More autopsy studies are needed to understand the pathogenesis of severe COVID-19

To the Editor — Since SARS-CoV-2 began spreading in late 2019, a total of 379 million cases and 5.7 million deaths have been reported so far, with the case-fatality rate of COVID-19 remaining steady at about 1–2% worldwide. After infection, most people with COVID-19 experience asymptomatic, mild or moderate forms of illness, and recover without apparent complications. However, roughly two to three weeks after infection, some people develop severe forms of COVID-19, with progressive respiratory failure, multisystem damage, and high morbidity and mortality (Fig. 1a).

Numerous studies that purport a so-called 'cytokine storm' and 'immune dysregulation' have sustained the rationale for treating severe forms of COVID-19 with various immune-system modulators (e.g., corticosteroids, monoclonal antibodies to interleukins, and inhibitors of cytokine pathways) and assorted anticoagulants. Some of these therapeutic approaches have been shown to improve clinical outcome, but others do not, and additional therapeutics based on an understanding of COVID-19 pathogenesis are still critically needed.

Two years into the pandemic, studies of the underlying mechanisms of COVID-19 pathogenesis remain surprisingly scarce. To understand the mechanism by which SARS-CoV-2 causes severe disease, the medical research community must prioritize direct tissue studies from autopsy. Several recent pathology studies have shed some light on the complex mechanisms of severe COVID-19, but multiple unknown factors remain that pose important questions to motivate further work.

Lung tissues from patients with fatal COVID-19 have revealed pathology cascades that include progressive diffuse alveolar damage, alveolar–capillary barrier damage, surfactant-production loss, and increased vascular permeability. Such findings typify those of severe acute respiratory distress syndrome. However, based on the detection of viral protein and RNA remnants, the same lung tissues also reveal novel pathology cascades that are distinct from those of pandemic influenza and SARS-CoV infection, and that arise from direct SARS-CoV-2 infection of respiratory epithelial and basal cells, alveolar type 1 and 2 cells, and capillary endothelial cells. Infection triggers pathways involved in the senescence pf epithelial and endothelial cells, impaired epithelial repair, increased procoagulants (e.g., PAI-1 or SERPINE1) in endothelial cells and neutrophils, coagulopathies from inhibition of fibrinolysis, and pulmonary fibrosis (Fig. 1b). The associated alveolitis and endotheliopathy culminates in dead lung acinar units that cannot replenish cells and thereby recover[1].

In another study, lung tissues from three patients with severe COVID-19 (who required and recovered after lung transplantation) have revealed similar pathology cascades, including the clearance of SARS-CoV-2 from lungs and concomitant progression to irreversible pulmonary fibrotic disease[2]. This study also showed that lung macrophages and fibroblasts expressed growth factors that drive self-sustaining cycles of cellular proliferation and fibrin deposition that resemble those of idiopathic pulmonary fibrosis. Brain tissues from a series of patients with SARS-CoV-2 infection revealed that microvascular cell damage is due to direct viral infection of brain endothelial cells. As demonstrated by a combination of human autopsy and animal-model studies, the main protease of SARS-CoV-2, M^{pro}, cleaves and ablates NEMO, an essential modulator of nuclear factor-κB, which, in turn, causes the death of human brain endothelial cells. The resulting central nervous system microvascular endotheliopathy damages the blood–brain barrier and may explain the neurological and psychological complications of COVID-19, including anosmia, epileptic seizures, encephalopathies, and strokes[3].

Studies of blood samples are also providing clues that can be linked to pathological findings. Plasma markers of endothelial cell injury and platelet activation were significantly more abundant in patients with severe COVID-19 than in less severely ill patients with COVID-19. Increases in

