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Original paper

Chest computed tomography signs associated with pejorative evolution in COVID-19 patients

Romain Auger[1,A,B,C,D,E,F], Paul-Armand Dujardin[2,A,C,D,E], Aurore Bleuzen[1,A], Juliette Buraschi[1,A], Natacha Mandine[1,B], Sylvain Marchand-Adam[3,D], Arthur Pearson[1,A,C,D,E], Gaëlle Derot[1,A,B,D,E,F]

[1]Department of Radiology, Centre Hospitalier Régional Universitaire de Tours, France
[2]CIC 1415, Centre Hospitalier Régional Universitaire de Tours, Inserm, Tours Cedex, France
[3]Department of Respiratory Medecine, Centre Hospitalier Régional Universitaire de Tours, France

Abstract

Purpose: The aim of this study was to evaluate how chest computed tomography (CT) can predict pejorative evolution in COVID-19 patients.

Material and methods: Data on 349 consecutive patients who underwent a chest CT either for severe suspected COVID-19 pneumonia or clinical aggravation and with COVID-19 were retrospectively analysed. In total, 109 had laboratory-confirmed COVID-19 infection by a positive reverse-transcription polymerase chain reaction (RT-PCR) and were included. The main outcomes for pejorative evolution were death and the need for invasive endotracheal ventilation (IEV). All the CT images were retrospectively reviewed, to analyse the CT signs and semiologic patterns of pulmonary involvement.

Results: Among the 109 COVID-19 patients, 73 (67%) had severe symptoms of COVID-19, 28 (25.7%) needed an IEV, and 11 (10.1%) died. The following signs were significantly associated with both mortality and need for IEV: traction bronchiectasis and total affected lung volume ≥ 50% ($p < 10–3$). Other CT signs were only associated with the need of IEV: vascular dilatation, air bubble sign, peribronchovascular thickening, interlobular thickening, and number of involved lobes ≥ 4 ($p < 10–3$).

Conclusions: On a chest CT performed during the first week of the symptoms, the presence of traction bronchiectasis and high values of affected lung volume are associated with the need for IEV, and with mortality, in COVID-19 patients.

Key words: COVID-19, chest CT, IEV, critical care, bronchiectasis.

Introduction

Coronavirus disease (COVID-19) has been spreading worldwide since December 2019 from Wuhan, Hubei Province [1]. The virus called SARS-Cov-2 belongs to the *Betacoronavirus* genus, is composed of a positive single-stranded RNA, and has a 50-200 nm diameter [2,3]. Bats are the natural reservoir for coronaviruses [4]. By April 26th 2020, more than 2,355,853 cases (of which 947,693 in Europe) and 164,656 deaths worldwide had been reported due to this pandemic [5]. By March 16th 2020 in France, 124,114 cases had been confirmed, with 22,614 deaths [6]. Fever, cough, fatigue, diarrhoea, dyspnoea, and myalgia are the most common symptoms, but the patients' condition can deteriorate rapidly, requiring intensive medical care [7,8]. Real-time reverse-transcription polymerase chain reaction (RT-PCR) is the standard reference to detect viral nucleic acid, but false-negative results have

Correspondence address:
Romain Auger, Department of Radiology, Le Centre Hospitalier Régional Universitaire de Tours, Tours, France, e-mail: romain.auger100@gmail.com

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A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

been reported and have led to a 66-80% sensitivity due to multiple factors, notably the quality of sampling [9]. Compared to RT-PCR, chest computed tomography (CT) is an easy-to-use and a faster method to diagnose and assess an early pulmonary COVID-19 infection [10]. Chest CT can also help to monitor the evolution and diagnose complications of COVID-19. Indeed, some authors have demonstrated the diagnostic value of chest CT in COVID-19 pneumonia describing compatible radiological signs [11-13]. Ai *et al*. evaluated chest CT diagnostic value in 1014 cases of suspected COVID-19 using RT-PCR as a reference, and they determined a sensitivity of 97% and negative predictive value of 83% [10]. Few authors have studied the prognostic value of chest CT. Yuan *et al*. found in a small sample of 27 patients (of whom 10 died) higher rates of consolidation and air bronchogram in the dead patients' group [14]. In a retrospective study, Zhao *et al*. found pleural effusions and architectural distortions to be CT signs potentially correlated with severe deterioration in a small population of severe or deceased patients (14/101 patients) [15]. Yang *et al*. proposed a pulmonary inflammation load score, which was higher in patients with severe COVID-19 in comparison with patients who had a mild form of the disease [16]. However, despite these elements, few studies have shown whether there was a relation between some early chest CT signs and the need for invasive endotracheal ventilation (IEV).

