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Scientific letter

Evolution of Radiologic Alterations in Patients With Covid-19 Pneumonia and Fibrosis at 6 Months

Evolución de las alteraciones radiológicas en pacientes con neumonía covíd-19 y presencia de fibrosis a los 6 meses

Dear Editor,

COVID-19 disease caused by SARS-COV-2 has been a turning point in the humanity history. The clinical course has been variable since symptoms like common cold until bilateral pneumonia.[1] Radiologically alterations in thoracic CT (computed tomography) have been ground-glass opacities with or without consolidations, crazy paving or interlobular septal thickening. The long-term alterations were ground glass, reticular pattern, traction bronchiectasis and parenchymal bands.[1,2] If we compare with SARS-CoV, at 6 months, ground glass was observed in 76%, parenchymal bands in 59%, reticular pattern in 71% and consolidations in 3%. After 1.5 years, ground glass disappeared in most patients, persisting in 21% and parenchymal bands in 25%.[3,4] 15 years after primary infection, only 4% showed radiological alterations.[5] To date, the risk factors described in COVID-19 infection associated with persistence of radiological alterations, including fibrosis, have been advanced age, male sex, type 2 diabetes, obesity, severity of the disease, smoking and chronic alcoholism.[4,6,7] Alteration of diffusion capacity (DLCO) is the most frequent pulmonary functional alteration described and is directly related to the severity of the acute disease. The aim of our observational, prospective, single center study was to describe CT changes during COVID-19 pneumonia and evaluate fibrosis at 6 months describing changes in chest CT and functional respiratory impairment in all adult patients, non-vaccinate, being discharged from hospital after COVID-19 pneumonia. For further analysis, according to the findings of the control thoracic CT 6 months after discharge, patients will be divided into two groups: group 1 with pulmonary fibrosis and group 2 without pulmonary fibrosis. The presence on follow-up chest CT of parenchymal bands, irregular interfaces or traction bronchiectasis will be considered evidence of fibrosis. The study (version 5.0; December 2020) was approved by the Ethics Research Committee from Castellón General University Hospital.

We included 64 males (59%) and 45 females (41%) aged 6435 ± SD 13.43 years old. If we analyze clinical characteristics between groups, female sex (p-value 0.049), elderly patients (p-value 0.007), presence of arterial hypertension (p-value 0.036) and a longer hospital stay (p-value 0.022) are more frequent in fibrosis group. The comparison between initial CT and CT at 6 months shows that bilateral ground glass (OR 0.13; IC 0.04–0.44), unilateral (OR 0.06; IC 0.01–0.45) and bilateral (OR 0.01; IC 0–0.11) consolidations and bilateral crazy paving (OR 0.02; IC 0–0.16) and initial score, described by Francone et al.[8] (OR 0.7; IC 0.64–0.77) decrease at 6 months in a statistically significant way. In contrast, architectural distortion (OR 12.8; IC 2.91–55.9) tend to increase over time (Table 1). If we compare the initial findings according to the presence of fibrosis or not at 6 months (Table 1) we can see that the presence of bronchial dilatation is more frequent in the fibrosis group (20% vs 3.4%), as well as the presence of subpleural curved line (40% vs 14%) and parenchymal bands (44% vs 17%). The initial score was higher in the fibrosis group (p-value 0.001).

If we compare the radiological findings at 6 months (Table 1) we can see that the presence of bilateral ground glass, reticular pattern, bronchial dilatation, subpleural curved line, parenchymal bands, traction bronchiectasis, architectural distortion and score were higher in the fibrosis group.

At 6 months, the proportion of patients with lung diffusion impairment (DLCO < 80%) was 54.6% followed by forced vital capacity (FVC) decrease (28%) and forced expiratory volume in 1 second (FEV_1) decrease (21%). Although this decrease was greater in the fibrosis group at 6 months there were no significant differences between groups.

More than four years after SARS-CoV-2 pandemic, there are still unknowns to be resolved, such as the long-term sequelae and the associated risk factors. To this end, it is very important to identify, at an early stage, those patients will be more likely to present alterations over time. In accordance with the literature, we have found that older patients with comorbidities (specifically arterial hypertension) and longer hospital stay were significantly associated with presence of fibrosis at 6 months.[6,9] In contrast to that published by Valenzuela C et al.[10] in our study, female sex was associated with the fibrosis group. As published by Bakhsh N et al.[11] and Fabbri L et al.,[12] the most frequent initial radiological alteration was the presence of bilaterally ground glass (94%), bilateral consolidations (36%) followed by crazy paving (28%). We have described that the presence of bronchial dilatation, subpleural curved line and parenchymal bands in the initial CT are significantly associated with the fibrosis group at 6 months. As suggested by Yu M et al.[6] they could be early predictors of pulmonary fibrosis. The same is described by Babar et al.[13] and Bakhsh et al.[11] where traction bronchiectasis, reticular pattern and septal thickening are associated with the fibrosis group. In evolutionary CT studies at 6 months and 1 year[13] the presence of ground glass and consolidations decrease with time. In our case, the decrease in ground glass and consolidations of the initial CT compared to CT at 6 months was statistically significant (p-value < 0.001).

