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COVID-19 infection and the kidney

Lucas Alvarez-Belon[1]
Alexander Sarnowski[2]
Lui G Forni[3]
Author details can be found at the end of this article
Correspondence to:
Lui G Forni; luiforni@nhs.net

Abstract

Despite initial reports, renal involvement, including acute kidney injury, has emerged as a serious complication of COVID-19 disease, particularly in critically ill patients. The reported prevalence varies considerably, which may reflect reporting practices, although differences in pre-existing comorbidities and socioeconomic factors, and differences between ethnic groups, almost certainly contribute. Renal involvement may present as an active urinary sediment or as changes in serum creatinine levels and urine output leading to acute kidney injury. In common with acute kidney injury complicating critical illness, the cause is often multifactorial and often presents as part of a multiorgan dysfunction syndrome. Treatment is, in the main, supportive, with kidney replacement therapy required in nearly 25% of reported cases. Few data currently exist as to the long-term burden of COVID-19-associated acute kidney injury but evidence suggests that only approximately one-third of patients are discharged with recovered renal function.

Key words: Acute kidney injury; COVID-19; Critical illness; Kidney replacement therapy

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Introduction

In early 2020 a cluster of cases of pneumonia in the Hubei Province of China was ascribed to a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By 11 March 2020, alerted by the spread and virulence of the disease that it caused – COVID-19 – the World Health Organization characterised it as a pandemic. As of mid-September 2020, over 29 million cases of COVID-19 had been confirmed globally and it is responsible for over one million associated deaths (Huang et al, 2020). Many cases of COVID-19 disease are asymptomatic, but clinical presentation following infection ranges from a mild upper respiratory tract infection to those requiring critical care with features of acute respiratory distress syndrome (Wang et al, 2020a; Zhu et al, 2020).

The primary pulmonary pathology appears to show diffuse alveolar damage, but there is also evidence of direct viral cytopathy, implying a direct causative role of virus-induced damage rather than part of a generalised inflammatory response. What has become clear is that, particularly in severe cases of infection, a combination of systemic inflammatory dysregulation, multiorgan injury and disseminated microangiopathic involvement can occur, resulting in an unpredictable disease course (Richardson et al, 2020).

These systemic effects, together with the use of mechanical ventilation and potential exposure to nephrotoxic agents (exposure to which has been linked to acute kidney injury in non-COVID-19 settings), has resulted in acute kidney injury being a commonly recognised feature in the critically ill patient with severe COVID-19 disease. Moreover, the development of acute kidney injury is now recognised as an independent risk factor for all-cause deaths in patients hospitalised with COVID-19 and is the most common extrapulmonary organ injury in those with COVID-19 (Cheng et al, 2020; Gupta et al, 2020; Pei et al, 2020; Richardson et al, 2020).

Epidemiology

Given the predominance of respiratory symptoms, few data were initially available on the incidence of renal involvement in COVID-19 disease, with some reports suggesting that renal involvement was uncommon. One early report from China, of 116 hospitalised patients with proven SARS-CoV-2 infection, failed to identify any patients meeting the Kidney Disease Improving Global Outcomes (KDIGO) criteria for acute kidney injury

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(Wang et al, 2020b). However, subsequent data from Europe and the USA have reported that over 40% of cases have abnormal proteinuria at hospital admission; acute kidney injury affects approximately 20–40% of those admitted to intensive care, with kidney replacement therapy commonly needed (Cheng et al, 2020). Meta-analyses confirm this, with an overall incidence of acute kidney injury of 10% (95% confidence interval 8–13%) in patients with COVID-19, associated with a higher fatality rate (Shao et al, 2020). Pre-existing chronic kidney disease was found in 5.2% and end-stage kidney disease in 2.3%. Hyperkalaemia was the most frequent renal complication (incidence of 12.5%) and kidney replacement therapy was needed in 6.8% (Kunutsor and Laukkanen, 2020). This discrepancy in reported rates of renal involvement in patients with COVID-19 may partly be explained by an initial reporting bias towards more immediate outcomes.

