# Thrombolysis of late acute pulmonary embolism post-COVID-19

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## ABSTRACT

Late pulmonary embolism (PE) in COVID-19 occurs weeks after SARS-CoV-2 infection and has been reported even in patients presenting mild influenza syndrome. There is no reliable explanation for its occurrence, but it appears to involve the persistence of viral inflammatory changes associated with phospholipid exposure and the release of potentially thrombogenic membrane microparticles. Thrombolysis with plasminogen activators, especially alteplase, is well established in high-risk PE cases and considered in intermediate-high risk events. These drugs promote benefits such as pulmonary reperfusion, pulmonary artery pressure reduction, and right ventricular (RV) stabilization. However, there are few reported cases of thrombolysis in PE secondary to COVID-19. We present the case of an adult female patient without significant risk factors for thrombogenic events diagnosed with mild COVID-19 who, on day 18, after symptom onset, evolved with PE associated with RV instability and underwent thrombolysis with intravenous alteplase successfully.


**Keywords:** COVID-19, SARS-CoV-2, Pulmonary embolism, Thrombolysis, Alteplase.

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## INTRODUCTION

*Coronavirus Disease-2019* (COVID-19) is a zoonosis whose etiological agent is the β-coronavirus SARS-CoV-2. It can manifest as mild influenza to severe acute respiratory syndrome (SARS) accompanied by different degrees of inflammatory response and coagulation changes, sometimes determining thrombotic events[1,2].

Complications such as pulmonary embolism (PE) and venous thromboembolism (VTE) have been described mainly in critically ill patients with acute-phase COVID-19[1, 3, 4]. However, PE can occur over four weeks, even in patients who have manifested mild flu-like symptoms[5–8].

In cases with PE with instability or high risk, fibrinolytic therapy with plasminogen activators (t-pA), mainly alteplase, is indicated in addition to therapeutic doses of heparins[9]. However, there is a scarcity of publications regarding thrombolysis in events related to COVID-19[2,10].

In this report, we present the case of an adult female patient diagnosed with mild COVID-19 who, on day 18, after the onset of symptoms, developed PE associated with right ventricular (RV) instability and underwent successful thrombolysis with intravenous alteplase.

The alteplase in PE is well established, and the benefits include, in addition to pulmonary reperfusion, hemodynamic stability[9,11]. It has been used in prolonged infusion on an experimental basis in refractory cases of SARS-CoV-2 SARS but with transient effects.[12,13]. Experiences reporting its success when used for thrombolysis are critical to benefit other patients. Therefore, we hope to contribute to the medical literature and clinical practice by reporting our experiences.

This study was approved by the Ethics and Research Committee of the institution - CAAE 47111121.9.0000.5442/ report 4.908.967.

### *Clinical case*

G.L.R., female, white, 37 years old, born in São Paulo (SP), four children, housewife. She denied smoking, alcohol, or drug use. No history of comorbidities, personal or family history of VTE, pregnancy loss, cancer, surgery in the last three months, or recent immobilization. She had been using daily combined oral contraceptives for over ten years: cyproterone + ethinylestradiol (2 mg/0.035 mg). She was not immunized against influenza or SARS-CoV-2.

She sought the Respiratory Center at Hospital do Servidor Público Municipal de São Paulo (HSPM), complaining of fever for one day, dyspnea, chest pain, and left lower limb (LLL) pain.

She had a history of influenza syndrome 18 days prior to hospital admission, with a positive *Reverse Transcription-Polymerase Chain Reaction* (RT-PCR) for COVID-19 performed in a health center at the onset of symptoms. She was acyanotic, afebrile (37.3ºC), with oxygen saturation (Sat02) of 88% on room air (r.a.), respiratory rate (RR) of 25 ipm, and a vesicular murmur (VM+) with crackling bibasilar rales. Cardiac auscultation with normal rhythmic sounds, without murmurs, heart rate (HR) of 147 bpm, and blood pressure (BP) 113x73 mmHg (MAP: 85 mmHg). Pain on palpation of the left calf, however, without edema or other phlogistic signs.

