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Pathophysiology of COVID-19-associated Acute Kidney Injury: implications for research and therapeutic strategies

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The authors declare no competing interests.

Abstract

Although in patients with COVID-19 respiratory failure and hypoxemia are the primary causes of admission to intensive care units, kidney involvement is also common. While any specific pathophysiology of underlying COVID-related acute kidney injury (AKI) remains largely unknown, in keeping with most AKI seen in critical care, the cause is likely multifactorial although recent findings have highlighted potential pathophysiological pathways. Here, we will discuss the currently available evidence behind the different proposed mechanisms of AKI complicating COVID-19 infection, including the histopathological findings highlighting the similarities and contrast with that known from the pathophysiology of AKI in non-COVID-related sepsis. Where performed, histopathological studies commonly demonstrate acute tubular injury, although as observed in patients with sepsis associated AKI this is often mild despite significantly deranged function. Systemic hemodynamics instability very likely contributes to tubular injury. Furthermore, although the cytokine storm syndrome has been much lauded, evidence shows lower levels of circulating cytokines (including Interleukin-6, TNF-a, etc.) compared to acute respiratory distress syndrome (ARDS) due to causes other than COVID-19, septic shock or other cytokine release syndromes. Tissue inflammation and local immune cell infiltration (including macrophages and dendritic cells) have been repeatedly observed and may play a critical role, as may endothelial injury and microvascular thrombi. Decreased viral clearance and an impaired type 1 interferon response have been reported in severe COVID-19 patients. Findings of higher RNA load of SARS-CoV2 in patients who died with AKI compared to those without AKI suggest a contribution of viral invasion in the kidneys even though this

issue remains controversial. In light of these observations, the potential pathophysiological mechanisms of COVID-19-related AKI may provide insights into therapeutic strategies.

Key-points:

- Over a quarter of patients hospitalized with COVID-19 have been reported to develop AKI.
- Low molecular weight proteinuria, Fanconi syndromes and histological findings point out toward tubular injury.
- Kidney biopsies from patients with COVID-19 and AKI inconsistently reported viral invasion but constant acute tubular injury.
- Collapsing glomerulopathy has been identified in subset of patients mostly without severe respiratory symptoms and high-risk APOL1 genotypes.
- Regional inflammation, endothelial injury and renal microthrombi were reported but their implication in the pathogenesis of COVID-associated AKI remains uncertain.
- Anti-inflammatory drugs (i.e. steroids, IL-6 receptors blockers) appear to limit progression toward severe AKI.

Introduction:

The severe acute respiratory coronavirus 2 (SARS-CoV-2) was first described in December 2019 and is responsible for the disease coronavirus 2019 (COVID-19) which has led to the global pandemic. The pulmonary manifestations of COVID-19 are well described but it is increasingly recognized that AKI is a common complication of the disease, often presenting at hospital admission. Whilst initial reports from China suggested relatively low rates of kidney involvement[1–4], subsequent reports from the United States and Europe indicate much higher rates of AKI particularly in the intensive care setting (ICU) with up to 45% requiring kidney replacement therapy (KRT)[5–8]. It is known that mortality in hospitalized patients with COVID-19 and AKI is higher than those without renal involvement[8,9]. As with all AKI in the context of multi-organ failure requiring ICU admission, mortality in patients admitted to the ICU with COVID-19 associated AKI requiring KRT is especially high[10]. Anecdotal reports of lack of renal recovery in those who survive compared to other forms of AKI is of particular concern[9,7,10] but long-term patient outcomes are not yet fully understood as this is complicated by prolonged hospital admissions as well as a lack of reported follow-up. Ascertaining the true epidemiology of COVID-19 associated AKI is difficult due to differences in underlying co-morbidities of the populations examined as well as possible variations in practice and methods of AKI measurement. Age, past medical history of hypertension, diabetes have repeatedly been associated with a higher risk of AKI in this setting. Chronic Kidney Disease (CKD) is a well identified risk factor for AKI in hospitalized patients, and was indicated as the most relevant risk factor for AKI requiring KRT in 3099 critically ill patients with COVID-19[9]. Indeed, several epidemiologic studies worldwide clearly demonstrated that CKD represents a relevant and independent risk factor for a worse outcome in COVID-19. In a recent case-control study

comparing COVID-19 patients with the Danish general population matched for age, gender and comorbidities, lower eGFR levels were associated with an increased rate of hospital-diagnosed COVID-19 and death[10]. OpenSAFELY project from ERA-EDTA analyzed variables associated with COVID-19 death in about 17 millions of patients: of note, CKD (HR 2.52 for patients with eGFR <30 mL/min/1.73 m2) was one of the most prevalent comorbidities associated with a worse outcome[11]. Moreover, CKD is often associated with other comorbidities such as diabetes, hypertension and obesity linked to an increased mortality rate[3]. In this clinical scenario, the high mortality observed in comorbid and elderly patients may be related to a reduced renal functional reserve (RFR), the capacity of the kidney to increase GFR in response to stress and strongly dependent on functioning nephron mass[12]decreased GFR and RFR levels may support the development of AKI as assessed by epidemiologic studies. In 4020 consecutive hospitalized patients with COVID-19 in Wuhan (China), 285 (7.09%) of them were identified as AKI. Both early and late forms of AKI were characterized by an increased risk of in-hospital mortality: moreover, CKD, older age and levels of inflammatory biomarkers were associated with increased risk of late AKI[13]. In 1603 consecutive patients admitted to a University Reference Hospital in Spain, 43.5% of patients elevated serum creatinine at admission had previous CKD and 11.4% developed AKI[14]. In 777 patients hospitalized in Genoa (Italy), AKI developed in 176 (22.6%): of these, 79 (45%) showed an acute worsening of a preexisting CKD, and 21 (12%) required kidney replacement therapy. Independent variables for AKI development were the presence of CKD, C-reactive protein (CRP) and ventilatory support[15]. Nevertheless, it is clear that the pathophysiology is multifactorial and different sub-phenotypes of COVID-associated AKI exist. In this review, we will discuss the current understanding of the pathophysiology of

COVID-19 associated AKI exåmining potential mechanisms as well as non-specific factors related to critical illness (Figure 1).

