Glomerular Diseases

Review Article

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Current Understanding of Clinical Manifestations of COVID-19 in Glomerular Disease

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Coronavirus disease · Glomerular disease · Chronic kidney disease · Glomerular injury · Collapsing glomerulopathy

Abstract
Background: The novel coronavirus disease (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an evolving pandemic with significant mortality. Information about the impact of infection on glomerular disease patients in particular has been lacking. Understanding the virus's effect in glomerular disease is constantly changing. This review article summarizes the data published thus far on COVID-19 and its manifestations in pre-existing and de novo glomerular disease. ***Summary:*** While patients with glomerular disease may be at higher risk of severe COVID-19 due to their immunosuppressed status, some data suggest that a low amount of immunosuppression may be helpful in mitigating the systemic inflammatory response which is associated with high mortality rates in COVID-19. There have been a few case reports on COVID-19 causing glomerular disease relapse in patients. Multiple mechanisms have been proposed for kidney injury, proteinuria, and hematuria in the setting of COVID-19. More commonly, these are caused by direct tubular injury due to hemodynamic instability and hypoxic injury. However, the cytokine storm induced by COVID-19 may trigger common post-viral glomerular disease such as IgA nephropathy, anti-GBM, and ANCA vasculitis that have also been described in COVID-19 patients. Collapsing glomerulopathy, a hallmark of HIV-associated nephropathy, is being reported SARS-CoV-2 cases, particularly in patients with high-risk APOL1 alleles. Direct viral invasion of glomerular structures is hypothesized to cause a podocytopathy due to virus's affinity to ACE2, but evidence for this remains under study. ***Key Messages:*** Infection with SARS-CoV-2 may cause glomerular disease in certain patients. The mechanism of de novo glomerular disease in the setting of COVID-19 is under study. The management of patients with existing glomerular disease poses unique challenges, especially with regard to immunosuppression management. Further studies are needed to inform clinician decisions about the management of these patients during the COVID-19 pandemic.

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Introduction

As COVID-19 spread across the globe, journals have been flooded with case reports and experience studies describing its clinical manifestations. Clinicians and pa-

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tients have struggled to understand the potential disease-specific risks for people with rare diseases. For patients with glomerular disease, this virus may have a unique impact – both in terms of its risks and implications for glomerular disease treatment decisions, and its potential to induce de novo disease.

Patients with glomerular disease may be at higher risk of severe disease due to their immunosuppressed status and chronic kidney disease (CKD) comorbidities [1]. Moreover, the unchecked systemic inflammatory response induced by COVID-19 infection may put patients at risk of a glomerular disease flare. COVID-19 attracted the interest of glomerular disease experts due to its affinity to angiotensin-converting enzyme 2 (ACE2) which is expressed on podocytes and proximal tubules [2]. This raised the possibility of inducing de novo glomerular disease by direct invasion of podocytes, though this remains speculative at this time. Regardless of the underlying mechanism, many reports have emerged describing collapsing glomerulopathy (CGP) and other glomerular diseases in the setting of COVID-19.

In this review, we aim to consolidate the information from the rapidly expanding literature published to date on COVID-19 infection and to answer common clinical questions about glomerular disease patients during the COVID-19 pandemic. Furthermore, we summarize reports discussing de novo glomerular disease in the setting of COVID-19.

Are Patients with Glomerular Disease More Likely to Contract COVID-19 and Suffer Worse Complications if They Do?

Patients with glomerular disease may be particularly vulnerable to COVID-19, given their CKD and immunosuppressed state as comorbidities. While there have been several reports indicating that CKD puts COVID-19 patients at high risk of severe COVID-19 disease [1, 3], there has been a dearth of studies looking into glomerular disease, specifically as a risk factor. A nationwide Korean case-control retrospective study [3] of 219,961 individuals tested for COVID-19 aimed to describe the effect of underlying comorbidities on the risk of infection and severity of COVID-19. There were in total 16 patients identified with glomerular disease, only one of whom was reported to have severe infection. While the study did show that patients with glomerular disease had an increased risk of contracting COVID-19 compared to those without glomerular disease (OR 1.377), it did not demonstrate any association of glomerular disease with severe complications of COVID-19. This finding is limited by the small number of patients with glomerular disease identified in the study population. Another case-control study of 120 patients from an international registry for glomerular disease and COVID-19 across several centers in North America, Europe, and Australia investigated the effect of glomerular disease on the clinical course of COVID-19 infection [4]. This study matched patients with glomerular disease (N = 40) who were infected with COVID-19 with age- and sex-matched controls (N = 80) infected with COVID-19 around the same time period but did not have any glomerular disease or CKD. Despite a higher rate of hospitalizations in the control group, patients with glomerular disease were found to have a higher rate of acute kidney injury (AKI [39% vs. 14%]) and a higher mortality rate (15% vs. 5%, OR 6.33). In the case group, immunosuppression status, level of proteinuria, and GFR at presentation were not correlated with the risk of death. This is not consistent with other studies that have shown an association of AKI and proteinuria with mortality in COVID-19 [1, 5]. This study supports concerns for higher risk of severe infection in glomerular disease but raises questions as to what may be the principal driving risk factors.

The effect of immunosuppression on the severity of COVID-19 infection is complex. On the one hand, suppression of the immune system reduces the ability to mount a host immune response to combat the virus. COVID-19 infection can also lead to lymphopenia and may therefore exacerbate the state of lymphopenia induced by some antimetabolite immunosuppressive therapy. On the other hand, the systemic inflammatory response in COVID-19 is hypothesized to be a major determinant of severity of disease. This led to the belief that a small amount of immunosuppression may be beneficial in mitigating an unchecked inflammatory response to the virus. Indeed, early therapies proposed to control the severity of COVID-19 included immunosuppressive therapy. Most notably, a randomized controlled trial of dexamethasone in COVID-19 patients requiring oxygen or ventilator therapy has been shown to reduce 28-day mortality [6]. This is in contrast to the earlier studies citing higher hospitalization [7] and mortality rates [8] in patients on chronic steroids for treatment of rheumatologic disease. Other immune-regulating medications which are not as commonly used in patients with glomerulonephritis (GN) as have been used in treatment of COVID-19. IL-6 receptor blockers such as tocilizumab have been hypothesized to reduce the inflammatory response and disease

severity. Single-center observational studies have shown some improvement in oxygenation and survival when tocilizumab is used, though there is some concern about increased risk of superinfection [9, 10]. Medications such as calcineurin inhibitors have been shown to inhibit SARS-CoV-2 viral replication in vitro due to the virus having active cyclophilin pathways [11], but their clinical effect on patients with COVID-19 has not been studied further.

