COVID-19 and kidney disease: insights from epidemiology to inform clinical practice

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Abstract

Over the course of the COVID-19 pandemic, numerous studies have been conducted across a range of settings to address the challenges faced by kidney patients and their caregivers worldwide. Areas of concern included how to best protect in-centre haemodialysis patients and mortality risks related to acute transplantation. However, being able to draw meaningful conclusions has proven difficult because of barriers to aspects of care, data limitations, and problematic methodological practices.

In many settings, access to SARS-CoV-2 testing varied systematically between patient groups, while incidence varies over time and place because of differences in population prevalence, targeted public health policies, and vaccination. The absence of baseline kidney function data posed problems in the classification of chronic kidney disease and acute kidney injury, potentially compromising generalizability. Findings require attentive appraisal in terms of confounding, collider bias and chance.

Moving forward in both this pandemic and beyond, sustainable and integrated research infrastructure is needed in settings across the world to minimize infection transmission and both prevent and plan for short- and long-term complications. Registries can support real world evaluation of vaccines and therapies in patients with advanced kidney disease while also being able to monitor for rare complications.

Introduction

The abrupt arrival of the COVID-19 pandemic in early 2020 posed unforeseen challenges for kidney patients and care providers worldwide. Day-to-day priorities shifted towards rapidly reconfiguring services to best protect in-centre haemodialysis patients who were unable to strictly adhere to social distancing policies due to their need to attend treatment, as well as deciding how to navigate acute transplantation, with concerns that it placed recipients at heightened risk of postoperative death. In addition, some critical care units became overwhelmed with an unprecedented demand for acute kidney replacement therapy. Despite effective treatments for severe disease and the rapid development of vaccines, many of these challenges persist with novel variants, while lessons also need to be rapidly absorbed to make the structural improvements to better deal with future crises.

To best inform clinical care, numerous epidemiological studies have been conducted across a range of settings and continue to do so. Studies have evolved from small single-centre case series to large registry and population-wide cohorts, but have encountered methodological challenges due to barriers to various aspects of care, data limitations and problematic designs. For example, some comparisons may not have adequately accounted for variation in healthcare delivery, temporal trends, and geographical factors in relation to the pandemic.Meta-analyses which use aggregated outcomes from such misleading comparisons may not be able to factor in these limitations. This was well-acknowledged by the authors of a meta-analysis of 348 studies.[1] Well-designed large studies with high data quality are therefore likely to prove more reliable and informative.

In this narrative review, we discuss a range of epidemiological challenges posed by the pandemic when timely research was needed in the face of an unprecedented public health challenge (Box 1). We have reviewed an extensive portion of the available literature, selecting studies for their public health relevance as well as for their ability to inform future research endeavors and study design. Major challenges conducting research in populations

with kidney disease, some of which are driven by barriers to healthcare are outlined in Table 1. In addition to outlining epidemiological design issues, key findings of important studies are highlighted in Boxes 2, 3 and 4. Future research may, of course, overcome design limitations of existing studies and reshape understanding further.

An important problem encountered in many COVID-19 studies is "collider bias".[2] As summarized in Figure 1, collider bias occurs when the risk factor or exposure of interest (e.g. kidney transplantation) and the factors on the pathway to the outcome of interest (e.g. disease severity on the pathway to death) both influence the mechanisms behind selection into a study sample population. Causal inference based on analyses of such a selected study sample are then not generalizable to the wider population of interest and, depending on the circumstances, not internally valid due to selection bias.

Epidemiological studies require well-defined study populations in whom outcome events (e.g. infection with SARS-CoV-2) are determined as accurately as possible. While people on long-term kidney replacement therapy are generally captured through registries, in populations with chronic kidney disease (CKD) and acute kidney injury (AKI), a lack of data on baseline kidney function becomes problematic. In this review, we will first discuss challenges of ascertaining COVID-19-related outcomes in the dialysis and transplant populations before expanding the discussion to more complex scenarios where there are challenges in defining people with CKD or AKI (the "denominators").

Studies have found high mortality from COVID-19 in patients with kidney disease, especially in those on kidney replacement therapy.

Evidence on how to mitigate risks to patients with kidney disease is often of poor quality due to the challenges in conducting epidemiological research in often fragmented health settings.

Studied associations may often be distorted due to collider bias

Recognizing epidemiological challenges enables an assessment of study quality and helps identify studies that have contributed robust findings to the literature.

To confront challenges wrought by future pandemics, a sustainable and integrated infrastructure is needed worldwide to generate evidence on minimizing infection transmission, preventing adverse outcomes, and planning for complications.

Box 1 Key points discussed in this review

COVID-19 and dialysis

Capturing incidence in in-centre haemodialysis

Generally, there is high-quality data on the incidence of COVID-19 among patients receiving maintenance haemodialysis. The first outbreak in haemodialysis was described from Wuhan[3], with several more reports emerging as the pandemic spread to other parts of the world[4-7]. Compared to the general population, in-centre haemodialysis patients were more exposed to SARS-CoV-2 infection, especially during lockdowns, as they needed to attend three times weekly for treatment. This may have included shared patient transportation to/from home as well as interaction with other patients and dialysis staff despite infection control procedures, especially when asymptomatic screening was unavailable[8] and when personal protective equipment may have been lacking[9]. It is therefore unsurprising that incidence has been found to be greater in dialysis patients than in the general population with the age-standardized estimate >4-fold greater at 2.5% by May 2020 in Flanders[10].

Furthermore, up to the end of August 2020 in England, 11.2% of in-centre haemodialysis patients tested positive for SARS-CoV-2 compared to only 2.9% of home dialysis patients[11]. However, diagnosis depends on the availability of testing, with greater access for in-centre haemodialysis patients in some settings compared to either the general population or home dialysis patients due to regular asymptomatic screening or testing for milder symptoms as part of infection control processes.

Estimates of SARS-CoV-2 incidence are heavily influenced by the sampling frame, both temporally and geographically because of differences in population prevalence, targeted public health policies, infectivity of virus variants, and vaccination. For example, in places where COVID-19 quickly became a major public health threat early in 2020, local attempts at detecting infection were more rapidly implemented than in other areas. As such, regional estimates cannot be reliably extrapolated to entire countries, as demonstrated across France where up to early May 2020, nationwide incidence was 3.3% but as high as 10% in some regions[12].