Functional tests at 6 months usually show a decrease in diffusion related to radiological involvement in 39% and 31% at 12 months.[14,15] In our study, 55% have decrease in DLCO. In the fibrosis group the decrease was higher (64%).

There are limitations to this study. The first is the low number of patients collected. Second, there is no histological confirmation

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Table 1
Description of initial and 6 months CT according to signs of fibrosis at 6 months.

	Initial CT				6 months CT				Univariant logistic regression Initial vs 6 months CT $N = 109$		
Variables	$N = 109$	Non fibrosis $N = 59$	Fibrosis $N = 50$	p-Value	$N = 109$	Non fibrosis $N = 59$	Fibrosis $N = 50$	p-Value	OR	CI	p-Value
Ground-grass opacity, n (%)											
No	3 (2.8%)	1 (1.7%)	2 (4.0%)	0.8	19 (17%)	16 (27%)	3 (6.0%)	0.003			
Unilateral	3 (2.8%)	2 (3.4%)	1 (2.0%)		7 (6.4%)	6 (10%)	1 (2.0%)		0.37	0.06, 2.27	0.3
Bilateral	103 (94%)	56 (95%)	47 (94%)		83 (76%)	37 (63%)	46 (92%)		0.13	0.04, 0.44	0.001
Consolidaction, n (%)											
No	60 (55%)	38 (64%)	22 (44%)	0.10	107 (98%)	58 (98%)	49 (98%)	0.7			
Unilateral	10 (9.2%)	4 (6.8%)	6 (12%)		1 (0.9%)	1 (1.7%)	0 (0%)		0.06	0.01, 0.45	0.007
Bilateral	39 (36%)	17 (29%)	22 (44%)		1 (0.9%)	0 (0%)	1 (2.0%)		0.01	0.00, 0.11	<0.001
Crazy paving, n (%)											
No	70 (64%)	41 (69%)	29 (58%)	0.4	108 (99%)	59 (100%)	49 (98%)	0.5			
Unilateral	8 (7.3%)	3 (5.1%)	5 (10%)		0 (0%)	0 (0%)	0 (0%)		0.00	0.00, Inf	>0.9
Bilatreal	31 (28%)	15 (25%)	16 (32%)		1 (0.9%)	0 (0%)	1 (2.0%)		0.02	0.00, 0.16	<0.001
Reticular pattern, n (%)											
No	91 (83%)	52 (88%)	39 (78%)	0.2	92 (85%)	57 (97%)	35 (71%)	<0.001			
Yes	18 (17%)	7 (12%)	11 (22%)		16 (15%)	2 (3.4%)	14 (29%)		0.88	0.42, 1.83	0.7
Inverse halus, n (%)											
No	106 (97%)	58 (98%)	48 (96%)	0.6	108 (100%)	59 (100%)	49 (100%)				
Yes	3 (2.8%)	1 (1.7%)	2 (4.0%)		0 (0%)	0 (0%)	0 (0%)				
Air bubble, n (%)											
No	105 (96%)	58 (98%)	47 (94%)	0.3	105 (97%)	57 (97%)	48 (98%)	>0.9			
Yes	4 (3.7%)	1 (1.7%)	3 (6.0%)		3 (2.8%)	2 (3.4%)	1 (2.0%)		0.75	0.16, 3.43	0.7
Bronchial dilatation, n (%)											
No	97 (89%)	57 (97%)	40 (80%)	0.012	104 (95%)	59 (100%)	45 (90%)	0.017			
Yes	12 (11%)	2 (3.4%)	10 (20%)		5 (4.6%)	0 (0%)	5 (10%)		0.39	0.13, 1.14	0.086
Bronchial wall thickening, n (%)											
No	108 (99%)	59 (100%)	49 (98%)	0.5	109 (100%)	59 (100%)	50 (100%)				
Yes	1 (0.9%)	0 (0%)	1 (2.0%)		0 (0%)	0 (0%)	0 (0%)				
Prominent vessels, n (%)											
No	107 (98%)	58 (98%)	49 (98%)	>0.9	107 (98%)	58 (98%)	49 (98%)	>0.9			
Yes	2 (1.8%)	1 (1.7%)	1 (2.0%)		2 (1.8%)	1 (1.7%)	1 (2.0%)		1.00	0.14, 7.23	>0.9
Pleural thickening, n (%)											
No	106 (97%)	58 (98%)	48 (96%)	0.6	108 (99%)	59 (100%)	49 (98%)	0.4			