Clinical and biological Features of COVID-19-associated AKI

The incidence and severity of AKI in the setting of COVID-19 infection depends on the clinical setting. Most studies utilize the KDIGO (Kidney Disease Improving Global Outcomes) consensus definition of AKI and several studies have reported that upwards of 30-50% of all patients hospitalized with COVID-19 related illnesses develop some form of AKI with the proportion increasing in those requiring intensive care[11,9,12,3,13,7.]In a meta-analysis, among hospitalized COVID-19 patients the pooled incidence of AKI was 28.6% [(95% CI 19.8-39.5]) in the USA and Europe and 5.5% (95% CI 4.1-7.4) in China[16]. Among patients admitted to the ICU, 46% were reported to have AKI, with up to 78% in those requiring intubation[17]. Additionally, amongst those in the ICU, kidney replacement therapy (KRT) was reported to be up to 20%[18–20,21,22]. In a large-scale retrospective observational cohort of a New York City Health Care System, 46% of 3,993 inpatients developed AKI with 39%, 19% and 42% having KDIGO Stage 1, 2 and 3 AKI respectively[19]. These data are mirrored in a separate and distinct New York based cohort of 3,854 patients with inpatient COVID-19 AKI (39.9% of the larger cohort) with 1644 (42.7%) having stage 1, 840 (21.8%) having stage 2 and 1370 (35.5%) having Stage 3 AKI[8]. In this second cohort which also included both ward and ICU patients, 638 of the 1,370 with Stage 3 AKI (46.5%, or 16.6% of total) received KRT. Importantly both of these studies are limited in that they only used the serum creatinine criteria of the KDIGO consensus definitions to identify those with AKI. Of note, wide geographic disparities in the incidence of AKI among US veteran patients hospitalized with COVID-19 have been reported ranging from

10% to 56%. Of note, rates of AKI declined over time (from 40% in March to 27% in July). This suggests that changes in patients management impacted the incidence rate of AKI[23].

Early reports of COVID-19 AKI noted the presence of hematuria and/or proteinuria[1,18] with one cohort study (n=701) noting that 44% of patients presented with proteinuria and 26% presented with hematuria[2] where greater amounts of hematuria or proteinuria (2-3+) had a stronger association with risk of hospital mortality in a "step wise dose effect" [2,18]. More recent cohort studies have demonstrated much higher rates of proteinuria (defined as a protein-creatinine ratio of > 0.5, 1+ or high on dipstick or >30 mg/dl on urinalysis) and hematuria (defined as 1+ or higher on dipstick / urinalysis) with 80% in patients with AKI[19]. Furthermore over 50% of those without AKI defined by KDIGO serum creatinine criteria had hematuria and over 70% presented with proteinuria. This presence of urinalysis abnormalities in those not meeting the definition of AKI suggests that kidney injury is occurring without significant functional change acutely. Fanconi syndrome (proteinuria, renal phosphate leak, hyperuricosuria and normo-glycaemic glycosuria) were reported to precede episodes of AKI[24](Figure 2). This presentation is in keeping with Stage 1S of a newly released AKI staging, when there is evidence of kidney injury that is not detected by creatinine and urine output criteria[25].

The proteinuria detected is of low molecular weight rather than albuminuria suggesting tubular origin rather than a reflection of glomerular injury and can identify patients in the early stage of AKI[26]. The contribution of underlying CKD is unknown, but the proportion of COVID-19 patients with proteinuria far exceeds the prevalence of stage 1 and 2 CKD in the general population[27]. Future studies are required to examine the role of other biomarkers of glomerular and tubular function to determine their association with serum creatinine-based AKI. Additionally, these data should be used in combination with the growing body of literature

describing the myriad of pathologic findings that have been seen on COVID-19 AKI kidney biopsies (e.g. collapsing glomerulosclerosis, thrombotic microangiopathy, direct viral tropism and classic tubular injury)[28–32](Figure 2). Integration of these pathologic findings with clinical data can potentially further inform the pathophysiology of COVID-associated AKI and recent evidence from France on biopsy data from 47 patients demonstrated that predominantly tubular damage is seen in cases with the most severe respiratory disease on ICU (66.7%) whereas collapsing glomerulopathy and focal segmental glomerulosclerosis was not seen in critically ill patients but in 70.6% of cases not in the ICU[33]. More than 2 co-existing comorbidities were seen in over 60% of cases and the occurrence of collapsing glomerulopathy was highly correlated with the expression of high-risk *APOL1* genotypes.

Current understanding of the Pathophysiology of COVID-19-associated AKI

The pathophysiology of COVID-19-associated AKI involves local and systemic inflammation and immune responses, endothelial injury and coagulation activation as well as activation of the renin-angiotensin-aldosterone system[30,34]. Direct viral infection with renal tropism of the virus has also been proposed but remains controversial[35]. Non-specific factors common in critical illness such as mechanical ventilation, hypoxia, hypotension, low cardiac output or nephrotoxic agents may also be responsible in the most severely affects patients (Table 2).

Insights from Renal Histology

Autopsy studies demonstrate that acute tubular injury is by far the most common finding (Table 1). Of note, tubular autolysis is a confounding factor in post-mortem renal histology for acute tubular injury[30,3]67/30/2021 1:25:00 PM. Postmortem kidney biopsies in patients with stage 2 or 3 AKI

and COVID-19 revealed that all patients had acute tubular injury with focal acute tubular necrosis

mostly mild, illustrating a relative uncoupling between histological injury and decline of renal function, a finding previously reported in non-COVID sepsis[37]. No evidence of glomerulonephritis, vasculitis or thrombotic microangiopathy nor significant viral presence were observed. In another autopsy series among 9 patients in the United Kingdom, evidence of acute tubular injury was noted in all patients with viral load quantified by use of qRT-PCR observed in 3 patients and detection of viral RNA only in one (11%)[38,39].

Renal biopsies among 17 patients with AKI (n=15) or proteinuria but mild COVID-19 symptoms for most, revealed acute tubular injury (n=14, 82%), collapsing glomerulopathy (n=7, 41%) and endothelial injury/thrombotic microangiopathy (n=6, 35%) were the most common histologic findings[40] (Table 1). One case showed acute glomerulonephritis with no evidence of direct infection of the kidney by SARS-CoV-2. A recent series from France demonstrated tubular injury in the sickest cohort whereas glomerular pathology was restricted to the non-ICU patients[33]. Of note, most biopsies were performed several weeks after onset of COVID-19 symptoms. This is in line with most biopsy studies failing to show significant SARS-CoV-2 infection of the kidney. Previous studies reported direct viral tropism but concerns have been raised regarding the methods used and the possibility of virus-like images such as normal vesicles from intracellular organelles and multivesicular bodies leading to false positive results[35,41,42,43]. However, Braun et al reported infective virus in an autopsied kidney that could replicate in vitro in non-human primate kidney tubular epithelial cells[44]. In this autopsy series, the authors further identified that 23 of 32 patients with AKI (72%) showed viral RNA in the renal tissue while only 3 of 7 (43%) were found in patients without AKI. In another autopsy

study among 6 COVID-19 patients using microdissection, SARS-CoV-2 was found in different kidney compartments, particularly in the glomerulus[42]. Viral RNA and protein were also detected using in situ hybridization with confocal microscopy. The presence of SARS-CoV2 particles have been sporadically observed in the urine too[32,45,46]. This suggest concomitant release by damage tubular cells or filtration of fragments of the virus since the high molecular weight of SARS-CoV2 (600-kDa) should not allow it to be filtered the glomerular membrane[47]. To conclude, viral particles have been found in kidney tissue although the direct role of the virus in the development of AKI remains controversial.

