COVID-19-associated AKI

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Purpose of review
While it is now widely established acute kidney injury (AKI) is a common and important complication of coronavirus disease (COVID-19) disease, there is marked variability in its reported incidence and outcomes. This narrative review provides a mid-2022 summary of the latest epidemiological evidence on AKI in COVID-19.

Recent findings
Large observational studies and meta-analyses report an AKI incidence of 28–34% in all inpatients and 46–77% in intensive care unit (ICU). The incidence of more severe AKI requiring renal replacement therapy (RRT) in ICU appears to have declined over time, in data from England and Wales RRT use declined from 26% at the start of the pandemic to 14% in 2022. The majority of survivors apparently recover their kidney function by hospital discharge; however, these individuals appear to remain at increased risk of future AKI, estimated glomerular filtration rate (eGFR) decline and chronic kidney disease. Importantly even in the absence of overt AKI a significant proportion of survivors of COVID-19 hospitalisation had reduced eGFR on follow-up.

Summary
This review summarises the epidemiology, risk factors, outcomes and treatment of COVID-19-associated AKI across the global pandemic. In particular the long-term impact of COVID-19 disease on kidney health is uncertain and requires further characterisation.

Keywords
acute kidney injury, coronavirus-19 disease, critical care, epidemiology, outcomes, SARS-CoV-2, treatment

INTRODUCTION

Severe acute respiratory coronavirus 2 (SARS-CoV-2), the viral pathogen that causes coronavirus disease (COVID-19), was first described in December 2019. Since then, there have been 514,000,000 cases and 6,250,000 deaths worldwide [1]. Although its effects on the kidneys were initially understated, rapid proliferation of research on this topic has helped shape a clearer understanding of the incidence and severity of kidney disease during COVID-19 disease.

Despite this, there remains a significant degree of variability in reports of the incidence and outcomes of acute kidney injury (AKI) in COVID-19. This is hardly surprising, conducting research during the COVID pandemic posed many methodological challenges, pressure to release data quickly and many studies have significant biases or variable quality [2▪]. Furthermore, the nature of the disease has altered since 2020 both in terms of baseline susceptibility, treatment and characteristics of the prevalent viral variant. Thus many early reports may lack relevance to the current clinical environment or have been superseded by large, better quality studies. Finally, geographic and temporal differences in the association between COVID and AKI undoubtedly exist but remain poorly characterised.

This narrative review provides a mid-2022 summary of the latest evidence on AKI in COVID-19. The pathophysiology of AKI has been extensively discussed [3]; overall conventional risk factors and mechanistic pathways of AKI appear to still hold with relatively weak evidence for a strong effect role of direct viral infection [4]. However, detailed discussion of AKI pathogenesis in COVID-19 is outside the scope of this clinical review, where we focus on

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KEY POINTS

- Up to a third of inpatients and the majority in ICU with COVID-19 develop AKI, although this incidence may be declining now compared to the first wave.
- The risk factors for AKI in COVID-19 are similar to those outside of COVID-19 and presence of underlying CKD is a particularly significant risk factor.
- Even mild AKI (stage 1) is associated with an increased risk of mortality, although the majority of survivors recover their kidney function by hospital discharge.
- Inpatients with COVID-19 are at increased risk of future AKI, eGFR decline and chronic kidney disease, even in the absence of overt AKI at time of infection.
- The important therapies to treat AKI are maintaining proper fluid balance, pharmaceuticals that reduce disease progression and renal replacement therapy according to standard indications.

the epidemiology, risk factors, outcomes and treatment of COVID-19 associated AKI.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN COVID-19

The first report describing the incidence of hospital inpatient COVID-19-associated AKI during the initial outbreak in China was published on January 24th, 2020, and described a low incidence of 7% [5]. Other studies from China in early 2020 reported similarly low rates, with a meta-analysis of predominantly Chinese studies published before May 2020 showing an overall incidence in hospitalised patients of 4.5%, ranging from 0.5% to 29% [6]. However, more subtle kidney abnormalities were more common; in a cohort of 333 patients, 65.8% had dipstix proteinuria at presentation, but only 4.7% developed overt AKI [7]. In contrast, initial reports from the USA and Europe reported significantly higher rates of inpatient AKI between 19% and 65% [8–10]. Subsequently large observational studies and meta-analyses, predominantly examining reports from the first COVID-19 wave, have reported an AKI incidence of 28–34% [11▪,12▪,13,14].

