

Renal Considerations in COVID-19: Biology, Pathology, and Pathophysiology

MEGHAN E. KAPP^{ID},* AGNES B. FOGO^{ID},* CANDICE ROUFOUSE^{ID},† BEHZAD NAJAFIAN^{ID},‡ JAI RADHAKRISHNAN^{ID},§
 SUMIT MOHAN^{ID},§ SARA E. MILLER,¶ VIVETTE D. D'AGATI,|| JEFFREY SILBERZWEIG^{ID},# TAREK BARBAR^{ID},#
 TULASI GOPALAN,# VESH SRIVATANA^{ID},# MICHELE H. MOKRZYCKI,** JUDITH A. BENSTEIN^{ID},†† YUE-HARN NG^{ID},‡‡
 KRISTA L. LENTINE^{ID},§§ VIKRAM AGGARWAL^{ID},¶¶ JEFFREY PERL,||| PAGE SALENGER^{ID},## JAY L. KOYNER^{ID},***
 MICHELLE A. JOSEPHSON,*** MICHAEL HEUNG^{ID},††† JUAN CARLOS VELEZ,‡‡‡ ALP IKIZLER^{ID},§§§ ANITHA VIJAYAN^{ID},¶¶¶
 PREETHI WILLIAM^{ID},||| BIJIN THAJUDEEN^{ID},### AND MARVIN J. SLEPIAN^{ID}****

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged into a worldwide pandemic of epic proportion. Beyond pulmonary involvement in coronavirus disease 2019 (COVID-19), a significant subset of patients experiences acute kidney injury. Patients who die from severe disease most notably show diffuse acute tubular injury on postmortem examination with a possible contribution of focal macro- and microvascular thrombi. Renal biopsies in patients with proteinuria and hematuria have demonstrated a glomerular dominant pattern of injury, most notably a collapsing glomerulopathy reminiscent of findings seen in human immunodeficiency virus (HIV) in individuals with apolipoprotein

L-1 (APOL1) risk allele variants. Although various mechanisms have been proposed for the pathogenesis of acute kidney injury in SARS-CoV-2 infection, direct renal cell infection has not been definitively demonstrated and our understanding of the spectrum of renal involvement remains incomplete. Herein we discuss the biology, pathology, and pathogenesis of SARS-CoV-2 infection and associated renal involvement. We discuss the molecular biology, risk factors, and pathophysiology of renal injury associated with SARS-CoV-2 infection. We highlight the characteristics of specific renal pathologies based on native kidney biopsy and autopsy. Additionally, a brief discussion on ancillary studies and challenges in the diagnosis of SARS-CoV-2 is presented. *ASAIO Journal* 2021; 67:1087–1096

From the *Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee; †Department of Immunology and Inflammation, Centre for Inflammatory Diseases, Imperial College, London, UK; ‡Department of Laboratory Medicine & Pathology, University of Washington Medicine, Seattle, Washington; §Division of Nephrology, Columbia University Medical Center, New York, New York; ¶Department of Pathology, Duke University School of Medicine, Durham, North Carolina; ||Department of Pathology and Cell Biology, Columbia University, New York, New York; #Division of Nephrology, Weill Cornell Medical College, New York, New York; **Division of Nephrology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; ††Department of Medicine, New York University Tisch Hospital, New York, New York; ‡‡Division of Nephrology, University of Washington, Seattle, Washington; §§Division of Nephrology (9-FDT), Center for Abdominal Transplantation, St. Louis, Missouri; ¶¶Division of Nephrology, Northwestern Medicine, Chicago, Illinois; |||Division of Nephrology, University of Toronto, Toronto, Ontario, Canada; ##Dialysis Clinics Incorporated, Nashville, Tennessee; ***Department of Nephrology, University of Chicago, Chicago, Illinois; †††Division of Nephrology, Department of Medicine, University of Michigan, Ann Arbor, Michigan; ‡‡‡Department of Nephrology, Ochsner Health System, New Orleans, Louisiana; §§§Division of Nephrology, Vanderbilt University Medical Center, Nashville, Tennessee; ¶¶¶Department of Medicine – Nephrology, Washington University School of Medicine in St. Louis, St. Louis, Missouri; ||||Division of Cardiology, Banner University of Arizona, Tucson, Arizona; ###Division of Nephrology, Banner University of Arizona, Tucson, Arizona; ****Departments of Medicine and Biomedical Engineering, Sarver Heart Center, University of Arizona, Tucson, Arizona.

Submitted for consideration December 2020; accepted for publication in revised form June 2021.

Disclosures: The authors have no conflicts of interest to report.

Correspondence: Marvin J. Slepian, Department of Medicine and Biomedical Engineering, Sarver Heart Center, University of Arizona, 1501 North Campbell Avenue, Tucson, AZ 85724. Email: slepian@email.arizona.edu.

Copyright © ASAIO 2021

DOI: 10.1097/MAT.0000000000001530

Key Words: COVID-19, acute kidney injury, biology, pathology, pathophysiology, glomerular disease, acute tubular injury

The emergence of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), with its consequential disease manifestation coronavirus disease 2019 (COVID-19), has led to a worldwide pandemic of epic proportion.¹ As of this writing (April 26, 2021), there have been more than 147 million COVID-19 cases worldwide, with greater than 3.1 million deaths, with more than 572,000 of those in the United States.¹ Sadly, now more than a year since the initial description of COVID-19 in the United States, we have faced an accelerating, rapidly rising infection rate with significant morbidity and mortality, with new cases slowly declining as vaccines are being administered.¹

Although the primary manifestation of COVID-19 has been respiratory, with a spectrum ranging from tracheobronchitis, patchy lung parenchymal involvement, to full suppurative infiltration, diffuse consolidation and severe acute respiratory distress syndrome, multiple organs are affected in COVID-19.^{2,3} Renal involvement, with acute renal dysfunction and a sudden demand and strain placed on dialysis, was particularly noted early in the pandemic.⁴ *De novo* renal impairment in COVID-19 may present as a rise in serum creatinine, acute kidney injury (AKI), proteinuria, and hematuria.⁵ Various mechanisms have been proposed for kidney injury, including ischemia related to severe pulmonary dysfunction, high levels of circulating proinflammatory cytokines, and possible direct infection of the renal parenchyma by SARS-CoV-2 virus.⁶ Yet, our understanding of the spectrum of renal involvement remains incomplete.

The American Society for Artificial Organs (ASAIO) has long been focused on systems, advances, and strategies for management of organ dysfunction through use of support or replacement therapeutics. With the emergence of COVID-19, ASAIO initially assembled a whitepaper addressing advanced pulmonary and cardiac support.⁷ With recognition of the significance and emerging spectrum of renal involvement in COVID-19, ASAIO has reached out broadly to the wider renal community, and has established a broad writing group to assemble knowledge and provide a resource document focused on the evolving understanding of renal involvement in COVID-19. We here address the biology, pathology, and pathophysiology of SARS-CoV-2 infection and associated renal involvement. We particularly report herein on new pathologic observations based on biopsy and autopsy studies.

Molecular Biology

Coronavirus was first described and named by Tyrrell *et al.*⁸ in 1967, as a generally round, enveloped, nonsegmented virus of 80–125 nm in size with a large genome of 30 kb in size. Coronaviruses early on were recognized to cause respiratory illness, though also resulting in gastroenteritis and necrotizing enterocolitis in children and hepatitis in mice.^{9–11} Over time four genera of enveloped positive-sense single-stranded ribonucleic acid (RNA) coronaviruses have been described: alpha, beta, gamma, and delta. In recent years, new emergent beta coronaviruses have been described including SARS and Middle Eastern respiratory virus (MERS). Some patients with MERS and SARS also experienced AKI but were not reported to show nephrotic syndrome and the spectrum of glomerular lesions described below for COVID-19, and risks potentially related to apolipoprotein L-1 (APOL1) risk allele variants for those infections are not described.