Collapsing glomerulopathy

Collapsing glomerulopathy was reported in several patients with COVID-19 (Table 1), described initially as COVID-19 associated nephropathy (COVAN) mostly in patients with non-severe respiratory symptoms of COVID-19 and isolated AKI or presenting with glomerular proteinuria[29,31,33]. Collapsing glomerulopathy has previously been described in various conditions including HIV and other viral infection infections (e.g. parvovirus B19, cytomegalovirus and Epstein–Barr virus). Collapsing glomerulopathy is associated with high-risk APOL1 genotypes, mostly in black patients. The true incidence of collapsing glomerulopathy and its contribution versus other underlying conditions (e.g. hypertension, CKD) toward the risk of COVID-associated nephropathy is unknown. Although the exact pathophysiology in COVAN remains unknown, it may share common mechanisms with HIV-infected patients with podocyte injury through disruption of autophagy and mitochondrial homeostasis [30].

Endothelial injury and dysfunction, coagulation activation

Biomarkers of coagulation and fibrinolysis activation (e.g. fibrinogen, D-dimer) have been repeatedly associated with an increased risk of death in COVID-19 patients. Autopsy studies report a 9-fold higher incidence of observed micro- and macrovascular thrombosis in lungs from COVID-19 patients compared to influenza pneumonia[48] and systemic micro- and macrovascular thrombosis have been repeatedly reported in COVID-19 in other organs, including the kidneys[49–51]. Many critical illnesses are associated with microvascular and endothelial injury but SARS-CoV2 is believed to have a specific impact on the endothelial activation. Post-mortem studies report vascular endothelialitis in COVID-19[48,52] and suspicion of viral infection of renal endothelial cells[52], but the use of electronic microscopy lacks specificity to confirm endothelial infection and evidence of direct viral infection of renal endothelial cells is lacking. Increase in plasma biomarkers of endothelial injury (sE-selectin, sP-selectin, Ang-2, sICAM-1, VWF antigen) and platelets (soluble thrombomodulin) and activation has been associated with poor prognosis[53,54,55]. Microvascular inflammation is known to trigger endothelial activation, leading to vasodilation, increased vascular permeability and pro-thrombotic conditions in other conditions[56–58]. Complement activation, as suggested by increased circulating levels of soluble C5b9 and C5a and by tissue deposition of C5b9 and C4d in lung and kidney tissues [5960,61], has been proposed to contribute to further promote inflammation and coagulation pathways in COVID-19. Release of damage-associated molecular patterns (DAMPs) from necrotic cell death may further contribute to endothelial injury in COVID-19[62]. SARS-CoV2 was furthermore shown to bind to platelets ACE2, activate platelets and promote immunothrombosis[63–65], making platelet activation a potential player in the pathophysiology of COVID-associated AKI[66,67]. Circulating prothrombotic autoantibodies targeting phospholipids and phospholipid-binding proteins have been reported[68]. In a cohort of 172 COVID-19 patients hospitalized, higher titers of

antibodies were associated with lower estimated glomerular filtration rate. *In vitro* studies confirmed that autoantibodies are potential drivers of endothelial cell activation contributing to the thrombo-inflammatory effects observed in severe COVID-19[69].

However, macro and microthrombi were inconsistently observed in the kidneys, or involving a small proportion of renal capillaries. A small autopsy study from New-York observed images of thrombotic microangiopathy within the glomeruli in only one of 7 cases[50]. In other cases, only rare small glomerular platelet aggregates were observed. In another kidney biopsy series with mild COVID-19 symptoms, evidence of glomerular acute endothelial cell injury were observed in 6 patients, most of them showing laboratory features of thrombotic microangiopathy (TMA)[40]. Of note, no evidence of peritubular vascular injury was observed. Neutrophils and neutrophil extracellular traps (NETs), frequently aggregating with platelets, were observed in many organs including the kidneys, despite sporadic presence of virus on histology, suggesting a role of inflammation in the development of intravascular thrombi[70]. Cases of renal artery thrombosis were anecdotally reported[71,72]. Finally, patients with severe COVID-19 often present with chronic comorbidities associated with chronic endothelial dysfunction and decreased activity of endothelial nitric oxide synthase and bioavailability of nitric oxide, a major vasodilator and antithrombotic factor[73].

Immune and inflammatory response

Several alterations of both innate and adaptive immune response following SARS-CoV-2 infection have been reported. *Immunosenescence,* a term used to define innate and adaptive immunological alterations occurring with aging, is characterized by *inflamm-aging*, a low-grade inflammatory state that may play a key role in the determination of organ dysfunction, and by

ineffective T cell response and antibody production. These features have been reported in COVID-19 and may explain partially the increased mortality in the elderly and comorbid population due to an inefficient viral clearance, enhanced cytokine/chemokine release, endothelial damage and activation of the coagulation and complement cascades[74].

The enhanced release of inflammatory mediators by immune and renal resident cells was firstly identified as a key mechanism of tissue damage. The inflammatory mediators in COVID-19 patients can bind to specific receptors located on renal endothelial and tubular epithelial cells causing a direct injury (e.g. activation of the death receptor pathway of apoptosis mediated by TNF/TNF-Receptor, Fas/Fas-Ligand activation)[75,76]: these findings have been observed in experimental models and measuring plasma cytokines in sepsis-associated AKI, but their role in COVID-19-associated AKI should be still clearly demonstrated.

Other studies evidenced the key role of type I IFN response by innate cells to suppress viral replication and activate the immune response : SARS-CoV-2 infection can triggers specific pathways finally leading to suppression of IFN release and IFN-treated patients improved viral clearance with a concomitant significant reduction of IL-6 and CRP[77].Inborn errors of type I IFN immunity showed IFN-alpha levels < 1 pg/ml allowing identification of genotypes at high risk of severe disease[78,79]. Another fascinating observation from the same group demonstrated that some patients of the cohort had autoantibodies directed to type I IFN, suggesting an autoimmune theory at the basis of the inefficient blockade of SARS-CoV-2 infection due to low IFN plasma levels and justifying the ongoing clinical trials based on therapeutic IFN administration[80].

However, a note of caution should be emphasized on the role of IFN in COVID-19-associated kidney damage: from one side, IFN blockade may limit the systemic inflammatory reaction due to SARS-CoV-2 replication; on the other hand, IFNs are well known mediators of glomerular

injury. Indeed, IFN-α and IFN-β exert differential effects on podocytes and parietal epithelial cells, enhancing podocyte loss and promoting glomerulosclerosis[81]. Moreover, different inflammatory stimuli can lead to the development of proteinuric diseases that may be ascribed to podocyte injury following cytokine release and activation of type 1 IFN signalling[82]. Finally, the above-mentioned expression of APOL1 risk alleles may promote damage through inflammatory-mediated podocyte death and glomerular scarring [83].

