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REVIEW ARTICLE

COVID-19 Survival and its impact on chronic kidney disease

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Up to 87% of patients hospitalized with coronavirus disease 2019 (COVID-19) experience chronic sequelae following infection. The long-term impact of COVID-19 infection on kidney function is largely unknown at this point in the COVID-19 pandemic. In this review, we highlight the current understanding of the pathophysiology of COVID-19-associated kidney injury and the impact COVID-19 may have on long-term kidney function. COVID-19-induced acute kidney injury may lead to tubular injury, endothelial injury, and glomerular injury. We highlight histopathologic correlates from large kidney biopsy and autopsy series. By conducting a comprehensive review of published literature to date, we summarize the rates of recovery from COVID-19-associated-AKI. Finally, we discuss how certain genetic differences, including *APOL1* risk alleles (a risk factor for collapsing glomerulopathy), coupled with systemic healthcare disparities, may lead to a disproportionate burden of post-COVID-19-kidney function decline among racial and ethnic minority groups. We highlight the need for prospective studies to determine the true incidence of chronic kidney disease burden after COVID-19. (Translational Research 2022; 241:70–82)

Abbreviations: AKI = acute kidney disease; aOR = adjusted odds ratio; ATN = acute tubular necrosis; COVAN = COVID-19-associated-nephropathy; COVID-19 = coronavirus disease 2019; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = ratio; TMA = thrombotic microangiopathy

INTRODUCTION

As of September 30, 2021, over 233 million patients worldwide have been infected with SARS-CoV-2 virus and over 4.7 million people have died.[1] Coronavirus disease 2019 (COVID-19) is a respiratory illness that ranges in severity from asymptomatic or mild upper respiratory symptoms to respiratory failure and death. The acute manifestations of COVID-19 have been well described and severe COVID-19 can cause multi-organ injury and failure.[2-4]

Recently, there has been increased coverage in the lay and scientific press about the chronic health consequences of COVID-19 in survivors. Accumulating data suggest that surviving patients may experience a wide array of persistent symptoms referred to as post-acute sequelae of SARS-CoV-2 (PASC) or long COVID. Some studies suggests that symptoms of COVID-19 persist beyond 8-12 weeks in up to 25% to 50% of patients with mild COVID-19 (not requiring hospitalization) and up to 87% of patients hospitalized for

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COVID-19.[5-7] In a large study of >1300 hospitalized patients with COVID-19 who survived and were discharged home with home health care services, only 40% of patients were independent in all activities of daily living by 30 days.[8] Chronic fatigue is the most commonly reported long-term symptom, affecting up to 69% of survivors.[9] Long-term symptoms can also affect the lungs, leading to exercise intolerance and chronic cough. Neuropsychiatric long-term effects have been reported in 33% to 61% of patients and include chronic headache, depression, insomnia, and memory and concentration impairment. Persistent cardiometabolic complications include chest pain or tightness.[5] Vaccinated individuals are susceptible to breakthrough infection and the effects of long COVID as well; up to 19% of individuals with breakthrough cases have reported having at least one symptom of long COVID (loss of smell, cough, fatigue, weakness, shortness of breath, or myalgia persisting beyond 6 weeks).[10]

In this review, we examine the current understanding of the pathophysiology of kidney injury in COVID-19 infected patients and its potential long-term effects on the kidney, which may promote chronic kidney disease (CKD) incidence and progression after COVID-19. We explore how acute kidney injury (AKI), as well as chronic and end-stage kidney disease (ESKD), are significant risk factors for mortality from COVID-19. Finally, we explore how racial and ethnic disparities may contribute to CKD risk in COVID-19 survivors.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN HOSPITALIZED PATIENTS WITH COVID-19

AKI is common in patients hospitalized for COVID-19. A recent systematic review and meta-analysis of 54 publications that included 30,639 patients found that the pooled prevalence of AKI was 28% (95% CI 22%−34%) among hospitalized patients and 9% (95% CI 7%−11%) required dialysis for AKI (Stage 3D).[11] Stage 3D AKI is even more common among patients with COVID-19 who require intensive care; in a multicenter study in the United States, Gupta *et al.* found that 637 of 3,099 patients (21%) admitted to intensive care required renal replacement therapy for AKI.[12] Well-designed studies prior to COVID-19 estimated that only 5% of patients in intensive care typically require RRT.[13] Several studies have compared the risk of AKI and need for dialysis in patients hospitalized with COVID-19 to patients hospitalized with other respiratory infections (i.e. influenza.) and found a substantially higher risk in COVID-19.[14-16] However, over time, the rate of AKI in hospitalized patients with COVID-19 appears to be declining; Charytan *et al.* determined there was a 32.5% AKI incidence in patients hospitalized in New York City in March 2020, which decreased to 17.2% of hospitalized patients with COVID-19 in August 2020.[17] Dellepiane and colleagues showed that AKI rates in a NYC healthcare system continued to fall though fall and winter of 2020.[18]

As for other conditions, preexisting CKD is an important risk factor for AKI. A prospective cohort study of 701 patients with COVID-19 found that the incidence of AKI was significantly higher in patients with elevated baseline creatinine than in patients with normal baseline creatinine (11.9% vs. 4.0%).[19] A study of 3,993 hospitalized patients in New York City found that CKD was an independent predictor of severe AKI (adjusted odds ratio [aOR] 2.8, 95% CI 2.1 to 3.7).[20,21]

Even though AKI is a common adverse sequela of COVID-19, it is widely underrecognized by the public. While most Americans are aware of effects of COVID-19 commonly reported in the media, such as acute respiratory failure, pneumonia, and acute respiratory distress syndrome (58%, 54%, 52%, respectively), a National Kidney Foundation-Harris Poll survey conducted in May 2020, found that only 17% of Americans are aware that COVID-19 can result in AKI. This is not unique to COVID-19 related AKI, as awareness of kidney disease is low in other settings, including among the lay public, healthcare workers, and even among patients who develop AKI and CKD.[22-25] Lack of awareness of the risks of COVID-19-associated kidney disease may hinder efforts to ensure appropriate post-AKI follow-up to diminish the effects of kidney disease on the individual and society.

