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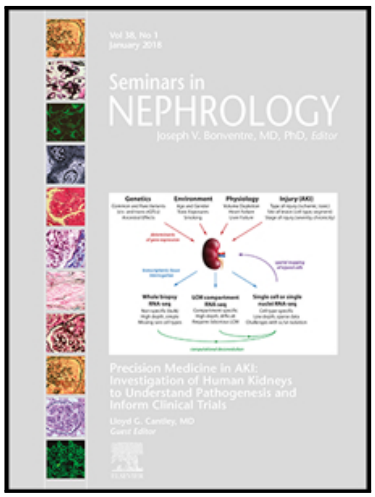

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COVID-19 and the Kidney: Recent Advances and Controversies

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Abstract

Kidney involvement is common in 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 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: 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 SARS-CoV-2 virus with ACE2 to prevent viral cell entry; and 3) the identification of high-risk patients for adverse outcomes in order to inform long-term outpatient management. Patients at particularly high risk for adverse kidney outcomes include those with *APOL1* high-risk genotype status, and biomarkers of injury, inflammation, and tubular health and repair measured in both the blood and urine may hold prognostic significance.

Key Words

acute kidney injury, *APOL1,* chronic kidney disease, COVID-19

Introduction

The SARS-CoV-2 virus has continued to affect people across the world for over 2 years,[1,2] with the novel coronavirus disease of 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 decline 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 aim to synthesize recent advances in the study of COVID-19–associated kidney injury while highlighting a 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 to AKI in other clinical settings

In an editorial published early in the course of the global pandemic, Kellum et al.[12] 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 histopathological 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 and colleagues[15] compared COVID-19–associated AKI with sepsis-associated AKI using a multi-omics approach. These investigators interrogated 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 (s-AKI) and 7 with non–sepsis-associated AKI (ns-AKI). All 17 patients who died from COVID-19 had evidence of at least mild acute tubular injury on histopathological examination. Using spatial transcriptomics and proteomic analysis, these authors found similar patterns of decreased oxidative phosphorylation, with upregulation in the ceramide signaling pathway and microvascular dysfunction/inflammation similar to that seen in s-AKI, findings not observed in ns-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 (**Figure 1**). Comparison groups included patients after cardiac surgery (from the TRIBE-AKI [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 stage 1, 2, and 3 AKI, respectively, had KIM-1 levels above the 90th percentile of reference. Similarly, among kidney donors

after brain death, 70%, 80%, and 90% of patients with stage 1, 2, and 3 AKI, respectively, had MCP-1 levels above the 90th percentile of reference. In general, the degree of kidney inflammation in the setting of COVID-19–associated AKI was comparable to 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.[12,16,17] Moledina et al.[16] demonstrated that COVID-19 was associated with AKI even after adjusting for key demographic factors, inflammatory markers, use of vasopressors, and other potential confounders indicating illness severity, compared with patients admitted within the same timeframe who were COVID-19–negative (adjusted hazard ratio [aHR]: 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 and colleagues[17] 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 demonstrated 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 (aHR: 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 is the temporal trend in AKI incidence as new strains have emerged. Following the initial wave of the pandemic, later waves have been associated with less disease severity including mortality in general,[18] with decreasing AKI incidence.[19]

Similar to Alexander et al,[15] Volbeda and colleagues[20] sought to compare COVID-19– and sepsis-associated AKI beyond clinical outcomes and histopathology, measuring differential mRNA 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.[18] found differential gene expression by clinical setting, with mRNA expression of the genes for NGAL and KIM-1 significantly lower in patients with COVID-19, compared with patients with bacterial sepsis, which is somewhat counterintuitive given the higher degree of tubular injury seen on histopathology in patients with COVID-19. Furthermore, these investigators found less kidney inflammation and endothelial cell activation in patients with COVID-19 compared with patients with bacterial sepsis, based on the relative lack of upregulation of E-selectin, VCAM-1, and 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,[21] 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.[22] Indeed, early post-mortem findings in patients with severe COVID-19 demonstrated acute tubular injury being nearly universally present on histology.[14,23] Later studies of kidney biopsy findings in critically ill patients with COVID-19 similarly demonstrated acute tubular injury as a prominent histological finding (**Table 1**).[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.[28] Hassler and colleagues[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 were likely artifact.[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–PCR, or in situ hybridization.

