Pathophysiology of COVID-19- associated acute kidney injury

Key points:

- Over a quarter of patients hospitalized with coronavirus disease 2019 (COVID-19) have been reported to develop acute kidney injury (AKI).
- Low molecular weight proteinuria, Fanconi syndrome and histological findings point towards tubular injury.
- Analyses of kidney biopsy samples from patients with COVID-19 and AKI have inconsistently reported viral infection of kidney cells.
- Collapsing glomerulopathy has been identified in patients with high- risk *APOL1* genotypes, mostly in those without severe respiratory symptoms.
- Regional inflammation, endothelial injury and renal microthrombi have been reported but their implication in the pathogenesis of COVID- associated AKI remains uncertain.
- Anti- inflammatory drugs (for example, steroids and IL-6 receptor blockers) seem to limit the development of severe AKI in patients with COVID-19.

Introduction:

The pulmonary manifestations of COVID-19 are most prominent, but acute kidney injury (AKI) is also now recognized as a common complication of the disease, and is often evident at hospital admission.

Although initial reports from China suggested relatively low rates of kidney involvement, subsequent reports from the USA and Europe indicate much higher rates of AKI, particularly in the intensive care setting, with up to 45% of patients in the intensive care unit (ICU) requiring kidney replacement therapy (KRT).

Mortality among hospitalized patients with COVID-19- associated AKI (COVID-19 AKI) is higher than for those without kidney involvement.

As with all instances of AKI in the context of multi-organ failure requiring ICU admission, mortality among patients admitted to the ICU with COVID-19 AKI requiring KRT is especially high.

Age, history of hypertension and diabetes mellitus have been repeatedly associated with a higher risk of AKI in patients with COVID-19.

Chronic kidney disease (CKD) is a well identified risk factor for AKI in hospitalized patients, and was indicated to be the most relevant risk factor for AKI requiring KRT in 3,099 critically ill patients with COVID-19.

Indeed, several epidemiological studies have clearly demonstrated that CKD represents a relevant and independent risk factor for worse outcomes in COVID-19.

Moreover, CKD is often associated with other comorbidities such as diabetes mellitus, hypertension and obesity, which have also been linked to mortality in patients with **COVID-19.**

In this clinical scenario, the high mortality observed in comorbid and elderly patients may be related to a reduction in renal functional reserve (RFR), an impaired capacity of the kidney to increase GFR in response to stress and reduced functioning nephron mass.

Decreased GFR and RFR levels may also support the development of AKI, as suggested by epidemiological studies.

Both early and late forms of AKI (that is, AKI at presentation and AKI developing after presentation) were associated with an increased risk of in-hospital mortality.

Moreover, CKD, older age and levels of inflammatory biomarkers were associated with an increased risk of late AKI.

Independent variables for AKI development were the presence of CKD, C- reactive protein level and requirement for ventilatory support.

Nevertheless, it is clear that the pathophysiology is multifactorial and different sub-phenotypes of COVID-19 AKI exist.

In this Review, we discuss current understanding of the pathophysiology of COVID-19 AKI, examining potential mechanisms by which SARS- CoV-2 infection might induce direct and indirect effects on the kidney, and factors that are not specific to COVID-19 but may influence kidney function through haemodynamic changes and/or organ crosstalk (Fig. 1)

Features of COVID-19 AKI

Epidemiology

The reported incidence and severity of AKI in the setting of COVID-19 depends on the clinical setting and definitions used.

Most studies have used the Kidney Disease Improving Global Outcomes (KDIGO) consensus definition of AKI and several studies that have used this definition have reported that upwards of 30–50% of hospitalized patients with COVID-19 develop some form of AKI, with the proportion increasing in those requiring intensive care.

Worldwide, among patients admitted to the ICU, an estimated 29% have AKI; this proportion is up to 78% in those requiring intubation.

Other studies have reported that up to 20% of patients in the ICU required KRT.

Of note, wide geographical disparities in the incidence of AKI among US veteran patients hospitalized with COVID-19 have been reported, ranging from 10% to 56%.

This finding, combined with evidence that rates of COVID-19 AKI have declined over time (from 40% in March 2020 to 27% in July 2020) with similar findings reported in a New York study, suggests that **changes in patient management** have had a positive impact on kidney outcomes and the incidence of AKI among patients with COVID-19.

