting dyspnea was associated with higher BMI, CPAP, VM or ECMO, number of initial symptoms, preexisting stroke and chronic pulmonary disease, with the risk decreasing with the increase of time after acute infection. Persistent memory loss was associated with the number of initial symptoms, preexisting renal insufficiency and diabetes, and its risk increased with the increase of time after acute infection. Persisting sleep disturbances were associated with higher BMI, hospitalization for COVID-19, number of initial symptoms, preexisting anxiety and chronic pulmonary disease and its risk increased with the increase in time after acute infection. Persisting muscle pain was associated with hospitalization for COVID-19, number of initial symptoms and chronic pulmonary disease. Persisting difficulty in concentration was associated with smoking and number of initial symptoms, and its risk decreased with the increase in time after acute infection and was also lower in the case of SARS.CoV-2 vaccination before acute infection. Finally, persisting joint pain or swelling was associated with higher BMI and with preexisting chronic pulmonary disease, but its risk was lower for younger age and in the presence of

Table 1 General description and differences between women and men in demographics, comorbidities, vaccination status and characteristics of acute infection

	All	Women	Men	*p*
N (%)	755	366 (48.5)	389 (51.5)	
Age (years, mean, SD)	61.7 (13.2)	60.5 (13.6)	62.7 (12.8)	**0.025**
Body mass index (kg/m^2, mean, SD) (*n*: 730)	27.4 (5.3)	27.2 (6.0)	27.6 (4.6)	0.289
Current smoking (*n*, %) (*n*: 704)	70 (9.9)	38 (11.2)	32 (8.7)	0.268
Comorbidities (mean number, SD)	1.6 (1.5)	1.5 (1.4)	1.7 (1.6)	0.274
Any	552 (73.1)	273 (74.6)	279 (71.7)	0.374
Neoplastic disease	56 (7.4)	26 (7.1)	30 (7.7)	0.750
Ischemic heart disease	65 (8.6)	20 (5.5)	45 (11.6)	**0.003**
Heart failure	30 (4.0)	9 (2.5)	21 (5.4)	**0.039**
Renal failure	46 (6.1)	22 (6.0)	24 (6.2)	0.927
Stroke	26 (3.4)	7 (1.9)	19 (4.9)	**0.025**
Anxiety	70 (9.3)	47 (12.8)	23 (5.9)	**0.001**
Depression	47 (6.2)	33 (9.0)	14 (3.6)	**0.002**
Chronic liver diasease	10 (1.3)	4 (1.1)	6 (1.5)	0.589
Respiratory failure or COPD	53 (7.0)	19 (5.2)	34 (8.7)	0.056
Diabetes	101 (13.4)	44 (12.0)	57 (14.7)	0.289
Hypertension	363 (48.1)	160 (43.7)	203 (52.2)	**0.020**
Obesity	156 (20.7)	73 (19.9)	83 (21.3)	0.637
Autoimmune diseases	72 (9.5)	54 (14.8)	18 (4.6)	**<0.001**
Asthma	30 (4.0)	17 (4.6)	13 (3.3)	0.360
Atrial fibrillation	23 (3.0)	7 (1.9)	16 (4.1)	0.079
OSAS	17 (2.3)	5 (1.4)	12 (3.1)	0.112
Other major conditions	45 (6.0)	17 (4.6)	28 (7.2)	0.139
Vaccinated*(*n*: 583)				**0.014**
Before infection	123 (21.1)	75 (26.0)	48 (16.3)	
After infection	263 (45.1)	120 (41.7)	143 (48.5)	
Not vaccinated	197 (33.8)	93 (32.3)	104 (35.3)	
Acute infection pandemic phase				**0.001**
Pre-omicron	533 (70.6)	238 (65.0)	295 (75.8)	
Omicron	222 (29.4)	128 (35.0)	94 (24.2)	
Hospitalised during acute phase	511 (70.6)	211 (60.6)	300 (79.9)	**<0.001**
Admitted to intensive care unit	87 (12.0)	25 (7.2)	62 (16.5)	**<0.001**
WHO COVID severity grade				**<0.001**
Mild (grade 1)	211 (27.9)	129 (35.2)	82 (21.1)	
Moderate (grade 2)	152 (20.1)	78 (21.3)	74 (19.0)	
Severe (grade 3)	246 (32.6)	104 (28.4)	42 (36.5)	
Critical (grade 4)	124 (16.4)	39 (10.7)	85 (21.9)	
Unknown	22 (2.9)	16 (4.4)	6 (1.5)	
Respiratory assistance				**<0.001**
None	244 (32.3)	149 (40.7)	95 (24.4)	
Low-flow O_2	151 (20.0)	72 (19.7)	79 (20.3)	
High-flow O_2	79 (10.5)	32 (8.7)	47 (12.1)	
CPAP	165 (21.9)	64 (17.5)	101 (26.0)	
Mechanical ventilation	74 (9.8)	28 (7.7)	46 (11.8)	
ECMO	8 (1.1)	2 (0.5)	6 (1.5)	
Unknown	34 (4.5)	19 (5.2)	15 (3.9)	