Laboratory tests (Table 1), a rapid test for Influenza (negative), and an electrocardiogram (ECG) of 12 derivations (sinus tachycardia) were carried out. In addition to chest computed tomography (CT), a pulmonary artery angiography (angio-CT) and venous Doppler ultrasound (US) of the LIP were requested, considering PE with high probability (Wells 7.5 points).

Chest CT characterized a high probability image for COVID-19 with the presence of peripheral and bilateral ground-glass opacities and consolidations with an estimated involvement of > 50% of the lung parenchyma (Figure 1).

Angio-CT revealed extensive pulmonary thromboembolism in the main pulmonary arteries, in lobar, segmental, and bilateral subsegmental branches (Figure 2). Deep venous thrombosis in the popliteal vein and left posterior tibial veins was confirmed by the US.

On reevaluation, although an improvement was reported, dyspnea, chest pain, and tachycardia persisted (HR: 124 bpm), RR: 24 ipm, Sat02 93% on a non-rebreather mask at 10 liters/minute. On further pulmonary auscultation, there was a progression of crackling rales up to 1/3, mainly on the right.

A "*point of care*" echocardiogram (POCUS) was performed by an experienced professional that demonstrated RV free wall hypokinesia (McConnell's Sign) with its reduced systolic function, as well as pulmonary artery systolic pressure (PSAP) estimated

**Table 1.** Laboratory Tests.

| | Parameters | Result | Reference Values* |
|---|---|---|---|
| **Arterial blood gas on admission** | pH | 7.38 | 7.35 – 7.45 |
| | $pCO_2$ | 40mmHg | 35 – 45mmHg |
| | $PaO_2$ | 69mmHg | 80 – 100mmHg |
| | $HCO_3$ | 21mmol; | 22 – 26mmHg |
| | BE | -3.2 | -3 - +3 |
| | Total CO2 | 21,9 mmol/L | 23 – 27 mmol/L |
| | Sat02 | 88% | 95-98% |
| | Fi02 | 21% | 21% |
| **Admission blood count** | Hemoglobin | 13.3g/dL | 13 - 17.5g/dL |
| | Hematocrit | 39.2% | 37 - 50% |
| | Total Leukocytes | 8200mm³ | 3500 - 10500mm³ |
| | Bastions | --mm³ | 0 - 84000mm³ |
| | Segmented | 6970mm³ | 1700 - 7000mm³ |
| | Lymphocytes | 902mm³ | 1000 - 3000mm³ |
| | Platelets | 261000mm³ | 150000 - 450000mm³ |
| **Other laboratory tests** | Admission D-dimer | 3025ng/mL | Até 198ng/mL |
| | Post-thrombolysis D-dimer** | 1569ng/mL | Até 198ng/mL |
| | Lactate Dehydrogenase (LDH) | 354U/L | 125 – 220U/L |
| | C-reactive protein (CRP) | 23,67mg /L | Inferior a 1mg/dL |
| | High sensitivity troponin | <0.01µg/mL | Até 0, 026µg/mL |
| | Glutamic-oxalacetic transaminase (TGO) | 9U/L | 5 – 34U/L |
| | Glutamic-pyruvic transaminase (GPT) | 44U/L | 0 – 55U/L |
| | Urea | 17mg/dL | 15 – 45mg/dL |
| | Creatinine | 0,72mg/dL | 0,7 – 1.25mg/dL |
| | Sodium | 136mmol/L | 136 -145mmol/L |
| | Potassium | 4.6mmol/L | 3.5 – 5.1mmol/L |
| | Prothrombin time (PT) | 13.8 segundos | Sem referência |
| | *International Normalized Ratio (INR)* | 1.2 | 0.80 – 1.25 |
| | Activated Partial Thromboplastin Time (aPTT) | 39s | 20 – 40s |

* Values standardized by the laboratory.

** Collected 24 hours after thrombolysis.

at 49 mmHg (RV ≤ 35 mmHg) using tricuspid valve regurgitant flow measurement.