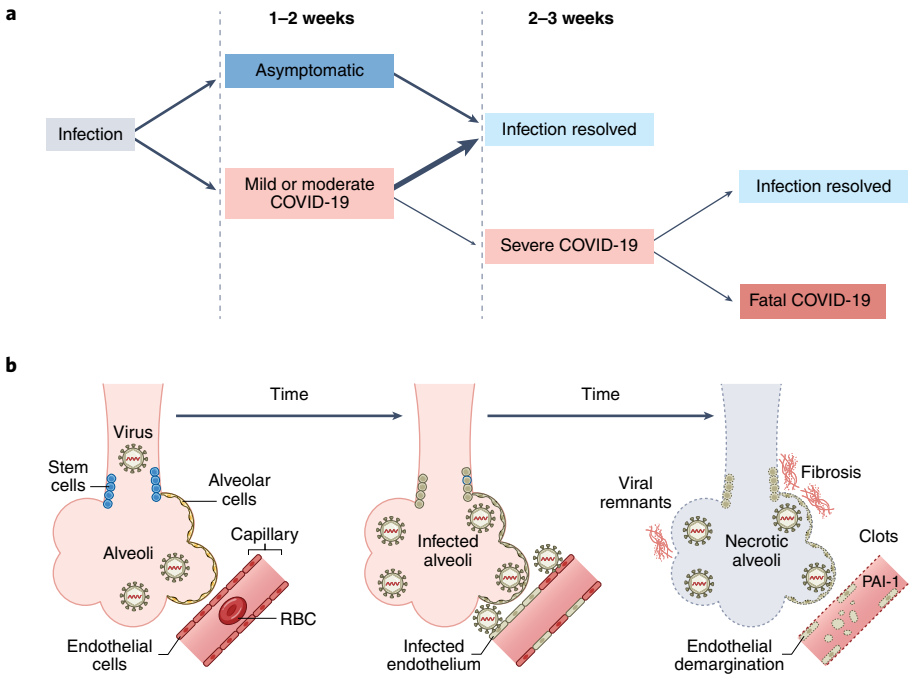

Fig. 1 | Time course of SARS-CoV-2 infection. Typical time course from initial SARS-COV-2 infection to severe COVID-19, during which most infections resolve (thick arrow), while a minority go on to develop severe COVID-19 (**a**), and corresponding time course of SARS-CoV-2 infection within lung acinar units (**b**). End-stage pulmonary disease is associated with dead alveolar cells, dead epithelial stem cells, demarginated endothelial cells, neutrophils with increased expression of PAI-1, widespread clotting, and severe pulmonary fibrosis. RBC, red blood cell.

Box 1 | Outstanding questions for pathology studies of COVID-19

1. Can biomarkers be identified and used to predict progression to severe COVID-19?
2. Are COVID-19 coagulopathies due to pre-existing systemic endotheliopathies or a cause of them?
3. Are there thresholds that pertain to viral loads, viral byproducts, and/or respiratory epithelial tissue damage beyond which severe or fatal disease progresses?
4. What therapies might be identified to preempt or blunt damage from the initiation of downstream severe or fatal endotheliopathies and coagulopathies by COVID-19-related damage cascades?
5. After apparent recovery from COVID-19, will recovered people show an increased risk of strokes and pulmonary, renal, and cardiac failure in the following years?

PAI-1 and von Willebrand factor were further associated with increases in soluble P-selectin and soluble CD40 ligand, which supports an endotheliopathy, as observed in the pathology studies noted above. In addition, increased concentrations of von Willebrand factor and soluble thrombomodulin suggest that such markers may be used to assess the severity of endothelial damage and predict morbidity and mortality[4]. However, clinical trials comparing therapeutic anticoagulation to standard prophylactic therapies have not demonstrated benefits[5]. Conversely, more-aggressive forms of anticoagulation have been associated with more adverse bleeding events in hospitalized patients, which calls for a better understanding of the underlying mechanisms of COVID-19 coagulopathies[6].

Several multi-omics reports, based on serial blood samples from patients with COVID-19, stratified disease outcomes with a broad array of metabolic and immunological markers, including plasma protein and metabolite levels, secreted and cell-surface protein levels, white-blood-cell transcriptomes, gene sequences encoding T cell and B cell receptors, and single-cell RNA sequencing. This identified metabolic and immunological profiles that shift with increasing severity of COVID-19[7,8]. Two other recent blood-sampling studies using proteomics and single-cell sequencing emphasized the hypercytokinemia in COVID-19 and the critical role of monocyte and neutrophil activation in severe COVID-19, as confirmed by autopsy studies[9,10]. Collectively, these data suggest a myeloid-associated immunopathology as a key component of disease severity.

The studies highlighted above employed molecular-pathology, clinical-trial, and systems-biology approaches to provide various 'snapshots' of lung, brain, vascular, and immunological damage. Although they suggest a time course of dysregulation, dysfunction, and destruction by progressively severe COVID-19, they further invite important and intriguing questions (Box 1). Fundamentally, why some people progress to severe forms of COVID-19 after a two- to three-week period remains unclear, as is the underlying role of known risk factors such as obesity, diabetes, and age. Such questions can be answered only with autopsy studies.

Clinician-scientists and their colleagues must deal with many challenges, many of which have been amplified during the pandemic. We believe that for airborne infectious diseases such as COVID-19, the hesitation to perform autopsies and tissue retrieval presents one of the foremost challenges. Such undertakings require planning, consent, and appropriate biosafety precautions in place that few pathology departments at hospitals are equipped to accomplish. However, without additional tissue-based studies, it will be all the more challenging to address the questions posed in Box 1. The lack of well-developed animal models for experimental pathogenesis studies further supports the need for additional autopsy studies in humans.

Vaccines remain the best option for controlling the COVID-19 pandemic, but variants of concern such as Omicron continue to emerge that will probably decrease vaccine efficacy. COVID-19 has both acute manifestations and post-acute manifestations (sometimes called 'long COVID'); given the unknown outcomes of endotheliopathies and coagulopathies in COVID-19, there may be 'time bomb' manifestations of COVID-19 whereby unforeseen clinical events such as increased incidences of cerebrovascular, myocardial, and kidney disease appear months after recovery from initial infection. Better, practical diagnostics and treatments for COVID-19 are desperately needed, and tissue-based pathology studies are vital for providing direct clues of how to understand the pathogenesis of the virus, and how to mitigate its impact. ❐

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Competing interests

The authors declare no competing interests.