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Residual pulmonary infiltrates, symptoms and diffusion impairment at 1-year after severe COVID-19 infection have different associated factors

Rosario Menéndez[1,2,3,4], Raúl Méndez[1,2,3,4], Ana Latorre[1,2], Paula González-Jiménez[1,2,4], Germán Peces-Barba[5], María Molina[6], Pedro Pablo España[7], Estela García[8], Angélica Consuegra-Vanegas[9], Ana Pando-Sandoval[10], Carolina Panadero[11], Juan Marco Figueira-Gonçalves[12], David De la Rosa[13], Oriol Sibila[14], María Dolores Martínez-Pitarch[15], Nuria Toledo[16], Pilar Cejudo[17], Wanda Almonte-Batista[18], Abigail Macías-Paredes[19], Diana Badenes[20], Eli Nancy Pérez-Rodas[21], Javier Lázaro[22], Sarai Quirós[23], Rosa Cordovilla[24], Irene Cano-Pumarega[3,25], Antoni Torres[3,14] & on behalf of RECOVID[1]

From the [1]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [2]Instituto de Investigación Sanitaria La Fe (IISLAFE), Valencia, Spain; [3]CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [4]The University of Valencia, Valencia, Spain; [5]Hospital Fundación Jiménez Díaz, Madrid, Spain; [6]Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain; [7]Hospital de Galdakao-Usansolo, Galdakao, Spain; [8]Hospital de Cabueñes, Gijón, Spain; [9]Hospital Universitario de A Coruña, A Coruña, Spain; [10]Hospital Universitario Central de Asturias, Oviedo, Spain; [11]Hospital de Getafe, Getafe, Spain; [12]Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; [13]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [14]Hospital Clínic, Barcelona, Spain; [15]Hospital Lluís Alcanyís, Játiva, Spain; [16]Hospital Son Espases, Palma, Spain; [17]Hospital Virgen del Rocío, Sevilla, Spain; [18]Hospital de Albacete, Albacete, Spain; [19]Hospital de Sant Jaume, Calella, Spain; [20]Hospital del Mar, Barcelona, Spain; [21]Hospital Dos de Mayo, Barcelona, Spain; [22]Hospital Royo Villanova, Zaragoza, Spain; [23]Hospital de Basurto, Bilbao, Spain; [24]Hospital Universitario de Salamanca, Salamanca, Spain; and [25]Hospital Universitario Ramón y Cajal, IRYCIS), Madrid, Spain

Abstract. Menéndez R, Méndez R, Latorre A, González-Jiménez P, Peces-Barba G, Molina M, et al. Residual pulmonary infiltrates, symptoms and diffusion impairment at 1-year after severe COVID-19 infection have different associated factors. *J Intern Med.* 2023;**294**:69–82.

Introduction. After severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia, patients may show lung sequelae on radiology and functional impairment at the 1-year follow-up. We aimed to describe the persistence of symptoms, radiological alterations, or reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) at 1-year follow-up in patients from the Spanish Registry RECOVID.

Methods. RECOVID collected symptom and radiological and functional lung tests data on hospitalized patients with coronavirus disease 2019 during the acute phase and at the 6- and 12-month follow-up visits.

Results. Of the 2500 enrolled survivors (90% admitted to the ward), 1874 had follow-up visits for up to a year. Of these, 42% continued to present with symptoms, 27% had radiological sequelae and 31% had reduced D_{LCO}. Independently associated factors included female sex, asthma and the requirement for invasive or non-invasive mechanical ventilation. Complete radiological resolution was 72.2% at 12 months; associated factors with incomplete recovery were age, male sex, oxygen or respiratory support, corticosteroids and an initial SpO_2/FiO_2 <450 or CURB-65 ≥2. Reduced D_{LCO} was observed in 31% of patients at 12 months; associated factors were older age, female sex, smoking habit, SpO_2/FiO_2 <450 and CURB-65 ≥2 and the requirement of respiratory support.At 12 months, a proportion of the asymptomatic patients showed reduced D_{LCO} (9.5%), radiological findings (25%) or both (11%).

Conclusions. The factors associated with symptom persistence, incomplete radiological resolution and

D_{LCO} <80% differed according to age, sex, comorbidities and respiratory support. The burden of symptoms, reduced D_{LCO} and incomplete radiological resolution were considerable in patients with SARS-CoV-2 pneumonia at the 1-year follow-up after hospitalisation.

Keywords: COVID-19, RECOVID, SARS-CoV-2, SEPAR

Abbreviations: CI, confidence intervals; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; D_{LCO}, diffusing capacity of the lung for carbon monoxide; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IRCU, intermediate respiratory care unit; NIMV, non-invasive mechanical ventilation; OR, odds ratio; RECOVID, Spanish COVID-19 Registry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen

Introduction

After an acute phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a considerable number of patients develop persistent symptoms and pulmonary sequelae [1–4]. Post discharge – mainly after severe episodes – these individuals maintain symptoms and present with alterations in radiographic images and reduced respiratory function [5, 6]. These observations have raised concerns, and as a result, created a strong interest in identifying the factors associated with the persistence of sequelae in episodes of SARS-CoV-2 infection with varying initial degrees of severity, including mild to moderate pneumonia, and extending beyond those admitted to the intensive care unit (ICU).

Impairment and reduction in pulmonary diffusion and residual radiological lung infiltrates are among the most frequently reported alterations, a finding consistent with the fact of lungs being the main target organs of SARS-CoV-2 pneumonia. However, these lung sequelae do not completely correlate with symptom persistence [7]. Patients with mild to moderate pneumonia can experience long-term functional symptoms as well [8]. Under these circumstances, identification of patients facing a higher risk of developing long coronavirus disease 2019 (COVID-19) and sequelae is pertinent [9]. Similarly, information regarding the different factors involved in persistence of symptoms, residual lung images and reduced diffusing capacity of the lung is lacking.

Specific persistent symptoms and pulmonary sequelae are important concerns. Direct repercussions may include a greater risk of exacerbation in patients with chronic diseases. As in patients with community-acquired pneumonia, there may be additional risks of new pulmonary diseases, cardiovascular events, readmission and late mortality [10, 11].

