

EDITORIAL

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# COVID-19: spot urine rather than bronchoalveolar lavage fluid analysis?

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Severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), has infected over 130 million people and caused more than 2.8 million deaths globally (as of April 4th 2021, according to WHO data). Identifying risk factors and prognostic markers for the development of COVID-19 disease and its sequelae is urgent in order to enable early identification and monitoring of high-risk patients.

While COVID-19 is most commonly characterized as a respiratory illness, extrapulmonary manifestations are a prominent part of its clinical spectrum. Kidney involvement is common in COVID-19. Hematuria, proteinuria, and acute kidney injury (AKI) are frequently reported in hospitalized COVID-19 patients, with incidence rates of 11.3–40.9%, 42.1–43.9%, and 5.1–36.6%, respectively, and they are associated with mortality [1]. The ACE2 receptor, which is the cellular entry point for SARS-CoV-2, is similarly expressed on bronchial and alveolar epithelial cells, as well as on podocytes and renal tubular epithelial and endothelial cells; therefore, direct viral tissue damage is a plausible mechanism of kidney injury (Fig. 1; [1–9]).

The parallelism between the bronchoalveolar and tubuloglomerular processes in COVID-19 is not surprising, since these structures are ontogenetically closely related and simultaneous lung and kidney damage patterns have been observed in other clinical conditions. This phenomenon is referred to by the umbrella term “pulmonary–renal syndromes”, which summarizes diverse disease

states associated with alveolar hemorrhage and glomerulonephritis. A known prototype of pulmonary–renal syndromes is Goodpasture disease, which is an autoimmune condition associated with the NC1 domain of the alpha-3 chain of type IV collagen, but the restricted tissue distribution of the alpha-3 chain generally limits injury to the glomeruli and alveoli. Autoimmunity has also been implicated in COVID-19-associated glomerular injury mediated by immunocomplexes of the viral antigen or virus-induced immunological effects, indicated by the development of collapsing glomerulopathy in subjects infected with SARS-CoV-2 who have high-risk variants of the *APOLI* genotype [1].

In contrast to the bronchoalveolar compartment, the tubuloglomerular compartment is accessible at any time for non-invasive diagnostics that involve urine analysis. There are two important questions concerning the use of urine analysis for COVID-19:

1. Can a differential urine analysis be used to predict COVID-19-associated AKI, and can it provide information on whether the kidney damage is caused by viral cytopathogenicity, by local/systemic immune reactions, or by alternative mechanisms?
2. Does the tubuloglomerular damage pattern mirror the bronchoalveolar damage pattern and, thus, allow characterization and assessment of the stage of the pulmonary disease process by means of serial urine analysis?

Prospective multicenter trials would be required to answer these questions. Specifically, analysis of pulmonary/renal functional parameters as well as biomarker expression by urine analyses would be required to inform

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(See figure on next page.)

**Fig. 1** Pulmonary–renal damage patterns of COVID-19. Clinical and histopathological data of COVID-19-associated ARDS and AKI indicate common etiological factors, including direct virus-mediated cell damage, endothelial damage and thrombo-inflammation, dysregulation of the immune response and hyperinflammation, and dysregulation of the renin–angiotensin–aldosterone system. In addition, use of mechanical ventilation, hemodynamic instability, volume overload, superimposed sepsis, and collapsing glomerulopathy have all been implicated in glomerular disease and tubular damage in COVID-19. In contrast to bronchoalveolar lavage fluid, urine is accessible at any time point for non-invasive assessment of organ involvement. The urinary tubuloglomerular pattern may mirror the bronchoalveolar damage pattern and, thus, allow characterization and assessment of the stage of the pulmonary disease by means of serial urine analysis. The table summarizes potential candidate urinary markers that could inform lung injury in the setting of COVID-19-associated ARDS. However, it is unclear which marker is most accurate for this purpose and what cut-offs are needed, and this requires further investigation. The left histopathological image shows diffuse alveolar damage with hyaline membranes at the alveolar walls as morphologic correlate of ARDS. The right histopathological image shows acute tubular injury with flattened brush borders and cytoplasm of the epithelial cells in dilated tubules as morphologic correlate of AKI. *ACE2* angiotensin-converting enzyme 2, *AKI* acute kidney injury, *ARDS* acute respiratory distress syndrome, *COVID-19* coronavirus disease 2019, *IGFBP7* insulin-like growth factor-binding protein 7, *IL* interleukin, *PAI-1* plasminogen activator inhibitor-1, *NGAL* neutrophil gelatinase-associated lipocalin, *RAAS* renin–angiotensin–aldosterone system, *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2, *TIMP-2* tissue inhibitor of metalloproteinases-2, *TNFR* tumor necrosis factor receptor