This is illustrated by data from the case mix programme database of the Intensive Care National Audit and Research Centre. Initial reports in April cited an 80% mortality in patients with COVID-19 receiving kidney replacement therapy on the intensive care unit, early in the national surge of COVID-19 hospital admissions (Intensive Care National Audit & Research Centre, 2020a). However, with further data acquisition, including more completed episodes, the observed mortality rate had dropped to 56.8% by early September 2020, with kidney replacement therapy needed in 26.7% of cases (Intensive Care National Audit & Research Centre, 2020b). This reflects the fact that the data report on completed episodes, that is discharge from the intensive care unit (either non-survival or survival), and patients with COVID-19 who survived to discharge from intensive care and who had received kidney replacement therapy during their admission had a median duration of 31 days stay, in contrast to 9 days for those survivors who did not require kidney replacement therapy (regardless of whether or not they had acute kidney injury). Hence, early data were influenced by those patients who died early in their disease course. Furthermore, many publications on COVID-19 do not include definitions or staging of acute kidney injury, nor information regarding renal recovery or follow up, and the distinction between de novo acute kidney injury and acute kidney injury superimposed on pre-existing chronic kidney disease is rarely made. As such, it is difficult to compare rates of acute kidney injury based solely on the number of hospitalised patients.

Although much attention has focused on the development of acute kidney injury, the presence of new haematoproteinuria, which may not be associated with functional disturbance but does imply renal damage, is commonplace. This was shown by a reported incidence of proteinuria in 65.8% and haematuria in 41.7% of 333 patients presenting with COVID-19. Only 4.7% of this cohort met the KDIGO criteria for acute kidney injury, and the presence of an active urinary sediment was associated with an increased risk of inpatient mortality (Pei et al, 2020).

Risk factors for renal involvement

Reports from the USA and China suggest that factors which predispose to acute kidney injury in critically ill patients with COVID-19 and acute respiratory distress syndrome are consistent with known risk factors for acute kidney injury in the critically ill, including a higher severity of illness, a history of diabetes, high body mass index and a history of heart failure (Panitchote et al, 2019). These findings are consistent with the risk factors for renal involvement being determined by premorbid condition, disease-associated factors and iatrogenic factors.

Comorbidities commonly associated with renal susceptibility to injury, such as diabetes mellitus, hypertension, cardiovascular disease, pre-existing renal disease and advanced age, are demonstrable risk factors in the development of COVID-19-associated acute kidney injury, as is male sex (Cheng et al, 2020; Hirsch et al, 2020; Mohamed et al, 2020). High body mass index has also been linked to COVID-19-associated acute kidney injury and is suggested to be a predictor of more severe acute kidney injury (Mohamed et al, 2020). There also appears to be variation in ethnic predisposition to acute kidney injury in patients with COVID-19. American data suggest a higher relative incidence in the black population, which may be the result of a combination of genetic susceptibility, socioeconomic factors and increased comorbidities (Mohamed et al, 2020) (**Table 1**).

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Table 1. Potential risk factors for COVID-19-associated acute kidney injury	
Patient factors	Older age
	Male sex
	Race
	Raised body mass index
Comorbidities	Diabetes mellitus
	Hypertension
	Cardiovascular system disease
	Baseline chronic kidney disease
Disease or treatment related	High severity of illness
	Ventilation strategies
	Rhabdomyolysis
	Nephrotoxins

The presence of elevated levels of biomarkers of systemic inflammation, including C-reactive protein, ferritin and lactate dehydrogenase, is associated with the development of acute kidney injury, as is the severity of disease and progression to mechanical ventilation (Pei et al, 2020). In a cohort of over 5000 patients from the USA, 89.7% of mechanically ventilated patients developed acute kidney injury with 23.2% receiving kidney replacement therapy, in contrast to a 21.7% incidence of acute kidney injury and 0.2% requirement for kidney replacement therapy in non-ventilated patients (Hirsch et al, 2020). The use of nephrotoxic agents as well as adopting a fluid restrictive resuscitation policy may also precede the development of acute kidney injury in patients with COVID-19.

Pathophysiology

The emergence of acute kidney injury as a common complication of COVID-19 disease has prompted a search for a common pathophysiological mechanism. However, data so far suggest that a single mechanism is unlikely to be responsible. The kidney impairment observed is likely to be the result of several processes occurring either in isolation or in tandem, in keeping with acute kidney injury observed from other causes such as sepsis (Figure 1) (Kellum et al, 2020). The occurrence of new active urinary sediment is common – in a study subset of 646 patients with acute kidney injury that had urinalysis performed, proteinuria and haematuria was seen in over 40% of cases (Hirsch et al, 2020). This may occur without significant functional change and therefore assessing renal injury only through classical markers of acute kidney injury may miss some cases of significant new injury.

