



Post-acute COVID-19 syndrome and kidney diseases: what do we know?

Sidar Copur¹ · Metehan Berkkan¹ · Carlo Basile² · Katherine Tuttle^{3,4} · Mehmet Kanbay⁵

Received: 22 January 2022 / Accepted: 20 February 2022 / Published online: 16 March 2022
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Abstract

COVID-19, a disease caused by a novel coronavirus (SARS-CoV-2), is a major global threat that has turned into a pandemic. Despite the emergence of multiple vaccination alternatives and developing therapeutic options, dramatic short- and long-term clinical outcomes have been recorded with more than 250 million infected people and over 5 million deaths as of November 2021. COVID-19 presents various respiratory, cardiovascular, neuropsychiatric, musculoskeletal and kidney features during the acute phase; nevertheless, renal involvement in the post-infection period has recently been emphasized. The present review aims to evaluate the growing literature on kidney involvement in the SARS-CoV-2 infection along with clinical features reported both in the acute phase of the infection and in the post-acute COVID-19 period by assessing potential pathophysiological frameworks explaining such conditions. Chronic kidney disease and development of acute kidney injury (AKI) in the course of initial hospitalization are associated with high mortality and morbidity rates. Moreover, growing evidence suggests a decline in renal function in the 6-to-12-month follow-up period even in patients without any signs of AKI during the acute phase. Despite such concerns there are no guidelines regulating the follow-up period or therapeutic alternatives for such patient population. In conclusion, the burden of COVID-19 on the kidney is yet to be determined. Future prospective large scale studies are needed with long follow-up periods assessing kidney involvement via multiple parameters such as biopsy studies, urinalysis, measurement of serum creatinine and cystatin C, directly measured glomerular filtration rate, and assessment of tubular function via urinary β^2 -microglobulin measurements.

✉ Carlo Basile
basile.miulli@libero.it

Sidar Copur
scopur14@ku.edu.tr

Metehan Berkkan
mberkkan16@ku.edu.tr

Katherine Tuttle
katherine.tuttle@providence.org

Mehmet Kanbay
drkankay@yahoo.com

² Associazione Nefrologica Gabriella Sebastio,
Martina Franca, Italy

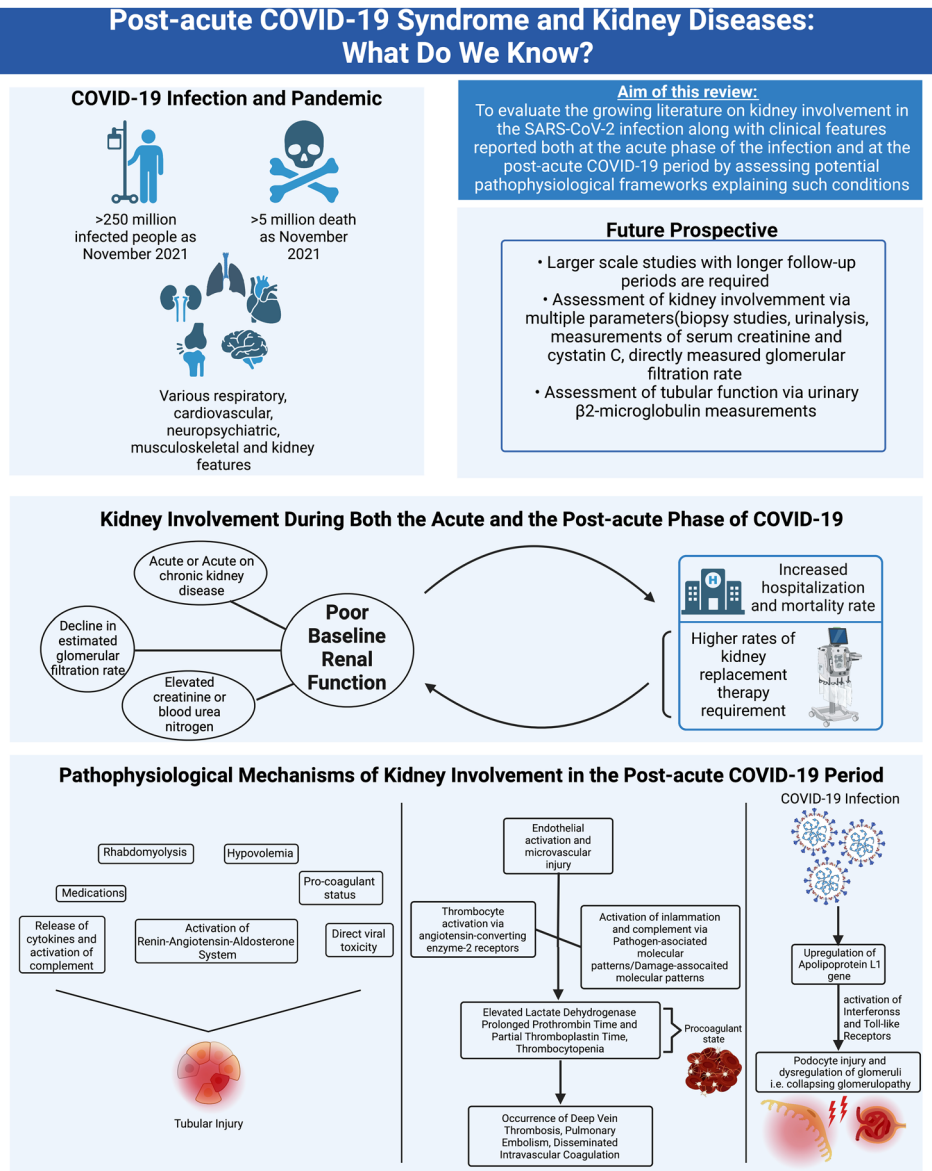
³ Division of Nephrology, University of Washington, Seattle,
WA, USA