The Spanish COVID-19 Registry (RECOVID) conducted a 12-month follow-up of hospitalized episodes, gathering data on different determinants including host characteristics such as age, sex and comorbidities; initial episode severity, including oxygenation, inflammation and lymphocyte response; treatment setting, including conventional room, intermediate respiratory care unit (IRCU) or ICU; and treatment administered for respiratory failure. We hypothesized that lung sequelae and/or persistent symptoms may arise from different components or associated factors.

The objective of this study was to evaluate the factors associated with symptom persistence, chest radiographic infiltrates and functional deterioration in discharged survivors of COVID-19 at 6- and 12-month follow-ups. Separate analyses of the related factors would enable gauging of the potential impact of the following: (1) host characteristics, including age, sex, smoking habit and comorbidities; (2) initial severity per analytical parameter and CURB-65 scale; and (3) treatment administered for respiratory failure, comprising oxygen and requirements of respiratory support (invasive or non-invasive mechanical ventilation [IMV or NIMV]).

Patients and methods

Design

The Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) Spanish Registry for Hospitalised COVID-19 (RECOVID) is a registry of patients hospitalized in 2020 (March–November) from 49 Spanish hospitals with a confirmed reverse transcriptase–polymerase chain reaction diagnosis of SARS-CoV-2. Patients with COVID-19 registered in the pneumology service of each participating centre (stratum) were identified. To achieve a more representative cohort of patients, including different geographical areas, each centre recruited groups of 50 randomly selected patients before entering the data. Only three hospitals recruited consecutive patients. The study received approval from the Ethics Committee (Comité Ètic d'Investigació Clínica) of Hospital Sant Pau, Barcelona on 29 April 2020 and locally from the various participating centres.

An electronic database hosted on the web platform Xolomon was created to collect general characteristics and common data with specific sections designed in the form of sub-notebooks. In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and Organic Law 3/20 18 of 5 December, patient confidentiality and identity were protected using a code.

The study used a data monitor to review inconsistencies and missing data and prepare follow-up questions for each hospital. To deem each case valid, a minimum of 70% of completed data regarding the fundamental variables were necessary.

Database protocol, follow-up and outcome variables

The database protocol contained data related to general demographics, smoking habit (current or former smokers vs. those who had never smoked), comorbidities (chronic obstructive pulmonary disease [COPD], asthma, liver disease, chronic kidney disease, dementia, hypertension, heart disease and diabetes mellitus) and previous treatments. We considered three different periods for data collection: the acute phase at diagnosis and two follow-up visits post-discharge in survivors (at 6 and 12 months). Data recorded at the time of COVID-19 diagnosis and during hospital admission included initial symptoms, analytical data, comorbidities, radiological patterns and treatment. To assess initial severity, we used the CURB-65 scale, and for respiratory insufficiency, we collected data on peripheral blood oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratios. Moreover, we recorded the initial admission setting (conventional ward, IRCU or ICU) and the highest respiratory support required for respiratory insufficiency during the hospital stay (low-flow oxygen, reservoir, high-flow oxygen, continuous positive airway pressure [CPAP], NIMV or IMV).

The follow-up database comprised clinical check-up visit data at 6 and 12 months, including information related to symptoms, analytical variables and complementary explorations. Radiological studies (chest radiography or computed tomography [CT]) were performed depending on the indications and data of the patients. Depending on the judgement of the physician in charge, the diffusion capacity of the lungs for carbon monoxide (D_{LCO}) was tested to assess lung function.

Outcome variables: The primary aim of our study was to determine the complete or incomplete resolution of clinical symptoms, radiological infiltrates and D_{LCO} (<80% of predicted) after COVID-19 hospitalisation. Additionally, we evaluated mortality after discharge. The associated factors evaluated were grouped into three categories: (1) age, sex, smoking habit and comorbidities; (2) initial episode severity per CURB-65, SpO_2/FiO_2, lymphopenia and C-reactive protein (CRP) level >60 mg/L; and (3) highest respiratory support during hospital stay: no oxygen, low-flow oxygen, high-flow oxygen, CPAP, NIMV and IMV. Clinical resolution was defined as the complete resolution of symptoms, such as dyspnoea, fatigue, weakness, asthenia, myalgia, cough, headache, anosmia and ageusia. Furthermore, we evaluated the persistence of any alteration on chest radiographs and/or CT scans to determine the degree of resolution on the radiological images. Lung function tests, spirometry and D_{LCO} were considered abnormal if the results were <80% of the predicted values. We recorded mortality after discharge and the need for rehospitalisation during follow-up visits.

Statistical analysis

The nature of RECOVID – a registry created during the pandemic – entails the existence of lost data. Descriptive analyses of the qualitative and quantitative variables were performed without any imputation of missing data.

Categorical variables were expressed as percentages, whereas quantitative variables were expressed as either means ± standard deviation or medians with 25th and 75th percentiles. For univariate comparisons, we used the chi-square test and either the Mann–Whitney *U* or Kruskal–Wallis test. ANOVA was performed to compare the three populations. To explore the associated factors with outcome variables (persistence of symptoms, incomplete radiological resolution or D_{LCO} <80%), odds ratio (OR) 95% confidence intervals (CI) were calculated for each outcome variable.

Three logistic regression analyses were performed with each outcome variable as the dependent variable. Independent variables were grouped for each model: The first model included host characteristics, such as age, comorbidities and smoking habit; the second model, initial variables or severity as assessed per SpO_2/FiO_2, CURB-65 ≥2, lymphopenia (<724 cells/μL) and CRP >60 mg/L; and the third model, the highest respiratory support required during hospital stay stratified as no oxygen, low-flow oxygen, high-flow oxygen, NIMV (including CPAP) and IMV and corticosteroids.

