Acute Pulmonary Embolism In Non-Hospitalized Covid-19 Patients Referred To CTPA By Emergency Department

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Abstract

Objectives: To evaluate the prevalence of acute pulmonary embolism (APE) in non-hospitalized COVID-19 patients referred to CT pulmonary angiography (CTPA) by Emergency Department.

Methods: From March 14 to April 6, 2020, 72 non-hospitalized patients referred by Emergency Department to CTPA for COVID-19 pneumonia were retrospectively identified. Relevant clinical and laboratory data and CT scan findings were collected for each patient. CTPA scans were reviewed by two radiologists to determinate the presence or absence of APE. Clinical classification, lung involvement of COVID-19 pneumonia and CT total severity score were compared between APE group and Non-APE group.

Results: APE was identified in 13 (18%) CTPA scans. The mean age and D-dimer of patients from APE group were higher in comparison with Non-APE group (74.4 vs. 59.6 years, p=0.008 and 7.29 vs. 3.29 µg/ml, p=0.011). There was no significant difference between APE and Non-APE groups concerning clinical type, COVID-19 pneumonia lung lesions (ground-glass opacity: 85 vs. 97%; consolidation: 69 vs. 68%; crazy paving: 38% vs. 37%; linear reticulation: 69 vs. 78%), CT severity score (6.3 vs. 7.1, p=0.365), quality of CTPA (1.8 vs. 2.0, p=0.518) and pleural effusion (38% vs. 19%, p=0.146).

Conclusions: Non-hospitalized patients with COVID-19 pneumonia referred to CT-scan by Emergency Departments are at risk of APE. Presence of APE was not limited to severe or critical clinical type of COVID-19 pneumonia.

Introduction

The 2019 coronavirus disease (COVID–19) epidemic linked to the new SARS-CoV–2 respiratory virus which appeared in Wuhan in China in December 2019 has rapidly spread around the world, to the point of becoming a global pandemic as declared by the WHO on March 11, 2020 [1–2]. The diagnosis of COVID–19 is essential to limit the spread of the virus and is confirmed by RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) SARS-CoV–2. The sensitivity of the RT-PCR test was evaluated between 42 and 71% [3–4]. Non-contrast chest CT has shown better sensitivity (up to 98%) than RT-PCR for the diagnosis of COVID–19 pneumonia [5]. This excellent sensitivity together with a high specificity in an epidemic context (from 73 to 100%) [6] makes it possible to envisage the use of the chest CT as a complementary means of diagnosing COVID–19 alongside RT-PCR [7–8]. Non-contrast chest CT also allows assessing the severity of the pulmonary involvement [9–10] and could play a key role in therapeutic efficacy evaluation in combination with clinical information [11].

The place of Computed Tomography pulmonary angiography (CTPA) in the evaluation of COVID–19 pneumonia remains more limited. It is reserved for patients whose clinical condition has deteriorated in order to search for an Acute Pulmonary Embolism (APE) [12]. Several published studies seem to confirm the association between COVID–19 and APE in hospitalized patients with severe to critical form [13–18].

In our practice, we have found cases of APE in non-hospitalized COVID–19 patients referred to CTPA by our Emergency Department.

The objective of our study was to retrospectively assess the prevalence of APE in non-hospitalized COVID–19 patients referred to CTPA by the Emergency Department.

Material And Methods

Case selection

All requests for chest CT scans for suspicion or assessment of COVID–19 pneumonia in non-hospitalized patients presenting in the Emergency Department of our hospital between March 14, 2020 and April 6, 2020 were retrospectively analyzed. Patients diagnosed with COVID–19 who underwent CTPA were included in our study. To have a final diagnosis of COVID–19, patients had to either have at least a positive RT-PCR for SARS-CoV–2, or a combination of compatible clinical findings and a chest CT with typical COVID–19 pneumonia features. Patients were divided into two groups: an APE group for patients with an acute pulmonary embolism discovered by CTPA and a Non-APE group for patients without acute pulmonary embolism.

This study was approved by the ethics committee of our institution and the requirement for informed consent was waived.

Clinical and biological data

The following clinical and laboratory data were extracted from our medical records: patient history, age, sex, body mass index (BMI), symptoms (fever (>37.5°C), cough, dyspnea, desaturation, chest pain, asthenia, myalgia, and diarrhea), delay between onset of symptoms and CT-scan, D-dimer and CRP (c-reactive protein) when available.