A relevant piece of the puzzle in innate immune response to viral infections is represented by the activation of the complement cascade although persistent and uncontrolled activation of the complement system may promote an inflammatory process finally leading to tissue injury. It has been shown that plasma levels of the soluble form of C5b9 and of the anaphylatoxin C5a were significantly higher in patients with COVID-19, particularly in the most severe forms of disease[84]. Complement may act in combination with other mediators contributing to the triggering of inflammation, coagulation and endothelial damage. Recent studies evidenced the activation of the complement cascade in different organs, including the kidney: C3c and C3d were detected in renal arteries and in glomerular capillaries of COVID-19 biopsies, and C3d was also observed in the tubular compartment. Staining for the membrane attack complex C5b-9 was positive in peritubular capillaries, renal arterioles, and tubular basement membrane. These findings suggest the activation of the lectin and classical pathways in peritubular capillaries and renal arteries, whereas the alternative pathway seems to play a key role in tubular damage [60]. Macor and coworkers confirmed multi-organ complement activation, in particular complement deposits were observed in tubular epithelial cells and vessels with only mild C5b-9 staining in glomeruli[61]. Complement activation seems to have a predominant role in COVID-19-associated endothelial dysfunction: C5a fraction can directly bind to C5aR located on endothelial cells

inducing the upregulation of Tissue Factor (TF) and loss of thrombomodulin, thus inducing activation of coagulation, exocytosis of P-selectin and ultra-large multimers of von Willebrand factor leading to increased platelet adhesion and aggregation. C5b-9 also contributes to endothelial dysfunction, increased vascular permeability, triggering of inflammation and coagulation[59,85,86]. Moreover, the binding of C5a on specific receptor present on tubular epithelial cells leads to DNA methylation of genes involved in cellular senescence, thus potentially promoting AKI persistence and progression toward CKD due to early fibrosis processes[87]. Taken together, these findings suggest that COVID-19 can be considered a thrombo-inflammatory disease and that the blockade of the complement cascade seems to be one of the potential therapeutic options to limit AKI, multiple organ failure and disease severity[88]. In a small cohort of hemodialysis patients, levels of plasma C3a and C5a were elevated prior to clinical deterioration in patients who developed severe disease suggesting that complement activation preceded severe symptoms[89]. Several studies also addressed the presence of an inadequate adaptive immune response: CD4+ and CD8+ T lymphopenia represent typical features of the most severe forms of COVID-19[90]. Other alterations of immune cells found in severe COVID-19 are the depletion of plasmacytoid dendritic cells, a major source of IFN-alpha, and of eosinophils[91]. A significant decrease of NK cell count was also noticed[91]. An intriguing hypothesis is the potential therapeutic approach represented by the increased expression of the antioxidant and anti-senescent transcription factor Nuclear factor (erythroid-derived 2) -like 2 (Nrf2). Nrf2 is maintained in an inactive state in the cytosol by association with its inhibitor protein KEAP1 (Kelch-like ECH-associated protein 1): in response to oxidative stress such as that observed in viral infections, KEAP1 is inactivated and Nrf2 is released to induce Nrf2-responsive genes able to protect against stress-induced cell death. On this basis, Nrf2 has been

suggested as the master regulator of tissue damage during infection. These pathways have been shown to be suppressed in biopsies from COVID-19 patients and Nrf2 agonist drugs can induce a distinct IFN-independent antiviral activity[92]: randomized clinical trials based on the administration of senolytic drugs in COVID-19 patients are currently ongoing[93]. Up to now, the protective role of Nrf2 activation in COVID-19-associated AKI is merely speculative: however, recent data from experimental AKI in other settings generated this hypothesis. Indeed, Noel et al. demonstrated that increased T cell expression of Nrf2 induced renal functional and histologic protection associated with significant lower levels of TNF-alpha, IFN-gamma and IL-17[94]. In addition, in ischemic and nephrotoxic models of AKI, Nrf2-deficiency has been shown to enhance susceptibility to tissue injury, confirming the role of this transcription factor as a potential therapeutic target[95]. Evaluating humoral immunity, some groups of COVID-19 patients exhibited a decreased B cell percentage and a concomitant increase of circulating plasmablasts [96]. As already underlined, a specific antibody response with a significant IgG component is essential to control viral infection: however, the above-mentioned mechanisms of immune senescence may lead to T cell exhaustion as well as to the aberrant production of tissue-specific autoantibodies. As reported for the formation of anti-IFN autoantibodies, immunosenescence may be responsible for a theory of autoimmune response directed to the soluble form of ACE2 that acts as a *dummy receptor*: the soluble form of ACE2 (sACE2) present in the blood and in extracellular fluids may act as an inactivator molecule for SARS-CoV-2 as described for other types of pathogenic viruses[97]. However, the high affinity of SARS-CoV-2 spike protein for ACE2 may lead to the formation of SARS-CoV-2-sACE2 complexes and to the consequent development of anti-ACE2 autoantibodies that can target tissue ACE2 creating vasculitis-like lesions after the early infective phase of the virus[98,99]. More recent studies reinforced the fact that

COVID-19 can be characterized by the presence of a robust autoimmune response with IgM directed to ACE2, the receptor allowing viral entry into the cells: purified anti-ACE2 IgM are able to activate complement in endothelial cells as observed in autopsy lung histology studies, thus confirming the angiocentric pathology of the most severe cases of disease[100]. Of note, anti-ACE2 IgM production has been associated with a robust anti-SARS-CoV-2 spike protein IgG response, suggesting the possible presence of an anti-idiotype IgM response cross-reacting with ACE2[98]. Considering the wide expression of ACE2 in different organs including the kidney, a role of anti-ACE2 autoantibodies cannot be excluded, leading to ACE1/ACE2 ratio modulation with the consequent worsening of tissue edema, inflammation and damage[101]. However, this theory remains to be validated. Furthermore, the relevant homology between ACE and ACE2 proteins may lead to the cross-reactivity with ACE receptor[102]. Lastly, Wang et al., using a high-throughput autoantibody discovery technique called Rapid Extracellular Antigen Profiling (REAP), showed in COVID-19 patients the production of autoantibodies directed to different extracellular and secreted immune-related or tissue-specific proteins, re-enforcing the relevant role of autoimmunity in the pathogenic mechanisms of lung and distant organ damage [103,104].