Severe acute respiratory syndrome coronavirus 2 also belongs to the beta coronavirus group.⁶ The surface of SARS-CoV-2 has club-like projections which afford its crown-like structure. The spike protein in coronavirus determines tissue tropism of the virus, enabling viral entry promoting cell to cell spread.¹² Severe acute respiratory syndrome coronavirus 2 enters the body mainly through the nasal and laryngeal mucosa, subsequently reaching the lungs where it replicates rapidly. Although the principal mode of transmission is droplets spread by coughing or sneezing, other routes of transmission, that is, fecal-oral route, are possible. Major target organs for the virus that have been described, beyond the lung, include but are not limited to heart, gastrointestinal tract, and kidney.⁷ The average incubation period for COVID-19 ranges between 2 and 14 days, with a mean of 5.2 days, and a mean case fatality rate of 3.31% among confirmed cases.¹³

The host receptor responsible for providing access to SARS-CoV-2 into cells is the angiotensin-converting enzyme 2 (ACE2) receptor.¹⁴ The kidneys have abundant ACE2 receptors, predominantly located in podocytes, mesangial cells, parietal epithelium of Bowman's capsule, proximal cell brush border, and collecting duct.⁶ Angiotensin-converting enzyme 2 expression in kidney tissue is higher than that of lung tissue and the binding affinity of SARS-CoV-2 to ACE2 receptors is 10–20 times higher than SARS-CoV.¹⁵ Angiotensin-converting enzyme 2 mediates the cleavage of angiotensin-I and angiotensin-II into angiotensin-(1-9) and angiotensin-(1-7), respectively. Angiotensin-(1-7)

exerts vasodilatory, antiproliferative, and anti-inflammatory activity counterbalancing the adverse effects of angiotensin-II-like vasoconstriction, proliferation, and inflammation. Binding of SARS-CoV-2 to ACE2 leads to depletion of ACE2 activity disrupting the physiologic balance ACE/ACE2 with consequential loss of the protective effects of angiotensin-(1-7) and accumulation of angiotensin-II. This promotes glomerular dysfunction, vasoconstriction, and inflammation resulting in AKI.^{16–18} Other potential mechanisms for organ involvement include a receptor related to the transmembrane serine protease (TMPRSS) gene and invasion through CD147-spike protein. Transmembrane serine protease primes viral surface spike protein promoting the fusion of virus and host cell membrane, whereas CD147-spike protein is a transmembrane glycoprotein expressed on proximal tubular epithelial cells and inflammatory cells.¹⁹

Risk Factors for AKI in COVID-19

Risk factors for development of AKI include ventilator support, use of vasopressor drugs, increased age, male sex, multiple comorbidities (especially diabetes mellitus, hypertension, and cardiovascular disease), severe disease, higher body mass index, non-O blood group type, and African American race.^{20–22} Other features of increased risk include leukocytosis, lymphopenia, thrombocytopenia, prolonged activated partial thromboplastin time, and higher levels of inflammatory markers: D-dimer, procalcitonin, aspartate aminotransferase, and lactic dehydrogenase.²³ Most AKI occurred in 7 days from admission to hospital with faster onset in patients who had elevated serum creatinine at baseline.²⁴ Acute kidney injury was reported in nearly 3-fold more patients with pre-existing kidney disease (11.4% vs. 4%).²⁴ Acute kidney injury is also more common in those with higher systolic blood pressure and potassium levels and lower serum albumin.²⁵ Higher rates of AKI have been documented in critically ill patients including those with higher sequential organ failure assessment (SOFA) score, renal SOFA score, cardiovascular SOFA score, and lower partial pressure of oxygen/fraction of inspired oxygen.²⁶

Pathophysiology

The pathophysiology of renal involvement in COVID-19 is not fully understood. The most common causes of AKI in COVID-19 infection appears to be a combination of volume depletion, synergistic effects of virus-induced direct cytotoxic effect, and cytokine-induced systemic inflammatory response. These result in intrinsic injury to the kidney in the form of tubular injury, acute interstitial nephritis, and *de novo* glomerular disease. Indirect processes associated with AKI include downstream consequences of infection such as endothelial injury, rhabdomyolysis, ischemic thrombi, inflammation, and complement dysregulation.²⁷ Hemodynamic instability (caused by hypovolemia or hypotension) or injury caused by nephrotoxic drugs likely contribute to AKI as well. Potential mechanisms of tubular injury include hemodynamic disturbances such as central venous pressure elevation, increased intrathoracic pressure, and high positive end-expiratory pressure (PEEP) which result in reduction of effective renal perfusion pressure.²⁸ Hemodynamic decompensation and shock compound respiratory decompensation leading to ischemic acute tubular injury (ATI).^{20,29} Cardiorenal syndrome from right ventricular

failure secondary to COVID-19 pneumonia or left ventricular dysfunction lead to tubular injury over time. Other causes of tubular injury include macrophage activation syndrome, microemboli and microthrombi as a result of dysregulation of coagulation homeostasis, and endothelialitis, leading to renal microcirculatory dysfunction. Impairment of gas exchange and severe hypoxemia seen in acute respiratory distress syndrome patients have been associated with AKI.^{6,20,29,30} African American individuals with COVID-19 may present with new nephrotic range proteinuria and AKI along with respiratory illness.³¹ Collapsing glomerulopathy appears to be a manifestation of an inflammatory response by a susceptible host, that is, with risk allele variants of APOL1, rather than direct parenchymal injury caused by the virus.

Severe acute respiratory syndrome coronavirus 2 activates macrophages which induce cytokine storm leading to the activation of coagulation factors and aggregation of erythrocytes leading to microvascular damage which compounds the hypercoagulable state triggered by the inflammatory milieu related to the infection.²⁷ Levels of proinflammatory cytokines that are elevated include interleukin-1 β , interleukin-1RA, interleukin-7, interleukin-8, interleukin-9, interleukin-10, fibroblast growth factor, granulocyte-macrophage colony-stimulating factor, interferon- γ , granulocyte colony-stimulating factor, interferon- γ -inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein one alpha, platelet-derived growth factor, tumor necrosis factor α , vascular endothelial growth factor.³² These cytokines induce endothelial and tubular dysfunction in the kidneys. Histopathological evidence based on postmortem examination of kidneys has demonstrated the presence of cluster of differentiation 68 (CD68)-positive macrophage infiltration in the tubules and interstitium as well as complement 5b-9 deposition, CD8+ T lymphocyte cells, and CD56+ (natural killer) cells.^{33,34}

Clinical Presentation of COVID-19–Associated Kidney Disease

The clinical presentation of COVID-19–related kidney disease reflects the underlying pathology. Patients with AKI may present with proteinuria or hematuria in addition to elevations of serum creatinine and blood urea nitrogen.⁵ The reported rates of AKI are variable, with estimates of >20% of hospitalized patients and >50% of patients in the intensive care unit.³⁵ Such patients are not typically biopsied since their clinical presentation and disease course resemble other patients with AKI in the setting of critical illness. In a study of 442 hospitalized patients with COVID-19 in China, proteinuria was present in 43.9% (with 30% having $\geq 2+$ on dipstick) with significant hematuria demonstrated in 11.3% patients.²³ Nephrotic syndrome is uncommon in COVID-19 and such patients are likely biopsied more commonly, and thus glomerular diseases appear to be over-represented in biopsy series. For example, in the series of 17 patients reported by Kudose *et al.*,³⁶ 88% presented with AKI or AKI superimposed on chronic kidney disease, and 53% had nephrotic syndrome. A variety of pathologic entities were reported including 10 glomerular diseases. Collapsing glomerulopathy is the entity that appears to be directly related to a COVID-19–associated hyperinflammatory state in predisposed individuals with APOL1 risk alleles. The striking similarity in kidney pathology between human immunodeficiency

virus (HIV)–associated nephropathy (HIVAN) and the collapsing glomerulopathy of COVID-19 has led to the suggestion that the eponym “COVAN,” that is, COVID-associated nephropathy, should be applied.³¹ Patients with COVAN present with AKI and nephrotic syndrome. In some series, manifestations of COVID-19 were mild or resolving at the time of kidney biopsy.³⁷ The clinical course is variable; however, a significant proportion of patients were either dialysis-dependent or with chronic kidney disease at the end of follow-up.^{36,38} None of the patients were treated with immunosuppressive therapy specifically target to COVAN.