ACUTE, CHRONIC AND END-STAGE KIDNEY DISEASE AS RISK FACTORS FOR MORTALITY FROM COVID-19

Preexisting CKD and ESKD have been among the most reproducible and robust predictors of severe and critical illness in patients with COVID-19. A prospective cohort study of 701 hospitalized patients with COVID-19 showed that patients with kidney disease had a 2 to 4-fold higher risk for in-hospital death depending on how kidney disease is defined. Proteinuria and hematuria of any degree, elevated baseline blood urea nitrogen, elevated serum creatinine, and AKI greater than stage 2 (≥ 2-fold rise from baseline)

were all associated with in-hospital death after adjustment for age, sex, disease severity on admission, comorbidities, and lymphocyte count.[19] Chan *et al.* found a 50% mortality rate among patients with AKI, compared to 8% in patients without AKI.[26] Gupta *et al.* found that critically ill patients requiring renal replacement therapy for AKI had a 55% mortality rate.[27] Among critically ill patient who require both mechanical ventilation and dialysis, mortality rates exceed 70%.[28]

A meta-analysis conducted in 2020 from four studies including 1,389 unique patients found a significant association between CKD and severe COVID-19 [OR 3.03 (95% CI 1.09−8.47), $I2 = 0.0\%$, Cochran's Q, $P = 0.84$], despite the fact that none of the studies found this association individually.[29] A separate meta-analysis with data from 9 studies found that CKD was associated with a greater risk of mortality (unadjusted RR 3.25 [1.13 to 9.28]).[30] The OPENSAFELY study analyzed approximately 17 million adults in England from February 1, 2020 to May 6, 2020 and found that eGFR 30-60 and eGFR <30 were associated with a 1.33 and 2.52 increased risk of mortality from COVID-19 in fully adjusted models.[31]

Logistical factors involved in how patients with CKD and ESKD access care may have additionally placed these patients at higher risk of acquiring COVID-19 during the first-wave of the pandemic. Patients with ESKD were unable to quarantine due to their need for dialysis and frequent health care interactions. According to a midsize national dialysis provider, in clinics with at least 1 case of COVID-19 during the first 3 months of the pandemic in the United States, 5.5% of all patients at those clinics became infected.[32] Severity was very high in the dialysis population as well: a retrospective cohort study of 7,533 patients with ESKD receiving dialysis in California found that among their 133 COVID-19 infected patients on dialysis, 57% of required hospitalization.[33] Per existing literature, mortality rates in patients with ESKD who were hospitalized for COVID-19 have ranged from 21%−32%.[33-37] The risk of mortality among patients on dialysis who were admitted to the intensive care unit due to COVID-19 exceeds 50%.[38]

Finally, patients with CKD and ESKD may be less likely to be eligible for COVID-19 treatments or trials. Remdesivir, the only antiviral therapy currently approved for hospitalized patients in the United States, was not initially studied in patients with eGFR < 30 mL/min/1,73m^2 due to concerns regarding accumulation of the drug, its active metabolite, and its cyclodextrin carrier.[39] However, multiple small case series have suggested remdesivir may be safe in patients with eGFR < 30 mL/min/1,73m^2 or on dialysis.[40-42] A *post hoc* analysis of clinical trial data showed that patients treated with remdesivir had less kidney function decline; 30% of patients receiving placebo experienced a decline in creatinine clearance, whereas only 15% of patients on a 5-day remdesivir course experienced a decline in creatinine clearance.[43] Studies summarizing the inclusion and exclusion criteria of clinical trials of therapeutics for COVID-19 have noted that kidney disease is an exclusion criteria in approximately half of trials.[44,45] Thus, in addition to being at high risk for poor outcomes, there is a lack of adequate evidence to inform treatment decisions in this group of high-risk patients.

There is likely a bidirectional relationship between COVID-19 and CKD: CKD increases the risk of severe COVID-19 and increased severity of COVID-19 leads to increased risk of acute and chronic kidney dysfunction. Patients with a high burden chronic comorbidities and frailty, and patients who are immunosuppressed, are at increased risk of both progressive CKD and severe COVID-19.

INCIDENT AND PROGRESSIVE CKD AS A LONG-TERM COMPLICATION OF COVID-19

Though the risk of AKI has been well characterized; the longer term sequela of COVID-19 on kidney function is unknown.[46] A study that used electronic health records from the Veterans Health Administration to conduct a high-dimensional assessment of long COVID reported increased risk of adverse kidney manifestations, including AKI, CKD, and urinary system infections that occurred even after the first 30 days following diagnosis of COVID-19.[47] Potential mechanisms driving CKD progression after COVID-19 can be largely grouped into three categories: unresolved tubular injury, micro or macrovascular injury, or podocytopathy/collapsing glomerulopathy (**Fig 1**).