Several reasons may underlie the initial discrepancy in reported rates of AKI. Observed mortality was considerably lower in early studies from China suggesting the threshold for admission was likely lower, leading to lower in-hospital disease severity [15]. Furthermore, the incidence of inpatient AKI in China has been reported to be lower prior to the pandemic, potentially suggesting under-recognition of AKI or lower baseline susceptibility in the Chinese in-patient population [16,17].

As expected, AKI was more prevalent in patients admitted to the intensive care unit (ICU). This increased incidence and severity of AKI in ICU is likely a product of the effect of more severe disease on the kidneys and the presence of additional risk factors specific to multiorgan failure like mechanical ventilation. Even in early meta-analyses that predominantly included studies from China, the ICU AKI incidence was 22% [18]. Further analyses that included more global studies estimated an ICU AKI incidence of 46–77% [12▪,19,20▪]. AKI in the ICU was generally more severe, the incidence of AKI stages 1, 2 and 3 in all inpatients was 44–66%, 19–20% and 14–34%, respectively, compared to 20–22%, 20–24%, 36–57% in ICU [11▪,12▪,19,20▪]. Importantly, patients admitted to ICU are at risk of AKI progression; an observational study from the UK showed that 36.7% of patients with no AKI or stage 1 AKI progressed to AKI stage 2/3 after 48 h [19].

The rate of AKI in inpatients with COVID-19 has been shown to be significantly higher than historical cohorts of acutely hospitalised patients [21]. However, this may reflect a more severe disease than non-COVID hospitalities. In the critically ill there was no difference in the rate of AKI or use of renal replacement therapy (RRT) in COVID-19 patients when compared to patients with other respiratory viruses requiring critical care [including viruses that target the Angiotensin converting enzyme 2 receptor and those that do not] [22]. Moreover, around one-third of patients also develop AKI in other types of sepsis such as community-acquired pneumonia with 49%, 21% and 30% developing stage 1, 2 and 3 AKI, respectively, suggesting that the incidence of AKI is not wholly dissimilar to other severe infections [23].

AKI in COVID-19 can also be sub-classified by timeframe; they can either develop within the first 24–48 h (community acquired AKI, CA-AKI) or after the first 24–48 h (hospital-acquired AKI, HA-AKI). Out of those that present with AKI, 51–72% present with CA-AKI and 28–49% present with HA-AKI [24,25]. The severity of the AKI was comparable between CA-AKI and HA-AKI although more patients with CA-AKI were admitted to ICU [24]. HA-AKI, however, is associated with significantly higher mortality than CA-AKI [24,25], which is consistent with observations in non-COVID AKI [26]. Further, the presence of new-onset AKI in ICU predicts increased mortality in patients with less severe disease, but not in those who have the highest sequential organ failure assessment (SOFA) scores [27]. These findings show that the presence of HA-AKI serves as an early indicator of development systemic multiorgan failure and subsequent death.

There is significant geographic variation in reported incidence of AKI. Along with the low

incidences in China, the incidences of reported AKI in parts of Africa and Southern India are peculiarly low with most reports stating an incidence between 4 and 7% [28–31]. In contrast, the AKI incidence rate of 36–50% in South America was comparable with those observed in Europe and Northern America [32,33]. This variation likely exists due to significant differences in demographics, hospitalisation, access to ICU and assessment of kidney function. There, however, is yet to be a comprehensive meta-analysis outlining the differences in the COVID-19 incidence between geographic and economic regions.