⁴ Providence Medical Research Center, Providence Health
Care, Washington, USA

⁵ Division of Nephrology, Department of Medicine, Koc
University School of Medicine, Istanbul, Turkey

¹ Department of Medicine, Koc University School
of Medicine, Istanbul, Turkey

Graphical abstract



Keywords Acute kidney injury · Chronic kidney disease · COVID-19 · End-stage kidney disease · Post-acute COVID-19 syndrome

Introduction

COVID-19, a disease caused by a novel coronavirus (SARS-CoV-2), is a major global human threat that has turned into a pandemic [1, 2]. It is the second one among the latest outbreaks caused by a coronavirus family member, following the severe SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV. COVID-19 presents various respiratory, cardiovascular, neuropsychiatric, musculoskeletal and kidney features during the acute infection phase; nevertheless, renal involvement in the post-infection period has recently been highlighted. Despite the emergence of multiple vaccination alternatives and developing therapeutic options, dramatic short- and long-term clinical outcomes have been recorded with more than 250 million infected people and over 5 million deaths as of November 2021 [3, 4]. The most common presenting symptoms include shortness of breath, fatigue, fever and cough, all of which are commonly observed between days 4 and 5 from exposure [5]. The most common causes of mortality and morbidity among infected patients are respiratory complications followed by cardiovascular events; nevertheless, pathological investigations and autopsy studies demonstrated the involvement of almost all systems, including: central and peripheral nervous, gastrointestinal, musculoskeletal and renal systems [6]. In addition to cardiovascular and respiratory comorbidities, chronic kidney disease (CKD), diabetes mellitus and immunocompromising disorders are associated with higher hospitalization and mortality rates [7].

Although various pharmaco-therapeutic alternatives including chloroquine/hydroxychloroquine, favipravir, azithromycin, lopinavir-ritonavir, molnupravir, and ivermectin have been proposed for the treatment of COVID-19, few antiviral agents such as remdesivir and nirmatrelvir-ritonavir have been approved by the US Food and Drug Administration to date [8]. Data on their safety are limited: studies so far have shown significant adverse reactions with remdesivir (high serum liver enzymes and serum creatinine, respiratory failure), chloroquine (retinal toxicity), ivermectin (neurotoxicity and psychosis), and favipravir (high serum liver enzymes) [9, 10].

The present narrative review aims to evaluate the growing literature on kidney involvement in COVID-19 along with clinical features reported both in the acute phase of infection and in the post-acute COVID-19 period by assessing potential pathophysiological frameworks explaining such conditions: in January 2022 we started our literature search in three databases, PubMed/Medline, Web of Science and Google Scholar. The titles and abstracts of all studies found were individually assessed with regard to their suitability for this narrative review. After deleting unrelated articles and studies the full texts of all remaining studies were individually assessed.