Unresolved tubular injury contributing to CKD risk. Possible direct viral effects on the kidney from SARS-CoV-2 include endothelial damage from viral entry and complement activation, local inflammation/cytokine release, and collapsing glomerulopathy. The indirect effects of COVID-19 that can lead to AKI include volume depletion, hypotension/shock, rhabdomyolysis, as well as the common causes of in-hospital AKI, such as nephrotoxin exposure and sepsis.[46] An early autopsy series of patients who died due to COVID-19 in China found acute tubular injury ranging from mild to severe in all 26 patients studied.[48] The first autopsy series in the United States also found that acute tubular injury was the most prominent finding on light microscopy.[49]

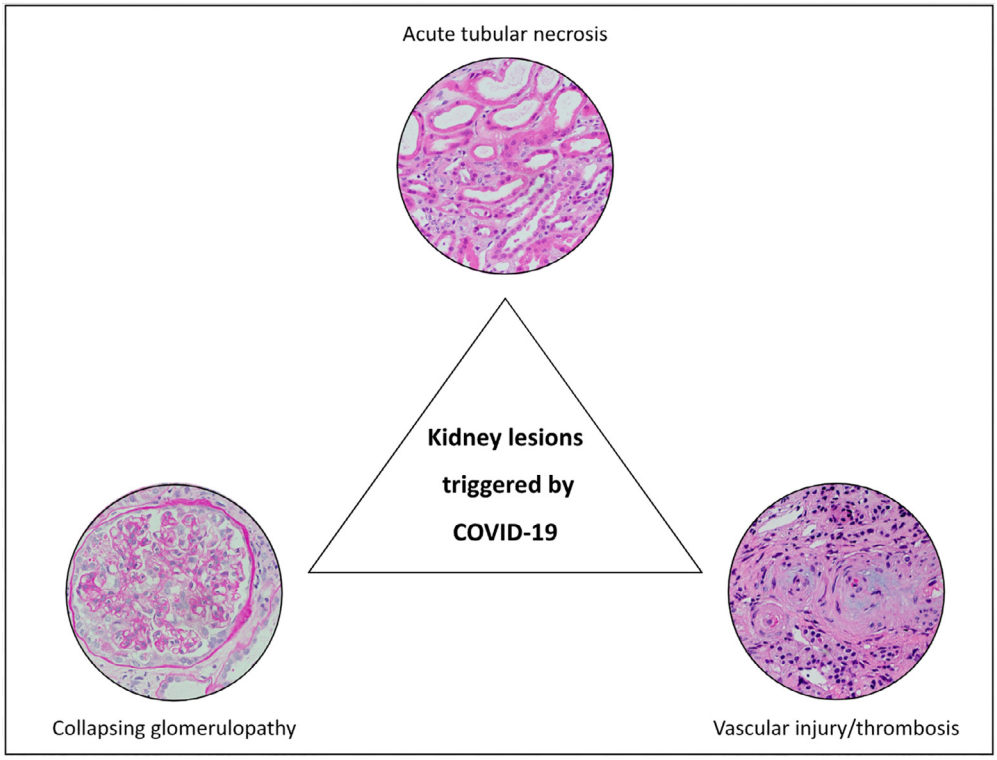


Fig 1. Pathologic findings in COVID-19 associated acute kidney injury. Representative histology (hematoxylin and eosin staining) of the three most-common kidney lesions associated with COVID-19, including acute tubular necrosis, collapsing glomerulopathy, and vascular injury and thrombosis.

Given the potential for severe AKI, the risk of CKD from unresolved acute tubular necrosis (ATN) may affect a significant number of patients with severe COVID-19 who survive to hospital discharge.

Acute tubular injury is most likely caused by local and systemic response to COVID-19 that can lead to hypotension, activation of the renin−angiotensin system, endothelial injury, activation of coagulation pathways, and mitochondrial injury.[49-51] Local release of cytokines in response to damage-associated and pattern-associated molecular patterns leads to recruitment of inflammatory cells and tissue damage. Neutrophil extracellular traps released by activated neutrophils have an important role in viral clearance, but they also contribute to local inflammation, immunothrombosis, and tissue damage.[52] Additionally, there are non-specific hemodynamic alterations that lead to AKI in COVID-19. Dehydration from poor oral intake and gastrointestinal manifestations can activate the renin-angiotensin system and impair renal perfusion. There is also a substantial burden of hospital-acquired AKI; patients with severe COVID-19 are commonly exposed to nephrotoxic medications and those who become critically ill may develop shock, low cardiac output, hypoxia, and hypotension.

Rhabdomyolysis is a rare but reported consequence of COVID-19 that may also lead to acute tubular injury via myoglobin precipitation and free radical release.[53] May *et al*. found that 8 of 240 (3.3%) of native kidney biopsies performed in patients with COVID-19 had myoglobin cast nephropathy, which was significantly elevated compared to the 0.1% incidence of myoglobin cast nephropathy in their biopsy database consisting of 63,575 controls.[54] The likelihood of AKI recovery in patients with myoglobin cast nephropathy is unknown.

To summarize the available literature reporting AKI recovery in patientst hospitalized with COVID-1, we performed a literature review using the natural library of medicine. Using the search terms “AKI recovery” or “Renal recovery” and “COVID-19″ we identified 60 articles. After the exclusions shown in **Fig 2**, we identified 24 unique cohort studies with ≥ 50 cases of hospitalized patients with COVID-19-related AKI that reported AKI recovery rates (**Table I**).[12,14,16,17,20,55-73] Although “full recovery” is variably defined in these studies, the proportion of surviving patients that experience a full recovery by hospital discharge ranges between 19% to 79%, with the majority of studies reporting that that >50% of survivors experience “kidney recovery” by hospital discharge.[16,20,56] Among

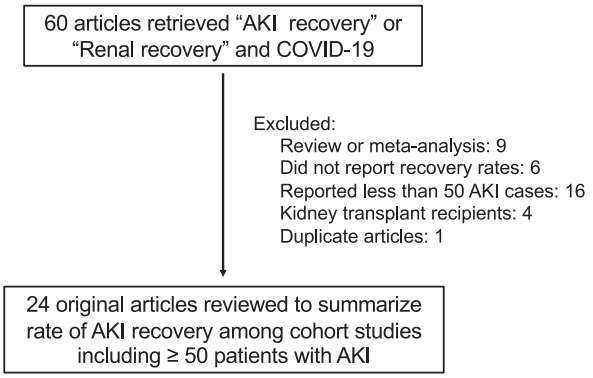


Fig 2. Identification of articles reporting AKI recovery rates in patients with Severe COVID-19