Seroprevalence studies may improve insight into past burden of SARS-CoV-2 infection in dialysis. A study from London found seropositivity in 18.7% of patients without symptoms and therefore not tested by polymerase chain reaction (PCR), and in 19.0% of those who were symptomatic but PCR-negative[8]. A survey of over 28,000 haemodialysis patients in July 2020 from across the US found seropositivity at 9.3% after standardization for age, sex, and region, ranging from 0% in seven states to 34% in New York[13]. However, this is likely to be an underestimate as it does not include patients who died from COVID-19 before July 2020, or patients who did not seroconvert or lost their antibodies. This study found that past infection was associated with black and/or Hispanic ethnic backgrounds, poverty, urbanicity and population density[13], after adjustment for age and sex, consistent with ethnic disparities in SARS-CoV-2 incidence seen in England[14].

Mortality in patients receiving maintenance dialysis

Mortality among dialysis patients was consistently high in the early stages of the pandemic. While few deaths were reported from Wuhan[3], early published case series from Lombardy warned of high mortality after COVID-19 in dialysis patients[4,5]. Approximately 20%-25% of infected dialysis patients died within 1 month[1,15,16]. During the peak of the pandemic, excess mortality (compared to all-cause mortality in the same period in previous years) on dialysis was 30% (i.e. 1.3-fold) in the US and the UK[14,17]. Not all of these deaths were formally diagnosed as being due to COVID-19. For example, as outlined by the World Health Organization, International Classification of Diseases-10 and -11 codes were in a state of constant evolution[18] and in the US, it was only several months into the pandemic that COVID-19 became an officially recognized cause of death on the national death notification form used to categorize all deaths in patients with end-stage renal disease (ESRD). Furthermore, given the understandable focus of health systems worldwide on the most acute care, it is difficult to establish retrospectively how much this excess mortality was driven by a lack of access to timely diagnosis and care.

The proportion of patients who died in the weeks and months following COVID-19 are even more striking when placed in the context of other acute illnesses that are common in dialysis patients: before the COVID-19 pandemic, approximately 8.5% of those hospitalized for cardiovascular disease died during hospitalization or within 30 days of discharge[19], while 13% died during index hospitalization from pre-pandemic infections or within 30 days of discharge[20].

The European Renal Association COVID-19 Database (ERACODA), a prospective voluntary registry of 98 centres, found that age, frailty, vascular cause of kidney disease, obesity and heart failure were associated with increased mortality in dialysis patients[21]. Notably, dialysis patients who were waitlisted for transplantation (or being worked-up) were found to have 81% lower mortality than those not for transplantation. Registry data from England and

Wales up to June 2020 additionally found that Asian ethnicity and being on kidney replacement therapy for over 5 years were associated with increased mortality for COVID-19 in in-centre haemodialysis[15].

Practice and care delivery-related factors

Concerns about the potential increased exposure to SARS-CoV-2 coupled with increased mortality risk prompted dialysis services worldwide to implement infection control measures at very short notice. Policies have largely been implemented in the absence of established evidence and outside the setting of prospective trials. Consequently, observational analyses are insufficient to derive definitive causal conclusions on which processes are most effective.

An audit of >5700 patients undergoing in-centre haemodialysis across centres in London found that the wearing of facemasks by asymptomatic patients was associated with decreased risk of hospital admission for suspected infection[22]. Units nursing a larger number of haemodialysis patients and with fewer side rooms suitable for sequestration were associated with worse outcomes, while isolation strategies (which varied by unit) were not although statistical power was limited. Some reports also identified high rates of infection among nursing staff which may exacerbate transmission to patients as well as the ability to safely deliver services[6,9]. During outbreaks in the absence of vaccination, in some settings, the weekly frequency of in-centre dialysis sessions was reduced (e.g. from three to two sessions per week) to limit patients' exposure at treatment centres and while using public or shared hospital transport to commute for dialysis[23]. It is unknown whether such measures were beneficial. The lack of dedicated transport for patients with confirmed or suspected SARS-CoV-2 infection also led to hospitalization for "social reasons" which will impact on studies which assume hospitalization as a measure of COVID-19 severity.

Many dialysis units now use regular asymptomatic surveillance testing to pre-emptively diagnose and isolate infected patients to minimize transmission to other dialysis patients. This means that, at present, patients found to have infection may be asymptomatic in contrast to the start of the pandemic when only symptomatic patients were tested.

COVID-19 and kidney transplantation

Challenges in comparing COVID-19 incidence in kidney transplant recipients with other populations

Incidence estimates in transplant recipients depend on the availability of SARS-CoV-2 PCR testing, which in many settings was predominantly limited to hospitalized disease in the early stages of the pandemic[24-26]. Higher reported incidence in kidney transplant recipients compared to the general population may be due to having less capacity to physically distance due to unavoidable health and social care interactions, or due to greater access to testing because of more severe disease or established relationships with healthcare providers[10,27]. Viral shedding may also persist for longer in transplant recipients which might yield higher sensitivity from PCR testing compared to the general population[28-31].

Regional and national registries including from Colombia, England, Flanders, France, and Wales consistently found higher incidence in dialysis or wait-listed patients compared to transplant recipients[10,24,32-34]. A possible explanation for this is that dialysis patients predominantly dialyse in-centre and were more exposed to SARS-CoV-2 compared to transplant recipients who knew that they were vulnerable and were able to physically distance themselves more effectively. Furthermore, in-centre haemodialysis patients were more likely to be screened for asymptomatic infection or be tested for mild symptoms as there were infection control imperatives to prevent transmission between patients within haemodialysis units.