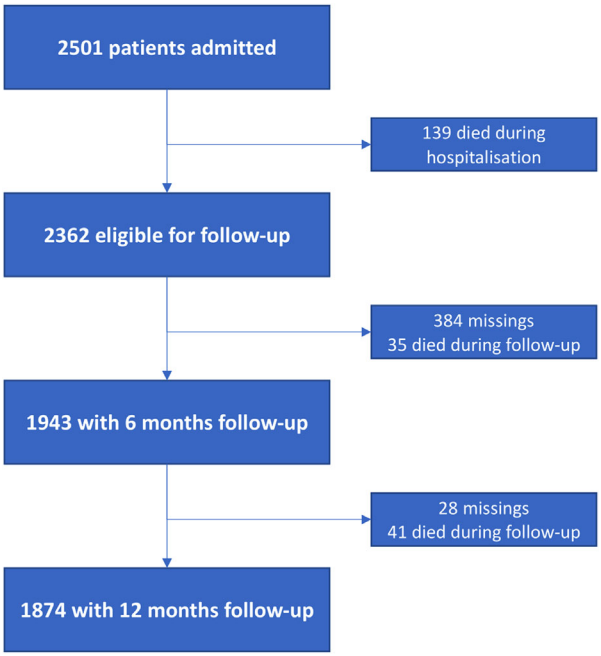

Fig. 1 *Flow chart.*

Results

General cohort characteristics

Of the initial 49 hospitals participating in the RECOVID Registry, 30 centres declined to participate in the follow-up sub-study (Fig. 1). Table 1 shows the baseline characteristics of 1943 patients at 6 months (available radiological data in 1413 patients and D_{LCO} in 748 patients) and 1874 patients at 12 months (available radiological data in 1285 patients and D_{LCO} in 755 patients) (Table 2). Of the patients who were followed up at 12 months, 227 were transferred to the ICU after being initially admitted to the ward or IRCU. At the 6-month follow-up, 35 of the 1978 patients who had survived an acute COVID-19 episode died, and 41 (of 1874 patients in total) died between the 6- and 12-month follow-ups.

Six-month follow-up: clinical features, imaging findings and lung function tests

In individuals without clinical resolution, dyspnoea and fatigue were the most frequently reported symptoms; these were more common in women, patients with asthma, and patients requiring respiratory support with high-flow nasal oxygen (HFNO), NIMV or IMV. Figure 2a depicts the ORs of the analysed factors. Chest radiography was performed in 1328 patients, and chest CT was performed in 764 patients. Complete resolution of the infiltrates was observed in 815 (57.6%) patients who underwent chest radiography and/or CT. In patients with incomplete resolution, radiological findings showed persistent infiltrates (29%), interstitial lung disease (3.6%) and newly diagnosed emphysema (1.9%). We observed significant differences in patients with incomplete resolution, who presented with a higher percentage of comorbidities (COPD and cardiac and arterial hypertension), ICU admission and a higher initial CURB-65 score. Regarding respiratory support, a larger proportion of patients treated with IMV, NIMV or HFNO showed incomplete resolution. Figure 2b shows the ORs of the analysed factors.

The lung function test D_{LCO} was performed in 784 patients, with abnormal results (<80% of predicted) in 384 patients (48.9%). The patients with reduced diffusing capacity of the lungs were older, had a higher percentage of smokers and had a higher prevalence of COPD and cardiac diseases. With respect to initial severity, these individuals had a higher CURB-65 score, presented with lymphopenia more frequently and received IMV, NIMV

Table 1. *Follow-up at 6 months*

	Incomplete radiological resolution			D_{LCO} <80%			Symptoms		
	No ($N = 815$)	Yes ($N = 598$)	*p*-Value	No ($N = 364$)	Yes ($N = 384$)	*p*-Value	No ($N = 777$)	Yes ($N = 907$)	*p*-Value
Age (years)									
≥80	56 (7.24%)	68 (11.37%)	<0.001	8 (2.20%)	14 (3.65%)	0.002	72 (9.27%)	70 (7.72%)	0.448
65–79	238 (29.20%)	287 (47.99%)		121 (33.24%)	172 (44.79%)		274 (35.26%)	334 (36.82%)	
<65	517 (63.44%)	242 (40.47%)		233 (64.01%)	197 (51.30%)		414 (53.29%)	501 (55.24%)	
Sex (male)	442 (54.23%)	379 (53.34%)	0.003	234 (64.29%)	221 (57.82%)	0.051	494 (63.58%)	501 (55.24%)	<0.001
Comorbidity									
Smoking	264 (32.39%)	220 (37.79%)	0.065	123 (33.79%)	159 (41.41%)	0.042	265 (34.11%)	337 (37.16%)	0.193
COPD	33 (4.05%)	56 (9.36%)	<0.001	7 (1.92%)	33 (8.59%)	<0.001	38 (4.89%)	61 (6.73%)	0.108
Asthma	76 (9.33%)	48 (8.03%)	0.412	27 (7.42%)	31 (8.07%)	0.731	48 (6.18%)	92 (10.14%)	0.003
Heart disease	71 (8.71%)	97 (16.22%)	<0.001	28 (7.69%)	51 (13.28%)	0.019	79 (10.17%)	113 (12.46%)	0.285
Diabetes	134 (16.44%)	102 (17.06%)	0.791	53 (14.56%)	71 (18.49%)	0.151	130 (16.73%)	150 (16.54%)	0.650
Hypertension	273 (33.50%)	255 (42.64%)	0.002	116 (31.87%)	157 (40.89%)	0.020	280 (36.04%)	360 (39.69%)	0.512
Renal disease	30 (3.68%)	23 (3.85%)	0.787	12 (3.30%)	16 (4.16%)	0.523	31 (3.99%)	36 (3.97%)	0.968
Initial admission									
Ward	736 (90.31%)	502 (83.95%)	<0.001	318 (87.36%)	318 (82.81%)	0.163	711 (91.51%)	735 (81.04%)	<0.001
IRCU	41 (5.03%)	20 (3.34%)		15 (4.12%)	19 (4.95%)		15 (1.93%)	67 (7.39%)	
ICU	38 (4.66%)	76 (12.71%)		30 (8.24%)	47 (12.24%)		51 (6.56%)	104 (11.47%)	
Absolute lymphocyte count <724 cells/μL	196 (24.05%)	170 (28.43%)	0.007	89 (24.45%)	134 (34.90%)	0.005	198 (25.48%)	260 (28.67%)	0.484
CRP ≥60 mg/L	282 (35.60%)	170 (28.43%)	0.206	123 (33.79%)	137 (35.68%)	0.620	274 (35.26%)	307 (33.85%)	0.195
SpO_2/FiO_2 <450	271 (33.25%)	220 (36.79%)	<0.001	121 (33.24%)	152 (39.58%)	0.020	270 (34.75%)	346 (38.15%)	0.107
CURB-65 ≥2	108 (13.25%)	132 (22.07%)	<0.001	45 (12.36%)	77 (20.05%)	0.002	117 (15.06%)	176 (19.40%)	0.071
Respiratory support									
No oxygen	218 (26.75%)	74 (12.38%)	<0.001	88 (24.18%)	52 (14.54%)	<0.001	179 (23.04%)	157 (17.31%)	<0.001
Nasal cannula/ Venturi mask	368 (45.15%)	226 (37.79%)		142 (39.01%)	115 (29.95%)		334 (42.99%)	330 (36.38%)	
Reservoir	46 (5.64%)	53 (8.86%)		31 (8.52%)	19 (4.95%)		52 (6.69%)	61 (6.73%)	
CPAP	7 (0.86%)	7 (1.17%)		2 (0.55%)	4 (1.04%)		4 (0.51%)	6 (0.66%)	
HFNO	61 (7.48%)	62 (10.37%)		26 (7.14%)	48 (12.50%)		65 (8.37%)	87 (9.59%)	
NIMV	17 (2.09%)	21 (3.51%)		19 (5.22%)	25 (6.50%)		12 (1.54%)	70 (7.72%)	
IMV	67 (8.22%)	103 (17.22%)		42 (11.54%)	102 (2.60%)		69 (8.88%)	167 (18.41%)	

