Pathophysiology and Pathology of Acute Kidney Injury in Patients With COVID-19

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Acute kidney injury (AKI) is common among hospitalized patients with Coronavirus Infectious Disease 2019 (COVID-19), with the occurrence of AKI ranging from 0.5% to 80%. The variability in the occurrence of AKI has been attributed to the difference in geographic locations, race/ethnicity, and severity of illness. AKI among hospitalized patients is associated with increased length of stay and in-hospital deaths. Even patients with AKI who survive to hospital discharge are at risk of developing chronic kidney disease or end-stage kidney disease. An improved knowledge of the pathophysiology of AKI in COVID-19 is crucial to mitigate and manage AKI and to improve the survival of patients who developed AKI during COVID-19. The goal of this article is to provide our current understanding of the etiology and the pathophysiology of AKI in the setting of COVID-19.
Key Words: AKI, COVID-19, Collapsing GN, Pathology, Kidney failure

Acute kidney injury (AKI) has been reported to be a common complication among hospitalized patients with Coronavirus Disease 2019 (COVID-19), with the occurrence of AKI ranging from 0.5% to 80%.[1–5] The understanding of the pathophysiology of AKI in the setting of COVID-19 is rapidly evolving; review of the current literature has demonstrated several etiologies: (1) prerenal azotemia, (2) proximal tubular injury, (3) glomerulopathy, (4) thrombotic microangiopathy, and (5) complications from the treatment of COVID-19. The pathogenesis of kidney injury in patients infected with severe acute respiratory virus-2 (SARS-CoV-2) is multifactorial (Fig 1).

Case 1

A 26-year-old man presented with acute shortness of breath and fevers. He was hospitalized and diagnosed with COVID-19. His body mass index on admission was 39 kg/m^2. On the urinalysis, he had hematuria and proteinuria. The spot urine to protein creatinine ratio was 1.2 g/g of protein/creatinine. His serum creatinine was 2.9 mg/dL (baseline of 0.8 mg/dl). His urine sediment showed muddy brown casts and hyaline casts. He had a prior medical history of obstructive sleep apnea. His clinical condition worsened as his inflammatory markers rose (ferritin, C-reactive protein, D-Dimer). He was intubated and transferred to the intensive care unit. Kidney function deteriorated, and he became anuric. Dialysis was initiated. A kidney sonogram showed no hydronephrosis; right kidney was 13 cm, and left kidney was 14 cm.

PRERENAL AZOTEMIA

Patients with COVID-19 often present with fever, volume depletion, and shortness of breath. In addition, around 10% of patients with COVID-19 experienced at least one gastrointestinal symptom (nausea, vomiting, or diarrhea),[6,7] all of which contributed to fluid losses. In a study from New York, 66% of the patients with AKI had a urine Na of <35 mmol/L, suggestive of a prerenal state or low effective arterial blood volume from heart failure or liver cirrhosis.[2] Based on a study by Mohamed and colleagues, prerenal azotemia accounted for 9-10% of AKI in patients with COVID-19.[8] While most cases of prerenal AKI were

from hypovolemia, some cases of AKI resulted from acute cardio-renal syndrome associated with COVID-19.[9]

ACUTE TUBULAR INJURY

Evidence to date shows that the vast majority of AKI cases in patients with COVID-19 were related to acute tubular injury. From a single-center study in the United States (US),[8] greater than 60% of AKI cases were attributed to acute tubular injury either from ischemic or toxic tubular injury. Several publications examining native kidney biopsy and autopsy have demonstrated acute tubular injury as the most common pathologic finding in patients with COVID-19 and concomitant AKI.[10–14] Acute tubular injury may occur in the setting of prolonged volume depletion and hemodynamic states that reduce kidney perfusion. In severe COVID-19, viral infection in type II alveolar cells results in immune cell recruitment, which

produce an abundance of cytokines that can lead to circulatory collapse.[15] From our background knowledge of sepsis-induced AKI, the exact pathophysiology of this illness is not known. However, it is generally accepted that it results from multifactorial injuries. This form of AKI has components of ischemia-reperfusion injury, direct inflammatory injury, coagulation and endothelial cell dysfunction, and apoptosis.[16] Table 1 and Figure 2 summarize the kidney biopsy findings in patients with COVID-19 and AKI that have been published at the time of writing this article (September 2020). Based on this series, the median age of 9 patients who developed acute tubular injury was 63 years (interquartile range [IQR], 54 to 69). The median peak serum creatinine was 4.8 mg/dL (IQR, 4.4 to 5.8). Two out of the 9 patients died, and among those who survived, one patient remained on dialysis upon discharge. It is important to note that kidney biopsies are typically not carried out for patients with a clinical diagnosis of acute tubular injury. Thus, the kidney biopsy series that have been published reflect "for-cause" biopsies and may not reflect the full extent of acute tubular injury in COVID-19.

