**Pulmonary Thromboembolism in COVID-19: Venous Thromboembolism or Arterial Thrombosis?**

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**Abstract**

**Background**

Coronavirus disease 2019 (COVID-19) in hospitalized patients is frequently complicated by pulmonary thromboembolism (PTE).

**Purpose**

To investigate CT pulmonary angiography (CTPA) findings of PTE in COVID-19 and its association with clinical and radiological conditions.

**Materials and Methods**

This retrospective study includes 109 hospitalized patients with COVID-19 who underwent CTPA for suspected PTE from March 20 to May 3, 2020. Data were collected from our PACS. CTPA

findings of PTE were evaluated. Based on the presence or absence of PTE, patients were divided in two groups and the clinical and radiological conditions were compared using Mann-Whitney U test and $\chi^2$ test.

**Results**

Study population comprised 82M/19F, mean age 64.1±15.0 [95% confidence interval CI:60.4-67.6] years. CTPAs were performed 19.8±6.1 [95% CI:18.1-20.2] days after the symptom onset and 10.5±3.8 [95% CI:10.2-12.9] days after the admission. Patients with PTE were 41/101(40.6%). PTE was mostly bilateral or only right (37/41[90.2%]), mainly involved segmental (37/41[90.2%]) or subsegmental (25/41[61.0%]) arteries, and affected mainly the lower lobes branches (30/41[73.2%]). Parenchymal segments supplied by segmental arteries with PTE showed a prevalent consolidation pattern (25/37[67.6%]). Deep vein thrombosis (DVT) was present only in 5/41(12.2%). Comparing groups with and without PTE, no significant difference was observed in age, gender, onset symptoms, comorbidities, tumor history, use of respiratory supports, activated partial thromboplastin time, prothrombin time and DVT. Conversely, differences were evaluated in CT lesion score (15.7±1.4 [95% CI:15.3-16.1] vs 14.1±1.1 [95% CI:13.8-14.4], p=0.035); d-dimer (p<0.001); lactate dehydrogenase (LDH) (p<0.001), and C-reactive protein (CRP) (p=0.042).

**Conclusion**

PTE in COVID-19 involves mainly the segmental and sub-segmental arteries of segments affected by consolidations in patients with more severe lung disease. We hypothesize that the development of PTE in COVID-19 might be a pulmonary artery thrombosis due to severe lung inflammation and hypercoagulability rather than thromboembolism.

Summary Statement

Pulmonary thromboembolism in hospitalized patients with COVID-19 involves mainly the segmental and sub-segmental arteries of the segments affected by consolidations, in patients with more severe COVID-19 pneumonia as scored by CT and with increased laboratorial biomarkers (d-

dimer, LDH and CRP). Moreover COVID-19 triggers a hypercoagulable state. These findings contribute to the discussion between pulmonary artery thrombosis versus venous thromboembolism.

Key Points

- Pulmonary thromboembolism (PTE) is frequently observed in COVID-19 patients, mainly involving the segmental (90.2%) and sub-segmental arteries (61.0%) of pulmonary segments affected by a consolidation pattern (67.6%).

- Patients with more severe COVID-19 lung disease (higher CT lesion score, d-dimer, LDH and CRP) tend to be more affected by PTE.

- We hypothesize that the development of PTE in COVID-19 could possibly be a pulmonary artery thrombosis due to severe lung inflammation and a hypercoagulable state rather than common thromboembolism.

**Introduction**

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019 [1]. Real-time reverse transcription polymerase chain reaction (RT-PCR) of viral nucleic acid is regarded as the reference standard in the diagnosis of COVID-19 [2]. CT imaging is helpful in the early detection of COVID-19 pneumonia, in the differentiation among clinical stages, and could provide information about disease progression [3, 4].

As described by a recent study, blood hypercoagulability is common among hospitalized COVID-19 patients [5]. In particular, the effect of SARS-CoV-2 infection on pulmonary coagulation is regulated by different pathophysiological mechanisms [6]. It has been reported that coagulation is activated in response to proinflammatory cytokines and it is accelerated by the dysfunction of endothelial cells induced by infection [7]. In addition, hypoxia, a common finding in severe

pneumonia, can stimulate thrombosis not only through increasing blood viscosity, but also via a hypoxia-inducible transcription factor-dependent signaling pathway [8]. For these reasons, anticoagulation therapy in severe COVID-19 patients has been recommend [9, 10]. Despite systematic thromboprophylaxis, Klok et al. [11] reported an incidence of 31% for thrombotic complications in intensive care unit patients with COVID -19.

