PERSPECTIVES

A call to action to evaluate renal functional reserve in patients with COVID-19

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Cantaluppi V, Guglielmetti G, Dellepiane S, Marengo M, Mehta RL, Ronco C. A call to action to evaluate renal functional reserve in patients with COVID-19. Am J Physiol Renal Physiol 319: F792–F795, 2020. First published September 24, 2020; doi:10.1152/ajprenal.00245.2020.—Coronavirus disease 2019 (COVID-19) poses an unprecedented challenge to world health systems, substantially increasing hospitalization and mortality rates in all affected countries. Being primarily a respiratory disease, COVID-19 is mainly associated with pneumonia or minor upper respiratory tract symptoms; however, different organs can sustain considerable (if not terminal) damage because of coronavirus. Acute kidney injury is the most common complication of COVID-19-related pneumonia, and more than 20% of patients requiring ventilatory support develop renal failure. Additionally, chronic kidney disease is a major risk factor for COVID-19 severity and mortality. All these data demonstrate the relevance of renal function assessment in patients with COVID-19 and the need of early kidney-directed diagnostic and therapeutical approaches. However, the sole assessment of renal function could be not entirely indicative of kidney tissue status. In this viewpoint, we discuss the clinical significance and potential relevance of renal functional reserve evaluation in patients with COVID-19.

acute kidney injury; chronic kidney disease; COVID-19; renal function

Coronavirus disease 2019 (COVID-19) is straining healthcare systems worldwide, causing an unprecedented rise in hospitalizations and difficult choices for resource allocation. Among the numerous life-threatening complications related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, interstitial pneumonia is the most common and leads to acute respiratory distress syndrome (ARDS), requiring ventilation support and admission to an intensive care unit. COVID-19 pneumonia is often associated with multiorgan injury; in particular, kidney failure occurs in 20% of patients with ARDS and prolongs their hospital stay and increases mortality (4, 7).

Italy is one of the countries most affected by COVID-19, with 242,363 total cases and 34,026 deaths (as of July 9, 2020). The Italian Istituto Superiore di Sanità recently reported the characteristics of COVID-19 deaths updated to July 9, 2020: the median age was 82 yr old (interquartile range: 74–88 yr old) and 66.2% had hypertension, 29.8% had diabetes, 27.7% had ischemic heart disease, 15.8% had heart failure, 10.4% had stroke history, and 16.8% had chronic obstructive pulmonary disease (7). Of interest, 20.3% of patients that died had a previous diagnosis of chronic kidney disease (CKD), an increasingly prevalent condition recognized as a public health concern worldwide (7a). Similar findings have been reported in the United States by the Center for Disease Control and Prevention; among 10,647 patients that died as consequence of COVID-19, 20.9% had underlying CKD (26).

Beside this tight association with CKD, COVID-19 is also a direct cause of de novo renal injury: at hospital admission, 43.9–65.8% of patients have proteinuria and 26.7–41.7% of patients have hematuria (4, 15). In a cohort of 333 hospitalized patients from China, renal complications were found in 75.4% of cases, even if only 7.5% met acute kidney injury (AKI) criteria. Of note, any renal involvement was associated with a 10× mortality increase (15). Two studies from the New York City area analyzed data from 5,449 and 5,700 hospitalized patients with COVID-19 and confirmed the incredibly high frequency of AKI in severely affected individuals. One study reported an AKI incidence of 89.7% in patients requiring ventilator support (10). In the other study, AKI and a need for renal replacement therapy were observed in 72.1% and 14.1%, respectively, of patients that subsequently died (17a). In the Italian data, a need of renal replacement therapy was reported in 22.6% of patients who died, and renal failure was the most common extrapulmonary complication.

These results suggest that both acute and chronic impairment of renal function associate with worse outcomes in SARS-CoV-2 infection and raise important questions on the underlying mechanisms. CKD increases the risk of chronic injury in the other organs, potentially favoring a more severe COVID-19 phenotype (4). A NHANES study showed that both obstructive and restrictive lung dysfunction are common in presence of CKD stage ≥3 (14). Similarly, cardiovascular mortality risk displays a negative linear correlation with glomerular filtration rate (GFR); the cooccurrence of renal and cardiac disease has been defined as cardiorenal syndrome, and it is well established that any dysfunction in either induces injury in the other (17). CKD also leads to diffuse tissue senescence and has been associated with muscle wasting, bone frailty, and dementia (13). Furthermore, CKD acts as a double-edged sword on the immune system. The uremic milieu suppresses the adaptive immunity and increases the incidence of infections and cancer; by converse, the innate immune response is chronically activated, resulting in inflammation and further tissue damage (13).
In COVID-19-associated AKI, severe ARDS may increase renal injury through different mechanisms including alterations of gas exchange and impaired hemodynamics; additionally, ventilation-induced barotrauma is associated with the release of nephrotoxic cytokines by the lung epithelium. This condition is so common that the term “ventilator-induced kidney injury” has been proposed, and AKI biomarkers are detectable in urine soon after mechanical ventilation is started (9). In the most severe forms of COVID-19, it is evident that there is a significant increase of inflammatory cytokines; among them, IL-6 has a central pathogenic role, and monoclonal antibodies have been tested to target the cytokine itself or its receptor (8). During AKI, the renal epithelium releases a massive amount of IL-6 into the bloodstream (>100-fold increase compared with baseline), and CKD is associated with higher circulating IL-6 levels as a consequence of the above-mentioned chronic inflammation coupled with reduced renal clearance (1, 23). Additionally, SARS-CoV-2 could directly infect renal cells; Su et al. (24) reported viral-like inclusions in both podocytes and tubular cells, but these data need further validation (2). However, more recent data have questioned a direct infection of renal tissue (21).