Hyperinflammation has been associated with COVID-19.[15] The type of hyperinflammation observed in patients with severe COVID-19 is similar to hemophagocytic syndrome-related cytokine release. Secondary hemophagocytic lymphohistiocytosis is an underrecognized, hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure. In adults, secondary hemophagocytic lymphohistiocytosis is most commonly triggered by viral infections and occurs in 3.7–4.3% of patients with sepsis and is sometimes referred to as macrophage activation syndrome.[17,18] Cardinal features of this syndrome include unremitting fever, cytopenias, and hyperferritinemia. Pulmonary involvement such as acute respiratory distress syndrome (ARDS) occurs in approximately 50% of patients with secondary hemophagocytic lymphohistiocytosis.[19] A cytokine profile resembling this hemophagocytic syndrome is associated with COVID-19 severity, characterized by increased interleukin (IL)-2, 6, 7, granulocyte colony–stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. Many studies have now shown high ferritin levels as a predictor of mortality.[20] The incidence of AKI during hemophagocytic lymphohistiocytosis is high (62% [59/95]), of whom 59% (35/59) require kidney replacement therapy. The main causes of AKI in patients with hemophagocytic lymphohistiocytosis are acute tubular injury (49%), hypoperfusion (46%), tumor lysis syndrome (29%), or hemophagocytic lymphohistiocytosis–associated glomerulopathies (17%).[21,22] Similar patho-

physiology of hyperinflammation could lead to acute tubular injury seen with COVID-19. The proinflammatory IL-6 is thought to be the principal cytokine that drives hyperinflammation in many of these syndromes. Among patients with COVID-19, the plasma concentration of IL-6 has been shown to be increased in those with ARDS.[23] Cytokine overproduction is also thought to mediate a crosstalk between the lung and kidney leading to bidirectional damage.[24] Injured kidney tubular epithelium leads to an upregulation of IL-6. Human and animal studies have shown increased levels of serum IL-6 in patients with AKI, and this was associated with higher alveolar-capillary permeability and pulmonary hemorrhage.[25,26] ARDS has been shown to induce kidney medullary hypoxia, which may act as an additional insult to tubular epithelial cells.[24]

Tubular injury from rhabdomyolysis[10] and a severe form of hyperinflammation[27] should be considered in the differential diagnosis of AKI in patients with COVID-19. Patel and colleagues.[27] reported a series of patients with hypermetabolism-related AKI, with striking elevations in uric acid, phosphorus, and potassium levels; lactate-negative anion gap; metabolic acidosis; and drastic decreases in serum albumin levels. There was no evidence of tumor lysis syndrome or rhabdomyolysis. While severe acute tubular injury associated with sepsis can present with rapid AKI, such hypercatabolic states in COVID-19 can also be the cause of severe prerenal azotemia and tubular injury.

Proximal tubular damage leading to AKI along with several electrolyte disorders has been described as well. In a cohort of 49 patients requiring hospitalization in a large academic hospital in Belgium, the investigators found evidence of proximal tubule dysfunction in a subset of patients with COVID-19, as attested by low-molecular-weight proteinuria (70-80%), neutral aminoaciduria (46%), and defective handling of uric acid (46%) or phosphate (19%).[28] Among these 49 patients, 22% developed AKI. At the structural level, 6 kidney autopsy samples from patients with COVID-19 showed prominent tubular injury, including in the initial part of the proximal tubule, with loss of brush borders, epithelial cell necrosis, collections of intraluminal debris, and a marked decrease in the expression of megalin in the brush border.[28] Interstitial disease was not as common as tubular injury, observed only in 2 out of the 6 patients.[28]

CLINICAL SUMMARY

- The most common cause of kidney injury in patients with COVID-19 is acute tubular injury.

- Collapsing glomerulopathy is a recognized glomerular pathology associated with COVID-19 that most commonly affects individuals with high-risk *APOL1* polymorphisms.

- Other glomerular pathology associated with COVID-19 might be coincidental or a "second hit" phenomenon.

- It is unclear at this point if SARS-CoV-2 directly infects the kidney.

Case 2

A 67-year-old man presented with acute shortness of breath and fever. He was hospitalized and diagnosed with COVID-19. On the urinalysis, he had hematuria (moderate with 10-20 RBCs) and proteinuria (4+). The 24-hour urine showed 19 g of proteinuria. His serum creatinine was 2.0 mg/dL (baseline of

1.1 mg/dL). He had a prior medical history of diabetes mellitus type 2, hypertension, and gout. His clinical condition worsened as his ferritin, C-reactive protein, and D-Dimer increased. He was intubated and transferred to the ICU. His kidney function deteriorated, and he became anuric. Dialysis was initiated. A kidney sonogram revealed no evidence of hydronephrosis; right kidney was 14.5 cm, and left kidney was 16 cm.

GLOMERULAR DISEASES

Glomerular diseases have been reported in association with COVID-19. Collapsing glomerulopathy (CG) is the most common form of glomerular disease, but other forms have been reported with variable frequencies.[10,11,29–37] CG has emerged as a distinct pathology associated with SARS-CoV-2 infection, which seems to specifically affect individuals of African ancestry who have high-risk *APOL1* genotypes (G1/G1, G1/G2, or G2/G2). To date, 24 cases of CG have been published in patients with COVID-19. A total of 18 of 22 of the cases mentioned had *APOL1* polymorphisms (12/18 with homozygous G1/G1 and 6/18 with heterozygous G1/G2). All cases presented with AKI or nephrotic syndrome; 23/24 (96%) patients were of Black race or of African or African-American heritage, and 1 patient was of Asian (Indian) origin. Most of the cases, 19/24 (79%), were from the United States and remaining from Europe, whereby 10/24 (42%) patients remained dialysis-dependent, and 20/24 (83%) patients were alive at the time of this writing (September 2020). Among those who were off of dialysis, the median serum creatinine upon discharge was 2.9 mg/dL (IQR, 2.6 to 3.6).