Note: Baseline characteristics, initial severity and highest respiratory support during hospital stay. Data are presented as *N* (%).
Abbreviations: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, C-reactive protein; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IRCU, intermediate respiratory care unit; NIMV, non-invasive mechanical ventilation; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen ratio.

Table 2. *Follow-up at 12 months*

	Incomplete radiological resolution			D_{LCO} <80%			Symptoms		
	No ($N = 929$)	Yes ($N = 356$)	p-Value	No ($N = 520$)	Yes ($N = 235$)	p-Value	No ($N = 986$)	Yes ($N = 730$)	p-Value
Age (years)									
≥80	70 (7.53%)	33 (9.27%)	<0.001	10 (1.92%)	8 (3.40%)	0.002	92 (9.33%)	49 (6.72%)	0.120
65–79	280 (30.14%)	171 (48.03%)		175 (33.65%)	108 (45.96%)		354 (35.90%)	266 (36.44%)	
<65	574 (61.79%)	151 (42.42%)		332 (63.85%)	119 (50.64%)		524 (53.13%)	411 (56.30%)	
Sex (male)	511 (55.01%)	239 (67.13%)	<0.001	351 (67.50%)	144 (61.28%)	0.123	618 (62.67%)	421 (57.67%)	0.012
Comorbidity									
Smoking	299 (32.19%)	150 (42.13%)	0.001	182 (35.00%)	118 (50.21%)	<0.001	343 (34.79%)	265 (36.30%)	0.592
COPD	35 (4.05%)	36 (10.11%)	<0.001	10 (1.92%)	17 (7.23%)	<0.001	46 (4.67%)	47 (6.44%)	0.114
Asthma	82 (8.83%)	28 (7.87%)	0.582	31 (5.96%)	19 (8.08%)	0.276	63 (6.40%)	71 (9.73%)	0.012
Heart disease	86 (9.26%)	58 (16.29%)	0.002	37 (7.11%)	37 (15.75%)	0.001	104 (10.55%)	80 (10.96%)	0.747
Diabetes	150 (16.15%)	56 (15.73%)	0.691	82 (15.77%)	47 (20.00%)	0.151	161 (16.33%)	112 (15.34%)	0.319
Hypertension	329 (35.41%)	142 (39.89%)	0.507	178 (34.23%)	107 (45.53%)	0.040	359 (36.41%)	275 (37.67%)	0.506
Renal disease	31 (3.34%)	18 (5.06%)	0.143	14 (2.69%)	9 (3.83%)	0.422	39 (3.95%)	28 (3.84%)	0.855
Initial admission									
Ward	827 (89.02%)	304 (85.39%)	<0.001	428 (82.31%)	180 (76.60%)	0.025	888 (90.06%)	588 (80.55%)	<0.001
IRCU	51 (5.49%)	9 (2.53%)		37 (7.12%)	14 (5.96%)		34 (3.45%)	48 (6.58%)	
ICU	51 (5.49%)	43 (12.08%)		5 (10.38%)	41 (17.45%)		64 (6.49%)	93 (12.94%)	
Absolute lymphocyte count <724 cells/μL	233 (25.08%)	110 (30.90%)	0.026	152 (29.23%)	75 (31.91%)	0.499	263 (26.67%)	212 (29.04%)	0.843
CRP ≥60 mg/L	312 (33.58%)	108 (30.34%)	0.395	198 (38.08%)	88 (37.45%)	0.835	323 (32.76%)	295 (40.41%)	0.704
SpO_2/FiO_2 <450	317 (34.12%)	128 (35.96%)	<0.001	191 (36.73%)	96 (40.85%)	<0.001	333 (33.77%)	284 (38.90%)	0.875
CURB-65 ≥2	117 (12.59%)	86 (24.16%)	<0.001	67 (12.88%)	44 (18.72%)	0.017	153 (15.52%)	131 (17.95%)	0.609
Respiratory support									
No oxygen	240 (25.83%)	36 (10.11%)	<0.001	103 (19.81%)	18 (7.66%)	<0.001	216 (21.91%)	132 (18.08%)	<0.001
Nasal cannula/ Venturi mask	417 (44.87%)	142 (39.89%)		191 (36.73%)	64 (27.23%)		416 (42.19%)	265 (36.30%)	
Reservoir	56 (6.03%)	37 (10.39%)		47 (9.04%)	18 (7.66%)		65 (6.59%)	48 (6.58%)	
CPAP	7 (0.75%)	3 (0.84%)		1 (0.19%)	4 (1.70%)		7 (0.71%)	5 (0.68%)	
HFNO	78 (9.15%)	29 (8.15%)		48 (9.23%)	32 (13.62%)		87 (8.82%)	65 (8.90%)	
NIMV	23 (2.48%)	11 (3.09%)		43 (8.27%)	15 (6.38%)		34 (3.45%)	45 (6.16%)	
IMV	68 (7.32%)	80 (22.47%)		72 (13.85%)	73 (31.06%)		88 (8.92%)	152 (20.82%)	

Note: Baseline characteristics, initial severity and highest respiratory support during hospital stay. Data are presented as N (%).
Abbreviations: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, C-reactive protein; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IRCU, intermediate respiratory care unit; NIMV, non-invasive mechanical ventilation; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen ratio.