Clinical classification

All cases were divided into four groups: minimal, moderate, severe, and critical according to whether there were clinical symptoms, severity of pneumonia, respiratory failure, shock, other organ failure, based on the Diagnosis and Treatment Plan of COVID–19 issued by National Health Commission (7th ed.) (in Chinese) [7].(1) Mild type: mild clinical symptoms without pneumonia in imaging; (2) moderate type: fever, respiratory tract and other symptoms with pneumonia in imaging; (3) severe type: respiratory distress, respiratory rate ≥ 30 times/min; in resting state, oxygen saturation ≤ 93%; PaO2/FiO2≤300mmHg; (4) critical type: respiratory failure requiring mechanical ventilation, shock and other organ failure requiring ICU monitoring and treatment.

CT acquisition

CT-scans were acquired in the supine position on a 64-MDCT (Revolution EVO, GE Healthcare). The CT-scanning range covered the area from the apices to the bases of the lungs. The examination began by performing an unenhanced low-dose cranio-caudal series with deep-inspiration breath-holding. The acquisition parameters were: 120 kVp, tube current modulation with a noise index setting of 50 (80–300 mA); ASIR-V, 40%; pitch, 1.531; rotation time, 0.35 seconds. The examination was completed with a caudal-cranial breath-hold CTPA without deep inspiration in order to avoid a transient interruption of contrast19], with intravenous administration of 50 ml of iodinated contrast medium at 4 to 5 ml/sec followed by a flush of 20 ml of physiological saline solution using a bolus-tracking technique. The CTPA acquisition parameters were: 100 kVp; tube current modulation with a noise index setting of 30 (140–480 mA); ASIR-V 50%, pitch, 1.531; rotation time, 0.35 seconds. The images were reconstructed with slice thickness of 1.25 mm and LUNG filter for the unenhanced low-dose series and 0.625 mm and SOFT filter for the CTPA. All images were archived and sent to our institution's Picture and Archiving Communication System.

Image analysis

All patient images were anonymized and CT-scans were randomized for interpretation on SyngoVia post-processing workstations (VB30, Siemens Healthcare). The images were reviewed by two radiologists with 10 and 12 years of experience in thoracic imaging (CB and EP). The images were reviewed independently with a final decision made by consensus. During image interpretation, the radiologists were able to change the viewing window, to zoom in or out on the images, use multiplanar reformations in any plane, and use maximal intensity projection or minimal intensity projection reformations. They were not made aware of the patient's clinical data.

For the CTPA images, the evaluation criteria were: quality of the CTPA based on the degree of opacification of the pulmonary arteries and the presence or absence of significant respiratory movement artifacts [20] (1 = excellent quality; 2 = satisfactory quality allowing a correct interpretation of all the pulmonary arteries; 3 = unsatisfactory quality not allowing a correct interpretation of all the pulmonary arteries), presence or not of acute pulmonary embolism (defined by the presence of a defect filling the lumen of a pulmonary artery on at least two consecutive axial sections [21]), most proximal position of the pulmonary embolism (main, lobar, segmental or subsegmental pulmonary arteries), topography of pulmonary emboli in the five pulmonary lobes, presence or absence of CT signs of severity (Right ventricle / left ventricle ratio of $\geq$1 [22]).

For the lung images, the evaluation criteria were: presence or absence of ground glass opacity (GGO), consolidation, crazy paving, linear opacities (including subpleural curvilinear opacities) and pleural effusion. According to the proportion of each pattern in comparison with the totality of the lung opacification, cases were classified as GGO dominant or consolidation predominant, if the proportion of each one of the patterns was respectively greater than 50% of the total [23]. A quantitative score was used to estimate the pulmonary involvement of all these abnormalities on the basis of the percentage of the total lung involved per lobe. For each of the five lung lobes, the lobar involvement was classified as

none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%), with corresponding scores of 0, 1, 2, 3, or 4. The total severity score (TSS) was reached by summing the five lobe scores (range from 0 to 20) [11].

Statistical analysis

Continuous variables were presented as means with standard deviation and extreme values in parentheses and compared by Mann-Whitney U test between APE and Non-APE groups. Categorical variables were presented as numbers and percentages and were compared by Fisher's exact test between both groups. Two-sided $p<0.05$ was considered statistically significant. Statistical analysis was done using R for Windows software (version 3.6.3, R foundation for Statistical Computing).