In this study, our main objective was to assess whether some chest CT signs were associated with pejorative evolution (defined as a need for IEV or death), in COVID-19 patients.

Material and methods

Study design

Ethical approval of this monocentric retrospective study was delivered by the review board of our hospital. We used the data of a cohort of 349 patients included from March 19t^{h} to April 28th 2020, which was created to study the diagnostic value of chest CT for COVID-19.

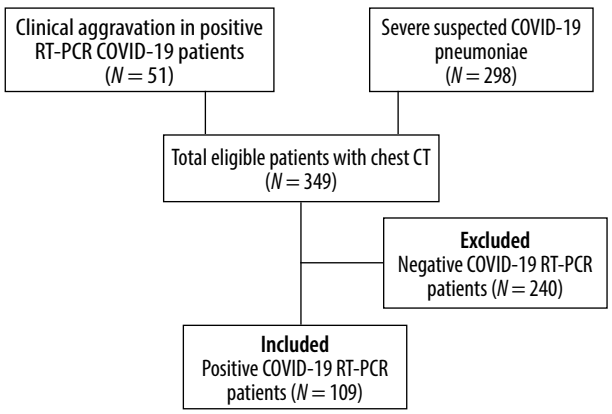

Figure 1. Flow-chart of the 109 patients included in the study

The patients were included in the cohort if they had a chest CT, either for suspected COVID-19 pneumoniae with severe symptoms or for clinical deterioration during a COVID-19 infection that had been confirmed with a positive RT-PCR. We included in our study 109 patients who had a positive COVID-19 RT-PCR.

The patient selection and inclusion process are represented in a flow diagram in Figure 1. The clinical severity scale was assessed according to the Chinese Centre of Disease Control and Prevention describing four groups of severity in the COVID-19 disease: uncomplicated illness, moderate pneumonia with dyspnoea, severe pneumonia, and acute respiratory distress syndrome (ARDS) [17,18].

RT-PCR test and clinical synthesis

Coronavirus nucleic acid was collected with nasopharyngeal swab or/and bronchial aspiration. RT-PCR was performed using gene amplification RdRpE, and/or N (CNR Pasteur technic, AllPlex Seegene, Bosphore Anatolia; depending on availabilities). For patients who presented a high clinical probability of infection, two or three RT-PCR tests were performed if the previous results were negative, with a minimum of 48-72 hours between samples.

If one RT-PCR was positive, COVID-19 diagnosis was confirmed. In the case of multiple chest CTs, we used the one that was closest, timewise, to the first positive RT-PCR. All patients were included, whatever the time between positive RT-PCR and chest CT.

Primary outcome

The primary outcome was pejorative evolution, which we defined as use of IEV or death.

Chest computed tomography protocol

Chest CT was performed for all patients. Images were obtained in supine position by one of the two following CT scanners: an Aquilion Prime 160 (Toshiba, Japan) or a Somatom Force CT VB10 (Siemens Healthiners, Germany). The scanning parameters were as follows: tube voltage 120 kV, automatic dose modulation (30-210 mAs), matrix 512 × 512, pitch 0.35-0.99, slice thickness 0.5 mm, and field of view 500 mm × 500 mm. A 0.5 mm slice thickness was used after image reconstruction. When a pulmonary embolism was suspected, iodinated contrast media (300 mg/l) was intravenously injected (3 to 4 ml/s) according to patient weight, with bolus tracking in the main pulmonary artery. Reconstructed images were archived and transferred to the informatic network.

Chest computed tomography image analysis

Images were reviewed by two radiologists, according to the consensual signs described in COVID-19 [7], and

a final decision reached by consensus. Clinical history was available for interpretation.

Chest CT signs were analysed according to the Fleishner Society glossary [19]: ground glass-opacities (patchy, nodular or mixed), crazy paving (thickened intralobular and interlobular lines in a ground glass opacity), subpleural curvilinear bands, consolidation areas, air bubble sign, vascular dilatation, traction bronchiectasis, reticular interlobular thickening, pleural effusion, pleural thickening, number of involved lobes, inferior predominance, laterality, lung localisation (subpleural, central or dual distribution), compatible CT aspect of acute respiratory distress syndrom, compatible CT aspect of organizing pneumonia, compatible CT aspect of cardiac failure, lymphadenopathy, emphysematous lesions, bronchial thickening, endobronchial secretion, centrilobular nodule, and total affected lung volume (0%, < 10%, ≥ 10 – < 25%, ≥ 25 – < 50%, ≥ 50 – < 75%, ≥ 75%). The cut-off values for lung volume involvement were chosen in accordance with the recommendations of the French Society of Radiology [20].