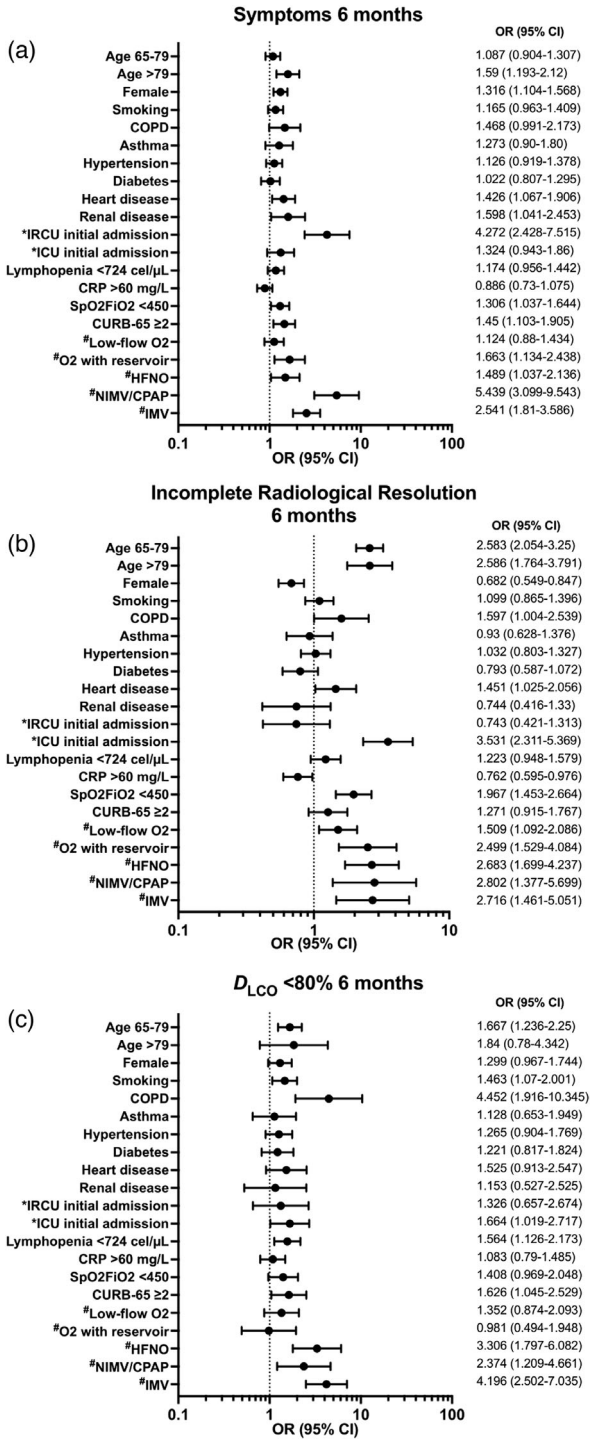

Fig. 2 *Univariate analysis at 6 months: (a) symptoms, (b) incomplete radiological resolution and (c) D_{LCO} <80%. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, C-reactive protein; D_{LCO}, diffusing capacity of the lung for carbon monoxide; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IRCU, intermediate respiratory care unit; NIMV, non-invasive mechanical ventilation; OR, odds ratio; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen.*

or HFNO more often. Figure 2c depicts the OR of the analysed factors.

Twelve-month follow-up: clinical features, imaging findings and lung function tests

Symptoms resolved in 57.4% of the survivors. In individuals without clinical resolution, dyspnoea and fatigue were the most frequently reported symptoms; these were more common in women, patients with asthma, and patients requiring respiratory support with HFNO, NIMV or IMV. Figure 3a depicts the ORs of the analysed factors. Complete resolution of the infiltrates on chest radiography or CT was seen in 912 (72.2%) patients. However, 356 patients showed incomplete resolution, presenting with persistent infiltrates (16.1%), interstitial lung disease (2.9%) and newly diagnosed emphysema. In the latter group of patients, the percentage of comorbidities (COPD or cardiac-related) was higher; 42.1% of these individuals smoked. This series of patients also exhibited the most severe initial episodes with a higher number of cases of ICU admission, CURB-65 ≥2 and requirement of respiratory support with IMV, NIMV or HFNO (Fig. 3b). Of the patients with incomplete radiological resolution, 65.5% received treatment with corticosteroids compared with 45.4% in the other group. Patients who required more respiratory support and/or ICU admission received more corticosteroids, indicating greater disease severity.

Of the 755 patients who underwent the lung function test D_{LCO}, 235 (31.1%) presented with abnormal results; those with reduced diffusing capacity of the lung were older, more often smokers/ex-smokers, and presented with COPD, cardiac diseases and arterial hypertension. With respect to initial severity, these individuals had a higher CURB-65 ≥2 and lower SpO_2/FiO_2 and more frequently received IMV and HFNO (Fig. 3c).

