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# Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19

To the Editor,

Between February and March 2020, the *Journal of Thrombosis and Haemostasis* has published four papers addressing the intricate, complex, and still little understood relation between COVID-19 and thrombogenesis.[1-4]

SARS-Cov-2 induces in severe cases a cytokine storm that ultimately leads to the activation of coagulation cascade, causing thrombotic phenomena.[5] There is a further strong link between abnormal coagulation parameters (D-dimer and fibrin degradation products) and mortality. Tang et al described that 71.4% of nonsurvivors and 0.6% of survivors showed evidence of disseminated intravascular coagulation (DIC), suggesting that DIC is a frequent occurrence in severe COVID-19.[4] The frequency of DIC in these patients is much higher than that reported for severe SARS.[6]

There are ongoing widespread discussions among intensivists on the possible use of anticoagulant therapy, especially in severe patients with elevated D-dimer levels. Tang et al showed that the use of heparin for 7 days or more resulted in decreased mortality in severe cases, especially in those with a sepsis-induced coagulopathy score >4 or D-dimer >6 fold of upper normal limit.[2]

A pathological substrate confirming the presence and frequency of pulmonary thrombi in severe COVID-19, to provide more rationale to therapeutic management, is missing. Although the number of fatalities is in the range of tens of thousands worldwide, autopsy studies are scarce and limited to a few organs.[7,8]

It is understandable that few autopsy descriptions have been presented so far. Few centers have skilled pathologists to perform autopsies, not to mention the great risk of contagion during the procedure and the need for special security facilities in the autopsy rooms. In China, for instance, where the disease started, Zhu et al described that, since 2000, almost no autopsies have been performed in 8 hospitals in large Chinese cities.[9] Mostly a neglected procedure, the autopsy rapidly regains its importance when novel diseases arise and can be extremely useful in revealing patterns of tissue damage, systemic involvement, and for further research on the pathogenesis of the disease.

São Paulo is the epicenter of COVID-19 cases in Brazil, with 304 deaths through April 6, 2020. Our large tertiary academic Clinical Hospital of the Faculty of Medicine of the University of São Paulo has allocated all of its 900 beds to receive patients with COVID-19 and, unfortunately, it is expected that a large number of deaths will still occur. Since February 2020, our group has performed minimally invasive autopsies in fatal cases of COVID-19 to characterize the pathology and pathogenesis of this new disease. We have developed a procedure for performing ultrasound-based minimally invasive autopsies that samples tissues from several organs and, at the same time, reduces the risks of the autopsy procedure. In fact, ultrasound-based minimally invasive autopsies was applied during the recent 2018 yellow fever epidemic in Sao Paulo, Brazil, and showed full diagnostic agreement with conventional autopsy.[10] For COVID-19 cases, we analyze histological samples from lungs, kidneys, heart, liver, spleen, brain, skin, and skeletal muscle. The procedure was approved by the institution's ethics board and was performed after informed consent from the next of kin. Here, we present some preliminary autopsy results that may provide new insights into the relation between COVID-19 and DIC.

To date, we have studied 10 fatal cases, 5 men and 5 women, with a mean age of 67.8 years (33-83 years). Eight patients were older than age 60 years and seven had comorbidities, including arterial hypertension, diabetes mellitus, ischemic heart disease, and chronic obstructive pulmonary disease. The average hospital stay was 5.4 days (0-15 days).

The general pulmonary histological picture in fatal cases of COVID-19 is exudative/proliferative diffuse alveolar damage, with intense epithelial viral cytopathic effects involving alveolar and small airway epithelium, and little lymphocytic infiltration (Figure 1A). We