Abbreviations: AKI = acute kidney injury, COVID-19 = coronavirus disease 2019.

those with AKI severe enough to require RRT, most survivors can discontinue RRT prior to hospital discharge, with continued dependence on RRT at hospital discharge ranging from 8% to 34% of surviving patients (**Table I**).[12,20,55,58,59] Though only a small number of publications provide post-discharge kidney function follow-up, the available literature suggests that among those surviving 30-90 days, kidney recovery rates are very high, ranging from 75% to 91%.[14,56,57] A prospective, uncontrolled cohort study followed 95 patients with AKI who survived 4 months and found new-onset CKD had developed in only 2 patients (2.1%);[69] this suggests that the vast majority of patients with COVID-19 induced AKI who survive will recover kidney function.

Table I. AKI recovery in COVID-19 associated AKI.

Reference	Population	Recovery
Overall AKI		
Birkelo, Kidney Int, 2021[14]	AKI	1024 hospitalized veterans with AKI, among those surviving > 90 days, 91% recovered to within 20% BL SCr
Ng Am J Kid Dis 2020[55]	AKI	3216 patients with AKI, 51% survived, among survivors, 74% with at least partial recovery (< 33% from peak Scr or < stage 1 AKI)
Chan J Am Soc Nephrol 2021[20]	AKI	1835 patients with AKI, 832 discharged alive, 65% to SCr within ≤0.3mg/dL and within 25% of BL SCr
Bowe Clin J Am Soc Nephrol, 2021[56]	AKI	1655 hospitalized veterans with AKI, 47% recovered to within 0.3mg/dL of BL SCr at discharge
Strohbehn, Kidney Int Rep, 2021[16]	AKI	251 patients with AKI, 56% recovered to within 20% of BL SCr by discharge
Zhang, BMC Infectious Diseases 2021[57]	New-onset elevated SCr during COVID-19 hospitalization	143 patients discharged alive, during a 4-month median follow-up 91% normalized (serum creatinine ≤84 μmol/L (0.95mg/dL) in women, ≤104 μmol/L (1.18 mg/dL) in men with negative urine protein)
Nugent, JAMA Open Net, 2021[60]	AKI	786 patients with AKI, 182 were discharged alive, 82.4% recovered by discharge
Sang, BMC Pulm Med, 2020[61]	AKI	92 patients with AKI, 16 (17%) improved by discharge
Hittesdorf, Blood Purif, 2021[62]	AKI in ICU	76 patients with AKI, 48 were discharged alive, 77% recovered to within 1.5-fold BL by discharge, 82% by 90 days
Moledina, Am J Kid Dis, 2021[63]	AKI	796 patients with AKI, 462 (58%) recovered to within 1.5-fold BLby discharge, and
Teoh, JASN, 2021[64]	AKI	66 patients with AKI, complete recovery (within 1.5-fold BL) noted in 87% by 30 days and 92% by 90 days
Saggi, Clin Med Insightts Circ Respir Pulm Med, 2020[65]	AA patients with AKI	75 patients with AKI, 65% experienced either a 50% increase in eGFR or discontinued RRT by discharge.
Charytan, Kidney Int Rep, 2021[17]	AKI	1386 patients with AKI, 678 (49%) were discharged alive. 523 (77%) recovered to within 0.3mg/dL above BL SCr
Abdallah, Saudi J Kidney Dis Transpl, 2021[66]	AKI in ICU	61 patients with AKI, 37 (61%) were discharged alive, 11 had full or partial recovery and 26 remained on RRT
Rahimzadeh, Kidney Blood Press Res, 2021[67]	AKI	194 patients with AKI, 117 (60%) were discharged alive, only 28% recovered to within 0.3mg/dL of baseline by hospital discharge and 72% did not fully recover by discharge
Lumlertgul, Ann Intensive Care, 2021[68]	AKI in ICU	240 patients with AKI, 158 (66%) were discharged alive and 82% recovered to within 1.5-fold BL SCr by discharge and 91% recovered by 90 days
Sampathkumar, J Assoc Physicians India, 2021[73]	AKI	Among 52 hospitalized patients with AKI 29 (55%) were discharged alive. AKI recovered in 41% by hospital discharge and 72% followed 4-6 weeks post-discharge

(*continued*)

Table I. (*Continued*)