Before vaccination commenced, seroprevalence studies provided an insight into the underestimation of SARS-CoV-2 infection by PCR testing in kidney transplant recipients. By early July 2020 at a centre in London, 3.9% of recipients had tested positive by PCR but additionally including those with antibodies increased the estimate to 10.8%[35]. However, serological surveys may also underestimate incidence as immunosuppressed patients may be less likely to seroconvert or may experience waning of antibodies more rapidly. A study from New York City up to late July 2020 found that 20.3% of recipients who had tested positive by PCR did not have detectable antibodies at a median of 44 days after diagnosis; seropositivity without PCR-positivity was associated with younger age, no diabetes and better graft function[25]. The overall incidence was 23.4% when combining PCR testing with antibodies, lower than the 33% seroprevalence in the local general population on a governmental survey. This difference may be due to less seroconversion in asymptomatic or mildly symptomatic transplant recipients or due to adherence with social distancing because of clinical vulnerability; seroconversion studies conducted have included few, if any, non-hospitalized kidney transplant recipients[36-41]. It should be noted that serological surveys of transplant recipients may not be representative if some groups of patients were less likely to attend for testing than others (e.g. those more cautious about risks of transmission while attending).

Mortality comparisons are affected by differences in access to testing and severity of infection at detection

Early studies with biased-low SARS-CoV-2 incidence estimates (fewer patients with mild or asymptomatic disease were diagnosed) may have overestimated the rates of outcomes such as death. For example, a single-centre study found that its mortality reduced from 32% to 15% after including cases identified through positive serology[35], but as seroconversion rates in non-hospitalized recipients is unknown, this may still be an overestimate[36-41].

Analyses of risk factors for death in transplant recipients therefore need to be scrutinized as to who data represents in terms of barriers in access to testing and care (Table 1). The most consistently identified pre-existing risk factors for death in transplant recipients are age, diabetes, cardiovascular disease, and deceased donor organ[16,25,26,35,42-46]. Ethnic inequalities in outcomes have also been found in some settings[46]. Some studies have reported associations between immunosuppression reduction and mortality, but this is likely due to confounding by indication (i.e. more unwell patients have their immunosuppression reduced).

As the pandemic has progressed, studies have investigated whether mortality in transplantation is comparable to other populations after accounting for age and comorbidity but such studies may be susceptible to collider bias (Figure 1A). As non-kidney solid organ transplant recipients are relatively rare, some studies have investigated overall mortality outcomes in all solid organ transplant recipients rather than disaggregated reports for each organ; while kidney transplantation is overwhelmingly more common, reports may be biased by better outcomes in liver recipients (the next most transplanted organ), potentially due to less comorbidity and immunosuppression[27,34].

Outcomes among transplant recipients requiring intensive care are poor . However, a propensity-score matched comparison that matched kidney transplant recipients and non-transplant patients on age, comorbidities and drugs across 68 intensive care units in the US found similar mortality at 40%[47]. This appears in line with several similar observational studies comparing kidney or solid organ transplant recipients matched to non-transplant patients[48-54]. However, these findings should be interpreted with caution as there are considerable risks of collider bias and residual confounding. Some studies have been small, limiting the effectiveness of matching on covariables[50,52]. Diagnosis, clinical presentation, hospitalization, and treatment thresholds may also be different for transplant recipients compared to the general population. For instance, some studies found more transplant

recipients without oxygen requirements during admission[51,55] and this may in part be due to many transplant recipients being admitted for predominantly gastrointestinal symptoms and/or graft impairment associated with a more favorable prognosis[56,57]. One study reported that 21% of general population comparators with COVID-19 had “do not resuscitate” orders, compared to only 9% of transplant recipients with COVID-19, suggesting fundamental differences[55]. In some studies, transplant recipients were more likely to be treated with tocilizumab[51,52,55], which has since been demonstrated to be beneficial in reducing mortality in severe COVID-19[58]; similarly, many studies were based on data from early in the pandemic before corticosteroids were routinely used in hospitalized COVID-19, while many transplant recipients would have already been on prednisolone as part of their immunosuppression regimen.

Large studies in unselected populations have demonstrated poorer outcomes in transplant recipients. A study of primary care electronic health records linked to death registry data from England up to early May 2020 found that being an organ transplant recipient was associated with 3.5-times more death from COVID-19 after taking account of recorded comorbidities[59], in line with registry data from Flanders, Italy and Sweden[10,27,60]. In another study, even after taking account of comorbidities indicated from electronic health records, transplant recipients from the US had almost twice the risk of mortality compared to non-transplant patients[61].

Using mortality data to decide on kidney transplantation during the pandemic

Of particular interest to clinicians and policymakers is whether recipients are at greater risk of death than those on the transplant waiting list as this might inform whether to resume or continue transplantation activity, especially given the higher absolute long-term risks of being infected and dying from COVID-19 seen in in-centre haemodialysis patients[11].

Again, it is essential to consider differential access to testing and care when making comparisons. A study from a hospital network in New York found 3.6-times greater odds of death in patients on the waiting list when compared to transplant recipients, but a much greater proportion of recipients had no oxygen requirement during admission suggesting less severe respiratory disease[42]; this is the opposite of findings from ERACODA, which showed a 5% mortality in waitlisted patients compared to 21% in recipients and 25% in all dialysis patients irrespective of waitlisting status[21]. In England, mortality was 26% in transplant recipients compared to 10% in those on the waiting list[34].

Another important consideration when deciding to continue transplanting during the pandemic is the initial increased risk to recipients in the weeks and months after surgery; time since transplantation is an important factor that simpler comparisons between waitlisted and transplanted patients may ignore. Several studies have reported mortality rates greater than 30%, thought to be due to more aggressive immunosuppression as well as more frequent healthcare interactions in the early post-transplant period[21,43,56,62]. A large centre in London found mortality amongst kidney transplant recipients in their first year 24% after additionally including seropositive cases, compared to just 7% in those on the waiting list[44]. However, a report from several transplant centres across India found only 15% of recipients transplanted during 2020 who developed COVID-19 died although the mean age in the transplanted population was only 39 years with 95% from living donors[63]; in Italy, there was little difference with 24% mortality in solid organ transplant recipients within 4 months of transplantation and 27% overall[27]. A meta-analysis described 30% mortality <15 months after transplantation compared to 20% at 16-60 months during the COVID-19 pandemic[64]. In view of generally high mortality after getting infected, local decision making on whether transplantation can proceed should be guided by high quality local data on infection risks in the hospital and on dialysis units.