Few studies and isolated clinical cases of COVID-19 pneumonia with pulmonary thromboembolism (PTE) have been recently published [12 – 16]. Poissy et al. [15] postulated an increased prevalence of PTE in COVID-19 patients and Danzi et al. [16] suggested that severe COVID-19 pneumonia could be a precipitant factor for acute PTE in the absence of major predisposing factors.

The awareness of such complication is essential because it could cause clinical deterioration [17]. Therefore, the aim of this study is to investigate computed tomography pulmonary angiography (CTPA) findings of PTE in patients with COVID-19 and its association with clinical and radiological conditions.

**Materials and Methods**

*Study population*

All procedures performed on studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Our study protocol was approved by the Institutional Review Board of our Hospital; written informed consent was waived. No industry support was given.

This retrospective study includes 109 hospitalized patients with COVID-19 confirmed by RT-PCR on oropharyngeal swab, who underwent CTPA for suspected PTE from March 20 to May 03, 2020. Data were collected from the PACS of "Infermi" Hospital Rimini, a tertiary center in Northern Italy. All CTPAs were performed due to the sudden onset of clinical deterioration with unexplained worsening of dyspnea, symptoms suggestive for PTE, d-dimer elevation, or in case of mismatch

between clinical worsening and chest radiograph stability. Eight patients with non-diagnostic CTPA were excluded: 5 because of motion artifacts and 3 due to attenuation values in the mean pulmonary artery (MPA) lower than 250 HU; this threshold is considered optimal for PTE evaluation [18, 19]. Our final cohort was composed by 101 patients.

*CT acquisition protocol and post-processing*

CT examinations were performed using a 64-row multi-detector CT scanner (Lightspeed VCT, GE Healthcare U.S.); patients laid in supine position with arms elevated. A 20-gauge cannula was inserted into a superficial vein of the right antecubital fossa, connected to a two-way power injector. All patients were examined with the same standardized protocol, based on two acquisitions from the lung apices to the costophrenic recess; first a non-contrast-enhanced scan, then a contrast-enhanced scan. The scan parameters were tube voltage 120 kVp with automatic tube current modulation, pitch = 0.95, matrix = 512×512 pixels, and field of view = 350 mm×350 mm. A volume of 70 ml of contrast medium (Iomeprol, 400 mgI/ml; Bracco Imaging, Milan, Italy) was injected at a flow rate of 4 ml/s with a bolus tracking technique, followed by 40 ml of saline solution at the same rate. A circular region of interest (ROI) was placed within the MPA; the acquisition started automatically when a threshold of 100 HU (Hounsfield Units) was reached. All images were reconstructed with a slice thickness of 0.625-1.250 mm with the same increment, using an iterative reconstruction algorithm. The lung parenchyma was evaluated using a sharp filter with window/level of 1200/-600 HU and mediastinal structures were evaluated using a softer filter with window/level of 350/50 HU. Multi-planar reconstruction and maximal intensity projection were also generated.

*CT evaluation*

Two radiologists in consensus (one with more than 5 years, and the second with more than 20 years of experience in chest imaging) retrospectively evaluated the CT examinations.

A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities based on the area involved. Each lobe was visually scored from 0 to 5 as: 0, no involvement; 1, <5% involvement; 2, 25% involvement; 3, 26%-49% involvement; 4, 50%-75% involvement; 5, >75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) [20]. The following diagnostic criteria for PTE were used: intraluminal filling defects or non-visualization of the pulmonary arteries compared to the contralateral side. The obstruction CT index was calculated as described by Qanadli et al. [21]. Pulmonary artery diameter and right ventricle dilatation were evaluated.