Post-acute COVID-19 syndrome

Presence and/or persistence of symptoms, not attributable to any other disease, 8–12 weeks after the onset of COVID-19, define the post-acute COVID-19 syndrome [11]. The most common symptoms include fatigue, joint and muscle pain, fever, dyspnea and cough; furthermore, multiple system involvement has been reported [11]. An observational study conducted on 1250 US patients showed that over 32% of them experienced persisting or new-onset symptoms; more than 15% required re-hospitalization with more than 6% of mortality [12]. Similar rates of mortality, re-hospitalization and persistent symptoms have also been reported in some European studies [13, 14]. In a large scale study including more than 1300 hospitalized patients, only 40% were independent in their activities within 30 days of discharge [15]. The most common cardiovascular symptoms were chest pain, myocarditis and palpitations, while the most common neuropsychiatric symptoms included anxiety-depression, sleep disturbances and headache [16, 17]. The main pathophysiological mechanisms underlying the post-acute COVID-19 syndrome are immunological and inflammatory alterations, virus-specific pathophysiological changes and other common post-infectious sequelae depending on the organ system involved.

Direct kidney involvement in COVID-19

The genome of SARS-CoV-2 is a positive-sense single-stranded RNA of less than 30 kb that encodes 14 open reading frames including envelope, spike, nucleocapsid, matrix and accessory proteins [18]. The spike protein is involved in the attachment of the viral envelope to the angiotensin converting enzyme 2 (ACE2) receptors via an N-terminal S1 subunit and fusion of the viral envelope to the host cell membrane via a C-terminal S2 subunit [19]. A step referred as priming occurs after the attachment to the ACE2 receptors. Through this route the spike protein is cleaved by endosomal proteases (19) [19]. At this route of the viral entry SARS-CoV-2 requires a transmembrane protease serine 2 (TMPRSS2), similarly to the other members of the coronavirus family. The ACE receptors and the TMPRSS2 are co-localized in the kidney mostly in the epithelial cells of the proximal tubules and collecting ducts, with additional presence in the podocytes and mesangial cells, though to a lesser degree (Fig. 1) [20]. Despite not being the most common entry route for SARS-CoV-2, another potential route that depends on the receptor CD147 commonly expressed on the proximal tubular epithelial cells has been identified. These findings are supported by the inhibition of the viral