Provided transplant patients can shield themselves in the community, and have effective antibody responses after vaccination, and if absolute numbers of hospital acquired infections can be minimized, then centres may be able to safely continue to transplant.

Critical illness

Meta-analyses have reported that 25%- 29% of kidney transplant recipients with COVID-19 were admitted to an intensive care unit[64,65]. However, there has been variability in access to critical care and some studies have therefore reported on composite outcomes of death or mechanical ventilation, with no difference when comparing solid organ transplant recipients to matched non-transplant patients in one study[49], and a trend towards increased rates in transplant recipients in another[54]. Compared to patients on the transplant waiting list, studies from the US and the UK have shown similar proportions of patients requiring mechanical ventilation[42,62].

Kidney graft-related outcomes

Kidney transplant recipients have baseline serum creatinine measurements available from routine consultations, and so changes during admission with COVID-19 indicating AKI will generally be reliably detected. AKI appears to be more common in transplant recipients with reports as high as 75-83% in some reports from a small number of centres[29,66,67]. One study from the US found solid organ transplant recipients were 3.5-times more likely to require dialysis than non-transplant patients[54].

Early multicentre reports of graft loss ranged from 12% across London[62] to 4% in the French registry[45], while data from Sweden up to November 2020 reported it at 5%[60]. Registries with linkages in place to COVID-19 testing data may be able to provide updated reports in the context of more widespread testing in future but may not have access to sufficient detail about disease severity and management to investigate possible pathophysiological processes and whether outcomes in transplantation are different to outcomes in non-transplant patients.

Potential alternative mechanisms in transplant patients include the exacerbation of microthrombotic complications by calcineurin inhibitors, while infection and cessation of antiproliferative drugs might lead to allosensitization and acute rejection. A large single-centre study from São Paulo found that 19% of transplant recipients alive 28 days after the onset of symptoms had persistent graft impairment; 30% underwent biopsy with acute rejection seen in 35% and tubular injury seen in all[29]. A single-centre from New York City reported on 18 biopsies done up to May 2021, finding vascular rejection in 36%, including in the first month after COVID-19[68]. There have also been reports of cytomegalovirus and BK polyomavirus activation after COVID-19 by single centres[69,70], as well as reports of new donor-specific antibodies[71]. Observational studies from single centres are susceptible to selection bias based on variation in clinical decision making and the availability and timing of investigations such as biopsies and anti-HLA testing.

In a study of primary care electronic health records from England, during the initial height of the pandemic, being a recipient of a solid organ transplant or of maintenance dialysis was associated with over 3.5-fold increased risk of death from COVID-19 compared to people without transplant and without dialysis respectively[59].

In patients receiving maintenance dialysis, COVID-19 was associated with an 8-fold increase risk of death. Approximately 20% of infected dialysis patients die within 1 month, a substantially higher percentage than for other infections or many cardiovascular events[1,15,16].

There was a nearly 30% excess mortality among maintenance dialysis patients, relative to historical trends, during the initial height of the pandemic in the US and the UK[14,17].

Meta-analyses have reported that more than 1 in 5 kidney transplant recipients die after infection with COVID-19. Risk of death varied by time since transplantation: nearly 1 in 3 whose transplant occurred within the previous 15 months died, compared with roughly 1 in 5 whose transplant occurred 16-60 months previously[64,65].

Approximately 9 in 10 maintenance dialysis patients seroconverted after immunization with the BNT162b2/Pfizer and mRNA-1273/Moderna vaccines, but titres rapidly decreased in the ensuing months, suggesting the need for additional doses[72].

Kidney transplant recipients have more persistent viral shedding compared to non-kidney transplant recipients, which might result in higher PCR testing sensitivity relative to the general population[28-31].

Box 2 Key clinically relevant study findings on COVID-19 in relation to dialysis patients and kidney transplant recipients

COVID-19 and chronic kidney disease

Challenges with determining estimates of COVID-19 incidence in CKD

Estimating the incidence of COVID-19 is especially difficult in people with CKD who are not on kidney replacement therapy. In many settings, access to SARS-CoV-2 testing may have depended on temporal and geographical variations, and severity or perceived risk, while in others, there may have been access to universal screening (e.g. in nursing homes)[73]. In addition, the "denominator population" – the total number of individuals with CKD within a given population – is typically unknown as CKD is often under-reported due to incomplete coding, underdiagnosis in groups perceived to be at lower risk (e.g. younger people and those without diabetes or cardiovascular disease), and infrequent measurement of albuminuria[74]. Patients with diagnosed CKD may have been more likely to be tested due to more frequent interaction with health services, causing a collider bias.

Reliability of estimates of COVID-19-related mortality in patients with CKD

Previous validation studies in the UK have found that the prevalence of estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2 can be reliably estimated using UK primary care electronic health records[75]. Analysis of such data from over 17 million adults in England up to early May 2020 found that people with eGFR 30-60 ml/min/1.73m^2 were at 33% greater risk of death with more than double the risk in those with eGFR <30 ml/min/1.73m^2 [59]. This finding may have been partly due to limited critical care resources during the early peak of the epidemic in England with consequently reduced access for people considered to be at greater risk of poor outcomes such as those with CKD.

A study using data from the National Health Service Digital Trusted Research Environment in England found that of over 2.3 million individuals identified with CKD (mostly stages 3-5) from a population of over 54 million, there were over 46,000 excess deaths between March

2020 and March 2021, not just driven by COVID-19 itself but also related to the marked multi-morbidity seen amongst people with CKD[76].

Critical illness

The Global Burden of Disease collaboration identified CKD as the most prevalent risk factor worldwide for severe COVID-19 requiring critical care[77]. If CKD was a condition that occurred in isolation of others, a naïve calculation would mean that removing CKD would decrease the proportion of the global population at increased risk of severe COVID-19 from 22% to 17%[77]. However, this may be an underestimate as the availability of critical care varies between clinical settings and over time, especially when health services have been stretched.

Kidney complications

In acute settings in which serum creatinine measurements can be obtained easily, AKI is more readily detectable in hospitalized patients. The International Severe Acute Respiratory and emerging Infections Consortium World Health Organization Clinical Characterization Protocol UK (ISARIC-WHO CCP-UK), a large prospective cohort comprising patients admitted to over 250 hospitals in Britain with COVID-19 up to early December 2020 found that patients with underlying CKD were 66% more likely to develop AKI and over three times more likely require acute kidney replacement therapy[78]. Studies evaluating the risk of ESRD in CKD patients after surviving COVID-19 are currently lacking.