*Clinical and laboratory analysis*

For each patient age, sex, onset symptoms (fever, cough, dyspnea, myalgia or fatigue, diarrhea, nausea and vomiting), number of comorbidities, smoking history, and oncologic history were collected. Moreover, for each patient, the following laboratory tests were collected within 48 hours after the CT examinations: activated partial thromboplastin time (aPTT), prothrombin time (PT), lactate dehydrogenase (LDH), C-reactive protein (CRP), d-dimer. The use of mechanical respiratory support, presence of deep venous thrombosis (DVT) and the type of therapy were annotated. Finally, the CT score of the pulmonary lesions at non-contrast acquisition was collected. Venous duplex-ultrasound of the lower extremities was performed routinely in all patients.

*Statistical analysis*

A dedicated statistical software was used (MedCalc v19.1.6, MedCalc Software, Ostend, Belgium). Continuous variables were displayed as mean ± standard deviation and categorical variables were reported as counts and percentages. CTPA findings suggestive of PTE were evaluated. Based on the presence or absence of PTE, patients were subdivided in two groups. Group 1, with PTE, and Group 2, without PTE. Age, sex, onset symptoms, such as fever, cough, dyspnea, number of comorbidities,

smoking history, oncologic history, use of ventilatory support, aPTT, PT, LDH, CRP, d-dimer, presence of DVT, and CT score were compared between two groups, using Mann-Whitney U test and χ2 test, respectively, for continuous and categorical variables. This was a convenience sample; therefore, no statistical power analysis was done a priori for comparing the distribution of variables between Groups 1 and 2. A p-value <0.05 was defined as statistically significant.

## Results

### Patient Population

Among the 101 included patients, 82 (81.2%) were male and 19 (18.8%) female, mean age 64.1 ± 15.0 [95% confidence interval CI: 60.4-67.6]. The main onset symptoms were fever (70.3%) and cough (56.4%). Rates of other onset symptoms, number of comorbidities, smoking history and tumor history are illustrated in Table 1.

In both groups the most frequent tumor in patients with positive oncologic history was prostate cancer. Laboratory tests within 48 hours after the CT examinations for PTE, such as aPTT, PT, LDH, CRP and d-dimer, the use of respiratory supports, the presence of DVT and CT score are summarized in Table 2. All patients were treated with antivirals, anticoagulants, and hydroxychloroquine. Thromboembolism prophylaxis consisted of subcutaneous enoxaparin 4000 I.U.

### PTE findings

CTPAs were performed 19.8 ± 6.1 [95% IC: 18.1-20.2] days after the symptom onset and 10.5 ± 3.8 [95% IC: 10.2-12.9] days after the admission. PTE was observed in 41/101 patients (40.6%), 35 males, 6 females; in 20 (48.7%) it was bilateral, in 17 (41.5%) only right, and 4 (9.8%) only left. PTE involved only the pulmonary trunk in 1/41 (2.4%), the main pulmonary arteries in 9/41 (22.0%), lobar arteries in 21/41 (51.2%) cases. Segmental arteries were involved in 37/41 (90.2%)

and sub-segmental arteries in 25/41 (61.0%) cases. The arteries for the upper lobes were involved in 5/41 (12.2%), for the middle lobe and the lingula in 6/41 (14.6%) and for the lower lobes in 30/41 (73.2%). Parenchymal segments supplied by segmental arteries with PTE showed predominant consolidation pattern in 25/37 (67.6%), predominant ground-glass pattern in 11/37 (29.7%), and no opacities in 1/37 (2.7%).The number of cases with exclusively involvement of segmental arteries was 14/41 (34.1%) and exclusively involvement of subsegmental arteries was 8/41 (19.5%). The mean obstruction CT index was 31.5% ± 14%. Dilatation of pulmonary artery was observed in 7/41 (17.0%) patients and dilatation of the right ventricle in 2/41 (4.9%).

*Comparison between groups with and without PTE*

Comparing groups with and without PTE, no statistically significant difference was observed in age, sex, presentation symptoms such as fever, cough and dyspnea, number of comorbidities, smoking or oncologic histories, use of ventilatory support, aPTT, PT, or presence of DVT. Conversely, differences were noted in the CT score (15.7±1.4 [95% IC: 15.3-16.1] vs 14.1±1.1 [95% IC: 13.8-14.4], p=0.0350); d-dimer (p<0.001); LDH (p<0.001) and CRP (p=0.0420). Results are showed in Table 3.