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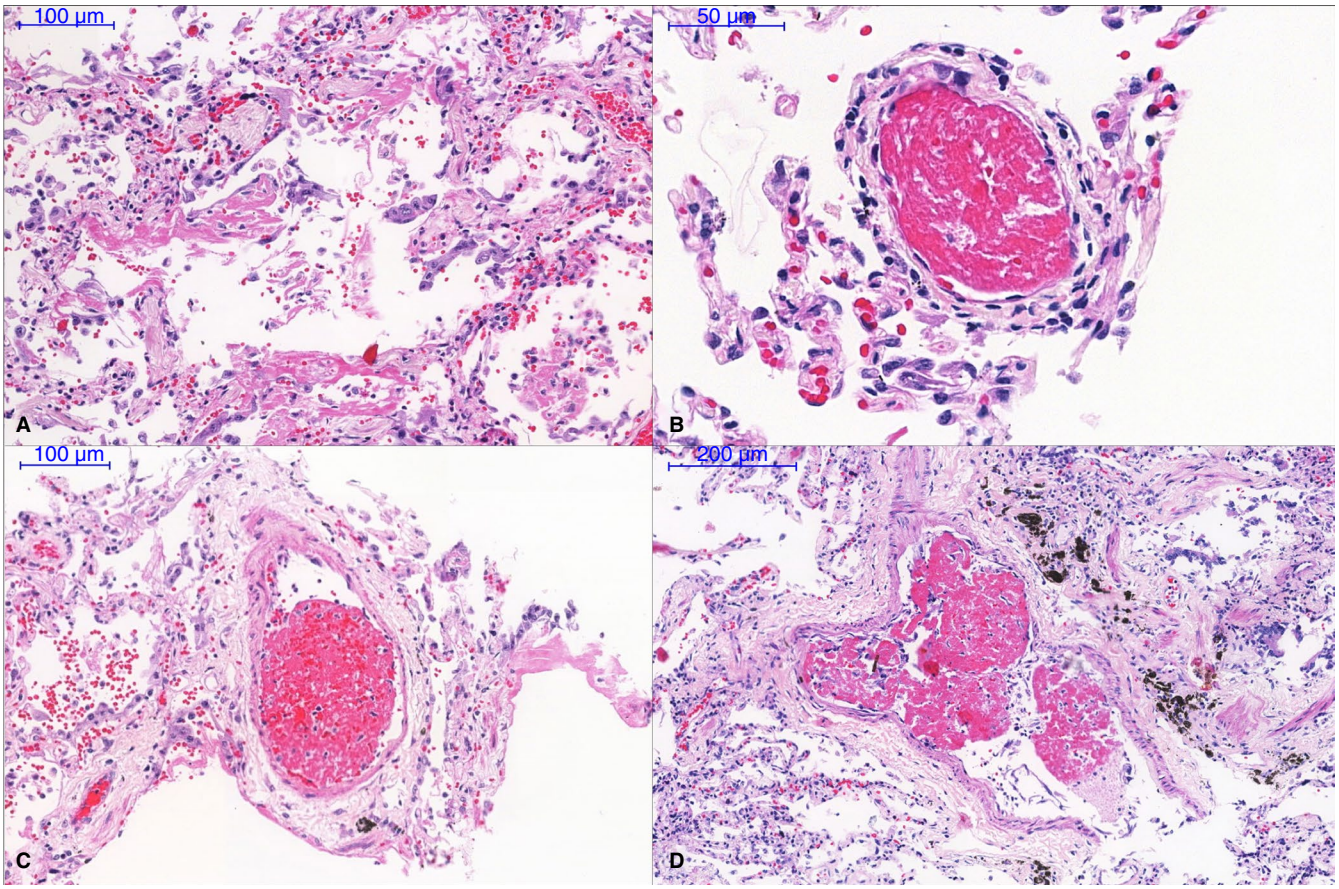


**FIGURE 1(A)** Diffuse alveolar damage in fatal COVID-19. (B-D) Fibrinous microthrombi in small-sized pulmonary arterioles, observed in 8 of 10 patients.

observed a variable number of small fibrinous thrombi in small pulmonary arterioles in areas of both damaged and more preserved lung parenchyma in 8 of 10 cases (Figure 1B-D). Endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries are other indicators of activation of the coagulation cascade. In addition, small fibrinous thrombi were rarely found in the glomeruli and superficial dermal vessels. There were few and small foci of alveolar hemorrhage, and pulmonary infarctions were not observed. Signs of secondary bacterial pneumonia were observed in six cases. Because these are postmortem transthoracic biopsies, we do not have access to large vessels and therefore cannot exclude or confirm pulmonary embolisms.

In summary, our pathological observations support the current concept of hypercoagulative status in these critically ill patients, showing that the frequency of pulmonary microthrombosis is high. Hopefully, these findings may shed light on the complex therapeutic decisions on this subject.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

M Dolhnikoff: study design, data analysis, and draft of the manuscript. AN Duarte-Neto: study design, tissue sample and data analysis. RA de Almeida Monteiro: study design, tissue sample. LFF da Silva: study design, data analysis, and figure. EP de Oliveira: clinical data collection. PHN Saldiva: study design, tissue sample, and data analysis. T Mauad: study design, data analysis, and draft of the manuscript. EM Negri: data analysis and draft of the manuscript.

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# Reply to "Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy"

We have just read with interest the article recently published in your Journal and titled "*Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy*" by Tang et al[1] In this article, it is suggested that those patients with COVID-19 that accomplish the Sepsis-Induced Coagulopathy (SIC) criteria, and receive anticoagulant treatment would present a reduction of mortality rates. It is well known that both shock and disseminated intravascular coagulation (DIC) are the two major causes of organ dysfunction in sepsis.[2] Furthermore, DIC is a strong predictor of mortality in patients with sepsis, independently of the severity of sepsis.[2]

In 2017, the International Society of Thrombosis and Haemostasis (ISTH) developed a Sepsis-Induced Coagulopathy (SIC) score. It was defined for clinical practice to facilitate early recognition of DIC in the setting of the sepsis, and to better identify those patients that are candidates for anticoagulation therapies.[3] The SIC score criterion consider using the platelet count (a value lower than $100 \times 10^3/mm^3$ platelets), PT ratio and four items of the total Sequential Organ Failure Assessment (SOFA) score that defines organ dysfunction: respiratory SOFA (PaO2/FIO2), cardiovascular SOFA (Hypotension), hepatic SOFA (bilirubin) and renal SOFA (creatinine or urine output). Therefore, the existence of thrombopenia from the SOFA score is not taken into account for the SIC score as it is already included as a criterion.

In the article published in your Journal, Tang et al mention that "*the SOFA score was developed by an international group of experts to describe the time course of six organ dysfunction using a limited number of routinely measured variables*". Considering our above explanation, using together for the patient's mortality evaluation the total SOFA score with its total six variables (which includes the existence of thrombopenia) and the SIC score (which includes the platelet count as per the CID criteria) would make to count the same item twice for a patient.

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