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Kidney involvement is common in coronavirus disease-2019 (COVID-19), and our understanding of the effects of COVID-19 on short- and long-term kidney outcomes has evolved over the course of the pandemic. Initial key questions centered on the spectrum and degree of acute kidney injury (AKI) in patients hospitalized with severe COVID-19. Investigators worldwide have explored the association between COVID-19–associated AKI and short-term outcomes, including inpatient mortality and disease severity. Even as treatments evolved, vaccinations were developed, and newer viral variants arose, subsets of patients were identified as at continued high risk for major adverse kidney outcomes. In this review, we explore key topics of continued relevance including the following: (1) a comparison of COVID-19–associated AKI with AKI developing in other clinical settings; (2) the ongoing controversy over kidney tropism in the setting of COVID-19 and the potential for competitive binding of the severe acute respiratory syndrome coronavirus 2 virus with angiotensin converting enzyme-2 to prevent viral cell entry; and (3) the identification of high-risk patients for adverse outcomes to inform long-term outpatient management. Patients at particularly high risk for adverse kidney outcomes include those with APOL1 high-risk genotype status. Biomarkers of injury, inflammation, tubular health, and repair measured in both the blood and urine may hold prognostic significance.

T he severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has continued to affect people across the world for over 2 years,1,2 with the novel coronavirus disease-2019 (COVID-19) pandemic persisting as new variants have arisen.3 Acute kidney injury (AKI) has been well described in patients with COVID-19, especially in patients hospitalized with severe COVID-19 early in the pandemic.4-6 We and others have explored risk factors for both short- and intermediate-term adverse kidney outcomes in patients hospitalized with COVID-19,7,9 and more recent work has explored longer-term effects of COVID-19 on kidney function.10,11 However, with SARS-CoV-2 variants arising over time and continued concerns about future strains evading vaccine-mediated immunity, it becomes increasingly important to identify the patients at greatest risk for severe COVID-19 and adverse post–COVID-19 outcomes. From a kidney standpoint, such major adverse kidney events (MAKE) include the risk of COVID-19–associated AKI and long-term accelerated decrease in kidney function. Central to the question of MAKE in the setting of COVID-19 is the kidney tropism associated with SARS-CoV-2 infection, given the high expression of angiotensin converting enzyme-2 (ACE2) receptors in the kidney, a continued area of controversy. In this review, we synthesize recent advances in the study of COVID-19–associated kidney injury while highlighting several areas of ongoing and future research: the comparison of COVID-19–associated AKI with AKI in other clinical settings; kidney tropism in the setting of COVID-19; and active research to identify key subgroups of patients at the highest risk for major adverse kidney events, including AKI and long-term CKD.

COVID-19–ASSOCIATED AKI IN COMPARISON WITH AKI IN OTHER CLINICAL SETTINGS

In an editorial published early in the course of the global pandemic, Kellum et al12 identified several similarities and distinctions between AKI associated with COVID-19 compared with other causes of sepsis. They also raised the question of whether COVID-19–associated AKI should be conceptualized or managed differently from general sepsis-associated AKI, which set the framework for future studies. Early studies evaluating histopathologic evidence of kidney tissue at autopsy suggested acute tubular injury as the predominant cause of AKI in the vast majority of patients dying from COVID-19, with the clear caveat being that these studies were conducted using postmortem samples.13,14 Alexander et al15 compared COVID-19–associated AKI with sepsis-associated AKI using a
multi-omics approach. These investigators investigated kidney tissue from 17 patients who died from COVID-19 compared with samples from 14 patients without COVID-19, which served as controls: 7 with sepsis-associated AKI and 7 with non-sepsis-associated AKI. All 17 patients who died from COVID-19 had evidence of at least mild acute tubular injury on histopathologic examination. Using spatial transcriptomics and proteomic analysis, these investigators found similar patterns of decreased oxidative phosphorylation, with up-regulation in the ceramide signaling pathway and microvascular dysfunction/inflammation similar to that seen in sepsis-associated AKI, findings not observed in non-sepsis-associated AKI.

Outside of infectious etiologies of AKI, we sought to compare the degree of kidney injury and inflammation in patients with COVID-19 with AKI in other clinical settings (Fig. 1). Comparison groups included patients after cardiac surgery (from the Translational Research Investigating Biomarker Endpoints in AKI Study cohort), patients after brain death before kidney donation (Deceased Donor Study cohort), and patients in the setting of exercise stress (marathon-associated AKI). Using pre—cardiac surgery biomarker levels as a reference, we noted that among patients with COVID-19—associated AKI, 40%, 50%, and 60% of patients with stages 1, 2, and 3 AKI, respectively, had kidney injury molecule-1 (KIM-1) levels higher than the 90th percentile of reference. Similarly, among kidney donors after brain death, 70%, 80%, and 90% of patients with stages 1, 2, and 3 AKI, respectively, had monocyte chemoattractant protein-1 (MCP-1) levels higher than the 90th percentile of reference. In general, the degree of kidney inflammation in the setting of COVID-19—associated AKI was comparable with other clinical settings.