Post-mortem studies

Acute tubular injury is often a predominant finding on histopathological examination of post-mortem tissue, which could also explain the haematoproteinuria observed in many patients, although the protein excretion is often low level (≤100 mg/dl). Unsurprisingly, background changes secondary to diabetes and hypertension are common albeit mild, and there have been occasional reports of findings compatible with collapsing focal segmental glomerulosclerosis (Santoriello et al, 2020). Glomerular pathology such as collapsing focal segmental glomerulosclerosis may be implicated in those with higher grade proteinuria, with several cases reports of this in the literature which may be closely associated with the presence of the APOL1 allele (Peleg et al, 2020). As well as the systemic effects of infection there is also evidence of direct viral tropism affecting the kidney, with viral particles seen in the tubular epithelium (Su et al, 2020), and post-mortem studies have demonstrated renal tropism (that is direct infection of the kidney) in patients with COVID-19, with an

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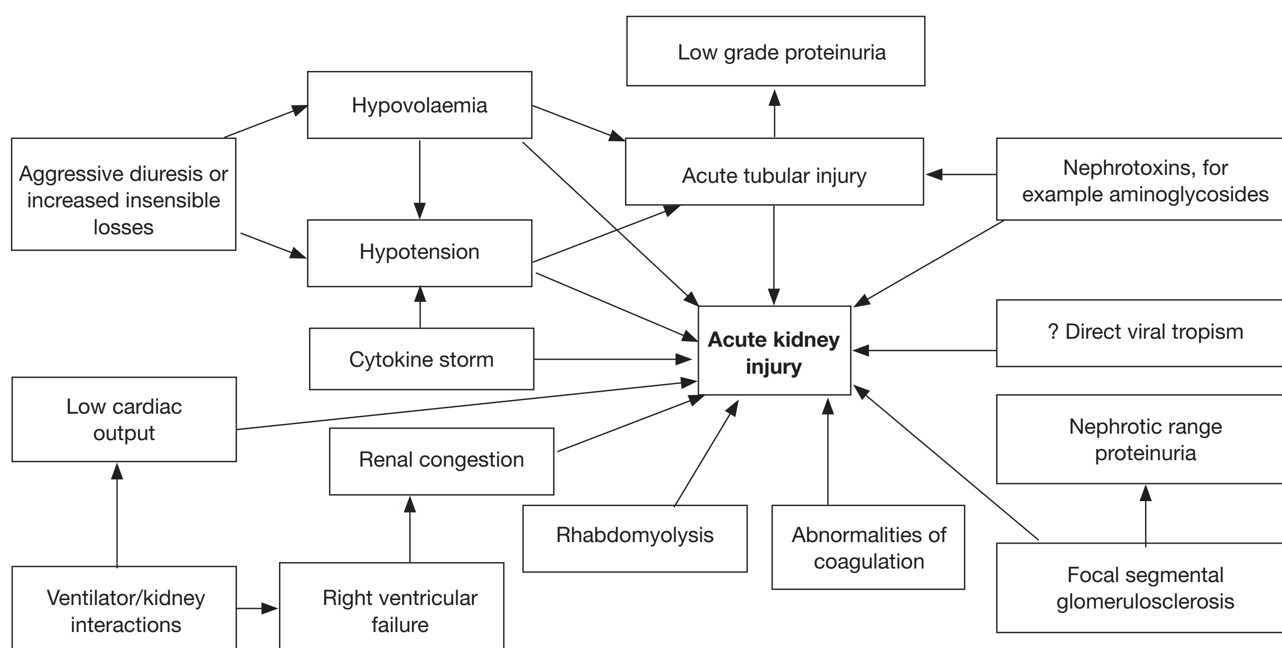

Figure 1. Potential pathophysiological mechanisms behind the development of COVID-19-associated acute kidney injury.

association with disease severity and development of acute kidney injury (Braun et al, 2020). Evidence of upregulation of the ACE2 protein (a protein thought to be responsible for viral entry into cells) has also been demonstrated in renal tissue (Su et al, 2020).

Thromboembolic complications

Patients with COVID-19 and acute respiratory distress syndrome have high rates of severe thromboembolic complications and endotheliitis despite anticoagulation (Ackermann et al, 2020). Indeed, fibrin thrombi in the glomerular capillary loops with associated endothelial damage have been observed as has thrombotic microangiopathy. Furthermore, endothelial dysfunction is a key risk factor for COVID-19-associated coagulopathy, characterised by high D-dimer levels and microvascular damage. Direct viral activation of the complement system may also contribute to endothelial dysfunction and coagulopathy, as may acquired pro-thrombotic conditions.

Rhabdomyolysis

Rhabdomyolysis has also been reported as complicating the initial course of COVID-19 disease, occurring in 7–20% of patients with evidence of acute kidney injury (Pei et al, 2020).