The impact of immunosuppressive therapy used in glomerular disease and COVID-19 infection remains speculative as few studies have analyzed the effect of maintenance or induction therapies in the setting of active COVID-19 infection. The closest parallels exist with kidney transplantation and rheumatologic disease. Elias et al. [12] conducted a prospective study of 1,216 kidney transplant recipients, followed for a 2-month period. These patients were being treated with calcineurin inhibitors (86%), steroids (83%), antimetabolites (92%), or belatacept (9%). Sixty-six patients (5%) contracted COVID-19 (compared to 0.3% observed incidence in France at the time). These patients had a significantly higher mortality rate (24% compared to 1% in the overall study population). Risk factors for contracting COVID-19 included nonwhite ethnicity, obesity, asthma, chronic pulmonary disease, and diabetes. Single center reports have communicated similarly high mortality rates in transplant patients [13, 14]. The COVID-19 Global Rheumatology Alliance was formed to collect the experience of rheumatologists across the world by creating a registry of patients with rheumatologic diseases who contracted COVID-19. They most recently published a summary report of 600 cases from their registry [7]. The patients were from 40 different countries, and 7% of them had CKD. Forty-six percent of patients were hospitalized, and 9% died. In their cohort, prednisone doses ≥10 mg/day were associated with higher odds of hospitalization, and tumor necrosis factor inhibitors were associated with lower odds of hospitalization. Other immunosuppressants used in treatment of glomerular disease such as B cell depleting rituximab may impede a humoral response to infection. There have been case reports of severe infections and mortality with COVID-19 in rheumatoid arthritis patients on rituximab [15]. It is worth noting, however, that in a prospective study of 159 pediatric patients with nephrotic syndrome treated with anti-CD20 therapy during the period of February to April 2020 in Italy [16], none developed COVID-19 symptoms during the study period. This is despite reduced IgG levels and CD19+ cells, as well as known infections in cohabitants of 6 of the study participants. These results show a surprisingly low number of severe infections in a pediatric patient cohort with depleted B cells in a high-risk infectious region and highlight the importance of age as a risk factor for severe COVID-19 [17]. No evidence-based conclusions can be drawn at this time with regard to the risk of specific immunosuppressive therapy in patients with glomerular disease. More data have been published in the context of transplantation and rheumatologic diseases, where immunosuppressive regimen and comorbid conditions may be different than in glomerular disease.

The vast majority of data thus far with regard to glomerular disease and COVID-19 infection risk and disease severity has been limited to case reports and small retrospective observational studies. Reports published early in the epidemic are biased by the limited testing available, underestimating the true prevalence of disease and potentially overestimating the rate of severe disease. The data reported suggest that patients with glomerular disease may be at a higher risk of contracting severe COVID-19 disease than the general population, but further investigation is required. Of particular concern is the limited information regarding the influence of specific immunosuppressive therapy on disease severity as this may dictate treatment decisions for these patients.

Are Patients with Glomerular Disease at Risk of Having Disease Relapse if They Contract COVID-19?

There are several risk factors for glomerular disease relapse in the setting of COVID-19 infection. COVID-19 induces a hyperimmune response in some patients which may hypothetically trigger a glomerular disease flare. For decades, it has been observed that non-COVID viral infections are implicated in relapse of nephrotic syndrome in pediatric patients [18] and IgA nephropathy. While the mechanism of disease flare is not fully understood, it is thought to be due to a dysregulated immune response to infection. Patients may also be particularly vulnerable to a flare-up in the setting of withholding some of their immunosuppressive medication to allow a host immune response to the virus. Conversely, some have hypothesized that the lymphopenia induced by SARS-CoV-2 may have a protective effect against glomerular disease progression [19].

Published case reports of glomerular disease relapse during COVID-19 have included flare-ups in diseases that are known to relapse after a viral infection, such as IgA nephropathy [20] and steroid-dependent minimal

change disease [21] in the pediatric population. Recurrent disease seemed to occur whether or not these patients were on maintenance immunosuppressive therapy. None of these patients developed severe disease, and they all responded to glucocorticoid therapy with no severe complications. There was also a report of recurrent anti-glomerular basement membrane (anti-GBM) disease after COVID-19 infection [22]. This patient's last relapse was 5 years prior to presentation, and she was not on any maintenance immunosuppression at the time of her hospitalization. She presented with respiratory distress, hemoptysis and hypoxia, AKI, as well as worsening hematuria and nephrotic range proteinuria. SARS-CoV-2 PCR was positive with an elevated cycle threshold, and anti-GBM titers were negative. She had evidence of ground-glass opacities on imaging, but she did not require intubation. Despite a negative anti-GBM antibody in the serum, a kidney biopsy showed 3/7 glomeruli with fibrocellular crescents and fibroid necrosis, and linear deposits of IgG, IgM, and C3 along the glomerular basement membrane. She was treated with steroids, 1 dose of cyclophosphamide and 2 doses of rituximab, as well as 7 sessions of plasma exchange. With relapse of hemoptysis 1 week after resolution of symptoms, she received an additional 7 sessions of plasma exchange. This was a more aggressive regimen than she had received in the past for flares. While she recovered from a respiratory standpoint, the patient remained dialysis-dependent at time of discharge. These cases highlight the importance of keeping glomerular disease on the differential in the appropriate clinical setting, especially in patients with known prior disease.

What Is the Role of ACE2 as a Risk Factor for Kidney Injury in COVID-19?