**Discussion**

Blood hypercoagulability is a common finding among hospitalized patients with COVID-19 [5]. The effect of COVID-19 on pulmonary coagulation and the resulting development of PTE could be due to proinflammatory cytokines, endothelial dysfunction and hypoxia [6, 8]. Several papers report high incidence of PTE in COVID-19, ranging from 22% to 39% [10, 11, 12, 13, 14, 15, 17, 22]: the awareness of such complication is of vital importance, because it can lead severe clinical deterioration.

We carried out a retrospective study to investigate CTPA findings of PTE in hospitalized patients with COVID-19 and its association with radiological and clinical parameters. In our study, thromboembolism was confirmed in a high percentage of patients (40.6%). The overall prevalence of PTE in our series is higher relative to that previously reported in the literature (22% - 39%) [10, 11, 12, 13, 14, 15, 17,22]. A possible explanation of this high frequency is that we collected patients from the beginning of the pandemic, who did not undergo appropriate prophylaxis. Our findings differ from the study of Grillet et al. [12] who reported lower PTE incidence (23%) in patients with severe COVID-19. The two studies differ in some aspects; in the latter, information about d-dimer was not collected and association between CT severity score and PTE was not attempted. Our study confirmed that more severe COVID-19 pneumonia, as scored by CT, and increased laboratorial biomarkers (d-dimer, LDH and CRP) were more commonly associated with PTE. However, Grillet et al. [12] did report an association between invasive mechanical ventilation and male gender with PTE, which was not evident in our cohort.

We hypothesized that PTE is a common complication of severe COVID-19 pneumonia occurring a few weeks after symptoms onset. In support of our hypothesis, we carried out a literature review about PTE in previous similar pandemics caused by SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). SARS-CoV infection has been responsible for various coagulation abnormalities and multiple vascular thromboses commonly seen in lungs, suggesting that an underlying thrombophilic state can induce pulmonary artery thrombi formation [23]. In the same way, hematological manifestations of MERS include thrombocytopenia and coagulopathy with an associated status of disseminated intravascular coagulation at different sites, including the pulmonary arteries [24].

In the present study, PTE was mostly bilateral (48.7%) or only involving the right lung (41.5%); it often involved the small caliber peripheral pulmonary arteries, such as segmental (90.2%) or subsegmental (61.0%) branches, as already described by Chen et al [22], especially in the lower lung lobes. Because of the small caliber of the vessels involved, the main PTE finding was vascular

cut-off. Indeed, it is of interest to note that parenchymal segments supplied by segmental arteries with PTE often showed prevalence of CT consolidation pattern 25/37 (67.6%). Besides, the number of exclusively segmental arteries (34.1%) or only subsegmental arteries involved (19.5%) is higher than those reported in non-COVID-19 series [25, 26]. These sites seem to correspond to the most common distribution of COVID-19 opacities [27]. Using a parallel rationale, Zotzmann et al. [28] suggested that subpleural consolidations in COVID-19 should prompt further diagnostic workup due to the potential occurrence of PTE.

In our study lower extremity venous Duplex Ultrasound (DUS) was performed in all hospitalized patients; interestingly, DVT was rarely concomitant with PTE (12.2%). When comparing groups with and without PTE, no differences were noted in the presence of DVT (p=0.9820). However, we cannot exclude that thrombi arising from different body regions could have contributed to the PTE observed in our series, since DUS would miss thrombi residing in the abdominopelvic or upper limbs. Besides, we cannot exclude that patients who had DVT with no PTE could have developed PTE later on, since a hypercoagulable state is also present in these patients.