Table 1
(*Continued*)

Variables	Initial CT				6 months CT				Univariant logistic regression Initial vs 6 months CT $N = 109$		
	$N = 109$	Non fibrosis $N = 59$	Fibrosis $N = 50$	*p*-Value	$N = 109$	Non fibrosis $N = 59$	Fibrosis $N = 50$	*p*-Value	OR	CI	*p*-Value
Yes	3 (2.8%)	1 (1.7%)	2 (4.0%)		1 (0.9%)	0 (0%)	1 (2.0%)		0.33	0.03, 3.20	0.3
Subpleural curved line, n (%)											
No	81 (74%)	51 (86%)	30 (60%)	0.002	72 (66%)	57 (97%)	15 (30%)	<0.001			
Yes	28 (26%)	8 (14%)	20 (40%)		37 (34%)	2 (3.4%)	35 (70%)		1.49	0.83, 2.67	0.2
Parenchimal bands, n (%)											
No	77 (71%)	49 (83%)	28 (56%)	0.004	65 (60%)	58 (98%)	7 (14%)	<0.001			
Yes	32 (29%)	10 (17%)	22 (44%)		44 (40%)	1 (1.7%)	43 (86%)		1.63	0.93, 2.86	0.089
Hypoatenuating line, n (%)											
No	106 (97%)	56 (95%)	50 (100%)	0.2	108 (99%)	59 (100%)	49 (98%)	0.5			
Yes	3 (2.8%)	3 (5.1%)	0 (0%)		1 (0.9%)	0 (0%)	1 (2.0%)		0.33	0.03, 3.20	0.3
Interphases sign, n (%)											
No	107 (98%)	58 (98%)	49 (98%)	>0.9	107 (99%)	58 (100%)	49 (98%)	0.5			
Yes	2 (1.8%)	1 (1.7%)	1 (2.0%)		1 (0.9%)	0 (0%)	1 (2.0%)		0.50	0.04, 5.60	0.6
Honey combing, n (%)											
No	106 (97%)	58 (98%)	48 (96%)	0.6	106 (97%)	58 (98%)	48 (96%)	0.6			
Yes	3 (2.8%)	1 (1.7%)	2 (4.0%)		3 (2.8%)	1 (1.7%)	2 (4.0%)		1.00	0.20, 5.07	>0.9
Traction bronchiectasis, n (%)											
No	98 (90%)	56 (95%)	42 (84%)	0.1	89 (82%)	54 (92%)	35 (70%)	0.004			
Yes	11 (10%)	3 (5.1%)	8 (16%)		20 (18%)	5 (8.5%)	15 (30%)		2.00	0.91, 4.41	0.085
Architecture distortion, n (%)											
No	107 (98%)	59 (100%)	48 (96%)	0.2	88 (81%)	57 (97%)	31 (62%)	<0.001			
Yes	2 (1.8%)	0 (0%)	2 (4.0%)		21 (19%)	2 (3.4%)	19 (38%)		12.8	2.91, 55.9	<0.001
Score[8]											
Mean (SD)	11.65 (4.09)	10.59 (4.27)	12.90 (3.53)	0.001	5.26 (4.09)	3.53 (3.55)	7.30 (3.76)	<0.001	0.70	0.64, 0.77	<0.001

Acronyms: computed tomography(CT), confidence interval (CI), odds ratio (OR).

of fibrosis, although the radiographic findings on thoracic CT are highly suggestive. Last one, only patients who have been hospitalized have been included in the study, which means that they have presented a more severe infection, and this could lead to a selection bias for the distribution and extension of pulmonary lesions. Therefore, these findings could not be generalized to the entire COVID-19 infected population.

To conclude, 45% of patients hospitalized for pneumonia secondary to SARS-CoV-2 present signs of fibrosis at 6 months. These findings confirm the need for follow-up of patients over a longer period to clarify whether these changes will persist over time.

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Authors' contributions

Cuenca Peris, Selene has contributed to the literature search, study design, data interpretation, has done all study assessments. Marco Domenech, Santiago F has contributed to interpretate all tomographic images and Marín Royo, Margarita, has contribute to interpretate lung functional studies. All authors had contributed to article writing and editing and approved its submission.

Conflicts of interest

The results presented have not been published previously. The authors declare no competing interests.

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