SARS-CoV-2 has been of particular interest in studying de novo glomerular disease due to its affinity to ACE2, which is the main entry point for SARS-CoV-2 into cells. ACE2 is found in the apical surface of proximal tubular cells and, to a lesser extent, on podocytes and mesangial cells [23–25]. This led to the hypothesis that AKI is mediated by direct viral invasion of tubular cells or podocytes. Fusion of the viral envelope with cellular membranes requires priming of the viral S proteins by the host cell's transmembrane serine protease 2 (TMPRSS2) [26]. While the kidney expresses low levels of TMPRSS2, tubular cells express other related proteases which may facilitate viral S protein priming [27]. More recently, a single-cell transcriptome co-localization analysis showed relatively high co-expression of ACE2 and TMPRSS2 on podocytes and proximal tubular cells [28], signaling a potential mechanism for cellular entry.

Despite the plethora of hypothesized mechanisms for viral entry into podocytes and proximal tubular cells, direct viral invasion as the pathogenesis of AKI remains controversial as no study has definitively documented viral invasion of the renal tissue. In fact, most studies published to date have reported the lack of viral particles on biopsy specimens in patients with AKI by either immunohistochemistry or ultrastructural examination by electron microscopy [29–32]. Furthermore, significant viral-mediated interstitial inflammation was not often seen. Several publications initially reported viral structures on kidney biopsies, in either proximal tubular epithelial cells [33, 34] or podocytes [35–37], where foot process effacement was found in 1 case [35] and CGP in another [37]. However, it is worth noting that ultrastructure findings of direct viral invasion on renal histology did not correlate with SARS-CoV-2 nucleoprotein antibody or RNA in these studies. Whether the coronavirus-like particles which were seen on biopsy are evidence of direct viral invasion of renal tissue was challenged in follow-up commentary [38, 39]. Multivesicular bodies, structures identified on biopsies since the 1960s, can be mistaken for coronavirus particles. Multivesicular bodies are of unclear significance, but some have hypothesized that they may represent podocyte endocytosis with intracytoplasmic microvesicles. They are coated by clathrin which gives them a "corona"-like appearance.

While direct visualization of viral particles has been controversial, SARS-CoV-2 RNA was detected by reverse transcriptase polymerase chain reaction (RT-PCR) in renal tissue obtained postmortem from patients with COVID-19 [40, 41]. The study by Braun et al. [40] included SARS-CoV-2-negative controls. RNA load correlated with kidney injury and disease severity. While the specificity of RNA detected by RT-PCR is high, tissue homogenization required for RT-PCR may have introduced virus RNA from the blood into the specimens. In another case report, SARS-CoV-2 RNA was detected by RT-PCR in a kidney biopsy specimen of a kidney-pancreas transplant recipient, and RNA in situ hybridization identified viral RNA in tubular cells and interstitium, even when blood samples tested negative [42]. Nonetheless, the majority of case series published have reported negative RT-PCR and RNA in situ hybridization findings on biopsy or postmortem analysis [30, 32, 43–49]. Validation studies are needed to confirm direct viral entry into renal cells and its implication in causing kidney injury in COVID-19 infection.

Aside from direct viral invasion, viral tropism to ACE2 may mediate kidney injury by shifting the balance of pro-inflammatory systemic effects of ACE against the anti-inflammatory actions of ACE2 (Fig. 1). ACE leads to the activation of the angiotensin type 1 (AT1) receptor through the ACE-angiotensin II-AT1 axis. AT1 causes vasoconstriction and salt and water retention and promotes apoptosis, inflammation, and fibrosis. ACE2 has been studied as an important mediator in mitigating the effects of AT1 through the formation of angiotensin 1–7 and its action on the Mas receptor. The Mas receptor promotes vasodilation and natriuresis, decreases cell proliferation, and has anti-inflammatory effects. An imbalance of ACE/ACE2 expression has been implicated in a variety of disease, most notably diabetes and hypertension [25]. In animal studies, deletions in ACE2 genes or administration of ACE2 inhibitors in mice leads to glomerulosclerosis or worsening of diabetic nephropathy [23, 50]. Kidney biopsies of patients with diabetic kidney disease demonstrate decreased expression of ACE2 [51]. SARS-CoV infection has been shown to downregulate ACE2 expression [52]. It is hypothesized that a similar process occurs in SARS-CoV-2. This decreases the protective effects of ACE2 against the pro-inflammatory ACE-angiotensin II-AT1 axis. This imbalance between ACE/ACE2 effects is thought to contribute to the pathogenesis of organ injury in COVID-19 [53]. This mechanism of injury provided the impetus for studying recombinant soluble ACE2 for treatment of severe COVID-19 infection [54].

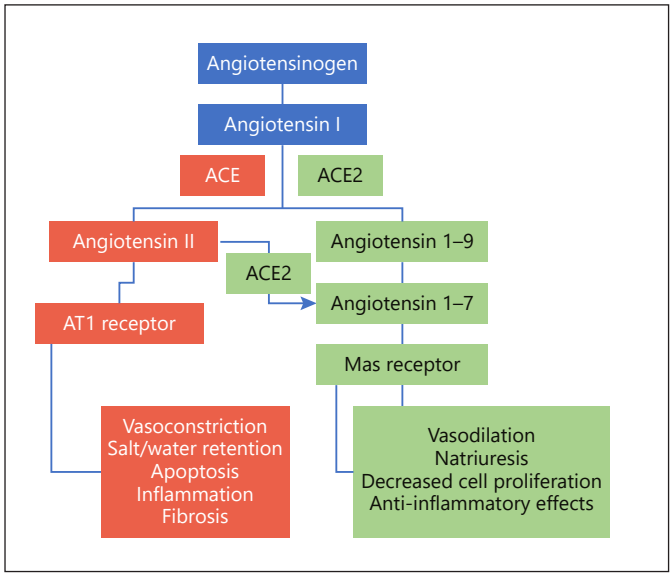

Fig. 1. Schematic of the effects of ACE and ACE2 in the renin-angiotensin system. The ACE-AngII-AT1 axis is facilitated by ACE action. It is shown on the left side of the figure, highlighted in red, and leads to vasoconstriction, fluid retention, and an inflammatory state. ACE2, on the other hand, aids in the degradation of angiotensin II and ultimately activates the Mas receptor, which has opposing anti-inflammatory effects leading to vasodilation, natriuresis, and decreased cell proliferation. ACE2, angiotensin-converting enzyme 2; AT1, angiotensin type 1.