Despite a number of similarities, however, several studies have highlighted how COVID-19—associated AKI is distinct in several respects from AKI in other settings, including its transmissibility, rapidity of infection, and disease severity. The incidence of AKI incidence has been observed to be increased in patients with COVID-19 compared with AKI from bacterial sepsis, severe influenza infection, or in the general hospitalized population. Moledina et al showed that COVID-19 was associated with AKI even after adjusting for key demographic factors, inflammatory markers, use of vasoressors, and other potential confounders indicating illness severity, compared with patients admitted within the same timeframe who were COVID-19—negative (adjusted hazard ratio [HR], 1.40; 95% CI, 1.29-1.53). These results further suggested the existence of mechanisms leading to AKI in the setting of COVID-19 that extend beyond general hospitalized AKI. Strohbehn et al used a historical cohort of patients with severe influenza infection as a more suitable comparison group to investigate adverse kidney outcomes in patients with severe COVID-19. These investigators showed that compared with patients hospitalized with influenza, patients hospitalized with COVID-19 had a greater risk of AKI incidence (HR, 1.58; 95% CI, 1.29-1.94), higher overall mortality (adjusted HR, 7.17; 95% CI, 4.78-10.76), and less AKI recovery at the time of hospital discharge. One
notable limitation for many of these translational and clinical studies surrounding COVID-19-associated AKI was the temporal trend in AKI incidence as new strains have emerged. After the initial wave of the pandemic, later waves have been associated with less disease severity, including mortality in general,\textsuperscript{18} with decreasing AKI incidence.\textsuperscript{19}

Similar to Alexander et al,\textsuperscript{15} Volbeda et al\textsuperscript{20} sought to compare COVID-19- and sepsis-associated AKI beyond clinical outcomes and histopathology, measuring differential messenger RNA gene expression in a similarly sized cohort of patients (6 with COVID-19—associated AKI, 27 with bacterial sepsis—associated AKI, and 12 reference samples from total nephrectomy). Volbeda et al\textsuperscript{20} found differential gene expression by clinical setting, with messenger RNA expression of the genes for neutrophil gelatinase-associated lipocalin (NGAL) and KIM-1 significantly lower in patients with COVID-19, compared with patients with bacterial sepsis, based on the relative lack of up-regulation in patients with COVID-19 compared with patients with bacterial sepsis, based on the relative lack of up-regulation of E-selectin, vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1).

**KIDNEY TROPISM IN COVID-19: EVIDENCE FOR AND AGAINST DIRECT KIDNEY INVOLVEMENT**

Based on previous studies from the early 2000s with the SARS-CoV-1 virus,\textsuperscript{3} it was quickly established that SARS-CoV-2 viral entry into cells occurs through the ACE2 receptor, which is highly expressed in the proximal tubule and, to a lesser extent, in the distal tubule and collecting duct.\textsuperscript{22} Indeed, early post-mortem findings in patients with severe COVID-19 showed acute tubular injury being nearly universally present on histology.\textsuperscript{14,23} Later studies of kidney biopsy findings in critically ill patients with COVID-19 similarly showed acute tubular injury as a prominent histologic finding (Table 1).\textsuperscript{24-27} However, it remained unclear to what extent such viral entry might have a direct impact on kidney injury and whether inhibition of viral entry at the level of the ACE2 receptor would make a clinically meaningful difference.\textsuperscript{28} Hassler et al\textsuperscript{28} argued that the detection of virus or viral particles within kidney tissue has been inconsistent, with a number of studies showing no presence of viral protein present on immunohistochemistry in biopsy studies, with the argument that viral-like proteins seen in post-mortem studies likely were artifacts.\textsuperscript{26,27,29} These investigators summarized the differences noted across several biopsy-based or postmortem tissue-based studies on the presence of either the spike protein or RNA using a variety of techniques, including immunohistochemistry, immunofluorescence, reverse-transcription polymerase chain reaction, or in situ hybridization.

In March of 2020, Batlle et al\textsuperscript{30} postulated that a soluble form of ACE2 competitively could bind to SARS-CoV-2, thereby preventing binding of the virus to the ACE2 receptor to limit viral entry and replication. However, studies would be required to provide evidence for these hypotheses in vitro and later in organoids and in vivo animal studies.