lung injury and potentially use renal stress/damage patterns to support diagnosis. Serial urine analyses may include: (1) traditional markers of tubuloglomerular and vascular barrier dysfunction; (2) markers of coagulation/fibrinolysis; (3) cytokine profiles indicative of immunological damage mechanisms; (4) markers of renin–angiotensin–aldosterone system activation potentially reflecting viral cell infectivity; and (5) alveolar and tubular stress/damage biomarkers indicating acute and permanent structural tissue damage. These urine parameters would then be associated with pulmonary, renal, and systemic parameters and their course, as well as the features of biopsy (and autopsy) tissue samples of both organs. Finally, these biomarker profiles would require validation in subsequent prospective studies in terms of their sensitivity and specificity.

Surprisingly, although a few studies have reported the use of urinary biomarkers to prognosticate COVID-19-associated critical illness and AKI [1], there is a paucity of data examining their value to monitor the pattern of COVID-19-associated lung damage. Various ARDS biomarkers indicative of different pathways of injury have been identified, but none of these have been studied in urine samples from ARDS patients [8].

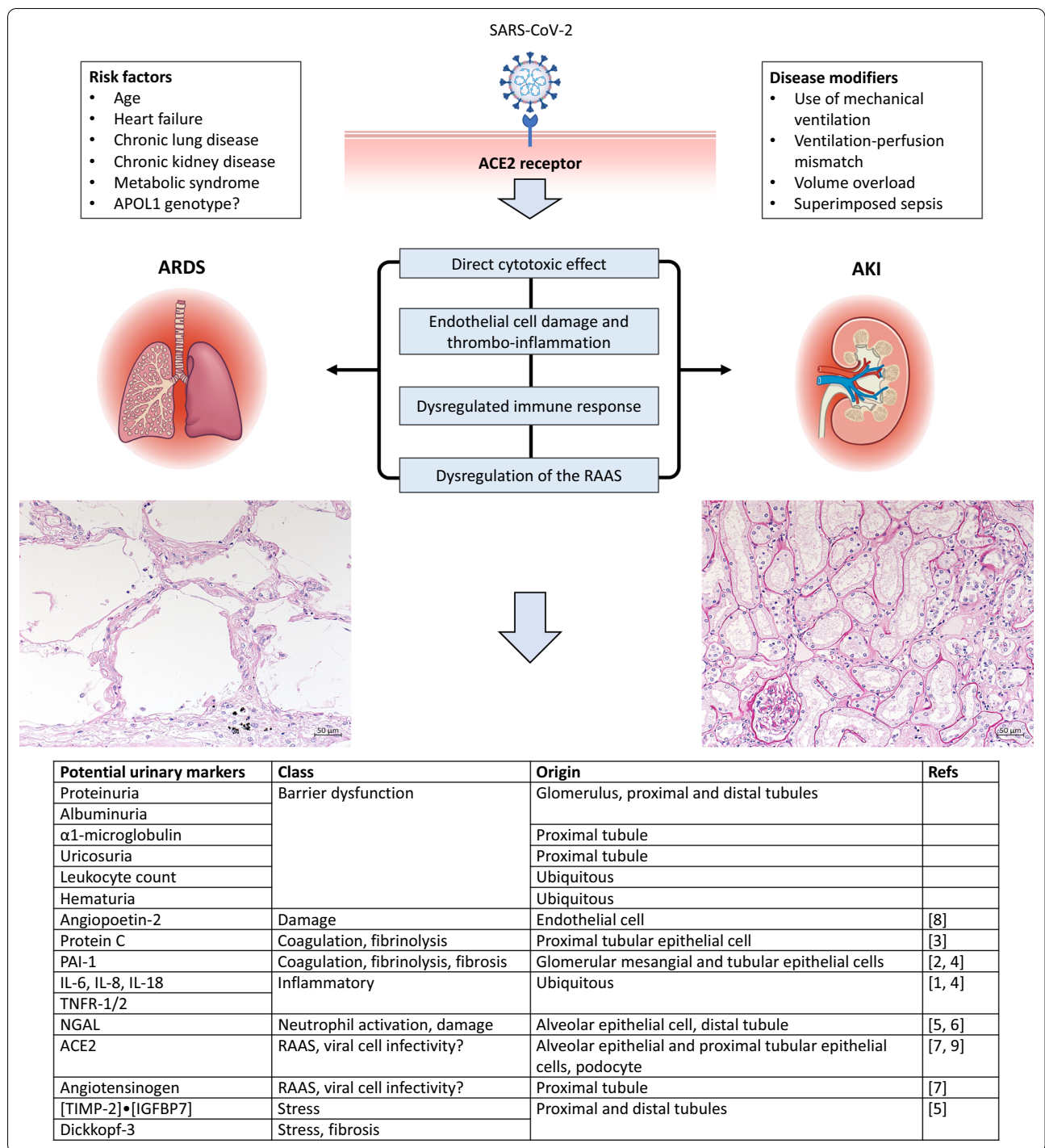
Disruption of the alveolar-capillary barrier is a pathological hallmark of ARDS that is associated with accumulation of protein-rich inflammatory edematous fluid in the alveolar space, and is associated with disease severity; this feature is also seen in COVID-19-associated ARDS [10]. Likewise, SARS-CoV-2 causes tubular barrier dysfunction [11], and features of proximal tubule dysfunction (e.g., proteinuria,  $\alpha$ 1-microglobulin excretion, uricosuria) are independently associated with risk of respiratory failure and AKI [11–13]. In a small study on COVID-19 patients, proteinuria was found to be significantly correlated with the driving pressure, indicating its potential role as a surrogate marker of lung strain in