SD: standard deviation; *COPD:* chronic obstructive pulmonary disease; *OSAS:* obstructive sleep apnea syndrome; $O_{2:}$ oxygen; *CPAP:* continuous positive airway pressure; *ECMO:* extracorporeal membrane oxygenation. * any dose. Significant p values are expressed in bold

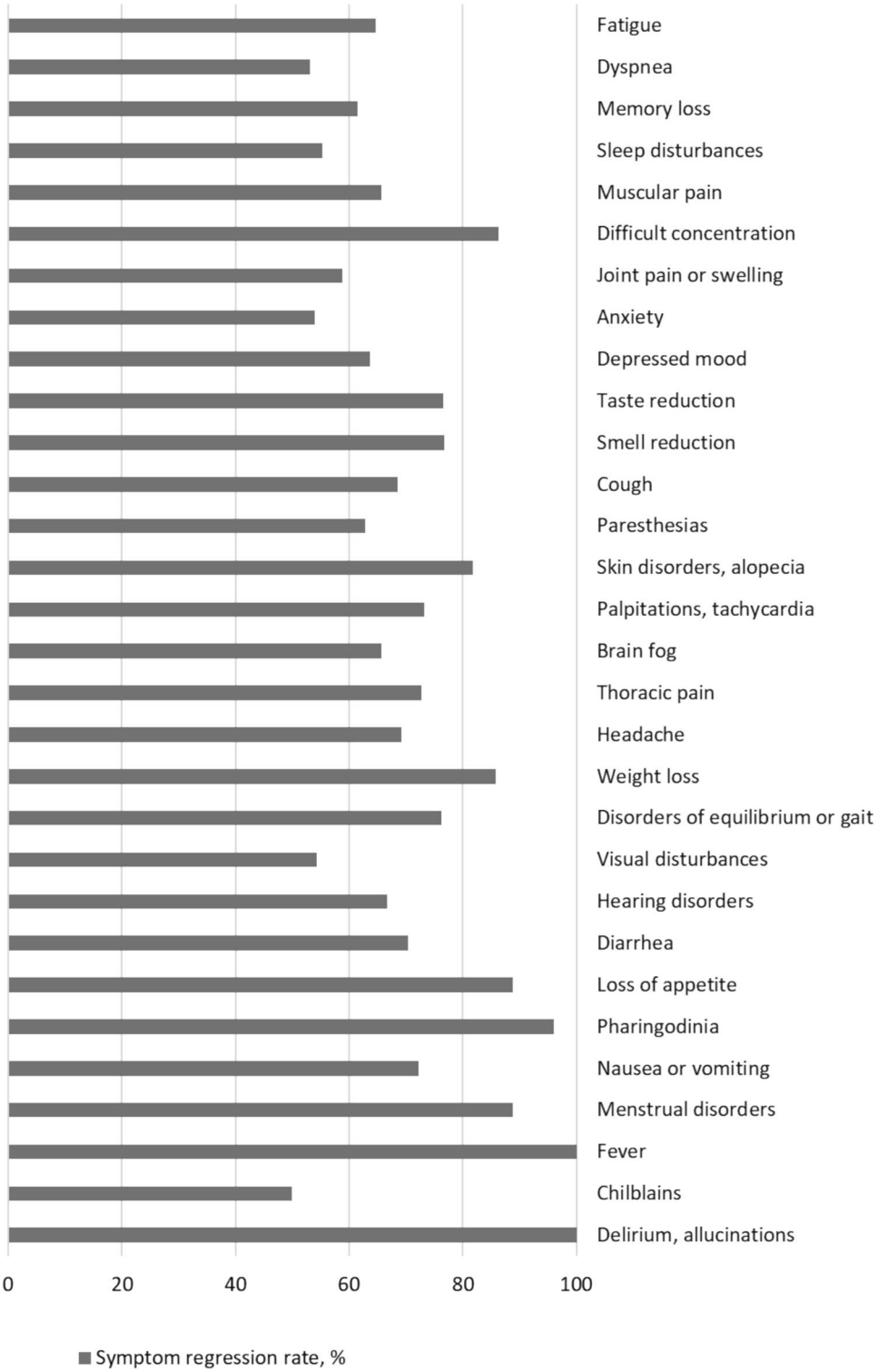

Fig. 1 Regression rate of individual symptoms between the first and second evaluation

autoimmune diseases. Adjusted odds ratios for all the above associations are shown in Table 2.

Reinfection

We also evaluated the possible role of SARS-CoV-2 reinfection in persistence of symptoms. A reinfection was recorded in 81 cases (10.7%), with the date of reinfection occurring before the first evaluation (36, 4.8%), between the first and