Arterial and venous thromboembolic complications

COVID-19 has been found to induce a prothrombotic state leading to increased risk of venous and arterial thromboembolic events in the general population[79]. There are conflicting findings as to whether people with CKD are at greater risk of thromboembolic events compared to those with intact kidney function. Studies to date have been limited with either no well-defined documentation of CKD at baseline, variable definitions, or lacking in systematic follow-up. A prospective multihospital registry of over 4900 hospitalized patients with COVID-19 from New York found that CKD was associated with more than double the risk of a composite of venous or arterial thromboembolic events and all-cause mortality within 90 days of hospital discharge[80]. However, this study did not mention the definition of CKD. Another study with well-defined pre-existing CKD before critical care admission due to COVID-19, found that the occurrence of thromboembolic events in critical care was similar in people with and without pre-existing CKD[81].

COVID-19 and kidney outcomes in the general population

Acute kidney injury

AKI in patients with COVID-19 is strongly associated with increased risk of short-term outcomes such as in-hospital death[78]. Variations in rates of AKI may reflect different national and regional policies regarding hospital admission which in turn may complicate comparisons between different settings. For example, patients from China had fewer comorbidities and were admitted for less severe disease, which may be why initial reports on the incidence of AKI were low[82]. Analysis of over 40,000 hospitalized patients in the ISARIC-WHO CCP-UK study found that 31.5% of patients developed AKI, which was associated with pre-existing CKD, black ethnicity, and tachypnoea at presentation, while increased mortality correlated with AKI severity[78]. It remains unknown whether the prevention or treatment of AKI can reduce the risk of outcomes such as in-hospital mortality or long-term

renal complications. AKI may instead be a “prognostic factor” reflecting disease severity or reduced renal reserve.

Many published studies have not included clear definitions or staging of AKI, or information on renal recovery or follow up. The distinction between AKI in people with premorbid normal kidney function and AKI superimposed on pre-existing CKD is also rarely made.
Urine output is reported infrequently outside of critical care settings, which may also contribute to underestimation of the incidence of AKI. A lack of baseline serum creatinine measurements prior to hospital admission impedes the ability to identify those who have pre-existing CKD but may not have been tested, and therefore diagnosed previously. This in turn creates challenges for the reliable diagnosis and staging of AKI. The assumption of eGFR 75 mL/min/1.73 m^2 for patients without baseline serum creatinine measurements could overestimate the incidence of AKI (older people are likely to have lower baseline eGFR)[83], whereas using the lowest serum creatinine value during the hospitalization as the baseline could underestimate incidence. Such misclassification may distort the association between AKI and outcomes such as in-hospital mortality and long-term kidney outcomes. Sensitivity analyses can be utilized to examine whether different definitions and assumptions change study conclusions.

Impacts of AKI on healthcare systems

During peaks of COVID-19, health systems faced an increased demand for kidney replacement therapy due to AKI. ISARIC-WHO CCP-UK reported that 2.6% of people hospitalized with COVID-19 required kidney replacement therapy[78], while intensive care registry data found it was required in up to 27% of patients admitted to critical care up to August 2020 in the UK[84]. In some settings, this led to unforeseen shortages of dialysis machines and/or consumables[85]. Supply chains may have been compromised due to lockdowns or workforce challenges, further threatening local shortages[86]. More recent

studies have reported a reduced need for kidney replacement therapy, and this may be due to improvements in fluid management or the use of drugs such as dexamethasone[29]. Dialysis starts decreased during the peak of the pandemic in some settings which may be due to competing mortality of high-risk patients with CKD who, without COVID-19, would have progressed to dialysis; reduction in transplantation may also have led to reduced availability in in-centre haemodialysis capacity[87,88].

In some resource-limited settings, the high mortality rate for ventilated patients with severe AKI has caused local physicians to consider it almost futile to commence kidney replacement therapy. It has been suggested that employing a wider variety of modalities (continuous veno-venous haemofiltration, prolonged intermittent renal replacement therapy, sustained low efficiency dialysis and acute peritoneal dialysis) may allow a greater number of patients to receive kidney replacement therapy[89]. In addition, strategies such as moderating treatment intensity to conserve fluids, lowering blood flows to reduce citrate consumption, or running accelerated therapy at higher clearance to treat more patients per machine could form part of a local response[86]. In the absence of clinical trials, evaluating outcomes of these strategies is challenging without meticulous data capture in large multicentre registries.

De-novo immune-mediated kidney disease

Case reports have been accumulating to suggest that COVID-19 may induce de-novo immune-mediated kidney diseases such as IgA nephropathy[90], vasculitis[91], membranous nephropathy[92], minimal change disease[93], and collapsing focal segmental glomerulosclerosis[94,95]. Larger studies are needed to quantify the extent of these associations, using for example, the incidence of disease before and after the pandemic within histopathology registries[96]. Because patients may be less likely to undergo biopsy during the COVID-19 pandemic, the strength of association may be underestimated. Another

approach would be to compare individuals with and without COVID-19 for the development of de-novo immune-mediated kidney disease within a (nested) cohort. However, patients with COVID-19 may be more likely to be followed up and investigated (e.g. for serum creatinine, urinary abnormalities and blood pressure) and, therefore, more likely to be diagnosed than those without COVID-19 leading to overestimation of the association.

Long-term kidney outcomes

There has been a gradual increase in the number of studies focusing on post-COVID-19 complications, some of which include the incidence or progression of kidney diseases[97,98]. Investigating rare outcomes such as ESRD requires very large cohorts. Healthcare systems with well-established databases with linkages to other data sources allow the initiation of kidney replacement therapy to be used as the outcome definition for ESRD. However, many patients with CKD stage 5 (eGFR <15 ml/min/1.73m^2) may not need to initiate dialysis until or unless kidney function worsens substantially and/or symptoms appear. Moreover, initiation of dialysis may sometimes be the result of severe AKI rather than progression to ESRD; distinguishing acute effects (such as those from COVID-19) from true progression of underlying CKD to ESRD can be challenging to differentiate depending on the data source.