Cytokine storm

It has been proposed that the ‘cytokine storm syndrome’ plays an important pathogenic role in COVID-19-associated organ dysfunction, including acute kidney injury, although what constitutes a cytokine storm remains ill-defined. Simplistically, it may be viewed as an excessive or uncontrolled release of pro-inflammatory cytokines, although there is little understanding as to the events that may precipitate this or indeed the contribution that such an event has to pathogenesis (Tisoncik et al, 2012). Elevated levels of cytokines have been documented in patients with COVID-19 disease, with meta-analysis demonstrating that higher IL-6 levels are significantly associated with adverse clinical outcomes. However, levels are considerably higher in patients with the chimeric antigen receptor (CAR) T cell therapy cytokine release syndrome or with sepsis than those seen in patients with COVID-19. In addition, cytokine assays are not well standardised, and comparisons between studies using different assays are often not possible. An alternative explanation may be that these moderately elevated levels of cytokines reflect critical illness, rather than a ‘storm’ per se, an argument borne out by data suggesting that in critically ill patients with COVID-19 and acute respiratory distress syndrome, circulating cytokine levels were lower than those in patients with bacterial sepsis

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and similar to those in other critically ill patients, suggesting that COVID-19 disease may not be characterised by a cytokine storm (Kox et al, 2020).

Indirect mechanisms of renal injury

Volume depletion and dehydration, with resulting reduction in renal perfusion, is likely to contribute to renal injury through increased insensible fluid losses, aggressive diuresis to manage pulmonary complications and gastrointestinal symptoms. This is evidenced by changes in specific gravity and sodium excretion supporting this mechanism (Hirsch et al, 2020). Exposure to nephrotoxic medications may also contribute to tubular injury. Elevated intrathoracic pressure from invasive positive pressure ventilation can reduce cardiac output and renal perfusion, as well as causing impaired right ventricular function, resulting in renal venous congestion (Joannidis et al, 2020).

Assessment of patients with COVID-19

As outlined, renal involvement is common in patients with COVID-19 and may occur at any time before or during hospital admission. Initial assessment should include a full medical history and comorbidities, including factors that further increase the risk of acute kidney injury (such as chronic kidney disease, heart failure, liver disease, diabetes, previous history of acute kidney injury, age 65 years or over). Clinical assessment should record fluid status by clinical examination (for example, peripheral perfusion, capillary refill, pulse rate, blood pressure, postural hypotension, jugular venous pressure, or pulmonary or peripheral oedema) as well as fluid balance (fluid intake, urine output and weight). Baseline investigations include full blood count, serum urea, creatinine and electrolytes (sodium, potassium, bicarbonate). Assessment should include, and may only be manifest through, changes in urinary sediment rather than functional markers such as creatinine; as such, urinalysis is mandatory (Selby et al, 2020). Medication review should be performed and those that can cause or worsen acute kidney injury should be stopped during the acute illness unless essential. Pharmacist advice on optimising therapy is recommended.

Hospitalised patients should be assessed daily for acute kidney injury through monitoring of fluid status and fluid balance. Current recommendations are that serum urea, creatinine and electrolyte levels (sodium, potassium, bicarbonate) are measured at least every 48 hours or more often if clinically indicated (for example, in those at increased risk of acute kidney injury, in those who have sustained acute kidney injury and those with electrolyte abnormalities) (Selby et al, 2020). Nephrology advice should be considered where there is diagnostic uncertainty about the cause of acute kidney injury, which may need further tests or imaging. This may include cases with significantly abnormal urinalysis results, as these may be a sign of COVID-19-induced kidney damage or other intrinsic renal disease. Further specialist advice may also be sought where fluid management needs are complex, the acute kidney injury continues to progress despite initial management or the patient has the usual indications for kidney replacement therapy (including life-threatening hyperkalaemia, refractory fluid overload or severe metabolic acidosis), particularly if there is no urine output.

