International Journal of Infectious Diseases 125 (2022) 287–293

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Characteristics of long-COVID among older adults: a cross-sectional study

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ARTICLE INFO

Article history:
Received 14 July 2022
Revised 8 September 2022
Accepted 27 September 2022

Keywords:
COVID-19
SARS-CoV-2
Post-COVID-19
Long-COVID
Long-lasting symptoms
Older adults

ABSTRACT

Objectives: To describe long-COVID symptoms among older adults and to assess the risk factors for two common long-COVID symptoms: fatigue and dyspnea.
Methods: This is a multicenter, prospective cohort study conducted in Israel, Switzerland, Spain, and Italy. Individuals were included at least 30 days after their COVID-19 diagnosis. We compared long-COVID symptoms between elderly (aged >65 years) and younger individuals (aged 18-65 years) and conducted univariate and multivariable analyses for the predictors of long-COVID fatigue and dyspnea.
Results: A total of 2333 individuals were evaluated at an average of 5 months (146 days [95% confidence interval 142-150]) after COVID-19 onset. The mean age was 51 years, and 20.5% were aged >65 years. Older adults were more likely to be symptomatic, with the most common symptoms being fatigue (38%) and dyspnea (30%); they were more likely to complain of cough and arthralgia and have abnormal chest imaging and pulmonary function tests. Independent risk factors for long-COVID fatigue and dyspnea included female gender, obesity, and closer proximity to COVID-19 diagnosis; older age was not an independent predictor.

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https://doi.org/10.1016/j.ijid.2022.09.035

Conclusion: Older individuals with long-COVID have different persisting symptoms, with more pronounced pulmonary impairment. Women and individuals with obesity are at risk. Further research is warranted to investigate the natural history of long-COVID among the elderly population and to assess possible interventions aimed at promoting rehabilitation and well-being.

Introduction

Long-COVID has been reported to affect a substantial portion of survivors of COVID-19, including those who experienced mild acute disease (Carter *et al.*, 2022; Chen *et al.*, 2022; Yan *et al.*, 2021). In many of the cases, the affected individuals experience debilitating symptoms that affect their physical and cognitive function, impairing their quality of life. Recent longer-term follow-up studies show that many individuals do not experience full recovery even 1 year after infection (PHOSP-COVID Collaborative Group, 2022; Zhang *et al.*, 2021). Often, rehabilitation is required to restore the prefunctional capacity of patients with long-COVID; however, no drug or nondrug intervention has been proven effective (Schneider, 2020). The most common long-COVID symptoms are fatigue and dyspnea, followed by others, including chest pain, myalgia, impaired memory or concentration, and neuropsychiatric symptoms (Michelen *et al.*, 2021; Schou *et al.*, 2021; Yelin *et al.*, 2022).

Although older adults constitute a large proportion of individuals infected with severe COVID-19, thus far, little is known about the prevalence and risk factors of symptomatic long-COVID among this population. In most cohorts reporting on long-COVID, the mean age of participants was less than 60 years (Huang *et al.*, 2021a, 2021b; PHOSP-COVID Collaborative Group, 2022), and only a few single-center studies addressed specifically older adults with long COVID.

To identify current needs and consequent health care system response, it is imperative to broaden our knowledge on long-COVID in older adults. We aimed to describe the prevalence of long-COVID symptoms among older adults and to explore independent risk factors for two of the most common long-COVID symptoms: fatigue and dyspnea.

Methods

Study design and population

This study was a multicenter, prospective cohort study, conducted at five multidisciplinary hospital-based COVID-19 recovery clinics in Israel, Switzerland, Spain, and Italy (Pisa and Modena). Data were collected at the first clinic visit in most centers (Israel, Italy, and Spain) and by telephone interview in one center (Switzerland). Consecutive adult (aged ≥18 years) individuals visiting the clinics between May 2020 and March 2021 were included. To be enrolled for a visit, patients were required to have a polymerase chain reaction-proved COVID-19 diagnosis at least 30 days before the clinic visit.

