

AKI during COVID-19 infection: specific or non-specific renal injury?

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The global COVID-19 pandemic has been challenging health systems worldwide since 2020. Although essentially a respiratory illness, it can also be accompanied by several extrapulmonary manifestations. These conditions include thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, gastrointestinal symptoms, hepatocellular injury, neurologic illness, hyperglycemic disorder, and acute kidney injury (AKI), among others.

Renal involvement in COVID-19

Current knowledge suggests a bidirectional relationship between COVID-19 and the kidneys. Patients on dialysis and kidney transplant recipients have been identified as groups at higher risk of adverse outcomes from COVID-19. Conversely, patients with severe COVID-19 are at increased risk of AKI. Initial studies reported an extremely high AKI prevalence among hospitalized COVID-19 patients, even exceeding 30%. Also, AKI is more common among COVID-19 than in other hospitalized patient populations, including septic patients. Predictors of COVID-19-associated AKI include old age, male sex, black race, existing diabetes, obesity, hypertension, and lower baseline eGFR. Development of AKI is associated with higher odds of longer hospital stay, mechanical ventilation and mortality.

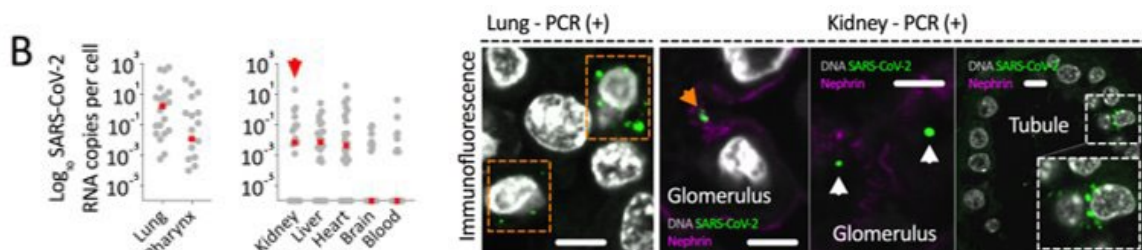


Figure 1. Renal tropism of SARS-CoV2

Several studies presented convincing data that the SARS-CoV2 virus exhibits tropism for organs other than the lungs, as viral particles were detected in the pharynx, heart, liver, brain and kidneys. The SARS-CoV2 viral load in different renal compartments showed preferential targeting of glomerular cells, but viral RNA and protein were also found in tubular cells. It appears that SARS-CoV2, similar to HIV, cytomegalovirus, Epstein-Barr virus and parvovirus B19, can lead to collapsing focal segmental glomerulosclerosis through direct toxic viral effects on podocytes, especially in the setting of overexpression of APOL1 risk variants. This particular SARS-CoV2-related kidney injury was named „COVAN“ denoting severe COVID-19-associated AKI with nephrotic range proteinuria. The presence of SARS-CoV-2 RNA in the kidneys was associated with older age, a higher number of comorbidities, AKI development, disease severity and increased risk of premature death, thus linking renal tropism to AKI and overall clinical outcome.

A large collaborative study by Jansen et al. examined direct viral effects on the kidney independent of systemic effects of COVID-19 infection by infecting human-induced pluripotent stem-cell-derived kidney organoids with SARS-CoV2. The infection led to increased collagen 1 protein expression and upregulation of profibrotic signalling pathways indicating cell injury and subsequent fibrosis, while the SARS-CoV2 protease inhibitor was able to mitigate the effects of viral infection of kidney cells. These data elucidate the possible mechanism for the occurrence of tubule-interstitial fibrosis within COVID-19-associated AKI and identify the possible therapeutic target to reduce tissue damage and organ failure. Omer et al. also explored SARS-CoV-2 interactions with kidney tubular cells on kidney organoids but failed to detect a cytopathic effect and cell death in affected cells that were strongly present in SARS-CoV-2-infected kidney clone cells from African green monkeys used as controls.