Compatible CT aspect of organising pneumonia (OP) was defined as consolidation (nodular, linear, perilobular, or peribronchovascular), subpleural curvilinear bands, halo sign, and/or atoll sign [21]. Traction bronchiectasis was defined as bronchial dilatations, with irregular contours, cylindrical, tubular, or fusiform, focalised in the areas affected by the ground glass opacities (GGO), consolidation, or crazy paving [22].

Statistical analysis

Statistical analysis was performed with Matlab® R2007b (MathWorks Inc., Natick, USA). Qualitative variables were reported with number and percentage, and quantitative variables with mean and standard deviation.

In the included patients, we compared the frequency and extent of COVID-19 chest CT signs, between the deceased and survivor groups and between the IEV and non-IEV groups.

The followings chest CT signs and patterns were analysed: GGO, crazy paving, consolidation area, subpleural curvilinear bands, traction bronchiectasis, vascular dilatation, air bubble sign, interlobular thickening, total volume (50-100% vs. < 50%), compatible aspect of OP, compatible CT aspect of ARDS, distribution (subpleural, central, and dual – i.e. central and subpleural), inferior localisation, and number of involved lobes (0 to 3 vs. 4 or 5 involved lobes). For statistical analysis, the 50% total volume involvement cut-off and the number of involved lobes (< 4 vs. ≥ 4) were chosen based on a previous study by Yang *et al*., which found that these cut-offs were associated with the severity of the disease [16].

Association between chest CT signs and pejorative evolution in COVID-19 patients was evaluated using vs. tests when applicable (all theorical numbers superior to 5) and Fisher's exact test otherwise. All test results with a p-value < 0.05 were considered statistically significant.

Results

Clinical and population characteristics

From March 19th to April 28th, 2020 a total of 109 patients with a positive RT-PCR were included in the study. Their clinical and demographic characteristics are shown in Table 1. Among them, 73 (67%) had severe symptoms (severe pneumonia or ARDS as described above), 28 (25.7%) had IEV, and 11 (10.1%) died. The mean time interval between the RT-PCR test and chest CT was inferior to 1.5 days.

Table 1. Clinical and demographic characteristics of the 109 patients included

Variable	Value
Age (years)	64.6 ± 17.2
Male sex	61 (55.6%)
Comorbidity	81 (74.0%)
Clinical severity	
Mild	12 (11.0%)
Moderate	24 (22.0%)
Severe	46 (42.2%)
Mild ARDS	1 (0.9%)
Moderate ARDS	15 (13.7%)
Severe ARDS	11 (10.1%)
ICUH	39 (35.7%)
IEV	28 (25.7%)
Death	11 (10.1%)
Life status unknown at the end of the study	11 (10.1%)
Number of unknown RT-PCR before CT	55 (50.5%)
Average time between first symptom and CT (days)	6.2 ± 5.1
Average time between first symptom and CT among patients in ICUH (days)	5.9 ± 4.3
Average time between CT and RT-PCR (days)	1.42 ± 2.00
Average time between RT-PCR and CT if RT-PCR results are not known (days)	1.49 ± 2.48
Average time between RT-PCR and CT if RT-PCR results are known (days)	2.11 ± 2.38
Average time between admission and CT (days)	1.10 ± 2.15

Qualitative values are indicated as number and percentages. Quantitative values are indicated as mean and standard deviation. Comorbidity corresponds to the following: age > 65 years, chronic respiratory disease, dialysis, cardiac insufficiency NYHA 3 or 4, history of cardiac diseases (arterial hypertension, coronaropathy, stroke, cardiac surgery), cirrhosis (≥ Child B), diabetes with complications or requiring insulin therapy, immunosupression (chemotherapy, biotherapy, immunosuppressive corticotherapy, uncontrolled HIV or CD4 < 200/mm^3, metastatic cancer, all types of graft), BMI > 40, or pregnancy.
ARDS – acute respiratory distress syndrome, ICUH – intensive care unit hospitalisation, IEV – invasive endotracheal ventilation, RT-PCR – reverse-transcription polymerase chain reaction, CT – computed tomography.