In patients with non-COVAN biopsy findings, for example, with membranous nephropathy, it is likely that they had pre-existing kidney disease and were biopsied incidentally during COVID-19. However, since COVID-19 represents a state of altered immunity, immune-mediated renal disease could potentially flare or present for the first time in this situation, for example, the multisystem inflammatory syndrome in children.

Finally, evidence of isolated proximal tubular dysfunction has also been reported in COVID-19. In a cohort of 49 hospitalized patients, proximal tubule dysfunction was present in a significant proportion of patients and included low-molecular-weight proteinuria (70–80%), neutral aminoaciduria (46%), and defective handling of uric acid (46%), or phosphate (19%). These manifestations were independent of pre-existing comorbidities, glomerular proteinuria, nephrotoxic medications, or viral load. Biopsy findings showed prominent tubular injury, including in the initial part of the proximal tubule.³⁹

Pathology

Renal Biopsy Findings

Kidney biopsies performed in patients with COVID-19 have revealed diverse glomerular and tubular disorders. The most common findings in biopsy series are ATI and *de novo* collapsing glomerulopathy, and more rarely, thrombotic microangiopathy (TMA). Other diverse immune-mediated glomerular disorders have also been described, and in some cases, development of SARS-CoV-2 infection causes exacerbation of pre-existing autoimmune and alloimmune conditions.

Acute Tubular Injury

In two biopsy series reported, four of 14 native kidney biopsies and two of three allograft biopsies reported from Columbia University Medical Center and five of 10 biopsies performed in hospitalized patients with COVID-19 from Northwell Hospital Systems showed ATI as the sole pathologic process. In both series combined, totaling biopsies from 27 patients, rhabdomyolysis and myoglobin casts were an identifiable etiology in only two cases of ATI (one from each center).^{36,40} Other potential etiologies included exposure to nephrotoxins, hypoxemia, and severe hemodynamic instability. However, in several cases, no obvious etiology could be found, and COVID-19 symptomatology was not considered severe, implicating yet unidentified triggers. Importantly, no case of ATI had evidence of direct viral infection of renal tubular cells by electron microscopy (EM) or *in situ* hybridization for SARS-CoV-2 RNA or by definitive virus by EM (discussed later).^{36,40,41}

Interestingly, both series described ATI as a background finding in association with other glomerular and vascular processes, discussed in detail later. The two patients with TMA had other potential underlying causes, including exposure to gemcitabine and complement disorder, suggesting that COVID-19 may potentiate endothelial injury leading to overt TMA in patients with predisposing conditions.⁴⁰

Collapsing Glomerulopathy

Collapsing glomerulopathy was the first glomerular disease to be identified in SARS-CoV-2–infected patients. Collapsing glomerulopathy occurring in association with COVID-19 has been reported in patients of African descent from the United States, France, and Switzerland.^{31,36,40,42–45} Collapsing glomerulopathy is a highly aggressive form of focal segmental glomerulosclerosis (FSGS) defined by implosive wrinkling and collapse of glomerular capillaries associated with hypertrophy and hyperplasia of glomerular epithelial cells, sometimes forming pseudocrescents that obliterate the urinary space (**Figure 1**). The tubulointerstitium displays ATI and focal tubular microcysts. Collapsing glomerulopathy was first well characterized in HIV-infected patients, where it is termed HIVAN. Patients typically present with nephrotic range proteinuria and acute renal failure, often accompanied by nephrotic syndrome. There may be rapid progression to irreversible renal failure while some patients present in a relatively chronic phase of collapsing glomerulopathy.³⁸

Similar to HIVAN, patients with so-called COVAN often have endothelial tubuloreticular inclusions, which are known as “interferon footprints” because they are induced in endothelial cells by exposure to ambient interferon. Interferon mRNA is not detected in kidney biopsies with collapsing glomerulopathy, consistent with renal pathology resulting from a systemic innate immune response to COVID-19.³¹ Collapsing glomerulopathy secondary to COVID-19 is thought to be induced by cytokine storm, including massive release of interferon and interleukins, in patients with a susceptible genetic background. Many collapsing glomerulopathy patients have relatively mild

symptoms of COVID-19 when they present with severe AKI and nephrotic proteinuria. Collapsing glomerulopathy occurring in the native kidney in the setting of COVID-19 has thus far only been identified in patients of African descent who carry two *APOL1* risk allele variants, G1 or G2.^{31,36,42,43} Such homozygosity or compound heterozygosity (G1/G1, G1/G2, or G2/G2) occurs in approximately 13–14% of African Americans.⁴⁶ The presence of *APOL1* risk alleles confers 29-fold higher odds of developing HIVAN in the African American population and 89-fold higher odds ratio in South African blacks.^{46,47} An exception is a single case report of collapsing glomerulopathy associated with COVID-19 occurring in the renal transplant recipient of a donor kidney carrying one *APOL1* risk allele.⁴⁸ Recent data suggest that even a single *APOL1* risk allele can cause dose-dependent–dominant cytotoxicity.⁴⁹ Activation of a viral program in podocytes bearing *APOL1* risk alleles upregulates *APOL1* expression and may cause podocyte injury and cell death *via* alteration in autophagy, mitochondrial function, energy metabolism, and potassium efflux.⁴⁹ Apolipoprotein L-1 risk alleles also confer risk for collapsing glomerulopathy among patients with other interferon-mediated forms of this lesion, including systemic lupus erythematosus with podocytopathy, hemophagocytic syndrome, and collapsing glomerulopathy in the setting of other viral infections such as parvovirus B19, cytomegalovirus, and Epstein-Barr virus.

To-date, no viral particles have been definitively identified in glomerular or tubular cells in patients with collapsing glomerulopathy due to COVID-19, using various techniques including *in situ* hybridization for viral RNA, RNAScope, immunohistochemistry for viral spike and nucleocapsid proteins, or demonstration of virions by EM.^{31,36,40,42,43,50} This represents a major difference between COVAN and HIVAN, in which HIV-1 viral RNA and DNA have been detected in glomerular podocytes, parietal epithelial cells, and tubular epithelial cells, leading to dysregulation of host genes governing cell cycle and differentiation.⁵¹

Other Glomerular Diseases

Two biopsy series were reported from the New York epicenter of the pandemic, one from Columbia University Medical Center and the other from Northwell Hospital Systems.^{36,40} A major difference between the two series is that all biopsies were performed on hospitalized patients in the Northwell series, where ATI predominated, whereas most biopsies were performed on an outpatient basis in the Columbia series, where glomerular disease predominated. In addition to five cases of collapsing glomerulopathy, a single case of minimal change disease associated with COVID-19 was reported in the Columbia series.³⁶ This African American patient presented with nephrotic syndrome and AKI. Genotyping revealed high-risk *APOL1* genotype; nonetheless, the patient responded to glucocorticoid therapy. Other glomerulopathies included two cases of membranous glomerulopathy of uncertain duration, one crescentic transformation of longstanding lupus nephritis, and one *de novo* antiglomerular basement membrane antibody nephritis.³⁶ While these cases may represent detection of renal disease during the time of COVID, some findings warrant postulation of an association. Antiglomerular basement membrane antibody nephritis is an extremely rare