### Studies of Kidney Tropism in COVID-19: In Vitro and in Kidney Organoids

Monteil et al\textsuperscript{31} tested this experimentally by adding human recombinant soluble ACE2 (ACE2 1-740) to Vero-E6 cells inoculated with SARS-CoV-2. With varying degrees of ACE2 1-740 administered over

| Study            | Acute Tubular Injury | Glomerular Findings                          | Other Findings |
|------------------|----------------------|----------------------------------------------|----------------|
| Kudose et al\textsuperscript{24} (n = 14)* | Present in 11/14 | - Collapsing FSGS in 5/14  
                     |                      |     MCD in 1/14  
                     |                      |     Membranous GN in 2/14  
                     |                      |     Anti-GBM in 1/14  
                     |                      |     LN class IV/V in 1/14  
                     |                      |     Diabetic nephropathy in 4/13  
                     |                      |     Membranous GN in 2/13  
                     |                      |     IgAN in 1/13  
                     |                      |     Crescentic GN in 1/13  
                     |                      |     “Healed” collapse in 1/10  
                     |                      |     Collapsing FSGS in 7/14  
                     |                      |     FSGS in 3/14  
                     |                      |     Diabetic neph. in 1/14  
                     |                      |     MCD in 1/14  
                     |                      |     Pigmented casts in 1/14  
                     |                      |     TRIs in 4/13  
| Nasr et al\textsuperscript{25} (n = 13) | Present in 13/13 |                      |                
| Sharma et al\textsuperscript{26} (n = 10) | Present in 10/10 |                      |                
| Akilesh et al\textsuperscript{27} (n = 14)* | Present in 12/14 |                      |                |

*Among native kidney biopsy specimens only.
Abbreviations: AIN, acute interstitial nephritis; COVID-19, coronavirus disease 2019; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; IgAN, IgA nephropathy; LN, lupus nephritis; MCD, minimal change disease; TMA, thrombotic microangiopathy; TRI, endothelial tubuloreticular inclusion.
time, these investigators showed significant reductions in SARS-CoV-2 viral load. These investigators then used human embryonic stem cells to generate kidney organoids with proximal tubular–like epithelial cells present. As expected, addition of ACE2 1-740 reduced SARS-CoV-2 entry into these human kidney organoids in a dose-dependent fashion.

Further research explored the use of a novel, bioengineered, soluble, human ACE2 with an extended duration of action as a means of reducing SARS-CoV-2 infectivity of kidney organoids. Wysocki et al specifically fused a human short ACE2 variant with an albumin-binding domain (ABD) to increase the duration of action. They found similar reductions in SARS-CoV-2 viral loads using the ACE2 1-740 tested by Monteil et al, with similar efficacy using a novel, shorter, soluble, human ACE2-ABD, with the added benefit of a longer duration of action.

Studies of Kidney Tropism in COVID-19: Murine Models

In a follow-up study, Hassler et al performed in vivo studies of their soluble ACE2-ABD protein linked via a dimerization motif hinge-like 4-cysteine dodecapeptide (DDC), which, in addition to a longer duration of activity, showed a greater binding affinity for SARS-CoV-2. Using a lethal murine model of COVID-19 in cytokeratin-18 gene promoter-driven angiotensin I-converting enzyme 2 (k18-hACE2) mice expressing human ACE2 and therefore susceptible to SARS-CoV-2 infection, the bioengineered ACE2–1–618-DDC-ABD was administered both intranasally and intraperitoneally. Compared with human ACE2 (ACE2 1-740) and their original bioengineered ACE2 (ACE2 1-618-ABD), ACE2–1–618-DDC-ABD had the greatest binding affinity to SARS-CoV-2. Mice receiving ACE2–1–618-DDC-ABD experienced less weight loss, with marked improvements in clinical scores and reduced mortality compared with untreated animals, with only 1 in 10 treated mice needing to be killed. Histologic analysis showed that the treated animals had less severe tubular injury, based on NGAL tissue staining, compared with untreated mice.

Clinically, the presence of SARS-CoV-2 in the urine as a marker of disease severity or adverse outcomes remains controversial, with conflicting evidence. Frithioff et al evaluated for the presence of SARS-CoV-2 RNA in 81 critically ill patients with polymerase chain reaction–proven COVID-19. They were able to detect viral RNA in only six (7%) patients, and they did not find any association between either the presence of the virus or viral load (range, 300-2,800 copies/mL) with disease severity or mortality. A later study by Caceres et al found that the presence of SARS-CoV-2 virus in the urine was associated with AKI and worse kidney outcomes in 52 patients hospitalized with COVID-19. Specifically, the presence of SARS-CoV-2 virus in the urine was associated with AKI incidence and that viral load correlated with subsequent mortality.

IDENTIFYING PATIENTS AT HIGHEST RISK FOR MAKE AND EVALUATION OF LONG-TERM KIDNEY FUNCTION AFTER COVID-19

APOL1 High-Risk Genotype Status and MAKE After COVID-19

Early case reports and case series, later supported by larger studies conducted as the pandemic progressed, showed an association between APOL1 high-risk genotype status and collapsing glomerulopathy in patients with COVID-19. COVID-19–associated nephropathy was the term used to describe this phenomenon, similar to human immunodeficiency virus–associated nephropathy, and with a potentially shared pathophysiology.