In March of 2020, Batlle and colleagues[30] postulated that a soluble form of ACE2 could competitively 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.[31] tested this experimentally by adding human recombinant soluble ACE2 (ACE2 1-740) to Vero-E6 cells inoculated with SARS-CoV-2 in vitro. With varying degrees of ACE2 1-740 administered over time, these investigators demonstrated 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.[32] Wysocki and colleagues specifically fused a human short ACE2 variant with an albumin-binding domain (ABD) to increase the duration of action.[32] They found similar reductions in SARS-CoV-2 viral loads using the ACE2 1-740 tested by Monteil et al.,[31] with similar efficacy using a novel, shorter human soluble 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, Batlle et al.[33] 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 k18-hACE2 mice expressing human ACE2 and therefore susceptible to SARS-CoV-2 infection,[34,35] 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 requiring euthanization. Histological 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. Frithiof et al.[36] evaluated for the presence of SARS-CoV-2 RNA in 81 critically-ill patients with PCR-proven COVID-19. They were able to detect viral RNA in only 6 (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.[37] 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,[38,39] later supported by larger studies conducted as the pandemic progressed,[29] demonstrated an association between *APOL1* high-risk genotype status and collapsing glomerulopathy in patients with COVID-19. COVID-19–associated nephropathy or COVAN was the term used to describe this phenomenon, similar to HIV-associated nephropathy or HIVAN and with a potentially shared pathophysiology.[40] Later studies explored clinical outcomes in patients with *APOL1* high-risk genotype status diagnosed with COVID-19 (**Table 2**). Larsen et al.[39] 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 and colleagues[41] investigated how *APOL1* risk variants associated with the incidence of AKI and death in patients hospitalized with COVID-19. Of 990 patients in the Veterans Affairs (VA) health care system of African ancestry who were hospitalized with COVID-19 between March 2020 and January 2021, 125 (12.6%) patients had 2 *APOL1* risk alleles. Among these patients, over 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 KDIGO 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 in-hospital mortality.[42,43] 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 acute kidney injury, both clinical and subclinical,[44-50] which is being increasingly investigated in the setting of COVID-19 (**Table 3**). Soluble tumor necrosis factor receptor 1 (sTNFR1) has been associated with adverse outcomes in patients with COVID-19, including COVID-19 severity[51] and intensive care unit (ICU) mortality.[52] With a focus on kidney-related outcomes, Ferrando and colleagues[9] investigated the prospective association between AKI in patients with COVID-19 and the biomarkers sTNFR1 and sTNFR1. A total of 122 patients with COVID-19 were consented at the time of ICU admission and followed 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. Furthermore, sTNFR1 and sTNFR2 levels trended higher by AKI stage ($P < 0.001$ and $P = 0.02$, 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 (AUC: 0.73; 95% CI: 0.62-0.84).

We have similarly shown that higher levels of plasma sTNFR1 and sTNFR2 are both strongly associated with increased risk of MAKE, defined in our study as development of 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 (AUC: 0.88). A cutpoint value for sTNFR1 of 3,005 pg/mL had a negative predictive value of 92%, suggesting that sTNFR1 may be used as a potential rule-out test for MAKE at the time of COVID-19 hospitalization.

Urine biomarker–enriched risk prognostication in COVID-19

Bezerra and colleagues[54] investigated the association of urinary biomarkers of kidney injury with death in patients admitted to the ICU with COVID-19. They measured urinary levels of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-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 cutpoint of 118.8 ng/mg Cr) were significantly associated with 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 death within 60 days of hospital admission).[7] We measured biomarkers using urine samples obtained

throughout the course of admission, demonstrating that higher levels of urinary NGAL, KIM-1, and MCP-1 were associated with MAKE (**Figure 2**). Conversely, higher levels of urinary epidermal growth factor (EGF), 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.[55] demonstrated, in a cohort of 444 patients in New York City, that urinary NGAL measured on admission for COVID-19 was strongly associated with AKI diagnosis and severity. Furthermore, a urinary NGAL level >150 ng/mL had 80% specificity and 75% sensitivity to diagnosed AKIN stages 2 or 3 AKI. Furthermore, NGAL levels on admission were associated with increased odds of sustained AKI, dialysis, death, and hospital length of stay.

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**).[56] Huang and colleagues[8] were among the first to report long-term outcomes 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 eGFR at follow-up, compared with only 13% of individuals

without COVID-19–associated AKI. Nugent et al.[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 decreased in eGFR over the course of follow-up compared with noninfected controls with hospitalized AKI (-14.0 mL/min/1.72 m^2; 95% CI: -25.1 to -2.9).

Using data from the VA health care system, Bowe and colleagues[58] evaluated MAKE up to 365 days after COVID-19 diagnosis in both the ambulatory and hospital settings. Compared with over 1.6 million patients without a diagnosis of COVID-19, nearly 90,000 patients who survived at least 30 days after COVID-19 diagnosis had a higher incidence of AKI and greater declines 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, excess eGFR decline was greatest in hospitalized patients who developed AKI, compared to hospitalized patients without AKI and the non-hospitalized population.