Can COVID-19 Infection Trigger de novo Glomerular Disease?

The exact mechanism of kidney injury in COVID-19 is likely multifactorial. We summarize some of the pathways described thus far in the development of kidney injury, proteinuria, and glomerular disease in COVID-19 (shown in Fig. 2). Early studies have noted a high incidence of proteinuria and hematuria in patients hospitalized with COVID-19 infection [1, 5], with as many as 65.8% of patients having proteinuria in the single-center study reported by Pei et al. [5]. Notably, these studies often did not include whether proteinuria was present prior to COVID-19 infection. Proteinuria has been associated with an increased risk of mortality in hospitalized patients [1, 55]. Proteinuria in patients with COVID-19 is primarily attributed to AKI and acute tubular necrosis in the setting of hypoxia, sepsis, and hemodynamic instability, as evident by several biopsy findings [43, 56]. Nonetheless, there remains a concern for the development of glomerular disease in these patients due to the dysregulated immune response associated with COVID-19. In an observational study of 161 patients admitted to the ICU with COVID-19 infection [57], 14 patients (9%) were found to have nephrotic range proteinuria, 6 of whom had de novo proteinuria. Of those 6, 3 were found to have CGP on biopsy, corresponding to about 2% of the entire cohort. Table 1 summarizes case series which reported histologic findings in either postmortem studies or kidney biopsies indicated for proteinuria or AKI in COVID-19-affected patients. The most prominent finding in postmortem studies is acute tubular injury. However, acute GN and fibrin thrombosis were notable in several patients.

The cytokine storm induced by COVID-19 can lead to a surge of inflammatory cells in organs causing tissue injury [58]. It is hypothesized that this dysregulated immune response can trigger acute glomerular autoimmune disease or endothelial damage which can induce thrombotic microangiopathy (TMA). Indeed, there have been a few cases of ANCA-associated GN [59, 60], IgA vasculitis

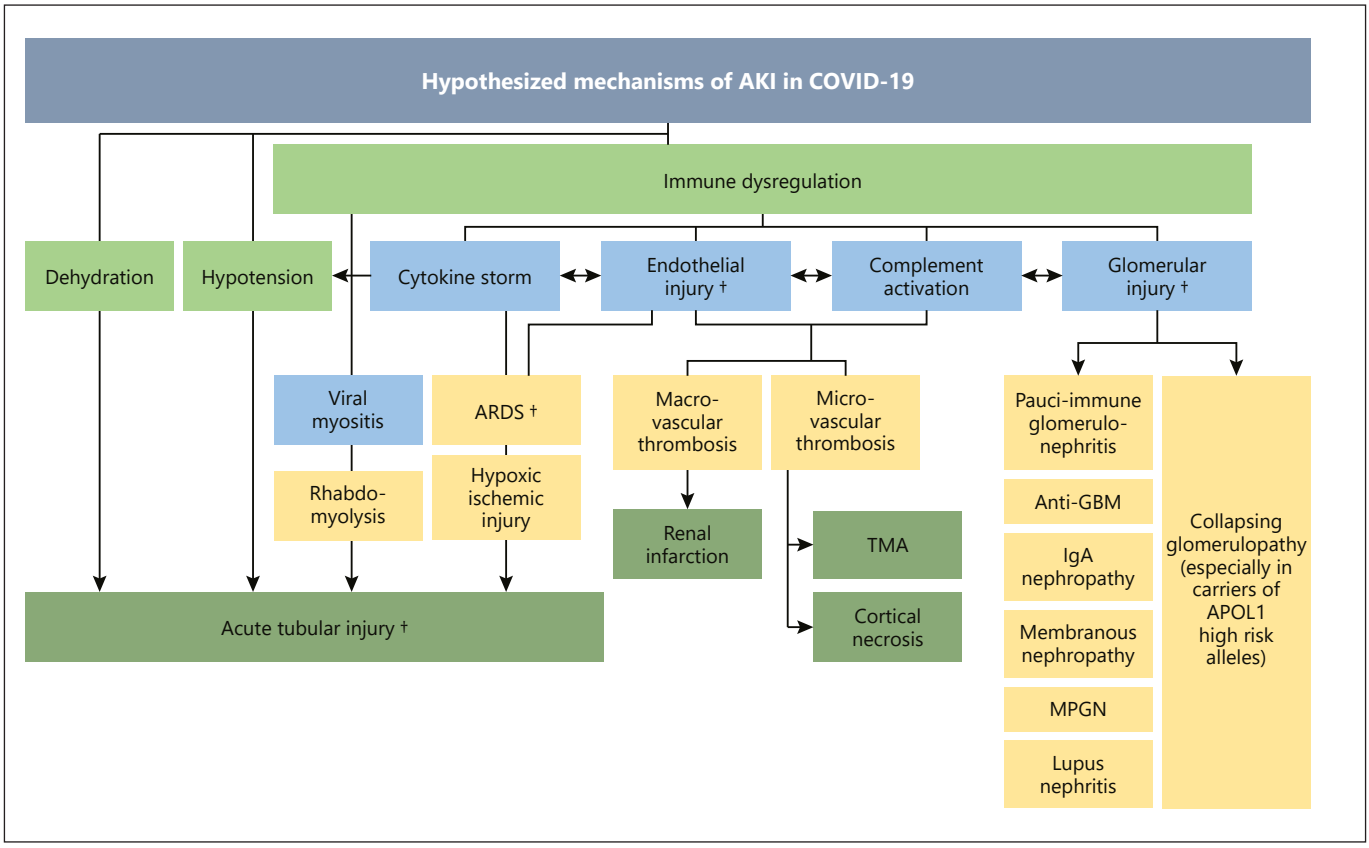

Fig. 2. Potential mechanisms of AKI in COVID-19: acute tubular injury is the principal cause of injury due to mechanisms previously recognized in other infections and critical illness. Hypercoagulability has also been established as a sequelae of COVID-19 – microvascular and macrovascular thrombotic renal events have been reported. Of interest is the glomerular injury that has been noted in those who exhibit AKI with nephrotic range proteinuria, alveolar hemorrhage, or vasculitis rashes. Finally, direct viral invasion as a cause of kidney injury remains speculative. Viral tropism to podocytes and proximal tubulars is hypothesized due to ACE2 expression on those particular cells. †Direct viral invasion of podocytes, proximal tubular cells, endothelial cells, and alveolar epithelial cells has been hypothesized to cause podocytopathy, proximal tubular injury, endothelial injury, and ARDS, respectively. ARDS, acute respiratory distress syndrome; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy; anti-GBM, anti-glomerular basement membrane; AKI, acute kidney injury.