Clinical features:

Early reports of COVID-19 AKI noted the presence of haematuria and/or proteinuria.

Severity of haematuria or proteinuria (2–3+ on dipstick) was associated with the risk of hospital mortality in a step- wise manner.

Furthermore, >50% of patients without AKI as defined by KDIGO serum creatinine criteria had haematuria and over 70% presented with proteinuria.

The presence of urinalysis abnormalities in those not meeting the definition of AKI suggests the existence of kidney injury without notable acute changes in kidney function.

Fanconi syndrome (characterized by proteinuria, renal phosphate leak, hyperuricosuria and normo-glycaemic glycosuria) has been reported to precede episodes of AKI (Fig. 2). This presentation is in keeping with stage 1S of new recommendations for AKI staging, when evidence of kidney injury exists that is not detected by creatinine and urine output criteria.

The proteinuria detected in patients with COVID-19 AKI is of low molecular weight rather than albuminuria, suggesting a tubular origin rather than glomerular injury, and can be used to identify patients with early- stage AKI.

The contribution of underlying CKD is unknown, but the proportion of patients with COVID-19 and proteinuria far exceeds the prevalence of stage 1 and 2 CKD in the general population.

Future studies are required to determine the association of biomarkers of glomerular and tubular function with serum creatinine- based AKI in the context of COVID-19 AKI.

Evidence from a study of biopsy data from 47 patients in France demonstrated that kidney injury seen in cases with the most severe respiratory disease in the ICU is predominantly tubular (66.7%); by contrast, **collapsing glomerulopathy and focal segmental glomerulosclerosis** were not seen in critically ill patients but were observed in 70.6% of cases not in the ICU[34].

More than two coexisting comorbidities were seen in over 60% of cases and the occurrence of collapsing glomerulopathy correlated highly with the expression of **high- risk *APOL1* genotypes**.

Pathophysiology of COVID-19 AKI

The pathophysiology of COVID-19 AKI is thought to involve local and systemic inflammatory and immune responses, endothelial injury and activation of coagulation pathways and the renin–angiotensin system[31,35].

Direct viral infection with renal tropism of the virus has also been proposed but remains controversial[36].

Non-specific factors that are common in critically ill patients, such as mechanical ventilation, hypoxia, hypotension, low cardiac output and nephrotoxic agents, might also contribute to kidney injury and/or functional decline in the most severely affected patients (Box 1).

Insights from renal histology

Collapsing glomerulopathy

Endothelial dysfunction and coagulation

The immune and inflammatory response

Inflammation
Interferon
Complement
Adaptive immunity
Humoral immunity

The role of cytokine storm syndrome

ACE2 and the renin–angiotensin system

Box 1 | **Factors that may contribute to COVID-19-associated acute kidney injury**

Acute tubular injury

- Regional inflammation
- Direct viral infection
- Renal compartment syndrome
- Tissue hypoxia hypoperfusion leading to hypoxaemia, hypotension, hypovolaemia and heart failure
- Nephrotoxic-induced injury (potentially associated with the use of antibiotics (vancomycin, aminoglycosides, colistin) or antivirals (remdesivir, ritonavir))
- Rhabdomyolysis

Vascular injury

- Endotheliitis
- Microthrombi
- Thrombotic microangiopathy

Glomerular injury

- Collapsing glomerulopathy (potentially caused by interferon-associated podocyte injury)
- Glomerulonephritis

Interstitial injury

- Acute interstitial nephritis; infiltration by immune cells
- Interstitial oedema

COVID-19, coronavirus disease 2019.