Reference	Population	Recovery
Morin, JAMA, 2021[69]	AKI	Among patients 95 patients with AKI surviving 4 months, only 2 (2.1%) developed new-onset CKD
Chaudhri, Kidney Blood Press Res, 2020[70]	AKI	63 patients with AKI, 79% had complete recovery (to BL or normal range) by hospital discharge
AKI requiring RRT		
Birkelo, Kidney Int, 2021[14]	AKI requiring RRT	1517 hospitalized veterans with AKI, 12% required acute RRT, 7% remained on RRT at discharge
Chen, Kidney Int, 2021[71]	AKI receiving acute PD	94 patients. 51 (54%) survived 30 days, 21 recovered off PD, 30 remained on PD.
Charytan, Kidney Int Rep, 2021[17]	AKI requiring RRT	237 received RRT for AKI, 66 were discharged alive, 41 (62%) discontinued RRT prior to discharge
Eriksson, J Crit Care, 2021[72]	AKI requiring RRT	82 patients in ICU with AKI requiring continuous RRT, 45 (55%) survived to hospital discharge. Among 42 patients with a post-hospitalization SCr, 31 (74%) recovered to within 1.5-fold BL SCr.
Ng, Am J Kid Dis, 2020[55]	AKI requiring RRT	638 had AKI requiring RRT, 108 were discharged alive, 36 (33%) of survivors remained on RRT
Chan J Am Soc Nephrol, 2021[20]	AKI requiring RRT	347 with AKI requiring RRT, 87 were discharged alive, 26 (30%) of survivors remained on RRT
Stevens, PLOS One, 2020[58]	AKI requiring RRT	115 patients with AKI requiring RRT, 57 were discharged alive, 10 (18%) of survivors remained on RRT
Gupta, J Am Soc Neph, 2021[12]	AKI requiring RRT in ICU	637 patients with AKI requiring RRT, 216 were discharged alive, 73 (34%) of survivors remained on RRT, 26% had partial AKI recovery, 40% complete AKI recovery (within 0.35mg/dL BL)
Stockmann, Kidney Int, 2021[59]	AKI requiring RRT in ICU	74 with AKI requiring RRT, 37 were discharged alive, 3 (8%) of survivors remained on RRT, 23 (62%) had full AKI recovery at median of 151 days

All publications that reported on the outcomes of ≥50 patients with COVID-19-associated-AKI were included in this table. Abbreviations: AKI, acute kidney injury; AA, African American; SCr, serum creatinine; RRT, renal replacement therapy; ICU, intensive care unit; BL, baseline; PD, peritoneal dialysis

However, it is important to note that serum creatinine level is an insensitive marker of kidney damage; and estimates of recovery must take into account that patients often lose muscle mass during the course of critical illness, which may make creatinine-based eGFR estimates less reliable.[69] Although in many patients serum creatinine returns to near-normal levels following AKI, the kidneys may not completely recover and studies with longer follow-up are needed.

Finding the appropriate populations to compare rates of AKI recovery and eGFR decline after hospitalization is challenging. A cohort study of 182 hospitalized patients with COVID-19 associated AKI found a greater rate of post-hospitalization eGFR decline compared to 1,430 hospitalized patients with AKI not associated with COVID-19, even after adjustment for comorbidities and AKI severity.[74] in contrast, two studies that compared AKI outcomes in patients with COVID-19 to patients hospitalized with influenza found very similar rates of medium to long-term recovery and eGFR decline.[14,16] Notably, most observational studies of AKI recovery have very high rates of loss to follow-up; thus, to understand the burden of CKD and eGFR decline, prospective studies that include assessment of blood and urine biomarkers are necessary.

Micro or macrovascular injury/endothelial activation contributing to CKD risk. Early autopsy reports suggested that microvascular injury may occur in multiple organs, with prominent endothelial lung injury demonstrated on autopsies.[75] Segmental fibrin microthrombi were also observed in the glomeruli of the first kidney autopsy data from China.[48] Since then there have been multiple case reports of thrombotic microangiopathy (TMA) identified by kidney biopsy and autopsy in patients with COVID-19.[76-81] However, May *et al.* reviewed 240 native kidney biopsies and found that only 3.3% had evidence of TMA, which was not significantly elevated compared to the non-COVID-19 infected kidney biopsy control cohort.[54]

Thrombocytopenia, elevated LDH, and D-dimer are common in COVID-19, and may be a feature of disseminated intravascular coagulation. At the cellular level, it has been postulated that platelet activation may be part of the etiology of the prothrombotic state

seen in COVID-19, as SARS-CoV-2 can bind to platelets via angiotensin-converting enzyme 2, activating platelets.[82] Severe COVID-19 may lead to cytokine release syndrome, macrophage activation, and release of pathogen-associated and damage-associated molecular pattern molecules that lead to release of tissue factor and activation of coagulation factors.[83] Complement activation may also upregulate tissue factor and lead to loss of thrombomodulin which promotes hypercoagulability.[53,84] Emerging evidence suggest that excessive formation of neutrophil extracellular traps plays an important role in the pathophysiology of endothelial injury and immunothrombosis that characterize severe cases of COVID-19.[52,85-87] COVID-19 triggered endothelial dysfunction may exacerbate underlying chronic diseases that are associated with chronic endothelial dysfunction and are major causes of CKD, such as hypertension, diabetes, and atherosclerosis.

Macro-vascular thrombosis can also occur in COVID-19. Pulmonary embolisms, strokes, right ventricular thromboses, aortic thromboses, and kidney-related macrovascular events have all been documented in patients with COVID-19.[88] Renal artery thrombosis and renal vein thrombosis have both been documented, including cases with associated renal infarction; however, these are likely rare events.[88-92]

Collapsing glomerulopathy and podocytopathy contributing to CKD risk. Collapsing glomerulopathy is a well-documented complication of viral infections, most commonly human immunodeficiency virus infection (HIV), Epstein-Barr virus, cytomegalovirus, and parvovirus B19.[93] Recently, it has been reported that SARS-CoV-2 infection may be an additional "viral hit" that can cause collapsing glomerulopathy.[94]

Collapsing glomerulopathy is characterized by segmental or global glomerular tuft collapse with hypertrophy and hyperplasia of the overlying podocytes.[95-98] Collapsing glomerulopathy is associated with high-risk *APOL1* genetic variants (G1/G1, G2/G2, or G1/G2). The vast majority of cases of documented COVID-19 associated collapsing glomerulopathy have been reported in patients of West African or African-American descent. It is estimated that 10% to 15% of African-American individuals have two high risk *APOL1* alleles, suggesting that a large proportion of the U.S. black population may be at risk for collapsing glomerulopathy.[99] May *et al.* reported that of 44 of 48 (92%) of patients with COVID-19-associated collapsing glomerulopathy had high-risk *APOL1* genotypes.[54]