[61–63], immune complex GN [64], and systemic lupus erythematosus [65] in patients with COVID-19. Of particular interest is the de novo nephrotic syndrome seen in some cases of COVID-19 infection [28]. New case reports have emerged revealing CGP as a cause of nephrosis in a subset of patients (the online supplementary table lists case reports published to date; for all online suppl. material, see www.karger.com/doi/10.1159/000518276). CGP is especially important in SARS-CoV-2 as it has been associated with an APOL1 risk variant which is commonly found in patients of African ancestry [66], a demographic which has been disproportionately affected by COVID-19 [67]. In the following sections, we present a summary of case reports published to date describing glomerulopathy findings in patients with COVID-19.

Focal Segmental Glomerulosclerosis and Collapsing Glomerulopathy

Focal segmental glomerulosclerosis (FSGS) is a heterogeneous disease by which multiple biological mechanisms can result in a specific pattern of injury on kidney biopsy. In a study analyzing kidney findings in 26 postmortem COVID-19 patients in China, 2 were found to have FSGS associated with severe arteriosclerosis. Both of these patients had a history of diabetes and proteinuria [35]. These findings are likely consistent with pre-existing secondary FSGS, rather than a primary glomerular disease. Determining baseline proteinuria prior to infection is valuable in order to distinguish cases with de novo proteinuria, especially since nephrotic range proteinuria can be found in those patients with diabetes, hyperten-

Table 1. Summary of biopsy and autopsy case series describing range of kidney pathology found in patients with COVID-19 [112]

Author	Biopsy indications	Sample size	Race	Biopsy findings	Viral inclusions?
Akilesh et al. [44]	88% AKI 64% proteinuria	17 14 native 3 allograft	8 Black 5 Hispanic 3 White 1 Asian	13 acute tubular injury 11 FSGS, with 7 CGP 7 TMA (1 of which in an allograft with rejection) 1 minimal change 1 IgA nephropathy 1 post-infectious GN 1 mesangial immune complex deposition 1 active antibody-mediated rejection 1 chronic active antibody-mediated rejection	No ultrastructure evidence of viral particles in all specimens SARS-CoV-2 nucleocapsid and RNA negative in 4 patients
Braun et al. [40]	Postmortem, 39 with information about kidney function, of those, 32 had AKI	63 native	Not reported	N/A	SARS-CoV-2 RNA in 23/32 patients with AKI and 3/7 patients without AKI
Golmai et al. [29]	Postmortem, 100% with Stages 2–3 AKI	12 native	6 Hispanic 3 Black 3 White	12 acute tubular injury 1 mild acute interstitial nephritis 1 renal oxalosis 1 medullary urate deposition	No
Kudose et al. [30]	88% AKI 53% nephrotic range proteinuria	17 14 native 3 allograft	12 Black 3 White 1 Asian 1 Hispanic	5 ATN 5 CGP 1 minimal change 2 membranous nephropathy (1 PLA2R positive) 1 lupus nephritis (class IV + V) 1 anti-GBM 1 T cell-mediated rejection 1 cortical infarction	No
Santoriello et al. [32]	Postmortem 94% with AKI	42	24 Hispanic 5 Black 3 White 10 other/ unknown	19 ATN (11 unable to assess due to autolysis) 1 collapsing FSGS 1 idiopathic nodular glomerulosclerosis 1 IgA nephropathy (chronic liver disease) 4 fibrin thrombi (focal, <5% of glomeruli) 3 arterial fibrin thrombi 35 moderate-severe arteriosclerosis 7 diabetic glomerulosclerosis	No
Sharma et al. [31]	100% AKI 60% nephrotic range proteinuria	10 native kidney biopsies	5 Black 3 Hispanic 2 White	5 ATN 1 collapsing FSGS with ATN 1 myoglobin cast nephropathy with ATN 1 crescentic GN with ATN 2 TMA (1 with ATN and 1 with cortical necrosis)	No
Shetty et al. [112]	100% AKI 100% nephrotic range proteinuria	6 5 native kidneys 1 allograft	6 Black	3 CGP 6 podocytopathy 6 protein overload tubulopathy 4 tubuloreticular inclusion	Unknown
Su et al. [35]	Postmortem 9/26 with known AKI, 8/26 unknown	26 native kidneys	Not reported	26 acute tubular injury (17 moderate-severe, 9 mild-moderate) 2 FSGS (both with history of diabetes) 1 IgA nephropathy 3 pigmented casts 15 moderate-severe arteriosclerosis 1 diffuse + 2 focal segmental fibrin thrombus 2 dense deposits 5 subendothelial expansion	Yes in 7 with coronavirus-like particles (proximal tubules, podocytes, distal tubules), 3 with positive SARS-CoV-2 nucleoprotein antibody
Werion et al. [34]	Postmortem All with proteinuria, 2 required RRT	6 native kidneys	Not reported	6 ATN, 5 with proximal brush border loss 5 erythrocyte aggregates in peritubular/ glomerular capillaries 1 single FSGS (tip variant) 2 mononuclear interstitial infiltrates	Yes, in proximal tubular cells' rough endoplasmic reticulum

Table 1 (continued)

Author	Biopsy indications	Sample size	Race	Biopsy findings	Viral inclusions?
Xia et al. [45]	Postmortem 100% AKI	10	Not reported	8 ATN 10 cytoplasmic vacuolization 2 glomerular ischemic sclerosis	RT-PCR SARS-CoV-2 RNA negative in 9 patients; 1 was not tested

CGP, collapsing glomerulopathy; AKI, acute kidney injury; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy; anti-GBM, anti-glomerular basement membrane; RT-PCR, reverse transcriptase polymerase chain reaction; GN, glomerulonephritis; PLA2R, phospholipase A2 receptor antibodies.

sion, and CKD, well-known factors associated with severe COVID-19 infection [68, 69]. Indeed, Mohamed et al. [57] found in their 1-month-long observational cohort that as many as half of the patients admitted to the ICU with AKI and nephrotic range proteinuria had pre-existing high-grade proteinuria prior to COVID-19 infection.