Results

Patient selection

The results of the patient selection process in our study are shown in Figure 1. From March, 14 2020 to April 6, 2020, 211 patients were referred by the Emergency Department to undergo a chest CT for suspicion or assessment of COVID–19 pneumonia. 146 (69%) patients had a final diagnosis of COVID–19 and 72 (49%) patients underwent CTPA and were included in our study. 13 (18%) patients had APE (APE group) versus 59 (82%) without APE (Non-APE group). Of the 72 patients included in the study, 58 (80%) patients had a positive RT-PCR for SARS-CoV–2, 10 (14%) did not have RT-PCR (including three from the APE group) and 4 (6%) had a diagnosis based on the typical clinical and radiological presentation of COVID–19 with RT- PCR results negative for SARS-CoV–2 (including two from the APE group).

Demographic, clinical and biological characteristics

Demographic, clinical and biological characteristics of included patients are summarized in table 1. The group consisted of 54 men and 18 women with an average age of 62.3 years and an average BMI of 26.7 kg / m². Patients in the APE group were significantly older than those in the Non-APE group (74.4 vs. 59.6 years, $p = 0.008$) with a significantly lower BMI (24.0 vs. 27.3 kg/m², $p = 0.021$). There was no significant difference between the APE group and the Non-APE group in terms of male/female distribution and the time between the onset of symptoms and the time at which CTPA was performed (8.3 vs. 7.5 days, $p = 0.617$). The most frequently found symptoms were fever (71%), dyspnea (68%) and desaturation (67%), with no significant difference between the two groups. Six patients (three in each group) were followed for active neoplasia. The clinical classification type was identified as moderate for 32 (44%) patients and severe to critical for 40 (56%) patients, with no significant difference between both groups. Biologically, 7 (54%) patients in the APE group and 34 (57%) in the Non-APE group had a D-dimer test on the same day as the CT scan. A significantly higher D-dimer level was found in the APE group compared to the Non-APE group (7.29 vs. 3.29 µg/ml, $p = 0.011$). Only one patient in the Non-APE group had a normal D-dimer level (0.33 µg/ml), and none of those in the APE group. All the patients in the APE group had had a CRP test on

the same day as the CT scan as well as 56 (95%) patients in the Non-APE group, with no significant difference in CRP levels between the two groups (136 mg/l vs. 105 mg/l, p = 0.407). As of April 15, 2020, 38 (53%) patients had returned home, 21 (29%) were hospitalized and 13 (18%) had died, with a significant difference in the death rate among patients in the APE group compared to the Non-APE group (46% vs. 13%, p = 0,015).

Imaging findings

Imaging findings of included patients are summarized in table 2.

Of the 72 CTPAs, 13 (18%) patients presented APE. Two (15%) patients had main, four (30%) lobar and seven (55%) segmental APE. The segments most often affected were the right lower lobe (61%) and the left lower lobe (54%). Five (38%) patients had bilateral thrombi while eight (62%) had unilateral involvement only. Five (38%) CTPA showed the presence of a CT sign of severity with a RV>LV ratio greater than or equal to 1. The quality score for the interpretation of the CTPA was comparable between the APE and Non-APE groups (1.8 vs. 2.0, p = 0.518) with a similar proportion of insufficient quality (38% vs. 35%, p = 1).

Chest CT showed anomalies related to COVID–19 pneumonia in 71 (99%) of the 72 patients. One (1%) patient in the Non-APE group had a normal chest CT scan. No significant difference between the two groups was found in the number of patients with more than two lobes involved (92% vs. 90%, p = 1). There was significantly less involvement of the left upper lobe in the APE group compared to the Non-APE group (62% vs. 86%, p = 0.05). The frequency of involvement of the other lobes did not show any significant difference between the two groups. Both the APE and Non-APE groups showed similar proportions of GGO (85% vs. 97%, p = 0.147), of consolidation (69% vs. 68%, p = 1), of crazy paving (38% vs. 37%, p = 1), of linear reticulation (69% vs. 78%, p = 0.490) and of pleural effusion (38% vs. 19%, p = 0.146). The type of pulmonary involvement with a predominance of GGO or consolidation was equivalent between the APE and Non-APE groups (54% vs. 56%, p = 1 and 46% vs. 42%, p = 1). The TSS did not show a significant difference between the APE and Non-APE groups (6.3 vs. 7.1, p = 0.365). 58 (81%) patients had a TSS lower than 10 with no significant difference between the two groups (85% vs. 80%, p = 1).