Cases of COVID-19 associated collapsing glomerulopathy typically present with AKI, heavy proteinuria, and hypoalbuminemia.[95,100-105] Acute tubular injury is also found in the vast majority of cases of COVID-19 associated collapsing glomerulopathy.[54] COVID-19 associated collapsing glomerulopathy can occur in patients with mild respiratory symptoms suggesting that, unlike COVID-associated ATN or rhabdomyolysis, the risk of COVID-19 associated collapsing glomerulopathy is not directly correlated to the severity of respiratory symptoms related to COVID-19.[95]

Some patients have presented with minimal change disease or focal segmental glomerulosclerosis without collapsing features on biopsy, suggesting that there may be a spectrum of podocytopathy affecting patients with COVID-19. May *et al.* performed APOL1 genotyping on black or Hispanic patients who developed other forms of focal segmental glomerulosclerosis or minimal change disease and found that 8 of 11 (72.7%) had high risk APOL1 genotypes, suggesting there may be a spectrum of APOL1 related kidney disease triggered by COVID-19.[54] It is likely that cases of COVID-19 associated collapsing glomerulopathy and podocytopathy reported in the literature represent a severe phenotype of this disease. Prospective studies are needed to determine the incidence of proteinuria after COVID-19. Furthermore, because collapsing glomerulopathy may occur in patients with mild COVID-19, even patients who do not require medical attention may still be at risk of developing overt or subclinical collapsing glomerulopathy that may only be detected by incidental lab testing months or years after infection. This is a particularly important consideration given the high prevalence of high risk *APOL1* genotypes among African-Americans.[99]

The exact mechanism by which SARS-CoV-2 infection leads to collapsing glomerulopathy has not been elucidated. Antiviral pathways, particularly interferon gamma upregulation, may be important inducers of kidney disease in individuals with the high-risk *APOL1* genotype.[53,94,106] There has been conflicting evidence as to whether viral particles and RNA from SARS-CoV-2 are directly deposited in the kidney.[107] Evidence for and against direct viral infection was well summarized recently by Hassler and colleagues.[108] In their review of studies to date, the presence of SARS-CoV-2 was suggested by at least one of the methods used (immunohistochemistry, RT-PCR, or *in situ* hybridization) in kidneys from 102 of 235 patients who underwent biopsy (43%).[108] The largest series of kidney biopsies by May *et al.* was unable to confirm SARS-CoV-2 RNA by *in situ* hybridization.[54] There is remaining uncertainty, with a need for more kidney biopsy data, particularly earlier in the disease course. However, even without direct invasion, viral-induced changes in the microenvironment surrounding the podocytes (increased cytokine production) can trigger collapsing glomerulopathy.[98] *APOL1* risk alleles may

also play a mechanistic role—viral infections stimulate host interferon production which stimulates *APOL1* gene expression, potentially exacerbating the deleterious effects of *APOL1* polymorphism on kidney function and leading to collapsing glomerulopathy.[109]

May *et al*. sought to determine if COVID-19 associated collapsing glomerulopathy was enriched in patients with COVID-19 by conducting a multi-center study that compared 240 native kidney biopsies obtained in COVID-19 infected patients to a 5-year U. S. kidney pathology database as a control.[54] They found that collapsing glomerulopathy occurred in 25.8% of the COVID-19 cases compared to 1.8% in the overall 5-year database and 28% of patients with HIV. This study highlights the importance of benchmarking against control patients. It is also possible that some kidney pathologies develop randomly and concurrently with COVID-19, which is challenging to know when relying on case reports and case series that may suffer from publication bias. Prospective studies with carefully matched controls will be needed to estimate the risk of new-onset proteinuria and glomerular disease after COVID-19.

RACIAL AND ETHNIC DISPARITIES AND THE RISK OF CKD AFTER COVID-19

COVID-19 has disproportionately affected racial and ethnic minority populations in terms of both overall infection and disease mortality rates. Black and Latinx patients are more likely than white patients to test positive for COVID-19.[110] As of June 2021, the CDC reported that 28.8% of COVID-19 cases in the U.S. occurred in Hispanic or Latinx individuals, despite only representing 18.5% of the population. **Fig 3A** shows the breakdown of COVID-19 cases in the U.S. as well as the breakdown of the overall U.S. population.[111] Among hospitalized patients, Black patients were less likely than white patients to become severely ill or die; however, Black patients had a higher out-of-hospital COVID-19 mortality rate, and the overall mortality rate in Black Americans is over twice the COVID-19 mortality rate in white Americans.[110,112] Sickle cell disease, which primarily affects people of African descent, may also be a risk factor for hospitalization and death from COVID-19.[112,113] COVID-19 associated kidney disease already appears to be affecting blacks disproportionately; in the study by May *et al.* black patients were disproportionately impacted, making up 44.6% of the 240 native COVID-19 kidney biopsies, compared to 15.4% of patients in the U.S. biopsy database that served as a control.