Moreover, between the two groups with and without PTE, no difference was observed according symptoms at presentation of COVID-19, number of comorbidities, oncologic history or use of respiratory support. Thus, we hypothesize that the development of PTE in severe COVID-19 pneumonia could be related to severe lung inflammation rather than to common risks factors for PTE or DVT. Considering potential limitations related to the narrow statistical power of our small sample, these preliminary findings - as also stated by previous authors [15] - may support the hypothesis that filling defects seen in pulmonary artery branches could be related to thrombosis rather than thromboembolic phenomena in COVID-19. This could have clinical implications as this hypothesis could support the indication of anticoagulant therapy as part of the first line therapeutic approach, regardless of traditional risk factors for DVT [29, 30]. Our assumption seems to be confirmed by the significant higher values of d-dimer (p<0.001), LDH (p<0.001), CRP(p=0.0420) and CT lesion score (p=0.0350). Further studies are still needed to settle the discussion between the

thrombosis versus embolic hypothesis, as well as to evaluate the prognostic role of PTE in these patients and to evaluate the management of anticoagulants.

Our study has some limitations. First, it was retrospective and monocentric, leading to increased risk for selection bias. Second, the influence of the therapies was not evaluated. Third, study design and relatively small sample size of patients with PTE have limited power to definitively address the thrombosis versus embolism conundrum.

## Conclusion

PTE is frequently observed in COVID-19 patients and mainly involves the segmental and subsegmental arteries supplying the lung parenchyma affected by consolidation. Patients with more severe COVID-19 pneumonia, as scored by CT, and with increased laboratorial biomarkers (d-dimer, LDH and CRP) were more commonly affected by PTE. These findings are in keeping with other observations showing that COVID-19 triggers a hypercoagulable state, and also contribute to the discussion between pulmonary artery thrombosis versus venous thromboembolism as potential hypotheses for this phenomenon.

**Compliance with ethical standards**

Conflict of interest

The authors declare no potential conflict of interest associated with this study.

Ethical standards

All procedures performed on studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was waived due to the COVID-19 emergency situation.

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**Table 1. Clinical features of patient population.**

| Features | | All patients (n=101) |
|---|---|---|
| Age (y) | | 64.1 ± 15.0 [95% CI: 60-67] |
| Sex | | |
| | Male | 82 (81.2%) |
| | Female | 19 (18.8%) |
| Symptoms | | |
| | Fever | 71 (70.3%) |
| | Cough | 57 (56.4%) |
| | Dyspnea | 32 (31.7%) |
| | Myalgia or fatigue | 46 (45.5%) |
| | Diarrhea | 8 (7.9%) |
| | Nausea and vomiting | 4 (4.0%) |
| Number of Comorbidities | | 1.2 ± 0.3 [95% CI: 1.2-1.3] |
| Smoking History | | 25 (24.8%) |
| Positive Oncologic History | | 20 (19.8%) |

Abbreviations. – n: number; CI: confidence interval.

**Table 2. Laboratory tests within 48 hours of the CT examinations for PTE; use of ventilatory support; radiological investigation**

| Laboratory tests | | All patients (n=101) |
|---|---|---|
| | aPTT (s) | 25.2 ± 2.1 [95% CI: 24.8-25.6] |
| | PT (s) | 12.8 ± 1.9 [95% CI: 12.3-13.3] |
| | LDH (U/L) | 334 ± 59 [95% CI: 322-345] |
| | CRP (mg/L) | 125 ± 45 [95% CI: 116-133] |
| | D-dimer (ng/mL) | 6643 ± 468 [95% CI: 5714-7572] |
| Ventilatory support | | |
| | Non-invasive ventilation | 76 (75.2%) |
| | Invasive ventilation | 25 (24.8%) |
| Radiological investigations | | |
| | Deep Venous Thrombosis | 11 (10.9%) |
| | CT score | 14.5 ± 1.1 [95% CI: 13.9-15.1] |

Abbreviations. – n: number; CI: confidence interval; aPTT: activated partial thromboplastin time; PT: prothrombin time; LDH: lactate dehydrogenase; CRP: C-reactive protein.