Diagnosed DVT in the LIP and PE of intermediate-risk by *Pulmonary Embolism Severity Index* [(PESI) III - 87 points)] with RV instability. Thrombolysis with intravenous alteplase (actilyse®) at a dose of 100 mg was chosen, being 10 mg in intravenous bolus over 2 minutes followed by 90 mg in infusion pump over 2 hours. Subsequently, she was referred to the intensive care unit (ICU), where she remained for three days.

On the 6th day of hospitalization (IHD), she was discharged to the ward using a nasal O2 catheter at 2 liters/minute with Sat02 97%. An angio-CT protocol TEP control was requested with significant improvement of the PE pattern as described in Figure 3. A control transthoracic echocardiogram (TTEtt) was also performed with RV with preserved contractility [TAPSE of 18 mm (RV > 16 mm)], and PSAP estimated at 44 mmHg.

Subcutaneous (SC) enoxaparin 12h/12h (Versa®) was used during hospitalization. On the

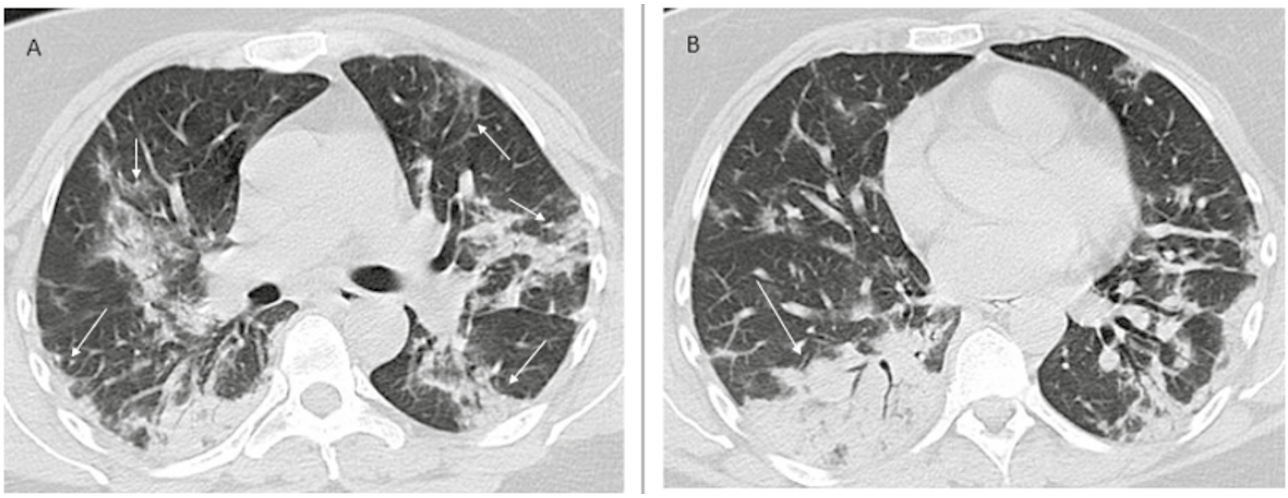


**Figure 1.** Conventional chest CT images in transverse section: (A) - in the arrow: focal ground-glass opacities with peripheral and bilateral distribution; (B) - in the arrow: Observable consolidations mainly in the right lobe. The findings are compatible with SARS-CoV-2 infection[14].

