A multi-center retrospective cohort study defines the spectrum of kidney pathology in Coronavirus 2019 Disease (COVID-19)

May, Rebecca M; Cassol, Clarissa; Hannoudi, Andrew; Larsen, Christopher P; Lerma, Edgar; et al; Luyckx, Valerie; Grosse, Phillipp

Abstract: Kidney failure is common in patients with Coronavirus Disease-19 (COVID-19) resulting in increased morbidity and mortality. In an international collaboration, 284 kidney biopsies were evaluated to improve understanding of kidney disease in COVID-19. Diagnoses were compared to five years of 63,575 native biopsies prior to the pandemic and 13,955 allograft biopsies to identify diseases increased in patients with COVID-19. Genotyping for APOL1 G1 and G2 alleles was performed in 107 African American and Hispanic patients. Immunohistochemistry for SARS-CoV-2 was utilized to assess direct viral infection in 273 cases along with clinical information at the time of biopsy. The leading indication for native biopsy was acute kidney injury (45.4%), followed by proteinuria with or without concurrent acute kidney injury (42.6%). There were more African American patients (44.6%) than patients of other ethnicities. The most common diagnosis in native biopsies was collapsing glomerulopathy (25.8%) which associated with high-risk APOL1 genotypes in 91.7% of cases. Compared to the five-year biopsy database, the frequency of myoglobin cast nephropathy and proliferative glomerulonephritis with monoclonal IgG deposits was also increased in patients with COVID-19 (3.3% and 1.7%, respectively), while there was a reduced frequency of chronic conditions (including diabetes mellitus, IgA nephropathy, and arterio nephrosclerosis) as the primary diagnosis. In transplants, the leading indication was acute kidney injury (86.4%), for which rejection was the predominant diagnosis (61.4%). Direct SARS-CoV-2 viral infection was not identified. Thus, our multi-center large case series identified kidney diseases that disproportionately affect patients with COVID-19, demonstrated a high frequency of APOL1 high-risk genotypes within this group, with no evidence of direct viral infection within the kidney.

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CONCLUSION: There is increased frequency of COVAN associated with a high-risk APOL1 genotype in COVID-19 patients. Proliferative glomerulonephritis with monoclonal immune deposits (PGMID), and myoglobin cast nephropathy were also enriched and chronic conditions were under-represented in this cohort (n=284 biopsies).

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A multi-center retrospective cohort study defines the spectrum of kidney pathology in Coronavirus 2019 Disease (COVID-19).

Rebecca M. May¹, Clarissa Cassol¹, Andrew Hannoudi², Christopher P. Larsen¹, Edgar Lerma³, Randy S. Haun¹, Juarez R. Braga⁴, Samar I. Hassen¹, Jon Wilson¹, Christine VanBeek⁵, Mahesha Vankalakunti⁶, Lilli Barnum¹, Patrick D. Walker¹, T. David Bourne¹, Nidia C. Messias¹, Josephine M. Ambruzs¹, Christie L. Boils¹, Shree S. Sharma¹, L. Nicholas Cossey¹, Pravir V. Baxi⁷, Matthew Palmer⁸, Jonathan Zuckerman⁹, Vighnesh Walavalkar¹⁰, Anatoly Urisman¹⁰, Alexander Gallan¹¹, Laith F. Al-Rabadi¹², Roger Rodby⁷, Valerie Luyckx¹³,¹⁴, Gustavo Espino¹⁵, Srivilliputur Santhana-Krishnan¹⁶, Brent Alper¹⁷,¹⁸, Son G. Lam¹⁹, Ghadeer N. Hannoudi²⁰, Dwight Matthew²¹, Mark Belz²², Gary Singer²³, Srikanth Kunaparaju²⁴, Deborah Price²⁵, Saurabh Chawla²⁶, Chetana Rondla²⁷, Mazen A. Abdalla²⁸, Marcus L. Britton²⁹, Subir Pau³¹, Uday Ranjit³⁰, Prasad Bichu³¹, Sean R. Williamson³², Yuvraj Sharma³³, Ariana Gaspert³³, Philipp Grosse³⁴, Ian Meyer³⁵, Brahmi Vasudev¹¹, Mohamad El Kassem³⁶, Juan Carlos Q. Velez³⁷,³⁸, Tiffany N. Caza¹