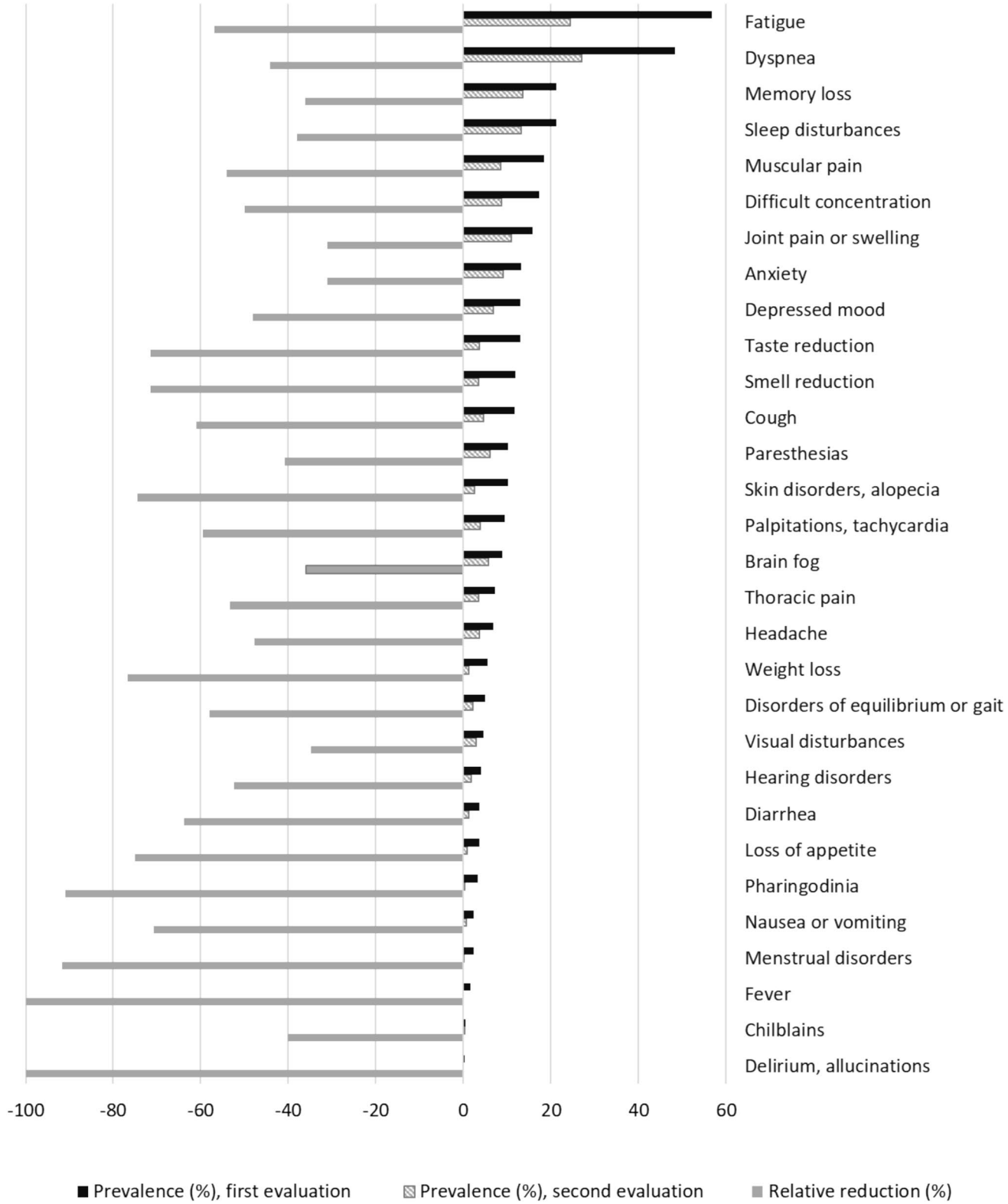

Fig. 2 Prevalence of individual symptoms at the first and second evaluation

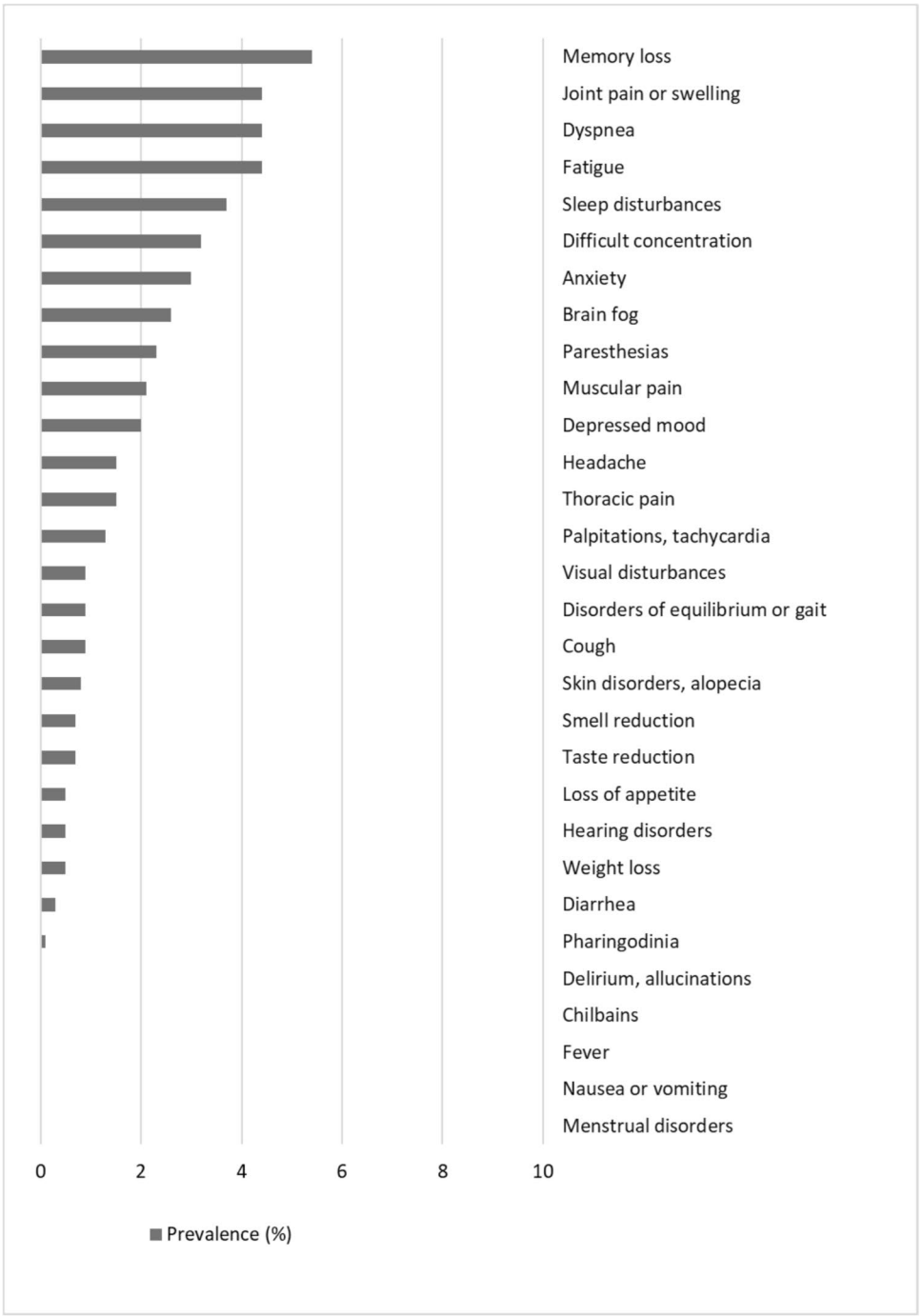

Fig. 3 Rate of new occurrence of individual symptoms at the second evaluation

second evaluation (17, 2.3%) or unknown (28, 3.7%). No association was found between reinfection and persistence of any symptom (persistence: 51.9% in patients with reinfection vs. 56.9% in patients without reinfection, $p = 0.423$) and between reinfection and persistence of the main individual symptoms considered (persistence for fatigue: 23.5% in patients with reinfection vs. 24.5% in patients without reinfection, $p = 0.939$; for dyspnea: 21.0 vs. 27.7%, respectively, $p = 0.196$; for memory loss: 9.9 vs. 14.1%, respectively, $p = 0.296$; for sleep disturbances: 18.5 vs. 12.6%, respectively, $p = 0{,}138$; for difficult concentration: 8.6 vs. 8.8%, respectively, $p = 0.973$; for muscular pain: 7.4 vs. 8.6%, respectively, $p = 0.715$; for articular pain or swelling: 6.2 vs. 11.4%, respectively, $p = 0.151$).

Antivirals, IL-6 inhibitors, and neutralizing monoclonal antibodies