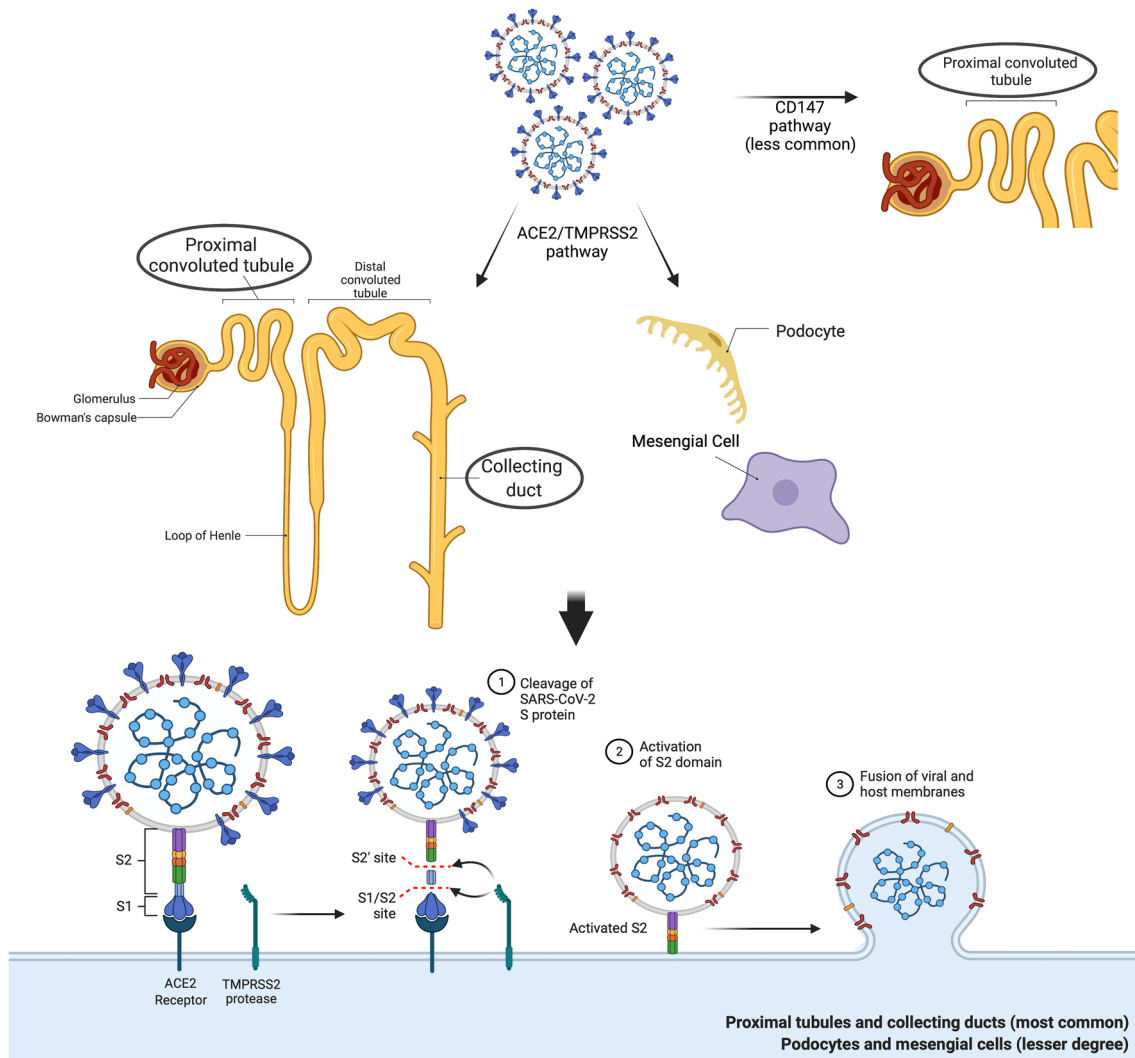


Fig. 1 Entry routes of the SARS-CoV-2 into the kidney cells

entry and amplification in certain cell lines incubated with meplazumab, an anti-CD147 antibody [21].

Although direct viral entry into the renal tissue has been shown in multiple studies and is supported by the presence of viral inclusion bodies on biopsy specimens, it is unclear whether the clinical kidney outcomes are caused by direct cytopathic effects, indirect mechanisms, or both [22, 23]. A detectable viral load has been observed by utilizing the RT-PCR method in certain autopsy specimens which may indicate direct cytopathic effects; nevertheless, it is important not to overlook the possibility of those viral inclusions being remnants of renal cell endocytosis or clathrin-coated vesicles, since not all inclusions include a viral RNA: such an example is observed in cases of COVID-19-associated collapsing glomerulopathy (Fig. 1) [24–27]. Therefore, further studies

are required to determine the underlying pathophysiology of kidney involvement in COVID-19.

Kidney involvement in the acute phase of COVID-19

High rates of acute kidney injury (AKI), elevated serum creatinine levels, electrolyte abnormalities and elevated serum urea levels have been reported in the acute phase of COVID-19, even though kidney involvement is not the most common cause of mortality or morbidity in COVID-19 patients [28–30]. Rates of AKI vary between 5 and 43% among infected patients through different pathophysiological mechanisms including acute tubular injury,

