Original Article

Development of prognostic models to estimate the probability of lung injury one year after COVID-19-related hospitalization —a prospective study

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Background: Long-term effects of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection still under study. The objectives of this study were to identify persistent pulmonary lesions 1 year after coronavirus disease 2019 (COVID-19) hospitalization and assess whether it is possible to estimate the probability that a patient develops these complications in the future.

Methods: A prospective study of ≥18 years old patients hospitalized for SARS-COV-2 infection who develop persistent respiratory symptoms, lung function abnormalities or have radiological findings 6–8 weeks after hospital discharge. Logistic regression models were used to identify prognostic factors associated with a higher risk of developing respiratory problems. Models performance was assessed in terms of calibration and discrimination.

Results: A total of 233 patients [median age 66 years [interquartile range (IQR): 56, 74]; 138 (59.2%) male] were categorized into two groups based on whether they stayed in the critical care unit (79 cases) or not (154). At the end of follow-up, 179 patients (76.8%) developed persistent respiratory symptoms, and 22 patients (9.4%) showed radiological fibrotic lesions with pulmonary function abnormalities (post-COVID-19 fibrotic pulmonary lesions). Our prognostic models created to predict persistent respiratory symptoms [post-COVID-19 functional status at initial visit (the higher the score, the higher the risk), and history of bronchial asthma] and post-COVID-19 fibrotic pulmonary lesions [female; FVC% (the higher the FVC%, the lower the probability); and critical care unit stay] one year after infection showed good (AUC 0.857; 95% CI: 0.799–0.915) and excellent performance (AUC 0.901; 95% CI: 0.837–0.964), respectively.

Conclusions: Constructed models show good performance in identifying patients at risk of developing lung injury one year after COVID-19-related hospitalization.

Keywords: Post-acute coronavirus disease 2019 syndrome (post-acute COVID-19 syndrome); respiratory

symptoms; radiological findings; fibrotic pulmonary lesions; respiratory functional test; clinical prediction models

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Introduction

The first cases of pneumonia of unknown origin were reported in Wuhan, Hubei, China, in December 2019 (1). In January 2020, a novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] was isolated in these patients. The disease caused by this virus was named coronavirus disease 2019 (COVID-19) (2). In October 2022, the World Health Organization (WHO) had confirmed near 620 million cases and 6.5 million deaths (3). This disease, associated with high hospitalization rates (4), represents a global threat to public health even in developed countries.

COVID-19 is associated with a wide variety of symptoms, ranging from asymptomatic infection to life-threatening complications such as acute respiratory distress (ARDS), multi-organic failure, and death (1,5-7). Some therapies (8) seem to improve prognosis, and the majority of patients recover from the disease. Other patients, however, are at a higher risk of developing severe pulmonary complications with potential long-term effects (9,10). Such is the case of patients with an advanced age and comorbidities (6). Apart from long-term health complications, patients may also experience a wide variety of symptoms (physical and mental) that may persist and impair their quality of life. These persistent symptoms constitute the so-called post-acute COVID-19 syndrome (11,12). Patients with post-acute COVID-19 syndrome need long-term follow-up. Considering their acquired disability, declined quality of life, and increased use of healthcare resources use, specific health programs should be designed for these patients.

Although the prevalence of this syndrome is not high, massive SARS-COV-2 infection may pose a serious public health problem, due to the intensive use of health resources that this syndrome involves. In the light of the inconsistent evidence currently available, it is necessary to develop tools that identify patients at a higher risk of developing lung injury after SARS-CoV-2 hospitalization. The use of these tools would facilitate the development of specific integral follow-up programs from which these patients would benefit.

The objectives of this study were to identify the persistent pulmonary lesions that long-stay patients developed one year after SARS-COV-2 infection and investigate whether it is possible to estimate the probability to develop persistent respiratory symptoms. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1565/rc).

Methods

Study design

This prospective study was conducted in a 1,000-bed tertiary university hospital serving a population of 450,000. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Santiago-Lugo (Registration No. 2020/305) and informed consent was taken from all the patients.

Following *American Thoracic Society* and *European Respiratory Society* (13) recommendations, the regional health system of Galicia *(Servicio Gallego de Salud)* promoted the creation of multidisciplinary post-COVID-19 units for the follow-up of patients who have been hospitalized for SARS-CoV-2 infection (14). In our center, post-COVID-19 Unit was composed of specialists from Internal Medicine and Pulmonology Departments.

Procedures

Sample collection for the diagnosis of COVID-19 was performed in accordance with WHO protocol (15). Criteria for hospitalization were the presence of pulmonary opacities on thoracic radiography, having a SaO_2 <95% and a respiratory rate >25/minute, and/or being a high-risk patient (subjects >60 years with comorbidities). In patients with mobility problems, diagnosis of pneumonia was established by lung ultrasound (16). Diagnosis of ARDS was established in accordance with Berlin definition (17).