The pathogenesis of COVID-19–associated CG is unclear. CG is a histopathological feature that has been associated with other viral infections; most characteristically seen in HIV-associated nephropathy (HIVAN), but also seen in Epstein-Barr virus, cytomegalovirus, and parvovirus B19.[38] How different viral infections would result in similar histopathological findings is worth exploring. Some have proposed a direct viral involvement in CG, particularly in HIVAN[39] and parvovirus B19,[40] and others suggest that this may result from the systemic response to infection and hyperinflammation.[41] In COVID-19, the inflammatory milieu may trigger or exacerbate immune-mediated diseases in predisposed patients.[6,10,11] Virus-induced hyperinflammation causes massive release of granulocyte colony–stimulating factor, various ILs, and interferons.[20,42,43]

APOL1 expression is upregulated by viral infections and other inflammatory diseases that activate interferons and toll-like receptor-3.[44] Viral infections stimulate host interferon production, and interferon is a potent stimulus to APOL1 gene expression.[44] Thus, in individuals with high-risk *APOL1* genotypes (which are most common in persons of West African ancestry), SARS-CoV-2 infection and the resulting hyperinflammation may act as a "second hit" that leads to podocyte dysregulation, injury, and CG.[45]

Other glomerular diseases, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis,[10,46,47] anti-glomerular basement membrane (GBM) disease,[48] and immunoglobulin A vasculitis without nephropathy[49]
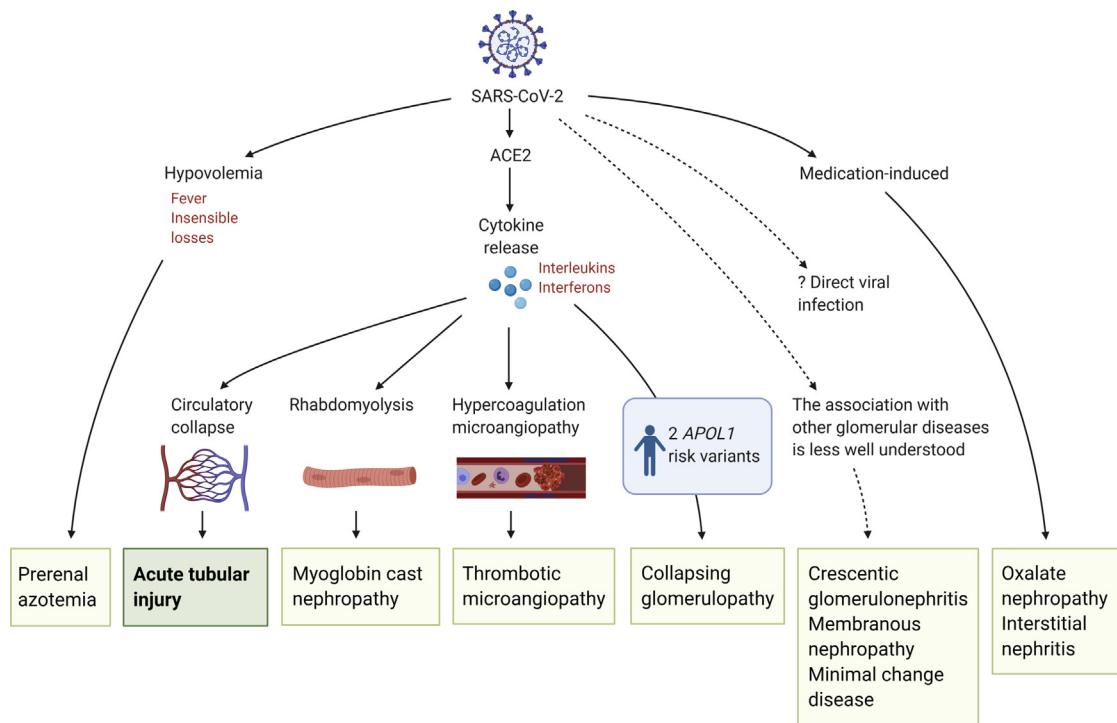
Figure 1. Various pathophysiological mechanisms associated with COVID-19–related acute kidney injury. Dashed line, the association is less well understood. Dark green box and bolded font, acute tubular injury is the predominant mechanism for acute kidney injury. ACE2, angiotensin-converting enzyme 2; COVID-19, Coronavirus Infectious Disease 2019; SARS-CoV-2, severe acute respiratory virus-2. (Figure 1 was created using Biorender.com.)

Table 1. Summary of Kidney Pathology Findings and Clinical Presentation of AKI Among Patients With COVID-19