We finally explored the possible role of three drug categories administered during acute infection on subsequent

Table 2 Variables associated with the persistence of symptoms in multivariable logistic regression models

	Persistence of at least one symptom		Fatigue		Dyspnea		Memory loss		Sleep disturbances		Muscle pain		Difficult concentration		Joint pain or swelling	
	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*
Female sex	1.58 (1.04–2.41)	0.031	2.15 (1.43–3.22)	<0.001	*		*		*		*		*		*	
Age >65 years	0.46 (0.29–0.75)	0.002	*		*		*		*		*		*		0.43 (0.23–0.80)	0.008
BMI (kg/m^2, per additional unit)	1.16 (1.10–1.23)	<0.001	1.07 (1.02–1.12)	0.004	1.12 (1.06–1.18)	<0.001	*		1.09 (1.03–1.16)	0.004	*				1.08 (1.02–1.15)	0.010
Current smoking							*				*		2.63 (1.03–6.73)	0.043	*	
SARS-CoV-2 vaccine pre-infection	*				*		*		*				0.20 (0.05–0.90)	0.036	*	
Infected during Omicron	*				*		*		*				*		*	
Severity grade of COVID-19[#]	*		*		*		*		*		*		*		*	
Hospitalised for COVID-19	2.65 (1.26–5.56)	0.010	2.10 (1.12–3.94)	0.021	*		*		4.41 (1.53–12.7)	0.006	3.57 (1.29–9.83)	0.014			*	