All adult patients (≥18 years) hospitalized for SARS-

CoV-2 infection were by Internal Medicine Unit. In the initial follow-up visit, complementary studies were performed (including, in all cases, a postero-anterior and lateral chest X-ray) to exclude the presence of subacute processes/lesions related to COVID-19. Patients were referred for pulmonology follow-up in the presence of exertional dyspnea, baseline SaO_2 ≤95% (unrelated to a previous known disease), pathological findings on chest X-ray (conducted at 6–8 weeks after discharge and not present prior to COVID-19), pulmonary embolism during hospitalization and/or discharge with home oxygen therapy.

Pulmonology department prepared a medical record and conducted the following studies: detailed physical examination, chest radiograph (2 projections), blood test (including immunoglobulins and alpha 1 antitrypsin), spirometry (with bronchodilator and gas diffusion test) and baseline SaO_2/arterial blood gas analysis. If all studies were unremarkable, the patient was discharged. If the patient exhibited abnormalities, depending on the type of finding, a thoracic high-resolution CT scan (HRCT) (CT angiography upon suspicion of pulmonary embolism) was performed. Six-minute walking test (6MWT) and/or a transthoracic echocardiogram were carried out to detect potential right ventricular dysfunction or pulmonary hypertension. All patients with abnormalities were follow-up. Patients younger than 18 years and those who declined to participate were excluded.

Demographic, clinical, radiological, and laboratory data, along with respiratory function test results were collected. Functional status was assessed using post-COVID-19 functional status scale (PCFS) (18). Spirometry and diffusion tests were carried out in accordance with current guidelines (19,20). Variables were expressed as percentages with respect to reference values (21,22). Reference values for 6MWT were obtained from standard guidelines (23). Findings on thoracic HRCT were classified in accordance with current recommendations (24). Diagnosis of a post-COVID-19 fibrotic pulmonary lesion was established based on the presence of a fibrotic lesions on thoracic HRCT with functional impact [forced vital capacity (FVC)% and/or diffusion capacity for carbon monoxide (DLCO)% <80% of the reference value], regardless of the presence or absence of clinical symptoms.

Statistical analysis

Continuous variables were described as median values and interquartile ranges. Categorical values were expressed as absolute and relative frequencies. Differences between baseline values and 1-year values were assessed using Wilcoxon test for continuous variables and the McNemar test for categorical values. Differences between the patients who stayed in a conventional hospitalization ward and those who were admitted to the critical care unit were assessed using the Mann-Whitney *U* test (continuous variables) and Chi-squared test (categorical variables). Logistic regression was used to estimate the probability of developing complications one year after discharge. Two prognostic models were built: one for persistent respiratory symptoms, and another for post-COVID-19 fibrotic pulmonary lesions. Based on a model containing all potential covariates, the variable with the least significant P value was removed and tested using the likelihood-ratio test until all variables left in the model (at alpha =0.05) contributed significantly to the model. Results are presented as odds ratio (OR) with 95% confidence intervals (CIs). Model performance was assessed in terms of calibration and discrimination. Calibration was assessed using the Brier score (25). The receiver operating characteristics (ROC) curves [and the corresponding area under the ROC curve (AUC)] were calculated to test discrimination. To correct optimism, internal validation was performed for each model using the bootstrap procedure with 1,000 bootstrapped samples (25). Analyses were carried out using pROC (26) and rms (27) software packages and ggplot plots (28), all available on the R free software (29). The analysis conforms to the reporting standards of TRIPOD (30).

Results

Between March 1, 2020, and July 31, 2021, a total of 22,749 patients received a diagnosis of COVID-19, of whom 2,053 needed hospitalization. *Figure 1* shows the inclusion flowchart. Patients characteristics are shown in *Table 1*. Of the 275 patients included, 42 were excluded in the initial pulmonology visit as they only had mild clinical symptoms and complementary studies were unremarkable. Follow-up of the remainder 233 patients was performed. Median age was 66 years [interquartile range (IQR): 56, 74], and 138 (59.2%) were male. Statistically significant differences were observed between the patients who stayed in a conventional hospitalization ward and those who stayed in CCU. The patients who stayed in the CCU were generally male, exhibited more extensive radiological lesions, had a longer mean stay, needed more frequently high-flow nasal cannulae, non-invasive ventilation (NIV), orotracheal