Discussion

COVID–19 disease presents many clinical forms, from cases of pauci- or asymptomatic patients to cases of severe forms of COVID–19 pneumonia which may lead to the patient's death [24]. The association between COVID–19 pneumonia and APE has already been described in patients hospitalized with severe to critical clinical type [13–18]. To the best of our knowledge, no study has yet evaluated the prevalence of APE in outpatients consulting to Emergency Department for clinical suspicion or degradation of COVID–19 pneumonia. One case describes the discovery of APE in a COVID–19 patient with a mild clinical form presenting to the Emergency Department for hemoptysis [25]. In our study, we focused on patients presenting to the Emergency Department for suspected or worsening COVID–19 pneumonia. Among these patients, many presented a deterioration of their clinical state with dyspnea (68%),

desaturation (67%) or chest pain (14%) but also an increase in D-dimer levels. These anomalies, although not specific, led us to complement our non-contrast chest CT scans with CTPA to eliminate APE. Of our 146 CT scans performed on COVID–19 patients, we complemented the examinations with 72 (49%) CTPA. Thirteen APE were discovered, representing a prevalence of 18% of the patients included in our study. Eight patients with APE had a severe to critical COVID–19 pneumonia but 5 of the 13 (38%) patients with APE had a moderate clinical form (Figure 2). These results seem to confirm the association between COVID–19 and APE, even in non-severe and non-hospitalized COVID–19 patients.

Several factors could explain this association. Radiologically, vascular thickening in ground-glass areas has been described in chest CT, which could correspond to a serious inflammatory response with vascular involvement leading to thrombosis [26]. Biologically, several studies have shown that COVID–19 patients tend to have higher D-dimer, fibrinogen and fibrin degradation product levels [27–28]. Zhou et al. also found in their study that a D-dimer level greater than 1 µg/ml was associated with fatal outcome of COVID–19 [29]. Other factors such as bed rest or confinement could also explain the onset of thromboembolic complications. In our study, three patients with APE had active cancer. Wider use of CTPA for COVID–19 patients seems to be advisable, with particular attention to COVID–19 patients with co-morbidities causing a higher thromboembolic risk.

Given the risks associated with the injection of iodinated contrast medium (renal failure and allergy) and the additional radiation dose due to CTPA, it does not seem reasonable to perform CTPA systematically with COVID–19 patients. In our study, we investigated whether the radiological manifestation of COVID–19 pneumonia in non-contrast chest CT scans could be associated with a higher rate of APE. The TSS of our patients' CT scans was on average 7/20, with no significant difference between the two groups. Only one (8%) patient in the APE group had a TSS greater than 10 and five (38%) had minimal lung damage with a score lower than 5. As for the TSS, our study did not show any significant difference concerning the type of lung lesions detected in COVID–19 patients with or without APE. Non-contrast chest CT therefore does not make it possible to differentiate the patients requiring complementary CTPA to search for APE. It is worth noting that in our protocol, CTPA was performed using breath-holding apnea without deep inspiration in order to obtain an optimal opacification of the pulmonary arteries by avoiding transient interruption of contrast [19]. But this acquisition without deep inspiration leads to ventilatory disturbances impeding detailed analysis of the pulmonary parenchyma, in particular the GGO. The unenhanced series with deep inspiration therefore remains necessary in order to have an optimal analysis of the pulmonary parenchyma for COVID–19 pneumonia (Figure 3).

Although the radiological manifestation of COVID–19 pneumonia does not allow for the selection of patients at risk of APE, we found a significantly higher D-dimer level in the APE group compared to the Non-APE group. The D-dimer level seems to be an important parameter in the management of COVID–19 patients, making it possible both to assess the severity of the disease [29] and to suspect APE. Given that the increase in the D-dimer level can be linked to COVID–19 disease, it would be interesting to evaluate on the basis of large-scale studies if there is a cut-off D-dimer level at which CTPA could be recommended to search for APE in COVID–19 patients [16]. Pending further data on D-dimer levels, we believe that all

patients with COVID–19 pneumonia and an increased level of D-dimer should benefit from CTPA to eliminate APE, whenever possible.