Non- specific factors

Organ crosstalk and lung–kidney interactions

Haemodynamic factors

Nephrotoxins

Extracorporeal membrane oxygenation

Similarities to non- COVID-19 AKI

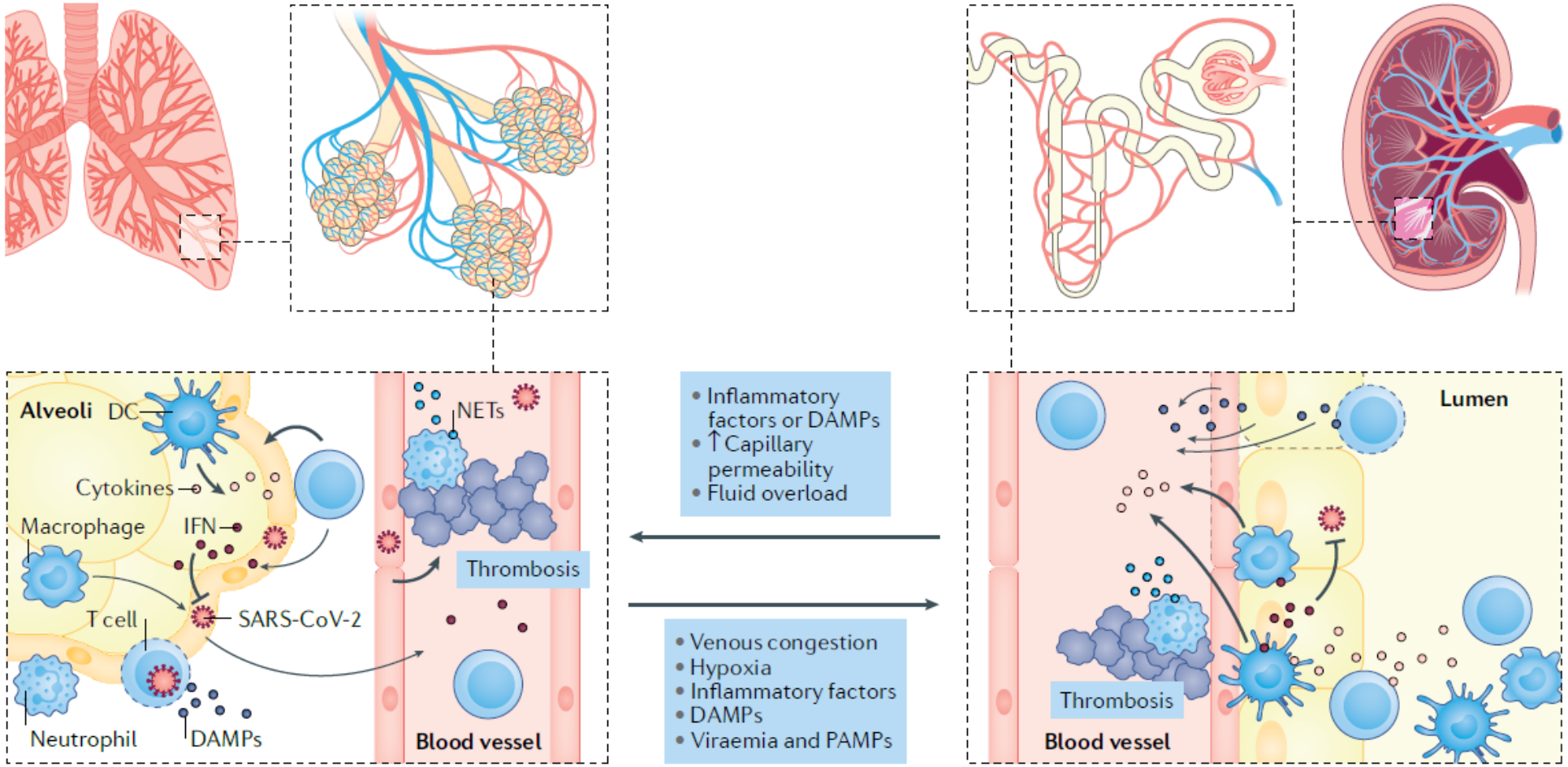

Fig. 1 | **Shared pathophysiology between lung and kidney injury in COVID-19.** Coronavirus disease 2019 (COVID-19)-associated acute respiratory distress syndrome involves regional inflammation with the recruitment of immune cells, including macrophages, effector T cells and polymorphonuclear neutrophils. Cytokines are released locally within the lung in response to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) and contribute to the further recruitment of inflammatory cells and tissue damage. Secretion of interferon (IFN) from immune cells contributes to viral clearance. Neutrophil extracellular traps (NETs), released by activated neutrophils, may also contribute to the local inflammatory response, pathogen clearance and thrombosis. Acute respiratory distress syndrome likely contributes to the development of acute kidney injury through systemic processes (for example, venous congestion and decreased cardiac output as a consequence of right-sided heart failure, high levels of intrathoracic pressure and hypoxia). Increased renal interstitial pressure due to tissue oedema is also likely to contribute to tubular injury. Release of DAMPs and PAMPs into the circulation contributes to regional inflammation within the kidney, the immune response and immune-mediated thrombosis. Direct infection of kidney cells has been observed in some patients and may also contribute to local inflammation and kidney damage. Conversely, acute kidney injury in other settings has been shown to contribute to promoting lung injury by stimulating regional inflammation, lung capillary permeability and fluid overload. DC, dendritic cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