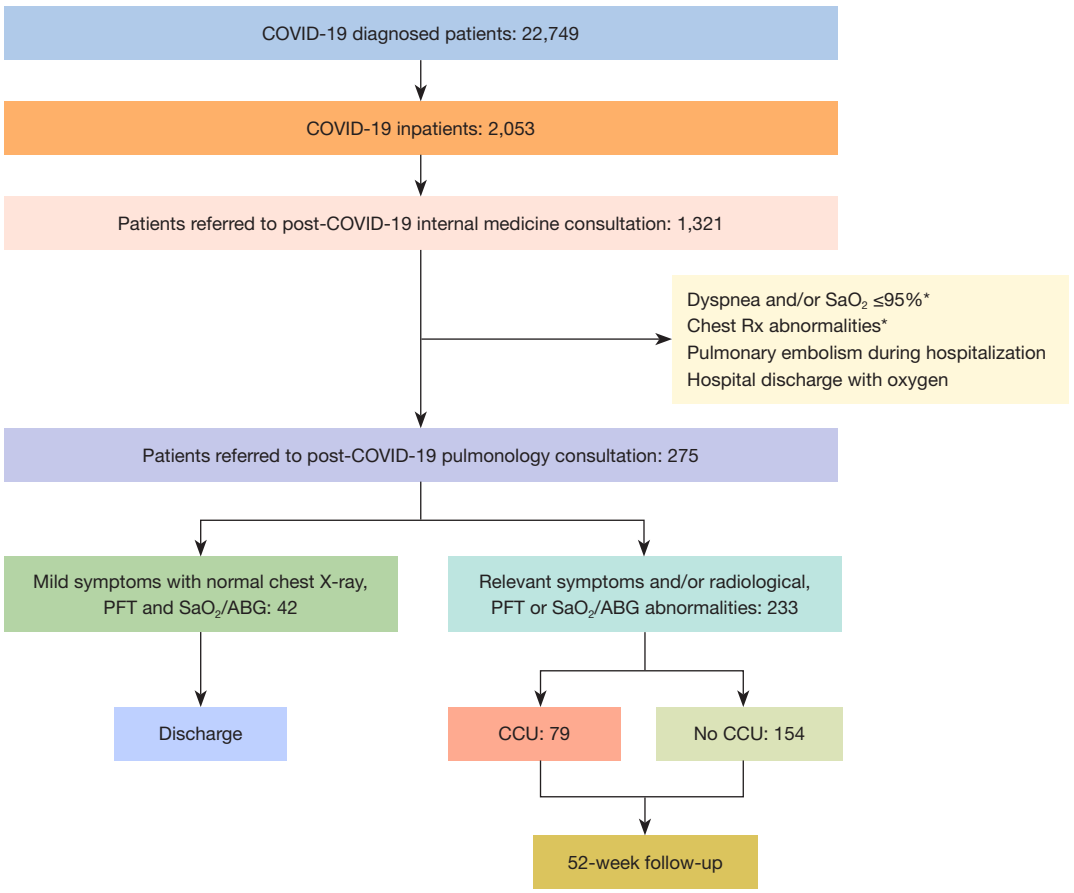

Figure 1 Action algorithm based on study design. *, no previous respiratory disease. COVID-19, coronavirus disease 2019; X-ray, radiography; PFT, pulmonary function testing; ABG, arterial blood gas analysis; CCU, critical care unit.

Table 1 Characteristics of patients during hospital admission

Characteristics	Total	Hospitalization ward	CCU	P
Total, n (%)	233	154 (66.1)	79 (33.9)	
Men, n (%)	138 (59.2)	83 (53.9)	55 (69.6)	0.029
Age (years), mean (IQR)	66 (56, 74)	64 (56, 75)	68 (56.5, 73)	0.073
Smoking (former or current), n (%)	119 (51.1)	77 (50.0)	42 (53.2)	0.749
Coexisting conditions, n (%)				
Hypertension	119 (51.1)	74 (48.1)	45 (57.0)	0.25
Diabetes	54 (23.2)	32 (20.8)	22 (27.9)	0.295
COPD	22 (9.4)	16 (10.4)	6 (7.6)	0.649
Asthma	26 (11.2)	17 (11.0)	9 (11.4)	1
ILD	13 (5.6)	12 (7.8)	1 (1.3)	0.065
OSA	53 (22.8)	30 (19.5)	23 (29.1)	0.101