**Table 3. Comparison between groups with (Group 1) and without (Group 2) Pulmonary Thromboembolism**

| | Group 1 (n=41) | Group 2 (n=60) | *p* |
|---|---|---|---|
| Age (y) | 64.4±13.6 [95% CI: 58.6-70.1] | 63.8 ± 16.6 [95% CI: 56.8-70.8] | 0.3140 |
| Sex (M/F) | 32/9 | 50/10 | 0.6832 |
| Fever (Y/N) | 30/11 | 41/19 | 0.7636 |
| Cough (Y/N) | 27/14 | 34/26 | 0.4716 |
| Dyspnea (Y/N) | 13/28 | 23/37 | 0.6375 |
| Comorbidities (n) | 1.5±0.2 [95% CI: 1.0-1.9] | 1.0 ± 0.2 [95% CI: 0.6-1.5] | 0.9860 |
| History tumor (Y/N) | 11/30 | 9/51 | 0.2260 |
| Smoking history | 11/28 | 14/46 | 0.8221 |
| aPTT (s) | 25.1±2.0 [95% CI: 18.2-29.7] | 25.6 ± 1.8 [95% CI: 20.3-29.1] | 0.1854 |
| PT (s) | 11.0±1.8 [95% CI: 10.5-12.3] | 12.2 ± 2.1 [95% CI: 10.9-15.0] | 0.1279 |
| LDH (U/L) | 378±50 [95% CI: 366-398] | 347±21 [95% CI: 336-349] | <0.001 |
| CRP(mg/L) | 169±20.0 [95% CI: 165-177] | 92±156 [95% CI: 83.5-91.0] | 0.0420 |
| d-dimer (ng/mL) | 11462 ± 2528 [95% CI: 10092–12033] | 2743 ± 568 [95% CI: 2688 – 3572] | <0.001 |
| NIV/IV | 28/13 | 48/12 | 0.2696 |
| DVT (Y/N) | 5/36 | 6/54 | 0.9820 |
| CT score | 15.7±1.4 [95% CI: 15.3-16.1] | 14.1±1.1 [95% CI: 13.8-14.4] | 0.0350 |