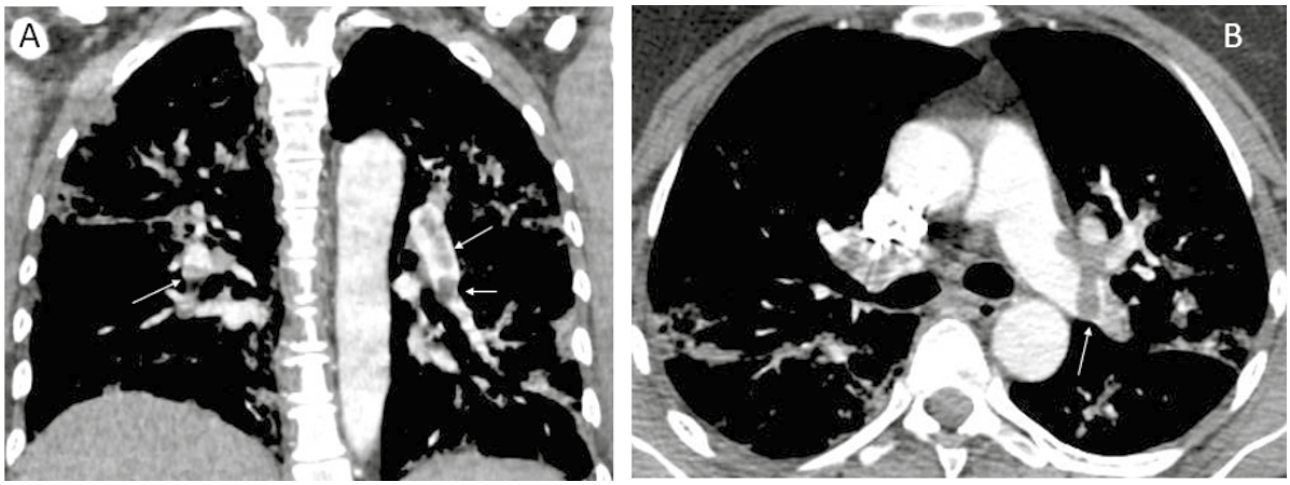


**Figure 2.** Pre-thrombolysis pulmonary artery CTA images. (A) Coronal view - in the arrow: filling failures in bilateral lobar, segmental, and subsegmental branches. (B) Cross-sectional view - in the arrow: extensive filling failure in the left main pulmonary artery.

8th IHD, after 24 hours of oxygen weaning, she was discharged with a prescription for Rivaroxaban (Xarelto®) and referred to outpatient follow-up.

## DISCUSSION

For this patient, the hypothesis of late PE secondary to COVID-19 occurred because she had no other risk factor or history that was more likely than SARS-CoV-2 infection. Although she had been in daily use of combined oral contraceptives for more than ten years, her history of flu-like syndrome with positive RT-PCR for the new coronavirus 18 days ago was sufficient to justify the VTE picture.

Furthermore, infections, including COVID-19, are associated with an increased risk of vascular events[1,2,15]. Long-term combined oral contraceptive use alone is a weak risk factor for VTE[16].

Thrombophilia testing is only recommended for patients who have VTE at a young age associated with a weak risk factor (minor surgeries, combined oral contraceptives, or immobility), a strong family history of VTE (first-degree relatives affected at a

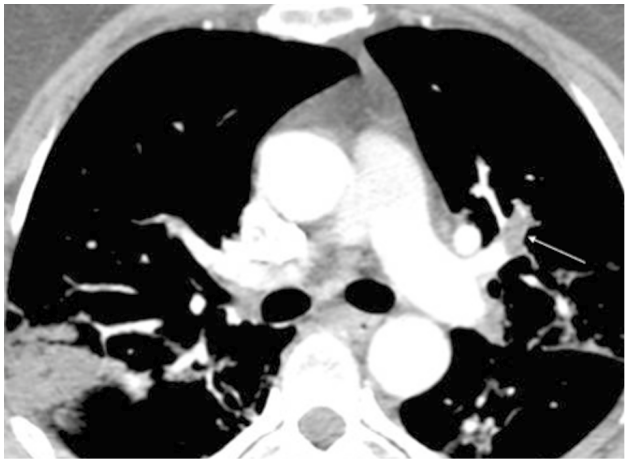

**Figure 3.** Cross-sectional CTA image of post-thrombolysis pulmonary artery. In the arrow: segmental filling failure to the upper lobe of the left lung.

young age), recurrent VTE events (especially at a young age), and VTE at unusual sites (splanchnic or cerebral veins)[16].

It is also noteworthy that antibodies such as anticardiolipin and lupus anticoagulant, among others, can be detected in the circulation during infection by SARS-CoV-2, with the possibility of inducing misdiagnosis of autoimmune diseases or thrombophilias[15,17]. It is thought that the circulation of these antibodies would be related to inflammatory activation and the procoagulant environment [17].