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	Hospitalization ward	CCU	p
Radiological data				<0.001
Normal	23 (9.9)	22 (14.3)	1 (1.3)	
One lobe	4 (1.7)	4 (2.6)	0 (0.0)	
Two lobes	197 (84.6)	119 (77.3)	78 (98.7)	
Bilateral	7 (3.0)	7 (4.6)	0 (0.0)	
Analytical parameters, mean (IQR)				
Peak CRP, mg/L‡	11.2 [5.1, 17.1]	8.38 [3.6, 14]	16.73 [11.2, 23.41]	<0.001
Peak D-dimer, ng/mL‡	1,364 [732.5, 4,002.5]	981 [594.3, 1,574]	3,918 [1,835.5, 13,266]	<0.001
Peak IL-6 pg/mL‡	40.5 [14, 197]	24 [9, 43]	281 [93, 1,254.5]	<0.001
Peak LDH, IU/L‡	574 [422.5, 724]	545 [403, 668.8]	669 [487.5, 842.5]	<0.001
Mean length of stay (days), mean (IQR)	13 (7, 24)	9 (6, 14.8)	31 (20, 60.5)	<0.001
HFNC, n (%)	56 (68.3)	3 (1.9)	53 (67.1)	<0.001
NIV, n (%)	17 (21.5)	0 (0.0)	17 (21.5)	1
OTI, n (%)	54 (68.4)	0 (0.0)	54 (68.4)	1
Tracheotomy, n (%)	18 (22.8)	0 (0.0)	18 (22.8)	1
ARDS, n (%)	131 (56.2)	53 (34.4)	78 (98.7)	<0.001
Mild	46 (35.4)	41 (77.4)	5 (6.5)	
Moderate	28 (21.5)	9 (17.0)	19 (24.7)	
Severe	56 (43.1)	3 (5.7)	53 (68.8)	
Dyspnea, n (%)				0.425
0	12 (5.2)	10 (6.5)	2 (2.5)	
1	108 (46.4)	72 (46.8)	36 (45.6)	
≥2	113 (48.5)	72 (46.8)	41 (51.9)	
PCFS scale, n (%)				<0.001
0	57 (24.5)	43 (27.9)	14 (17.7)	
1	65 (27.9)	38 (24.7)	27 (34.2)	
2	84 (36.1)	63 (40.9)	21 (26.6)	
≥3	27 (11.6)	10 (6.5)	17 (21.5)	

‡, maximum concentration during admission. CCU, critical care unit; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; OSA, obstructive sleep apnea; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; HFNC, high flow nasal cannulas; NIV, noninvasive ventilation; OTI, orotracheal intubation; ARDS, acute respiratory distress syndrome; PCFS, post-COVID-19 functional status.

intubation (OTI) and/or a tracheostomy. In addition, these cases generally developed ADRS and obtained higher scores on PCFS scale. Finally, CCU patients showed higher average of peak values of inflammatory markers.

Table 2 shows the level of dyspnea, radiological findings, respiratory function test results, and PCFS score in initial visit and at 52 weeks by type of hospitalization unit (conventional hospitalization ward *vs.* CCU). At the end of

Table 2 Clinical, radiological, pulmonary function and functional status at first consultation and at 52 weeks of follow-up

Characteristics	Initial			At 52 weeks			P		
	Total	Ward	CCU	Total	Ward	CCU	Total	Ward	CCU
Clinical									
Dyspnea (mMRC) , n (%)							<0.001	<0.001	0.004
0	12 (5.2)	10 (6.5)	2 (2.5)	87 (37.3)	55 (35.7)	32 (40.5)			
1	108 (46.4)	72 (46.8)	36 (45.6)	106 (45.5)	73 (47.4)	33 (41.8)			
≥2	113 (48.5)	72 (46.8)	41 (51.9)	40 (17.2)	26 (16.9)	14 (17.7)			
Radiological findings, n (%)									
Imaging test	X-ray	X-ray	X-ray	HRCT	HRCT	HRCT			
No consolidation	170 (73.0)	12 (83.8)	41 (51.9)						
Persistence of pulmonary lesions	63 (27.0)	25 (16.2)	38 (48.1)						
Ground glass opacities				33 (14.2)	10 (21.4)	23 (29.1)			
Unspecific radiological findings				24 (10.3)	10 (21.4)	14 (17.7)			
Predominantly fibrotic				27 (11.6)	6 (3.9)	21 (26.6)			
Respiratory function test, mean (IQR)									
FEV_1 (%)	98.5 [80.7, 115]	100.5 [79, 117.2]	97 [80, 111.2]	101 [83.5, 118]	101.5 [82, 118]	101 [86.2, 113.2]	<0.001	0.039	0.002
FVC (%)	99.5 [84, 117]	108 [91, 117]	97 [80, 111.2]	104 [88.7, 115.2]	106 [89.7, 120.2]	101 [86.2, 113.2]	<0.001	0.044	0.002
DLCO	69 [59, 82]	68 [54, 81]	74 [62.5, 82]	77 [63, 87.5]	74 [63, 86]	81.50 [69, 87.7]	<0.001	<0.001	<0.001
DLCO/AV	93 [77.5, 103]	86.50 [71.7, 96.5]	96 [87.5, 105]	99 [84.5, 111]	89 [79, 109]	102.50 [95.5, 113.7]	<0.001	0.001	<0.001
Functional status									
PCFS scale, n (%)							<0.001	<0.001	<0.001
0	57 (24.5)	43 (27.9)	14 (17.7)	115 (49.4)	73 (47.4)	42 (53.2)			
1	65 (27.9)	38 (24.7)	27 (34.2)	72 (30.9)	52 (33.8)	20 (25.3)			
2	84 (36.1)	63 (40.9)	21 (26.6)	30 (12.9)	21 (13.6)	9 (11.4)			
≥3	27 (11.6)	10 (6.5)	17 (21.5)	16 (6.9)	8 (5.2)	8 (10.1)			