Admitted to ICU	*				*						*		*			
CPAP, MV, or ECMO	2.90 (1.53–5.48)	0.001			2.27 (1.19–4.34)	0.013	*		*						*	
Months from acute COVID-19[#]	0.97 (0.95–0.99)	0.011	0.97 (0.94–0.99)	0.004	0.96 (0.94–0.98)	<0.001	1.04 (1.02–1.06)	0.001	1.03 (1.01–1.06)	0.013	*		0.94 (0.90–0.98)	0.003	*	
Number of symptoms at first visit[#]	1.18 (1.09–1.29)	<0.001	1.18 (1.11–1.27)	<0.001	1.20 (1.11–1.99)	<0.001	1.23 (1.13–1.34)	<0.001	1.20 (1.11–1.30)	<0.001	1.23 (1.13–1.34)	<0.001	1.36 (1.24–1.50)	<0.001	*	
Comorbidities (any)	*		*		*		*		*						*	
Number of comorbidities[#]	*		*		*		*		*				*			
Neoplasms	*		*		*											
Ischemic heart disease	*				*											
Heart failure	*		*		*											
Renal insufficiency	*		2.52 (1.09–5.82)	0.030	*		2.86 (1.03–7.95)	0.044	*							
Stroke					6.22 (1.49–25.9)	0.012										
Anxiety	3.63 (1.38–9.56)	0.009	*				*		3.21 (1.37–7.54)	0.006	*		*			
Depression	*		*		*		*		*				*			
Chronic liver disease							*		*							
Chronic pulmonary disease	4.16 (1.46–11.8)	0.007	2.71 (1.28–5.74)	0.009	3.01 (1.25–7.26)	0.014			2.71 (1.03–7.17)	0.044	2.84 (1.11–7.25)	0.029			3.31 (1.35–8.13)	0.009