Later studies explored clinical outcomes in patients with APOL1 high-risk genotype status diagnosed with COVID-19 (Table 2). Larsen et al showed, in a combined inpatient/outpatient cohort of 126 self-reported Black adult patients, that the presence of 2 APOL1 risk alleles (either homozygous G1/G1 or G2/G2 or heterozygous G1/G2) was associated with an increased risk of AKI incidence, AKI persistence, and need for kidney replacement therapy. More recently, Hung et al investigated how APOL1 risk variants were associated with the incidence of AKI and death in patients hospitalized with COVID-19. Of 990 patients in the Veterans Affairs health care system of African ancestry who were hospitalized with COVID-19 between March 2020 and January 2021, 125 (12.6%) patients had two APOL1 risk alleles. Among these patients, more than 50% developed AKI and nearly 20% died. Compared with patients without high-risk genotype status, those in the high-risk group had significantly higher odds of AKI incidence (odds ratio [OR], 1.95; 95% CI, 1.27-3.02) in fully adjusted analysis. Furthermore, these patients had significantly higher odds of developing Kidney Disease: Improving Global Outcomes stages 2 or 3 AKI (OR, 2.03; 95% CI, 1.37-2.99) and of mortality (OR, 2.15; 95% CI, 1.22-3.72). Notably, these investigators did not find any significant association between APOL1 high-risk genotype status and hematuria or proteinuria.

Blood Biomarker—Enriched Risk Prognostication in COVID-19

Clinically available biomarkers of disease severity, especially markers of inflammation such as D-dimer and C-reactive protein, have been associated with COVID-19 disease severity and short-term outcomes, including inhospital mortality. The use of novel biomarkers in both blood and urine has been studied extensively across
multiple clinical settings to improve the precision and
timeliness of AKI diagnosis, as well as to prognosticate
longer-term outcomes after AKI, both clinical and sub-
clinical,44-50 which increasingly is being investigated in
the setting of COVID-19 (Table 3). Soluble tumor necro-
sis factor receptor 1 (sTNFR1) has been associated with
adverse outcomes in patients with COVID-19, including
COVID-19 severity51 and intensive care unit (ICU) mor-
tality.52 With a focus on kidney-related outcomes, San-
cho Ferrando et al9 investigated the prospective
association between AKI in patients with COVID-19
and the biomarkers sTNFR1 and sTNFR2. A total of 122
patients with COVID-19 were consented at the time of
ICU admission and followed up longitudinally over the
course of their admission. Levels of sTNFR1 and
sTNFR2 were higher in patients with severe COVID-19
compared with healthy blood donors as controls. Fur-
thermore, sTNFR1 and sTNFR2 levels trended higher by
AKI stage \((P < .001\) and \(P = .02\), respectively). Finally,
sTNFR1 showed moderate to strong discrimination for
the prediction of 30-day mortality, after adjustment for
age and respiratory failure, as a marker of COVID-19
severity (area under the receiver operating characteristic
curve (AUC), 0.73; 95% CI, 0.62-0.84).

We similarly have shown that higher levels of plasma
sTNFR1 and sTNFR2 are both associated strongly with
increased risk of MAKE, defined in our study as devel-
oped AKI stage 3, dialysis, or death within 60 days
of admission in patients hospitalized with COVID-19.53
Furthermore, sTNFR1 showed strong discrimination for
the prediction of MAKE (area under the receiver operat-
ing characteristic curve, 0.88). A cut-point value for
sTNFR1 of 3,005 pg/mL had a negative predictive value
of 92%, suggesting that sTNFR1 may be used as a poten-
tial rule-out test for MAKE at the time of COVID-19
hospitalization.

### Urine Biomarker—Enriched Risk Prognostication in
COVID-19

Bezerra et al55 investigated the association of urinary
biomarkers of kidney injury with death in patients admi-
tered to the ICU with COVID-19. They measured urinary
levels of NGAL, KIM-1, MCP-1, and nephrin in patients
admitted to the ICU with COVID-19. In fully adjusted
Cox proportional hazards regression modeling, higher
levels of NGAL (above a cut-point of 118.8 ng/mg Cr)
were associated significantly with an increased risk of
death at 2 months.

Beyond mortality, our group has investigated the
association between urinary biomarkers of injury,
inflammation, and repair in patients hospitalized with
COVID-19 with MAKE (stage 3 AKI, new dialysis, or
dead within 60 days of hospital admission).7 We mea-
sured biomarkers using urine samples obtained through-
out the course of admission, showing that higher levels