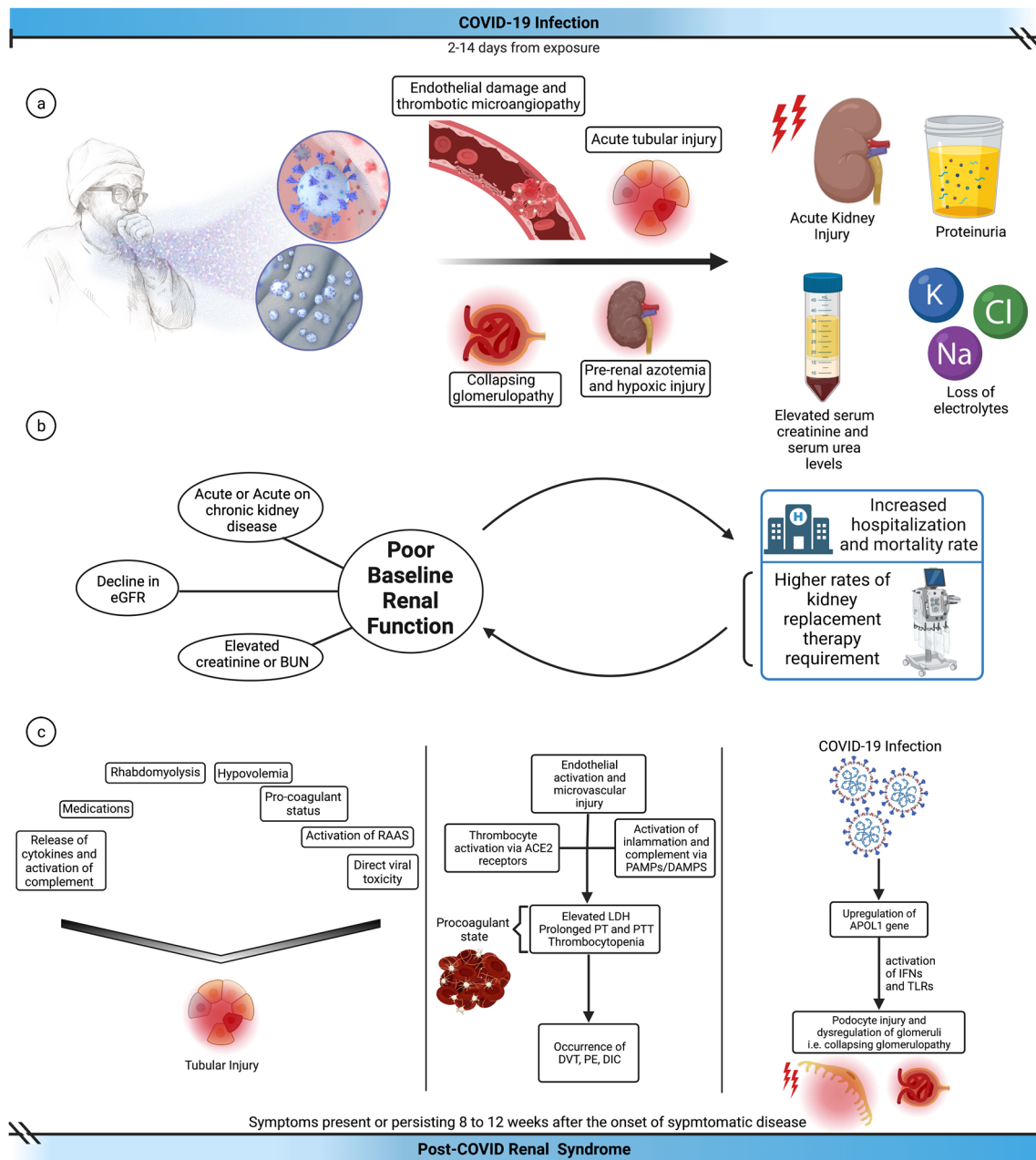


Fig. 2 Kidney involvement in COVID-19: **a** clinical features during the acute phase of COVID-19; **b** kidney involvement during both the acute and the post-acute phase of COVID-19; **c**. Pathophysiological mechanisms of kidney involvement in the post-acute COVID-19 period

endothelial damage, thrombotic microangiopathy, pre-renal azotemia, hypoxic injury and collapsing glomerulopathy (Fig. 2a) [6, 30]. A recent meta-analysis including 30,839 patients estimated AKI prevalence in 28% of them and the need for dialysis in 9% of the hospitalized patients; however, the rates of both AKI and need for dialysis were considerably higher in patients admitted to the intensive care units (Fig. 2b) [31]. Additionally, rates of AKI and need for dialysis were much greater during the course of COVID-19 compared to influenza respiratory infections,

as demonstrated by large scale comparison studies [32, 33]. Many mechanisms of kidney involvement in the acute phase of COVID-19 have been proposed: systemic factors including hemodynamic instability in response to sepsis or multi-organ failure (most commonly found in the so-called pre-renal AKI), cytokine-mediated injury and direct viral invasion, as described in the previous section. The main causes of pre-renal AKI in the acute phase of COVID-19 include hypotension, multi-organ failure, poor renal perfusion due to the effects of non-invasive or invasive

mechanical ventilation, rhabdomyolysis, hypovolemia due to poor oral intake or increased losses through various mechanisms including insensible perspiration or vomiting [34, 35].

