Response to: How important is the assessment of soluble ACE-2 in COVID-19?

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The role of angiotensin converting enzyme 2 (ACE2) in coronavirus disease 2019 (COVID-19) is matter of debate, because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes ACE2 on host cells as its entry receptor.[1] We recently reported that activity of the renin-angiotensin-aldosterone system and expression of ACE2 were not changed in patients with non-severe COVID-19 as compared to SARS-CoV-2 negative control subjects with similar symptoms.[2] Rojas and collaborators expand this view and demonstrate that ACE2 expression is likewise unaltered in patients with more severe COVID-19 (sequential organ failure assessment score 2.043; 4C mortality score 6.174) as compared to recovered COVID-19 patients or a historic control group.[3] Noteworthy, the authors found no correlation of ACE2 levels and viral load.[3]

ACE2 is a peptidase that mediates the breakdown of angiotensin II. The full-length form of ACE2 contains an extracellular catalytic domain, a structural transmembrane domain, and a small intracellular C-terminal domain. After binding of SARS-CoV-2 to the extracellular domain of membrane-bound ACE2, the virus/protein complex is internalized by the host cell. Accordingly, the affection of multiple organs in COVID-19 might be explained by the wide expression of ACE2 in different tissues, including lung, heart, kidney, or intestine. In contrast, the soluble form of ACE2 may bind SARS-CoV-2, but is not internalized due to the lack of the transmembrane domain[1]

This has different implications: Increased density of membrane-bound ACE2 may facilitate virus cell entry and thus be a risk factor for severe COVID-19. Interestingly, in two cohorts of patients with atrial fibrillation or heart failure, respectively, male sex was the strongest predictor of high levels of soluble ACE2, which might contribute to the higher risk of COVID-19 in males.[4] However, though it is assumed that plasma concentrations of soluble ACE2 reflect the total abundance of the membrane-bound form, this has not been proven, particularly not in COVID-19.[1,4] To date, it remains elusive whether plasma concentration of soluble ACE2 predicts the risk for SARS-CoV-2 infection and prospective studies would be

required to clarify. On the other hand, it has been proposed that accelerated cleavage of ACE2 during SARS-CoV-2 infection might decrease ACE2 abundance, leading to impaired angiotensin II breakdown and subsequent organ injury.[1] Although we cannot exclude local differences in tissue angiotensin II concentrations, the now available data on soluble ACE2 in patients with non-severe[2] or severe[3] COVID-19 strongly argue against this hypothesis. In summary, the available evidence suggests that soluble ACE2 is not related to disease severity and should not be considered as a valid biomarker predicting outcome in COVID-19.

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