Systemic fibrinolysis for acute pulmonary embolism complicating acute respiratory distress syndrome in severe COVID-19: a case series

A peculiar form of coagulopathy develops in patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with elevations in D-dimer levels (parallel with a rise in markers of inflammation), alterations in clotting times, and thrombocytopenia. Consequently, a high incidence of venous thrombo-embolism (VTE) as well as of pulmonary embolism (PE) has been reported, and linked to increased mortality, in both Chinese and European cohorts.

Clinically, this coagulation imbalance seems different from the classical disseminated intravascular coagulation with a bleeding diathesis, and results in a very high incidence of thrombotic and thrombo-embolic events with, prominently, VTE/PE of variable severity.

We hereby report a retrospective case series of four patients needing mechanical ventilation for SARS-CoV-2 infection, who were diagnosed with high-risk PE and underwent systemic fibrinolysis with full-dose alteplase, with rapid haemodynamic and respiratory success in three of them. Figures 1 and 2, as well as their legends, report the most relevant clinical characteristics. Detailed descriptions of the four cases appear in the Supplementary material online.

The described patients developed sudden haemodynamic instability, and the diagnosis of PE was made with bedside echocardiography, which showed either direct (‘thrombus in transit’, two patients) or indirect (right ventricular strain) signs of PE in all patients. Three cases had been treated with anticoagulants before PE: one case even suffered PE while on sodium heparin, one while on a full, weight-adjusted dose enoxaparin, and the third one 2 days after sodium heparin full anticoagulation was...
Computed tomography pulmonary angiography (CTPA) was performed in three cases for diagnostic confirmation, showing segmental and subsegmental embolic material in all cases, and a ‘saddle embolus’ in one. All four patients received 100 mg of alteplase over 2 h, followed by anticoagulation with sodium heparin. Three patients survived to discharge from the intensive care unit (ICU). None of the four cases experienced bleeding.

Only another small case series has reported the use of thrombolytics in COVID-19 PE patients, whereas fibrinolysis was not mentioned in other cohort studies. This is probably due to bleeding concerns because of the unfamiliar coagulopathy often associated with thrombocytopenia, occurring in up to 58% of subjects with severe disease, and the difficulty of disentangling the haemodynamic impact of PE from those of acute respiratory distress syndrome (ARDS) and pneumonia. Indeed, some authors disagree with a recent Consensus Document, and support catheter-directed treatment as a potential first-line therapeutic approach.

We believe that ARDS and VTE/PE are, in COVID-19 patients, strictly inter-related, and that pulmonary micro- and macrocirculatory thrombosis has a pathogenetic role. It is likely that the prevalence of imaging-evident PE (e.g. thrombi in pulmonary macrovascular) is higher than reported and dependent on the logistics and willingness to move highly infectious patients to an imaging suite. Evidence of ‘thrombus in transit’, but perhaps also indirect signs of right heart strain, might then prompt systemic fibrinolysis even if CTPA confirmation is not available or feasible.

**Supplementary material**

Supplementary material is available at European Heart Journal – Cardiovascular Pharmacotherapy online.

**Conflict of interest:** none declared.

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![Figure 2](https://example.com/figure2.png)

**Figure 2.** Clinical and imaging characteristics of patient 3 (A) and patient 4 (B–D). (A) Bedside echocardiography image taken in right parasternal short-axis view showing the aortic valve (AoV), the right ventricular outflow tract (RVOT), the pulmonary valve (PV), the main pulmonary artery (PA) trunk and its branches, the right PA, and the left PA. At the bifurcation level, a hypoechoic, billowing mobile large mass (see Supplementary material online, Video 2) is evident, indicating ‘thrombus in transit’ (red arrow). (B) Time course of D-dimer (green triangle and green line) and of activated partial thromboplastin time (aPTT, red circles and red line). The patient was on standard, nomogram-adjusted i.v. sodium heparin, which was substituted with 60 mg enoxaparin on 7 April due to low D-dimer levels. The diagnosis of pulmonary embolism suspected by echocardiography was confirmed by computed tomography (CT) on 9 April (black vertical dotted line). Alteplase 100 mg over 2 h was given and sodium heparin was then restarted. Pulmonary embolism and fibrinolysis were accompanied by a massive, albeit transient, rise in D-dimer levels. (C) CT pulmonary angiogram slice demonstrating embolus in the right inferior lobar artery (red arrow). (D) Lung CT scan demonstrating multiple, bilateral parenchymal ground-glass opacities.
Correspondence

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Roberta Della Bona¹, Alberto Valbusa¹, Giovanni La Malfa², Daniele Roberto Giacobbe³, Pietro Ameri¹,², Niccolò Patroniti³,⁶, Chiara Robba⁵, Vered Gilad¹, Angelo Insors¹, Matteo Bassetti³,⁵, Paolo Pelosi³,⁶, Italo Porto¹,²*, on behalf of the GECOVID study group¹

¹CardioThoracoVascular Department (DICATOV), Ospedale Policlinico San Martino – IRCCS, Genoa, Italy; ²Department of Internal Medicine and Medical Specialties (DIMI), University of Genoa, Genoa, Italy; ³Infectious Diseases Unit, Ospedale Policlinico San Martino – IRCCS, Genoa, Italy; ⁴Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; ⁵Department of Anesthesia and Intensive Care, Ospedale Policlinico San Martino – IRCCS, Genoa, Italy; ⁶Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

*Corresponding author. University of Genoa, Cardiovascular Unit, Department of Internal Medicine and Specialties (DiMI), Viale Benedetto XV, 10, 16132 Genoa, Italy. Tel. +39 010 5551, Email: italo.porto@unige.it

†Members of the GECOVID study group are listed in the Supplementary material online.