High rates of proteinuria and loss of electrolytes due to proximal tubular damage have been shown in a Belgian study conducted on 49 hospitalized patients [36]. Some studies have shown proteinuria [36, 37]. In most cases proteinuria was low in degree, whereas cases of collapsing glomerulopathy showed severe proteinuria. Additionally, the degree of proteinuria was found to be associated with the severity of COVID-19 in a study conducted on 45 subjects [38]. Studies analyzing the presence of hematuria are limited: hematuria was present in 26.7% of the 701 subjects enrolled in a study [39]. Both hematuria and proteinuria were positively correlated with in-hospital deaths in COVID-19 patients [39].

In addition to AKI or acute-on-chronic kidney disease operating through various mechanisms, patients with poor baseline kidney function, as shown by a low estimated glomerular filtration rate (eGFR) or elevated serum creatinine or blood urea nitrogen levels, had a poor prognosis in terms of hospitalization and mortality during COVID-19 [30, 39, 40]. Therefore, poor renal function is a bad prognostic factor in addition to being a complication of COVID-19 (Fig. 2).

Kidney involvement in the post-acute COVID-19 period

AKI and requirement for kidney replacement therapy (KRT) were relatively common features of severe COVID-19, especially in patients admitted to the intensive care unit, with up to 25% incidence; furthermore, both were important predictors of survival [41, 42]. Approximately 28% of hospitalized COVID-19 patients were also affected by AKI and 9% of them required KRT [31]. Nevertheless, studies investigating renal function during the post-acute COVID-19 period are limited in number and in terms of follow-up duration. A study conducted on 56 hemodialysis patients infected with SARS-CoV-2 with a follow-up period of 12 months demonstrated a higher mortality rate compared to 154 hemodialysis patients without COVID-19 (hazard ratio 3.0, $P < 0.01$), with 30% of mortality occurring during the initial hospitalization [43]. Another important finding of that study was the rapid decline in anti-SARS-CoV-2 IgG levels in the hemodialysis patients at the 12-month follow-up [43]. A Chinese study showed that 35% of the 1733 subjects recovering from COVID-19 and with a baseline eGFR > 90 ml/min/1.73 m² had a statistically significant decline in eGFR at the six-month follow-up, including 13% who did not demonstrate any signs of AKI during the initial hospitalization period [44]. Similar findings were observed in a study conducted on US veterans, in which the risk of a decline in renal function and urinary tract infections were

correlated with the severity of the initial COVID-19 infection [45]. Most of the patients demonstrated a variable degree of recovery of renal function and a decline in the need for KRT in a study conducted on 74 hospitalized COVID-19 patients with AKI requiring KRT during the post-acute COVID-19 period (median follow-up period of 151 days) [46]. Similar findings were reported in many other retrospective cohort or observational studies, in which only the presence of CKD at baseline appeared to be a risk factor for higher rates of KRT requirement [47, 48]. Additionally, higher rates of AKI, significant decline in eGFR, major adverse kidney events and end-stage kidney disease were observed in the 30-day survivors of COVID-19 compared to a non-infected control group in a study including 89,216 infected patients and 1,637,457 controls [49].

Kidney transplant patients are a population that is highly vulnerable to COVID-19 due to the use of immunosuppressive medications, low levels and shortened persistence of antibody titers following either vaccination or active infection, a pro-coagulant state caused by the CKD status and medications, and greater need for hospitalization and medical assistance. Kidney transplant patients are more prone to develop signs of kidney injury during the initial hospitalization period, in addition to higher rates of morbidity and mortality, compared to the general population [50]. Furthermore, almost 90% of the kidney transplant patients who survived COVID-19 developed general symptoms of post-acute COVID-19 syndrome, such as fatigue, malaise and joint pain. The most common laboratory findings included shortened activated partial thromboplastin time, elevated fibrinogen and D-dimer levels, all of which are consistent with a pro-coagulant state [51]. Rates of symptoms and laboratory abnormalities associated with the post-acute COVID-19 syndrome were statistically significantly higher in kidney transplant patients [51, 52]. Despite such findings, high rates of graft survival were reported in relatively large scale studies during the post-acute COVID-19 period [53]. However, some of the major limitations of these studies were the short follow-up period, the lack of biopsy-proven histopathological changes, and the lack of a clear cause-effect relationship. Additionally, there is no consensus on the therapeutic alternatives for patients with renal involvement in the post-acute period, despite the presence of certain recommendations regarding other organ systems, such as the cardiovascular, respiratory and neuropsychiatric ones.