Table 2. Chest CT signs for the 109 positive COVID-19 patients

Signs	Values
GGO	98 (89.9%)
Crazy paving	65 (59.6%)
Not systematised consolidation area	39 (35.8%)
Subpleural curvilinear bands	63 (57.8%)
Traction bronchiectasis	45 (41.3%)
Vascular dilatation	25 (22.9%)
Air bubble sign	12 (11.0%)
Interlobular thickening	14 (12.8%)
Compatible aspect of ARDS	7 (6.4%)
Compatible aspect of OP	59 (54.1%)
Compatible aspect of cardiac additional decompensation	6 (5.5%)
Lymphadenopathy	13 (11.9%)
Bronchial thickening	13 (11.9%)
Endobronchial secretion	7 (6.4%)
Centrilobular nodule	7 (6.4%)
Pneumothorax	2 (1.8%)
Pulmonary embolism	6 (5.5%)
Emphysematous lesions	5 (4.6%)
Systematised consolidation	6 (5.5%)
Pleural effusion	17 (15.6%)
Pleural thickening	4 (3.7%)
Bilateral involvement	102 (93.0%)
Unilateral involvement	3 (2.7%)
Subpleural localisation	104 (95.4%)
Central localisation	48 (44.0%)
Dual distribution	52 (47.7%)
Inferior localisation	75 (68.8%)
Number of involved lobes	4.2 ± 1.4
Volume (total affected lung)	0%: 5 (4.6%) < 10%: 13 (11.9%) ≥ 10 –25%: 24 (22.0%) ≥ 25 – < 50%: 31 (28.4%) ≥ 50 – 75%: 16 (14.7%) ≥ 75%: 20 (18.4%)
No CT signs	4 (3.7%)

All signs are described with number and percentage, except the number of involved lobes which is described with mean and standard deviation.
CT – computed tomography, GGO – ground glass opacities, ARDS – acute respiratory distress syndrome, OP – organising pneumonia.

Patients generally had chest CT on the same day or on the day after hospitalisation and a mean of 6.2 days after the first symptoms. Table 2 presents the chest CT signs of the 109 COVID-19 patients who had a positive RT-PCR. Seven (6.4%) patients did not show COVID-19 CT signs (normal CT or incompatible CT signs).

Table 3. Association between chest CT signs and use of IEV in comparison with the non-IEV group, among positive COVID-19 RT-PCR patients

Signs	IEV group ($n = 28$)	Non-IEV group ($n = 81$)	p-value
GGO	26 (92.2%)	72 (88.9%)	-
Crazy paving	19 (67.9%)	46 (56.8%)	-
Not systematised consolidation area	13 (46.4%)	26 (32.1%)	-
Subpleural curvilinear bands	12 (42.6%)	51 (63%)	-
Traction bronchiectasis	23 (82.1%)	22 (27.2%)	$< 10^{-3}$
Vascular dilatation	13 (46.4%)	12 (14.8%)	$< 10^{-3}$
Air bubble sign	6 (21.4%)	6 (7.4%)	0.039
Interlobular thickening	7 (25%)	7 (8.6%)	0.026
Compatible aspect of ARDS	7 (25%)	0 (0%)	$< 10^{-3}$
Subpleural localisation	28 (100%)	76 (93.8%)	-
Central localisation	17 (60.7%)	31 (38.3%)	-
Dual distribution	19 (67.9%)	33 (40.7%)	-
Inferior localisation	20 (71.4%)	55 (67.9%)	-
Compatible aspect of OP	13 (46.4%)	46 (56.8%)	-
Peribronchovascular thickening	8 (28.6%)	6 (7.4%)	6.10^{-3}
Number of involved lobes	4.8 (0.57)	2.53 (1.77)	$4.25.10^{-3}$
Total affected volume ≥ 50%	22 (78.5%)	15 (18.5%)	$< 10^{-3}$

CT – computed tomography, GGO – ground glass opacities, IEV – invasive endotracheal ventilation, ARDS – acute respiratory distress syndrome, OP – organising pneumonia, RT-PCR – reverse-transcription polymerase chain reaction, ICUH – intensive care unit hospitalisation. All signs are described with number and percentage, except the number of involved lobes which is described with mean and standard deviation. Dashes correspond to $p > 0.05$.