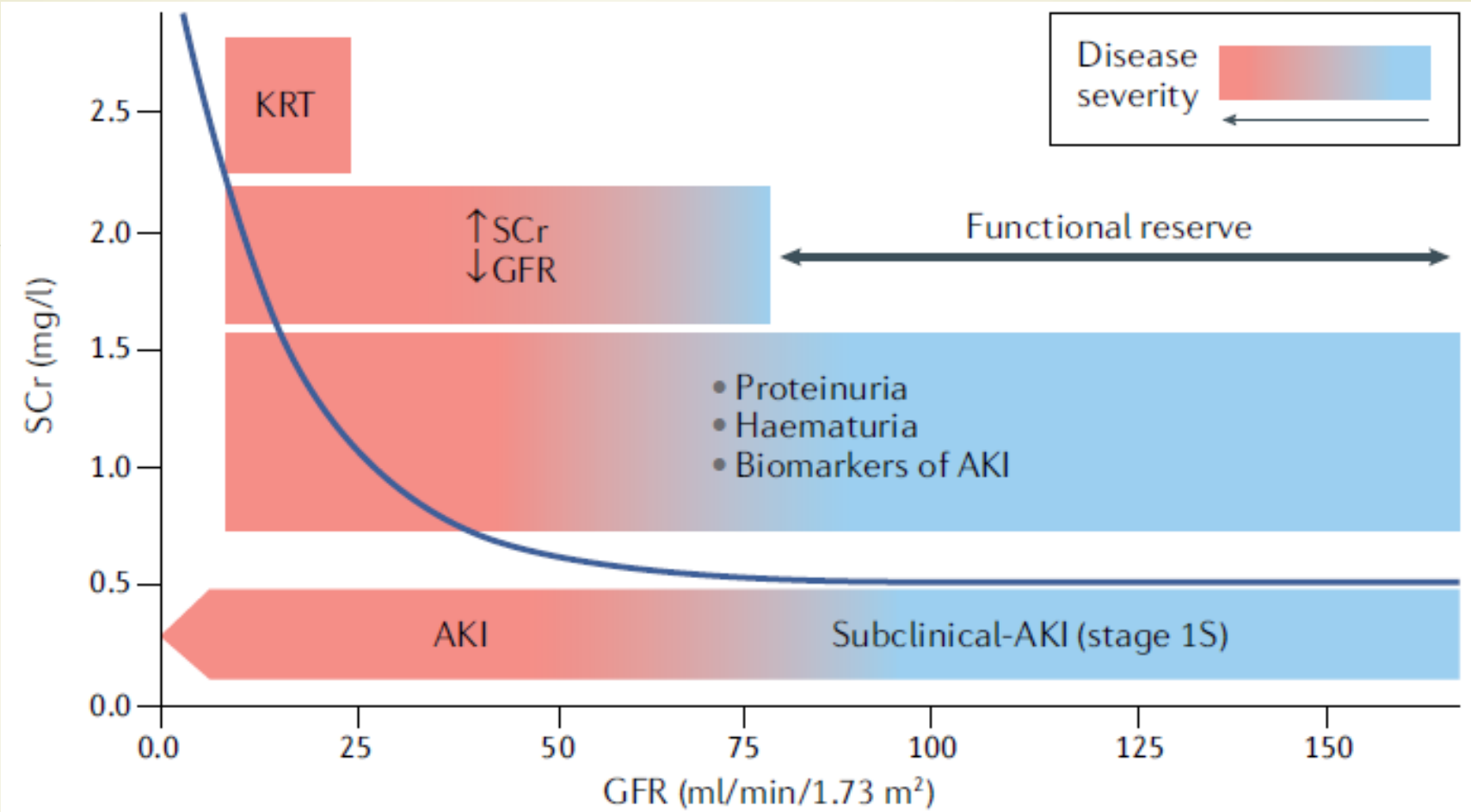

Fig. 2 | **Different stages of COVID-19-associated acute kidney injury.** Proteinuria and/or haematuria is indicative of kidney injury, even in the absence of a rise in serum creatinine (SCr) level or a drop in glomerular filtration rate (GFR). Further injury is associated with a drop in GFR and rise in SCr. Underlying chronic kidney disease or factors such as ageing limits the baseline functional reserve and can precipitate the development of acute kidney injury (AKI). Kidney replacement therapy (KRT) is required for severe cases of AKI. COVID-19, coronavirus disease 2019.

Implications for research and therapy

Non- kidney- specific strategies

Specific strategies for COVID-19 AKI

Box 2 | **Key research questions for COVID-19-associated acute kidney injury**

Epidemiology

- What is the risk of non-recovery?
- What are the factors associated with non- or partial renal recovery?
- Does the epidemiology of coronavirus disease 2019-associated acute kidney injury (COVID-19 AKI) differ from that of non-COVID sepsis-associated AKI?
- What are the biomarkers predicting development of COVID-19 AKI?
- What are the biomarkers predicting non-recovery from COVID-19 AKI?

Pathophysiology

- What is the contribution of direct viral infection to COVID-19 AKI?
- What is the contribution of endotheliitis, microthrombi and complement activation?
- What is the contribution of haemodynamic factors?
- Is collapsing glomerulopathy and/or podocyte injury triggered by interferon?
- Do the pathogenic mechanisms of COVID-19 AKI differ from those in non-COVID sepsis-associated AKI?
- What is the contribution of comorbidities including chronic kidney disease to AKI development?

Treatment

- Do different oxygenation and mechanical ventilation strategies affect kidney outcomes?
- Do anti-inflammatory drugs (e.g. steroids, anti-IL-6 antibodies) affect kidney outcomes?
- Can treatments that target ACE2 and therefore prevent viral entry prevent AKI?
- Can treatments that target viral clearance (e.g. interferon) affect kidney outcomes?
- Do treatments that modulate the renin–angiotensin–aldosterone system affect the long-term consequences of COVID-19 AKI?