Figure 4 depicts the percentage of patients at the 12-month follow-up presenting with either incom-

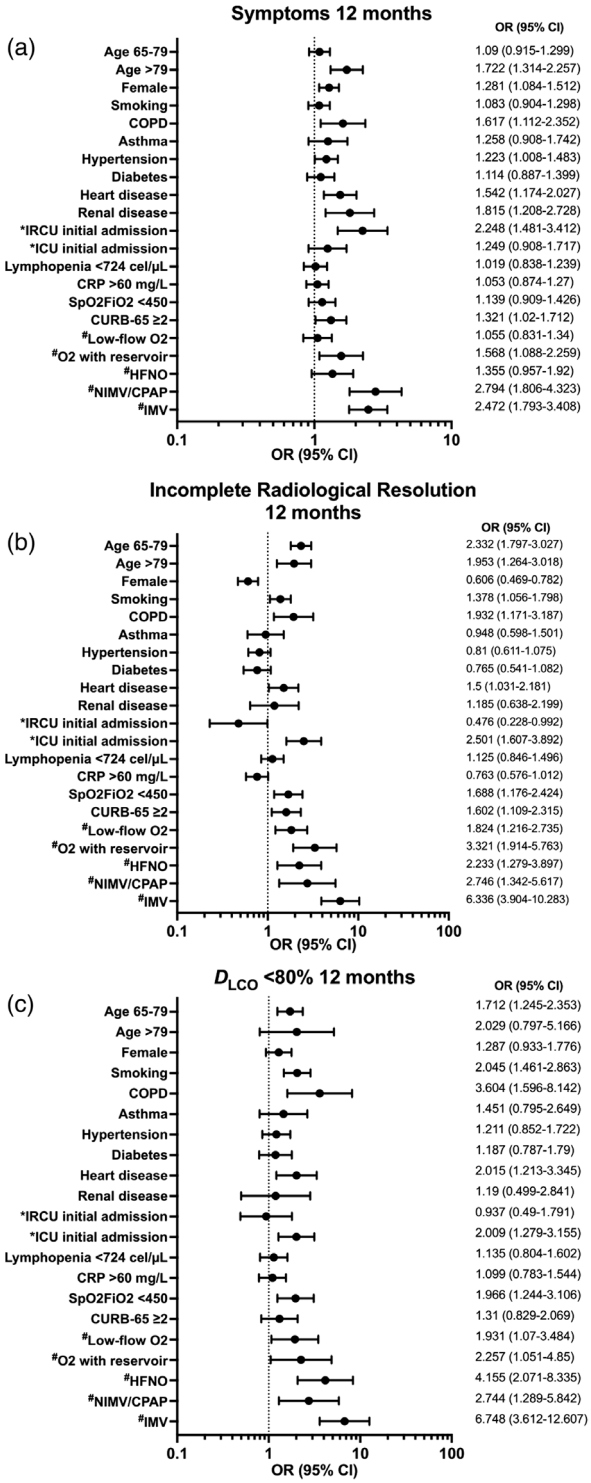

Fig. 3 *Univariate analysis at 12 months: (a) symptoms, (b) incomplete radiological resolution and (c) D_{LCO} <80%. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, C-reactive protein; D_{LCO}, diffusing capacity of the lung for carbon monoxide; HFNO, high-flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IRCU, intermediate respiratory care unit; NIMV, non-invasive mechanical ventilation; OR, odds ratio; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen.*

plete radiological resolution, reduced D_{LCO} or both (depending on the persistence of symptoms).

Multivariable analyses

Logistic regression analyses were performed for each independent variable at 12 months, including symptom persistence, incomplete radiological resolution and reduced D_{LCO} (Table 3). Three sets of independent variables were evaluated for each grouped independent variable as follows: (1) host characteristics, including age, sex, smoking habit and comorbidities; (2) initial severity as measured by the CURB-65 scale and some analytical parameters, such as lymphopenia, CRP >60 mg/L and SpO_2/FiO_2 <450, which were reported to be independently associated with outcomes [12]; and (3) respiratory failure treatment, including corticosteroids, oxygen treatment and respiratory support (low- and high-flow oxygen, CPAP, NIMV and IMV).

Discussion

The main findings of the present study were as follows: (1) At 12 months, 42.6% of hospitalized COVID-19 survivors presented with persistent symptoms, with dyspnoea and fatigue being the most frequent. Such persistence was more common in women, those with asthma, and those who required respiratory support with NIMV or IMV; (2) Complete resolution of lung infiltrates was noted in 72.2% of patients, and factors associated with persistence in lung imaging included older age, male sex, initial CURB-65 ≥2, SpO_2/FiO_2 and respiratory support; (3) Reduced diffusing capacity of the lung was present in 31.1% of patients and was associated with female sex, smoking habit, more severe initial episodes, corticosteroid treatment and a requirement of respiratory support; and (4) A proportion of asymptomatic patients still showed reduced D_{LCO} (9.5%), incomplete resolution on radiological images (25%) or both (11%) at 12 months.

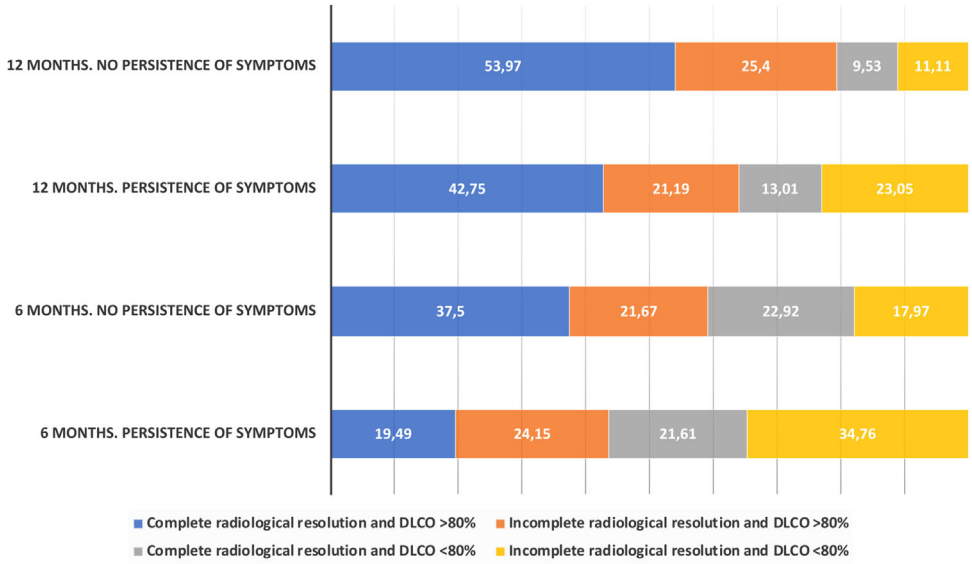

Fig. 4 *Percentage of patients at 12 months with incomplete radiological resolution, D_{LCO} <80%, or both, depending on the persistence of symptoms. D_{LCO}, diffusing capacity of the lung for carbon monoxide.*

The proportion of individuals with long COVID-19 symptoms ranges from 74.3% in ICU survivors to 10%–35% in outpatients [5, 13]. The persistence of symptoms remained high (42%) at 12 months in our cohort of hospitalized COVID-19 survivors (90% in the conventional ward), even though the 6-month follow-up showed recovery (63.9%) and most episodes were not critical. Our study revealed that a combination of factors was associated with the persistence of symptoms – female sex, the presence of asthma and the requirement for IMV during hospital stay were independent predictors, albeit not initial severity, as measured using the CURB-65 scale [14, 15].