¹ Arkana Laboratories, 10810 Executive Center Drive #100, Little Rock AR USA 72211
² University of Michigan, 500 S State Street, Ann Arbor, MI USA 48109
³ University of Illinois at Chicago College of Medicine / Advocate Christ Medical Center, Department of Internal Medicine, 1853 W Polk St, Oak Lawn IL USA 60612
⁴ University of Arkansas for Medical Sciences, Nephrology Division, 4301 W Markham St, Little Rock, AR USA 72205
⁵ AmeriPath Laboratories, Pathology, 225 N.E. 97th St #600, Oklahoma City OK USA 73114
⁶ Manipal Hospital – Bangalore, Department of Pathology, 98 HAL Old Airport Rd, Bangalore, Karnataka India 560017
⁷ Rush University Medical Center, Nephrology Division, 1620 W. Harrison St, Chicago IL USA 60612
⁸ University of Pennsylvania Perelman School of Medicine, Department of Pathology, 3400 Civic Center Blvd, Philadelphia PA USA 19104
⁹ University of California Los Angeles Health System, Department of Pathology and Laboratory Medicine, 140833 Le Conte Ave, Los Angeles, CA USA 90095
¹⁰ UCSF Medical Center, Department of Pathology, 505 Panassus Avenue, CA USA 92103
¹¹ Medical College of Wisconsin, 9200 W. Wisconsin Avenue, WDL Building L73, Milwakee, WI USA 53226
12 University of Utah School of Medicine, 50 N Medical Drive, Salt Lake City UT 84132
13 University of Zurich, Department of Pathology and Molecular Biology, University Hospital Zurich, Schmelzberstrasse 8091, Zurich, Switzerland
14 Brigham and Women’s Hospital, Renal Division, 75 Francis Street, Boston, MA USA 02115
15 Albuquerque Nephrology Associates, 4333 Pan American Fwy NE, Albuquerque, NM USA 87107
16 Renal Associates of West Michigan, 330 E Beltline Ave NE, Suite 100, Grand Rapids, MI USA 49509
17 Tulane University School of Medicine, Tulane University Hypertension and Renal Center of Excellence, 6823 St. Charles Avenue, New Orleans, LA USA 70118
18 Tulane School of Medicine, 1430 Tulane Ave, New Orleans, LA USA 70112
19 Nephrology and Hypertension Associated LTD, 1790 Barron Street, Oxford, MS USA 38655
20 Michigan Kidney Consultants, 44200 Woodward Ave, Suite 209, Pontiac, MI USA 48341
21 Shoals Kidney & Hypertension Center, 422 East Dr Hicks Boulevard, Suite A, Florence, AL USA 35630
22 Iowa Kidney Physicians PC, 1215 Pleasant Street, Suite 100, Des Moines, IA USA 50309
23 Midwest Nephrology Associates, 70 Jungermann Circle, Suite 405, St. Peters, MO USA 63376
24 Richmond Nephrology Associates, 7001 West Broad Street, Suite A, Richmond, VA USA 23294
25 Nephrology Associates of NE Florida, 2 Shircliff Way DePaul Bldg Suite 700, Jacksonville, FL USA 32204
26 Northwest Indiana Nephrology, 6061 Broadway, Merrillville, IN USA 46410
27 Georgia Nephrology, 595 Hurricane Shoals Road NW, Suite 100, Lawrenceville, GA USA 30046
28 The Kidney Clinic, 2386 Clower Street, Suite C105, Snellville, GA USA 30078
29 Nephrology & Hypertension Associates LTD, 1542 Medical Park Circle, Tupelo, MS USA 38801
30 Nephrology Associates of Central Florida, 2501 N Orange Avenue #53, Orlando, FL USA 32804
31 Nephrology Associates of Tidewater Ltd., Norfolk, VA USA 23510
32 Cleveland Clinic, 9500 Euclid Ave L25, Cleveland, OH USA 44195
33 Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI USA 48202
34 Kantonal Hospital of Graubunden, Loestrasse 170, CH-7000, Chur, Switzerland
35 Mt Auburn Nephrology, 8260 Pine Road, Cincinnati OH USA 45236
36 Mohamad El Kassem MD (private practice), Nephrology, Coral Springs, FL USA
37 Ochsner Health System, Deparment of Nephrology, 1514 Jefferson Hwy, New Orleans LA USA 70121
38 Ochsner Clinical School, The University of Queensland (Australia), Department of Nephrology, St. Lucia, QLD, AUS

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Corresponding author:
Tiffany Caza, MD/PhD
10810 Executive Center Drive #100
Little Rock, AR 72211
Phone: (501)-492-2695
Email: tiffany.caza@arkanalabs.com
Abstract.