Gu and colleagues[11] later investigated kidney function trends in a cohort of 1,734 hospitalized patients with COVID-19 out of China. Patients who experienced AKI had significantly greater declines in eGFR compared with patients without AKI. In particular, patients with KDIGO stage 3 AKI had a 17.8% (95% CI: 9.1-26.4) greater decline in eGFR compared with patients without AKI.

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, though 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.

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Conflicts of Interest
CRP serves as a member of the advisory board of and own equity in Renalytix AI. CRP is named as a co-inventor on a pending patent, “Methods and Systems for Diagnosis of Acute Interstitial Nephritis,”. SM has received consulting fees from the Dedham Group and research funding from Renalytix AI.

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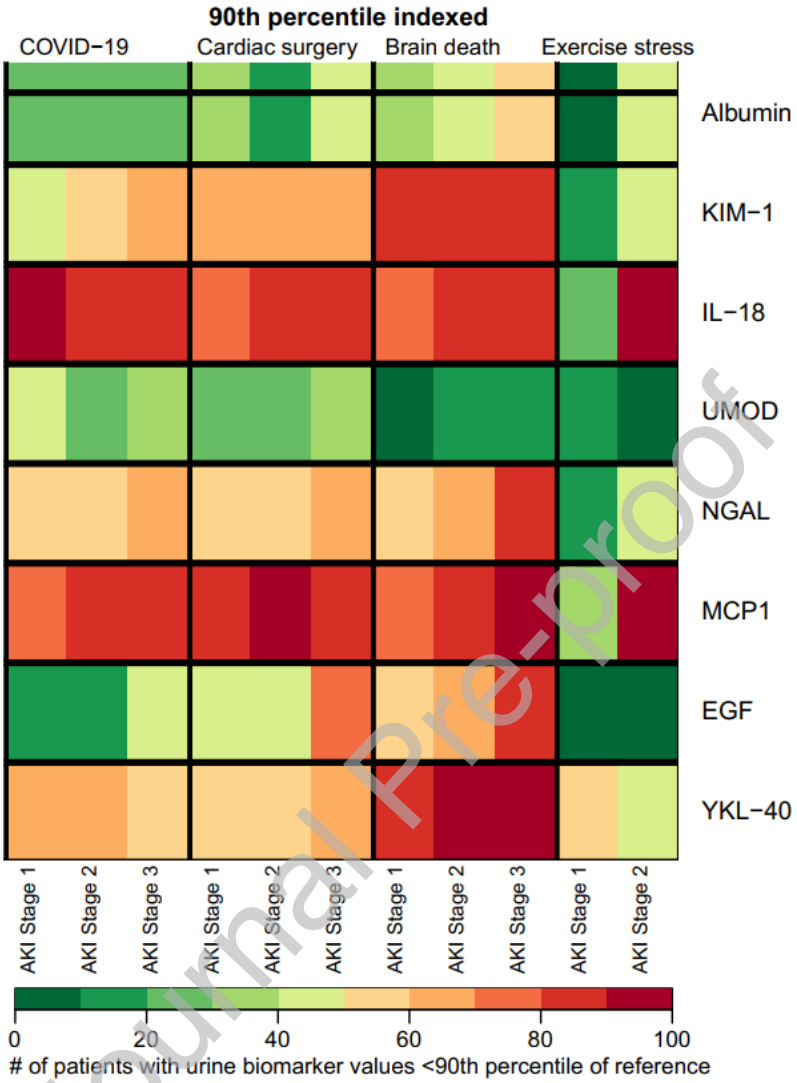

Figure 1. Heat map showing the percentage of patients with AKI in the setting of COVID-19, after cardiac surgery (TRIBE-AKI cohort), after brain death (DDS cohort), and in the setting of exercise stress (marathon-associated AKI). For exercise stress–associated AKI, blood and urine biomarkers were measured from biosamples obtained within 30 minutes of completing a marathon. The colors denote the percentage of patients by AKI stage with biomarker levels above the 90th percentile of the reference value, based on cardiac surgery preoperative values. Among patients with COVID-19–associated AKI, 40%, 50%, and 60% of patients with stage 1, 2, and 3 AKI, respectively, had KIM-1 levels above the 90th percentile of reference. Similarly, among kidney donors after brain death, 70%, 80%, and 90% of patients with stage 1, 2, and 3 AKI, respectively, had MCP-1 levels above the 90th percentile of the reference value. Note: Sample sizes by AKI stage: COVID-19: stage 1 (n = 56), stage 2 (n = 31), stage 3 (n = 20); cardiac