The Role of the Cytokine Storm Syndrome

Cytokine storm syndrome (CSS) is viewed as a life threatening condition with organs failure characterized by rapid proliferation and hyperactivation of all components of the immune system including T cells, macrophages, natural killer (NK) cells and the increased production and release of over 150 chemical mediators and inflammatory cytokines[105]. The inflammatory response of COVID-19 bears similarities to other conditions that are also referred to as exhibiting the CSS, including primary hemophagocytic lymphohistiocytosis (HLH)[106]. In severe COVID-19 infection, a CSS has been proposed as part of the "hyperinflammatory state" observed with marked elevations of acute phase reactants, lymphopenia, coagulation defects and in some cases of SARS-CoV2. Elevated levels of cytokines have been documented in patients with COVID-19 suggesting hyperactivation of the humoral immune response, including interleukin (IL)-6, as a critical mediator particularly for multiorgan dysfunction, including AKI[107,108]. A recent meta-analysis has reported that IL-6 levels are elevated and significantly associated with adverse clinical outcomes, including ICU admission, ARDS and death[109]. In these severe cases nearly three-fold higher serum IL-6 levels were observed within a range of 7.9-283 pg/ml although variable timing of IL-6 measurement, the type of assay as well as differences in the adjuvant immunomodulatory medications received, such as corticosteroids, may have affected both IL-6 response and patient outcomes. However, the levels observed are much higher in sepsis and non-COVID ARDS than that in COVID-19, approaching 10,000 pg/ml in CRS and over 20,000 pg/ml in sepsis[110]. A recent meta-analysis revealed that IL-6 levels in severe COVID-19 were lower than patients with sepsis, septic shock or hyperinflammatory ARDS[125]. A study from the Netherlands further compared proinflammatory cytokine levels (IL-6, IL-8 and TNF) in critically ill patients with COVID-19 vs other critically ill individuals[111]. The concentrations of circulating cytokines were lower in patients with

COVID-19 than in patients with bacterial sepsis and similar to other critically ill patients, even though patients with COVID-related ARDS had lower APACHE2 score, suggesting a lower severity of critical illness. These findings suggest, despite the initial enthusiasm, that COVID-19 may not be characterized by CSS and its role in the development of COVID-associated AKI therefore questionable. This has important implications for the rationale of using extracorporeal blood purification techniques as discussed further. Importantly, this does not exclude a role of regional inflammation in the pathogenicity of COVID-19. This is in line with high acute phase reactant inflammatory biomarkers levels including CRP in patients with COVID-19[125].

Role of ACE 2 and Activation of the renin-angiotensin-aldosterone system

Angiotensin-converting enzyme-2 (ACE2) allows virus entry into the cells. Of note, Kidney Injury Molecule-1/T cell immunoglobulin mucin domain 1 (KIM-1/TIM-1) was identified as an alternative tubular cells receptors for SARS-CoV2[112]. Renal cells also express serine 2 (TMPRSS2) an enzyme that is essential for the viral complex to enter the cell[42],[113]. TMPRSS2 co-localizes in the different renal cells compartment, although expression is increased in the distal tubules while ACE-2 is predominantly present in the proximal tubules[114,115,116]. Angiotensin-converting enzyme 2 (ACE-2), a widely distributed membrane-associated carboxypeptidase, can act as a receptor for virus entry for SARS-CoV-2.ACE-2 activity is the primary means of angiotensin-II metabolism by cleaving a terminal peptide to form angiotensin(1-7)[117,118]. Angiotensin(1-7) generally opposes the actions of angiotensin-II. It has been hypothesized that after SARS-CoV-2 binds to human ACE2, ACE2 becomes downregulated leading to increased angiotensin II action and a decrease of the angiotensin 1–7[119120,121]. This hypothesis is in line with a decrease of plasma angiotensin-II level observed in a

patient with COVID-19 after administration of human recombinant ACE2, which can bind SARS-CoV2[122]. Angiotensin-II elicits vasoconstriction, endothelial activation, platelet activation, and pro-inflammatory cytokine release[108]. Human recombinant soluble ACE2 lead also to a marked reduction in the inflammatory cytokine interleukin (IL)-6 and chemokine IL-8[122]. Lower plasma levels of Ang1 and Ang1-7 were reported in COVID-19 patients compared to healthy donors and non- ICU patients[109].

Importantly, while in the kidney angiotensin(1-7) formation from angiotensin-II appears predominantly mediated by ACE2, both plasma angiotensin(1-7) and angiotensin(1-7) formation in the lungs have been reported to be largely independent of ACE2. Of note, circulating levels of the soluble form of ACE-2 are very low[108]. This makes the kidney, in theory, more sensitive to ACE2 activity with respect to the angiotensin-II and (1-7) balance. Whether this imbalance between angiotensin II and 1–7 plays a direct role in the endothelial activation and COVID-19-associated AKI remains theoretical at present[123].

ACE2 genes polymorphisms have been described but there is no information on their relationship to AKI in COVID-19[124]. While some polymorphisms may lead to increased entry into the tubular epithelial cell (through ACE2), future study should explore if these genetic differences are associated with specific injury patterns found on biopsy / autopsy.

Altogether, these data suggest a specific interaction between ACE2 and angiotensin II in COVID-19. The interaction with the renin-angiotensin system may, however, depend on the severity of the disease where it represents an adaptative system to shock. Low levels of angiotensin-II may be associated with poorer outcome in critically ill patients. One small single center study among critically ill COVID-19 patients did show that AKI was associated with an increase in plasma renin levels[125]. This association between plasma renin levels and AKI was

observed in other critical care settings such as distributive shock or cardiac surgery as the consequence a relative deficit of an angiotensin-II (inducing a loop positive feedback on renin release)[125,126]. This is suggested by lower angiotensin-II levels observed in COVID-19 patients with ARDS[127].

The impact of withholding ACE-I/ARB in patients with COVID-19 has been intensely debated but does not appear to impact outcomes[128,129]. Recent work in murine models demonstrated that administration of captopril or telmisartan lead to a decrease in ACE2 protein expression in kidney isolated membranes with no effect on ACE2 activity in lung-isolated membrane[130]. Finally, in a recently published randomized controlled trial, discontinuation of the treatment had no impact on patient severity and renal function[131].

Non-specific renal damaging factors

Organ Cross talk and Lung Kidney Interaction

The pathophysiology behind lung-kidney interactions identified in other conditions is complex and comprises several putative mechanisms[132] that are likely to occur in severe COVID-19 patients especially those admitted in the ICU (Figure 1). Acute hypoxaemia may alter renal function and increase renal vascular resistance [73,133]that might contribute to renal hypoperfusion [134]and acute tubular injury observed In COVID-19[135].

Moreover, following AKI, a significant increase of inflammatory cytokines (e.g. IL-6) due to reduced renal clearance and increased production has been reported, with a possible contribution to the worsening of respiratory failure in a detrimental kidney-lung cross-talk[127].

In more severe patients, the use of mechanical ventilation can contribute to the development of AKI in patients with acute lung injury through immune mediated processes and haemodynamic effects[136]. Mechanical ventilation has been associated with an increased risk of AKI among COVID-19 patients. In the US a cohort of COVID-19 veteran patients, AKI was associated with more frequent mechanical ventilation use (odds ratio, 6.46; 95% CI, 5.52 to 7.57)[23]. Whether this reflects higher severity of the disease and systemic inflammation or a direct impact of mechanical ventilation is uncertain but is likely a combination of both.