Kidney failure is common in patients with Coronavirus Disease-19 (COVID-19) resulting in increased morbidity and mortality. In an international collaboration, 284 kidney biopsies were evaluated to improve understanding of kidney disease in COVID-19. Diagnoses were compared to five years of 63,575 native biopsies prior to the pandemic and 13,955 allograft biopsies to identify diseases increased in patients with COVID-19. Genotyping for APOL1 G1 and G2 alleles was performed in 107 African American and Hispanic patients. Immunohistochemistry for SARS-CoV-2 was utilized to assess direct viral infection in 273 cases along with clinical information at the time of biopsy. The leading indication for native biopsy was acute kidney injury (45.4%), followed by proteinuria with or without concurrent acute kidney injury (42.6%). There were more African American patients (44.6%) than patients of other ethnicities. The most common diagnosis in native biopsies was collapsing glomerulopathy (25.8%) which associated with high-risk APOL1 genotypes in 91.7% of cases. Compared to the five-year biopsy database, the frequency of myoglobin cast nephropathy and proliferative glomerulonephritis with monoclonal IgG deposits was also increased in patients with COVID-19 (3.3% and 1.7%, respectively), while there was a reduced frequency of chronic conditions (including diabetes mellitus, IgA nephropathy, and arterionephrosclerosis) as the primary diagnosis. In transplants, the leading indication was acute kidney injury (86.4%), for which rejection was the predominant diagnosis (61.4%). Direct SARS-CoV-2 viral infection was not identified. Thus, our multi-center large case series identified kidney diseases that disproportionately affect patients with COVID-19, demonstrated a high frequency of APOL1 high-risk genotypes within this group, with no evidence of direct viral infection within the kidney.
Introduction.

Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection, impacting 37% of patients hospitalized with COVID-19. Morbidity and mortality are significantly higher for COVID-19 patients with AKI, than those without kidney disease. Up to 40% of patients requiring mechanical ventilation need concurrent kidney replacement therapy (KRT), resulting in unprecedented numbers of patients requiring KRT and a shortage of dialysis units. In a study of over 10,000 patients in 920 hospitals, the frequency of in-hospital death was a staggering 73% in patients requiring both mechanical ventilation and dialysis.

Case reports, small case series, and autopsy studies have shown a wide spectrum of kidney manifestations in COVID-19 patients and have improved our understanding of kidney disease in this population. Reported manifestations in native biopsies include acute tubular injury (ATI), myoglobin cast nephropathy, thrombotic microangiopathy (TMA), acute interstitial nephritis, non-collapsing focal and segmental glomerulosclerosis (FSGS), collapsing glomerulopathy (also known as COVID-19 associated nephropathy, COVAN), membranous nephropathy, minimal change disease, acute pyelonephritis, oxalate nephropathy, immune complex-mediated glomerulonephritis/lupus nephritis, infection-associated glomerulonephritis, membranoproliferative glomerulonephritis, anti-GBM disease, IgA nephropathy, light chain cast nephropathy, arteritis, and crescentic glomerulonephritis. Acute T-cell mediated rejection, antibody-mediated rejection, calcineurin inhibitor nephrotoxicity, atheroemboli, collapsing glomerulopathy, and cortical necrosis have been reported in COVID-19 kidney allograft biopsies. Chronic conditions have also been reported, including diabetic nephropathy, obesity-related glomerulopathy, amyloidosis, and arterionephrosclerosis (Supplemental Tables 1 and 2). These studies have been useful to elucidate the need for kidney biopsy in COVID-19 patients for proper diagnosis and disease management. However, given a large spectrum of diagnoses, it is unclear which diseases are enriched in COVID-19 patients from small series and case reports. Additionally, single case reports can be subject to publication bias, reporting those with interesting or unusual clinical presentations.