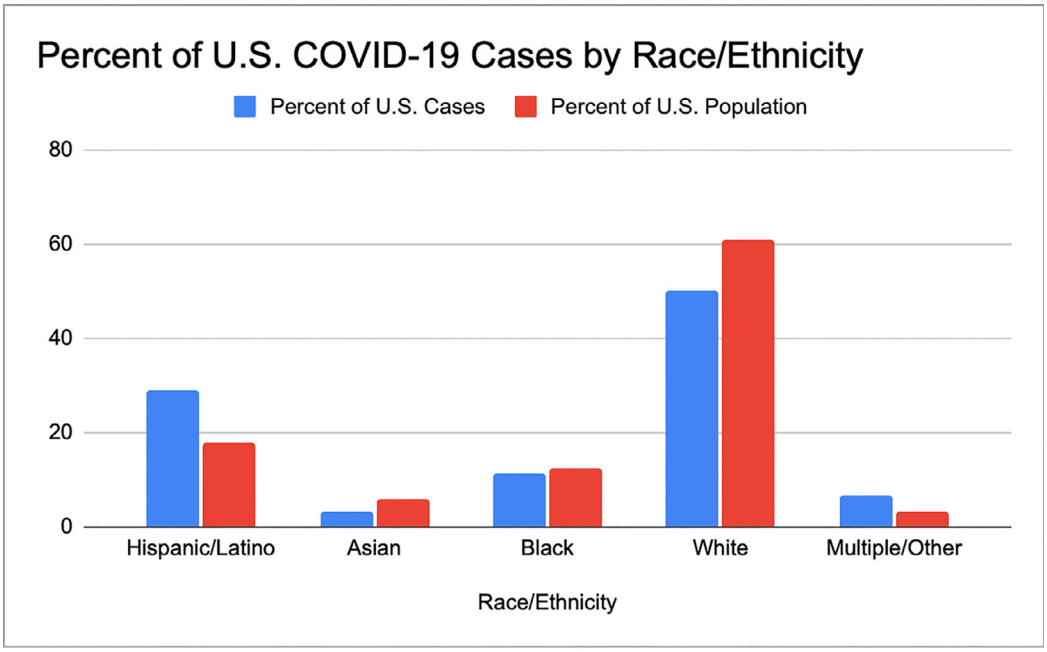
Disparities in post-hospital care may also affect the risk of CKD. It is recommended that patients with AKI (including COVID-19-associated AKI) receive post-hospital care with a nephrologist to ensure resolution of AKI, optimize blood pressure, and minimize exposure to potential nephrotoxins. There are well-documented disparities in post-hospitalization care in minority populations, thus disparities in access to subspecialty care and post-hospitalization follow-up may contribute to CKD burden faced by members of racial and ethnic minority groups affected by COVID-19.[114] The majority of Medicaid recipients are black or Latinx; Medicaid recipients are overall less likely to be transferred to a long-term care or skilled nursing facilities after being in the intensive care unit.[114] Black and Latinx patients are more likely to be discharged home, with black patients less likely than white patients to see improvements in their daily life after critical illness.[115-117] Black and Latinx patients who are discharged to a skilled nursing facility often go to facilities with higher readmission rates and lower rates of successful discharge into the community.[118] To minimize the risk of CKD after COVID-19-related AKI, it is critical to ensure patients have access to post-acute care and nephrology care when clinically indicated.

Disparities also manifest in differential rates of COVID-19 vaccination. As of June 20, 2021, the CDC reported that out of 92 million vaccinated people in the United States, 8.7% were black and 14.1% were Latinx despite these groups making up 12.5% and 18.5% of the U.S. population, respectively (**Fig 3B**).[111]

Clinicians and the public should be aware that the confluence of biological, social, and economic factors, as well as systemic and institutional racism, may lead to an increased burden of CKD in patients from racial and ethnic minority populations who develop COVID-19 (**Fig 4**).

CONCLUSION AND FUTURE DIRECTIONS

Kidney injury is an important and common adverse outcome of COVID-19. Both AKI and CKD are associated with severe COVID-19 and risk of death. COVID-19 may lead to CKD in survivors via unresolved acute tubular injury that occurs in patients with severe disease; as a result of podocytopathy, which has been strongly linked to high risk *APOL1* genotypes; or by causing endothelial or vascular injury, which promotes CKD progression. Although several studies suggest that AKI rates in COVID-19 may be higher than matched controls and recovery by hospital discharge may be lower than matched controls, medium to long-term recovery of AKI seems to be high among patients