Pathophysiological mechanisms of kidney involvement in the COVID-19 period

COVID-19 might affect the kidney in multiple ways and the contribution of these factors can vary over time. Many of the direct and indirect effects of SARS-CoV-2 may persist during recovery after hospital discharge and could lead to

repeat episodes of sepsis, recurrent AKI and increased risk of CKD. Furthermore, the relationship between COVID-19 and CKD is likely to be bidirectional. Mild CKD might increase the risk of COVID-19 and associated AKI, whereas increased severity of AKI might be associated with persistent kidney dysfunction, delayed recovery and/or need for long-term dialysis.

Various pathophysiological mechanisms including tubular injury, endothelial damage, inflammatory mediators, complement activation, micro- or macrovascular injury, and podocyte injury have been proposed to explain the renal features reported during the post-acute COVID-19 period (Fig. 2c).

Tubular injury

In addition to potential direct viral toxicity, local inflammatory processes including release of cytokines and activation of complement, medication-induced tubular injury, rhabdomyolysis, hypovolemia caused by fluid losses due to fever or diarrhea, hypotension or septic shock, pro-coagulant status, and activation of the renin–angiotensin–aldosterone system are all potential contributors to tubular injury (Fig. 2c) [6, 54, 55]. This hypothesis has been supported by numerous autopsy studies revealing high rates of acute tubular necrosis; one biopsy study conducted on 240 subjects demonstrated myoglobin cast nephropathy in 3.3% of patients [52]; additionally, two cases of biopsy-proven vitamin C-related oxalate nephropathy have been reported [56]. Lack of long-term follow-up periods, dependence on a single parameter, mostly serum creatinine to assess renal function, absence of urinalysis and relatively small study populations are major limitations of these studies. Nevertheless, we cannot underestimate the possibility of unresolved tubular injury that is not reflected in clinical or laboratory features.

Endothelial activation and microvascular injury

Commonly encountered during COVID-19, elevated lactate dehydrogenase levels, prolonged prothrombin and partial thromboplastin times, thrombocytopenia and occurrence of deep vein thrombosis or pulmonary embolism are features of a pro-coagulant state and/or disseminated intravascular coagulation (DIC) (Fig. 2c) [57]. Thrombocyte activation is thought to be the main mechanism for DIC in COVID-19, since SARS-CoV-2 can bind to thrombocytes via ACE2 receptors and activate certain signaling pathways [58]. Additionally, activation of inflammatory pathways and complement via the release of pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) molecules may lead to the release of pro-coagulant substances and tissue factors involved in the extrinsic pathway of coagulation [59]. Recent studies have demonstrated

a role of an excessive formation of neutrophil extracellular traps in a phenomenon referred to as immunothrombosis in severe cases of COVID-19 [60]. Additionally, features of thrombotic microangiopathy have been demonstrated in 3.3% of 240 patients [52]. Supporting evidence for thrombotic complications includes rare cases of renal artery or renal vein thrombosis leading to renal infarction [61].

Podocyte injury

Collapsing glomerulopathy is the most commonly reported glomerular disease in COVID-19 patients: it is associated with APOL1 gene polymorphisms especially in patients of African ancestry (Fig. 2c) [62]. Upregulation of the APOL1 gene via a viral infection leads to activation of interferon and toll-like receptors, thus leading to dysregulation of podocytes and glomeruli [63, 64]. Many other viral infections associated with interferon release, such as human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus and Parvovirus B19, have been linked to collapsing glomerulopathy [65–67]. Furthermore, rare cases of minimal change disease and focal segmental glomerulosclerosis have been reported in COVID-19 patients.

Other glomerulopathies

Rare cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane (GBM) disease and immunoglobulin A vasculitis without nephropathy have been reported in COVID-19 patients [68, 69].