During their clinic visit, the patients were interviewed by the attending physician and reported their long-COVID symptoms using a designated questionnaire, in which they were asked to rank each symptom on a 0-3 Likert scale (0 - not at all; 1 - mild; 2 - moderate; 3 - severe). We defined individuals with a high burden of long-COVID symptoms as those reporting at least three continuing symptoms. In addition, the patients, regardless of their symptoms, underwent a complete pulmonary function test (PFT) (spirometry, lung capacities, and diffusing capacity) during the clinic visit, according to the American Thoracic Society guidelines (Culver *et al.*, 2017). PFT measurements were expressed as the percentage of predicted normal values according to sex, age, and height, as measured during the visit. Abnormal diffusion was defined as carbon monoxide diffusing capacity <80% of the predicted value (Culver *et al.*, 2017).

We compared elderly individuals (aged <65 years) to the younger population (aged 18-65 years).

Data collection

Before the initiation of the study, shared data collection formats were drafted in collaboration between all the participating centers. A manual defining the variables of interest (including filling instructions, labels, and values) was sent to all collaborators. Data collection was implemented using research electronic data capture tools hosted at Yale University (Harris *et al.*, 2019). Information on demographics (age, marital status, and sex), pre-COVID-19 and post-COVID-19 physical activity, body mass index, smoking status, comorbidities, and characteristics of acute COVID-19 were assessed during the clinic visit. These were recorded by the attending physicians at the time of the clinic visit. For the current study, we retrieved these data from the patients' medical records. COVID-19 severity was defined following the World Health Organization's definitions (World Health Organization [WHO], 2020a). We used the World Health Organization guidelines on physical activity and sedentary behavior to define the individual's physical activity. Physically active individuals were those who undertook aerobic activity of >150 or >75 minutes per week for moderate or vigorous activities, respectively (WHO, 2020b).

Statistical analysis

We used descriptive statistics with measures of central tendency and dispersion to describe the study population. Comparisons were based on the classification of two age groups. The demographics and clinical parameters were compared between the groups implementing the Student's *t*-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for dichotomous variables. Univariate and multivariate analyses for risk factors for long-COVID fatigue and dyspnea were conducted, incorporating age as a variable in the analysis. The multivariable analysis was conducted using generalized estimating equation binary logistics to account for the study site as a random-effect variable. Variables that were not strongly correlated ($r < 0.4$) were entered into the multivariable model based on the univariate analysis (*i.e.,* those for which $P < 0.1$). Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from the multivariate model. Data analysis was performed using IBM SPSS version 28 (Armonk, NY, USA).

Ethical approval

The local research ethics committees of the participating centers approved the study protocol (RMC-0485-2020). All participating individuals signed written informed consent forms.

Table 1
Demographics and clinical characteristics of the study population.

	Valid cases (N = 2333)	Individuals aged 18-65 years (N = 1855) (79.5%)	Individuals aged >65 years (N = 478) (20.5%)	*P*-value[a]
Age (years), mean (SD)	51.25 (16.39)	45.32 (12.49)	74.25 (6.32)	<0.001
Women, N (%)	1145 (49.2)	956 (51.6)	189 (39.5)	<0.001
Body mass index, mean (SD)	27.8 (5.4), N = 952	27.6 (5.5)	28.8 (5.2)	0.388
Married, N (%)	644 (70.5), N = 914	512 (70.0)	132 (72.1)	0.579
Smokers, N (%)	644 (32.2), N = 2002	463 (29.5)	181 (41.9)	<0.001
Pre-COVID-19 physical activity				<0.001
Inactive, N (%)	289 (32.5), N = 888	199 (28.2)	90 (49.5)	
Partially active, N (%)	280 (31.5), N = 888	238 (33.7)	42 (23.1)	
Fully active, N (%)	319 (35.9), N = 888	269 (38.1)	50 (27.5)	
Background illnesses				
Diabetes mellitus, N (%)	213 (9.90), N = 2151	124 (7.1)	89 (21.4)	<0.001
Hypertension, N (%)	465 (23.4), N = 1983	247 (15.2)	218 (60.4)	<0.001
Obesity, N (%)	391 (26.8), N = 1460	275 (25.7)	116 (29.9)	0.106
Ischemic heart disease, N (%)	94 (4.8), N = 1957	45 (2.8)	49 (14.2)	<0.001
Hypothyroidism, N (%)	59 (5.7), N = 1044	42 (5.1)	17 (7.8)	0.123
Chronic kidney disease, N (%)	32 (2.2), N = 1487	12 (1.1)	20 (5.2)	<0.001
Chronic pulmonary disease, N (%)	129 (7.4), N = 1732	95 (6.4)	34 (13.5)	<0.001
Malignancy, N (%)	45 (2.6), N = 1732	28 (1.9)	17 (6.7)	<0.001
Charlson comorbidity score, median (IQR)	0 (0-2), N = 1406	0 (0-1)	2 (0-4)	<0.001
Regular use of angiotensin-converting enzyme inhibitors, N (%)	156 (15.8), N = 987	70 (9.1)	86 (39.1)	<0.001
Regular corticosteroid therapy, N (%)	15 (1.6), N = 944	10 (1.3)	5 (2.6)	0.208
Regular use of anticoagulation, N (%)	40 (4.2) N = 956	10 (1.3)	30 (14.9)	<0.001