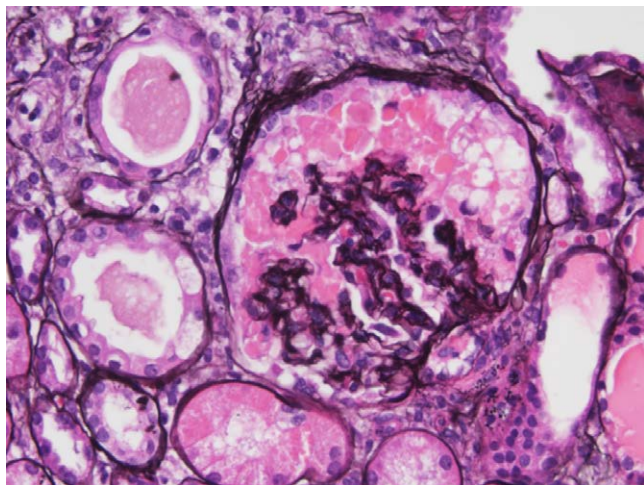


Figure 1. Collapse of glomerular tuft with overlying visceral epithelial cell hyperplasia with protein droplets diagnostic of collapsing glomerulopathy (Jones' silver stain, original magnification $\times 400$). [full color online](#)

glomerulonephritis, yet a 5-fold increased rate of new cases was described in London, United Kingdom, during the COVID-19 pandemic, of which half had detectable antibody to SARS-CoV-2.⁵² Pulmonary injury due to COVID-19, as proposed for influenza and other infectious insults, has been postulated to precede onset of antglomerular basement membrane antibody nephritis by exposing the cryptic target Goodpasture antigen, consisting of particular epitopes in COL4A3, in damaged alveolar capillary basement membranes. Thus, COVID-19 could initiate an aberrant adaptive immune response targeting the basement membrane. Hypercytokinemia due to COVID-19 may also promote heightened adaptive autoimmune and allo-immune responses that trigger crescentic transformation of longstanding stable lupus nephritis and acute T cell-mediated rejection in allografts of patients with preformed donor-specific antibodies.³⁶

Renal Findings at Autopsy

Postmortem examinations of patients who died from SARS-CoV-2 infection likely represent more severe manifestations of COVID-19, yet have shed light on the causes of AKI and are summarized in **Table 1**. Acute tubular injury is the leading cause of renal dysfunction, and in most cases, there are no distinguishing features of the ATI in this setting on light microscopy. There is tubular epithelial cell flattening, detachment of epithelial cells from the tubular basement membrane, and formation of granular casts (**Figure 2**). On occasion, myoglobin casts are noted (**Figure 3**) and a few reports have noted isometric tubular epithelial cell cytoplasmic vacuolation.^{2,41,55} In *Su et al*,⁵⁵ this could be attributed to mannitol and intravenous immunoglobulin administration, whereas *Farkash et al*.⁴¹ hypothesize that this could be related to viral infection of tubular epithelial cells; however, identification of virus in the tubular epithelial cell using a variety of methods has proven controversial.^{41,55} Interstitial inflammation is minor and confined to areas of interstitial fibrosis, without tubulitis; therefore, renal failure cannot be attributed to active tubulointerstitial nephritis. A substantial proportion of cases show areas of tubulointerstitial fibrosis, often in association with global glomerulosclerosis and arterial intimal thickening and was therefore attributed to hypertensive nephropathy.^{58,61}

Arterial thrombi have been described in a number of organs in severe COVID-19, including the kidney, in keeping with the clinical finding that patients with severe COVID-19 have features of a distinctive coagulopathy, with a combination of incomplete features from both disseminated intravascular coagulation and TMA.⁶² The thrombi likely contribute to some degree to organ dysfunction. Thrombi containing fibrin or platelets were noted in kidneys in several studies, but, in contrast to autopsies from patients with disseminated intravascular coagulation, were usually very focal, only affecting some arteries (**Figure 4**) and some glomeruli (**Figure 5**).⁶³ Endothelialitis affected the arteries in one study, leading to the suggestion that local endothelial cell injury might play a role in the pathogenesis of the intravascular thrombi. Platelet thrombi are also noted in microvasculature.^{54,59} Arteries often show features of pre-existing arteriosclerosis, with fibrous intimal thickening, as would be expected in an older age group with frequent

Table 1. Kidney Findings at Autopsy

	Type of Biopsy	Number of Cases: Total (Kidney)	Tubulointerstitium	Glomeruli	Blood Vessels
<i>Diao et al.</i> ⁵³	Autopsy	6	ATI (6/6); interstitial inflammation NOS (5/6)	Hypertensive glomerulosclerosis (3/6)	Endothelialitis in 2/2 (1/2 renal transplant)
<i>Varga et al.</i> ⁵⁴	Autopsy	3 (2)	ATI; pyelonephritis (2/26); pigmented casts possibly myoglobin (3/26); hemosiderin granules (4/26)	FSGS NOS (2/26); mesangial sclerosis (2/26); segmental fibrin thrombi (3/26); erythrocyte aggregation	Arteriosclerosis (25/26); erythrocyte aggregation in PTC; arteritis (1/26) attributed to pyelonephritis
<i>Su et al.</i> ⁵⁵	Autopsy	26	ATI (numbers not reported)	Diabetic nephropathy (numbers not reported)	Arteriosclerosis (numbers not reported)
<i>Bradley et al.</i> ⁵⁶	Autopsy	12	ATI (1/1)	Thrombi (3/17); mesangial sclerosis (2/17)	Arteriosclerosis (2/17)
<i>Farkash et al.</i> ⁴¹	Autopsy	1	ATI (1/15)	Microaneurysm (1/9); thrombi (1/9)	Arterial thrombi (4/9); arteriosclerosis (9/9)
<i>Menter et al.</i> ²	Autopsy	21 (15–17)	ATI (3/8)	Diffuse mesangial sclerosis (4/25); nodular mesangial sclerosis (2/25); congestion and platelet aggregation (numbers not reported)	Arteriosclerosis; congestion and platelet aggregation in vasa recta/PTC (numbers not reported)
<i>Martines et al.</i> ⁵⁷	Autopsy	8	ATI (9/9); myoglobin casts (1/9); tubular atrophy/interstitial fibrosis (2/9)	Diffuse mesangial sclerosis (2/12); nodular mesangial sclerosis (1/12)	Arteriosclerosis (11/12)
<i>Hanley et al.</i> ⁵⁸	Autopsy	10 (9)	ATI (6/25); calcium phosphate crystals (4/25)	Diffuse or nodular mesangial sclerosis (8/42); collapsing FSGS (1/42); secondary IgAN (liver disease; 1/42); thrombi (4/42)	Focal arterial thrombi (3/42); arteriosclerosis (42/42)
<i>Bryce et al.</i> ⁵⁹	Autopsy	67 (25)	ATI (12/12); mild active tubulointerstitial nephritis (1/12); oxalate crystals (1/12); urate crystals (1/12)		
<i>Golmai et al.</i> ⁶⁰	Autopsy	12	ATI (19/31); microinfarction (1/42)		
<i>Santoriello et al.</i> ⁶¹	Autopsy	42			

None of the studies show definitive evidence of coronavirus in the kidney. ATI, acute tubular injury; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; NOS, not otherwise specified; PTC, peritubular capillaries.