Haemodynamic Factors

The crosstalk between the cardiovascular system and kidneys is also likely to be a contributing to COVID-19 associated AKI. Rare cases of acute myocarditis[137,138] and myocardial injury[139] have been described in COVID-19 potentially resulting in impairment of cardiac function thereby potentially compromising kidney perfusion through decrease of cardiac output or renal vein congestion[140,141]. As in other forms of acute respiratory distress syndromes, use of high PEEP and/or tidal volumes leads to elevated intrathoracic pressure, increased right atrial pressure, increased right ventricular afterload and can decrease cardiac output[136]. Right heart dysfunction and increased venous pressures can result in increased interstitial and tubular hydrostatic pressure within the encapsulated kidney, which decreases net glomerular filtration rate (GFR) and oxygen delivery[142]. Indirect evidence of a contribution of hemodynamic factors has been the association of mechanical ventilation and vasopressors with the risk of AKI, and the frequent observation of acute tubular injury in COVID-19 patients[5,143,144].

Nephrotoxins

As with all patients at risk of AKI, drug stewardship with regard to potential renally damaging drugs should be paramount. COVID-19 associated AKI is in this regard, no different from AKI from other causes. In particular, administration of antibiotics such as vancomycin and aminoglycosides especially in the context of critical illness can play an important role in its aetiology[145,146]. Administration of nephrotoxins (i.e. vancomycine, colistine, aminoglycosides) has also been associated with an increased risk of AKI in COVID-19 patients[147].

There are uncertainties regarding the safety of antivirals used to treat COVID-19 in patients with AKI. Remdesivir is a nucleotide analog that inhibits viral RNA-dependent RNA polymerase and is predominantly renally excreted. Both efficacy and potential renal toxicity, through mitochondrial injury in renal tubular epithelial cells, have been proposed. Renal toxicity is most likely to occur after prolonged exposure or at high doses. A shorter recovery time from COVID-19 symptoms was reported in a randomized controlled trial of 1062 patients, a benefit mostly observed among patients treated early after onset of symptoms and not critically ill patients[148]. A decline in glomerular filtration rate was observed in 14% in the placebo group and 10% in the treated group, but patients with an eGFR of less than 30 ml/min were excluded thereby largely excluding patients with AKI. Of note, a more recently published randomized controlled trial failed to show a benefit of remdesivir on patient outcome[149]. Again, baseline eGFR was respectively 99 and 110 ml/min in the short (5 days) and extended duration (10 days) groups excluding patients with altered renal function at inclusion. A decline of creatinine clearance was seen in 30% of the control groups, 15%, in the short duration dose group and 26% in the extended duration dose group. Outside of clinical trials, some evidence of renal toxicity has however been identified. An analysis of the international pharmacovigilance post marketing databases of the World Health Organization revealed a statistically significant disproportionality

signal of renal toxicity, with a 20-fold higher risk of AKI compared to other drugs frequently used in COVD-19 ((hydroxychloroquine, tocilizumab, and lopinavir/ritonavir)[150]. Cases of AKI associated with lopinavir and low-dose ritonavir therapy in the course of COVID-19 management were also reported[151]. Finally, a potential nephrotoxic mechanism identified for other forms of AKI associated with viral infections is rhabdomyolysis, as described during the SARS-CoV2 pandemic[152,153].

Extracorporeal membrane oxygenation

Data of patients on extracorporeal membrane oxygenation (ECMO) requiring KRT has been 22 % and 46% in two European multicenter cohorts [154,155]. Potential factors associated with the use of ECMO that may worsen AKI include venous congestion, secondary infections, hemolysis, major bleeding and the inflammatory response to the extracorporeal circuit. Major bleeding occurred in 42% of patients, hemolysis in 13%, canula infection in 23 % and ventilator-associated pneumonia in 87% of patients in one cohort[150].

Comparison with current understanding of AKI among non-COVID-19 related sepsis and ARDS

The question arises whether sepsis associated AKI and COVID-19 associated AKI share similarities. Sepsis associated AKI is characterized by a drop in GFR whereas renal blood flow might range from reduced to increased blood flow[156]. Contributing factors to sepsis-associated AKI include regional inflammation, microvascular alterations and hemodynamic alteration (including periglomerular shunting, activation of tubuloglomerular feedback, increased interstitial and, thus, intratubular pressure)[157,158]. Filtered DAMPs and PAMPs are considered triggers of interstitial inflammation by activating TLR2 and TLR4 receptors located on the brush

border membrane of epithelial cells in the proximal tubule[159,160]. Additionally, glomerular leucocyte infiltration and intraglomerular thrombus formation are found indicating endothelial damage leading to increased permeability of the glomerulus (at least in animals) and albuminuria[161,162]. Inflammatory cytokines also have been shown to promote the release of ultra-large von Willebrand factor (ULVWF) multimers from endothelial cells and inhibit the cleavage and clearance of these pro-thrombotic agents by the metalloproteinase, ADAMTS13[162]. This, together with endothelial injury and shedding of the glycocalyx by inflammatory mediators may increase susceptibility to microthrombi formation, occlusion of glomerular and peritubular capillaries and prolonged exposure of tubular epithelial cells to inflammation and hypoxia. Correspondingly, postmortem kidney histology showed overall little alteration despite the profound impairment of renal function[163]. All these changes are consistent with findings in COVID-19 associated AKI. To summarize, the major differences with other types of sepsis, including viral sepsis[164], appear to be the inconsistent finding of virus particles in epithelial cells, and more prominent vascular alterations in COVID-19. The potential contribution of these factors is however not yet fully understood.

Severe COVID-19 patients present with ARDS, even though different sub-phenotypes have been reported. Endothelial injury and systemic release of pro-inflammatory mediators in ARDS (e.g. plasminogen activator inhibitor-1, IL-6 and soluble TNF receptors-I and II) has been associated with the development of AKI[165,166]. As above mentioned, concomitant hypoxemia may increase renal vascular resistance[167] and elevated central venous pressure[141], due to either right heart failure, high intrathoracic pressures and concomitant pulmonary vascular thrombi can result in increased interstitial and tubular hydrostatic pressure within the encapsulated kidney, compromising renal perfusion and GFR.

Implications for research and therapeutic strategies

A disease model that centers around regional inflammation, immunothrombosis, vascular pathology and potential direct viral renal toxicity has important implications for the ongoing search for therapeutics (Table 3)[168].