CGP is a distinct variant of FSGS characterized by podocyte hypertrophy and hyperplasia along with segmented or global glomerular collapse [70]. CGP has been associated with other infectious diseases such as HIV, CMV, EBV, and parvovirus B19 [71]. Tubuloreticular inclusions have been identified on biopsies showing CGP in COVID-19 [30, 72] (Table 2). Tubuloreticular inclusions are induced in response to interferon and are seen in the context of viral infections such as HIV or autoimmune disease such as systemic lupus erythematosus [73]. It is unclear why some patients may be at a higher risk of developing CGP during COVID-19. COVID-19 may present a "second hit" to patients who are predisposed to glomerular disease [74]. Among patients who develop frank nephrosis, a subset has been found to have high-risk APOL1 alleles, which is associated with FSGS and CGP [66].

Multiple case reports of CGP have been found in kidney biopsies of patients infected with SARS-CoV-2 [30, 37, 44, 47, 48, 72, 74, 75]. Table 2 summarizes the clinical and pathologic findings and outcomes in patients documented to have CGP. All but 2 of the patients in these case reports were black. Most cases were either heterozygous or homozygous for a high-risk APOL1 allele [72, 75]. A case report of a renal transplant patient who developed FSGS 2 months post-transplant after contracting COVID-19 revealed that the donor was homozygous for the high-risk APOL1 variant [76]. Interestingly, there was a case of CGP in a kidney transplant recipient with COVID-19, though neither the recipient nor the donor had high-risk alleles for APOL-1 [77]. This suggests that the high-risk APOL1 allele is not always necessary for CGP during COVID-19 infection. About half of the reported cases with biopsy-proven CGP thus far have required dialysis. This figure likely overestimates the rate of renal failure in CGP as it is the patients who develop severe AKI who are more likely to be biopsied and confirmed to have CGP. About 31% of those who underwent dialysis no longer required dialysis at the time of discharge, though there was significant residual renal injury (average creatinine at discharge 3.32 mg/dL) and persistent proteinuria (4.5 g/g). Patients with CGP post-COVID-19 will need to be followed up further to determine their ultimate clinical outcome.

Since much of the early COVID-19 literature related to kidney findings was reported on Chinese patients and then European patients, studying the effect of COVID-19 on different populations may reveal disproportionate incidence rates of AKI and glomerulopathies. Black Americans have a higher mortality from COVID-19 [67]. Early in the epidemic in Michigan, 40% of deaths due to SARS-CoV-2 were in Black patients, while they only make up 14% of the population [78]. While in Louisiana, 32% of the population is Black, and 70% of COVID-19 deaths were Black patients [78]. As COVID-19 literature continues to be published, there have been many case reports on CGP in Black patients, many with a high-risk APOL1 variant. Because of this large disparity, examining the relationship between CGP and COVID-19 severity and mortality in this population is an important future area of research.

Anti-Glomerular Basement Membrane

An environmental trigger has been hypothesized to be associated with anti-GBM disease as studies have shown spatial and temporal clustering of cases of anti-GBM disease [79]. Anti-GBM clusters have been noted during influenza outbreaks in the past [80, 81]. It is possible that tissue destruction in the setting of infection exposes basement membrane collagen antigen targets, triggering the formation of autoimmune antibodies against the GBM [82]. Prendecki et al. [83] noted an increase in incident cases of anti-GBM disease in North West London during

Table 2. Summarized characteristics of reported cases with CGP

Age, years (range)	53.2 (16–79)
Gender, *n* (%)	
Female	13 (26)
Male	37 (74)
Race, *n* (%)	
Black	48 (96)
Hispanic	1 (2)
Indian	1 (2)
APOL1 genotype, *n* (%)	
G1/G1	14 (28)
G1/G2	8 (16)
G2/G2	2 (4)
Wild type/G1	1 (2)
Transplant recipient G0/G0, donor G0/G2	1 (2)
Donor G1/G0, recipient G1/G1	1 (2)
Comorbidities, *n* (%)	
Hypertension	36 (72)
Diabetes	15 (3)
CKD	19 (38)
Obesity	11 (22)
Respiratory status, *n* (%)	
Mechanical ventilation	4 (8)
Nasal cannula	8 (16)
No oxygen requirement	6 (12)
Not reported	32 (64)
Renal function	
Average baseline creatinine	1.47 mg/dL
Dialysis requirement, *n* (%)	29 (58)
Average peak serum creatinine or creatinine at time of biopsy	9.04 mg/dL
Average proteinuria	9.3 g/g 7.18 g/d
Biopsy findings	
Glomerular collapse, % (% range)	33 (3–100)
Tubuloreticular inclusions present, *n*/*N* (%)	14/29 cases (48)
Viral inclusions or evidence of viral RNA on biopsy, *n*/*N* (%)	4/31 cases (13)
Renal-specific treatments	
Treatment with steroids for renal cause	1
Renal outcome	
Dialysis-dependent, *n* (%)	20 (40)
Average latest serum creatinine reported	3.32 mg/dL
Average latest proteinuria reported	4.5 g/g
Mortality, *n* (%)	
Alive	46 (92)
Death	2 (4)

CKD, chronic kidney disease; CGP, collapsing glomerulopathy.

the coronavirus epidemic. They report 8 new cases diagnosed in April 2020, representing an observed-to-expected case ratio of 5.64. Four of these cases had SARS-CoV-2 IgM antibodies in their serum, which suggests that this infection may play a role in causing this autoimmune disease, though this remains speculative. Kudose et al. [30] also reported 1 case of new onset anti-GBM nephritis in a COVID-19 patient. These are the first anti-GBM cases linked to COVID-19, and this possible causal relationship needs to be explored further.