We present the largest kidney biopsy series to date, encompassing 240 native and 44 allograft biopsies in an international collaborative effort to improve our understanding of kidney disease in COVID-19. We sought to determine which kidney diseases are enriched in patients with COVID-19 through comparison of this series to a pre-COVID-19 biopsy cohort.

Materials and Methods.

Study design.

A multi-center clinicopathologic study of kidney pathology in COVID-19 patients was initiated following approval by the Solutions institutional review board, with adherence to the principles of the Declaration of Helsinki. Multiple kidney pathologists and
nephrologists were invited to participate and formed the ‘COVID-19 Kidney Biopsy Consortium’. Biopsies were received from a total of nine institutions and were from the United States, Switzerland, and India. The participating centers included University of California at Los Angeles (n=2), University of California at San Francisco (n=2), University of Pennsylvania (n=2), Medical College of Wisconsin (n=1), Rush University (n=2), Ameripath Laboratories (n=7), University of Utah (n=2), University of Zurich (Switzerland, n=1), Manipal Hospital (Bangalore, India n=13), and the remaining cases were from Arkana Laboratories which were received from multiple nephrology practices among several states (n=252). Cases from March 2020 to March 2021 were included. A total of 284 biopsies from COVID-19 patients were evaluated, including 240 native biopsies and 44 allografts. Patients of all ages were included. Inclusion criteria included cases with a confirmed diagnosis of COVID-19 prior to kidney biopsy, requiring a positive RNA PCR for SARS-CoV-2 from a nasopharyngeal swab. Cases for which a diagnosis of COVID-19 preceded kidney biopsy by greater than 3 months were excluded. Additionally, native kidney biopsy cases in which there was a prior biopsy with the same diagnosis preceding COVID-19 were excluded. All biopsies with temporal association with COVID-19 were included to avoid selection bias. All cases in the series are novel and are not published in another manuscript.

For a control comparison cohort to compare demographics, biopsy indications, and disease frequencies, we utilized a database of kidney biopsies over a 5-year period prior to the pandemic in the United States, from 1/1/2015 – 1/1/2020. This included 77,530 biopsies overall, comprised of 63,575 native biopsies and 13,955 allograft biopsies. Due to the large number of biopsies in the database, we selected 100 cases a year (500 cases total) through use of a random number generator (https://www.random.org/integer-sets) to provide estimates of database characteristics.

Biopsies from patients with COVID-19 were also compared to diagnostic frequencies from 100 HIV-positive patients biopsied prior to the COVID-19 pandemic as a control for systemic viral infection. The cohort of HIV positive patients spanned a fourteen year period (2006-2020) to identify these 100 cases. The comparison cohorts included only cases from Arkana Laboratories. Arkana Laboratories receives biopsies from 40 states and is nearly representative of the biopsied population in the United States.

Statistics.

Categorical variables were compared using the $x^2$ statistic or Fisher's exact test as appropriate. T-tests were used to evaluate differences in continuous variables. Krusal-Wallis testing was utilized for evaluation of group differences. A cutoff of $p <0.01$ was considered significant.

Histologic processing of kidney biopsies.

Kidney biopsies were prepared by standard light microscopy, immunofluorescence (IF), and electron microscopy (EM) techniques as previously described$^{53}$. Formalin-fixed paraffin-embedded (FFPE) tissue sections were stained with hematoxylin and eosin
(H&E), Periodic acid–Schiff (PAS), Masson-Trichrome, and Jones methenamine silver (JMS). IF was performed on frozen tissue sections for IgG, IgA, IgM, C3, C1q, κ light chain, and λ light chains. Immunofluorescence microscopy was available for 283 or 284 cases. Transmission EM was evaluated for ultrastructural analysis and was available for 198 of 240 native and 34 of 44 allograft biopsies.

For the Arkana Laboratory cases, a Congo red stain was performed on all native biopsies of patients ≥49 years of age. Immunostains for C4d and SV-40 were performed on allograft biopsies. Additional immunostains were performed within some cases as indicated for diagnosis. These included myoglobin and hemoglobin for cases of ATI with eosinophilic granular or beaded casts, DNAJB9 for fibrillary glomerulopathy, serum amyloid P for confirmation of a diagnosis of membranous-like glomerulopathy with masked IgG kappa deposits (MGMID), IgG subclasses light chain restricted cases, and for membranous nephropathy subtyping with phospholipase A2 receptor (PLA2R), thrombospondin type 1 domain containing 7A (THSD7A), exostosin-1 (EXT1), and neural epidermal growth factor-like 1 (NELL1).