Table 2 (continued)

	Persistence of at least one symptom		Fatigue		Dyspnea		Memory loss		Sleep disturbances		Muscle pain		Difficult concentration		Joint pain or swelling	
	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*	AOR, 95% CI	*p*
Diabetes	*				*		2.41 (1.11–5.25)	0.026	*				*			
Hypertension	*		*		*				*							
Obesity	*		*		*		*		*						*	
Autoimmune diseases			*										*		0.27 (0.72–0.98)	0.047
Asthma	8.15 (1.59–41.6)	0.012														
Atrial fibrillation					*						*		*		*	
OSAS																
Other major conditions	*		*		*											
Reinfection									*							

The symbol * indicates all the variables included in each model according to prespecified criteria (sex and age plus any variable associated with the outcome at a significance level <0.15 in univariate analyses).

AOR: adjusted odds ratio; #: AOR per each additional unit; CI: confidence interval; SD: standard deviation; ICU: intensive care unit; CPAP: continuous positive airway pressure; VM: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; OSAS: obstructive sleep apnea syndrome

persistence and number of symptoms: antivirals (*n*: 136, 18.6%, mostly represented by remdesivir); IL-6 inhibitors (*n*: 65, 8.9%, with no information on individual drugs used); monoclonal neutralizing antibodies (*n*: 20, 2.7%, with no information on individual drugs used). Their administration had no effect on symptom persistence (any symptom: *p* values 0.413, 0.122 and 0.512, respectively) or on the number of persistent symptoms (*p* values: 0.729, 0.679 and 0.846, respectively).

Discussion

In this study, we provided longitudinal data on rate, timing and predictors of symptom persistence in a multicenter sample of 755 patients who presented persisting Long-COVID symptoms after a mean interval of 7 months from acute infection and were subsequently reevaluated after an additional 7 months, at a mean interval of 15 months after acute infection.

Men and women showed some clinical differences in the profile of comorbidities: males were slightly older and more likely to have experienced severe acute SARS-CoV-2 disease, a finding also reported in other studies [22]. An important and reassuring finding is that 44% of patients who were still symptomatic at the first evaluation, performed 7 months after acute COVID-19, were symptom free after an additional 7 months. It should also be underlined that patients with complete symptom regression were in two-thirds of cases polysymptomatic at first evaluation (on average, three symptoms per individual), indicating that the regression involved most commonly more than one symptom, translating into a mean regression rate among individual symptoms of 72%.

Comparing the above regression rates with existing literature is problematic, because in most of the published studies the design included a single time point for evaluation, the populations studied were heterogeneous, the number and type of symptoms collected not uniform and the follow-up time variable [13, 16, 23–31]. Restricting the field to studies with at least 12 months of follow-up and longitudinal data available to define trajectories, our data are overall consistent with the 51.2% reported subjective improvement in the study by Stalker [16], and slightly more favorable compared to the 67% persistence rate reported by Peter [23]. It should, however, be underlined that other studies have reported persistence rates around 40% [25, 29], higher than 75% [26, 30] and in some cases even higher than 90% [13]. In one of the few studies characterized by a longer follow-up, persistence rate was 23% at 2 years [31]. Despite the methodological issues that complicate possible comparisons, our data confirm that there is a progressive, although slow, regression of symptoms over time in most patients, but also that a significant proportion of cases remain symptomatic and that new symptoms that were previously not present may also arise with time, although infrequently.

