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.

they activate platelets and macrophages and disrupt alveolar endothelial integrity, promoting in-situ thrombosis in the lung vasculature. The temporal association of severe illness with the onset of humoral immunity is also explained by this phenomenon. Autoantibodies directed at phospholipids, possibly emerging through molecular mimicry or redox-related conformational changes of innate epitopes, could also play a prominent role in disease progression.[5]

As the initial viral load determines the strength and duration of the antibody response, it might be prudent to avoid downregulation of the innate immune response by immunosuppression during the early viral replication phase. However, if there is evidence of disease progression to the immunothrombotic phase, key treatment strategies include immunosuppression and anticoagulation to suppress the aberrant antibody response and lung-centric microthrombosis. Once immunothrombotic lung injury is fully established, with diffuse alveolar damage manifesting as clinical acute respiratory distress syndrome, neither antiviral therapy nor immunosuppression is likely to modify the disease trajectory, and the management would essentially be supportive.

RNAaemia seen at this stage might not have implications for therapy, but rather might be a marker of disease severity and immune paralysis, portending poor prognosis.

We declare no competing interests.

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Authors' reply

We thank Robin Cherian and colleagues for their interest in our Viewpoint[1] discussing the potential importance of RNAaemia in severe COVID-19 and its possible implications for refining therapy with a goal of improving survival.[1] We wish to emphasise that we acknowledge the value of immunosuppression, but we question the value of universal immunosuppression for all patients with moderate-to-severe COVID-19, and specifically in the subgroup of patients with ongoing alveolar viral replication as set out in figure 1 of our Viewpoint. We agree with Cherian and colleagues that viral shedding from the upper airways has ceased by the time patients develop severe disease, but our focus was specifically on alveolar viral territory replication in the face of strong immunosuppression.

As stated in our Viewpoint, culturable virus might be absent in the second week after symptom onset, when patients progress to severe illness, but nevertheless there is a subgroup of patients in whom upper airway viral replication persists. The impact of this on viral replication in the alveolus remains poorly defined, and alveolar viral replication is likely important for immunosuppression.[1] Cherian and colleagues point out a lack of topological correlation between the location of lung pathology and viral presence, but this is based on one small cross-sectional study,[2] so it is difficult to extrapolate from these data.

We fully agree with Cherian and colleagues that small-vessel immunothrombosis is central to the pathogenesis of COVID-19 pneumonia, but this nevertheless represents a strategy to restrict viral spread via containment of viral dissemination.[3] As set out in figure 3 of our Viewpoint,[1] we agree that immunosuppression works in several different ways, especially in patients in whom viral replication has ceased in the alveolar territory. We did not include the antibody response in our figure, and we fully agree that anti-SARS-CoV-2 antibody responses in the second week could contribute to immunopathology and could be another mechanism underlying immunosuppression, especially in patients without alveolar viral replication.[4]

Finally, we fully agree with Cherian and colleagues that very early immunosuppression might be detrimental and that once clinical acute respiratory distress syndrome has developed, medical therapy is also limited and antiviral agents to counteract RNAaemia would be of limited value.[1]

We declare no competing interests.

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