surgery: stage 1 (n = 456), stage 2 (n = 34), stage 3 (n = 31); brain death: stage 1 (n = 275), stage 2 (n = 93), stage 3 (n = 76); exercise stress: stage 1 (n = 9), stage 2 (n = 2). Abbreviations: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; DDS, Deceased Donor Study; EGF, epidermal growth factor; IL, interleukin; KIM-1, kidney injury molecule 1; MCP1, monocyte chemoattractant protein 1; NGAL, neutrophil gelatinase-associated lipocalin; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury; UMOD, uromodulin; YKL-40, chitinase-3-like protein 1.

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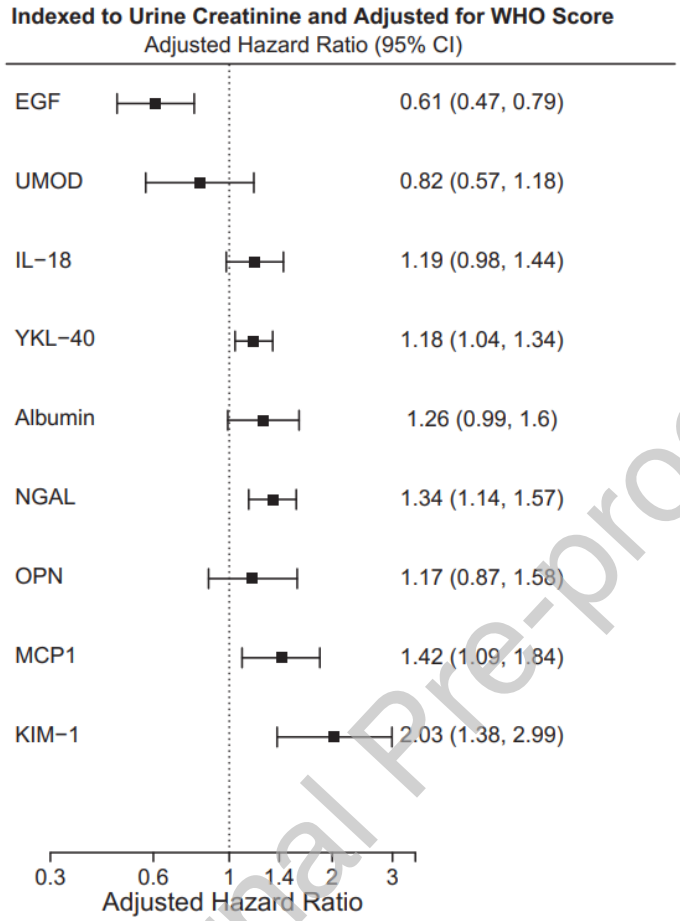

Figure 2. Risk of stage 3 AKI, new dialysis initiation, or death within 60 days of hospital admission by urinary biomarker level, indexed to urine creatinine and adjusted for World Health Organization disease severity scale. Abbreviations: AKI, acute kidney injury; EGF, epidermal growth factor; IL, interleukin; 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

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Table 1. Overview of histological findings on kidney biopsies from patients with COVID-19

Study	Acute tubular injury	Glomerular findings	Other findings
Kudose et al.[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	• Pigmented casts in 1/14
Nasr et al.[25] (n=13)	present in 13/13	• Collapsing FSGS in 8/13 • Diabetic Neph. in 4/13 • Membranous GN in 2/13 • IgAN in 1/13 • Crescentic GN in 1/13	• TRI's in 4/13
Sharma et al.[26] (n=10)	present in 10/10	• Crescentic GN in 1/10 • "Healed" collapse in 1/10	• TMA in 2/10 • Myoglobin casts in 1/10
Akilesh et al.[27] (n=14)*	present in 12/14	• Collapsing FSGS in 7/14 • FSGS in 3/14 • Diabetic Neph. in 1/14 • MCD in 1/14	• TMA in 6/14 • AIN in 2/14

*among native kidney biopsies only
FSGS = focal segmental glomerulosclerosis; GN = glomerulonephritis; IgAN = IgA nephropathy; LN = lupus nephritis; MCD = minimal change disease; TRI = endothelial tubuloreticular inclusion

