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Renal Prognosis of COVID-19 Associated Nephropathy

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INTRODUCTION

COVID-19 associated nephropathy (COVAN) is the most common cause of acute kidney injury (AKI) in Black patients with SARS-CoV-2 infection undergoing kidney biopsy. It presents with AKI and proteinuria, often nephrotic-range. The histopathology of COVAN is collapsing glomerulopathy (CG), the most severe form of focal segmental glomerulosclerosis.[1] The pattern of injury of CG is also seen in the setting of other infections (including human immunodeficiency virus, human T-cell lymphotrophic virus-1, filariasis, leishmaniasis, parvovirus B19, cytomegalovirus, and loa loa), autoimmune disease, ischemia, anabolic steroids, and therapeutic or recreational drugs.[2]

CG is most commonly described in patients with recent African ancestry due to genomic risk variants in the gene Apolipoprotein L1 (*APOL1*).[3] Many CG etiologies are considered to be "second hits" to underlying *APOL1* risk, for which SARS-CoV-2 is of no exception, with a high-risk genotype frequency of up to 91%−94% patients with COVAN.[4,5]

A poor prognosis of CG is demonstrated within multiple studies,[6,7] however, most CG triggers involve chronic conditions rather than a short-lived infection. In case series, patients with CG compared to non-collapsing focal segmental glomerulosclerosis had a higher serum creatinine, increased proteinuria, and worse prognosis.[8] At 5 years, all patients had progressive chronic kidney disease (CKD) or end-stage kidney disease (ESKD).[9]

Though overall CG has a poor prognosis, outcomes attributed to COVAN have not been extensively studied. A series of 23 patients showed a majority of COVAN patients had CKD at follow-up, although half of patients who initially required dialysis achieved dialysis independence.[5] A series of 6 cases showed similarly poor outcomes, with 5 of 6 patients developing ESKD or death.[3] Given that SARS-CoV-2 infection is rapidly cleared and may represent a self-limited "second-hit" to *APOL1* risk alleles, it is theoretically possible that remission could occur postviral clearance. Herein, we present a clinicopathologic case series to assess clinical outcomes in 43 patients with COVAN to further inform prognosis.

RESULTS

Clinical Presentation and Biopsy Findings

A total of 56 patients with biopsy-proven COVAN, diagnosed between March 2020 through March 2021, were identified from 3 institutions, with 43 patients having available outcome data for further analysis (See Supplementary Methods). The mean age was 52.8 ± 12.0 years and included 84.7% self-identified Black, 4.3% Hispanic, and 11.6% patients of unknown race. There was no sex predilection. Nineteen patients (44%) had pre-existing CKD. Comorbidities were common, including hypertension (76.7%), obesity (60%), smoking (7%), and diabetes mellitus (27.9%), with 81.4% having at least 1 condition. Most patients lacked additional risk factors for CG, however, 2 patients were found to be positive for human immunodeficiency virus (HIV) and 1 patient had concurrent lupus nephritis. The severity of COVID-19 infection (available in 33 patients) was mild in 3 patients, moderate in 17, and 13 had severe disease. Most patients who presented with COVID-19 were biopsied within 1 month (81.4%), including 69.8% within 2 weeks.

Most COVAN patients presented with AKI (90.7%). Nephrotic range proteinuria was present in 81.3%

Table 1. Clinical, pathologic, and laboratory data from patients with COVID19-associated nephropathy ($n = 43$)

Clinical parameter	Value
Age (mean ± SD; range)	52.8 ± 11.8; 30–78 yr
Sex	22/43 male, 21/43 female
Severity of COVID-19 ($n = 33$)	3 outpatients, 17 hospitalized, 13 required ICU care
Patient comorbidities	HTN 33 Pts, Smoking 2 Pts, Obesity 26 Pts, Diabetes 12 Pts
Patients with CKD at time of biopsy	19 (44%)
Patients with CKD at follow up	40 of 42 (1 deceased) (95%)
Biopsy indication	39/43 AKI + proteinuria; 4/43 proteinuria without AKI
Days between COVID and biopsy (mean ± SD)	15.4 ± 23.2
Days between biopsy and follow-up (mean ± SD)	244 ± 143
Patients on dialysis at time of biopsy	16 (37%)
Patients on dialysis at follow-up	14 (8 were on dialysis at time of biopsy) (33%)
Patients with kidney transplant at follow-up	0
Deceased patients	1
Laboratory parameter	Value
Creatinine at time of biopsy (mean ± SD; mg/dl); $n = 41$	7.0 ± 4.7
Creatinine at follow-up (mean ± SD; mg/dl); $n = 28$[a]	3.1 ± 1.9
Change in creatinine at follow-up (mean ± SD; mg/dl)	−3.1 ± 5.1, $P = 0.0002$ (Wilcoxon Signed Rank)
Proteinuria at time of biopsy (mean ± SD; g/day), $n = 26$	12.2 ± 10.9
Proteinuria at follow-up (mean ± SD; g/day); $n = 23$[a]	2.4 ± 2.7
Change in proteinuria at follow up (mean ± SD; g/day)	−7.01 ± 10.4, $P = 0.00001$ (Wilcoxon Signed Rank)
Albumin at time of biopsy (mean ± SD; g/dl), $n = 25$	2.4 ± 0.6
Albumin at follow-up (mean ± SD; g/dl), $n = 15$	3.7 ± 0.5