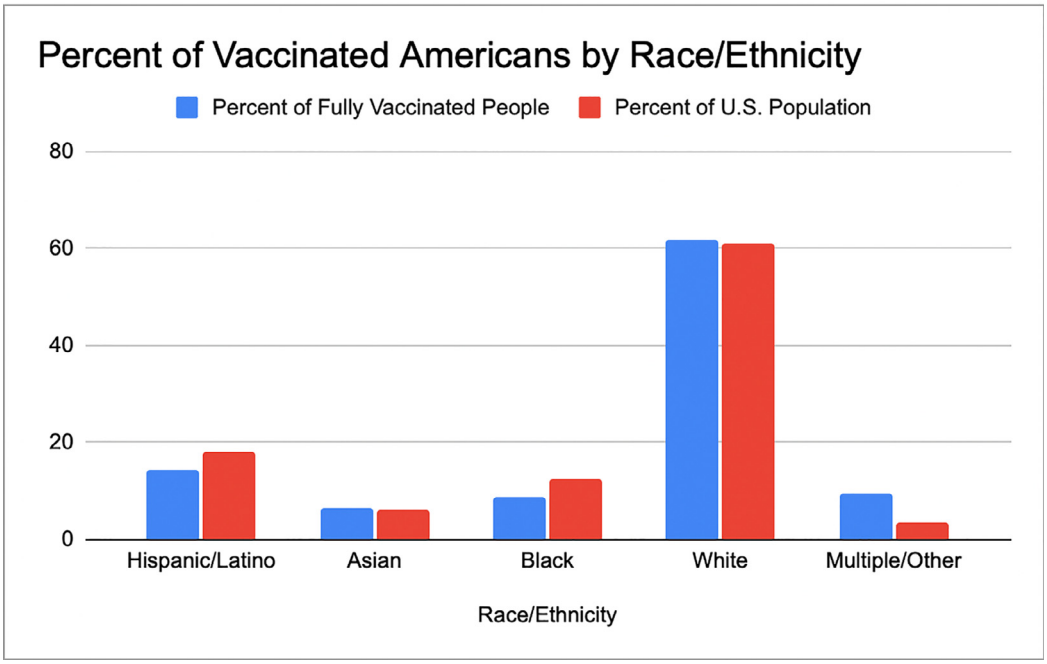


Fig 3A. Rate of COVID-19 infection among racial and ethnic groups in the U.S. population. The percentage of patients infected with COVID-19 broken down by self-reported racial and ethnic groups. The multiple/other group includes Native Americans, Pacific Islanders/Hawaiians, and other/multiple. The number of COVID-19 infected individuals is disproportionately high in Hispanic populations when compared to the percentage of the United States population this group makes up, according to data from the CDC accessed June 20, 2021.[111]. **Fig 3B** Rate of COVID-19 vaccination among racial and ethnic groups in the U.S. population. The percentage of COVID-19 vaccinated patients broken down by self-reported racial and ethnic groups. The multiple/other group includes Native Americans, Pacific Islanders/Hawaiians, and other/multiple. The COVID-19 vaccination rate is disproportionately low in Black and Hispanic groups when compared to the percentage of the United States population these groups make up, according to data from the CDC accessed June 20, 2021.[111]

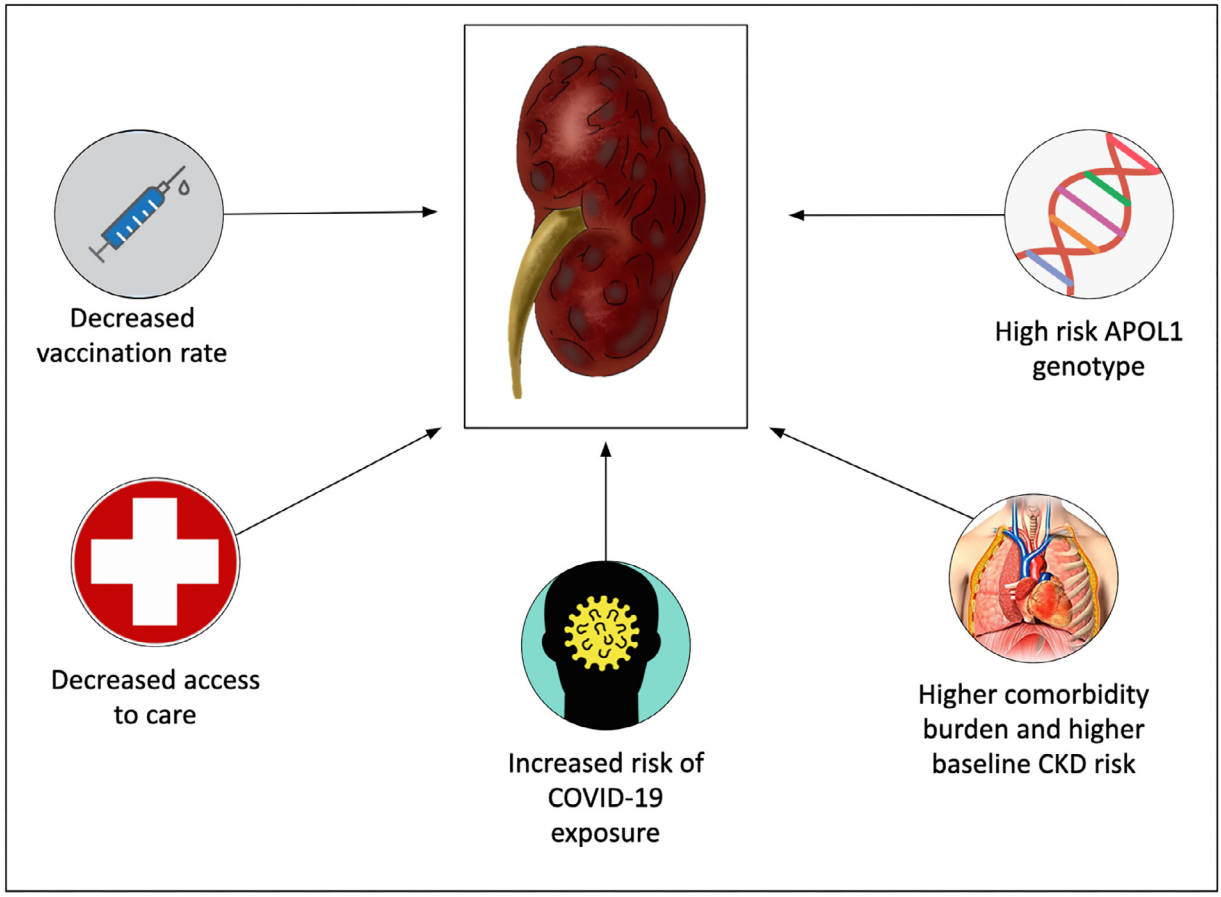


Figure 4. Factors contributing to increased risk of adverse kidney outcomes among racial and ethnic minorities. Several factors increase the risk of deleterious kidney outcomes in racial and ethnic minorities. These include decreased COVID-19 vaccination rate, decreased access to care, increased risk of COVID-19 exposure, higher comorbidity burden and baseline CKD risk, and increased prevalence of the high risk APOL1 genotype in these populations. Abbreviations: CKD = chronic kidney disease.

who are followed after hospital discharge. The true burden of CKD after COVID-19 has not yet been accurately ascertained, and we are limited in estimating CKD risk from observational datasets due to the high rates of loss to follow-up. Prospective studies that longitudinally measure kidney function and proteinuria are needed. Hopefully, this will be addressed through the Researching COVID to Enhance Recovery (RECOVER) cohort studies and other planned prospective studies.[119]

RESEARCH DATA

Not applicable

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