Notably, 80% of the survivors with persistent dyspnoea and/or fatigue did not require any oxygen flow (18%) or low-flow nasal cannula (36%) [2, 16], representing cases of mild to moderate episodes [12]. Only 20.6% of the patients required mechanical ventilation. However, symptoms are subjective and may be related to structural abnormalities due to incomplete recovery, physical deconditioning or anxiety or post-traumatic stress [17]. Gamberini et al. reported persistent dyspnoea in ICU survivors, which was only partially explained by functional respiratory tests, highlighting different mechanisms or reasons [18]. In fact, we found that the resolution of radiographic infiltrates was complete, and lung diffusion was >80% in 42% of the patients with persistent symptoms at 12 months.

Complete resolution of lung infiltrates was observed in 42.3% of patients at 6 months and in 72.2% at 12 months, showing the capacity for progressive recovery. In a cohort of ICU-admitted patients, Caruso et al. reported higher persistence of lung infiltrate on 72% of CT scans at 6 months [19]; this figure is similar to those described in other studies on critical episodes of IMV or acute respiratory distress syndrome [19]. Factors associated with incomplete radiological resolution at 12 months were age, higher initial severity and the requirement for NIMV/IMV. With respect to comorbid conditions, those with COPD, cardiac diseases and arterial hypertension showed lower resolution at 6 months; however, this difference was not significant at 12 months, suggesting a slower resolution in this series of patients. Interestingly, among those with residual radiological findings, 42% were smokers (and former smokers) and received more corticosteroid treatment, representing more severe initial episodes, greater infiltrates and higher inflammation. SARS-CoV-2 pneumonia episodes with poorer SpO_2/FiO_2 and CURB-65 $\geq$2 were independently associated with incomplete resolution. The effect of respiratory support was found to be increasingly dependent on the complexity of the requirement; the OR

Table 3. *Multivariable analysis*

Incomplete radiological resolution			D_{LCO} <80%		Symptoms	
Demographics	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)
Age	<0.001	1.031 (1.019, 1.043)	0.017	1.022 (1.004, 1.040)	0.650	1.002 (0.993, 1.011)
Sex (female)	0.003	0.638 (0.474, 0.858)	0.047	1.464 (1.005, 2.132)	0.022	1.305 (1.039, 1.640)
Smoking	0.359	1.150 (0.853, 1.550)	0.010	1.621 (1.121, 2.343)	0.445	1.096 (0.866, 1.388)
COPD	0.069	1.661 (0.961, 2.870)	0.132	1.999 (0.812, 4.922)	0.179	1.371 (0.866, 2.172)
Asthma	0.512	1.177 (0.724, 1.912)	0.083	1.785 (0.927, 3.438)	0.042	1.497 (1.016, 2.207)
Heart disease	0.078	1.436 (0.960, 2.147)	0.059	1.702 (0.979, 2.957)	0.665	1.078 (0.766, 1.519)
Diabetes	0.108	0.737 (0.508, 1.069)	0.579	1.132 (0.730, 1.757)	0.251	0.845 (0.633, 1.127)
Arterial hypertension	0.057	0.744 (0.549, 1.009)	0.610	1.104 (0.754, 1.617)	0.596	1.066 (0.841, 1.352)
Renal disease	0.921	0.968 (0.507, 1.847)	0.863	0.923 (0.368, 2.312)	0.880	0.960 (0.568, 1.624)
Severity	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)
Absolute lymphocyte count <724 cells/μL	0.174	1.304 (0.889, 1.911)	0.268	1.298 (0.818, 2.058)	0.643	1.069 (0.806, 1.418)
CRP >60 mg/L	0.205	0.788 (0.545, 1.139)	0.686	0.911 (0.582, 1.428)	0.283	0.866 (0.666, 1.126)
SpO_2/FiO_2 <450	0.007	1.685 (1.151, 2.465)	0.012	1.873 (1.148, 3.053)	0.840	0.973 (0.742, 1.275)
CURB-65 ≥2	<0.001	2.484 (1.647, 3.746)	0.021	1.893 (1.099, 3.263)	0.303	1.183 (0.859, 1.630)
Treatment	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)
Corticosteroids	<0.001	1.692 (1.269, 2.257)	0.866	0.968 (0.663, 1.413)	0.857	1.021 (0.811, 1.287)
O_2 nasal cannula/Venturi mask[a]	0.002	1.874 (1.249, 2.812)	0.025	1.955 (1.088, 3.514)	0.997	0.999 (0.754, 1.324)
O_2 reservoir mask[a]	<0.001	3.122 (1.773, 5.496)	0.039	2.257 (1.041, 4.895)	0.637	1.117 (0.706, 1.766)
HFNO/CPAP/NIMV[a]	0.008	2.006 (1.199, 3.358)	0.001	3.144 (1.628, 6.075)	0.032	1.496 (1.035, 2.164)
IMV[a]	<0.001	5.543 (3.356, 9.157)	<0.001	6.058 (3.199, 11.475)	<0.001	2.894 (1.988, 4.213)

Note: Follow-up at 12 months.
Abbreviations: COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRP, C-reactive protein; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation; SpO_2/FiO_2, peripheral blood oxygen saturation/fraction of inspired oxygen ratio.
[a]Reference no oxygen.

increased gradually from low-flow to high-flow oxygen/NIMV to IMV (OR, 1.87; CI, 2.01–5.54). Luger et al. reported that age (>60 years), critical episodes and male sex were factors related to persistence on CT at 12 months [20]. In our study, CT scans were not performed in all patients; therefore, the presence of small lesions not visible on chest radiographs may have been underestimated. The systematic use of dual-energy CT scans could help identify further radiological sequelae [21].