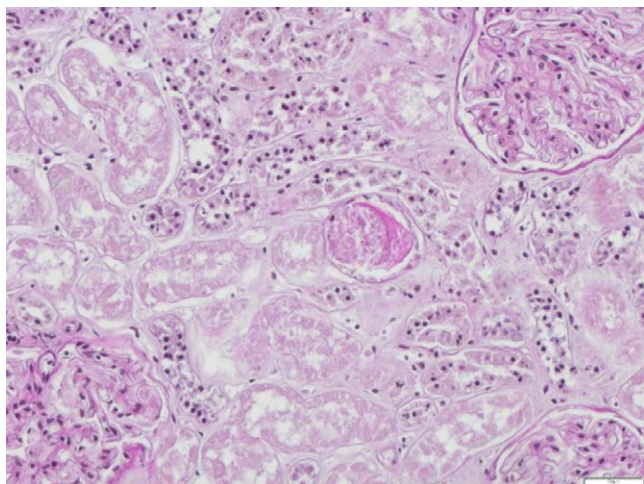


Figure 2. Acute tubular injury with cytoplasmic vacuolization, blebbing, and loss of brush border (periodic acid Schiff, original magnification $\times 200$). [full color online](#)

hypertension. The peritubular capillary network may contain red blood cell “rolls.”⁵⁵

Glomeruli most often show nonspecific features such as ischemic tuft shrinkage, which is often seen in association with severe ATI. Glomeruli in some cases show evidence of pre-existing renal disease, in the form of global glomerulosclerosis, focal and segmental glomerulosclerosis and diffuse or nodular mesangial sclerosis, in many cases due to diabetic nephropathy.^{2,43,54,56,58,59,61} In one case series, a single patient presented with features of collapsing focal and segmental glomerulosclerosis.⁶¹ In a single case in one report, a single glomerulus showed microaneurysmal change indicative of endothelial injury.⁵⁸

In summary, postmortem examinations have revealed the predominant causes of AKI in patients deceased with COVID-19 to be ATI, with a possible contribution of focal macro- and microvascular thrombi. Important negative findings for patient management and prognosis are the near-complete absence of virus-related collapsing FSGS, immune complex glomerulonephritis, and active tubulointerstitial nephritis. Although a few cases showed very focal vascular inflammation (one study), glomerular microaneurysmal change (**Figure 6**) (one study), and glomerular or arterial thrombosis, in no report were the

changes widespread. The findings are in most respects the same as those reported in sepsis-associated AKI.⁶³ Histological evidence of underlying chronic kidney disease is frequent and mostly related to hypertensive arterionephrosclerosis and diabetes.

Attempts to assign any of these postmortem findings specifically to the effects of COVID-19 would benefit from inclusion of adequate control (non-COVID-19-related) intensive care deaths for comparison, and the use of ancillary studies to identify virus and investigate pathophysiological pathways. Findings to date using immunohistochemistry, *in situ* hybridization and EM in the autopsy series are covered below. A major limitation of such ancillary studies is the often-advanced state of autolysis present in postmortem kidneys. Electron microscopy done on autopsy tissue shows profound alteration of cell membranes and cytoplasm, making identification of normal cellular structures or virus difficult.

Ancillary Studies

Electron microscopy is an important tool in detecting novel viruses and establishing their tissue tropism. Human coronavirus was first described by virologists Almeida and Tyrell⁶⁴ in 1967, using negative staining EM on human nasal and tracheal epithelial cells grown in culture and infected with “nasal washings from a patient with a cold.”⁸ Almeida and Tyrell⁶⁴ named the new virus coronavirus due to the presence of surface spikes, which on negative staining EM photographs “recalled the solar corona.”

Transmission EM has been used to document the ultrastructural features of active coronavirus replication in infected cell cultures.^{65,66} Infected cells contain an often conspicuous viral replicative organelle. The replicative organelle is induced in infected cells by viral nonstructural proteins, and comprises convoluted membranes, double-membrane vesicles and small open double-membrane spherules, all derived from, and remaining connected to, the endoplasmic reticulum (ER).^{67,68} Virions assemble in and acquire their membrane from the ER–Golgi intermediate complex, resulting in virions within cisternal spaces derived from this complex.⁶⁹ The virions are transported to the cell membrane within these vesicles, using the usual secretory route of the ER–Golgi complex, and are released by exocytosis. In transmission EM images of infected cells, SARS-CoV-2 virions measure

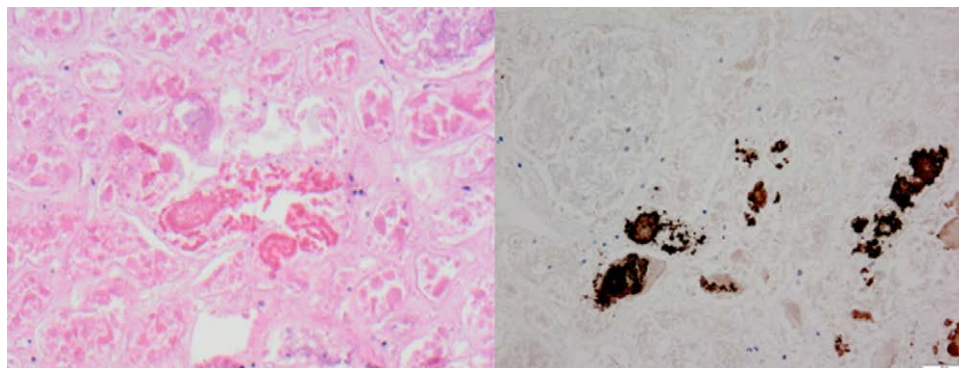


Figure 3. Intratubular globular casts (A) with acute tubular injury, which stain for myoglobin (B) by immunohistochemistry (A, hematoxylin and eosin, original magnification $\times 200$; B, antimyoglobin immunohistochemistry, original magnification $\times 200$).

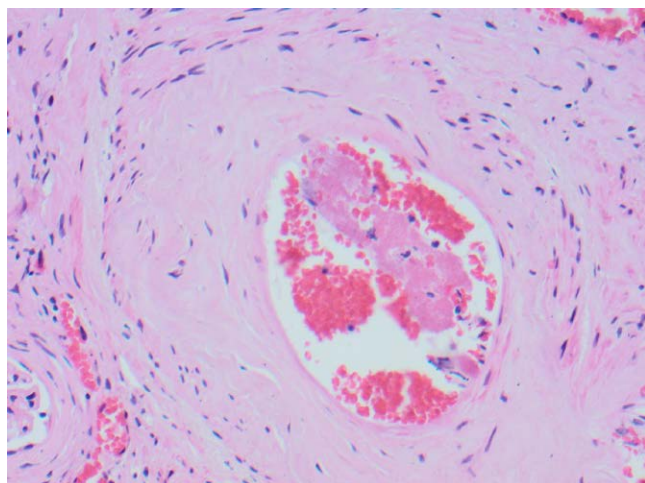


Figure 4. Intra-arterial fibrin thrombus with red blood cells (hematoxylin and eosin, original magnification $\times 200$). [full color online](#)

60–140 nm in diameter, with spikes 9–12 nm length and are found in membrane-bound vesicles within the cytoplasm or outside the cell, near the plasma membrane (**Figure 7**).⁷⁰ The helical viral nucleocapsid produces characteristic black dots within the virion.^{71–73}

Attempts have been made to apply transmission EM to human tissue samples, from both live and deceased patients to document active viral replication within tissues. As could be expected, lower airway samples have yielded the most convincing images of virions, in type II pneumocytes.⁵⁷

Tubular epithelial cells express the ACE2 receptor used for viral entry into cells, and *in vitro* investigations using kidney organoids illustrate the potential for viral replication in the human kidney.⁷⁴

A growing body of literature reports on corona virus-like particles in the kidneys of patients with COVID-19.^{2,41,45,54–56} However, these observations appear to not represent virions, with most of the intracellular structures depicted more likely representing subcellular structures that are part of the endosomal pathway, such as clathrin-coated vesicles and

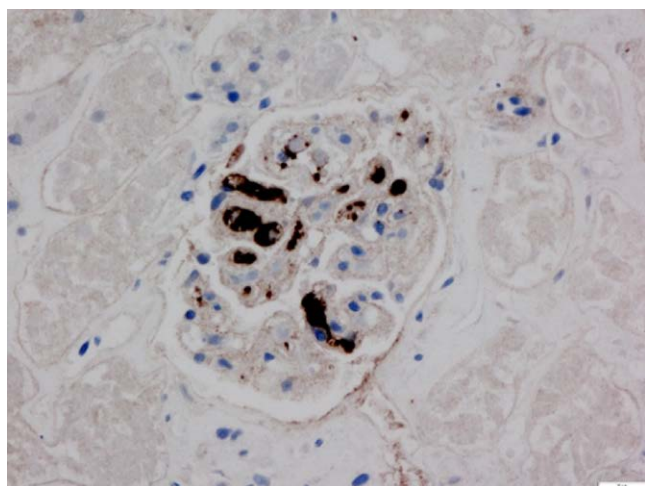


Figure 5. Thrombosis in glomerular capillary loops with CD61-positive staining (anti-CD61 IHC, original magnification $\times 200$). [full color online](#)