Currently, most observational studies report incidences of COVID-19 AKI during the period between March and August 2020 (i.e. wave 1 of the pandemic) but there are increasing numbers of studies reflecting the incidence from December 2020 to April 2021 (wave 2). Most papers describe the incidence and or severity to be declining [34,35]. This may be due to improved treatment of COVID-19 or increased recognition of less severe AKI in COVID-19. However, these findings are not universal [36] and further longitudinal studies or meta-analyses are necessary to validate these findings.

RISK FACTORS FOR DEVELOPMENT OF ACUTE KIDNEY INJURY IN COVID-19

Risk factors for AKI in COVID-19 can be classified as premorbid patient factors, factors identified at hospitalisation (biochemical and clinical parameters) and risk factors arising during hospitalisation. The majority of identified premorbid patient risk factors for AKI in COVID-19 are exposures known to be associated with increased risk of AKI occurrence and progression in general, outside of COVID-19. These include diabetes, chronic kidney disease (CKD), obesity, hypertension, male gender and increasing age. [11▪,37]. CKD in particular is now recognised as an important risk factor for development of severe COVID-19 requiring critical care admission, and it is estimated in the absence of CKD the burden of severe COVID-19 would fall from 22 to 17% [38]. A meta-analysis from Cai *et al.* also identified smoking, chronic pulmonary disease, cardiovascular disease and cancer as AKI risk factors; however, these latter associations were not borne out in the large observational International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) World Health Organisation (WHO) Clinical Characterisation Protocol study (CCP)-UK study [11▪,37]. Importantly many identified COVID-19 AKI risk factors have also been associated with adverse outcomes in COVID-19 in general, although the extent to which AKI is causative in these associations is uncertain.

The relationship between risk of AKI and non-White ethnic groups is unclear and any increased risk is likely multifactorial including socioeconomic factors, systemic inequalities, cultural factors and differing patterns of comorbid disease. In particular, in a large multivariable analysis an increased risk of AKI in Black patients with prior CKD was observed [11▪]; however, CKD diagnoses were recorded less in Black patients compared to White, possibly suggesting under-diagnosis of mild CKD in Black patients [11▪]. In the UK, South Asian background has been associated with more severe, stages 2 and 3, AKI, although interaction analysis suggests this might be mediated by CKD and diabetes. In contrast, some increased risk of AKI in Black patients appears to persist, even after adjusting for socioeconomic factors and underlying co-morbidities although these studies are still subject to confounding bias [21,39]. Genetic factors, such as the presence of high-risk genotypes of *APOL1,* which encodes an innate immunity protein, might partly account for increased risk of AKI in Black patients. *APOL1* genotypes found predominantly in individuals of African descent [40] are associated with increased risk of CKD [41]. Small case series have described the presence of collapsing glomerulopathy in Black patients with COVID-19 that have the high-risk genotype of *APOL1* [42]. However, previous studies have shown no association between the presence of high-risk *APOL1* genotypes and AKI [42,43]; therefore, further studies are required to elucidate this putative genetic link.

Another area of interest is the risk of AKI in patients on inhibitors of the renin-angiotensin system (RAS). At the start of the pandemic there was concern regarding the safety of angiotensin-converting enzyme inhibitors (ACEi) due to the link between the ACE2 receptor and SARS-CoV2. Subsequent studies showed no difference between patients on ACEi and COVID-19 progression and death. The link between RAS-blockers and AKI is less clear with some studies suggesting no association [39] but others finding some association even after adjustment for cofounders [11▪]. Even with adjustments, however, these studies are still at risk of confounding biases (e.g. degree of CKD or hypertension are often not accounted for in multivariate analysis) and future active comparator study designs will be required to investigate this further [2▪].