Case #	Pathology	Age	Sex	Race/ Ethnicity*	Kidney Presentation	SCr† (mg/dL)	Proteinuria (g/g)	KRT	Kidney outcome‡	Patient Outcome	Other	Risk Alleles	Country	Reference§
Acute tubular injury														
1	ATI	43	Female	Black	AKI	6.7	NA	Yes	NA	NA			USA	Kudose (JASN)[11]
2	ATI	54	Female	Hispanic	AKI	2.9	0.2	No	2.2	Alive	Kidney transplant		USA	Kudose (JASN)[11]
3	ATI	67	Male	White	AKI	5.7	NA	Yes	Dialysis-dependent	Alive			USA	Kudose (JASN)[11]
4	ATI	51	Male	Black	AKI	4.8	0.5	No	2.5	Alive			USA	Kudose (JASN)[11]
5	ATI	62	Male	Hispanic	AKI	6.3	NA	Yes	Dialysis-dependent	Died			USA	Sharma (JASN)[10]
6	ATI	69	Male	Hispanic	AKI, proteinuria	5.8	2.4	Yes	Dialysis-dependent	Died			USA	Sharma (JASN)[10]
7	ATI	76	Female	White	AKI	4.4	0.9	No	4.4	Alive			USA	Sharma (JASN)[10]
8	ATI	59	Male	AA	AKI	4.5	2.8	No	5.6	Alive			USA	Sharma (JASN)[10]
9	ATI	69	Female	AA	AKI, proteinuria	1.9	7.6	No	1.9	Alive			USA	Sharma (JASN)[10]
Collapsing glomerulopathy with acute tubular injury														
1	CG + ATI	46	Male	Black	AKI, NS	12.5	5.8	Yes	Dialysis-dependent	Alive	APOL1+	G1/G1	USA	Kudose (JASN)[11]
2	CG + ATI	62	Male	Black	AKI, NS	10.7	12.1	No	3.8	Alive	APOL1+	G1/G1	USA	Kudose (JASN)[11]
3	CG + ATI	62	Male	Black	AKI, Proteinuria	11.6	19.0	No	2.3	Alive	APOL1+	G1/G2	USA	Kudose (JASN)[11]
4	CG + ATI	57	Male	Black	AKI, proteinuria	4.9	6.2	No	4.9	Alive			USA	Kudose (JASN)[11]
5	CG + ATI	61	Male	Black	AKI, Proteinuria	15.0	9.0	Yes	Dialysis-dependent	Alive			USA	Kudose (JASN)[11]
6	CG + ATI	63	Male	Black	AKI, NS	4.9	12.7	Yes	Dialysis-dependent	Alive	APOL1+	G1/G1	USA	Wu (JASN)[31]
7	CG + ATI	64	Female	Black	AKI, NS	4.2	4.6	No	3.1	Alive	APOL1+	G2/G2	USA	Wu (JASN)[31]
8	CG + ATI	65	Female	Black	AKI, NS	2.9	13.6	Yes	Dialysis-dependent	Died	APOL1+	G1/G1	USA	Wu (JASN)[31]
9	CG + ATI	44	Male	Black	AKI, NS	11.4	25.0	Yes	Dialysis-dependent	Alive	APOL1+	G1/G1	USA	Wu (JASN)[31]
10	CG + ATI	37	Male	Black	AKI, NS	9.0	NA	Yes	Dialysis-dependent	Died	APOL1+	G1/G2	USA	Wu (JASN)[31]
11	CG + ATI	56	Male	Black	AKI, NS	6.7	3.6	Yes	2.8	Alive	APOL1+	G1/G1	USA	Wu (JASN)[31]

(*Continued*)

Table 1. Summary of Kidney Pathology Findings and Clinical Presentation of AKI Among Patients With COVID-19 (*Continued*)

Case #	Pathology	Age	Sex	Race/Ethnicity*	Kidney Presentation	SCr† (mg/dL)	Proteinuria (g/g)	KRT	Kidney outcome‡	Patient Outcome	Other	Risk Alleles	Country	Reference§
12	CG + ATI	67	Female	AA	AKI, NS	2.2	3.2	Yes	Dialysis-dependent	Alive	APOL1+	G1/G2	USA	Sharma (KM)[30]
13	CG + ATI	49	Male	AA	AKI, NS	4.8	2.5	Yes	Dialysis-dependent	Alive	APOL1+	G1/G2	USA	Sharma (KM)[30]
14	CG + ATI	56	Male	African	AKI, proteinuria	1.8	1.8	No	1.4	Alive	APOL1+	G1/G1	France	Courturier (CKJ)[35]
15	CG + ATI	52	Male	African	AKI, proteinuria	6.2	2.8	No	2.2	Alive	APOL1+	G1/G2	France	Courturier (CKJ)[35]
16	CG + ATI	28	Female	AA	AKI, NS	6.5	2.0	Yes	Off dialysis	Alive	APOL1+	G1/G1	USA	Magoon (KM)[29]
17	CG + ATI	56	Male	AA	AKI, NS	7.2	21.0	Yes	Off dialysis	Alive	APOL1+	G1/G1	USA	Magoon (KM)[29]
18	CG + ATI	63	Male	Black	AKI, NS	4.4	4.0	No	5.5	Alive	APOL1+	G1/G1	Switzerland	Kissling (KI)[32]
19	CG + ATI	44	Female	AA	AKI, NS	4.0	3.9	Yes	Dialysis-dependent	Alive			USA	Larsen (KIR)[34]
20	CG + ATI	77	Female	AA	AKI, Proteinuria	8.1	1.5	Yes	3.0	Alive			USA	Sharma (JASN)[10]
21	CG + ATI	71	Male	Asian	AKI, NS	4.4	18.4	Yes	Dialysis-dependent	Alive	Initial biopsy MCD, repeat biopsy was CG		USA	Gupta (BMCN)[36]
22	CG + ATI	54	Male	Black	AKI, NS	4.5	16.0	No	NA	Alive			USA	Gupta (BMCN)[36]
23	CG + ATI	49	Female	Black	AKI	8.7	20.0	Yes	2.8	Alive	APOL1+	G1/G1	France	Izzedine (IMJ)[37]
24	CG + ATI	38	Female	Black	AKI	11.7	19.0	No	2.9	Alive	APOL1+	G1/G1	France	Izzedine (IMJ)[37]
Others														
1	Myoglobin cast nephropathy	28	Male	Black	AKI	9.0	NA	Yes	1.2	Alive			USA	Kudose (JASN)[11]
2	Myoglobin cast nephropathy	60	Male	Hispanic	AKI	8.1	4.7	Yes	Dialysis-dependent	Died			USA	Sharma (JASN)[10]
3	Oxalate nephropathy	50	Male	White	AKI	5.8	0.2	Yes	4.0	Alive			Italy	Fontana (KIR)[61]
4	Oxalate nephropathy	71	Male	White	AKI	6.5	1.2	Yes	4.4	Alive			Italy	Fontana (KIR)[61]
5	LN Class 4 + 5	27	Female	Asian	AKI, NS	2.5	9.2	No	NA	Died	Systemic lupus erythematosus		USA	Kudose (JASN)[11]
6	MN (Plar2+)	72	Male	White	NS	0.8	8.8	No	1.3	Alive			USA	Kudose (JASN)[11]
7	MN (Plar2-)	70	Female	Black	AKI, Proteinuria	2.9	6.8	No	2.4	Alive	Endocrine cancer		USA	Kudose (JASN)[11]
8	MCD + ATI	25	Male	Black	AKI, NS	2.2	21.0	No	0.8	Alive	APOL1+	G1/G1	USA	Kudose (JASN)[11]
9	ANCA vasculitis	64	Male	AA	AKI, Proteinuria	7.9	5.0	Yes	2.4	Alive	MPO+		USA	Uppal (KIR)[47]

