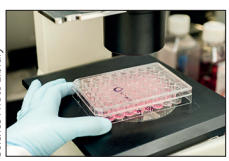
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pathologists in pursuit of the COVID-19 culprit



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Published Online June 8, 2020 https://doi.org/10.1016/S1473-3099(20)30449-7

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For the **Johns Hopkins University Coronavirus Resource Center** see https://coronavirus.jhu.edu/map.html

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 5·7 million confirmed cases and 350 000 deaths globally as of May 28, according to the Johns Hopkins University Coronavirus Resource Center. Despite the vast number of reports on the epidemiology, immunology, radiology, and management of COVID-19, few publications on the disease's pathology have so far been available, and most have been single-case reports or small case series.[1–3]

Initial reports of the disease focused on older patients with comorbidities; however, we are now witnessing cases in paediatric and young adult populations. The spectrum of clinical manifestations documented in the literature mirrors this expanded view of COVID-19 as well. In addition to pneumonia and respiratory failure, thromboembolic events (sometimes clinically unsuspected at death) are common, according to a 12-case autopsy series from Germany.[4] In addition, clinical studies have reported acquired coagulopathy in patients with COVID-19,[5–7] and a paediatric inflammatory syndrome linked to SARS-CoV-2 can also cause life-threatening cardiac issues.[8]

Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for SARS-CoV-2, allowing entry of the virus into host cells.[9] ACE2 is normally highly expressed in the lung, heart, ileum, kidney, and bladder. In the lungs, ACE2 is heavily expressed on ciliated airway epithelial cells and alveolar type 2 pneumocytes.[9] Endothelial cells, which comprise about a third of resident pulmonary cells, also express ACE2.[9] Thus, it has been hypothesised that SARS-CoV-2 undergoes haematogenous dissemination via infected pulmonary epithelium, followed by pulmonary endothelium. During this process, endothelial injury—inciting the coagulation cascade—and subsequent microvascular permeability occur. Levels of circulating ACE2 are higher in men than in women, which might account for the differences in severity and mortality between sexes.[9] Whether SARS-CoV-2 can bind to other targets is not known.

The host immune response mediates inflammation and cellular antiviral activity in a process crucial to the inhibition of viral replication and dissemination. However, excessive immune responses can be harmful and cause severe symptoms, especially in younger patients. Patients infected with SARS-CoV-2, and especially those requiring escalated levels of care, are reported to have higher plasma levels of proinflammatory cytokines.[9]

Careful observation and descriptive studies are vital to understanding disease manifestations. As integral members of care teams, pathologists work behind the scenes to form diagnoses on the basis of tissue biopsies, or to ascertain cause of death through autopsies. A thorough post-mortem evaluation can prove or disprove various postulated clinical events, with the potential to offer invaluable insights into the mechanism of disease. In *The Lancet Infectious Diseases*, Luca Carsana and colleagues[10] report the post-mortem findings from 38 autopsies done at two centres in northern Italy. They found diffuse alveolar damage to be the predominant pattern of lung injury. Although this series did not include any control cases (without COVID-19), diffuse alveolar damage is known to be a common pathway in acute lung injury caused by any severe infection. Thus, the additional unusual findings could be attributable to COVID-19.

Carsana and colleagues highlight that the prevalence and intensity of endothelial necrosis, increased megakaryocytes in alveolar capillaries, and widespread arteriolar fibrin–platelet thrombi are far more pronounced in cases of COVID-19 than in typical cases of diffuse alveolar damage resulting from other causes. These histopathological findings are substantiated by very high serum D-dimer levels, suggesting ante-mortem disseminated intravascular coagulation. Adding to this theory, some patients with COVID-19 present with ischaemic stroke[11] or deep vein thrombosis.[4] Despite these compelling findings, it is difficult to tease out the causal relationship among disseminated intravascular coagulation, diffuse alveolar damage, and pulmonary thrombotic microangiopathy. Regardless of the underlying mechanism, these findings suggest that anticoagulation might be an important therapeutic strategy.

An additional compelling and unique aspect of this study is the ultrastructural demonstration of coronavirus particles. The virions showed characteristic 13 nm projections and were identified along the plasmalemmal membranes or in cytoplasmic vesicles within type 1 and 2 pneumocytes, and rarely within

alveolar macrophages. Notably, these virions were not detected in the endothelial cells in this study, conflicting with the aforementioned mechanism of SARS-CoV-2 dissemination via infected pulmonary epithelium and endothelium. Also noteworthy is that co-infection with secondary microorganisms was uncommon in this series, possibly because of the rapidity with which death can occur in cases of COVID-19.

Despite the limitations inherent to retrospective descriptive studies, Carsana and colleagues[10] provide valuable information, corroborating clinical observations of coagulopathy, which could have implications on viable treatment strategies. Carsana and colleagues' work to provide these valuable findings amid the ongoing crisis should be lauded.

We declare no competing interests.

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Household studies provide key insights on the transmission of, and susceptibility to, SARS-CoV-2

Studies of household members and close contacts of individuals infected with a communicable disease such as COVID-19 are a key source of information for infectious disease epidemiologists. Exposure to an infectious individual is the most important risk factor for communicable diseases. In household studies, only individuals who have been exposed are included, allowing for careful examination of other individual-level risk factors and quantification of transmission probabilities. The study by Qin-Long Jing and colleagues[1] published in *The Lancet Infectious Diseases* provides important insights into factors affecting transmission from COVID-19 primary cases and susceptibility of their close contacts.

The considerable contact tracing effort undertaken in Guangzhou, China, by the Guangzhou Center for Disease Control and Prevention, enabled the comprehensive analysis by Jing and colleagues. Surveillance has shown that older individuals (aged ≥60 years) are disproportionately represented among diagnosed COVID-19 cases.[2] However, this observation might reflect the fact that older individuals are more likely to be infected or that they have greater severity of symptoms than younger individuals, making these individuals more likely to be diagnosed. In this retrospective cohort study, the close contacts of primary cases (all ages) were identified and quarantined, with nasal swabs collected on days 1 and 14 for RT-PCR testing.[1] Thus, typical biases associated with which individuals are exposed and which are tested were minimised. Compared with the oldest age group (≥60 years), the risk of household infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was lower among younger age groups (odds ratio [OR] 0·23 [95% CI 0·11–0·46] among individuals aged younger than 20 years; OR 0·64 [0·43–0·97] among individuals aged 20–59 years) and only 5% of contacts aged younger than 20 years were infected, which suggests that older age is associated with increased risk of infection conditional on exposure.[1]

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Published **Online**
June 17, 2020
https://doi.org/10.1016/S1473-3099(20)30514-4

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