Abbreviations. – n: number; CI: confidence interval; M/F: male/female; Y/N: yes/no; NIV: non-invasive ventilation; IV: invasive ventilation; DVT: deep venous thrombosis
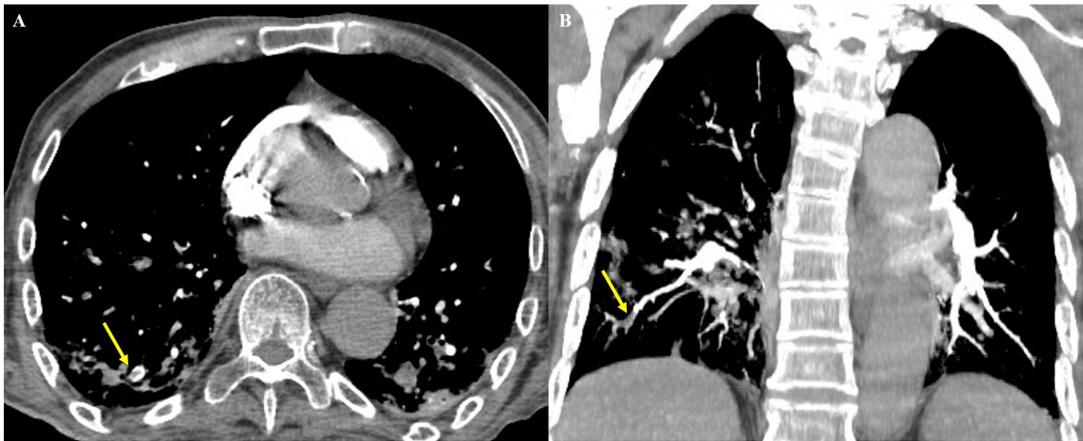
**Figures**
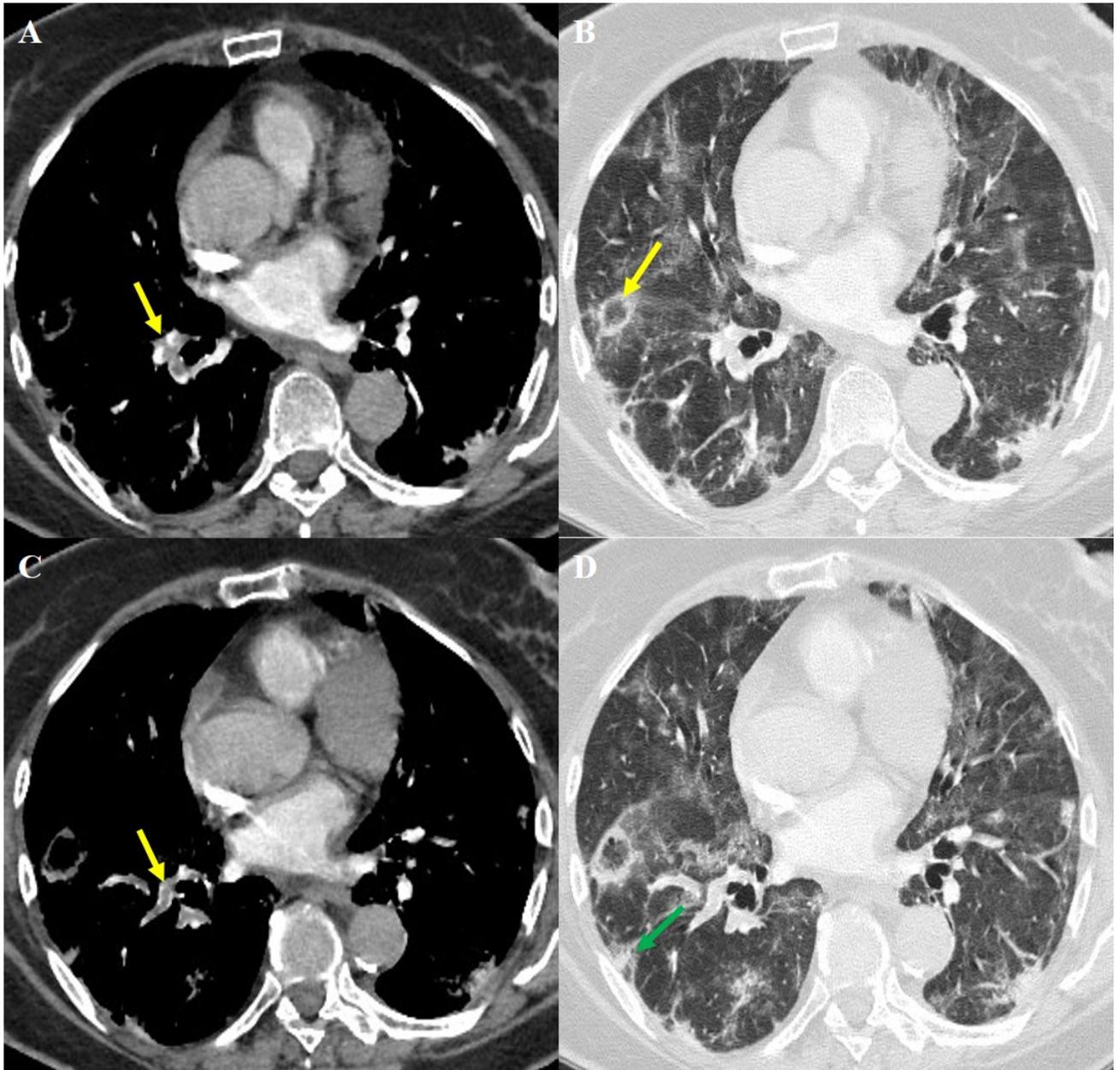