Autopsy data have found acute tubular necrosis, microvascular congestion, microvascular thrombi, hemosiderin deposits, lymphocyte infiltration, complement activation, and myosin casts in the kidneys of patients who died of COVID-19 (2). Surprisingly, relevant renal microvascular damage was also detected in individuals without clinically detected AKI (2).

These findings prompted us to suggest that the high mortality observed in comorbid and elderly patients is related to a reduced renal functional reserve (RFR). RFR is the capacity of the kidneys to increase GFR in response to stress and depends mainly on total nephron mass (19). Reduced preoperative RFR represents a risk factor for the development of AKI (11). A subclinical nephron mass loss is common during aging and in patients with renal or extrarenal systemic diseases but could be challenging to detect; studies performed on kidney donors have demonstrated how the acute loss of 50% of renal mass corresponds to a barely appreciable increase in serum creatinine (5). Therefore, in the presence of a normal GFR but reduced RFR, patients could be exposed to increased mortality risk and AKI episodes may favor CKD progression, thus triggering a vicious circle (Fig. 1). We believe that during hospitalization, the identification of patients with reduced RFR may allow a better stratification in terms of worse outcome and may prompt the initiation/anticipation of COVID-19 therapies supported by preliminary evidences (e.g., dexamethasone or remdesivir) (5a, 13a).

Technical problems may limit RFR assessment during hospitalization; RFR is commonly evaluated as GFR increase after oral or intravenous protein load. This approach has been studied under steady-state conditions and may not be applicable to patients with COVID-19. Different theories have been proposed to explain the GFR increase after protein load, the most common method to assess RFR: glomerular hyperfiltration may occur, leading to an increase of filtration fraction (18). In 1993, Woods and coworkers (25) suggested that an overall increase of renal blood flow and not a temporary variation of filtration fraction may represent the main mechanism of GFR increase. This theory seems to be supported by the observation of the decrease in renal vascular resistance in response to protein load with afferent arteriolar vasodilatation (20).

It is debatable as to whether a metabolic or a hemodynamic stressor is more appropriate for RFR assessment (6). A hemodynamic and noninvasive bedside method to estimate RFR has been recently proposed (20); mechanical abdominal pressure leads to a renal blood flow decrease and triggers autoregulatory mechanisms, which reduce the renal resistive index. The entity of renal resistive index variation correlates with RFR and could determine AKI susceptibility. This approach has no validation, and more extensive studies are required; however, it pinpoints kidney microvascular function, one of the main targets of renal COVID-19.

**Fig. 1. Hypothesis of glomerular filtration rate (GFR) decline and reduction of nephron mass (%) in patients with COVID-19.** Age and chronic comorbidities (green box and arrows) contribute to the GFR decline: COVID-19-associated acute kidney injury (AKI) may occur at any GFR value and may favor chronic kidney disease (CKD) progression and end-stage renal disease (ESRD). On the left (white) side, a normal baseline GFR (black line) is maintained until renal functional reserve (RFR) is preserved; however, RFR decreases (blue line) after AKI episodes. In contrast, on the right (gray) side, when RFR is spent, GFR (black line) decreases, leading to CKD progression and ESRD; at any GFR level, AKI episodes enhance CKD progression (red arrow). CV, cardiovascular; COPD, chronic obstructive pulmonary disease.
From an economic point of view, AKI is associated with an increased length of hospital stay and costs: in 2017, AKI total costs in the United States were estimated to be between $5.4 and $24 billion, with a further average increase of $40,000 for each patient when dialysis was needed (22). Moreover, the transition from AKI to CKD/end-stage renal disease (ESRD) leads to a further spread of medical costs due to the development of comorbidities. In these terms, worsening of renal function following hospitalization for COVID-19 (in particular for patients who experienced AKI) may cause a public health burden with future limitation to renal care access due to the excessive growth of the population with ESRD. Dedicated ambulatory followup is warranted to diagnose renal impairment and to prevent frequent rehospitalizations and CKD progression; however, serum creatinine may lead to some errors in data interpretation considering the well-known reduction of muscle mass during hospitalization, particularly in elderly individuals. In this setting, RFR with oral protein load can be a useful tool to discriminate patients more prone to evolve to CKD/ESRD. Moreover, RFR could be integrated with new biomarkers of renal function (pro- enkephalin, cystatin-C, or direct measure of renal function) (3, 12) and nephron mass (e.g., uromodulin) (16) able to improve the identification of CKD progression.

In conclusion, current evidence suggests the need to consider the clinical, social, and economic relevance of renal function evaluation in COVID-19. Both AKI and CKD are tightly associated with COVID-19-related death, and renal functional impairment may contribute to disease severity and may warrant earlier targeted or supportive therapeutic interventions. The lack of extensive data about renal function evaluation in patients with COVID-19 reminds us of the traditional Indian story of “The Elephant in the Village of the Blind”: when it is difficult to achieve the complete knowledge of a problem altogether, we need to evaluate the different variables and to interconnect them. As the 1932 Nobel Prize in Physics Werner Heisenberg said: “We have to remember that what we observe is not nature in itself, but nature exposed to our method of questioning.” In our opinion, evaluation of renal function and RFR are important pieces to decipher COVID-19-related AKI.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
V.C. conceived and designed research; M.M. prepared figures; G.G., M.D., S.D., V.C. drafted manuscript; V.C. and SD edited and revised the manuscript; R.M. and C.C. approved the final version of the manuscript.

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