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 al.[29]	Retrospective cohort study between March 2020 and March 2021	240 patients with PCR-positive COVID-19 who provided kidney biopsies, of whom 107 underwent *APOL1* genetic testing1	2 *APOL1* high-risk alleles (n = 65) vs 0 or 1 *APOL1* high-risk alleles (n = 42)	• Kidney pathology by high-risk allele status (2 vs. 0/1): ○ Increased FSGS lesions (*P* = 0.03) ○ Increased podocyte foot process effacement (*P* < 0.001) • 44/48 (91.7%) patients with collapsing GN had 2 high-risk alleles
Larsen et al.[39]	Retrospective cohort study between March 2020 and October 2020, New Orleans, LA	126 adult self-identified Black patients with PCR-positive COVID-19	2 *APOL1* high-risk alleles (n = 16) vs 0 or 1 *APOL1* high-risk alleles (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 al.[41]	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	2 *APOL1* high-risk alleles (n = 125) vs 0 or 1 *APOL1* high-risk alleles (n = 865)	Overall • aOR of AKI = 1.95 (95% CI: 1.27-3.02) • aOR of death = 2.15 (95% CI: 1.22-3.72) Patients with baseline eGFR > 60 mL/min/1.73 m^2 • aOR of AKI = 1.93 (95% CI: 1.15-3.26) • aOR of death = 2.51 (95% CI: 1.21-5.05)

AKI, acute kidney injury; aOR = adjusted odds ratio; GN = glomerulopathy; PCR = polymerase chain reaction

Table 3. Summary of studies showing biomarker-enriched prognostication of adverse kidney events

Study	Study Details	Patient Population	Control/Comparison Group	Biomarkers Tested	Kidney outcomes
Blood					
Ferrando et al.[9]	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 vs. control ($P < 0.001$) • sTNFR1 levels increase with increasing AKI stage ($P < 0.001$) • sTNFR2 levels increase with increasing AKI stage ($P < 0.02$)
Menez et al.[53]	Prospective cohort study between April 2020 and June 2020 in 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, IL-2, IL-10, IL-18, 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 al.[7]	Prospective cohort study between April 2020 and June 2020 in 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, interluekin-18, 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 al.[55]	Prospective cohort study between March 2020 and April 2020 in 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 2017-2019	Urinary NGAL	• NGAL at admission associated with AKI diagnosis ($p < 0.001$)
					• 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; Ang2 = angiopoietin 2, EGF, epidermal growth factor; 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; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; sFLT1 = soluble fms-like tyrosine kinase 1; sTNFR1/2 = soluble tumor necrosis factor receptor 1/2; UMOD, uromodulin; YKL-40, chitinase-3-like protein 1

Table 4. Long-term outcomes in COVID-19

Authors	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 in 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 • Decreased eGFR* in 13% of survivors without AKI at time of acute COVID-19
Nugent et al.[57]	Retrospective cohort study of patients hospitalized with COVID-19 surviving to discharge from March 2020 to August 2020 in 5 hospitals across CT and RI	178 patients who had AKI in the setting of COVID-19 during hospitalization	1,430 patients who had hospitalized AKI but did not have COVID-19	Patients with AKI and COVID-19, compared with patients with AKI and no COVID-19: • eGFR decline 14.0 mL/min/1.73m^2 greater • aHR of kidney recovery during follow-up, in those without AKI recovery at discharge = 0.57 (95% CI: 0.35-0.92)
Bowe et al.[58]	Retrospective cohort study of patients in the VA health care system with COVID-19, in both the ambulatory and hospital setting from March 2020 to March 2021	89,216 patients in the VA system with COVID-19 who survived at least 30 days from date of diagnosis	1.6 million ambulatory patients in the VA system over the same time period without COVID-19	COVID-19 survivors compared to noninfected controls: • aHR of AKI = 1.94 (95% CI: 1.86-2.04) • aHR of eGFR decline ≥ 30% = 1.25 (95% CI: 1.14-1.37) • aHR of ESKD = 2.96 (95% CI: 2.49-3.51) • aHR of MAKE = 1.66 (95% CI: 1.58-1.74)
Gu et al.[11]	ambidirectional cohort study of patients hospitalized with COVID-19, surviving to discharge from January 2020 to May 2020 in Wuhan, China	1,734 patients admitted to the hospital with COVID-19 who survived to hospital discharge	N/A	Patients with AKI compared to patients without AKI during acute COVID-19: • eGFR decline 8.3% greater (overall) • eGFR decline 17.8% greater (stage 3 AKI) • OR of reduced kidney function at follow-up = 4.60 (95% CI: 2.10-10.1)

*in patients without AKI and with eGFR above 90 at time of acute COVID-19, 13% had eGFR < 90 mL/min/1.73m^2 at the time of follow-up
AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; MAKE = major adverse kidney events (eGFR decline ≥50%, ESKD, or all-cause mortality); VA = Veterans Affairs