Our study had several limitations. First, the number of patients included was small. Other large-scale studies are needed to confirm our results and analyze whether other factors could help to optimize the indications for CTPA in COVID–19 patients. Second, certain medical or biological data were not available due to the retrospective nature of our study. Third, our study did not include a control group to compare the prevalence of APE in a group of patients with COVID–19 pneumonia versus other types of pneumonia. Finally, the CTPA quality scores showed that 36% of CT scans had an interpretation score of 3, i.e. not optimal for the analysis of all the pulmonary arteries. This was mainly due to respiratory artifacts in patients with dyspnea. It is therefore difficult to totally exclude the possibility that some patients may have had distal APE not seen in the CTPA.

In conclusion, our study showed an 18% prevalence of APE in non-hospitalized COVID–19 patients referred to CTPA by the Emergency Department. More studies are needed to determine which COVID–19 patients require CTPA as a complement to the non-contrast chest CT scan.

Declarations

The authors received no external funding for this research.

The authors declare no competing interests.

Abbreviations

APE: Acute pulmonary embolism

COVID-19: coronavirus disease 19

CTPA: Computed tomography pulmonary angiography

GGO: Ground glass opacities

RT-PCR: Reverse Transcription Polymerase Chain Reaction

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Tables

	All Patients (n=72)	APE group (n =13)	Non-APE group (n=59)	P value
Age (years)	62.3 ± 17.8 (22-92)	74.4 ± 15.0 (48-92)	59.6 ± 17.4 (22-92)	0.008
BMI (kg/m²)	26.7 ± 5.4 (16.1-51.2)	24.0 ± 3.5 (18.7-32)	27.3 ± 5.6 (16.1-51.2)	0.021
Gender (n)				1
Male	54 (75%)	10 (77%)	44 (75%)	..
Female	18 (25%)	3 (23%)	15 (25%)	..
Time to CTPA (days)	7.6 ± 4.2 (0-20)	8.3 ± 5.7 (0-19)	7.5 ± 3.9 (0-20)	0.617
Symptoms (n)				
Fever	51 (71%)	9 (69%)	42 (71%)	1
Cough	41 (57%)	6 (46%)	35 (59%)	0.537
Dyspnea	49 (68%)	10 (77%)	39 (66%)	0.529
Desaturation	48 (67%)	9 (69%)	39 (66%)	1
Chest pain	10 (14%)	2 (15%)	8 (14%)	1
Asthenia	29 (40%)	4 (31%)	25 (42%)	0.541
Myalgia	19 (26%)	3 (23%)	16 (27%)	1
Diarrhea	11 (15%)	1 (8%)	10 (17%)	0.381
Clinical type (n)				0.766
Moderate	32 (44%)	5 (38%)	26 (44%)	..
Severe-critical	40 (56%)	8 (62%)	33 (56%)	..
Biology				
D-dimer (µg/ml)[a]	3.61 ± 4.54 (0.33-20.00)	7.29 ± 6.34 (2.41-20.00)	3.29 ± 4.62 (0.33-20.00)	0.011
CRP (mg/l)[b]	111.9 ± 84.2 (2.1-345)	136.8 ± 105.8 (35.0-345.0)	105.0 ± 76 (2.1-331.0)	0.407
Outcome (n)				
Discharge	38 (53%)	4 (31%)	34 (58%)	0.124
Hospitalization	21 (29%)	3 (23%)	17 (29%)	1
Death	13 (18%)	6 (46%)	8 (13%)	0.015

Table 1. Demographic, clinical and biological characteristics of patients included in the study.

Except for p value, continuous variables are presented as mean ± standard deviation and extreme values in parentheses and compared by means of the Mann-Whitney U test between the APE group and Non-APE group. Categorical variables are presented as numbers and percentage in parentheses and compared by means of Fisher's exact test between the two groups. APE=acute pulmonary embolism; BMI=body mass index; CRP=c-reactive protein; CTPA=computed tomography pulmonary angiography.

[a] D-dimer were available for 7 (54%) patients in the APE group and 34 (57%) in the Non-APE group.

[b] CRP were available for all patients in APE group and 56 (95%) in Non-APE group.

Table 2. Chest CT findings for all patients and for APE vs. Non-APE groups.