(*Continued*)

Table 1. Summary of Kidney Pathology Findings and Clinical Presentation of AKI Among Patients With COVID-19 (*Continued*)

Case #	Pathology	Age	Sex	Race/ Ethnicity*	Kidney Presentation	SCr† (mg/dL)	Proteinuria (g/g)	KRT	Kidney outcome‡	Patient Outcome	Other	Risk Alleles	Country	Reference§
10	ANCA vasculitis	46	Male	Asian	AKI	2.9	NA	No	1.2	Alive	PR3+		USA	Uppal (KIR)[47]
11	ANCA vasculitis	25	Male	White	AKI	5.5	NA	No	NA	Alive	PR3+		Iran	Moeinzadeh (IJKD)[46]
12	Anti-GBM	48	Female	Black	AKI	20.0	3.1	Yes	Dialysis-dependent	Alive			USA	Kudose (JASN)[11]
13	Anti-GBM	45	Female	Asian	AKI	8.2	NA	No	NA	Alive			UK	Prendicki (KI)[48]
14	Anti-GBM	69	Female	White	AKI	32.0	NA	Yes	NA	Alive	MPO+		UK	Prendicki (KI)[48]
15	Anti-GBM	63	Female	White	AKI	15.0	NA	Yes	4.2	Alive	MPO+		UK	Prendicki (KI)[48]
16	Anti-GBM	72	Female	Black	AKI	15.5	NA	Yes	3.1	Alive			UK	Prendicki (KI)[48]
17	Anti-GBM	34	Female	White	AKI	3.2	NA	No	0.9	Alive	MPO+		UK	Prendicki (KI)[48]
18	IgA	78	Male	White	AKI, proteinuria	1.4	10.0	No	1.4	Alive	HSP-like skin findings		Spain	Suso (KIR)[50]
19	TMA	45	Female	AA	AKI, proteinuria	7.4	5.7	Yes	Dialysis-dependent	Died	Recent gemcitabine infusion		USA	Sharma (JASN)[10]
20	TMA	69	Female	White	AKI, proteinuria	7.8	1.4	Yes	Dialysis-dependent	Died	Atypical complement defect		USA	Jhaveri (KI)[54]

Abbreviations: AA, African American; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic autoantibody; anti-GBM, antiglomerular basement membrane; APOL1, apolipoprotein L1; ATI, acute tubular injury; CG, collapsing glomerulopathy; HSP, Henoch-Schonlein purpura; KRT, kidney replacement therapy; LN; lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; MCD, minimal change disease; MPO, myeloperoxidase; NA, not available; NS, nephrotic syndrome; PR3, proteinase 3; SCr, serum creatinine; TMA, thrombotic microangiopathy.

Abbreviations for the Journals: BMCN; *BioMed Central Nephrology*; CKJ, *Clinical Kidney Journal*; IJKD, *Iran Journal of Kidney Diseases*; IMJ, *Internal Medicine Journal*; JASN, *Journal of American Society of Nephrology*; KI, *Kidney International*; KIR; *Kidney International Reports*; KM, *Kidney Medicine*.

*Race/ethnicity are cited directly from the source article.

†Values refer to the peak serum creatinine (mg/dL).

‡Values refer to serum creatinine (mg/dL) upon discharge.

§Last name of first author, journal name and reference number.
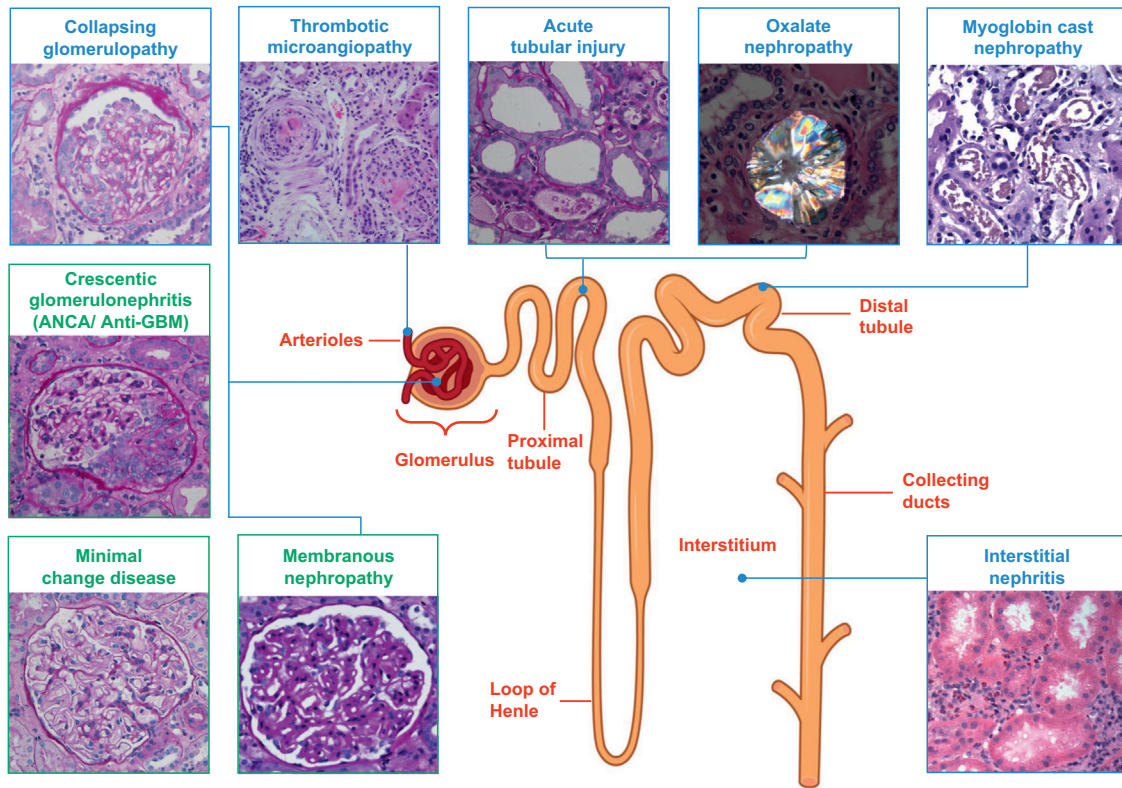
Figure 2. COVID-19–associated kidney disease: pathology findings. Green boxes, the association between COVID-19 and certain histopathological findings (crescentic glomerulonephritis, minimal change disease, and membranous nephropathy) are still putative. ANCA, antineutrophil cytoplasmic antibody; COVID-19, Coronavirus Infectious Disease 2019; GBM, glomerular basement membrane. (Figure 2 was created using Biorender.com.)