In our study, all symptoms decreased in frequency between the first and second evaluation, but the individual regression rates of the 30 symptoms showed differences that may have clinical relevance. Compared to a mean overall regression rate of 72%, rates of regression for dyspnea, anxiety and sleep disturbances were just a few units above 50%, while the rates of regression for difficult concentration and skin disorders were higher than 80%. Other authors have reported differential symptom persistence, with a higher persistence of pulmonary symptoms [16], sleep and memory disturbances [30], and fatigue [32]. Our findings, consistent with those reported above, identify some symptoms that deserve particular attention in terms of persistence and suggest different trajectories for individual symptoms.

A further objective of our study was to characterize the potential predictors of persistence. In univariate analyses, several demographic and clinical factors were associated with the persistence of symptoms, and some of these were confirmed in multivariable analyses that provided risk estimates adjusted for potential confounders.

Persistence of at least one symptom was associated with female sex, higher body mass index, hospitalization, intensive respiratory support during acute infection, number of symptoms at the first evaluation, anxiety, chronic pulmonary disease and asthma, and its risk reduced with advanced age and with the increase in time after acute infection. Although no precise overlapping with other studies was possible, due to differences in design and populations, the above findings are consistent with others that identified as predictors of overall symptom persistence female sex [12, 14, 15, 25, 29, 31, 33, 34], severity of acute disease [15, 23, 29, 31, 33, 34], higher body mass index [23, 25], comorbidities [14, 29] and initial polysymptomaticity [35]. In our study, advanced age did not increase but reduced the risk of overall persistence, as reported by Shah [34], but in contrast with other studies that identified advanced age as a risk factor for persistence [12, 15, 29, 33, 35]. In evaluating this difference, it should be considered that different studies evaluated different panels of symptoms and that not all the studies obtained estimates that controlled for confounders. In our study, the risk estimates for advanced age were adjusted for several other covariates, including comorbidities and severity of acute disease.

Time from acute infection was inversely associated with overall persistence, confirming the reassuring trend for a spontaneous general symptom regression over time. When evaluating individual symptoms in multivariable analyses, however, this association showed in some cases opposite directions, with the risk of persistence significantly declining over time for fatigue, dyspnea and difficulty in concentration, but increasing over time for memory loss and sleep

disturbances. This finding is consistent with the described increase with follow-up of some neurological or mental health symptoms [27, 28].

Persistence of the main individual symptoms showed several associations of potential relevance. Female sex was a specific risk factor for persistence of fatigue, which represents a frequent and often disabling manifestation of Long-COVID [36]. A higher body mass index was a significant risk factor not only for overall persistence of symptoms, but also for persistence of some important individual symptoms, such as fatigue, dyspnea, sleep disturbances and joint pain or swelling. This association is relevant because it identifies a potentially modifiable risk factor that influences persistence consistently and widely.

Severity of acute disease was a relevant risk factor not only for overall persistence of symptoms, but also for some individual key symptoms: patients hospitalized for COVID-19 had a higher risk of fatigue, sleep disturbances and muscle pain, and those who necessitated a more intensive respiratory support during acute disease had an increased risk of remaining symptomatic and of showing persistent dyspnea. Polysymptomaticity at first visit was also significantly associated with persistence of most of the individual symptoms considered, indicating that regression is less likely in the presence of multiple symptoms. Smoking, which only a few studies have reported as a risk factor for persistence [23, 31], was associated only with persisting difficulty in concentration. SARS-CoV-2 vaccination apparently had a limited role in preventing overall persistence, showing a protective effect only on the persistence of difficulty in concentration. The inverse association between advanced age and persistence of joint pain or swelling might indicate lower risk of inflammatory manifestations in elderly individuals. Reinfection, differently from other studies [17, 23, 37], had no apparent role in favoring persistence. Similarly, we found no significant protective effect on symptom persistence of the administration of antivirals, IL-6 inhibitors, and monoclonal neutralizing antibodies during acute infection. Other studies have already described no or limited effect of IL-6 inhibitors and neutralizing antibodies in this context [38–40]. Data on antivirals are more controversial [38, 41–45]. In our study, the most commonly used antiviral drug was remdesivir, and other antivirals, particularly nirmatrelvir, might be more effective [38]. Other interventions that we did not evaluate might also be beneficials [46, 47].