	All Patients (n=72)	APE group (n=13)	Non-APE group (n=59)	P value
CTPA quality score	2.0 ± 0.9 (1-3)	1.8 ± 1.0 (1-3)	2.0 ± 0.8 (1-3)	0.518
Chest CT severity score	7.0 ± 3.5 (0-15)	6.3 ± 3.7 (1-15)	7.1 ± 3.4 (0-15)	0.365
Lobe involvement (n)				
Left upper lobe	59 (82%)	8 (62%)	51 (86%)	0.05
Left lower lobe	64 (89%)	12 (92%)	52 (88%)	1
Right upper lobe	64 (89%)	10 (77%)	54 (92%)	0.151
Right middle lobe	58 (81%)	8 (62%)	50 (85%)	0.114
Right lower lobe	68 (94%)	13 (100%)	55 (93%)	1
More than two lobes	65 (90%)	12 (92%)	53 (90%)	1
Radiological findings (n)	68 (94%)	11 (85%)	57 (97%)	0.147
GGO	49 (68%)	9 (69%)	40 (68%)	1
Consolidation	27 (38%)	5 (38%)	22 (37%)	1
Crazy paving	55 (76%)	9 (69%)	46 (78%)	0.490
Linear reticulation				
Radiological pattern (n)	40	7 (54%)	33 (56%)	1
GGO > consolidation	31	6 (46%)	25 (42%)	1
Consolidation > GGO	1	0 (0%)	1 (2%)	..
Normal CT-scan				
Pleural effusion (n)	16 (22%)	5 (38%)	11 (19%)	0.146

Except for p value, continuous variables are presented as mean ± standard deviation and extreme values in parentheses and compared by means of the Mann-Whitney U test between the APE group and Non-APE group. Categorical variables are presented as numbers and percentage in parentheses and compared by means of Fisher's exact test between the two groups. APE=acute pulmonary embolism; CTPA=computed tomography pulmonary angiography; GGO=ground-glass opacity.

Figures

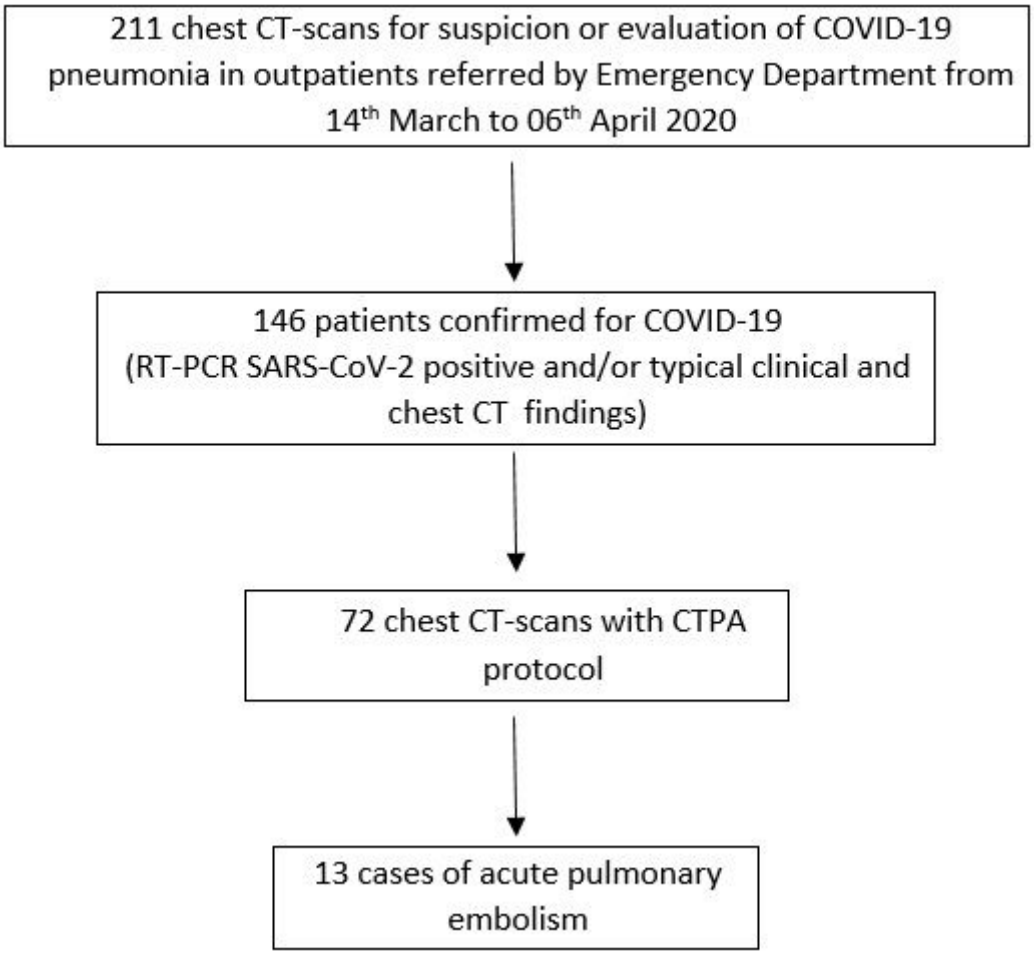

Figure 1

Graph showing the patient selection process for inclusion in our study.