[a] Calculated using Student's *t*-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.Abbreviation: IQR, interquartile range; N, number of patients.

Results

Overall, 2333 individuals were included. The mean age was 51 years (SD = 16), and 478 (20.5%) of them were older than 65 years. The average time interval between COVID-19 onset and clinic visits was 146 days (95% CI 142-150 days). Baseline characteristics of participants, according to age groups, are detailed in Table 1. The proportion of women aged over 65 years was lower than the proportion of women in the younger group (39.5% vs 51.6%, P <0.001). Older individuals were more likely to be smokers (41.9% vs 29.5%, P <0.001), not physically active (49.5% vs 28.2%, P <0.001), and had higher rates of comorbidities and medication use (Table 1).

Characteristics of acute COVID-19 in older adults compared with younger individuals

Compared with younger individuals, older participants experienced higher rates of severe COVID-19 (severe or critical 58.4% vs 24.4%, P <0.001), higher rates of hospitalization (79.1% vs 39.8%, P <0.001), and longer duration of hospital stay (mean = 18 days, SD = 14 days vs mean = 13 days, SD = 12 days, P <0.001). Dyspnea was the only symptom that was significantly more common in older adults with acute COVID-19 (64.3% vs 56.6%, *P*-value = 0.035) than higher proportions of sore throat, nasal congestion, headache, chest pain, and anosmia/ageusia, which are all more common in younger adults (Supplementary Table 1).

Manifestations of long-COVID in older adults compared with younger individuals

Older participants visited the recovery clinic about 1 month earlier than younger participants (mean = 123 days, 95% CI 113-134 days vs mean = 150 days, 95% CI 145-154 days, P <0.001) and had higher rates of symptoms (80.0% of older individuals reporting any symptom compared with 64.2% of younger individuals, P <0.001). Nevertheless, they had similar rates of high burden symptoms (34.1% in older individuals vs 32.8% in younger individuals, *P*-value = 0.678). Fatigue and dyspnea were the most common long-COVID symptoms in both age groups (fatigue: 38.7% among older individuals vs 39.4% among younger individuals, *P*-value = 0.779; dyspnea: 29.9% in older individuals vs 27.3% in younger individuals, *P*-value = 0.251). Headache, chest pain, palpitations, concentration impairment, and emotional distress were all more common in the younger age group, whereas cough and arthralgia were more common in older adults. Older participants were more likely to report an increase in their physical activity after COVID-19 (29.2% vs 8.2%, P <0.001), whereas younger patients tended to report a decrease (younger 28.8% vs older 16.3%, P <0.001). Older participants were more likely to have abnormal chest imaging at the time of assessment (23.2% vs 10.1%, *P*-value = 0.001) and impairments in PFT (including impaired forced expiratory volume in 1 second, total lung capacity, and carbon monoxide diffusing capacity) (Table 2).

The ranked severity of long-COVID symptoms in the general study population and the older adult population are provided in Supplementary Tables 2 and 3.

Risk factors for long-COVID fatigue among older adults

The univariate and multivariate analyses for long-COVID fatigue are displayed in Table 3. Female sex, smoking, obesity, and hypertension were associated with higher rates of long-COVID fatigue. Obesity (OR 1.586, 95% CI 1.115-2.255) and female sex (OR 2.073, 95% CI 1.572-2.734) were independently associated with long-COVID fatigue. Evaluation at a shorter time interval since the acute infection was also significantly associated with fatigue (OR 1.594, 95% CI 1.054-2.410). Older age did not associate with long-COVID fatigue (OR 0. 779, 95% CI 0.538-1.129) (Table 3).