Non-Kidney specific strategies for COVID-19

Several non-specific measures toward renal protection in COVID-19 are however expected to impact kidney outcomes, especially in the light of organ crosstalk. Early liberal intubation and mechanical ventilation had been advocated in the early stage of the pandemic. A more restrictive approach is now applied by many. Limiting indications for invasive ventilation, therefore limiting ventilator-induced lung injury, and the consequences of high levels of PEEP may have contributed to the decreasing rate of AKI over time [23,169]. Translating the large amount of data from non-COVID ARDS to COVID-related ARDS, strategies to avoid both excessive fluid depletion, and fluid overload leading to venous congestion are likely to protect the kidney in COVID-19.

As discussed previously, inflammatory organ injury may play an important role in the pathogenesis of COVID-19 with a subgroup of patients having markedly elevated inflammatory markers and so glucocorticoids have been postulated to mitigate inflammatory organ injury[170]. The RECOVERY trial showed a reduction in mortality in patients requiring ventilation or oxygen alone[171].Patients who received steroids (and not requiring KRT at randomization) were less likely to receive KRT compared to the control group (4.4% vs 7.5%, risk ratio-CI95% 0.61; 95% CI, 0.48- 0.76) suggesting a protective effect on the kidney. Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to IL-6

receptors thereby blocking IL-6 signally and reducing inflammation and improving organ failures[172]. Preliminary results from the RECOVERY trial suggested that treatment with tocilizumab in hospitalized patients with hypoxia and evidence of inflammation improved survival and chances of discharge from hospital at 28 days. Furthermore, there was also a significant reduction in the requirement for kidney replacement therapy suggesting beneficial effects on preventing AKI and/or promoting renal recovery[173].

Interferon therapy is one of the most promising approaches to improve viral clearance in the early stage of COVID-19. While small interventional trials reported encouraging results, more robust trials are needed to validate this hypothesis[174,175]. Of note, caution is mandated in populations at risk of collapsing glomerulopathy given the role of interferon in podocyte injury[31].

No evidence supports the use of convalescent plasma therapy so far. Potential safety concerns emerged due to circulating autoantibodies against type I interferons that can be present in plasma and associated with worse outcomes[7/30/2021 1:25:00 PM]. The high incidence of micro and macro thrombotic events in COVID-19 patients and the observation of microvascular thrombi calls for a better understanding of the anticoagulation strategies in COVID-19 patients but the impact on COVID-related AKI is unknown.

As above mentioned, cytokine storm is not observed in most patients and histology findings show a complex inflammatory response making extracorporeal cytokine removal unlikely to be superior to anti-inflammatory drugs to improve renal outcome in the vast majority of patients.

AKI requiring KRT has been reported to vary between 5 and 21% among severe COVID-19 patients, an incidence similar to other critical illnesses[16]. While no trial has been specifically investigating the impact of timing of KRT in COVID-19, several trials recently reported in non-COVID critical illness that a liberal use of KRT didn't improve survival but was associated with

more side effects and use of resources[177]. A restrictive use of KRT is furthermore highly relevant in a setting of a pandemic with limited critical resources.

Specific strategies for COVID-19-related AKI

Specific treatments or prevention of COVID-associated AKI are lacking so far. As for other critical illnesses, the understanding of the pathophysiology of COVID-associated AKI has been limited by the rare and limited access to kidney tissue and hemodynamics in humans. Animal models can overcome this limit but the translation of results to humans has long been debated. Reproducing COVID-19 in animals has been challenging, mostly due to interspecies characteristics. Mouse lack the ACE2 receptor binding to the viral for entry in the cell. Several strategies have been developed to overcome this issue, including spike protein modification of the virus to bind mouse ACE2 receptors or genetically modified mice expressing human ACE2[178,179]. The various expressions of human ACE2 in different tissues might limit the exploration of the role of viral infection to the kidney. Finally, these models often fail to reproduce severe diseases and didn't induce extrapulmonary organ damage, including the kidney. No renal damage nor infection of renal cells by the virus was detected in a model of syrian hamsters as well[178]. Other species have been used as well, including primates but kidney damage was not explored.

Finally, the specific interaction between SARS-CoV2 and ACE2 receptors deserves specific investigation. The direct blockage of ACE2 receptors might limit tissue infection including the kidney. Human recombinant soluble ACE2 (hrsACE2) has recently been shown to inhibit SARS-CoV-2 of engineered human blood vessel organoids and human kidney organoids[180]. Its use is currently under investigation in the clinical setting[122].

Conclusion

Acute tubular injury in COVID-associated AKI appears common but mild despite severely altered renal function. Endothelial injury, microvascular thrombi, local inflammation and immune cell infiltration have been repeatedly observed. It remains whether the pathophysiology of COVID-associated AKI differs from AKI among non-COVID sepsis. High incidence of thrombi and increase intravascular coagulation might be one the striking differences. Given the lung-kidney interactions, treatment and strategies preventing the progression of the disease and needs for mechanical ventilation such as steroids are very likely to protect the kidney. Regional inflammation certainly plays a role in COVID-related organ injury and data on steroids and IL-6 receptors antagonists appear promising to prevent severe AKI for future work should specifically investigate their impact on AKI and renal recovery. Kidney cells infection has been observed in several cohorts, including several weeks after the onset of disease, but its role in the development of AKI remains controversial. Of note, an impaired type 1 interferon response in severely ill COVID-19 patients was reported and might contribute to decrease viral clearance in kidney cells in a subset of patients. Collapsing nephropathy in COVID-19 patients was associated with APOL1 High-Risk Genotype. However, therapeutic strategies specifically targeting the kidney are still lacking. Recombinant soluble ACE2 were shown to prevent in vitro kidney viral infection and represent a potential promising specific treatment for COVID-associated AKI.

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Table 1. Summary of histological findings in COVID-19 patients. Only cohorts with more than 2 patients are reported. AKI, acute Kidney Injury; CKD. Chronic Kidney Disease.

Reference	n	Post-mortem	Age	Mechanical ventilation	Tubular injury	Acute glomerular Injury	Vascular injury	Viral inclusions	Technique of Virus detection	comments
Hanley et al.	9	Yes	73 years (IQR 52–79)	4/9	Yes (in 9/9)	No	Yes (44%) (rare thrombi in interlobular arteries in four patients)	viral genomic RNA in 3/5 patients. Subgenomic viral RNA transcript in one patient	Viral RNA	No evidence of underlying ch disease in any of the 9 patien
Schurink et al.	21	Yes	68 years (range 41–78)	16/21	Yes	No	Yes Three (14%) patients showed intravascular neutrophilic aggregates with platelets - One (5%) patient showed signs of endothelial - Glomerular microthrombi in one patient	SARS-CoV-2-positive cells in one patient (9%)	Immunohistochemical staining	Renal histopathological chan found in 12 (57%) patients
Golmai et al.	12	Yes	49-92 years	11/12	Yes (from mild to diffuse)	No	No	No	Immunohistochemical staining and in situ hybridization	-One patient had findings compati mild acute interstitial nephri - One patient exhibited renal oxalosis of ur cause, and a third had medul -n=3 kidney tranplants)ee
Akilesh et al.	17	No	54 years (range 34-77)	No	Yes (n=14)	Yes, collapsing glomerulopathy (n=7)	Yes, endothelial injury/thrombotic microangiopathy (n=6)	-	Electron microscopy	-n=15 had AKI; -n=11 proteinuria. -Two of the three transplant patients dev active antibody-mediated rej
Su et al.	26	Yes	69 years (range, 39–87)	Yes	Yes	No	Yes, erythrocyte aggregates obstructing the lumen of capillaries without platelet or	Yes (n=7)	Electron microscopy	9/26 had elevated serum cre