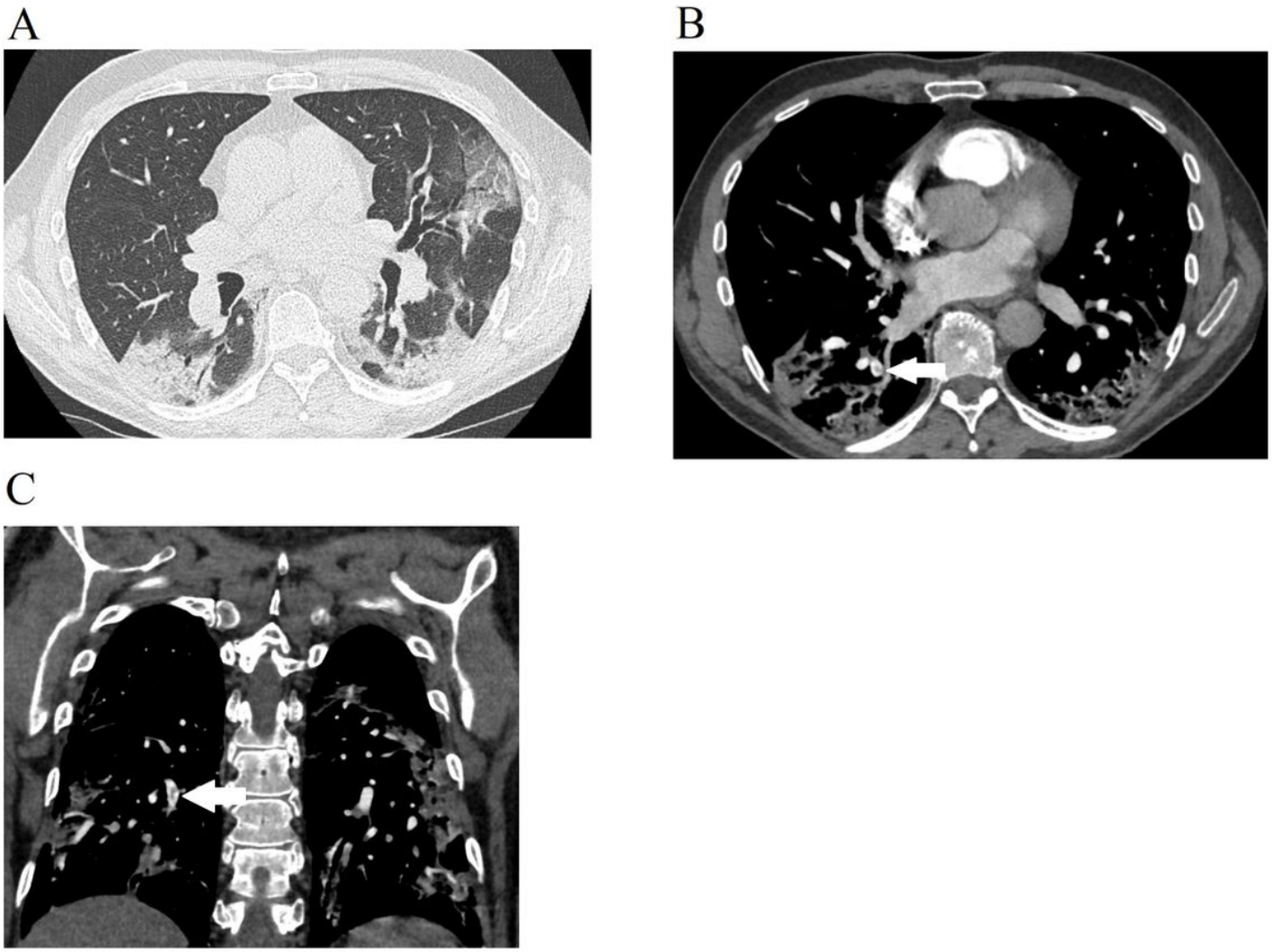

Figure 2

Segmental acute pulmonary embolism in COVID-19 patients. 61-year-old man presenting to the Emergency Department for fever and myalgia during 9 days with new onset of dyspnea without desaturation. The RT-PCR for SARS-CoV-2 was positive. Unenhanced chest CT-scan (a) revealed a typical COVID-19 pneumonia with a mild lung involvement (TSS of 7). CTPA in axial (b) and coronal reformation (c) showed a segmental acute pulmonary embolism of the right lower lobe (arrows). After two days of hospitalization, patient was discharged at home with a good outcome.