Risk factors for long-COVID dyspnea among older adults

Female sex, pre-COVID-19 physical activity status, obesity, hypertension, and COVID-19 severity were associated with higher rates of long-COVID dyspnea. Obesity (OR 1.690, 95% CI 1.198-2.382), female sex (OR 1.674, 95% CI 1.261-2.222), partial pre-COVID-19 physical activity (OR 1.632, 95% CI 1.163-2.290), and chronic pulmonary disease (OR 1.983, 95% CI 1.179-3.334) were independent risk factors for long-COVID dyspnea. Older age did not associate with long-COVID dyspnea (OR 0.695, 95% CI 0.476-1.013)

Table 2
Characteristics of the study population during the post-COVID-19 clinic visit.

	Valid cases (N = 2333)	Individuals aged 18-65 years (N = 1855) (79.5%)	Individuals aged >65 years (N = 478) (20.5%)	*P*-value[a]
Time from COVID-19 diagnosis to clinic visit (days), mean (SD)	146 (87), N = 1601	150 (87)	124 (83)	<0.001
Individuals who visited <60 days from diagnosis, N (%)	207 (12.9), N = 1601	172 (12.7)	35 (14.3)	0.474
Long-COVID symptoms[b]				
Any symptom, N (%)	1439 (67.2), N = 2141	1111 (64.2)	328 (80.0)	<0.001
≥3 symptoms, N (%)	575 (33.0), N = 1743	488 (32.8)	87 (34.1)	0.678
Fatigue, N (%)	916 (39.3)	731 (39.4)	185 (38.7)	0.779
Headache, N (%)	159 (6.8)	143 (7.7)	16 (3.3)	0.001
Chest pain, N (%)	205 (11.8), N = 1743	186 (12.6)	19 (7.5)	0.022
Dyspnea, N (%)	649 (27.8)	506 (27.3)	143 (29.9)	0.251
Palpitations, N (%)	111 (4.8)	102 (5.5)	9 (1.9)	<0.001
Cough, N (%)	265 (11.4)	197 (10.6)	68 (14.2)	0.027
Myalgia, N (%)	493 (21.1)	386 (20.8)	107 (22.4)	0.452
Arthralgia, N (%)	177 (7.6)	126 (6.8)	51 (10.7)	0.004
Hair loss, N (%)	91 (5.3), N = 1732	79 (5.3), N=1732	12 (4.8), N=1732	0.705
Concentration impairment, N (%)	446 (19.1)	370 (19.9)	76 (15.9)	0.045
Memory impairment, N (%)	479 (20.5)	368 (19.8)	111 (23.2)	0.102
Emotional distress, N (%)	401 (23), N = 1743	358 (24.1)	43 (16.9)	0.012
Anosmia, N (%)	363 (15.5)	299 (16.1)	63 (13.2)	0.114
Physical activity status at time of visit				<0.001
Worsened, N (%)	385 (26.8), N = 1427	347 (28.8)	38 (16.3)	
Remained unchanged, N (%)	885 (61.6), N = 1427	758 (63.0)	127 (54.5)	
Improved, N (%)	167 (11.6), N = 1427	99 (8.2)	68 (29.2)	
Pathological chest radiogram, N (%)	66 (12.5), N = 530	44 (10.1)	22 (23.2)	0.001
Pulmonary function tests				
FEV1 (%), mean (SD)	97 (16), N = 848	97 (15)	100 (20)	0.028
FEV1 <80% of expected, N (%)	90 (10.5), N = 848	67 (9.8)	23 (14.0)	0.114
FVC (%), mean (SD)	98 (16), N = 844	97 (15)	100 (20)	0.129
FVC <80% of expected, N (%)	90 (10.7), N = 844	69 (10.2)	21 (12.7)	0.338
FEV1/FVC, mean (SD)	87 (11), N = 833	86 (10)	88 (14)	0.104
FEV1/FVC <0.7, N (%)	29 (3.5), N = 833	20 (3)	9 (5.5)	0.113
TLC (%), mean (SD)	95 (14), N = 816	96 (14)	93 (15)	0.042
TLC <80% of expected, N (%)	107 (13.1), N = 816	76 (11.6)	31 (19.4)	0.009
DLCO (%), mean (SD)	90 (16), N = 826	91 (15)	85 (18)	0.001
DLCO <80% of expected	209 (25.3), N = 826	152 (22.7)	57 (36.3)	<0.001

[a] Calculated using Student's *t*-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables;
[b] For each symptom, individuals who reported moderate to severe intensity were counted as positive.Abbreviations: DLCO, Diffusing capacity for carbon monoxide; FEV1, Forced expiratory volume in 1 second; FVC, forced vital capacity; N, number of patients; TLC, total lung capacity.