Computed tomography signs and pejorative evolution

The frequency of chest CT signs and the calculated p-values of the corresponding χ^2 tests can be found in Table 3 (comparing the need for IEV and no-IEV groups) and Table 4 (comparing the deceased and survivor groups).

Traction bronchiectasis and total affected lung volume ≥ 50% were significatively associated with mortality ($p = 0.018$, and $p < 10^{-3}$, respectively), and IEV ($p < 10^{-3}$).

Vascular dilatation ($p < 10^{-3}$), air bubble sign ($p = 0.039$), interlobular ($p = 0.026$) and peribronchovascular thickening ($p = 6.10^{-3}$), and the number of involved lobes ≥ 4 ($p < 10^{-3}$) were associated with the need for IEV.

Discussion

In our study, we found that traction bronchiectasis and total affected lung volume ≥ 50% (Figures 2 A, B and 3), were significantly associated with death, among positive RT-PCR COVID-19 patients. Also, vascular dilatation, traction bronchiectasis, and lesional expansion (total affected lung volume ≥ 50% or ≥ 4 affected lobes) were

Table 4. Association between chest computed tomography signs and death in comparison with the surviving group, among positive COVID-19 RT-PCR patients

Signs	Deceased group ($n = 11$)	Surviving group ($n = 87$)	p-value
GGO	11 (100%)	77 (88.5%)	–
Crazy paving	7 (63.6%)	52 (59.8%)	–
Not systematised consolidation area	4 (36.4%)	29 (33.3%)	–
Subpleural curvilinear bands	4 (36.4%)	56 (64.4%)	–
Traction bronchiectasis	8 (72.7%)	31 (35.6%)	0.018
Vascular dilatation	3 (27.3%)	19 (21.8%)	–
Air bubble sign	2 (18.2%)	8 (9.2%)	–
Interlobular thickening	1 (9.1%)	12 (13.8%)	–
Compatible aspect of ARDS	1 (9.1%)	3 (3.4%)	–
Subpleural localisation	11 (100%)	82 (94.3%)	–
Central localisation	6 (54.5%)	33 (37.9%)	–
Dual distribution	6 (54.5%)	36 (41.4%)	–
Inferior localisation	6 (54.5%)	61 (70.1%)	–
Compatible aspect of organizing pneumonia	4 (36.4%)	52 (59.8%)	–
Peribronchovascular thickening	1 (9.1%)	9 (10.3%)	–
Number of involved lobes	4.4 (0.36)	2.54 (1.76)	–
Total affected volume ≥ 50%	7 (63.6%)	23 (26.4%)	$< 10^{-3}$

CT – computed tomography, GGO – ground glass opacities, RT-PCR – reverse-transcription polymerase chain reaction, ARDS – acute respiratory distress syndrome.
All signs are described with number and percentage, except the number of involved lobes, which is described with mean and standard deviation. Dashes correspond to $p > 0.05$.