The thromboembolic complications that occur in patients with COVID-19 in the acute phase, even without significant history or risk factors, seem to involve endothelial injury, platelet activation, cyclic inflammatory response mediated by TH1 and TH17 lymphocytes, cytokines (IL1-b, IL-17, IL-22, and TNFα), signaling pathways (hypoxia-induced; urokinase), which generate a state of hypercoagulability[1,3,4].

However, there is no reliable explanation for late thromboembolic events. One hypothesis is the persistence of viral changes associated with phospholipid exposure and the release of potentially thrombogenic membrane microparticles[8].

Late PE does not have a specific definition, but it is considered when it occurs weeks after SARS-CoV-2 infection and has been seen in patients with mild influenza syndrome, such as our patient. In the case series of Vechi et al. (2020), five patients with mild COVID-19, with no previous hospitalization and no history of VTE, after apparent improvement, developed PE in the third and fourth week after symptom onset[5].

In the study of Kanso et al. (2020), two patients previously hospitalized for COVID-19 who received adequate prophylactic anticoagulation also developed pulmonary thromboembolism days after hospital discharge. Both were in the second week after symptom onset[8].

Due to the high probability for PE with Wells of 7.5 points, we performed angio-CT that confirmed the hypothesis (Figure 3). This is the most commonly used test, detecting thrombi up to 1 to 2 mm in a specific segment. Conventional chest CT has very variable sensitivity and specificity in different series[9]. However, it is the most suitable imaging study to identify SARS-CoV-2 infection[14].

Regardless of the probability score used (Wells or Geneva), the proportion of PTE is 10% in low, 30% in intermediate, and 65% in high probability [9]. The European guideline recommends D-dimer in the low and intermediate probabilities, as it has a high negative predictive value in PE[9]. However, this test alone is not recommended as a predictor for embolism in patients with COVID-19, because the serum level may be altered from the beginning of the infection. Currently, it represents a marker for the severity and prognosis of this disease[1–3].

Additionally, Doppler US of the MIE confirmed ipsilateral venous occlusion. In up to 70% of confirmed PE cases, the cause is DVT. This finding is enough to justify anticoagulation without the need for further confirmatory tests[9].

Faced with a diagnosis of PE and being hemodynamically stable, that is, without shock or hypotension (high risk), we should preferably stratify by the PESI score[9]. The patient in question was classified as intermediate risk (87 points). In these cases, complementation is recommended with cardiac injury markers (troponins and natriuretic peptide - BNP) and RV dysfunction evaluation by echocardiography or angio-CT[9].

POCUS was performed and showed RV dysfunction (McConnell's sign), reduced systolic function, and pulmonary hypertension; however, troponin was negative. In our hospital, BNP is not routinely performed. Due to the echo finding and progression of crackling rales that could indicate circulatory shock or acute pulmonary edema, we under-stratified the patient into intermediate-high risk despite laboratory markers.

The "*point of care*" study can be an ally to investigate direct or indirect cardiac complications related to COVID-19 or even in the evaluation of RV dysfunction for stratification of PE as already used by the ECOtt. Despite the ease and speed with which the method is performed, it requires experienced professionals, should not be used alone in diagnosis, and additional studies are recommended[18,19].

The ECG allowed exclusion of acute myocardial infarction (AMI) with supra-ST, tachyarrhythmias, and ventricular overload. In our patient, sinus tachycardia corroborates the most common electrocardiographic alteration reported in PE. In some cases, the S1Q3T3 pattern can be found[9].

After excluding the differential diagnoses of dyspnea and chest pain, AMI, pleural or pericardial effusion, ruptured aortic aneurysm, among others, and confirming the diagnosis of PE, we opted for intravenous thrombolysis with alteplase. The patient in this case had no contraindication to thrombolytic therapy.

For high-risk PE cases, thrombolysis is formally indicated, and for intermediate high-risk cases, it should be considered[9,20]. The benefits of this therapy include, in the first days, restoration of pulmonary perfusion, decrease in pulmonary artery resistance and pressure with consequent improvement in RV function[9,11]. Therefore, we considered the patient eligible, and the benefits outweighed the risks.