(Table 4). Dyspnea was also significantly associated with a shorter time interval between acute illness and evaluation (OR 2.071, 95% CI 1.386-3.094) (Table 4).

Discussion

In this cohort of 2333 COVID-19 recoverees recruited from multinational COVID-19 recovery clinics at approximately 5 months after disease onset, 20.5% were older adults (aged >65 years). The proportion of women among the older group was lower than younger adults. As expected, older adults had higher rates of comorbidities. During the acute phase, the proportion of individuals with severe COVID-19 was higher among the older age group; consequently, they had a higher likelihood of hospitalization, chest radiogram abnormalities, and reduced pulmonary diffusing capacity at the time of clinic assessment. Older adults were more likely to report persisting symptoms at the time of assessment, with the most common symptoms being fatigue and dyspnea. This burden of persisting symptoms among older adults probably reflects the higher rates of severe COVID-19 and consequent hospitalizations and complications. It is likely that these well-known contributing factors for deconditioning among the elderly population (Covinsky *et al.*, 2011) added to the baseline risk for long-COVID among recoverees, leading to higher proportions of symptoms.

The differences in long-COVID manifestations between older and younger adults may also reflect the difference in baseline conditions, such as comorbidities, which are significantly more prevalent among the former. Although age and comorbidities are associated with COVID-19 severity, their impact on long-COVID may extend beyond the acute phase. For instance, the poorer age-adjusted pulmonary function found in our study among the older adults can be explained by a diminished pulmonary reserve with age (Lowery *et al.*, 2013), which likely protracts restoration of health after COVID-19. In addition, sarcopenia was postulated as one of the contributors to long-COVID (Piotrowicz *et al.*, 2021). In comparison to the younger adults, older individuals have lower skeletal muscle mass. These physiological differences consequent from the effects of aging on muscle fiber type and size (Deschenes, 2004). Because sarcopenia is associated with functional decline (Beaudart *et al.*, 2017), its effect on elderly individuals may be more substantial. It may also play a role in long-COVID, accounting for different effects and consequences of fatigue and dyspnea among younger and older individuals.

As for the somewhat less frequent symptoms, older patients were more likely to report cough and arthralgia, whereas younger patients were more likely to report headache, chest pain, concentration impairment, and emotional distress. Older age did not correlate with long-COVID fatigue or dyspnea. Among older adults, the independent risk factors for long-COVID fatigue included female sex, obesity, and proximity to the acute phase; whereas the risk factors for long-COVID dyspnea included the former as well as chronic obstructive pulmonary disease and pre-COVID partial physical activity status.

Table 3
Univariate analysis and multivariate Generalized Estimating Equations analysis of independent risk factors for long-COVID fatigue among older adults.