A cohort study of military veterans from the US compared over 89,000 COVID-19 survivors and over 1.6 million non-infected controls for the incidence of AKI, eGFR decline, ESRD, and major adverse kidney events (defined as eGFR decline ≥50%, ESRD, or all-cause mortality)[99]. COVID-19 survivors exhibited increased risk of all the studied outcomes, irrespective of whether they were admitted to intensive care, hospitalized, or non-hospitalized. Overall, the rate of ESRD was almost three times higher in survivors compared to individuals without known infection. Investigating eGFR decline can be affected by collider bias (Figure 1B), as only people with available eGFR measurement are selected. Serum

creatinine testing is more likely in people at risk of a rise in serum creatinine (e.g. people with diabetes or cardiovascular disease), so the strength of any association with SARS-CoV-2 infection may be distorted.

In another study, a cohort comprising 443 adults from Hamburg aged 45-75 years who had survived SARS-CoV-2 infection (over 90% of whom were non-hospitalized) were found to have a slightly lower median eGFR when compared to matched population-based controls recruited pre-pandemic[100]. However, this may be due to confounding by a higher proportion of underlying CKD in the SARS-CoV-2 group, and it is difficult to extrapolate the clinical significance of findings given the small magnitude of difference. The findings may also have been affected by selection bias as some participants were recruited through public announcement. Outcomes such as decline in kidney function (for example, decrease in eGFR below a certain cut-off such as <60 or <30 ml/min/1.73m^2)[101], time to percentage eGFR decline (e.g. 30%, 40% or 50%)[99,102], and longitudinal eGFR decline using linear mixed models[103] are likely to be more informative than median residual eGFR following infection. It should be noted that in survivors of severe COVID-19, particularly those with a prolonged, severe or complex course of illness, serum creatinine may estimate higher GFR due to changes in body composition and so true long-term impacts on eGFR may in turn be underestimated.

The pathophysiological processes which may lead to irreversible decline in kidney function remain unknown. Autopsy studies of COVID-19 patients have raised the possibility of direct infection of the kidney by SARS-CoV-2 causing upregulation of profibrotic cell signaling pathways. However, these findings are affected by collider bias as associations between COVID-19 and the histological features of CKD at autopsy are distorted because pre-existing CKD is a risk factor for severe COVID-19 (Figure 1C).

In individuals diagnosed with COVID-19, the risk of death among those with CKD stage 4/5 was 2.5-fold greater that of individuals with normal kidney function or with mild CKD (stage 1/2)[59].

In a large prospective cohort study from Britain, 31.5% of hospitalized patients developed AKI, which was associated with pre-existing CKD, black ethnicity, and tachypnoea at presentation. Mortality correlated with AKI severity and 2.6% of hospitalized patients required kidney replacement therapy[78].

The initial weeks of the pandemic were associated with decrease in the total number of individuals with newly registered ESRD. In the US, there was a 25% decrease in incident ESRD relative to historical projections in April 2020; by one year after the start of the pandemic, there were about 3.5% fewer prevalent ESRD patients in the US than would have been projected[87,88].

Among military veterans in the US, 30-day survivors of COVID-19 (compared with individuals who were not infected) had a 1.6-fold increased risk of a 50% decline in eGFR and a nearly 3-fold increased risk of developing ESRD[99].

Box 3 Key clinically relevant study findings on COVID-19 in relation to CKD and AKI

COVID-19 pharmacoepidemiology in kidney disease

Safety of existing drugs in COVID-19

At the beginning of the pandemic, concerns were raised regarding whether the use of angiotensin-converting-enzyme (ACE)-inhibitors increased the risk of severe COVID-19 in individuals due to upregulated expression of ACE2, a functional receptor for coronavirus entry into cells[104]. Because continuous use of ACE-inhibitors is essential for many patients with hypertension, CKD, ischaemic heart disease and heart failure, the best available evidence was immediately needed to respond to this safety concern. Observational studies from Lombardy[105] and New York[106] among several others[107-109], consistently suggested that there was no association between the used of ACE-inhibitors and the incidence and progression of COVID-19. This has since been confirmed by two randomized controlled trials comparing patients who continued and discontinued ACE-inhibitors during hospitalization for COVID-19 with no difference in outcomes such as COVID-19 progression and death[110,111].

Clinical trials are imperfect vehicles for detecting rare outcomes. Persistent safety concerns about commonly used drugs such as ACE-inhibitors[105-109] and non-steroidal anti-inflammatory drugs[112,113] can be rapidly investigated using administrative databases ("real world evidence"), which complements trials. However, as with other pharmacoepidemiological studies, caution is needed to deal with confounding by indication appropriately. For example, patients with and without an ACE-inhibitor prescription are systematically different in terms of comorbidities such as hypertension, CKD and heart failure. To reduce the influence of confounding by indication, an active comparator study design (e.g. comparing hypertensive patients on ACE-inhibitors with those on other antihypertensives) may be a more rigorous analytic approach.

Anti-COVID-19 therapies

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) international platform clinical trial has demonstrated mortality benefit with the use of dexamethasone, tocilizumab in the treatment of hospitalized COVID-19[58,114], while finding no benefit from therapies used

widely in patients with kidney disease early in the pandemic[115], including lopinavir-ritonovir, hydroxychloroquine and azithromycin[116-118]. Dexamethasone reduced the requirement of kidney replacement therapy by 39%[114], and tocilizumab by 28%[58]. This ongoing trial, currently investigating other repurposed therapies, has recruited over 45,000 participants. People with pre-existing kidney diseases are included but subgroup analyses have not been reported and would likely be underpowered. Participants can be considered unsuitable for randomization to specific therapies which may affect generalizability; for example, 28% of recruited participants with eGFR <30ml/min/1.73m^2 and a third of people with diabetes were considered unsuitable for randomization to dexamethasone[114]. While the RECOVERY trial can serve as a blueprint for rapidly determining effective therapies in future pandemics and other clinical settings, real-world analyses of inpatient prescription data are also required to support safety and efficacy in subgroups such as patients with kidney disease. Such pharmacoepidemiology requires specific methodological considerations to generate valid and reliable evidence such as active comparator study designs (to minimize confounding by indication) and valid definitions of outcomes[119].