							fibrinoid material. No evidence of vasculitis or interstitial inflammation			
Kudose et al.	17	No	54 years (range, 22–72)	9/17	Yes	Yes, (n=5 collapsing glomerulopathy, n=4 immune-mediated glomerular diseases)	Yes, Glomerular endothelial tubuloreticular inclusions in 6/10 cases	No	Immunohistochemical staining and in situ hybridization	15/17 had AKI
Santoriello et al.	42	Yes	71.5 years (range, 38–97	21/42	Yes (mild)	No, (n=1 collapsing focal segmental glomerulosclerosis)	Yes, Focal kidney fibrin thrombi in 14% cases	No	In situ hybridization of viral RNA	94% had AKI
Remmelink et al.	17	Yes	72 (62–77) years	11/17	Yes	No	No	Yes (n=10)	Viral RNA	Hemosiderin and/or pigmen seen in 12 of 17 patients
Xia et al.	10	Yes	57-82 years	yes	Yes	No, (occasional wrinkling of the glomerular basement membrane)	Yes, glomerular endothelial swollen (n=1), Intimal hyperplasia,	Yes (viral-like particles on EM)	Electronic microscopy	One patient with venous thro
Werion et al.	6	Yes	57 and 82 years	-	Yes	No	Yes erythrocyte aggregates in peritubular and/or glomerular capillaries in 5/6 patients	Yes (viral-like particles on EM)	Electronic microscopy	Focal infiltration of the inters mononuclear cells in 2/6 pat
Sharma et al.	10	No	45-77 years	4/10	Yes	Yes, collapsing glomerulopathy (n=1), pauci-immune crescenti	Yes, thrombotic microangiopathy (n=2)	No	Immunohistochemical staining	Eight patients had severe AKI requiring RRT

						c GN (n=1)				
Wu et al.	6	No	37-65 years	2/6	Yes (diffuse in 5/6)	Yes, collapsing glomerulopathy	Yes, focal peritubular capillaries red blood cell aggregates in n=1, swollen endothelial cells in n=3	No	Viral RNA	-3 patients had baseline stag - drug-induced acute intersti in n=1 -pleomorphic interstitial infiltrate of immu n=1
Ferlicot et al.	47	No	52-69	28/47	Yes (In ICU cohort)	Yes (In non-ICU cohort)	Thrombotic microangiopathy (1) Arterits (1)	No	Immunohistochemistry staining	
Dargelos et al.	3	No	63-72	3/3	Yes	Yes in the ethnic African patient	low degree of glonerular endothelial cell swelling	No	Viral RNA	strong ACE2 staining was observed in the apical brush border in proximal con tubules

Table 2. Proposed contributing factors of COVID-19-related acute Kidney injury

Acute tubular injury	-Regional inflammation -Direct viral infection -Renal compartment syndrome -Tissue hypoxia-hypoperfusion: hypoxemia-hypotension-hypovolemia-heart failure -Nephrotoxics: vancomycin, aminoglycosides, colistin, remdisivir, ritonavir -Rhabdomyolisis
Vascular injury	-Endotheliitis -Microthrombi -Thrombotic microangiopathy
Glomerular injury	-Collapsing glomerulopathy/podocyte injury by interferon -Glomerulonephritis
Interstitial injury	-Acute interstitial nephritis/infiltration by immune cells -Interstitial oedema

Table 3. Key research questions for COVID-19-related acute Kidney injury

Epidemiology	-What is the risk of non-recovery? -What are the factors associated to non or partial renal recovery? -Does epidemiology differ from non-COVID sepsis-associated AKI? -What are the biomarkers predicting development of COVID-19-related AKI? -What are the biomarkers predicting non-recovery from COVID-19-related AKI?
Pathophysiology	-What is the contribution of direct viral infection? -What is the contribution of endotheliitis, microthrombi and complement activation? -What is the contribution of hemodynamic factors? -Is collapsing glomerulopathy/podocyte injury triggered by interferon? -Do pathogenic mechanisms differ from non-COVID sepsis-associated AKI? -What is the contribution of comorbidities including CKD on AKI development?
Treatment	-Does different oxygenation and mechanical ventilation strategies impact renal outcomes? -Does anti-inflammatory drugs (e.g., steroids, anti-IL6) impact renal outcomes? -Can treatment targeting the ACE2 receptor prevent AKI? -Can treatment targeting viral clearance (e.g. interferon) impact renal outcomes?

	-Does treatment modulating the renin-angiotensin-aldosterone system impact long-term consequences of AKI? -Can extracorporeal blood purification therapies impact AKI development and progression?

Legends for Figures:

Figure 1. Current understanding of the shared pathophysiology between lung and kidney injury in COVID-19. COVID-19 associated acute respiratory distress syndrome (ARDS) involves regional inflammation with recruitment of immune cells including macrophages, effector T-cells and polymorphonuclear neutrophils. Cytokines are released in response to DAMPS (damage-associated molecular patterns) and PAMPS (pathogen-associated molecular pattern) locally and contribute to the recruitment of inflammatory cells and tissue damage. IFN (interferon) secretion contributes to viral clearance. NETs (neutrophil extracellular traps) have also been proposed to contribute to local inflammatory response, pathogen clearance and thrombosis generation. ARDS contributes to acute kidney injury through systemic factors (i.e. venous congestion and decrease of cardiac output due to right heart failure and high levels of intrathoracic pressure and hypoxia). Increase of renal interstitial pressure due to tissue oedema contribute to tubular injury (i.e. renal compartmental syndrome). Release into the circulation of DAMPs and PAMPS will contribute to renal regional inflammation and immune response and immune thrombosis. Direct infection of renal cells has been observed in some patients and may contribute to local inflammation and renal tissue damage. In turn, acute kidney injury in other settings has been shown to contribute to remote lung injury through increase lung inflammation, increase lung capillary permeability and fluid overload.

Figure 2. Representation of the different stages of COVID-19-associated acute kidney injury (AKI) across the severity stages of the disease. Proteinuria and/or hematuria indicates kidney injury even though serum creatinine hasn't raised, and glomerular filtration rate hasn't dropped. Further injury is associated with drop in GFR and rise in serum creatinine. Underlying

chronic kidney disease or aging amputates the baseline functional reserve and can precipitate occurrence of AKI at more severe stages during the course of the disease.