have been reported in patients with COVID-19. A total of 9 cases of ANCA vasculitis and anti-GBM disease have been reported, and 5 of 9 required dialysis. All 9 patients received treatment with various immunosuppressive therapy and are alive off dialysis at the time of discharge. A single case of immunoglobulin A nephritis has been reported.[50] Other glomerular diseases including membranous nephropathy and minimal change disease have been reported as well.[11] There are 2 possible explanations for seeing the variety of glomerular diseases in patients with COVID-19. One can postulate a predilection for a specific glomerular pathology for these patients and SARS-CoV-2 acted as a "second hit". Alternately, these processes could have been unrelated to SARS-CoV-2 and could represent incidental findings.

Case 3

A 57-year-old woman presented with fever, cough, and shortness of breath. She was hospitalized and diagnosed with COVID-19. Her laboratory parameters showed a serum creatinine of 3.0 mg/dL (baseline of 0.5 mg/dl). She clinically worsened leading to ICU admission and subsequent intubation. Her platelets decreased, and she developed anemia consistent with hemolysis. Her kidney function deteriorated, and she became anuric. Dialysis was initiated. A blood smear showed several schistocytes. Her coagulation profile was normal. Her serological profile for lupus and antiphospholipid syndrome was negative. After platelet transfusion, a kidney biopsy was performed.

THROMBOTIC MICROANGIOPATHY

The development of coagulopathy and disseminated intravascular coagulation (DIC) is a devastating complication in patients with sepsis that is associated with increased mortality.[51] The pathophysiology of DIC is complex and thought to occur by immune overactivation and disordered coagulation leading to pathologic organ dysfunction.[52] In patients with severe COVID-19, overall mortality is higher among those who developed DIC; 71.4% of nonsurvivors met the International Society on Thrombosis and Haemostasis diagnostic criteria for DIC, whereas only 0.6% of survivors met criteria for DIC.[53] One case of thrombotic microangiopathies (TMA) has been described in patients with COVID-19, with the kidney biopsy showing diffuse cortical necrosis and widespread glomerular microthrombi.[53] However, recent evidence suggests that signs and symptoms of severe COVID-19 resemble the pathophysiology and phenotype of complement-mediated TMA,[10,54,55] rather than sepsis-induced coagulopathy or DIC. To our knowledge and at the time of this writing in September 2020, no cases have been reported of kidney vein thrombosis associated with COVID-19;

Table 2. Method Used to Detect the Presence of SARS-CoV-2 in the Kidney

Study	Tissue Type	Positive Results/Total # of Cases Tested	Method of Detection
Su and colleagues[14]	Autopsy	3/6 IF	Anti-SARS-CoV nucleoprotein antibody (40,143-T62, Sino Biological, Beijing, China)
Puelles and colleagues[71]	Autopsy	Unclear number tested and number positive by ISH and IF	RNAscope 2.5 HD Duplex Assay (Advanced Cell Diagnostics, Newark, California, USA)
			2 commercially available antibodies for SARS-CoV-2 detection: spike glycoprotein antibody [3A2] (Abcam, ab272420) and SARS-CoV SΔ10 within S2 domain protein (Genetex, GTX632604)
Santoriello and colleagues[13]	Autopsy	0/10 ISH	RNAscope 2.5 HD Duplex Assay (Advanced Cell Diagnostics, Newark, California, USA)
Golmai and colleagues[12]	Autopsy	0/4 ISH	RNAscope 2.5 HD Duplex Assay (Advanced Cell Diagnostics, Newark, California, USA)
		0/12 IHC	Mouse anti-SARS-CoV-2 nucleocapsid protein (Clone 1C7, Bioss, Woburn, MA)
Bradley and colleagues[72]	Autopsy	2/4 IHC	Monoclonal antibody to the SARS-CoV-2 spike protein GeneTex, Irvine, CA
Sharma and colleagues[10]	Kidney biopsy	0/10 IHC	Mouse anti-SARS-CoV-2 nucleocapsid protein (Clone 1C7, Bioss, Woburn, MA)
Kudose and colleagues[11]	Kidney biopsy	0/16 ISH	RNAscope 2.5 HD Duplex Assay (Advanced Cell Diagnostics, Newark, California, USA)
		0/16 IHC	SARS-CoV SΔ10 within S2 domain protein (Genetex, GTX632604)
			Anti-SARs-CoV-2 nucleocapsid protein clone 001 (40,143-R001; Sino Biologic, Beijing, China)
Wu and colleagues[31]	Kidney biopsy	0/6 ISH	RNAscope 2.5 HD Duplex Assay (Advanced Cell Diagnostics, Newark, California, USA)

