New Insight for Kidney Biopsy Series in Cases with COVID-19-related Acute Kidney Injury

Sir,

I read with great interest the paper by Asgharpour *et al*., about kidney findings in coronavirus disease 2019 (COVID-19) cases. As they reported, acute kidney injury (AKI) is a common complication of COVID-19 that worsens the overall prognosis.[1] I thank them for presenting the representative and crucial data that needs clarification from specialists. Although several reports indicated the relationship between COVID-19, inflammatory response and accompanying systemic problems, this paper is one of the most comprehensive and systematic presentations in the literature.

Asgharpour *et al*., reviewed the kidney findings in patients with COVID-19, in addition to describing pathologies of other organ systems.[1] This paper reported that acute tubular necrosis (ATN) and glomerular involvement were detected in renal tissue analysis in patients with COVID-19. However, they declared that there is no evidence of viral particles on ultrastructural examination by electron microscopy; and researchers never detected severe acute respiratory syndrome coronavirus 2 *(SARS-CoV-2)* RNA successfully from renal tissue of infected patients.[1] In a recent report by Braun *et al*., *SARS-CoV-2* was isolated from one post-mortem sample of kidney in autopsy series from 63 patients that produced a 1000-times increase in viral RNA after 48 hours of cell infection *in vitro*; and they added that this finding showed that the virus maintains infective potential, even under post--mortem conditions.[2] Moreover, they found that this human-derived *SARS-CoV-2* shows replication in cultured kidney tubular epithelial cells of a non-human primate. In view of these findings, they suggested that renal cells can be targeted by *SARS-CoV-2* and renal tropism can be associated with disease severity.[2] In another study by Vijayan *et al.* that refers to the previous report, the authors present possible renal implications, and clinical outcomes of *SARS-CoV-2* infection of kidneys.[3] These reports declared that *SARS-CoV-2* mRNA, which may cause collapsing glomerulopathy as well as acute tubular injury, was detected in renal tissue.[2,3]

Previous reports focused on the importance of assessing renal functions in *SARS-CoV-2*, and they indicated that chronic renal failure is the strongest mortality reason for *SARS-CoV-2* infected patients. This was even more serious compared with other risk factors such as chronic heart or lung disease. Vijayan *et al*. speculated that these findings might be a reflection of kidney tropism by *SARS-CoV-2*.[3] According to the above reports, kidneys are important and risky targets of *SARS-CoV-2*; and this point should be kept in mind in addition to other organ systems' findings during the management of the disease.

The definition of viral pathogenic factors may play a key role in clarifying pathogenicity and treatment strategies. Variable cellular responses against virus and affected organs should be identified for describing symptoms and associated findings. So, I congratulate Braun *et al*.[2] for illuminating the possible kidney tropism of *SARS-CoV-2* and, I thank Asgharpour *et al*.[1] for the presentation of a comprehensive updated paper for patients with COVID-19-related kidney disease. I believe that the systemic reflections of the disease will be better understood by clarifying micro implications.

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AUTHORS' REPLY:

Sir,

We are thankful to Kaya for his interest in our paper and comments on it.[1,2] Kidney involvement in novel coronavirus disease 2019 (COVID-19) is one of the most common extra-pulmonary complications of this disease, which increases the morbidity and mortality. Currently, it is also one of the most extensively investigated areas in biomedical research. The incidence of acute kidney injury (AKI) in COVID-19 is significant and much attention is focused on it. Nonetheless, the data is still evolving; in particular, regarding the pathogenesis and

pathology of COVID-19-associated nephropathy (COVAN). The most contentious and as yet unsettled point is whether the virus induces renal injury directly by cytopathic effects or indirectly *via* immune response/systemic inflammatory response, hemodynamic and hypoxemic factors. Initially, when we were reviewing the literature, most studies were based on clinical and laboratory observations, with little information on pathology of kidney involvement. Subsequently, a number of small biopsy and autopsy-based studies and case reports were published, which started to unravel the underlying pathology and pathomechanisms of nephropathy in COVID-19 disease, *albeit* with conflicting results. Some researches found evidence of direct viral infection of the kidneys; whereas, others did not find the virus or viral products in kidney biopsies or autopsy samples. The first detailed study that found evidence of direct viral infection of the kidney parenchyma was based on autopsy of 26 patients dying of respiratory failure.[3] We mentioned its findings as ''Su *et al*. also found viral particles in podocytes and tubular epithelial cells on ultrastructural study of postmortem specimens from kidneys.''[2] However, this report was soon followed by critical reviews of these results; and doubts were casted on the nature of viral-like particles and RNA expression in post-mortem kidney tissues.[4,5] Regarding detection of RNA in kidney tissue, our statement of "Researchers have never detected the *SARS-CoV* RNA successfully from renal tissue of infected patients." was related to the predecessor of *SARS-CoV-2*, *i.e., SARS-CoV* and not *SARS-CoV-2*.[2] For the later, we mentioned as "More recently, the occurrence of viral RNA and viral products in kidney tissue and urine of symptomatic patients of COVID-19 infection has been documented in some studies.''[2] We hope the above clarifications settle the points raised by Kaya.[1] Although, the matter is still far from settled, currently the predominant view is that renal injury is mainly mediated by indirect effects rather than direct viral infection of the kidneys.

We concur with Kaya that COVID-19 disease is still evolving and its fuller spectrum is not completely known, till date. However, kidney has emerged as one of the main extra-respiratory targets of *SARS-CoV-2* virus. All components of kidney parenchyma have been reported to be involved in *COVAN*. Both host and viral factors shape the pathology and extent of the viral illness and its complications including COVAN, which portends a poor prognosis. As more and more data emerge on this topic, the picture will become clear as time passes.

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