	Univariate analysis (N = 2333)			Multivariate analysis	
	No post-COVID fatigue (N =1417)	Post-COVID fatigue (N = 916)	*P*-value	Odds ratio (95% CI)	*P*-value
Age >65 years	293 (20.7)	185 (20.2)	0.779	0.779 (0.538-1.129)	0.187
Women	651 (45.9)	497 (54.3)	<0.001	2.073 (1.572-2.734)	**<0.001**
Married, N = 916	256 (67.7)	389 (72.3)	0.135	-	-
Smoker, N = 2007	382 (33.9)	263 (29.9)	0.060	1.086 (0.787-1.498)	0.617
Pre-COVID-19 physical activity, N = 890			0.150	-	-
Inactive	106 (29.8)	183 (34.3)			
Partially active	125 (35.5)	156 (29.2)			
Fully active	125 (35.1)	195 (36.5)			
Background illnesses					
Diabetes mellitus, N = 2155	117 (9.2)	96 (10.9)	0.185	-	-
Obesity, N = 1465	245 (21.0)	220 (26.8)	0.003	1.586 (1.115-2.255)	**0.010**
Hypertension, N = 1985	168 (24.4)	223 (28.7)	0.064	1.185 (0.819-1.716)	0.368
Ischemic heart disease	50 (4.4)	44 (5.4)	0.287	-	-
Hypothyroidism, N = 1046	21 (4.7)	38 (6.4)	0.236	-	-
Chronic kidney disease, N = 1491	15 (2.1)	17 (2.2)	0.963	-	-
Chronic pulmonary disease, N = 1734	74 (7.1)	55 (7.9)	0.511	-	-
Malignancy, N = 1734	27 (2.6)	18 (2.6)	0.990	-	-
Otherwise healthy individuals, N = 1611	193 (23.8)	191 (23.9)	0.971	-	-
Regular use of angiotensin-converting enzyme inhibitors, N = 689	75 (18.2)	82 (14.2)	0.090	-	-
Regular corticosteroid therapy, N = 946	6 (1.5)	9 (1.6)	0.929	-	-
Regular use of anticoagulation, N = 958	19 (4.8)	21 (3.7)	0.403	-	-
Disease severity according to the WHO, N = 2209			0.227	-	-
Asymptomatic, mild, or moderate	904 (66.8)	571 (66.7)			
Severe	406 (30.0)	246 (28.7)			
Critical	43 (3.2)	39 (4.6)			
Less than 60 days from COVID-19 diagnosis to clinic visit, N = 1688	89 (8.9)	122 (17.8)	<0.001	1.594 (1.054-2.410)	**0.027**

Univariate analysis performed using Chi-square test; N = number of patients; goodness of fit test: Quasi Likelihood under Independence Model Criterion (QIC) = 1230.37. p value<0.001; constant: β = -1.530; risk for long COVID-19 fatigue: OR>1.

Long-COVID is reported to affect a considerable portion of COVID-19 recoverees, which is estimated to be at 10-30%, and symptoms may persist for longer than 1 year (Yelin *et al.*, 2022). A study from Wuhan, China reported fatigue, chest pain, anxiety, and myalgia in 8-28% of survivors 1 year after discharge (Zhang *et al.*, 2021). Similar to our findings, multiple studies rank fatigue as the most common long-COVID symptom (Aly and Saber, 2021; Michelen *et al.*, 2021; Proal and Marshall, 2018; Tosato *et al.*, 2021; Townsend *et al.*, 2020; Wostyn, 2021). Although older age is an established risk factor for severe acute COVID-19 (Gao *et al.*, 2021; Li *et al.*, 2020; Perrotta *et al.*, 2020), data on post-COVID sequela and long-COVID among the specific population of elderly individuals are lacking. In a recent cohort study of hospitalized individuals, older age harbored a greater risk for long-COVID at 1-3 months after acute disease. In our study, older age did not correlate with long-COVID. This difference can be explained by the fact that although the former study included hospitalized individuals, 52% of our cohort were not hospitalized during the acute phase. Similar to our study, the aforementioned study identified ongoing fatigue and impaired pulmonary diffusion capacity at higher rates among the older population. Female sex and high body mass index were also identified as risk factors for long-COVID among older adults (Bai *et al.*, 2021). A recent UK-based, multicenter, prospective study also found that female sex and obesity are risk factors associated with long-COVID, with a long-term follow-up of 1 year (PHOSP-COVID Collaborative Group, 2022). A suggested explanation is the association between obesity and multisystemic states (*i.e.*, proinflammatory, hormonal, and metabolic) that could promote the maintenance of systemic inflammation. The same study found that long -lasting systemic inflammation correlated with the severity of long-COVID symptoms (PHOSP-COVID Collaborative Group, 2022).

A cohort study assessing recoverees at 6 months after acute COVID-19 also identified an association between older age and pulmonary diffusion impairment, fatigue, and weakness (Huang *et al.*, 2021a). When the same cohort was followed up for a year, the risk for diffusion impairment surged by 30% per each additional decade of age. Similar to our study, no significant association was demonstrated between age and long-COVID fatigue (Huang *et al.*, 2021b).