CCU, critical care unit; mMRC, modified Medical Research Council dyspnea scale; HRCT, high-resolution computed tomography; IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; AV, alveolar volume; PCFS, Post-COVID-19 functional status; X-Ray, chest radiography.

follow-up, variables had improved significantly (P<0.001). Radiological findings were not compared, as chest radiography was performed in the initial visit, whereas a HRCT was performed in the final visit. *Figure 2A-2C* show differences between the two visits in terms of FEV1%, FVC% and DLCO% (median and IQR), and course of the patients between visits. PCFS scores at the initial visit and at week 52 are shown in *Figure 2D*.

Table 3 detail the demographic and clinical characteristics of patients with respiratory symptoms (dyspnea ≥2 on the mMRC), and post-COVID-19 fibrotic pulmonary lesions (dominantly fibrotic lesions with deterioration of respiratory

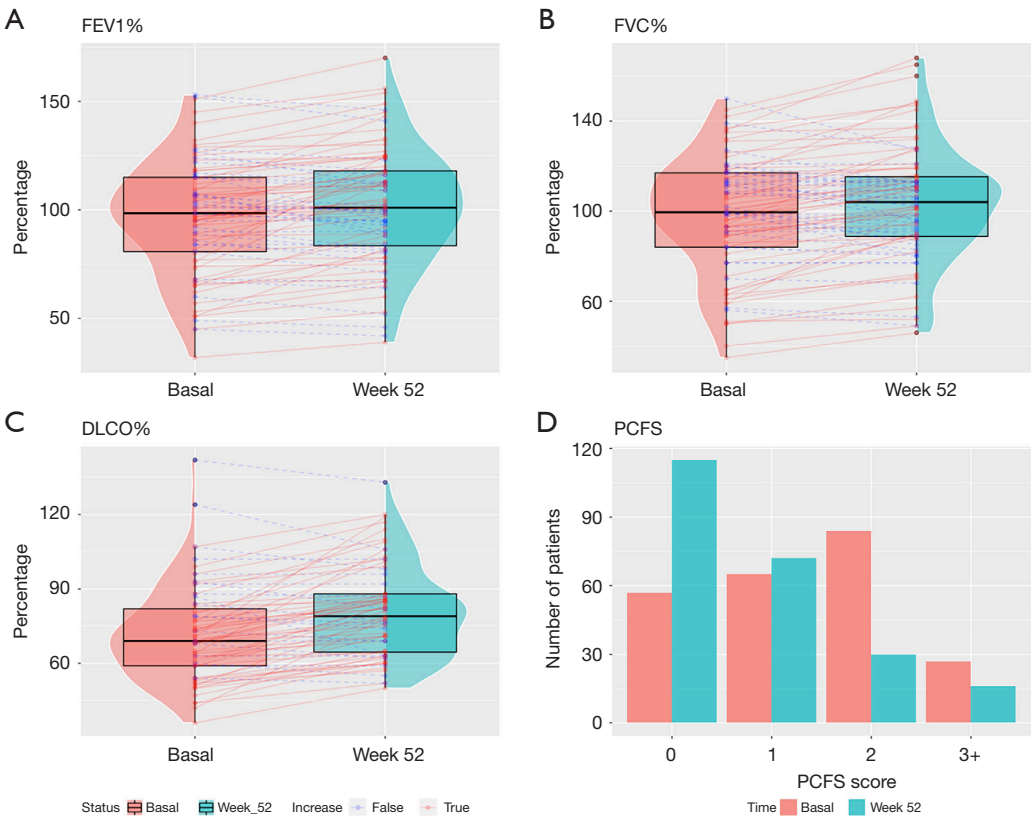

Figure 2 Temporary changes in the percentage of forced expiratory volume in 1 second (A), forced vital capacity (B), diffusion capacity (C), with respect to their theoretical value, and number of patients that obtained the same score on the post-COVID-19 functional scale (D) at baseline and at week 52. Data are expressed as median values and interquartile ranges. Solid red lines represent patients who experienced an increase in the percentage of that specific parameter, whereas dotted blue lines represent the patients who experienced a worsening. COVID-19, coronavirus disease 2019; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; PCFS, post-COVID-19 functional status scale.