AKI, acute kidney disease; CKD, chronic kidney disease; HTN, hypertension; ICU, intensive care unit; Pts, pateints.
[a]Patients on dialysis excluded from analysis, as follow-up creatinine and proteinuria measurements would not be accurate.

patients, with hypoalbuminemia in 95.8%. Thirteen patients (30%) required dialysis at presentation (Table 1). All patients with COVAN had a diagnosis of CG. Concurrent acute tubular injury was present in 95.3% (including patients with mild, moderate, or severe disease). Mean global glomerulosclerosis was 34.1% ± 25.9%. The degree of interstitial fibrosis and tubular atrophy was variable (Table 2). Of the patients with available data, 83% showed severe podocyte foot process effacement by electron microscopy (≥80% foot process effacement). The average foot process effacement overall was 62.6 ± 41.4%. Thirty-seven patients had an *APOL1* high-risk genotype (86%), 1 patient had 1 genomic risk allele, and 5 had no *APOL1* risk alleles. SARS-CoV-2 immunohistochemistry was performed in 38 patients and was negative in all cases (see Supplementary Methods). Ultrastructural investigation for virions was not performed, because viral particles can mimic intracellular structures and may show poor specificity.[S1–S3]

Outcome Data

The mean follow-up interval was 244 ± 143 days. Sixteen (37%) patients required dialysis at presentation, of which 8 developed ESKD and became dialysis-dependent at follow-up, whereas the remaining 8 were able to subsequently come off dialysis. Six additional patients required dialysis at follow-up, but did not at presentation. One patient died. Forty of 42 living patients developed progressive CKD with a mean eGFR of 26.6 ± 14.2 ml/min and a mean serum creatinine of 3.1 ± 1.9 mg/dl. Serum creatinine was significantly decreased overall at follow-up ($P = 0.0002$, Wilcoxon Signed Rank test). Twenty of 23 nondialysis patients (87%) with available data had persistent proteinuria (mean 2.4 ± 2.7 g/day), although overall proteinuria was significantly decreased from presentation ($P = 0.0001$, Wilcoxon Signed Rank test). Hypoalbuminemia resolved in 33%. Overall, 6.9% of patients had complete remission of proteinuria, 34.9% had partial remission, 25.6% had no remission, and 34.9% reached end-points of ESKD or death.

Therapies received by the patients included corticosteroids (prednisone or dexamethasone, $n = 12$), renin-angiotensin system blockade with angiotensin converting enzyme inhibitors or angiotensin receptor blockers ($n = 15$), diuretics ($n = 9$), antiviral treatment with remesivir ($n = 2$), convalescent plasma ($n = 1$), corticosteroids ($n = 12$), mycophenolate ($n = 2$), cyclosporine ($n = 1$), and methotrexate ($n = 1$).

Most patients treated with corticosteroids had moderate to severe COVID-19, with 11 of 12 requiring hospitalization, 4 of which needed intensive care. Four steroid-treated patients were on dialysis on presentation and 2 remained dialysis-dependent at follow-up. All patients not requiring renal repalcement therapy had renal dysfunction at follow-up with a mean creatinine of 2.6 ± 0.7 mg/dl and proteinuria of 3.4 ± 4.4 grams/day. Corticosteroid therapy is not the standard of care for CG because CG is a genetic form of focal segmental glomerulosclerosis rather than a primary podocytopathy.[S4] Nevertheless, given that there are no known effective therapies or randomized controlled clinical trials, corticosteroid use was attempted in 12 patients, but not found to have a significant benefit in this cohort.

Poor Prognostic Indicators

Patients who were dialysis-dependent at follow-up were older (mean age, 59.1 ± 13.9 years vs. 50.4 ± 10.7 years, *t*-test $P = 0.03$) and had a higher serum creatinine at

Table 2. Histopathologic data on kidney biopsies from patients with COVID-19-associated nephropathy