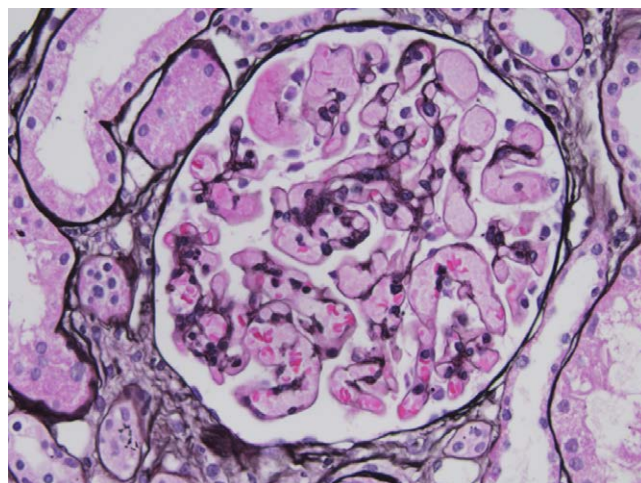


Figure 6. Mesangiolysis with loss of mesangial cells, dissolution of matrix, and microaneurysm formation (Jones' silver stain; original magnification $\times 400$). [full color online](#)

multivesicular bodies, whereas extracellular structures are likely exocytosed elements of this same pathway.^{71,75–78} With respect to telling virions apart from other subcellular structures, intracytoplasmic structures with a “corona” directly projecting into the cytoplasm (rather than into a cisternal space) are likely clathrin-coated vesicles, derived from either endocytosis, from the trans-Golgi network or from endosomes/endolysosomes (**Figure 8**).⁷⁶ Membrane-bound structures containing virus-sized structures but without internal dots, or of variable size, are more likely multivesicular bodies or other structures from the endosomal pathway.

It is notable that most of the observations of alleged virions have been made in tissue samples from postmortem examinations (**Table 2**). A major limitation of such investigations is the often-advanced state of autolysis, which leads to alterations of both membranes and cytoplasm, resulting in indistinct subcellular structures. This makes it particularly difficult in postmortem samples to distinguish virions from intracellular structures to which virions and their replicative organelles bear some resemblance. Tissue samples from live patients are better preserved, and with the exception of one study, virions were not identified in these samples.⁴⁵ On the other hand, it could be argued that live patient samples are typically from patients showing less severe viral infection. This controversy has illustrated the fundamental requirement in histopathological studies for both positive and negative biologic controls, together with “blinded” histological scoring.

Incontrovertible ultrastructural evidence of direct viral infection of renal parenchymal cells *in vivo* in humans is lacking, and it is possible that standard ultrastructural examination will be insufficient, and that immunoelectron microscopy and ultrastructural *in situ* hybridization will be needed to provide definitive evidence. However, these techniques are complicated and not usually applicable to routine samples obtained in a diagnostic histopathology department.

Detection of SARS-CoV-2 viral antigen in formalin-fixed paraffin-embedded tissue would facilitate not only clinical diagnosis of viral infection but would also allow studies to

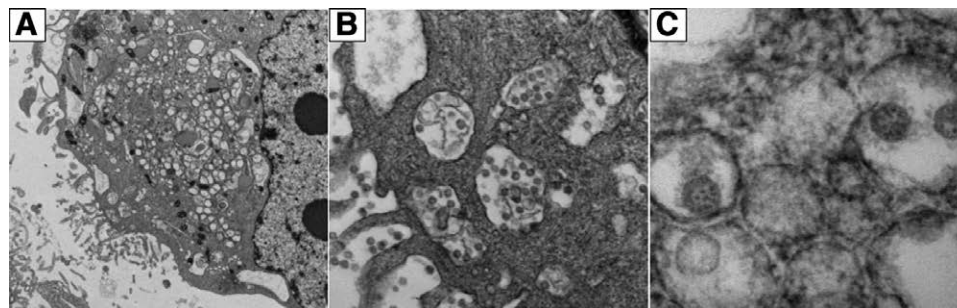


Figure 7. Transmission electron microscopy of SARS-CoV-2-infected Vero cells. **A:** Numerous intracellular vacuoles of dilated endoplasmic reticulum ($\times 1500$). **B:** Intracellular viral particles within the vacuoles and exocytosed viral particles outside the cell (left) ($\times 8000$). **C:** High magnification of vacuoles containing viral particles with cross-sections of nucleocapsids (small dots) ($\times 40,000$). Courtesy of Olivia Swann, Wendy Barclay and Linda Moran. SARS, severe acute respiratory syndrome coronavirus 2.

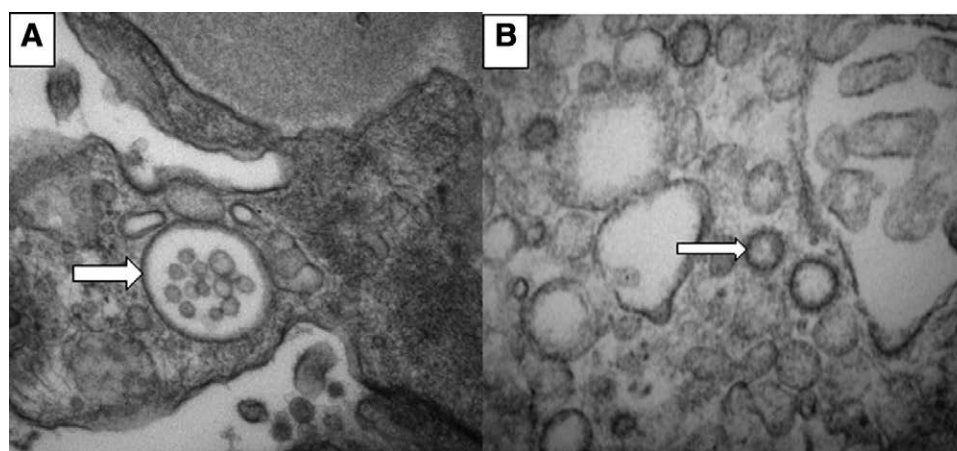


Figure 8. Transmission electron microscopy of coronavirus mimics. **A:** A multivesicular body containing small vesicles (arrow; $\times 10,000$). **B:** A clathrin-coated vesicle; note spikes around the exterior (arrow; $\times 40,000$).