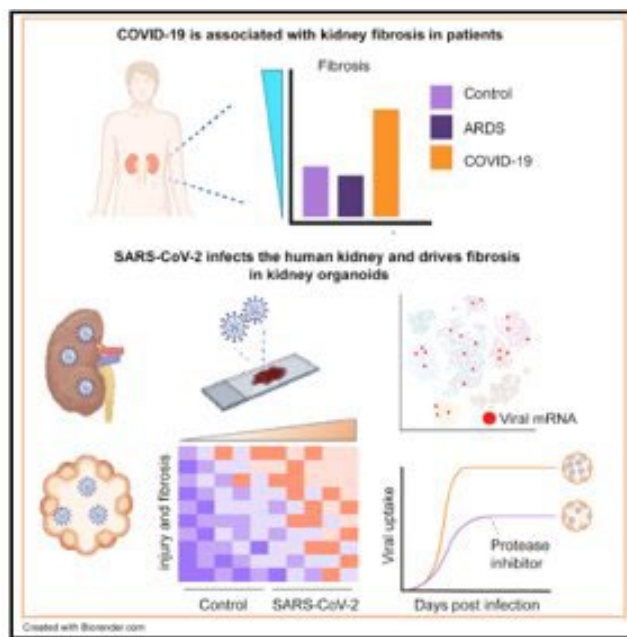


Figure 2. Molecular consequences of SARS-CoV2 renal tropism

The organoid model was also employed in the study by Garreta et al. to investigate the possible underlying mechanisms leading to worse outcomes in diabetic patients who contracted COVID-19. They observed a higher viral load, altered mitochondrial respiration and enhanced glycolysis in diabetic-like kidney organoids as compared to controls, resulting in higher SARS-CoV-2 infections in kidney biopsies from diabetic patients compared with non-diabetic cells. These results provided insights into diabetic-induced programming in the kidneys which increases susceptibility to SARS-CoV2 infection.

Similar to renal involvement, other extrapulmonary manifestations of COVID-19 have gained attention due to their links to clinical outcomes and potential long-term consequences. Namely, liver injury, demonstrated by disturbed liver function tests, was present in 2/3 of patients upon hospital admission and was not related to previous organ damage. Further analysis of transcription-, proteomic- and transcription factor-based activity profiles in hepatic autopsy samples in a multicentric study by Wanner et al. revealed similarities to the signatures associated with multiple other viral infections of the human liver. The research reported an association between SARS-CoV2 liver tropism and

proteomic and transcription factor activity regulation of interferon responses in COVID-19-associated systemic inflammation.

Longterm consequences of SARS-CoV2

Long-term post-COVID-19 kidney outcomes depend on disease severity and development of COVID-19-associated AKI, but most surviving patients exhibited an increased risk of adverse kidney outcomes in the post-acute phase of the disease. Individuals who recovered from mild to moderate infection still exhibited signs of the subclinical decline of renal function.

Timely identification of patients who could benefit from close monitoring and early start of renal replacement therapy to better manage fluid overload was crucial during pandemics. A group led by Gross proposed an algorithm for early detection of COVID-19-associated nephritis and capillary leak syndrome relying on coupling results from frequent urine sampling to detect albuminuria, hematuria and/or leukocyturia with low serum albumin (<20g/L) and antithrombin III ($\leq 70\%$). Patients with all findings positive were considered at high risk for decompensation and need for intensive care, including renal replacement therapy.

Intrinsic and extrinsic kidney signals in COVID-19-associated AKI

Despite much research on the association between COVID-19 and AKI, it remains unclear whether COVID-19-associated AKI is in any way different from AKI related to other causes. It appears that the underlying pathophysiological mechanisms of AKI development are similar to those in other systemic infections and include microvascular dysfunction, inflammatory response, and metabolic reprogramming as three fundamental mechanisms. However, it also seems that the SARS-CoV2 virus can modulate the renal response to a septic environment, while the potential contribution of direct viral toxicity still needs to be elucidated.

Key points

1. SARS-CoV2 exhibits multiorgan tropism directed at the heart, liver, brain and kidneys.
2. SARS-CoV2 renal tropism modulates renal molecular response to infection and contributes to the development of AKI.
3. Patients at risk of severe forms of COVID-19-associated AKI can be identified with timely repeated urinalysis coupled with serum albumin and antithrombin III levels.
4. Long-term follow-up studies are needed to assess the potential long-lasting consequences of COVID-19 on kidney function.

Further reading

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