

Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection represents a pandemic emergency of dramatic proportions.¹ The clinical course of SARS-CoV-2 infection often meets the criteria for acute respiratory distress syndrome (ARDS), with progressive severity ultimately leading to a rapid death.¹⁻³ The pathophysiology of ARDS in severe cases of SARS-CoV-2 infection is attributed to a hyperimmune reaction of the host.³ Since the early descriptions, it appeared that the progressive worsening lung function of patients infected with SARS-CoV-2 was potentially driven by host immune response.⁴

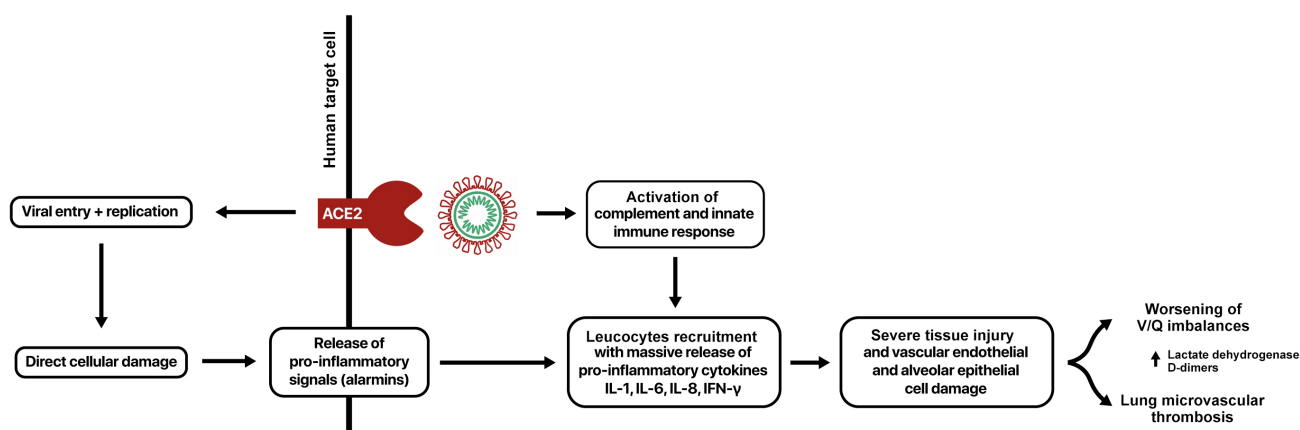
SARS-CoV-2 enters target cells through the cell surface receptor angiotensin-converting enzyme 2 (ACE2), which is expressed on the surface of lung epithelial cells and enterocytes of the small intestine. ACE2 is also present in arterial and venous endothelial cells and in arterial smooth muscle cells of multiple organs.⁵ Its replication causes direct

ABSTRACT

We suggest the use of MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as a new name for severe pulmonary coronavirus disease 2019 (COVID-19). We hypothesise that, in predisposed individuals, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis. This progressive endothelial thromboinflammatory syndrome may also involve the microvascular bed of the brain and other vital organs, leading to multiple organ failure and death. Future steps in the understanding of the disease and in the identification of treatments may benefit from this definition and hypothesised sequence of events.

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Figure 1. MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as an atypical acute respiratory distress syndrome working hypothesis



ACE2 = angiotensin-converting enzyme 2; IFN = interferon; IL = interleukin; V/Q = ventilation/perfusion.

cellular damage and release of pro-inflammatory alarmins from dying cells.⁶ In addition to this direct effect, viral particles may elicit innate immune responses of the host through different mechanisms, including the activation of alveolar macrophages and of the complement cascade through the lectin pathway. Moreover, locally formed immune complexes may have a role in further activating the complement system and boosting the inflammatory response, as suggested by the recent finding of a large number of activated plasma cells in the bronchoalveolar lavage of a patient with severe coronavirus disease 2019 (COVID-19) pneumonia.⁷

The activation of complement cascade not only directly causes endothelial damage but further recruits leucocytes via C3a and C5a formation, responsible for a massive local release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and interferon- γ .⁸ Within this massive host immune response, lymphocytes, resident macrophages, monocytes and neutrophils exert their potent pro-inflammatory functions, causing additional severe collateral tissue injury and massive vascular endothelial and alveolar epithelial cell damage and microvascular thrombosis.^{9,10} Functional implications of this peculiar ARDS pathogenesis include a progressive worsening of ventilation/perfusion imbalances and a loss of hypoxic vasoconstriction reflexes, with a marked component of microvascular pulmonary thrombosis, as suggested by lactate dehydrogenase and D-dimer elevations.¹¹ In the late stages of ARDS, the progression of endothelial damage with microvascular thrombosis can spread locally in the lung and potentially extends the systemic inflammatory reaction involving the microvascular bed of the kidneys, brain and other vital organs.¹²

Since the beginning of the pandemic in Italy, our hospital underwent a deep reorganisation to face the emergency, and we admitted to our institution more than 700 patients with severe SARS-CoV-2-induced pneumonia requiring oxygen therapy, including more than 100 patients admitted to the intensive care unit.¹³ After our experience in managing these patients and thanks to an extensive multidisciplinary input, we now propose a mechanism of lung damage, primarily explained by a dramatic alveolar endothelial damage leading to a progressive endothelial pulmonary syndrome with microvascular thrombosis, and suggest MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as an atypical ARDS working hypothesis (Figure 1).

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Competing interests

None declared.

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References

- World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim guidance. Version 1.2, 13 March 2020. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) . (viewed Apr 2020).
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.

POINT OF VIEW

- 3 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; doi: 10.1056/NEJMoa2002032. [Epub ahead of print].
- 4 Herold T, Jurinovic V, Arnreich C, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. *BMJ* 2020; doi: 10.1101/2020.04.01.20047381; [Preprint, 10 April 2020].
- 5 Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203: 631-7.
- 6 Yang D, Han Z, Oppenheim JJ. Alarmins and immunity. *Immunol Rev* 2017; 280: 41-56
- 7 Giani M, Seminati D, Lucchini A, et al. Exuberant plasmocytosis in bronchoalveolar lavage specimen of the first patient requiring extracorporeal membrane oxygenation for SARS-CoV-2 in Europe. *J Thorac Oncol* 2020; 10.1016/j.jtho.2020.03.008. [Epub ahead of print]
- 8 Monteleone G, Sarzi-Puttini P C, Ardizzone S. Preventing COVID-19-induced pneumonia with anticytokine therapy. *Lancet Rheumatol* 2020; doi: 10.1016/S2665-9913(20)30092-8. [Epub ahead of print]
- 9 Mastellos DC, Ricklin D, Lambris JD. Clinical promise of next-generation complement therapeutics. *Nat Rev Drug Discov* 2019; 18: 707-29.
- 10 Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med* 2017; 377: 562-72.
- 11 Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020; doi: 10.1164/rccm.202003-0817LE. [Epub ahead of print]
- 12 Tan CW, Low JGH, Wong WH, et al. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. *Am J Hematol* 2020; doi 10.1002/ajh.25822. [Epub ahead of print]
- 13 Zangrillo A, Beretta L, Silvani P, et al. Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: facing the COVID-19 pandemic emergency. *Crit Care Resusc* 2020. [Epub ahead of print]