There are few reports of thrombolysis in PTE secondary to SARS-CoV infection 2. A 47-year-old patient on mechanical ventilation who evolved with shock underwent a "*point of care*" echocardiogram that found a large thrombus migrating from the right atrium into the pulmonary circulation and acute RV dilation and dysfunction. Intravenous alteplase 100 mg was used over 2 hours with no intercurrences. After 20 days of hospitalization, he was discharged with oral rivaroxaban[10].

In another case, a young male patient with confirmed COVID-19 developed high-risk PE despite using prophylaxis for VTE. He also underwent thrombolysis with alteplase 100 mg intravenously over 2h. After a few weeks, he returned to work. This demonstrates the efficacy of this therapy in this new disease, which does not differ from the management of PE due to other causes[15].

Alteplase is a fibrin-specific recombinant tissue plasminogen activator; it induces the conversion of plasminogen into plasmin, promoting clot dissolution. Its half-life is up to 6 minutes. It can reduce pulmonary arterial pressure by an average of 30% after 2 hours of infusion. However, there is a risk of systemic bleeding[11].

Another t-pA, tenecteplase, is being used more frequently as clinical trials confirm its safety; however, reteplase lacks more evidence[11].

The t-pA in COVID-19 has also been used experimentally in patients with COVID-19 under mechanical ventilation due to acute respiratory distress syndrome (ARDS) refractory to therapeutic measures where cardiopulmonary bypass (ECMO) and advanced resources are limited. In one of these protocols, three patients received intravenous alteplase under infusion over 24 hours. Overall, transient improvement in oxygenation and PaO2/FiO2 ratio was observed with weak evidence[12,13].

Therapeutic heparinization is well established in PTE and is recommended for inpatients, including those undergoing thrombolysis[9]. It is also recommended in COVID-19 in a prophylactic manner. It is advocated that besides being anticoagulant, they would have cytoprotective, anti-inflammatory, and antiviral effects. This could reduce pulmonary microthrombosis, one of the alterations pointed out as responsible for PE and ARDS.[21] We used enoxaparin SC 12h/12h (Versa®) in our patient during hospitalization.

We consider the thrombolytic therapy in our case a success because there were no complications or bleeding, as well as the RV function was reestablished as shown in control ECHOtt, and areas of pulmonary occlusions decreased considerably in the post-thrombolysis CTA, in addition to the complete weaning from oxygen support, absence of need for mechanical ventilation and discharge to home.

We emphasize that the Angio-CT control TEP protocol was performed purely for scientific interest with the patient's consent after explaining all the risks. We do not recommend, and no evidence in the literature justifies its routine use to prove the effectiveness of thrombolytic therapy.

The changes in serum levels of LDH (354 U/L), CRP (23.67 mg/L), and D-dimer may reflect both the generalized inflammation by COVID-19 and the repercussion of PE. These tests and others such as PT, TTpa, ferritin, platelet count, and fibrinogen

have prognostic values and may also be indicators of complications in the infection by the new coronavirus (correlating them with the clinical picture)[1–3].

Oral anticoagulation after PE is recommended for all patients[9,20]. Direct factor Xa inhibitors such as rivaroxaban, or even vitamin K-dependent factor inhibitors, such as warfarin, can be used as anticoagulants. Although rivaroxaban has been widely used, the choice should be individualized according to socioeconomic characteristics, comorbidities, and the possibility of medical follow-up.

Given the favorable evolution and the success of the thrombolytic therapy, the patient was discharged with rivaroxaban (Xarelto®) and will be followed up in our outpatient clinics.

## CONCLUSION

PE is a complication in patients with COVID-19 in the acute phase or even weeks after SARS-CoV-2 infection. A young patient, without contraindications to thrombolysis, with low bleeding risk, may benefit from intravenous alteplase therapy when there is hemodynamic instability or intermediate risk associated mainly with RV dysfunction and/or markers of cardiac injury.

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**Conflicts of interest**
We declare that there are no conflicts of interest, fomentation, or donation from any private entity.

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