Clinical AKI risk factors on admission with COVID-19 are largely related to severity of the COVID-19 disease. This includes clinical parameters, such as high respiration rate (>20) and hypoxia; and blood biochemistry, such as high inflammatory markers (interleukin, IL-6, C-reactive protein, fibrinogen, high neutrophil:lymphocyte

ratio, low albumin) and evidence of end-organ damage (high lactate, deranged liver function tests, increased amylase and lactate dehydrogenase) [11▪,19,44]. Admission proteinuria is also associated with increased risk of AKI, and may be a marker for subclinical kidney injury [7,45]. A recent small study has also looked at the utility of other potential urinary biomarkers, such as neutrophil gelatinase-associated lipocalin and monocyte chemoattractant protein, finding these were associated with higher risk of adverse kidney outcomes (stage 3 AKI, dialysis, or death within 60 days) [46,47]. Some patients also had high urinary biomarkers but no biochemical AKI potentially indicating subclinical AKI, although the clinical significance of this is uncertain. Further studies are needed to investigate the prognostic utility of AKI biomarkers in COVID-19.

The risks for AKI as an inpatient are less well characterised but potentially include inappropriate fluid management at either extreme (either hypervolaemia secondary to excessive fluid resuscitation or hypovolaemia from conservative fluid management or over-diuresis), nephrotoxin exposure and other organ failure and their treatment [44,48▪]. Of the patients admitted to ICU, 59.2–81% and 39.2–43% of patients required vasopressor support and mechanical ventilation, respectively [19,20▪]. Mechanical ventilation, in particular, is associated with a higher risk of AKI [19] and is a well-recognised AKI risk factor in general [49].

OUTCOMES

The association between AKI and increased mortality in COVID-19 was evident in the earliest reports [50]. It is now widely accepted that even mild AKI (stage 1) confers increased risk of mortality and risk increases as the severity of AKI increases [11▪,20▪,44]. Cohort studies have shown an in-hospital mortality of around 40% of all patients with any AKI [11▪,44], which increases to 62% for patients with AKI in ICU [20▪]. The attributable mortality of AKI in COVID-19 is not well characterised and it remains unclear to what extent AKI is playing a causative role in risk for death or merely reflective of disease severity. A recent study by Morieri *et al.* showed that AKI was independently associated with increased mortality in a non-ICU setting (i.e. before a patient had clinically deteriorated to the point of ICU admission) and concluded causation over association [44]. However, there were many potential confounders and any exact contribution of AKI to risk of death will be inevitably context dependent including influences on clinician decision making.

Recovery of kidney function or development of CKD is, aside from death, the most consequential outcomes of AKI. However, data for kidney recovery were often incomplete or missing in studies, often due to lack of time for follow-up, and therefore not described in meta-analyses. Results from the authors' hospital system showed that only a minority (40.2%) of patients recovered kidney function by day 7 and the majority either relapsed (14.1%) or had persistent AKI (45.6%) and developed acute kidney disease (AKD) [14]. Risk factors for AKD included hypertension, cardiovascular disease and CKD [51].

By hospital discharge, however, the majority of survivors (74–84%) - even those admitted in ICU - showed biochemical recovery of kidney function [20▪,52,53]. The risk of nonrecovery by discharge is significantly higher in patients who developed stage 3 AKI and/or acute kidney disease [14,20▪,51]. Moreover, patients who had unresolved kidney injury at discharge had a significantly increased risk of mortality in the 10-months following discharge [54].

Several studies have attempted to further characterise the long-term sequelae of COVID-19 induced kidney injury post discharge. A large cohort study included 89 216 patients from the Veterans Health Administration who were 30-day survivors of COVID-19 and found that these patients were at increased risk of future AKI, eGFR decline (of more than 30–50%) and end stage kidney disease compared to controls (no COVID-19). Although the risk was higher if patients were hospitalised with AKI and/or admitted to ICU, risk of GFR decline existed even in patients who were hospitalised with COVID-19 but without overt AKI [55▪]. These results are consistent with previous reports from China that found 13% of patients who had normal eGFR at time of infection had reduced eGFR (<90) at 6 months follow-up [56▪]. These long-term outcomes could be a result of the subclinical kidney injury that has been extensively described in the literature [7,46] and highlights the importance of monitoring urinalysis results as well as lab biochemistry. It is however also possible that the mechanism of kidney injury in COVID-19 predisposes to worse long-term outcomes as studies have shown greater decrease in eGFR when comparing COVID-19-associated AKI with non-COVID-19-associated AKI [57]. This may be consistent with the general higher severity of COVID-19 associated AKI including greater need, use and duration of RRT.