- Can extracorporeal blood purification therapies affect the development and progression of COVID-19 AKI?

Conclusions

Acute tubular injury seems to be a common occurrence in patients with COVID-19 AKI, but is often mild, despite severely altered kidney function.

Endothelial injury, microvascular thrombi, local inflammation and immune cell infiltration have been repeatedly observed in patients with COVID-19 AKI; however, differences and similarities in the pathophysiology of COVID-19 AKI and non- COVID sepsis- associated AKI remain to be established.

A high incidence of thrombi and intravascular coagulation might be one striking difference.

Given the interactions between lung and kidney, treatment and strategies that prevent progression of the disease and need for mechanical ventilation are very likely to protect the kidney.

Regional inflammation contributes to COVID-19- associated organ injury; in line with this mechanism of organ injury, available data suggest that steroids and IL-6 receptor antagonists may be promising in preventing severe AKI, although further work is required to confirm these findings and assess their impact on renal recovery.

Direct viral infection of kidney cells has been observed in several cohorts, however, the role of direct viral infection in the development of AKI remains controversial.

Of note, an impaired type I interferon response in severely ill patients with COVID-19 has been reported and might contribute to the ineffective clearance of virus from kidney cells in a subset of patients. However, collapsing nephropathy in patients with COVID-19 seems to be associated with the high- risk *APOL1* genotype and may involve pathogenic pathways linked to interferon-mediated podocyte injury.

Despite advancing insights into the processes underlying kidney injury in COVID-19, however, therapeutic strategies that specifically target the kidney are lacking.

Human recombinant sACE2 has been shown to prevent viral infection of kidney cells in vitro, and might represent a promising specific treatment for COVID-19 AKI in the future.