Parameter	Total	No progression ($n = 29$)	Progression to ESKD ($n = 14$)	*P* value
Global glomerulosclerosis ($n = 43$)	34.1 ± 25.9%	25.0 ± 23.2%	52.9 ± 21.3%	
Interstitial fibrosis+Tubular atrophy ($n = 43$)				
Mild	14/43	13/29	1/14	0.017
Moderate	15/43	10/29	5/14	1.000
Severe	14/43	6/29	8/14	0.034
Arteriosclerosis ($n = 38$ with available data)				
None	6/38 (15.8%)	6/25	0/13	0.076
Mild	9/38 (23.7%)	6/25	3/13	1.000
Moderate	8/38 (21.1%)	6/25	2/13	1.000
Severe	15/38 (39.5%)	7/25	8/13	0.079
Arteriolar hyalinosis ($n = 39$ with data)				
None	16/39	14/26	2/13	0.037
Mild	9/39	5/26	4/13	0.45
Moderate	5/39	4/26	1/136/13	0.65
Severe	9/39	3/26		0.039

presentation (mean 9.4 ± 3.2 vs. 6.0 ± 5.0 mg/dl, *t*-test $P = 0.03$). On kidney biopsy, patients who required dialysis had increased global glomerulosclerosis (mean 52.9% vs. 25.0%, Fisher exact test $P = 0.0005$) increased frequency of moderate-to-severe interstitial fibrosis and tubular atrophy (Fisher exact test $P = 0.034$), and increased frequency of severe arteriolar hyalinosis (Fisher exact test $P = 0.039$). Sex, proteinuria at presentation, CKD at presentation, *APOL1* high-risk versus low-risk genotypes, and AKI requiring dialysis at presentation were not predictive of ESKD.

DISCUSSION

COVAN carries a significant disease burden for Black patients with SARS-CoV-2 infection. In our series, nearly all patients with COVAN had advanced CKD at follow-up, with most showing no remission or disease progression. Most patients with COVAN presented with AKI (91%) and had an *APOL1* high-risk genotype (86%), frequencies similar to those described previously.[4,5]

A high-risk *APOL1* genotype is an independent risk factor for development of AKI in Black Americans with COVID-19, with a 2-fold increased risk compared to patients without a high-risk genotype.[S5] It has been reported that copy number alterations can occur in *APOL1*, which may contribute to a toxic gain of function of *APOL1*.[S6] We evaluated for copy number alterations by digital droplet polymerase chain reaction (PCR) in the one patient containing 1 *APOL1* risk allele, although no copy number alterations were identified (data not shown). As a minority of patients develop COVAN independent of *APOL1* nephropathy, additional mechanisms may be at play in disease pathogenesis.

The renal prognosis of COVAN appears to be similar to what is reported for HIV-associated nephropathy (HIVAN), despite HIV being a persistent infection whereas SARS-CoV-2 infection is self-limited. Similar to COVAN, HIVAN is triggered with viral infection being a "second hit" to an underlying *APOL1* high risk genotype leading to systemic type I interferon activation, because most patients with both HIVAN and COVAN carry 2 *APOL1* risk alleles.[1,3,4] CG due to HIVAN results in >90% of patients developing CKD, and 40% with ESKD or death at <1 year.[S7] There is increased mortality in HIVAN[S7] compared to COVAN, although this may be due to opportunistic infections from acquired immune deficiency syndrome.

To date, there is only 1 large prior study examining renal prognosis of COVAN. This study included 23 patients, with no patients achieving full remission. In this series, most patients developed advanced CKD with a median serum creatinine of 2.5 mg/dl.[5] Approximately one-third of patients had partial remission with persistent renal dysfunction and subnephrotic proteinuria, one-third of patients had no remission, and one-third of patients progressed to ESKD. Half of patients with COVAN requiring dialysis at the time of presentation became permanently dialysis-dependent.[5] Our study largely recapitulates these data, with overall poor outcomes of COVAN, similar to other forms of CG.

Limitations

Limitations of our study include the retrospective design, for which not all clinical and laboratory data parameters were available. For most patients, there were no baseline pre-COVAN laboratory studies available for evaluation. Therefore, the prevalence of pre-existing CKD may be underestimated.

SARS-CoV-2 variant testing was not performed; however, these data were collected when the dominant SARS-CoV-2 variants were alpha and beta, prior to the delta and omicron variants. There was no standard treatment of either COVID-19 or COVAN, and antiviral

treatments were not widely available at this time. Another limitation of this study was that all patients with COVAN were infected by the alpha and beta variants of SARS-CoV-2, which are no longer the predominant strains of the virus. These data reflect COVID-19 cases prior to vaccine availability and monoclonal antibody therapies. However, COVAN is still a significant kidney disease and public health problem. Whereas these data include COVAN cases from March 2020 to 2021, we did not observe a decline in COVAN cases from March 2021 to 2022 (56 cases in 2020-2021 compared to 94 cases in 2021-2022) and a greater percentage of cases of CG can be attributed to COVAN (16.6% of cases compared to 24.9% of cases). Although this study is the largest to date, the sample size is small for a predictive analysis and conclusions may be premature, although our results are concordant with an independent study of COVAN outcomes.

CONCLUSION

In patients affected with COVAN, there is an overall poor prognosis, with most patients developing advanced CKD and one-third of patients with ESKD or death at <1 year. Though SARS-CoV-2 infection is often cleared within 2 weeks, this short-lived trigger did not lead to better outcomes than other causes of CG.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Supplementary Methods.

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