Nevertheless,it is highly relevant that incomplete resolutions or abnormal radiological findings at 12 months were significant (10.1%), even in patients not requiring oxygen therapy or in those treated with low-flow nasal cannula (38.9%); these individuals represented almost 50% of the group with radiological sequelae. Charfeddine et al. postulated that the sequelae were related to microcirculation or endothelial dysfunction [22]. Méndez et al. reported sustained elevated levels of proadrenomedullin after discharge [23]. García-Hidalgo et al. reported that the diffusion capacity and radiological features of survivors of SARS-CoV-2-induced acute respiratory distress syndrome were associated with specific miRNA profiles [24, 25].

Regarding analytical signs of severity and severity measured by CURB-65 scale, patients with initial lymphopenia (<724 cells/μL), higher CRP and CURB-65 $\geq$2 showed a higher percentage of incomplete radiological resolution at 6 months than at 12 months.

Impairment of D_{LCO} (<80% of predicted) was found in 48.9% of the patients at 6 months, and the percentage decreased to 31% at 12 months. In another study on hospitalized patients, impairment of D_{LCO} was 21% [26] and approximately 35% in survivors of critical episodes [18]. Associated factors related to decreased function were older age (>65 years), some comorbid conditions, an initial higher severity (CURB-65 $\geq$2), lower SpO_2/FiO_2 and a more frequent requirement of high-flow oxygen or IMV. Interestingly, women who showed a significant reduction in D_{LCO} at 6 months (55% vs. 48% in men) presented with non-significant differences at 12 months (34% vs. 29%), indicating a possibly slower recovery [27]. Notably, smokers and former smokers constituted the highest percentage of patients with decreased D_{LCO} levels (53% at 6 months and 50% at 12 months), underpinning the crucial need for smoking cessation after discharge to promote lung recovery.

It is important to mention the proportion of patients with persistent symptoms but no apparent residual radiographic sequelae or functional impairment to explain the dyspnoea or fatigue. Several mechanisms have been proposed to explain the persistence of symptoms, including alterations in mitochondrial metabolism, muscle damage, immune dysregulation, autoimmunity, endothelial dysfunction, occult viral persistence and coagulation activation [28, 29]. Conversely, some patients present with objectively incomplete resolution, albeit with no clinical expression. Some omics and other physiopathological studies may disentangle the varying clinical trajectories and expression. Marshall et al. postulated the role of diverse mechanisms and clusters in long COVID-19 [9].

In terms of study limitations, our cohort did not include outpatients with SARS-CoV-2 pneumonia. Furthermore, studies performed during the pandemic represented a real-life registry with overloaded wards and were not systematically performed; furthermore, decisions regarding radiological or functional test explorations varied based on the physicians in charge and limitations on the different services involved. As a result, not all patients underwent CT, and chest radiographs may not have indicated minimal residual sequelae. Hence, the incidence of radiological sequelae may have exceeded that observed in the present study. Additionally, the absence of baseline D_{LCO} data did not allow for the formulation of clinical conclusions.

The strengths of our study include a large multicentre cohort design, with the inclusion of different mild to moderate episodes and a higher percentage of patients with SARS-CoV-2 pneumonia. This allowed us to obtain a more comprehensive picture of the long-term consequences of episodes of varying severity. In addition, we analysed the different types of respiratory support apart from IMV required for respiratory failure.

Although there was progressive recyovery in symptoms and diffusing capacity of the lung and infiltrate resolution between 6 and 12 months, the number of cases of lung sequelae and prolonged COVID-19 symptoms was considerable. Factors associated with lower recovery were initial severity, comorbid conditions and complex respiratory support with different components of clinical, radiological or functional sequelae. Considering the large number of patients admitted to our hospital, this finding represents a high burden of

symptoms and lung sequelae (radiological or reduced D_{LCO}). This new scenario, with unknown repercussions in patients with mild to moderate episodes that do not require invasive respiratory support, may lead to a reduced quality of life, an increase in health resources and vulnerability to subsequent lung diseases or complications. The implications are significant given that the number of episodes treated outside the ICU is much higher than those cases that are critical.

Author contributions

Conceptualization-lead; data curation-equal; formal analysis-equal; funding acquisition-lead; methodology-equal; supervision-lead; writing-original draft-lead: Rosario Menendez. *Data curation-lead; formal analysis-equal; methodology-equal; writing-review and editing-equal*: Raúl Méndez. *Data curation-equal; methodology-equal; writing-review and editing-equal*: Ana Latorre. *Data curation-equal; writing-review and editing-equal*: Paula Gonzalez-Jimenez, Maria Molina, Pedro España, Estela García, Angélica Consuegra-Vanegas, Ana Pando-Sandoval, Carolina Panadero, Juan Figueira-Gonçalves, Oriol Sibila, María Martínez-Pitarch, Nuria Toledo, Pilar Cejudo, Wanda Almonte-Batista, Abigail Macías-Paredes, Diana Badenes, Eli Pérez-Rodas, Javier Lázaro, Sarai Quirós, Rosa Cordovilla, Irene Cano-Pumarega and Antoni Torres. *Data curation-equal; funding acquisition-equal; writing-review and editing-equal*: Germán Peces-Barba. *Formal analysis-equal; writing-review and editing-equal*: David de la Rosa.

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Son Espases. Nuria Toledo Pons. Luisa Ramón Clar, Hospital Univ. Torrejón. Alba Esperanza Barrios, Hospital Univ. Virgen del Rocío. Pilar Cejudo Ramos. Cecilia López Ramírez. Mirella Gaboli, Hospital Univ. Virgen Macarena. Virginia Almadana Pacheco, Hospital Univ. Arnau de Vilanova. Ferran Eduard Barbé Illa. Anna Clara, Hospital Virgen de la Luz. Nuria Gutiérrez González, Hospital Virgen de la Victoria. Eva Cabrera César.

Conflict of interest statement

The authors declare no conflict of interests.

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Correspondence: Rosario Menéndez, Pneumology Department, Hospital Universitario y Politécnico La Fe, Avda. Fernando Abril Martorell 106, 46026 Valencia, Spain.
Email: rosmenend@gmail.com