function) at 52 weeks, according to whether they stayed in a conventional hospitalization ward or in CCU. A total of 179 patients (76.8%) exhibited respiratory symptoms (including dyspnea ≥1 on the mMRC); 46 (25.7%) had a PCFS ≥2; 33 (14.2%) had ground-glass opacities (GGO); 24 (10.3%) had indeterminate radiological lesions; 27 (11.6%) showed fibrotic lesions on HRCT; and 57 (58.2%) had some pulmonary function parameter <80% of the predicted value. Twenty-two patients (9.4%) presented fibrotic lesions on HRCT and impairment of pulmonary function (FVC% and/or DLCO% <80% of its predicted value); therefore, they were considered to have post-COVID-19 fibrotic pulmonary lesions. CCU admission was not associated with a higher risk of developing persistent pulmonary lesions, except for fibrotic lesions on HRCT and post-COVID-19 pulmonary fibrotic lesions (P<0.001) (*Table 3*).

Following prognostic factors were included in Model 1: PCFS at initial visit (the higher the score, the higher the risk) and previous bronchial asthma. Model 2 for post-COVID-19 fibrotic pulmonary lesions included the following prognostic factors: being female; FVC% at the initial visit (the lower the FVC%, the higher the probability); and CCU stay (*Table 4*). Models 1 and 2 showed a good and excellent power of discrimination, respectively [AUC 0.857 (95% CI: 0.799, 0.915)] (*Figure 3A*) and [AUC 0.901 (95% CI: 0.837 0.964)] (*Figure 3B*), respectively. Their power of discrimination remained the same after adjustment for optimism bias using 1,000 bootstrap samples (AUC =0.844 for Model 1, and AUC =0.884 for Model 2). Calibration of the two models was excellent (Brier score of Model 1=0.118 and Model 2=0.060).

Table 3 Patients with respiratory symptoms and post-COVID-19 fibrotic pulmonary lesions at 52 weeks of follow-up

Characteristics	Total	Hospitalization ward	CCU	P
Demographic characteristics				
Total, n (%)	179	120 (67.0)	59 (33.0)	0.623
Male, n (%)	98 (54.8)	60 (50.0)	38 (64.4)	0.079
Age (years) (mean, IQR)	66 (55.5, 75)	64.5 (55.8, 76)	68 (55.5, 72.5)	0.813
Clinical characteristics, n (%)				
Dyspnea (mMRC ≥2)	40 (22.3)	26 (21.7)	14 (23.7)	0.815
Cough	64 (35.8)	39 (32.5)	25 (42.4)	0.245
Asthenia	28 (15.6)	22 (18.3)	6 (10.2)	0.192
Post-COVID-19 fibrotic pulmonary lesions, n (%)				
Dominantly fibrotic lesions with deterioration of respiratory function	22 (9.4)	4 (2.6)	18 (22.8)	<0.001

COVID-19, coronavirus disease 2019; CCU, critical care unit; IQR, interquartile range; mMRC, modified Medical Research Council dyspnea scale.

Table 4 Prognostic models for persistent symptoms and fibrotic lesions one year after SARS-CoV-2 infection

Prognostic model	OR	95% CI	P
Persistent symptoms			
Age	0.988	0.956–1.020	0.451
Gender (male)	0.604	0.267–1.369	0.225
PCFS			
0 (reference)	—	—	
1	4.349	1.881–10.054	<0.001
≥2	57.881	15.270–219.397	<0.001
Asthma	6.788	1.342–34.342	0.019
Post-COVID-19 fibrotic pulmonary lesions			
Age	1.01	0.968–1.055	0.633
Gender (male)	0.286	0.083–0.988	0.046
FVC%	0.94	0.915–0.966	<0.001
CCU	14.413	3.810–54.525	<0.001

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; 95% CI, 95% confidence interval; PCFS, post-COVID-19 functional status; FVC, forced vital capacity; CCU, critical care unit.

Figure 4 shows clinical scores for both models. The total score indicates the estimated individual risk of having post-COVID lung complications. For instance, a patient with a PCFS score of 1 (34 points) and asthma (49 points), obtains a total score of 83 points, which corresponds to a 95% probability of developing persistent respiratory symptoms. This model has a specificity of 0.94, with a positive predictive value of 0.97. Regarding post-COVID-19 pulmonary fibrotic lesions, being female (13 points); an initial FVC% of 80% (67 points); and no CCU admission (0 points), yields a total score of 80 points, which corresponds to a 10% probability of developing pulmonary fibrotic lesions.

