Figure 1. Scatterplots of measured ACR versus predicted median ACR for Alberta (A) kidney transplant recipients and (B) non transplant recipients show similar symmetrical distributions around the red diagonal line of identity, indicating unbiased prediction and similar accuracy. The predicted median ACR was calculated using the equations published in Weaver et al. on the basis of a simple linear spline for 2280 ACR/PCR pairs in 627 transplant recipients and 142,049 ACR/PCR pairs in 61,900 non transplant recipients (5% random sample of 7127 pairs shown for clarity).

Supplemental Figure 1. Simulated distribution of differences between predicted and measured values, with positive differences shown on a log scale and negative differences shown on a negative log scale.

References


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Possible Protective Effect of Renin-Angiotensin System Inhibitors in COVID-19 Induced Acute Kidney Injury

A recent article by Batlle et al. entitled “AKI in COVID-19: Emerging Evidence of a Distinct Pathophysiology” has discussed comprehensively the possible pathophysiology of AKI in novel coronavirus disease 2019 (COVID-19), a complication of COVID-19 that many have largely ignored.

Although the authors were right to avoid speculating about specific interventions until a full picture has been obtained, we feel that sound hypotheses with evidence extrapolated from the COVID-19 population may help in the design of clinical studies.

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trials or even prospective studies to better understand what works and what does not, since in the field of medicine it is always about testing hypotheses (without causing harm), especially amid this COVID-19 pandemic where many lives have been claimed due to complications in such a short period of time.

It has now been established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen for COVID-19, gains entry into host cells through an angiotensin-converting enzyme 2 (ACE2) protein, which is also abundantly expressed in the kidney. Authors have speculated about direct viral infection of the kidney, where SARS-CoV-2 gains entry through the ACE2 protein of the proximal tubule. In this sense, the use of renin-angiotensin system (RAS) inhibitors, including ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), may be protective toward kidney injury.

Firstly, ARBs could compete with SARS-CoV-2 for ACE2-expressing proximal tubular cells, block the binding, and hence the attachment of SARS-CoV-2 to ACE2, thereby inhibiting its entry into the cells. In this way, there may be less entry, if not entirely of no entry, of SARS-CoV-2 into proximal tubular cells. Thus, the proximal tubular cells at risk may be limited, and tubular function of the kidney may be better preserved. Secondly, downregulation of ACE2 upon viral invasion and subsequent increased production of angiotensin II seems to drive the occurrence of kidney injury. Both ACE inhibitors and ARBs could block the physiologic effect of angiotensin II.

The protective ability of RAS inhibitors may have been hinted in a prospective cohort study of 701 patients with COVID-19. Cheng et al. investigated the association between in-hospital medications (on admission and during hospitalization) and the development of AKI among patients with COVID-19. It was noted that none of the patients who were taking RAS inhibitors on admission or during hospitalization for COVID-19 developed AKI. In contrast, almost all patients with COVID-19 who had AKI were receiving antibiotics (35/36; 97%), a well known causative agent for AKI.

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**REFERENCES**


**Authors’ Reply**

In our Perspective article, we aimed to discuss the emerging mechanisms that might be involved in the pathophysiology of coronavirus disease 2019 (COVID-19)—associated AKI and emphasized the need for more information. At the time of writing, data were largely limited to the two studies from China reporting data from autopsies. We refrained from speculating about therapies because we felt that it would be premature and speculative.

We are not aware that angiotensin-receptor blockers could compete with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for angiotensin-converting enzyme 2 (ACE2) and block the binding of the virus. In fact, these agents do not bind to ACE2 and therefore any connection would have to be indirect. Some studies have shown upregulation of ACE2 by angiotensin-receptor blockers. The significance of this finding remains unclear regarding infectivity by SARS-CoV-2 and the course of COVID-19 and its manifestations, including AKI. Concerning the potential use of renin-angiotensin system (RAS) blockers to protect the kidneys in patients with COVID-19, we see pros and cons as is the case in other forms of AKI. Angiotensin II is upregulated in AKI in general and this may be exacerbated in COVID-19–associated AKI if ACE2 is suppressed as has been hypothesized. In this regard, the use of RAS blockers could be beneficial but one needs to be mindful of their hypotensive action that may