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See related Letters to the Editor, "Kidney Involvement in COVID-19: Need for Better Definitions," and "Authors' Reply," on pages 2224–2225 and 2225–2226, respectively.

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Kidney Involvement in COVID-19: Need for Better Definitions

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus outbreak in China at the end of 2019, increasing interest emerged regarding renal involvement during coronavirus disease 2019 (COVID-19). AKI with or without proteinuria is described in a variable percentage of patients with COVID-19, and several reports outlined an increased mortality risk in those with AKI.

The mechanisms of renal injury during COVID-19 are difficult to study due to the interference of several coexisting factors, such as polypharmacy, hypoxia, and cytokine storm. Just like severe acute respiratory syndrome coronavirus, SARS-CoV-2 virus entry into target cells is facilitated by the presence of angiotensin-converting enzyme 2 (ACE2) expressed in respiratory cells as well as renal tubular cells and podocytes, making the hypothesis of a direct renal infection particularly intriguing.

Farkash *et al.*[1] observed renal tubular vacuolization and virus-like inclusions in tubular cells by electron microscopy (EM) in the autopsy of a patient with COVID-19. Similar EM findings together with suggestive immunohistochemical stain for SARS-CoV-2 proteins in tubules were shown in a few patients from two independent Chinese COVID-19 autopsy

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cohorts (Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. [2020] Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection. 10.1101/2020.03.04.20031120).[2] However, the same immunohistochemical was not considered specific when used by others.[3] Of note, when specific and highly sensitive molecular methods for tissue viral identification were used (*i.e.*, RNAscope[3] or real-time PCR,[4] the presence of SARS-CoV-2 RNA could not be demonstrated within renal tissue, and none of the aforementioned autopsy studies included viral RNA isolation in the kidney.

Interestingly, viral nephropathies with direct tubular infection and viral replication within epithelial cells (*i.e.*, BK virus nephropathy) are usually associated with substantial viruria due to the direct release of viral particles in the tubular lumen following cytopathic cell injury. So far, there is no solid evidence of a correlation between urinary levels of SARS-CoV-2 viral copies and the degree of kidney injury in patients with COVID-19.[5] Moreover, the presence of viral particles by pure morphologic evaluation (EM) does not demonstrate by itself a direct cytopathic effect nor a replicative potential because it only supports viral entry. More specific morphologic correlates of viral cytopathy (nuclear atypia/dysmorphology and syncytia) have not been shown yet.

Three cases of collapsing glomerulopathy during SARS-CoV-2 infection have been reported,[6] presenting with severe kidney injury and variable proteinuria: in genetically predisposed subjects, increased levels of cytokines (*i.e.*, IFNs) in patients with COVID-19 are thought to drive podocyte injury, resulting in collapsing glomerulopathy as can be observed in other viral-associated nephropathies. Although in one case, the presence of virus-like particles in podocytes was observed by EM, the hypothesized mechanism of injury does not require direct kidney infection.

Taken together, these observations suggest that caution should be used when addressing the etiology of kidney dysfunction in patients with COVID-19 because unequivocal evidence of direct viral infection of the kidney is still lacking in these severe and acutely ill patients.

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Authors' Reply

We acknowledge the expertise of the letter writers and appreciate their critical comments. We agree with Delsante *et al.*[1] that there are weaknesses to each modality of detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in autopsy kidneys. Immunohistochemical staining can nonspecifically label areas of necrosis, electron microscopy relies on morphologic features only, and *in situ* hybridization and other RNA studies may be limited by autolysis or confounded by plasma contamination. Definitive proof of direct renal infection will likely require some combination of techniques, such as immunogold or serial sections with immunohistochemical and molecular detection of virus.[2,3]

We also agree with Miller and Goldsmith[4] that we cannot definitively exclude that the structures that we have reported in

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