With accumulating evidence of impaired seroconversion despite vaccination in dialysis patients and kidney transplant recipients (see below), studies are urgently required to evaluate the benefits from novel antibody and antiviral therapies which may reduce COVID-19 disease severity in these high-risk groups which may then support outpatient treatment pathways.[120] Sotrovimab has been found to markedly reduce hospitalization and death in high-risk patients with non-hospitalized COVID-19 within 5 days of symptom onset; while the trial defined high-risk to include patients with CKD, people with eGFR <60 ml/min/1.73m^2 comprised <1% of participants[121]. The RECOVERY trial recently reported that casirivimab-imdevimab reduced mortality in seronegative patients hospitalized with COVID-19[122]. A living systematic review and network meta-analysis (including 47 randomized-controlled trials up to 21 July 2021) concluded that casirivimab-imdevimab as well as some other antibody therapies may reduce hospitalization while convalescent plasma, intravenous

immunoglobulin and other antibody and cellular therapies are unlikely to provide meaningful benefit, although most studies did not seem to include patients with kidney diseases[123].

COVID-19 vaccines

Evidence on the efficacy and safety of COVID-19 vaccines in patients with kidney diseases has accumulated rapidly, including in kidney transplant recipients and those on dialysis[124,125]. The REnal Patients COVID-19 VACcination Immune Response (RECOVAC IR) study, which includes CKD patients not on dialysis, is ongoing[126]. Both patients with kidney transplantation and those on dialysis have been found to have an impaired response to vaccines compared with the general population[120,127,128]. In a prospective study, dialysis patients exhibited a higher seroconversion rate than kidney transplant recipients (>95% vs. 42%)[129]. A study of over 9000 dialysis patients found 87% developed a seroresponse to the BNT162b2/Pfizer and 96% to the mRNA-1273/Moderna mRNA vaccines but only 37% to Ad26.COV2.S/Janssen adenoviral vector vaccine between 14 and 74 days after completion of vaccination[130]. However, the authors found from longer-term follow-up that antibody responses for mRNA vaccines declined within six months[131], prompting policy changes to increase the routine vaccination series to include three primary doses.

A recent study found that a third dose of BNT162b2/Pfizer vaccine in kidney transplant recipients improved humoral immune responses but effectiveness on clinical outcomes such as death and hospitalization remain unknown[132]. An analysis of national transplant registry data from England found that while there were fewer deaths in recipients vaccinated with ChAdOx1-S/Oxford-AstraZeneca compared to recipients who were unvaccinated after SARS-CoV-2 infection, there was no reduction seen in those vaccinated with BNT162b2/Pfizer[133]. However, this may be due to residual confounding due to comorbidities or age (which was classified, somewhat crudely, as 16-49 or >50 years).

There have been case reports suggesting that COVID-19 vaccines may induce de novo or reactivation of intrinsic kidney diseases[134]. Large studies comparing patients with and without vaccination are needed to confirm these signals at a population level. However, in countries with high vaccine uptake rate and especially with prioritization based on clinical risk, there may be a very small pool to draw from in the comparison group, and patients with and without vaccination may be systematically different in health-related status and behaviors (i.e. healthy vaccinee bias).

Future directions

Potential directions for future research are outlined in Box 4 and a schema for overcoming practical challenges in Figure 2. Kidney doctors need to understand how their patients' data are "captured" (or not) in their local electronic healthcare data sources (such as primary and secondary care). If supported by validation studies and appropriate research ethics approvals, such electronic resources can allow for rapid evaluation of the safety and efficacy of therapies in real-world settings. Kidney disease registries need to be readily integrated with health systems to be able to receive real-time data to monitor outbreaks and help plan local infection control processes.

Nephrology and public health communities must come together to establish protocols for future pandemics, ideally relying on findings from representative patient populations. The ISARIC-WHO CCP-UK is a good example of a secondary care prospective study which was ready to be rapidly implemented to accumulate data from hospitals across Britain, having been designed several years earlier in anticipation of a pandemic[78].

Collider bias – a constant threat to such public health reporting efforts – can be avoided only by breaking down barriers to care and associated documentation of health needs. For example, using a defined cohort of pre-consented and engaged patients, there is no reason

why technological advancements cannot be developed together with patients to be able to gather symptoms data in real-time, especially where patients are in self-isolation.

Protocols should be in place, including randomized components, to be able to evaluate the efficacy of centre-level interventions where clinical equipoise exists. Such randomized trials are the gold standard to assess causality of interventions (e.g. temporary reduction to twice weekly dialysis to reduce exposure at infection epicentres or cessation of acute transplantation).

For patients with relatively rare conditions who are typically excluded from clinical trials, (e.g. people on kidney replacement therapy or with rare immune-mediated kidney diseases), there should be global trial protocols in place that allow participating disease registries to rapidly implement adequately powered treatment and vaccination trials when called upon. Registries with systematic, real-time capture of incident and relapsed intrinsic kidney disease, with linkages to other records in defined-catchment populations, are required to keep track of rare complications of infections and pharmaceuticals.

A stark imbalance is apparent between economically advanced nations and those less well-developed, in the capacity to conduct studies making use of comprehensive electronic health record sources in settings with universal provision of care for kidney diseases[135]. The pandemic has highlighted the importance of economic empowerment and targeted approaches to deliver equitable and sustainable global solutions and this should extend to the infrastructure to be able to conduct large-scale studies at speed. Not having the right tools to be able to utilize localized data for surveillance, planning and development may lead to unexpected costly consequences when it comes to the provision of care and premature loss of life.

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Figure 1 Collider bias

1A Collider bias can occur when investigating the association between kidney transplantation (risk factor) and death (outcome) in people hospitalized with COVID-19 (sample population). Restriction to a hospitalized population (red box) leads to associations between kidney transplantation and death which do not generalize to the wider population (red-dotted lines) because the indications for hospitalization may differ between transplant recipients and other patient groups. Similar problems arise when investigating associations in populations admitted to intensive care.