**Fig.1** 85 year-old-male, after 16 days of hospitalization in the intensive care unit with invasive ventilation  sudden increase of d-dimer value.
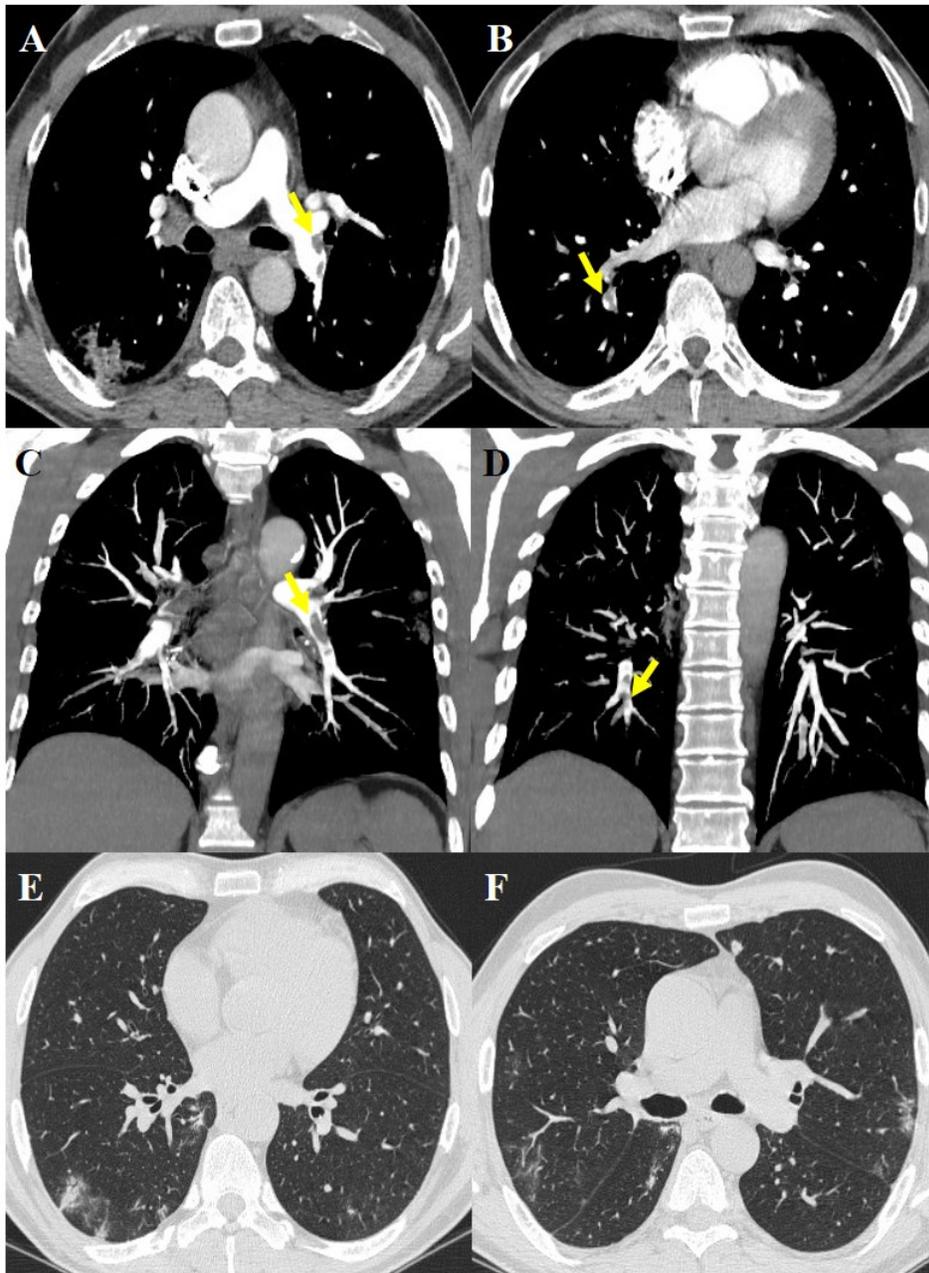
The images show pulmonary thromboembolism in the segmental arteries for the lower right lobe (yellow arrows) (A-C), lung parenchyma is characterized by reverse halo sign (yellow arrow) (B),

diffuse ground-glass and peripheral sub-pleural wedge-shaped consolidation in lower lung lobe (green arrow) (D).



**Fig.2** 71 year-old-female, after 21 days of hospitalization with non-invasive ventilation sudden dyspnea and increase of d-dimer value.

The images show pulmonary thromboembolism in the segmental and sub-segmental arteries for the lower right lobe (yellow arrow) (A), confirmed by MIP reconstruction (yellow arrow) (B).

**Fig.3** 63 year-old-male, after 17 days of hospitalization without respiratory support sudden increase of d-dimer value.

The images show pulmonary thromboembolism in the lobar arteries for the left lower lobe (yellow arrow) (A) and in the segmental arteries for the right lower lobe (yellow arrows) (B), confirmed by MIP reconstructions (yellow arrows) (C, D). Lung parenchyma is characterized by some peripheral sub-pleural bilateral ground-glass opacities and consolidations (E, F).