Abbreviations: IF, immunofluorescence; IHC, immunohistochemistry; ISH, in-situ hybridization.

although kidney arterial thrombosis leading to kidney infarction has been reported.[56-58]

TREATMENT-RELATED AKI

Certain treatment-related causes of AKI in patients with COVID-19 such as the use of antiviral agents leading to tubulointerstitial diseases[59,60] and 2 cases of biopsy-proven vitamin C–related oxalate nephropathy[61] have also been reported. In addition, kidney infarction has been postulated as a cause of AKI.[11,58] Trials of multiple molecules such as lopinavir/ritonavir, nucleoside analogues, remde-sivir, tenofovir, chloroquine phosphate, or hydroxychloroquine sulfate have been used in patients with COVID-19. Moreover, antibiotics, many of which have been implicated in AKI, are commonly given during hospitalization for COVID-19.[62] Thus, treatment-related complications need to be considered when determining the etiology of AKI.

AUTOPSY FINDINGS

In one of the first autopsy series published from China, 26 autopsies were performed for patients with COVID-19.[14]

These cases were all rapid autopsies with a postmortem interval of 6 or fewer hours, which reduces autolytic artifacts within tissue. All cases in the series showed mild to severe acute tubular injury. Acute tubular injury was characterized by a loss of the proximal tubular brush borders, vacuolar degeneration (nonisometric in most cases), frank epithelial cell necrosis (4 cases), pigmented granules within tubular cytoplasm (4 cases), and pigmented casts in tubular lumens (3 cases). There was evidence of glomerular ischemia in 7 cases, with 3 of the cases showing fibrin thrombi within the glomerular capillary loops. This was rarely associated with an overlying epithelial cell proliferation (pseudocrescent formation). No proliferative changes were identified within the glomeruli, such as endocapillary hypercellularity or true crescents. In another retrospective study of 81 patients in a single center in China, a total of 41 (50.6%) patients experienced AKI. Limited autopsy of 10 patients showed pathologic findings consistent with acute tubular injury.[4] More recently, several kidney autopsy series from New York were published. Combined data from Northwell Health and Columbia University Medical Center showed that 72% (31/43) in the autopsies were acute tubular injury with varying degrees of severity.[12] There was no evidence of glomerulonephritis, vasculitis, thrombotic microangiopathy, or classic viral nephropathy.

Another autopsy series of 9 patients from NYU was analyzed.[63] Other than findings consistent with acute tubular injury, the authors also reported platelet-rich fibrin microthrombi in scattered peritubular capillaries and venules in most cases. In one case, there was thrombotic microangiopathy within the glomeruli with large platelet-rich microthrombi, red cell fragmentation, and mesangiolysis. All the cases exhibited mild to moderate arteriolosclerosis, and one demonstrated arteriolar hyalinosis. No changes to glomerular vessels, foot processes, or GBM were observed on light or electron microscopy. Another autopsy series from the United Kingdom evaluated 10 patients. Interestingly, thrombotic features were observed in at least one major organ in all full autopsies, predominantly in the lung (8/9 [89%] patients), heart (5/9 [56%]), and kidney (4/9 [44%]). Evidence of acute tubular injury was noted in all 9 patients examined.[64]

DOES SARS-CoV-2 INFECT THE KIDNEY PARENCHYMA?

All the aforementioned histopathologic kidney biopsy and autopsy series have tried to identify if SARS-CoV-2 infects the kidney parenchyma. Each study used variable techniques, and the results and interpretation of the findings have led to controversy surrounding this question. In the first autopsy study from China by Su and colleagues,[14] ultrastructural analysis by electron microscopy was performed on 9 cases, with putative identification of particles that had the appearance of viral structures in 7 cases. An indirect immunofluorescence staining for SARS-CoV-2 nucleoprotein was performed in 6 cases, 3 of which showed positive staining in tubular epithelial cells. In 2 of these 3 cases, viral particles consistent with coronavirus were also identified. Soon after, Kissling and