In a nested case-control study performed in one of our participating COVID-19 recovery clinics, 141 younger adults (mean age = 47 years, SD = 13) underwent a multidimensional assessment for long-COVID fatigue, including cardiopulmonary exercise testing. The two independent risk factors for long-COVID fatigue identified through a multivariable analysis were long-COVID memory impairment and peak exercise heart rate (Margalit *et al.*, 2022). Those with significant long-COVID fatigue had, on average, lower peak exercise heart rate, although their physical performance was within the range of normal. This subtle deviation corresponds with the observed discrepancy between the suffering of inflicted individuals and the paucity of clinical findings on routine assessment tests.

Among the older age group in the current study, we found no association between long-COVID fatigue and cognitive aspects. This may stem from the fact that occupational requirements frequently unveil subtle cognitive impairments among the younger age group (Godeau *et al.*, 2021), whereas older individuals on retirement may detour this confrontation. Moreover, these subjective symptoms may be under reported among the elderly group be-

Table 4
Univariate analysis and multivariate Generalized Estimating Equations analysis of independent risk factors for long-COVID dyspnea among older adults.

	Univariate analysis (N = 2333)			Multivariate analysis	
	No post-COVID dyspnea (N = 1684)	Post-COVID dyspnea (N = 649)	*P*-value	Odds ratio (95% CI)	*P*-value
Age >65 years	335 (19.9)	143 (22.0)	0.251	0.695 (0.476-1.013)	0.063
Women	794 (47.1)	354 (54.5)	0.001	1.674 (1.261-2.222)	**<0.001**
Married, N = 916	375 (71.8)	270 (68.5)	0.277	-	-
Smoker, N = 2007	440 (31.9)	205 (32.7)	0.718	-	-
Pre-COVID-19 physical activity, N = 890			0.020		
Inactive	150 (30.8)	139 (34.5)		1.078 (0.769-1.512)	0.663
Partially active	173 (35.5)	108 (26.8)		1.632 (1.163-2.290)	**0.005**
Fully active	164 (33.7)	156 (38.7)		Reference	
Background illnesses					
Diabetes mellitus, N = 2155	117 (9.2)	96 (10.9)	0.185	-	-
Obesity, N = 1465	204 (23.2)	187 (32.0)	>0.001	1.690 (1.198-2.382)	**0.003**
Hypertension, N = 1985	303 (21.5)	162 (28.2)	0.001	-	-
Ischemic heart disease	65 (4.7)	29 (5.0)	0.784	-	-
Hypothyroidism, N = 1046	31 (5.0)	28 (6.5)	0.315	-	-
Chronic kidney disease, N = 1491	13 (1.4)	19 (3.4)	0.012	2.233 (0.847-5.887)	0.104
Chronic pulmonary disease, N = 1734	78 (6.2)	51 (10.5)	0.002	1.983 (1.179-3.334)	**0.010**
Malignancy, N = 1734	30 (2.4)	15 (3.1)	0.411	-	-
Otherwise healthy individuals, N = 1611	252 (24.5)	132 (22.7)	0.430	-	-
Regular use of angiotensin-converting enzyme inhibitors, N = 689	90 (16.1)	67 (15.6)	0.825	-	-
Regular corticosteroid therapy, N = 946	6 (1.1)	9 (2.1)	0.220	-	-
Regular use of anticoagulation, N = 958	24 (4.5)	16 (3.8)	0.589	-	-
Disease severity according to the World Health Organization, N = 2209			<0.001		
Asymptomatic, mild or moderate	1107 (69.0)	368 (60.8)		Reference	
Severe	445 (37.7)	207 (34.2)		1.121 (0.540-2.331)	0.759
Critical	52 (3.2)	30 (5.0)		1.958 (0.979-3.915)	0.057
Less than 60 days from COVID-19 diagnosis to clinic visit, N = 1688	125 (10.3)	86 (18.0)	<0.001	2.071 (1.386-3.094)	**<0.001**

[a]Calculated using chi-square; [b]N = number of patients; [c]goodness of fit test: Quasi Likelihood under Independence Model Criterion = 1175.01. P <0.001; constant: β = -2.954; risk for long-COVID-19 dyspnea: odds ratio >1.

cause individuals may disregard their long-COVID cognitive symptoms as age-related.