Table 2. Summary of Studies Including EM

	Number of Cases with EM	Main Pathology in Kidney	Coronavirus-Like Particles Reported*	Cell Type(s) with Coronavirus-Like Particles*
Live patient biopsy reports				
Peleg <i>et al.</i> ⁴³	1	Collapsing FSGS	No	Not identified
Gaillard <i>et al.</i> ⁴⁴	1	Collapsing FSGS	No	Not identified
Larsen <i>et al.</i> ⁴²	1	Collapsing FSGS	No	Not identified
Kissling <i>et al.</i> ⁴⁵	1	Collapsing FSGS	Yes	Podocyte
Kudose <i>et al.</i> ³⁶	17	Collapsing FSGS, ATI, TMA, anti-GBM, IC-GN	No	Not identified
Sharma <i>et al.</i> ⁴⁰	10	ATI, collapsing FSGS, ANCA vasculitis, TMA	No	Not identified
Roufousse <i>et al.</i> ⁷⁷	4 (2 cases/2 controls)	Rejection; ANCA vasculitis	No	Not identified
Cassol <i>et al.</i> ⁷⁸	15 (pre- and post-COVID-19 pandemic)	Variety of native and transplant diagnoses	No	Not identified
Akilesh <i>et al.</i> ⁷⁹	16 (native and transplant)	Collapsing FSGS, ATI, TMA	No	Not identified
Nasr <i>et al.</i> ³⁸	12	Collapsing FSGS, ATI	No	Not identified
Deceased patient autopsy reports				
Diao <i>et al.</i> ⁵³	2	ATI; interstitial inflammation	Yes	TEC
Varga <i>et al.</i> ⁵⁴	2	Vasculitis	Yes	Endothelium
Su <i>et al.</i> ⁵⁵	9	ATI; fibrin thrombi	Yes	TEC, podocyte
Bradley <i>et al.</i> ⁵⁶	Not reported	ATI	Yes	TEC, podocyte, endothelium
Farkash <i>et al.</i> ⁴¹	1	ATI	Yes	TEC
Menter <i>et al.</i> ²	2	ATI; thrombi	Yes	TEC, podocyte, endothelium
Martines <i>et al.</i> ⁵⁷	2	ATI	No	Not identified
Bryce <i>et al.</i> ⁵⁹	Not reported	ATI	No	Not identified

*Corona virus-like particles have been reported in the kidney on EM; however, they appear to not represent virions, but subcellular structures.

ANCA, antineutrophil cytoplasmic antibodies; Anti-GBM, antiglomerular basement membrane antibody disease; ATI, acute tubular injury; COVID-19, coronavirus disease 2019; EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; IC-GN, immune complex glomerulonephritis; TEC, tubular epithelial cell; TMA, thrombotic microangiopathy.

advance our understanding of the pathogenesis of its associated disease, COVID-19. As discussed, identification of the virus within renal biopsies and postmortem kidney samples by ultrastructure examination is complicated by confounding normal mimics of viral particles; thus, additional methods for viral detection are needed. In a limited study of two autopsies, SARS-CoV-2 RNA was detected from formalin-fixed paraffin-embedded tissue by quantitative reverse transcription-polymerase chain reaction in both cases.⁸⁰ SARS-CoV-2 viral genome was also successfully sequenced by next-generation sequencing in one of these cases. Although this study was performed on lung tissue, it demonstrates molecular testing from infected tissue with inactivated virus can detect viral RNA and SARS-CoV-2 genome sequencing can be successfully performed on formalin-fixed paraffin-embedded blocks. Testing methodologies more readily available to clinical pathology practices including immunohistochemistry and *in situ* hybridization with commercially available probes have been successfully implemented, though detection of the virus in kidney samples has not been demonstrated.^{50,81}

In summary, a significant subset of patients with COVID-19 experience AKI. Renal biopsy findings in patients with proteinuria and hematuria have demonstrated a glomerular dominant pattern of injury, most notably a collapsing glomerulopathy reminiscent of findings seen in HIVAN. In contrast, postmortem examination of kidneys from patients who died with COVID-19 show ATI as the main morphologic finding. Notably, detection of direct viral infection of the kidney parenchymal cells has not been definitely demonstrated, although clinical and histologic findings suggest this possibility, and there is no single pathognomonic lesion attributable to COVID-19.⁸² Much has been learned about this virus and its effects on the human body within the first months of the current pandemic, but more studies supported by molecular and immunohistochemical tests are needed to fully understand the mechanism of renal injury in this clinical setting.

References

1. Johns Hopkins Coronavirus Resource Center. Available at: <https://coronavirus.jhu.edu>.
2. Menter T, Haslbauer JD, Nienhold R, et al: Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 77: 198–209, 2020.
3. Zaim S, Chong JH, Sankaranarayanan V, Harky A: COVID-19 and multiorgan response. *Curr Probl Cardiol* 45: 100618, 2020.
4. Available at: <https://www.nytimes.com/issue/todayspaper/2020/04/20/todays-new-york-times>.
5. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19: Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382: 1708–1720, 2020.
6. Yuki K, Fujiogi M, Koutsogiannaki S: COVID-19 pathophysiology: A review. *Clin Immunol* 215: 108427, 2020.
7. Rajagopal K, Keller SP, Akkanti B, et al: Advanced pulmonary and cardiac support of COVID-19 patients: Emerging recommendations from ASAIO-A “living working document”. *ASAIO J* 66: 588–598, 2020.
8. Tyrrell DA, Almeida JD, Cunningham CH, et al: Coronaviridae. *Intervirology* 5: 76–82, 1975.
9. Subbarao K, Mahanty S: Respiratory virus infections: Understanding COVID-19. *Immunity* 52: 905–909, 2020.
10. Mortensen ML, Ray CG, Payne CM, Friedman AD, Minnich LL, Rousseau C: Coronaviruslike particles in human gastrointestinal disease. Epidemiologic, clinical, and laboratory observations. *Am J Dis Child* 139: 928–934, 1985.
11. Roth-Cross JK, Bender SJ, Weiss SR: Murine coronavirus mouse hepatitis virus is recognized by MDA5 and induces type I interferon in brain macrophages/microglia. *J Virol* 82: 9829–9838, 2008.
12. Shang J, Wan Y, Luo C, et al: Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A* 117: 11727–11734, 2020.
13. Onder G, Rezza G, Brusaferro S: Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 323: 1775–1776, 2020.
14. Perico L, Benigni A, Remuzzi G: Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. *Nephron* 144: 213–221, 2020.
15. Wrapp D, Wang N, Corbett KS, et al: Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367: 1260–1263, 2020.
16. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L: Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med* 46: 1339–1348, 2020.
17. Ni W, Yang X, Yang D, et al: Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* 24: 422, 2020.
18. Armaly Z, Kinaneh S, Skorecki K: Renal manifestations of Covid-19: Physiology and pathophysiology. *J Clin Med* 10: 1216, 2021.
19. Chueh TI, Zheng CM, Hou YC, Lu KC: Novel evidence of acute kidney injury in COVID-19. *J Clin Med* 9: E3547, 2020.
20. Hirsch JS, Ng JH, Ross DW, et al; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium: Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 98: 209–218, 2020.
21. Lim JH, Park SH, Jeon Y, et al: Fatal outcomes of COVID-19 in patients with severe acute kidney injury. *J Clin Med* 9: E1718, 2020.
22. Zietz M, Zucker J, Tatonetti NP: Associations between blood type and COVID-19 infection, intubation, and death. *Nat Commun* 11: 5761, 2020.
23. Fu J, Kong J, Wang W, et al: The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China. *Thromb Res* 192: 3–8, 2020.
24. Cheng Y, Luo R, Wang K, et al: Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 97: 829–838, 2020.
25. Chan L, Chaudhary K, Saha A, et al: AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 32: 151–160, 2021.
26. Rubin S, Orioux A, Prevel R, et al: Characterization of acute kidney injury in critically ill patients with severe coronavirus disease 2019. *Clin Kidney J* 13: 354–361, 2020.
27. Battle D, Soler MJ, Sparks MA, et al; COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group: Acute kidney injury in COVID-19: Emerging evidence of a distinct pathophysiology. *J Am Soc Nephrol* 31: 1380–1383, 2020.
28. Kopitko C, Medve L, Gondos T: Renoprotective postoperative monitoring: What is the best method for computing renal perfusion pressure? An observational, prospective, multicentre study. *Nephron* 139: 228–236, 2018.
29. Hassanein M, Thomas G, Taliencio J: Management of acute kidney injury in COVID-19 [published online ahead of print May 20, 2020]. *Cleve Clin J Med*. doi: 10.3949/ccjm.87a.ccc034.
30. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA: Is the kidney a target of SARS-CoV-2? *Am J Physiol Renal Physiol* 318: F1454–F1462, 2020.
31. 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* 31: 1688–1695, 2020.
32. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L: SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 54: 62–75, 2020.
33. Park MD: Macrophages: A Trojan horse in COVID-19? *Nat Rev Immunol* 20: 351, 2020.
34. Demaria O, Carvelli J, Batista L, et al: Identification of druggable inhibitory immune checkpoints on natural killer cells in COVID-19. *Cell Mol Immunol* 17: 995–997, 2020.