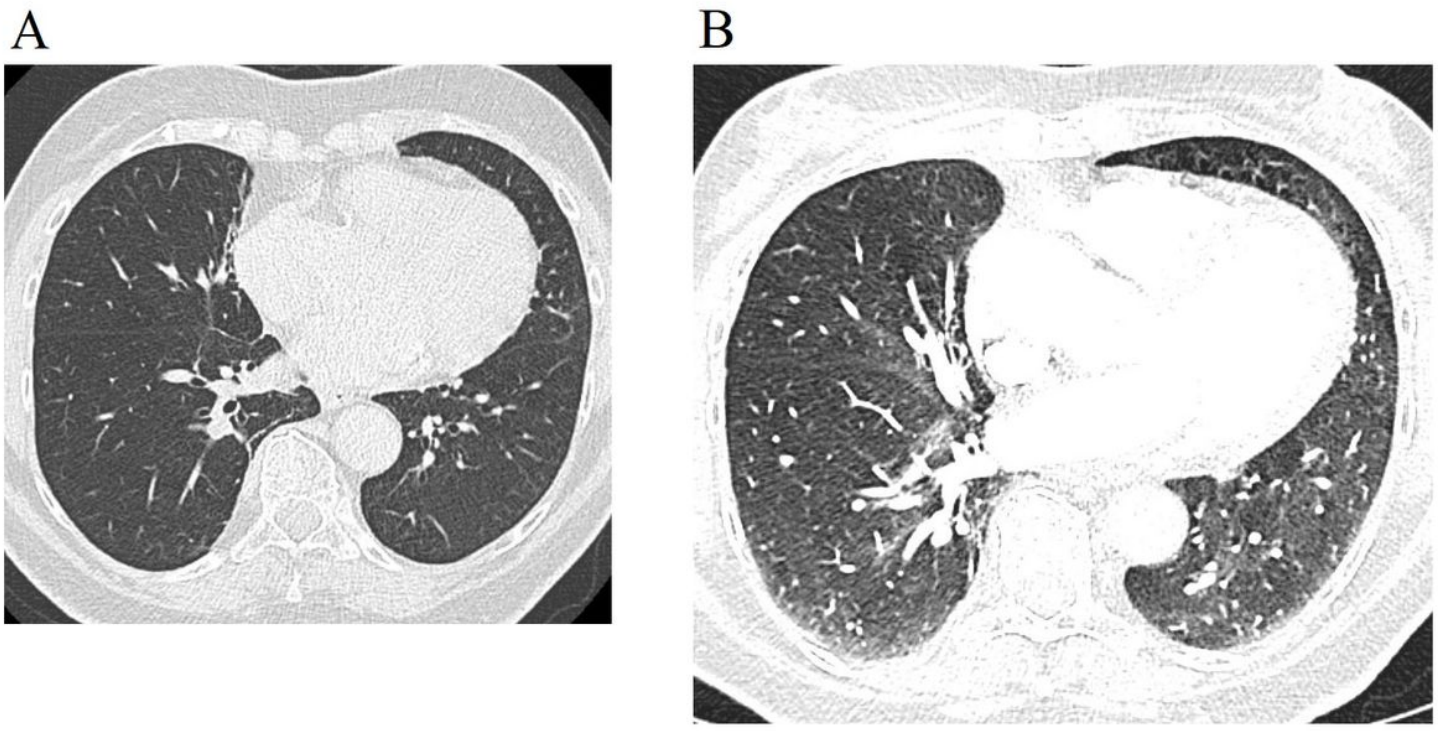

Figure 3

Comparison of lung findings in COVID-19 patients between unenhanced low dose chest CT (a) and CTPA (b) acquisitions. Unlike the unenhanced images, the CTPA images were not performed with deep inspiration to avoid the appearance of transient interruption of contrast. The CTPA series therefore includes ventilation disturbances which may resemble false GGO images (b). The unenhanced series with deep inspiration is necessary to allow correct analysis of the parenchyma in COVID-19 patients.