The risk of eGFR decline in nonhospitalised patients is less clear. Although the study including nonhospitalised Veterans showed a small but significantly increased risk in those infected with COVID-19 compared to control, this result was not replicated in a separate cohort study from Germany that included mainly adults who survived SARS-CoV2 infection [58]. As perhaps expected, the degree of eGFR decline

at 6 and 12 months corresponds with the AKI severity during admission; there was a decline of 6.02%, 15.99% and 17.79% for AKI stage 1, 2 and 3, respectively [59].

It is also important to consider that the true decline in serum creatinine-based eGFR may be underestimated for patients who had long, severe and complex admissions due to the reduction in muscle mass leading to spurious elevation in calculated eGFR-creatinine [60]. However, this important consideration has not been widely considered in COVID-19 studies looking at kidney function and it is therefore likely that the burden on kidney disease during and after COVID-19 is larger than appreciated, particularly in the patients who experienced more severe illness.

TREATMENT

The therapies to treat AKI in COVID-19 can be split into supportive measures, in particular maintaining proper fluid balance; COVID-specific pharmacotherapy, in particular antivirals and immunosuppressants and RRT.

The paradigm of fluid therapy in COVID-19 has shifted significantly since the start of the pandemic. Some groups initially advocated for an early negative volume balance with a conservative fluid resuscitation strategy, a based-on treatment of non-COVID-19 ARDS patients [11▪,61,62]. However, this approach neglected the fact that COVID-19 patients generally presented without shock and nonrespiratory organ failure and were thus less likely to receive aggressive fluid resuscitation. In contrast COVID-19 patients may be more susceptible to dehydration, due to inability to easily access or imbibe oral fluids and increased fluid losses. It should be stressed, however, that when it occurs fluid overload remains harmful to the kidney in COVID-19 and this risk may be more marked in sicker patients, so in the ICU positive fluid balance in COVID-19 patients is associated with adverse outcomes including AKI progression [19]. An individualised approach to fluid therapy in COVID-19 has therefore been recommended [48▪]. Other than this, in the absence of good evidence to the contrary, the principles of managing COVID-19 AKI remain the same as AKI in other settings [48▪].

Pharmaceutical management of COVID-19, such as antivirals and immunosuppressants, should theoretically reduce the risk of AKI by reducing disease progression. There is little evidence to suggest that the then most commonly used antiviral, remdesivir, is associated with decreased incidence of AKI [11▪] and recent pharmacovigilence studies have instead suggested increased incidence [63]. Currently remdesivir is not used in patients with eGFR<30 due to the theoretical risk of the cyclodextrin derivative, sulfobutylether-beta-cyclodextrin, accumulating, although this risk may have been overstated [64]. Other pharmaceuticals with hypothesised antiviral effects that were used earlier on in the pandemic, such as azithromycin, lopinavir/ritonavir and hydroxychloroquine, showed no reduction in progression to RRT [65–67].

In contrast, the platform RECOVERY trial has shown that use of dexamethasone and later the use of tocilizumab on a background universal dexamethasone use both reduce receipt of RRT [68,69]. While observational studies have shown varying results with some describing increased risk of renal deterioration in patients on dexamethasone [20▪] and some describing decreased risk [19], these studies are very susceptible to inclusion bias and results from large randomized controlled trials remain the gold-standard. Although the RECOVERY trial has found that the combination of casirivimab and imdevimab reduces 28-day mortality for those who were seronegative, there appears to be no reduction in renal replacement therapy receipt [70]. There is also no evidence that convalescent plasma reduces mortality or progression to RRT [71].