Thrombotic Microangiopathy

COVID-19 has been known to induce a hypercoagulable state, leading to micro- and macrovascular thrombosis [84, 85]. Complement-mediated TMA in SARS-CoV-2 is thought to be triggered by the cytokine release and host

immune response following infection. This results in endothelial cell dysfunction, activation of the complement cascade, and microvascular thrombosis [86]. Renal-associated TMA has been identified on kidney biopsies in COVID-19-affected patients [31, 44, 87]. Of note is a case series of 17 patients with COVID-19 who had kidney biopsies done for AKI or proteinuria [44]. This study identified 4 patients with severe hypertension and AKI and laboratory results consistent with TMA (anemia, thrombocytopenia, elevated LDH, and low haptoglobin with normal ADAMTS-13); however, 3 of the 4 patients had other confounding conditions such as hypertension, illicit drug use, or exposure to cytotoxic therapy. One of them had low C3 with normal C4, indicative of activation of the alternative complement pathway. TMA has only been identified on biopsy in a small subset of patients with COVID-19. That said, a study examining 3 postmortem kidney biopsies in COVID-19 demonstrated increased tubular C5b-9 deposition in these specimens [49], raising suspicion that tubular injury may be due to complement activation. Clinical trials for the use of eculizumab and C5aR inhibitors in the treatment of severe COVID-19 are ongoing [88]. Further studies are needed to identify how complement inhibition or systemic anticoagulation can affect patient outcomes from a renal standpoint.

Treatment-Associated Glomerulonephritis

Several treatment options are currently being investigated to minimize the morbidity and mortality associated with COVID-19 infections. Some of these drugs have been known to have renal adverse events, including AKI, proximal renal tubular acidosis, autoimmune GN, and TMA. Izzedine et al. [89] included a chart of renal adverse events associated with drugs that may be potential COVID-19 treatment options. Of particular interest are monoclonal antibodies such as adalimumab (tumor necrosis factor inhibitor), in phase IV trials, and bevacizumab (vascular endothelial growth factor inhibitor), in phase II/III trials, both of which have been implicated in causing an autoimmune GN. Bevacizumab has also been known to cause a TMA. Leflunomide has also been reported to cause anti-GBM or an autoimmune GN.

What Treatment Strategies Have Been Recommended for Glomerular Patients during COVID-19?

Treatment of glomerular disease patients during the COVID-19 pandemic introduced several challenges for treating physicians. The severity of COVID-19 in patients with hypertension and diabetes who are on RAAS inhibitors, along with the virus's affinity to ACE2 receptors, called into question a potential harmful association between RAAS inhibitor use and severity of infection [90]. Further case-control studies and cohort studies with propensity score matching have not demonstrated any association with RAAS inhibitor use and severity of infection [91–93]. Due to lack of convincing evidence of harm of RAAS inhibition during COVID-19, and preponderance of evidence for their benefit in treatment of chronic renal and cardiac disease [94], several professional societies recommend continuing RAAS blockade throughout the epidemic, including the American College of Physicians [95] and the Renal Association, UK [96].

Balancing the risk and benefit of immunosuppression during the COVID-19 introduces yet another treatment dilemma. While there have yet to be evidence-based guidelines for treatment, there have been some expert recommendations published addressing the handling of immunosuppression during this pandemic [97–99]. With limited data on which to base treatment decisions, these expert and consensus recommendations are largely based on clinical experience and weighing the risk and benefit of holding immunosuppression: keeping glomerular disease in check while minimizing the risk of acquiring COVID-19 infection. For patients who are stable, then postponing initiation of drug therapy may be more appropriate. For patients who are on therapy and contract COVID-19, then reducing or discontinuing antimetabolites is recommended to lower their immunosuppression [97]. Decreasing or withdrawing antimetabolites, at least in hospitalized patients, has also been the primary strategy for physicians caring for transplant patients [12, 13]. Efforts should also focus on social distancing measures and minimizing patient visits to the hospital, by encouraging the use of telemedicine, limiting blood draws, and reserving kidney biopsies to critical cases. Further studies are needed to establish guidelines on which treatments may be safe to administer or withhold during this pandemic.

The advent of vaccines against SARS-CoV-2 brought about optimism for protection against severe infection with COVID-19. Unfortunately, patients receiving treatment for glomerular disease were excluded from 78% of trials with non-live attenuated vaccines. Furthermore, patients with CKD were excluded from 16% of trials [100]. Although immunosuppressed patients were given priority in receiving vaccination [101], little is known about their ability to mount an effective im-

Table 3. Summary of studies documenting incidence of glomerular disease after COVID-19 vaccination