colleagues described a case of CG with negative reverse transcriptase-polymerase chain reaction for SARS-Co-V-2 in kidney biopsy tissue, but they reported findings suggestive of viral particles on electron microscopy.[32] Another autopsy case report by Farkash and colleagues also suggests the presence of viral particles by electron microscopy in the tubular epithelial cells; no immunohistochemistry or in situ hybridization was performed in this case.[65] Several articles followed, however, disputing whether the particles identified were virus in origin and suggested multivesicular bodies or clathrin-coated vesicles have an identical appearance.[66–70] Three of the 6 patients in an autopsy series described in the publication by Puelles and colleagues showed a detectable SARS-CoV-2 viral load in all kidney compartments examined by reverse transcriptase-polymerase chain reaction.[71] The authors report positive results by in situ hybridization and indirect immunofluorescence with confocal microscopy.[71] In another series from Belgium, the authors found transmission electron microscopy identified particles resembling coronaviruses in vacuoles or cisternae of the endoplasmic reticulum in proximal tubule cells. They interpreted the presence of virions in proximal convoluted tubules and rare podocyte virions as the evidence of direct viral infection of the kidney.[28] On the other hand, data from Northwell Health and Columbia University Medical Center in New York, describing a total of 52 autopsy cases and 29 kidney biopsies from living patients, report negative results by immunohistochemistry or in situ hybridization in all tested cases.[10–13] In the Columbia series, rare tubular epithelial staining (<1 in 200 cells) with low-intensity dot-like positivity was described in many cases, in the setting of a high background staining, and substantially less intense than the staining in lung specimens from autopsies with COVID-19. The authors conclude that the rare equivocal staining may represent nonspecific staining or low viral abundance. Virus-like particles were commonly identified on electron microscopy, but unequivocal features of coronavirus were not seen, as previously described.[67,69] An autopsy series from Washington state in the United States included 14 patients, with focally positive immunohistochemistry findings in 2 out of 4 tested kidney samples; they also describe viral-like particles in 3 of 3 cases with electron microscopy examination.[72] The various methods used to detect the presence of SARS-CoV-2 as reported by these studies are summarized in Table 2.

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) to gain entry to the host cell.[73] Access to the cellular ultrastructure needed for viral replication is also dependent on proteases such as transmembrane serine protease 2 (TMPRSS2) and furin.[74] ACE2 is expressed in the kidney and is localized to the apical brush border of proximal tubular cells with some expression in the distal tubule, interlobular arteriole endothelium, and vascular smooth muscle.[75,76] Lower expression of ACE2 is found in the glomerulus and is predominantly seen in podocytes. Some have postulated that the virus could enter the kidney via ACE2. However, SARS-CoV-2 uses TMPRSS2 in addition to ACE2 to be primed to gain entry

into host cells. TMPRSS2 is primarily expressed in the distal nephron as opposed to the proximal tubule where ACE2 is expressed.[77] This, at least in the basal state, would prove difficult as these 2 proteins are expressed in different tubule compartments. It remains to be determined if ACE2 or TMPRSS2 expression is altered in SARS-CoV-2 infection and thus allow for coexpression in the kidney tubules. An alternative route of entry could be from immune cells such as macrophages or in podocytes. Furthermore, perturbations in components of the renin-angiotensin system could lead to increases in the proinflammatory angiotensin (Ang) II signaling. This is because ACE2 is a critical counter-regulatory enzyme that converts Ang II into Ang-(1-7). Ang-(1-7) functions to attenuate inflammation by signaling through the Mas receptor.[78] Preclinical research on SARS-CoV-1 in a mouse model showed reductions in ACE2 protein in the lungs of mice after infection with SARS-CoV-1 and after spike protein enhanced lung injury.[79] Furthermore, they showed reduction in lung injury in this model after treatment with an angiotensin-receptor blocker. It is unclear if this occurs in humans and what the clinical significance of these findings are. Moreover, controversy exists as to whether the use of inhibitors of the renin-angiotensin enzyme are helpful or harmful in the context of COVID-19.[80] Ongoing clinical trials are currently underway. This is discussed in more detail by Edmonston and colleagues in this issue of ACKD.[81]

In summary, although direct viral infection of the kidney is possible, it is certainly not a common or even widespread finding reported (Table 2). In fact, SARS-CoV-2 is detected uncommonly by immunohistochemistry or *in situ* hybridization. Electron microscopy is a suboptimal method of detection as it relies solely on morphology and the particle size, leaving room for confusion with normal cellular structures.

MANAGEMENT

Treatment and management of patients with COVID-19–associated AKI is generally similar to those of patients with AKI associated with septic shock. Conservative management of volume overload, metabolic acidosis, and hyperkalemia can be attempted before considering initiation of dialysis. In cases of CG, TMA and other glomerular diseases, careful management of COVID-19, and specific glomerular pathology might be prudent. Shaikh and colleagues discuss the management of COVID-19-associated AKI in this issue of ACKD.[82]

OUTCOMES

Other recent publications have reported on the association of AKI with in-hospital death among those hospitalized with COVID-19.[1,3,83] Early reports from Wuhan, China, found that the risk of death was increased with AKI.[84] Based on a recent publication from New York of approximately 9600 hospitalized patients with COVID-19, the risk of in-hospital death was increased with AKI even after adjusting for baseline demographic, comorbid conditions, and illness severity (HR 3.4 for AKI-not requiring dialysis, HR 6.4 for AKI-requiring dialysis).[85] The Study of the

Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) is a US-based multicenter retrospective cohort study of patients admitted to the ICU. This study found that in 637 patients with AKI requiring dialysis, 55% died within 28 days of ICU admission compared with only 19% of patients without AKI; among patients with Kidney Disease: Improving Global Outcomes (KDIGO) stage 1 and 2 AKI, the 28-day mortality was 34% and 46%, respectively. Among the 216 patients with AKI requiring dialysis who survived to hospital discharge, 73 (34%) remained dependent on dialysis at discharge, and by 60 days of follow-up, 18% remained dialysis-dependent.[86] Despite the heterogeneity of published studies in terms of geographical location, patient population, and severity of illness, it is clear that AKI is associated with increased risk of death among patients with COVID-19.

CONCLUSION

In summary, AKI is not uncommon in patients hospitalized with COVID-19 with an incidence of around 37%. The most common cause of kidney injury in patients with COVID-19 is acute tubular injury. CG is a recognized glomerular pathology associated with COVID-19 that most commonly affects individuals with high-risk *APOL1* polymorphisms. Other glomerular pathology associated with COVID-19 might be coincidental or a "second hit" phenomenon. At the time of this writing (September 2020), it is unclear if the SARS-CoV-2 directly infects the kidney.

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