Future perspectives

The burden of COVID-19 on the kidney is yet to be determined. The COVID-19 pandemic is likely to have a long-term impact even on patients who have not been infected by the virus, owing to delays in care for chronic diseases, such as CKD, diabetes and hypertension. This area is understudied but might have the largest impact at the population level and could disproportionately affect vulnerable individuals, particularly those with low socioeconomic status and poor access to health care. Studies are urgently needed to investigate this area and confirm the importance of measures to catch up on preventive care for at-risk individuals [67]. To gain a better understanding of the effects of COVID-19 on the kidney, large integrated health-care systems and collaborations that enable rapid collection and analysis of clinical, laboratory and diagnostic data should continue to provide access to their databases for researchers who are investigating the long-term sequelae of COVID-19. Translational studies in which patients with COVID-19 undergo data and

Table 1 Ongoing clinical trials investigating the long-term effects of COVID-19 on the kidney

Study	Study type	Recruitment status/results	Study population	Country	Outcomes
Kidney Involvement in COVID-19 (COVKID) NCT04355624	Multi-center, prospective, observational cohort	Recruiting/No results posted	Patients with COVID-19	France	Rate of kidney involvement 3 months after COVID-19
Institut de Recherches Cliniques de Montréal (IRCM) Post-acute COVID-19 (IPCO) Research Clinic (IPCO) NCT04736732	Prospective, observational cohort	Recruiting/No results posted	Patients with COVID-19	Canada	Evaluation of the short- and long-term kidney involvement within 24 months
Global Assessment of Acute and Chronic Kidney Disease Incidence and Outcomes in Patients with COVID-19 NCT04491227	Multi-center, retrospective, cohort	Enrolling by invitation/no results posted	Patients with COVID-19 with acute and chronic kidney dysfunction	US Bolivia Canada Chile India UK	AKI incidence; dialysis requirement; recovery of kidney function up to 12 months
Kidney in Coronavirus Disease 2019 Registry (Kidney-COVID19) NCT04797091	Single-center, retrospective, case-control	Recruiting/no results posted	Patients with SARS-CoV-2-infection	Germany	Analysis of the effects of SARS-CoV-2-infection on the kidney by means of estimated glomerular filtration rate and serum creatinine after 6 months
KIDney Injury in Times of COVID-19 (KIDCOV) NCT04705766	Multi-center, prospective, cohort	Recruiting/no results posted	Individuals with current SARS-CoV-2 test results recorded	US	Testing predictive value of kidney injury molecules for kidney outcomes within 12 months
Long-Term Cardio-Vascular Risk Assessment in CKD and Kidney Transplanted Patients Following SARS-COV-2 (CARDIO SARS) NCT05125913	Multi-center, prospective, case-control	Recruiting/no results posted	CKD stage 3 to 5 patients, dialysis patients and kidney transplant patients with COVID-19	Romania	Doubling of serum creatinine and 40% decline in glomerular filtration rate after 6, 12, 24 months
Follow-up of patients with Covid-19. (TeleRea'nCo) NCT04609839	Single-center, prospective, case-only	Recruiting/no results posted	Patients admitted to the intensive care unit for COVID-19	France	Assessment of the presence of renal sequelae during 12 months following the patient's discharge from the intensive care unit
Long-Term Outcome in ICU-Treated COVID-19: New Chronic Diseases NCT05075096	Multi-center, retrospective, case-control	Not yet recruiting	All patients with COVID-19 admitted to the intensive care unit	Sweden	Assessment of the severity of COVID-19 on development of chronic kidney disease within 1 year
REassement After Hospitalization for Sars-COV-2 disorder (REHCOVER) NCT04443257	Single-center, prospective, cohort	Enrolling by invitation/No results posted	Adults hospitalized within 3–6 months for COVID-19	France	Incidence or worsening of renal disease within 3–6 months after COVID-19
One-year Outcomes in Survivors of the Severe COVID-19 Pneumonia (CO-Qo-ICU) NCT04401111	Single-center, prospective, cohort	Recruiting	Patients treated for COVID-19 in the intensive care unit	France	Evaluation of renal function during the first year after the patient's discharge from the intensive care unit

biospecimen collection during hospitalization and recovery are key to understanding clinical and biological outcomes and for investigating mechanisms [67]. Future prospective large scale studies are needed with long follow-up periods assessing renal function via multiple parameters such as biopsy studies, urinalysis, measurement of serum creatinine and cystatin C, directly measured GFR, and assessment of tubular function via urinary β^2 -microglobulin measurements. Several ongoing clinical trials are investigating this issue (Table 1). In the meantime, careful follow-up of kidney function should be performed in COVID-19 patients with prioritization of those who had AKI or are affected by CKD.

Acknowledgements Mehmet Kanbay gratefully acknowledges the use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency of Turkey, Presidency of Strategy and Budget. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Presidency of Strategy and Budget.

Funding No funding agency granted the present study.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No verbal and written informed consent was necessary for this study.

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