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**Table 2. Summary of Cohort Studies Investigating APOL1 High-Risk Genotype Status and Kidney Outcomes in COVID-19**

| Study | Study Details | Patient Population | Comparison Groups | Outcomes |
|-------|---------------|--------------------|------------------|----------|
| May et al29 | Retrospective cohort study between March 2020 and March 2021 | 240 patients with PCR-positive COVID-19 who provided kidney biopsy specimens, of whom 107 underwent APOL1 genetic testing | Two APOL1 high-risk alleles (n = 65) versus zero or one APOL1 high-risk allele (n = 42) | Kidney pathology by high-risk allele status (two versus zero/one) |
| Larsen et al39 | Retrospective cohort study between March 2020 and October 2020 (New Orleans, LA) | 126 adult self-identified Black patients with PCR-positive COVID-19 | Two APOL1 high-risk alleles (n = 16) vs zero or one APOL1 high-risk allele (n = 110) | aOR of AKI, 4.4 (95% CI, 1.1-17.5) aOR of persistent AKI, 3.5 (95% CI, 1.1-11.6) aOR of kidney replacement therapy, 5.0 (95% CI, 1.0-24.4) |
| Hung et al41 | Retrospective cohort study between March 2020 and January 2021 | 990 adult participants of African ancestry in the VA Health System with PCR-positive COVID-19 | Two APOL1 high-risk alleles (n = 125) versus zero or one APOL1 high-risk allele (n = 865) | Overall aOR of AKI, 1.95 (95% CI, 1.27-3.02) aOR of death, 2.15 (95% CI, 1.21-3.72) aOR of kidney replacement therapy, 2.05 (95% CI, 1.21-3.42) |

Abbreviations: AKI, acute kidney injury; aOR, adjusted odds ratio; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephropathy; PCR, polymerase chain reaction; VA, Veterans Affairs.
| Study | Study Details | Patient Population | Control/Comparison Group | Biomarkers Tested | Kidney Outcomes |
|-------|---------------|---------------------|--------------------------|-------------------|----------------|
| **Blood** Sancho Ferrando et al⁹ | Prospective cohort study between March 2020 and September 2020 from the Uppsala PRONMED study cohort | 122 patients admitted to the hospital with COVID-19, with blood samples drawn within 6 days of ICU admission | 25 healthy blood donors | Plasma sTFNR1, sTNFR2 | • Significantly increased sTNFR1 and sTNFR2 in COVID-19 versus control \(P < .001\) • sTNFR1 levels increase with increasing AKI stage \(P < .001\) • sTNFR2 levels increase with increasing AKI stage \(P < .02\) |
| **Menez et al⁵³** | Prospective cohort study between April 2020 and June 2020 (Baltimore, MD, New Haven, CT, and New York, NY) | 576 patients admitted to the hospital with COVID-19, taking first available plasma sample for biomarker measurement | N/A | Plasma sTNFR1, sTNFR2, NGAL, YKL-40, KIM-1, IL2, IL10, IL18, sFTL1, TNF-α, Ang2 | Higher aHR of MAKE by increase in biomarker: • sTNFR1, 2.30 (95% CI, 1.86-2.85) • sTNFR2, 2.26 (95% CI, 1.73-2.95) Model discrimination for MAKE • AUC of sTNFR1, 0.88 (95% CI, 0.85-0.91) • AUC of sTNFR2, 0.83 (95% CI, 0.80-0.87) |
| **Urine** Menez et al⁷ | Prospective cohort study between April 2020 and June 2020 (Baltimore, MD, and New Haven, CT) | 178 patients admitted to the hospital with COVID-19, with urinary biomarkers measured on all available urine samples (n = 218 samples) | N/A | Urinary EGF, UMOD, IL18, YKL-40, albumin, NGAL, OPN, MCP-1, KIM-1 | Lower aHR of MAKE by increase in biomarker • EGF, 0.61 (95% CI, 0.47-0.79) • Higher aHR of MAKE by increase in biomarker • YKL-40, 1.18 (95% CI, 1.04-1.34) • NGAL, 1.34 (95% CI, 1.14-1.57) • MCP-1, 1.42 (95% CI, 1.09-1.84) • KIM-1, 2.03 (95% CI, 1.38-2.99) |
| **Xu et al⁵⁴** | Prospective cohort study between March 2020 and April 2020 (New York, NY) | 440 patients presenting to the Columbia University emergency department with COVID-19 | Historical cohort of 426 patients admitted to Columbia University between 2017 and 2019 | Urinary NGAL | NGAL at admission associated with AKI diagnosis \(P < .001\) • NGAL >150 ng/mL to diagnose stage 2/3 AKI - Sensitivity, 75% - Specificity, 80% • NGAL <150 ng/mL to rule out stage 2/3 AKI Negative predictive value, 0.95 (95% CI, 0.92-0.97) |

*Combined model containing NGAL, KIM-1, and proteinuria.

Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; Ang2, angiopoietin 2; AUC, area under the receiver operating characteristic curve; COVID-19, coronavirus disease 2019; EGF, epidermal growth factor; IL, interleukin; KIM-1, kidney injury molecule 1; MAKE, major adverse kidney events (stage 3 AKI, dialysis, death within 60 days of hospital admission); MCP-1, monocyte chemoattractant protein 1; N/A, not applicable; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; PRONMED, inflammatory mediators of acute kidney injury in intensive care; sFLT1, soluble fms-like tyrosine kinase 1; sTNFR1/2, soluble tumor necrosis factor receptor 1/2; TNF, tumor necrosis factor; UMOD, uromodulin; YKL-40, chitinase-3-like protein 1.
of urinary NGAL, KIM-1, and MCP-1 were associated with MAKE (Fig. 2). Conversely, higher levels of urinary epidermal growth factor, a marker of intact distal tubular repair and a surrogate for healthy repair mechanisms in the kidney, were associated with decreased risk of MAKE. Similarly, Xu et al.\textsuperscript{54} showed, in a cohort of 444 patients in New York City, that urinary NGAL measured on admission for COVID-19 was associated strongly with AKI diagnosis and severity. Furthermore, a urinary NGAL level greater than 150 ng/mL had 80% specificity and 75% sensitivity to diagnose acute kidney injury network stages 2 or 3 AKI. Furthermore, NGAL levels on admission were associated with an increased odds of sustained AKI, dialysis, death, and hospital length of stay.

![Figure 2. Risk of stage 3 AKI, new dialysis initiation, or death within 60 days of hospital admission by urinary biomarker level, indexed to urine creatinine and adjusted for the World Health Organization disease severity scale. Abbreviations: AKI, acute kidney injury; EGF, epidermal growth factor; IL, interleukin; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein 1; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; UMOD, uromodulin; WHO, World Health Organization; YKL-40, chitinase-3-like protein 1 Figure reprinted with permission from Menez et al.\textsuperscript{7}](image)

**LONG-TERM KIDNEY FUNCTION AFTER COVID-19**

Within months of the start of the pandemic, various groups investigated intermediate- to long-term health consequences after recovery from acute COVID-19, variously termed long-COVID syndrome, post-COVID-19 syndrome, and post-acute sequelae of COVID-19, among others (Table 4).\textsuperscript{56} Huang et al.\textsuperscript{54} reported long-term outcomes of up to 6 months after acute COVID-19 in patients surviving to hospital discharge. These investigators showed that patients commonly experienced long-term sequelae after recovery from the acute phase of COVID-19, including persistent dyspnea, fatigue, and weakness. In the subset of patients with available follow-up laboratory data, 35% of individuals who had experienced COVID-19–associated AKI had decreased estimated glomerular filtration rate (eGFR) at follow-up evaluation, compared with only 13% of individuals without COVID-19–associated AKI. Nugent et al.\textsuperscript{57} later investigated longer-term kidney function in patients with hospitalized AKI in the setting of COVID-19 compared with patients who experienced hospitalized AKI without COVID-19. After adjusting for demographic factors, baseline comorbidities, peak creatinine value in the hospital, and need for acute dialysis, patients with COVID-19–associated AKI had a greater decrease in eGFR over the course of follow-up evaluation compared with noninfected controls with hospitalized AKI (-14.0 mL/min per 1.72 m\textsuperscript{2}; 95% CI, -25.1 to -2.9).

Using data from the Veterans Affairs health care system, Bowe et al.\textsuperscript{58} evaluated MAKE for up to 365 days after a COVID-19 diagnosis in both the ambulatory and hospital settings. Compared with more than 1.6 million patients without a diagnosis of COVID-19, nearly 90,000 patients who survived for at least 30 days after COVID-19 diagnosis had a higher incidence of AKI and greater decreases in eGFR. Furthermore, patients with COVID-19 were more likely to develop end-stage kidney disease (HR, 2.96; 95% CI, 2.49-3.51). Not unexpectedly, among patients diagnosed with COVID-19, an excess eGFR decrease was greatest in hospitalized patients who developed AKI, compared with hospitalized patients without AKI and the nonhospitalized population.

Gu et al.\textsuperscript{11} later investigated kidney function trends in a cohort of 1,734 hospitalized patients with COVID-19 in China. Patients who experienced AKI had significantly greater decreases in eGFR compared with patients without AKI. In particular, patients with Kidney Disease: Improving Global Outcomes stage 3 AKI had a 17.8% (95% CI, 9.1-26.4) greater decrease in eGFR compared with patients without AKI.
| Study               | Study Details                                                                 | Patient Population                                                                 | Control/Comparison Group                                                                 | Outcomes                                                                                     |
|---------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Huang et al^8       | Ambidirectional cohort study of patients hospitalized with COVID-19, surviving to discharge from January 2020 to May 2020 (Wuhan, China) | 1,733 patients admitted to the hospital with COVID-19 who survived to hospital discharge | N/A                                                                                       | • Persistent fatigue or weakness in 63% of survivors  
• Anxiety/depression in 23% of survivors  
• Decreased eGFR in 35% of survivors at follow-up evaluation  
• Decreased eGFR* in 13% of survivors without AKI at time of acute COVID-19  

^In patients without AKI and with an eGFR higher than 90 at the time of acute COVID-19, 13% had an eGFR less than 90 mL/min per 1.73 m^2 at the time of follow-up evaluation.  

Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MAKE, major adverse kidney events (estimated glomerular filtration rate decrease ≥50%, end-stage kidney disease, or all-cause mortality); N/A, not applicable; VA, Veterans Affairs. |
SUMMARY

The long-term impact of COVID-19 after initial recovery from the disease has become more evident over time, with an increasing focus on the identification of patients at the highest risk for long-term adverse outcomes. Our conceptualization of COVID-19–associated kidney injury as a distinct entity has been informed by studies worldwide, although similarities exist between this and other infectious and inflammatory clinical scenarios. With proof-of-concept studies in vitro leading to newer studies in kidney organoids and mouse models, there is compelling evidence that a soluble form of ACE2 as a competitive binder to SARS-CoV-2 may decrease infectivity and improve clinical outcomes. However, further studies in human subjects are essential before firm clinical implications can be determined. Research in therapeutic discovery for patients with COVID-19 and to identify the patients most at risk for MAKE remains essential. Such research will be increasingly important as new SARS-CoV-2 variants continue to emerge, the lessons from which may be applicable beyond COVID-19 in the future.

REFERENCES

1. Bhatraju PK, Ghassemi BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med. 2020;382(21):2012-22.

2. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ. 2020;369:m1996.

3. Otto SP, Day T, Arino J, et al. The origins and potential future of SARS-CoV-2 variants of concern in the evolving COVID-19 pandemic. Curr Biol. 2021;31(14):R918-29.

4. Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol. 2020;32(1):151-60.

5. Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med. 2020;180(11):1436-47.

6. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738-42.

7. Menez S, Moledina DG, Thiessen-Philbrook H, et al. Prognostic significance of urinary biomarkers in patients hospitalized with COVID-19. Am J Kidney Dis. 2022;79(2):257-67. e251.

8. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from a hospital: a cohort study. Lancet. 2021;397(10270):220-32.

9. Sancho Ferrando E, Hanslin K, Hultström M, Larsson A, Frithiof R, Lipsey M. Soluble TFN receptors predict acute kidney injury and mortality in critically ill COVID-19 patients: a prospective observational study. Cytokine. 2022;149:155727.

10. Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z. Acute kidney injury in a national cohort of hospitalized US veterans with COVID-19. Clin J Am Soc Nephrol. 2021;16(1):14.

11. Gu X, Huang L, Cui D, et al. Association of acute kidney injury with 1-year outcome of kidney function in hospital survivors with COVID-19: a cohort study. EBioMedicine. 2022;76:103817.

12. Kellum JA, Nadim MK, Forni LG. Sepsis-associated acute kidney injury: is COVID-19 different? Kidney Int. 2020;98(6):1370-2.

13. Golmai P, Larsen CP, DeVita MV, et al. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. J Am Soc Nephrol. 2020;31(9):1944.

14. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27.

15. Alexander MP, Mangalaparthi KK, Madugundu AK, et al. Acute kidney injury in severe COVID-19 has similarities to sepsis-associated kidney injury: a multi-omics study. Mayo Clin Proc. 2021;96(10):2561-75.

16. Moledina DG, Simonov M, Yamamoto Y, et al. The association of COVID-19 with acute kidney injury independent of severity of illness: a multicenter cohort study. Am J Kidney Dis. 2021;77(4):490-9.

17. Strohbehn IA, Zhao S, Seethapathy H, et al. Acute kidney injury incidence, recovery, and long-term kidney outcomes among hospitalized patients with COVID-19 and influenza. Kidney Int Rep. 2021;6(10):2565-74.

18. Bechman K, Yates M, Mann K, et al. Inpatient COVID-19 mortality has reduced over time: results from an observational cohort. PLoS One. 2022;17(1):e0261142.

19. Charytan DM, Panth S, Khanri M, et al. Decreasing incidence of acute kidney injury in patients with COVID-19 critical illness in New York City. Kidney Int Rep. 2021;6(4):916-27.

20. Volbeda M, Jou-Valencia D, van den Heuvel MC, et al. Comparison of renal histopathology and gene expression profiles between severe COVID-19 and bacterial sepsis in critically ill patients. Crit Care. 2021;25(1):202.

21. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.

22. Hammang I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.

23. Santoriello D, Khairallah P, Bombacca AS, et al. Postmortem kidney pathology findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):2158-67.

24. Kudose S, Batal I, Santoriello D, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):1959-68.

25. Nasr SH, Alexander MP, Cornell LD, et al. Kidney biopsy findings in patients with COVID-19, kidney injury, and proteinuria. Am J Kidney Dis. 2021;77(3):465-8.

26. Sharma P, Uppal NN, Wanchoo R, et al. COVID-19-associated kidney injury: a multi-omics study. Mayo Clin Proc. 2021;96(10):1758-67.

27. Hassler L, Reyes F, Sparks MA, Welling P, Batlle D. Evidence for inhibition of SARS-CoV-2 and against direct kidney infection by SARS-CoV-2 in patients with COVID-19 and the kidney. Kidney Int Rep. 2021;6(4):1944.

28. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020;181(4):905-13. e907.