Discussion

The results of this study reveal that a high proportion of patients hospitalized for COVID-19 have a risk of experiencing persistent respiratory symptoms, impaired pulmonary function, changes in pulmonary functional status or fibrotic pulmonary lesions on radiological studies a year after infection. Prognostic factors of persistent respiratory symptoms after COVID-19 include PCFS at the initial

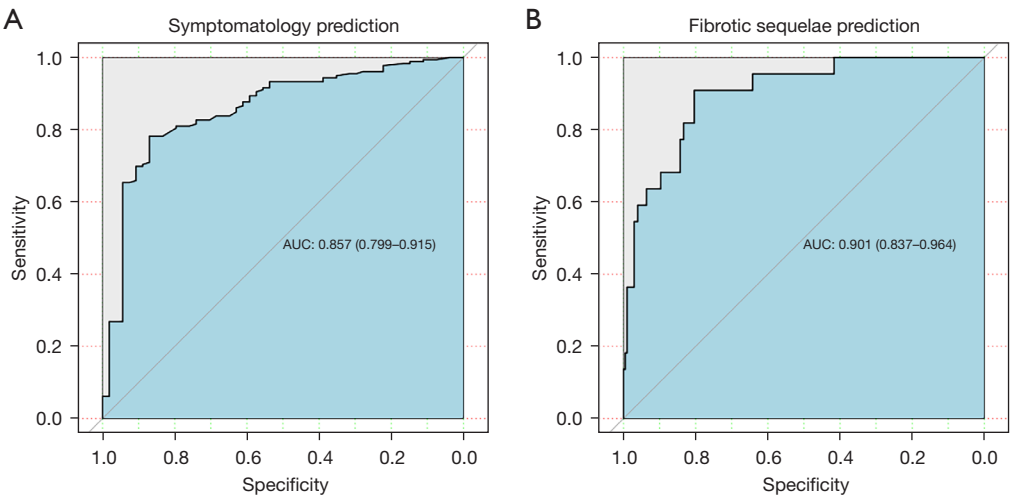

Figure 3 ROC curve and corresponding Area under the curve [AUC (95% confidence interval)] for: (A) risk for persistent symptoms (post-COVID functional status and history of asthma); (B) risk for pulmonary fibrotic changes (forced vital capacity and hospitalization in critical care unit). ROC, receiver operating characteristic; AUC, area under the area; COVID, coronavirus disease.

Prognostic model for persistent symptoms									
PCFS	Score	Asthma	Score	Total score	Probability (%)	SE (%)	SP (%)	PPV (%)	NPV (%)
0	0	0	0	0	35	77	23	50	50
1	34	1	49	34	70	67	93	97	46
≥2	100			83	95	6	94	97	42
				100	97	7	98	92	24
				149	99	7	98	92	24

Prognostic model for post-COVID-19 fibrotic pulmonary lesions											
Gender	Score	FVC%	Score	CCU	Score	Total score	Probability (%)	SE (%)	SP (%)	PPV (%)	NPV (%)
Female	13	30	100	No	0	80	10	91	79	32	99
Male	0	60	80	Yes	28	89	20	64	92	45	96
		80	67			94	30	55	97	60	95
		100	53			99	40	36	97	61	93
		110	47			103	50	36	98	62	93
		130	33			108	60	32	99	75	93
						112	70	18	99	77	92
						118	80	14	100	100	91
						127	90	0	100	100	90

Figure 4 Clinical scores for both models. PCFS, post-COVID-19 functional status; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; COVID-19, coronavirus disease 2019; FVC, forced vital capacity; CCU, critical care unit.

visit and history of bronchial asthma. Sex, percentage of FVC with respect to initial visit and CCU stay are prognostic factors of post-COVID-19 fibrotic pulmonary lesions.

As many as 76.8% of patients [179] had dyspnea (≥1 of mMRC), cough or asthenia a year after SARS-CoV-2 infection, which is consistent with the results of other series (31,32). These symptoms are not specific of COVID-19 (31) and, as demonstrated by our results, usually improve over time (33). The reasons why symptoms persist are still unclear. Potentially associated factors include damage to the affected organs, persistent low-grade inflammation, endothelial dysfunction or the presence of viral reservoirs (34) promoted by severe psychological trauma (specially in patients who stayed in the CCU) (35). Thus, post-COVID-19 dyspnea has been associated with hyperventilation syndrome, a form of dysfunctional breathing (36,37). This complication usually occurs in

absence of organic respiratory disease and affects patients quality of life. Cough has been suggested to be secondary to activation of vagal sensory nerves (38,39).