High rates of use of RRT were a feature of early phases of the pandemic perhaps driven by a desire to address fluid overload and severity of illness [61]. However, these rates have declined over time likely due to a mixture of a maturing clinical treatment consensus, novel treatments and improvements in processes of care. This was reflected in both the ISARIC WHO CCP-UK study where the usage of RRT peaked in April 2020 and the Intensive Care National Audit and Research Centre data, which showed that the use of RRT in ICU has steadily declined from 26.8% at the start of the pandemic to 14.1% in 2022 (Table 1). [11▪,72] Globally, the prevalence of RRT in those who had COVID-19 was around 9% in all inpatients and 19% for those admitted to ICU [12▪]. There is a significantly increased risk of mortality in those started on RRT and up to 67% of patients receiving RRT went on to die [11▪,19,20▪]. However, this is not unexpected given that the vast majority of RRT in COVID-19 occurs in the setting of multiorgan failure with 84–95% of patients receiving RRT also receiving mechanical ventilation [72]. In survivors of RRT-requiring AKI, on-going dialysis was required in 8–33% at discharge, and up to 52% of patients had a discharge creatinine of 1.5 times above baseline [14,19,20▪,52]. It is still unclear what proportion of these patients will recover kidney function long term.

Table 1. Table highlighting the characteristics of patients admitted to the intensive care unit in England, Wales and Northern Ireland with AKI and COVID-19 between August 2020 to January 2022

	up to 31 Aug 2020	1 Sep 2020-30 Apr 2021	1 May 2021-21 Jan 2022
Number in ICU	10953	25847	16727
Age (mean)	58.8	58.6	54.6
APACHE II (mean)	15.8	13.0	14.1
Number RRT	2929 (26.8%)	4308 (16.7%)	2273 (14.1%)
Mortality with RRT	56%	69%	57%
MV in those with RRT	95%	90%	84%
Virus	Original	Alpha	Delta/omicron
Hospital Treatment	Supportive care	Steroids	steroids & IL-6 antagonists
Community prevention	Lockdown	Lockdown	Vaccination

CONCLUSION

Although research into AKI in COVID-19 has developed significantly and rapidly over the last couple of years (summarised in Fig. 1), many uncertainties remain. The greatest of these is the long-term impact of COVID-19 on future kidney health and development of CKD. The sheer number of COVID-19 admissions has led to a large rise in the number of in-hospital episodes of severe AKI and early evidence suggests many of these patients will develop CKD. On-going research of the long-term outcomes is therefore urgently needed to explore the impact of

FIGURE 1. Schematic representation of the incidence, risk factors, treatment and outcomes of patients with COVID-19 and AKI in the community, hospital, ICU and post-discharge. Image credits: Panel 1 Green Street, Newham author Steve Daniels https://commons.wikimedia.org/wiki/Category: Green_Street,_Newham#/media/File:Green_Street_-_geograph.org.uk_-_2200969.jpg *Creative Commons Attribution-Share Alike 2.0 Generic license*
Panel 2 Royal London Hospital author Matt from London https://en.wikipedia.org/wiki/Royal_London_Hospital#/media/File:Royal_London_Hospital_redevelopment.jpg *Creative Commons Attribution 2.0 Generic license*
Panel 3 Covid-19 ICU patient in Sao Paulo author Gustavo Basso https://en.wikipedia.org/wiki/COVID-19_pandemic#/media/File:Covid-19_SP_-_UTI_V._Nova_Cachoeirinha.jpg *Creative Commons Attribution-Share Alike 4.0 International license*
Panel 4 Arvin McCray, first COVID-19 patient goes home aft 50 days Milwaukee VA Medical Center https://commons.wikimedia.org/wiki/File:Arvin_McCray,_first_COVID-19_patient_goes_home_aft_50_days_%2849860636542%29.jpg *As a work of the U.S. federal government, the image is in the public domain.*

this under-recognised aftermath of the COVID-19 pandemic. Furthermore, future waves of COVID-19 are likely and better understanding and management of AKI in this context will be an important part of improving both short- and long-term outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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