29. Wysocki J, Ye M, Hassler L, et al. A novel soluble ACE2 variant with prolonged duration of action neutralizes SARS-CoV-2
infection in human kidney organoids. J Am Soc Nephrol. 2021;32 (4):795.
33. Hassler L, Wysocki J, Gelarden I, et al. A novel soluble ACE2 protein provides lung and kidney protection in mice susceptible to lethal SARS-CoV-2 infection. J Am Soc Nephrol. 2022;33 (7):1293-307.
34. Winkler ES, Bailey AL, Kafai NM, et al. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. Nat Immunol. 2020;21(11):1327-35.
35. Golden JW, Cline CR, Zeng X, et al. Human angiotensin-converting enzyme 2 transgenic mice infected with SARS-CoV-2 develop severe and fatal respiratory disease. JCI Insight. 2020;5(19): e142032.
36. Frithiof R, Bergqvist A, Järhult JD, Lipcsey M, Hultström M. Presence of SARS-CoV-2 in urine is rare and not associated with acute kidney injury in critically ill COVID-19 patients. Crit Care. 2020;24(1):587.
37. Caceres P, Savickas G, Murray S, et al. High SARS-CoV-2 viral load in urine sediment correlates with acute kidney injury and poor COVID-19 outcome. J Am Soc Nephrol. 2021;32(10):2517-28.
38. Wu H, Larsen CP, Hernandez-Arroyo CF, et al. AKI and collapsing glomerulopathy associated with COVID-19 and APOL1 high-risk genotype. J Am Soc Nephrol. 2020;31(8):1688.
39. Larsen CP, Wickman TJ, Braga JR, et al. APOL1 risk variants and acute kidney injury in black Americans with COVID-19. Clin J Am Soc Nephrol. 2021;16(12):1790.
40. Velez JCQ, Caza T, Larsen CP. COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol. 2020;16(10):565-7.
41. Hung AM, Shah SC, Bick AG, et al. APOL1 risk variants, acute kidney injury, and death in participants with African ancestry hospitalized with COVID-19 from the million veteran program. JAMA Intern Med. 2022;182(4):386-95.
42. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med. 2021;26(3):107.
43. Garibaldi BT, Füksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19. Ann Intern Med. 2020;174(1):33-41.
44. Parikh CR, Coca SG, Thiessen-Philbrook H, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol. 2011;22(9):1748-57.
45. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Urinary biomarkers and progression of AKI in patients with cirrhosis. Clin J Am Soc Nephrol. 2014;9(11):1857-67.
46. Coca SG, Garg AX, Thiessen-Philbrook H, et al. Urinary biomarkers of AKI and mortality 3 years after cardiac surgery. J Am Soc Nephrol. 2014;25(5):1063-71.
47. Moledina DG, Isguven S, McArthur E, et al. Plasma monocyte chemotactic protein-1 is associated with acute kidney injury and death after cardiac operations. Ann Thorac Surg. 2017;104 (2):613-20.
48. Menez S, Moledina DG, Garg AX, et al. Results from the TRIBE-AKI study found associations between post-operative blood biomarkers and risk of chronic kidney disease after cardiac surgery. Kidney Int. 2021;99(3):716-24.
49. Vijayan A, Faubel S, Askenazi DJ, et al. Clinical use of the urine biomarker [TIMP-2] x [IGFBP7] for acute kidney injury risk assessment. Am J Kidney Dis. 2016;68(1):19-28.
50. Tidbury N, Browning N, Shaw M, Morgan M, Kemp I, Matata B. Neutrophil gelatinase-associated lipocalin as a marker of postoperative acute kidney injury following cardiac surgery in patients with pre-operative kidney impairment. Cardiovasc Hematol Disord Drug Targets. 2019;19(3):239-48.
51. Palacios Y, Ruiz A, Ramón-Lueng LA, et al. Severe COVID-19 patients show an increase in soluble TNFR1 and ADAM17, with a relationship to mortality. Int J Mol Sci. 2021;22(16):8423.
52. Mortaz E, Tabarsi P, Jamaati H, et al. Increased serum levels of soluble TNF-α receptor is associated with ICU mortality in COVID-19 patients. Front Immunol. 2021;12:592727.
53. Menez S, Coca SG, Moledina DG, et al. Plasma TNFR1 predicts major adverse kidney events in hospitalized patients with COVID-19 [abstract]. Am Soc Nephrol Kidney Week. 2021.
54. Xu K, Shang N, Levitman A, et al. Elevated neutrophil gelatinase-associated lipocalin is associated with the severity of kidney injury and poor prognosis of patients with COVID-19. Kidney Int Rep. 2021;6(12):2979-92.
55. Bezerra GF, Meneses GC, Albuquerque PL, et al. Urinary tubular biomarkers as predictors of death in critically ill patients with COVID-19. Biomark Med. 2022;16(9):681-92.
56. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021;11(1):16144.
57. Nugent J, Aklila A, Yamamoto Y, et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. JAMA Netw Open. 2021;4(3):e211095.
58. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. J Am Soc Nephrol. 2021;32(11):2851.