PCFS is a recently developed score for assessing functional limitations and status in COVID-19 survivors after hospitalization (18,40). In our study, PCFS improved significantly over time [median 2, (IQR: 1, 2) in the initial visit *vs.* 0 (IQR: 0, 1) in the final visit; P<0.001). Hence, in the initial visit, 47% of patients [111] had a PCFS ≥2, but only 19.8% maintained this score at 52 weeks [46] (P<0.001). Consistently with our results, the study by Taboada *et al.* (40) showed that 24.7% of patients obtained a PCFS ≥2 at 6 months. In terms of radiological findings, pulmonary abnormalities were classified as dominantly fibrotic, GGO and with indeterminate course (24). Fibrotic abnormalities are irreversible and have more severe effects. They result from a pathological reconstruction of the alveolar epithelium associated with destruction of normal pulmonary architecture (33,38). In the COMEBAC study, 19.3% of patients had small fibrotic lesions 4 months after hospitalization, with mild deterioration of pulmonary function (38). In our study, only 27 patients (11.6%) had fibrotic lesions. This rate, however, is very likely to be influenced by the timing of measurements, the number of patients that developed ARDS and stayed in CCU in each series and the number of patients who needed OTI. These factors have been associated with a higher risk for fibrotic lesions (38). The percentage of patients with GGO (14.2%) and lesions of indeterminate course (10.3%) in our series was slightly lower than in previous studies. GGO are associated with inflammation of the lung parenchyma and are potentially reversible, although they can be observed 12 months after COVID-19 diagnosis. Indeterminate lesions have a poorly differentiated course profile.

In total, 58.2% of cases had values <80% of the predicted for any pulmonary function parameter. In contrast, the median values of FVC% and FEV1% exceeded that threshold (80%), both at the initial visit and at 1 year. Only the median of baseline DLCO% was <80% of its value of reference both, at the initial visit (65%) and at 52 weeks (77%), although values improved significantly (P<0.001). Consistently, the study by Wu *et al.* in hospitalized patients who did not need NIV revealed a slight deterioration of DLCO% and FVC% at 3 months [median values (IQR) 77% (67–87%) and 92% (81–99%) of predicted values, respectively]. These parameters improved progressively at 6 months [DLCO 76% (68–90%) and FVC 94% (85–104%)] and at 12 months [DLCO 88% (78–101%) and FVC 98% (89–109%)] (32). In a systematic review of seven articles including 380 patients after hospitalization for SARS-COV-2 infection, the pulmonary function parameter that deteriorated most significantly was DLCO% (41). Our results support the hypothesis that the pulmonary function parameter most severely affected by COVID-19 is DLCO% (38). In this sense, we used the expression "post-COVID-19 fibrotic pulmonary lesions", which indicates the presence of fibrotic lesions on HRCT with concurrent deterioration of pulmonary function. This concept, which is possibly arbitrary and still poorly defined, defines patients more likely to experience more severe lung injury secondary to SARS-COV-2 infection. The fact that this subgroup of patients only accounts for a small percentage of the total sample (9.4%), along with the fact that patients only experienced a mild deterioration of pulmonary function, suggest that predominantly fibrotic lesions do not cause relevant changes in respiratory function parameters, except for DLCO.

Our prognostic models for the identification of persistent symptoms and patients with a higher risk of developing post-COVID-19 fibrotic pulmonary lesions include five parameters: PCFS score at the initial visit; history of asthma to detect persistent respiratory symptoms; female sex; FVC% at the initial visit and CCU stay. The two models showed a good (AUC 0.857; 95% CI: 0.799–0.915) and excellent (AUC 0.901 95% CI: 0.837–0.964) power of discrimination, respectively. These models can be very useful in clinical practice, as they are easy to use and the variables included are measured in routine laboratory tests. Our models will help physicians determine risk and adopt early follow-up measures. The variables included in the model for persistent respiratory symptoms are associated with high ORs. The same occurs with the variables of the prognostic model for fibrotic pulmonary lesions. Hence, a 1-point increase in baseline FVC% leads to a 6% decrease (OR 0.940) in the probability of developing fibrotic lesions. In addition, CCU stay multiplies by 14 the probability of having these lesions one year after infection. We decided to build two models upon realizing that functional status and history of asthma are enough for the prognosis of persistent respiratory symptoms; in contrast, the prognosis of post-COVID-19 fibrotic pulmonary lesions requires the analysis of a wider variety of variables (factors associated with the deterioration of pulmonary function along with a history of COVID-related CCU stay).

This study has some limitations. Firstly, it is a single-center study without external validation and is based on

a small sample of patients. Secondly, the abnormalities observed on HRCT and lung function test cannot be completely attributed to diffuse alveolar damage secondary to infection of the lung parenchyma by SARS-COV-2 and/or subsequent ARDS.

Conclusions

In conclusion, although values prior to SARS-COV-2 infection were not available, the results of this study suggest that a high percentage of patients hospitalized for COVID-19 develop pulmonary lesions though with a low pulmonary function impact. Follow-up these patients is necessary, especially if they have risk factors. Our models identify patients with a high risk of developing persistent respiratory symptoms or post-COVID-19 pulmonary fibrosis with a high accuracy, which could be very useful in clinical practice. Further, longer studies are needed to determine the long-term impact of these complications. External validation of these models is also needed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Santiago-Lugo (Registration No. 2020/305) and informed consent was taken from all the patients.

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