35. Nadim MK, Forni LG, Mehta RL, et al: COVID-19-associated acute kidney injury: Consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 16: 747–764, 2020.
36. Kudose S, Batal I, Santoriello D, et al: Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol* 31: 1959–1968, 2020.
37. Shetty AA, Tawhari I, Safar-Boueri L, et al: COVID-19-associated glomerular disease. *J Am Soc Nephrol* 32: 33–40, 2021.
38. Nasr SH, Alexander MP, Cornell LD, et al: Kidney biopsy findings in patients with COVID-19, kidney injury, and proteinuria. *Am J Kidney Dis* 77: 465–468, 2021.
39. Werion A, Belkhir L, Perrot M, et al; Cliniques universitaires Saint-Luc (CUSL) COVID-19 Research Group: SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. *Kidney Int* 98: 1296–1307, 2020.
40. Sharma P, Uppal NN, Wanchoo R, et al; Northwell Nephrology COVID-19 Research Consortium: COVID-19-Associated kidney injury: A case series of kidney biopsy findings. *J Am Soc Nephrol* 31: 1948–1958, 2020.
41. Farkash EA, Wilson AM, Jentzen JM: Ultrastructural evidence for direct renal infection with SARS-CoV-2. *J Am Soc Nephrol* 31: 1683–1687, 2020.
42. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA: Collapsing glomerulopathy in a patient with COVID-19. *Kidney Int Rep* 5: 935–939, 2020.
43. Peleg Y, Kudose S, D'Agati V, et al: Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep* 5: 940–945, 2020.
44. Gaillard F, Ismael S, Sannier A, et al: Tubuloreticular inclusions in COVID-19-related collapsing glomerulopathy. *Kidney Int* 98: 241, 2020.
45. Kissling S, Rotman S, Gerber C, et al: Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int* 98: 228–231, 2020.
46. Kopp JB, Nelson GW, Sampath K, et al: APO1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 22: 2129–2137, 2011.
47. Kasembeli AN, Duarte R, Ramsay M, et al: APO1 risk variants are strongly associated with HIV-associated nephropathy in Black South Africans. *J Am Soc Nephrol* 26: 2882–2890, 2015.
48. Lazareth H, Péré H, Binois Y, et al: COVID-19-related collapsing glomerulopathy in a kidney transplant recipient. *Am J Kidney Dis* 6: 590–594, 2020.
49. Datta S, Kataria R, Zhang JY, et al: Kidney disease-associated APO1 variants have dose-dependent, dominant toxic gain-of-function. *J Am Soc Nephrol* 31: 2083–2096, 2020.
50. Best Rocha A, Stroberg E, Barton LM, et al: Detection of SARS-CoV-2 in formalin-fixed paraffin-embedded tissue sections using commercially available reagents. *Lab Invest* 100: 1485–1489, 2020.
51. Rednor SJ, Ross MJ: Molecular mechanisms of injury in HIV-associated nephropathy. *Front Med (Lausanne)* 5: 177, 2018.
52. Predecki M, Clarke C, Cairns T, et al: Anti-glomerular basement membrane disease during the COVID-19 pandemic. *Kidney Int* 98: 780–781, 2020.
53. Diao B, Wang C, Wang R, et al: Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. *Nat Commun* 12: 2506, 2021.
54. Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395: 1417–1418, 2020.
55. Su H, Yang M, Wan C, et al: Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 98: 219–227, 2020.
56. Bradley BT, Maioli H, Johnston R, et al: Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: A case series. *Lancet* 396: 320–332, 2020.
57. Martines RB, Ritter JM, Matkovic E, et al; COVID-19 Pathology Working Group: Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. *Emerg Infect Dis* 26: 2005–2015, 2020.
58. Hanley B, Naresh KN, Roufousse C, et al: Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: A post-mortem study. *Lancet Microbe* 1: e245–e253, 2020.
59. Bryce C, Grimes Z, Pujadas E, et al: Pathophysiology of SARS-CoV-2: Targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. medRxiv. Preprint posted online May 22, 2020. doi: 10.1101/2020.05.18.20099960.
60. 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* 31: 1944–1947, 2020.
61. Santoriello D, Khairallah P, Bomback AS, et al: Postmortem kidney pathology findings in patients with COVID-19. *J Am Soc Nephrol* 31: 2158–2167, 2020.
62. Levi M: COVID-19 coagulopathy vs disseminated intravascular coagulation. *Blood Adv* 4: 2850, 2020.
63. Lucas S: The autopsy pathology of sepsis-related death. *Curr Diagn Pathol* 13: 375–388, 2007.
64. Almeida JD, Tyrrell DA: The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. *J Gen Virol* 1: 175–178, 1967.
65. Knoop K, Kikkert M, Worm SH, et al: SARS-coronavirus replication is supported by a reticulovascular network of modified endoplasmic reticulum. *PLoS Biol* 6: e226, 2008.
66. Snijder EJ, Limpens RWAL, de Wilde AH, et al: A unifying structural and functional model of the coronavirus replication organelle: Tracking down RNA synthesis. *PLoS Biol* 18: e3000715, 2020.
67. Hagemeyer MC, Monastyrska I, Griffith J, et al: Membrane rearrangements mediated by coronavirus nonstructural proteins 3 and 4. *Virology* 458–459: 125–135, 2014.
68. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, et al: Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. *J Virol* 80: 5927–5940, 2006.
69. Fung TS, Liu DX: Human coronavirus: Host-pathogen interaction. *Annu Rev Microbiol* 73: 529–557, 2019.
70. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team: A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 382: 727–733, 2020.
71. Goldsmith CS, Miller SE, Martines RB, Bullock HA, Zaki SR: Electron microscopy of SARS-CoV-2: A challenging task. *Lancet* 395: e99, 2020.
72. Harcourt J, Tamin A, Lu X, et al: Severe acute respiratory syndrome coronavirus 2 from patient with coronavirus disease, United States. *Emerg Infect Dis* 26: 1266–1273, 2020.
73. Goldsmith CS, Miller SE: Modern uses of electron microscopy for detection of viruses. *Clin Microbiol Rev* 22: 552–563, 2009.
74. 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* 181: 905–913.e7, 2020.
75. Calomeni E, Satoskar A, Ayoub I, Brodsky S, Rovin BH, Nadasdy T: Multivesicular bodies mimicking SARS-CoV-2 in patients without COVID-19. *Kidney Int* 98: 233–234, 2020.
76. Miller SE, Brealey JK: Visualization of putative coronavirus in kidney. *Kidney Int* 98: 231–232, 2020.
77. Roufousse C, Curtis E, Moran L, et al: Electron microscopic investigations in COVID-19: Not all crowns are coronas. *Kidney Int* 98: 505–506, 2020.
78. Cassol CA, Gokden N, Larsen CP, et al: Appearances can be deceiving - viral-like inclusions in COVID-19 negative renal biopsies by electron microscopy. *Kidney360* 1: 824, 2020.
79. Akilesh S, Nast CC, Yamashita M, et al: Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. *Am J Kidney Dis* 77: 82–93.e1, 2021.
80. Sekulic M, Harper H, Nezami BG, et al: Molecular detection of SARS-CoV-2 infection in FFPE samples and histopathologic findings in fatal SARS-CoV-2 Cases. *Am J Clin Pathol* 154: 190–200, 2020.
81. Liu J, Babka AM, Kearney BJ, Radoshitzky SR, Kuhn JH, Zeng X: Molecular detection of SARS-CoV-2 in formalin-fixed, paraffin-embedded specimens. *JCI Insight* 5: 139042, 2020.
82. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN: COVID-19 and the kidney: What we think we know so far and what we don't. *J Nephrol* 33: 1213–1218, 2020.