Unveiling the extent of long-COVID and its characteristics among the older population is particularly important because, the older age of recoverees was associated with long-term impairment in quality of life and functional capacity (Tleyjeh *et al.*, 2022).

Our study has several limitations. First, older participants had a higher proportion of severe COVID-19 and a consequent higher proportion of hospitalizations. This prevents concrete inference as to whether differences are exclusively related to age or confounded by disease severity. This possible limitation has been partly controlled by the multivariable analysis; however, it still limits the generalizability of our findings. Studies that include a larger sample of older outpatients (during acute COVID-19) are needed. Second, residual confounding is also a concern because we did not have baseline chest imaging and PFT for reference. Accordingly, the impaired pulmonary function observed among older individuals could be possibly related to reduced capacity at baseline. Nevertheless, older adults also experienced a high acute COVID-19 burden of respiratory symptoms. Accordingly, it is reasonable to assume that the abnormal imaging and diffusing capacity are at least partially related to COVID-19 itself. Third, two of the five included centers did not collect full demographics, background conditions, and COVID-19-related parameters. However, this limitation did not differentiate between patients, and the sample size yielded sufficient statistical power (Peduzzi *et al.*, 1995).

In conclusion, older individuals report higher rates of long-COVID manifestations, with somewhat different persisting symptoms and more pronounced pulmonary impairment. Women and individuals with obesity are at risk. The somewhat higher burden of long-COVID symptoms among older adults is likely to be multifactorial. Higher rates of severe COVID-19 with subsequent deconditioning and diminished baseline muscle mass and pulmonary reserve, as well as comorbidities, are assumed to play a role. Further prospective long-term follow-up research is warranted to investigate the natural history and recovery patterns of long-COVID among the elderly population. The exceedingly high numbers of COVID-19 recoverees together with the high prevalence of long-COVID among the elderly population indicate a need for clinical attention and resource allocation for long-COVID among older adults. Possible interventions aimed at promoting rehabilitation and well-being of this susceptible population should be assessed in comparative trials.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

This work was supported in part by Prof. Amnon Shashua's research fund, Tel Aviv University - Faculty of Medicine Research Funds, and by the Israel Insurance Association Research Fund, grant no. 050-351-010. The funding organizations had no role in the planning, writing, or analyzing of the data in this study.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of the four centers (approval numbers: Israel 0458-20-RMC; Italy CEAVNO n. 1768; Spain PR374/20; Switzerland CER 2020-01273).

Author contributions

Israel: Leonard Leibovici, Dana Yelin, and Dafna Yahav conceived the study idea, designed the study, planned the statistical analysis,

verified the underlying data, and drafted the manuscript; Ili Margalit contributed to the underlying research protocol, designed the study, planned the statistical analysis, collected data, and drafted the manuscript; Vered Daitch designed the study, planned the statistical analysis, performed the statistical analysis, and writing the manuscript; Muhammad Awwad collected data and drafted the manuscript, Irit Shapira-Lichter and Donna Abecasis contributed to the underlying research protocol; all authors contributed to manuscript revision and read and approved the submitted version.

Switzerland: Mayssam Nehme contributed to the underlying research protocol, data collection, and review of the manuscript; Idris Guessous contributed to the underlying research protocol, data collection, and supervision of the work in Switzerland; Pauline Vetter and Laurent Kaiser contributed to the underlying research protocol and data collection; all authors contributed to manuscript revision and read and approved the submitted version.

Spain: Carlota Gudiol contributed to the underlying research protocol, coordinated the study in Spain, and writing of the manuscript; Jaume Bordas-Martínez contributed to the underlying research protocol, collected data, and reviewed the manuscript; Xavier Durà-Miralles and Dolores Peleato-Catalan contributed to the underlying research protocol and collected data; all authors read and approved the final version of the manuscript.

Italy: Pisa: Marco Falcone contributed to the underlying research protocol, collected data, reviewed the manuscript, and supervised the work in Pisa; Giusy Tiseo, Laura Carrozzi, and Francesco Pistelli contributed to the underlying research protocol, collected data, and reviewed the manuscript; Modena: Cristina Mussini, Giovani Guaraldi, and Jovana Milić contributed to the underlying research protocol, collected data, and reviewed the manuscript.

Informed consent statement

All patients signed or gave oral informed consent before participation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.035.

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