Author	Age, years	Gender	Race	Underlying glomerular disease	Baseline proteinuria	COVID-19 vaccine	Renal findings	Timing of symptoms	Biopsy findings	Treatment	Outcome
Glomerular disease flare											
Mancianti et al. [108]	39	M	W	Minimal change	None	BNT-162b2	Proteinuria 8 g/day AKI (Cr 1.8 mg/dL)	8 days after 1st dose	MCD	Steroids	AKI and proteinuria resolved
Negrea et al. [109]	38	F	W	IgA nephropathy	0.63 g/day	mRNA-1273	Gross hematuria Proteinuria 1.4 g/day Cr stable	Hematuria 8–24 h after 2nd dose Proteinuria 3 weeks after 2nd dose	N/A	None	Hematuria resolved after 3 days
Negrea et al. [109]	38	F	W	IgA nephropathy	0.43 g/day	mRNA-1273	Gross hematuria Proteinuria stable Cr stable	8–24 h after 2nd dose	N/A	None	Hematuria resolved after 3 days
Rahim et al. [110]	52	F	A	IgA nephropathy	1 g/g	mRNA-1273	Gross hematuria Proteinuria 4.2 g/g Cr stable	24 h after 2nd dose	N/A	None	Resolved proteinuria and hematuria in 1 week
Aydin et al. [111]	66	F	NR	MN, PLA2R unknown 8 yr remission	None	Sinovac	Edema Cr 2.78 mg/dL UPCR 9.42 mg/mg PLA2R 120.53 RU/mL	2 weeks after 1st dose	N/A	NR	NR
De novo glomerular disease											
Lebedev et al. [104]	50	M	NR	N/A	N/A	BNT-162b2	Edema, anasarca Proteinuria 6.9 g/day AKI (Cr 6.6 mg/dL)	4 days after 1st dose	MCD	Steroids	AKI resolved in 1 week UACR 155 mg/g
D'Agati et al. [105]	77	M	W	15 yr T2DM	None	BNT-162b2	Edema, anasarca Proteinuria 23.2 g/day AKI (Cr 3.17 mg/dL)	7 days after 1st dose	MCD + ATN	Steroids	3 wk follow-up, Cr 3.74 mg/dL, proteinuria 18.8 g/day
Sekar et al. [106]	52	M	W	N/A	N/A	mRNA-1273	Microscopic hematuria AKI (Cr 8.41 mg/dL) 1+ proteinuria ANCA PR3 positive	2 weeks after 2nd dose	Pauci-immune crescentic GN	Steroids, rituximab, cyclophosphamide	Dialysis
Anderegg et al. [107]	81	M	NR	N/A	N/A	mRNA-1273	Proteinuria (subnephrotic) AKI (not quantified) ANCA-PR3 positive	Unclear, biopsy 22 days after second dose	Pauci-immune crescentic GN	Steroids, cyclophosphamide, pheresis	Renal function improved over 3 wk
Anderegg et al. [107]	39	M	NR	N/A	N/A	mRNA-1273	Gross hematuria AKI (not quantified) Proteinuria present (not quantified in report)	Immediately after 2nd dose	Crescentic IgA nephritis	Steroids, cyclophosphamide	AKI resolved, Proteinuria improved Micro-hematuria persisted

AKI, acute kidney injury; Cr, serum creatinine; GN, glomerulonephritis; MCD, minimal change disease; MN, membranous nephropathy; NR, not reported; PLA2R, phospholipase A2 receptor antibodies; T2DM, type 2 diabetes mellitus; UPCR, urine protein creatinine ratio; UACR, urine albumin creatinine ratio.

munogenic response to the vaccines. A study of 242 renal transplant patients in France who received the mRNA-1273 vaccine demonstrated that only 10.8% of patients demonstrated seroconversion 28 days after receiving the vaccine [102]. As expected, a decreased immunosuppression regimen, a longer time from transplantation, and better renal function were associated with higher rates of seroconversion. Similarly, we expect that patients on lower doses of immunosuppression are more likely to mount an immune response to SARS-CoV-2 vaccines. Of particular concern is the use of anti-CD20 agents which may significantly depress a patient's ability to form antibodies. A study of antibody response to mRNA vaccines in patients with rheumatologic and musculoskeletal diseases, and a reduced antibody response was noted in patients on rituximab or mycophenolate [103]. If possible, timing the vaccine with a period of lowest immunosuppression feasible may optimize vaccine immunogenicity.

As vaccines became widely available, several case reports have been published documenting de novo glomerular disease (minimal change disease [104, 105], ANCA vasculitis [106, 107], and crescentic IgA [107]), or flares of known glomerular disease (minimal change [108], IgA nephropathy [109, 110], primary membranous nephropathy [111]) after administration of mRNA-based or inactivated SARS-CoV-2 vaccines. These cases and their outcome are summarized in Table 3. While the timing of glomerular disease occurrence in relation to the vaccine is suggestive of a causal association, these findings may have been coincidental with mass vaccination. The overwhelming efficacy of COVID-19 vaccination suggests that the benefit of vaccination likely outweighs the potential associated risks in this high-risk immunosuppressed cohort. However, close clinical monitoring post-vaccination is likely indicated. Overall, studies focusing on the vaccine immune response in patients with glomerular disease are imperative in order to better care for these patients and manage their immunosuppression accordingly.

Conclusion

We examined the current literature to summarize the information available to inform the care of patients with glomerular disease in the setting of the COVID-19 pandemic. This is a patient population at high risk of complications from the infection itself, as well as from their kidney disease if immunosuppressive therapy plans are altered. As glomerular disease is rare, aggregating data across multiple studies is needed. We reviewed the evidence around several key clinical questions. But, like many rare diseases, the evidence guiding care remains sparse for glomerular disease.

Very limited studies have assessed risk of glomerular disease patients contracting the virus, but generalizable data are not available. Urgent studies are needed to understand the effectiveness of various health behaviors to reduce the risk of infection in this population. Higher quality data do support the risk of a more severe disease course in patients with CKD which likely applies to glomerular disease patients. However, specific studies assessing the relative risk in glomerular disease as compared to other causes of CKD are needed. Many case reports have now surfaced for glomerular disease relapse as well as de novo disease which may result from a number of different mechanisms. In patients who did undergo a biopsy, pathologic diagnoses vary, but FSGS and TMA are most commonly reported along with tubular injury. Data on immunosuppressive management in terms of mitigating risk of infection, severity of COVID-19 disease, risk of disease relapse, and treatment of relapsed or de novo disease are not currently available but also deserve study.

The understanding of COVID-19 pathogenesis and clinical presentation is rapidly evolving as cases are reported from centers across the globe and as the pandemic reaches more diverse populations. Coordinated collaborations across centers are likely the most efficient way to generate the evidence needed to support treatment decisions in glomerular disease.

Conflict of Interest Statement

Dr. Mariani has received fees for advisory boards from Reata Pharmaceuticals, Retrophin Inc, and Calliditas.

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Author Contributions

Data acquisition: A.S. and S.S. Data analysis and/or interpretation: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors.

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