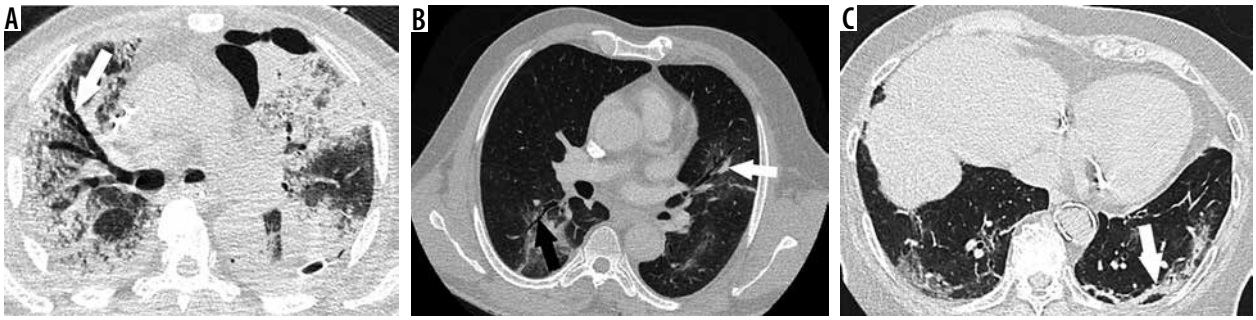

Figure 2. Chest computed tomography (CT) in positive reverse-transcription polymerase chain reaction COVID-19 cases. **A)** A 74-year-old man in intensive care unit hospitalisation (ICUH) with endotracheal ventilation, 11 days after first symptoms, massive traction bronchiectasis (white arrow) in the entire right lung, large areas of ground glass opacities (GGO) and subpleural consolidation, with ≥ 75% of total affected lung. Note a left anterior loculated pneumothorax and a left posterior pleural effusion drain. **B)** A 57-year-old man in ICUH, 13 days after first symptoms, dual distribution areas (subpleural and central) of GGO in the lingula and the right inferior lobe with traction bronchiectasis (black arrow) and vascular dilatation (white arrow), with 50-75% of total affected lung. **C)** A 67-year-old man in ICUH, 10 days after first symptoms, CT aspect of organised pneumonia (white arrow) with bilateral posterior subpleural curvilinear bands

significantly associated with IEV. Semiological CT anomalies like traction bronchiectasis, vascular dilatation, and bubble sign are consistent with indirect signs of acute pulmonary fibrosis, and they could explain the rapid clinical deterioration of some patients. Indeed, vascular dilatation could be due to endothelial lesions with inflammatory vasodilatation or maybe to parenchymal retractions associated with fibrosis. The air bubble sign is more frequent in the IEV group and could correspond to a bronchioloalveolar dilatation due to fibrosing damage or a previous existing cyst revealed by the diffuse infection [22]. Our findings are consistent with those of a study that had a similar sample size, i.e. in 60 patients showed that at least four affected lobes was correlated with death in critically ill patients [23]. Feng *et al.* also demonstrated that more lung lobes were involved in the severe and critical groups than in the moderate group; their findings are also consistent with our study [24].

We also observed patterns compatible with OP in more than 50% of patients (Figure 2 C). This concurs with a study by Copin *et al.* [25], which found an association between OP and fibrosis lesions in a pulmonary autopsy of a COVID-19 patient and described it as a specific histologic pattern of acute fibrinous and OP.

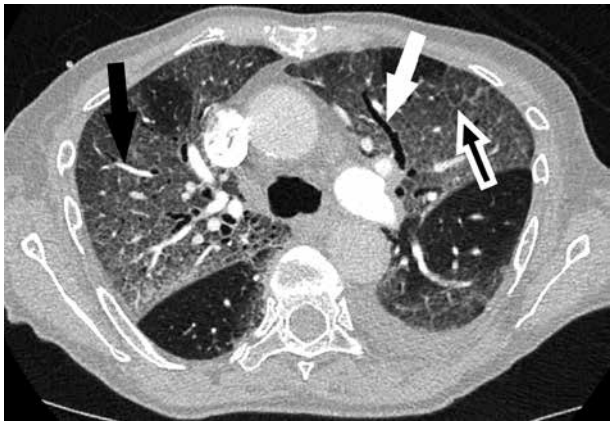

Figure 3. Chest computed tomography of a 76-year-old man in intensive care unit hospitalisation, 10 days after first symptoms, bilateral, large, and patchy ground glass opacities with crazy paving (white underlined dark arrow), traction bronchiectasis (white arrow) and vascular dilatation (dark arrow), with 50-75% of total affected lung

The significantly higher frequency of interlobular and peribronchovascular thickening in the IEV group could be due to alveolar interstitial oedema, similar to what can be observed in congestive heart failure, or due to the interstitial spreading of the inflammation [26]. However, unlike Zhao *et al.*, lymphadenopathy and pleural effusion were not associated with a pejorative evolution in our cohort [15].

The frequency and type of chest CT signs are similar to previous studies except for consolidation and traction bronchiectasis, more prevalent in our study probably due to the clinical severity of our patients [13,22,27-29].

This study has some limitations. First of all, it was a retrospective study. Also, because only one CT scan was included per patient, no CT aspect evolution analysis could be performed; however, the rapidity of evolution of symptoms might be another predictive factor of pejorative evolution. Additionally, we decided to routinely review each COVID-19 scan collectively to maximise our diagnostic value for the patients; therefore, the interobserver agreement was not studied. Finally, it is possible that some signs are not associated with pejorative evolution because of the relatively small number of deaths in our cohort. All these points would be interesting to investigate in future studies.

Conclusions

Interestingly, the presence of traction bronchiectasis and focal vascular dilatations are associated with a pejorative evolution: pulmonary fibrosis lesions could play a part in the physiopathology of COVID-19 pneumonia. High values of affected lung volume were also associated with a pejorative evolution, which concurs with the current literature on the subject.

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Conflict of interest

The authors report no conflict of interest.

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