1B Collider bias will also occur when restricting data extraction when investigating long-term reduction in eGFR to those with available eGFR measurements and SARS-CoV-2 test results (red box). Infection is only partially observed due to limited access to testing (based on severity of disease early in the pandemic), and serum creatinine testing is more likely to be undertaken in people at risk of declining kidney function (e.g. people with diabetes, cardiovascular disease or on certain drugs), or in those at risk of, or suspected to have AKI. This means that associations may be altered by collider bias (red dotted lines).

1C Autopsy studies after COVID-19 are also at risk of collider bias. As only people who died after COVID-19 are selected (red box), and because pre-existing CKD is a risk factor for severe COVID-19, associations between COVID-19 and histological features of CKD at autopsy are affected by collider bias.

Figure 2 Challenges faced when conducting epidemiological research in kidney disease populations and potential solutions.

Quantifying long-term kidney impacts of COVID-19on the development and progression of CKD is a public health priority.

Pharmacological and non-pharmacological clinical trials are required for AKI survivors (after both COVID-19 and other causes) to investigate how to minimize the risk of adverse outcomes such as the development of CKD, further AKI, ESRD, heart failure and thrombotic events.

The risk of SARS-CoV-2 reinfection, and in particular the role that vaccination (including additional and booster doses) play on reducing risk of severe illness in patients with kidney disease requires greater understanding.

The effects of “long-COVID” in patients on dialysis and with kidney transplant should be studied, particularly in terms of whether this phenomenon represents an additional source of morbidity in a population with an already-high comorbidity burden.

The safety and efficacy of emerging drugs for COVID-19 (e.g. antibody therapies) should be evaluated specifically in patients with kidney disease. Patients with kidney disease (e.g. transplant recipients) may potentially be amongst those to benefit most from early intervention to reduce infection severity given vaccine responses may be impaired and mortality high.

Research is needed to establish whether drugs such as, for example, SGLT2 inhibitors are acutely renoprotective in the setting of COVID-19-related AKI.

Systematic multi-centre registries of intrinsic kidney diseases within well-defined catchment populations with capacity for linkage to data on infection and vaccination, should be established for the long-term to be able to determine rapidly whether infections and vaccines might induce *de novo* or reactivation of kidney disease.

Box 4 Possible directions for future research

Population	Barriers to accessing healthcare pre-pandemic	Barriers to COVID-19 testing	Barriers to accessing healthcare during the COVID-19 pandemic	Biases	Potential design solutions
Dialysis	Out-of-pocket costs to access care May vary between in-centre haemodialysis patients and home therapy patients	Universal testing limited by resources, government policy Variable testing approaches in different phases of the pandemic Less access to testing for home therapy patients compared to in-centre haemodialysis patients	AKI burden during the pandemic and shortages of dialysis resources/personnel Reduction in frequency of dialysis sessions to reduce exposure Lack of dedicated transport for infected/exposed patients and those with suspected infection (leading to hospitalization for "social reasons") Pressure to shift to home-based modalities	**Selection bias:** Where testing rates low, incidence falsely low; more severe cases likely to be tested so outcomes such as critical careadmission and death have falsely high rates	Investigating dialysis populations which use surveillance testing for infection control purposes (both denominator and SARS-CoV-2 infections systematically assessed in all patients)

Kidney transplant	May vary based on clinical characteristics (e.g. more recent recipients or individuals with advanced graft impairment or infectious complications may be seen more frequently than chronic recipients)	Reduction in follow-up visits to reduce exposure so less likely to be tested, especially early in pandemic and especially when not requiring hospital admission	Reduction in follow-up visits to reduce exposure; more likely to present late (or not at all) with COVID-19 and non-COVID-19 complications Well-established relationships with healthcare providers may have meant increased access compared to other groups Some transplant programmes suspended to minimize exposure of donors and recipients to healthcare settings and to minimize exposure of recipients to immunosuppression	**Selection bias:** Incomplete capture of SARS-CoV-2 infection resulting in underestimation of incidence and overestimation of mortality Biopsy series affected by clinical decision to perform biopsies **Misclassification:** Possible reduced SARS-CoV-2 seroconversion or premature antibody waning resulting in underestimation of seroprevalence **Collider bias:** Risk factor analyses in hospitalized populations affected by who is	Large prospective cohorts with regular testing to be able to estimate incidence of mild and asymptomatic infection Integration of international/national/regional transplant registries to include biopsy reports, rejection episodes and immunosuppression Report disaggregated outcomes for each organ Work with patients to capture symptoms and health needs at home, as opposed to only assessing those in hospital

				hospitalized and why; in several studies, more transplant recipients admitted without respiratory failure compared to other patients (e.g. due to gastrointestinal symptoms and/or graft impairment or as a precaution) so may be less likely to die	
Chronic kidney disease/acute kidney injury	Low rates of testing for albuminuria +/- eGFR resulting in underdiagnosis of CKD If CKD present, low awareness to diagnose/code CKD in records Limited healthcare resource Multiple co-existing	Universal testing in at risk groups limited by resources and government policies COVID-19 risk varying depending on time and area	Limited healthcare resource AKI burden during the pandemic with shortages of dialysis/personnel resources More CKD patients after the pandemic (newly recognized, due to COVID-19) but CKD may be simply not have been detected prior to infection	**Selection bias:** Lack of universal testing If testing rates low, incidence will be falsely low with more severe cases likely to be tested so outcomes (death, hospitalization, critical care admission etc.) are overestimated **Misclassification:** Due to Inaccurate/incomplete coding of CKD	If using electronic health records, validate captured kidney populations against external/gold standard data (e.g. surveys, registries) Ensure population-based infection surveillance studies are well-represented with patients from known high-risk groups Work with patients to capture symptoms/health needs, as opposed to only assessing those who are hospitalized

	conditions such as hypertension, diabetes and cardiovascular disease among patients with CKD		Reduction in clinic and hospital visits to reduce exposure; more likely to present late (or not at all) with COVID-19 and non-COVID-19 diseases	**Collider bias:** Those with severe disease more likely to be tested Inadequate follow-up testing of kidney function in people not considered to be at risk of CKD	

Table 1 Barriers to healthcare and potential study biases

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