Management of acute kidney injury in patients with COVID-19

The management of established acute kidney injury in patients with COVID-19 disease is supportive. There are few specific therapies, and no evidence to suggest that acute kidney injury in patients with COVID-19 should be managed differently to other causes of acute kidney injury in the critically ill (Reference Keys, 2012). As such, management should follow current consensus recommendations for acute kidney injury. In all patients, the aim should be to achieve and maintain euvolaemia and, where there is volume depletion, this may be corrected orally if tolerated or through intravenous fluid therapy. In the critically ill patient this may be better managed with dynamic haemodynamic assessment, which reduces the risk of acute kidney injury and respiratory failure (Douglas et al, 2020). The choice of fluid should be selected on an individualised basis, although the use of balanced

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solutions is preferred as part of an intravenous fluid management plan that is reviewed daily. The clinician should be aware that patients with COVID-19 who have acute kidney injury are at higher risk of hyperkalaemia and this should be managed according to local guidelines. Where respiratory support is needed in patients with severe COVID-19 and acute respiratory distress syndrome, a lung-protective mechanical ventilation strategy should be used. Positive end expiratory pressure levels should be individualised, minimising excessive pressures, as this may result in high systemic venous pressure and a reduction in kidney perfusion and subsequently glomerular filtration. The use of proning techniques does not seem to impact on the risk of acute kidney injury.

Kidney replacement therapy should be considered in the presence of emergent complications as noted above and not guided by the stage of acute kidney injury. Choice of modality will be driven by local resource availability, although continuous therapies may be better tolerated in patients with haemodynamic instability and facilitate improved volume and nutrition management. Given the hypercoagulable state seen in some patients with COVID-19 this may result in premature circuit failure, but there are no data to recommend one approach in favour of others. Of note, the unprecedented demand for kidney support has led to some centres using peritoneal dialysis to treat acute kidney injury in patients with COVID-19 who need kidney replacement therapy. To date there are no data on outcomes of acute peritoneal dialysis. Although evidence has shown survival benefit from the use of steroids in patients with COVID-19 disease requiring supplemental oxygen, there is little evidence to suggest any impact on renal function.

Extracorporeal blood purification techniques

Extracorporeal blood purification techniques have been proposed as a possible adjuvant therapy for critically ill patients with COVID-19 through the removal of circulating mediators which may be responsible for the severe immuno-inflammatory response seen in some patients with severe COVID-19 (Ronco and Reis, 2020). The rationale is that removal of immune mediators might mitigate organ failure through minimising organ injury. This has been proposed in the treatment of patients with severe sepsis characterised by hyperinflammation, cytokine release, endothelial dysfunction and hypercoagulability with the production of inflammatory molecules. However, given cytokine activation in particular is not as robust in patients with COVID-19, careful patient selection is necessary if such techniques are to be considered, particularly as they have not yet been formally studied. Techniques available include haemoperfusion and therapeutic plasma exchange, as well as direct removal of virus particles using heparan bonded columns. Although several case reports have suggested patient benefit, this is yet to be tested under randomised controlled conditions.

Long-term outcomes

There are few data on longer term outcomes following the development of acute kidney injury in patients with COVID-19. A study from the USA demonstrated that patients with COVID-19 and stage 3 acute kidney injury were more likely to experience in-hospital death compared with patients negative for COVID-19 with stage 3 acute kidney injury (52.1% vs 19.6%; relative risk = 3.8; 95% confidence interval = 2.6–3.9). Interestingly, fewer patients with COVID-19 and stage 3 acute kidney injury requiring kidney replacement therapy remained dialysis dependent than patients negative for COVID-19 or historical controls, but this may be explained through the competing risk of death and high mortality observed in patients with COVID-19 and stage 3 acute kidney injury (Fisher et al, 2020).

Conclusions

Kidney involvement in patients with COVID-19 infection is common and associated with worse outcomes in the critically ill. In keeping with acute kidney injury found in many other circumstances, the aetiology is varied and often multifactorial.

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Key points

- Despite early reports to the contrary, kidney involvement commonly complicates COVID-19 disease. In the critically ill this may mean almost 30% of patients require kidney replacement therapy.
- Risk factors for the development of severe acute kidney injury include higher severity of illness, a history of diabetes, high body mass index, black race, male sex, older age and a history of heart failure.
- Acute kidney injury in patients with COVID-19 appears to be of heterogenous origin with volume depletion, hypotension, acute tubular injury, ventilator-associated acute kidney injury and rhabdomyolysis among causative mechanisms.
- Active urinary sediment may exist; case reports have demonstrated the presence of focal segmental glomerulosclerosis and this should be considered where there is heavy proteinuria.
- Management of acute kidney injury is supportive and the usual steps should be taken to ensure optimal haemodynamic and volume status, with the use of kidney replacement therapy where indicated.

Author details

[1]Intensive Care Unit, Royal Surrey Hospital Foundation Trust, Guildford, UK

[2]Renal Unit, St George's Hospital, London, UK

[3]Department of Clinical and Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK

Conflicts of interest

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