With respect to comorbidities, the findings indicate a predominant role of chronic pulmonary disease that was associated with an overall four times increase in the risk of persistent symptoms, and with significantly increased risks for most of the individual symptoms considered. Attention should also be posed to anxiety and asthma, which significantly increased the overall risk of persistence, and to renal insufficiency, diabetes and stroke, which significantly increased the risk of persistence of some individual symptoms. An inverse association between autoimmune diseases and joint pain or swelling was found, possibly mediated by concomitant treatments for the underlying disease.

In terms of study limitations, our study only evaluated symptom trajectories and was not designed to estimate Long-COVID prevalence, because we already selected as an inclusion criterion the presence of Long-COVID symptoms. The definition of symptom trajectories, inevitably based on the availability of two time points, may have introduced some selection, because cases with spontaneous regression of symptoms may have more often not returned for follow-up visits compared to patients with persistence [23], with a possible underestimation of the actual regression rates. As for other studies, we also did not assess severity of symptoms, and symptom collection was based on patients' report, with a potential for information or recall bias. Finally, in the identification of predictors, we did not evaluate the possible impact of social determinants of health, such as economic, occupational and psychosocial factors, which are recognized as important cofactors affecting the risk of Long-COVID [23, 37, 48]. In evaluating role of reinfection, we also cannot exclude that some asymptomatic SARS-CoV-2 reinfections may have occurred, potentially affecting symptom persistence at re-evaluation.

In terms of strengths, our study was based on a large sample and assessed longitudinally a relatively large number of symptoms in trajectories that included time points distant from acute infection, with a relatively long follow-up compared to other studies. We also used a form specifically developed by WHO, with a comprehensive evaluation of demographic and clinical characteristics. The wide range of covariates considered allowed to identify in multivariable analyses possible determinants of persistence and provide risk estimates that were adjusted for a significant number of potential confounders. Finally, our study was conducted in multiple centers in different regions, with a variety of specialty clinics and settings of care that ultimately reinforced the external validity of the results.

In conclusion, in this population of patients already selected for Long-COVID manifestations, roughly half of the patients that were symptomatic at 7 months after acute infection were still symptomatic after an additional 7 months. Persistence of symptoms was associated with some comorbidities, demographic factors and severity of acute disease, and showed relevant differences among individual symptoms. Many of the available studies were based on a short-term evaluation [14, 27, 32, 33, 35], and the present study may therefore contribute to a better identification of the long-term trajectories of a relatively large number of symptoms. The identified predictors and patterns of persistence may also be relevant to patients and clinicians for prognosis, identifying some particular manifestations that

tend to persist longer than others. The differences in regression rates observed among specific symptoms draw attention to some particular risk factors and complement the findings of several studies based on cluster analyses that suggested that the different Long-COVID phenotypes are sustained by distinct disease mechanisms and pathways [11, 24, 37, 49, 50]. Such findings may provide a basis for future clinical and pathogenetic research.

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Author contributions MF was responsible for data acquisition, directly accessed and verified the underlying data reported in the manuscript, performed the analyses and drafted the manuscript. LEW was responsible for data acquisition. MF and GO were responsible for study design and conceptualization. LEW, PRQ, PB, DL, SF, SZ, PA, EB, ALF, PG and KL contributed to the data acquisition. All authors contributed to interpretation of results and review of the manuscript for intellectual content. All authors read and approved the final manuscript and accepted responsibility to submit for publication.

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Data availability The study data can be made available upon reasonable request. Ethics Committee consultation may be necessary to obtain permission to share. Requests to access the datasets should be directed to marco.floridia@iss.it.

Declarations

Conflict of interest None. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

Ethical approval The Italian National Ethics Committee approved the project (AOO-ISS—19/04/2022-0015066 Class: PRE BIO CE 01.00).

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