ARDS [13]. However, it is not clear whether the degree of proteinuria is correlated with the total protein concentration of bronchoalveolar lavage.

It has long been known that high tidal volume ventilation in classical ARDS is associated with the release of various mediators, which may play a role in mediating AKI [4]. There is also experimental evidence that injurious ventilatory strategies can induce alveolar damage and renal epithelial cell apoptosis and dysregulation of Fas ligands [14]. Furthermore, a correlation between changes in levels of soluble Fas ligand and serum creatinine can be observed in patients with classical ARDS. Thus, some data point to the existence of a link between respiratory failure, ventilatory strategies, biotrauma, circulating mediators, and AKI. The topic that needs to be investigated in the future is whether there is a link between urinary biomarkers and ARDS severity in COVID-19 beyond the effects of mechanical ventilation on the kidney.

Finally, detection of SARS-CoV-2 mRNA in post-mortem specimens is associated with shorter survival time and increased incidence of AKI, indicating renal tropism of SARS-CoV-2 [1]. One implication of this finding is that urine testing for viral mRNA might help in the risk stratification of COVID-19 patients, but current data indicate that viral shedding in urine is rare [15].

Analysis of urine samples is straightforward, and the samples are easy to obtain. Importantly, minimizing the use of bronchoalveolar lavage fluid analysis may reduce the risk of transmission of SARS-CoV-2 infection through aerosol generation during bronchoscopy. Future research should aim to investigate whether the pathogenicity pattern of the tubuloglomerular compartment as indicated by urine analysis corresponds to that of the bronchoalveolar compartment, and whether such urinalysis is suitable for serial assessment of SARS-CoV-2 disease severity.



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