**SARS-CoV-2 immunohistochemistry and in situ hybridization.**

Immunohistochemistry for SARS-CoV-2 was performed for expression of SARS-CoV-2 within 3-µm FFPE tissue sections on the Leica BOND III platform, using a SARS nucleocapsid mouse monoclonal antibody at 1:100 dilution (Thermo Fisher Scientific, cat #MA1-7404), as described previously.

For SARS-CoV-2 in situ hybridization (ISH), RNAscope was performed on unstained FFPE tissue sections on the Leica BOND-III platform using the Leica Bond RNAscope detection kit (cat # DS9790) by the standard manufacturer’s protocol. Commercially available RNA probes targeting nucleotides 21631-23303 of SARS-CoV-2 (ACDBio cat # 848568) were used for ISH. Positive and negative controls were evaluated with each sample. Peptidylprolyl isomerase B (PP1B), a house-keeping gene, was utilized as a positive RNA integrity control. Diaminopimelate B (DAPB), a bacterial gene, was used as a negative control. The tissue sections were counterstained with PAS following ISH.

**Histopathologic review.**

All cases were de-identified and pathology slides were evaluated at a single center (Arkana Laboratories) and were graded by nine nephropathologists. A subset of glass slides from the referring pathologist or whole slide images were reviewed. Light microscopic parameters evaluated included the presence or absence of mesangial expansion, mesangial hypercellularity, endocapillary hypercellularity, fibrinoid necrosis, crescents, segmental sclerosis, microangiopathic changes, and presence of capillary loop thrombi. If segmental sclerosis was present, the type according to the Columbia classification was specified. Tubulointerstitial parameters (for both native and allograft biopsies) were graded on a 0 to 3 scale according to the Banff classification.
parameters and included interstitial inflammation, edema, tubulitis, tubular injury, and the degree of interstitial fibrosis and tubular atrophy (IF/TA). Vascular parameters included evaluation of arteriosclerosis, arteriolar hyalinosis, endothelialitis, or microangiopathic changes. Arteriosclerosis and arteriolar hyalinosis were scored as mild (10-25% intimal fibrosis or luminal stenosis), moderate (25%-50%), or severe (>50%). Immunofluorescence was graded on a trace to 3+ scale for IgA, IgG, IgM, C3, C1q, C4d, kappa, and lambda light chains, with the character of deposits and compartment specified. For outside cases without IF slides, this information was recorded from the pathology reports. Electron microscopy included the evaluation of electron dense deposits (subepithelial, intramembranous, subendothelial, or mesangial), and degree of podocyte foot process effacement (estimated in percentages to the nearest 10% for all cases with segmental sclerosis; and as mild 10-25%, moderate 25-50%, severe >50% for the remainder).

Clinical evaluation.

Clinical parameters provided by the nephrologists included patient demographics (age, sex, and ethnicity), medical history for co-morbid conditions, and time of biopsy laboratory values. As data was abstracted from clinical records, it is unknown whether patients self-identified with the race provided in the chart. The indication for biopsy (AKI, proteinuria, proteinuria with acute kidney injury, hematuria, or AKI on chronic kidney disease, CKD) was obtained, as well as the time interval between COVID-19 diagnosis and biopsy. Severity of disease was noted, documented as 'mild' for outpatients or asymptomatic COVID-19 infection, 'moderate' for hospitalized patients, and 'severe' in those who required intensive care unit (ICU) admission with mechanical ventilation and/or kidney replacement therapy (KRT).

AKI was defined according to the KDIGO Clinical Practice Guideline for Acute Kidney Injury. In patients in which we did not have a known baseline serum creatinine value, we considered AKI to be present in there was >0.5 mg/dL creatinine above the reference range with no evidence of chronicity on biopsy, presence of oliguria, requirement for KRT, or a creatinine of >4.0 mg/dL (as this criterion alone meets KDIGO criteria for AKI class III). We did not separate AKI into KDIGO class I, II, or III as a baseline creatinine value was not available for some patients. CKD was defined as known pre-existing CKD in the patient's medical record or a prior GFR < 60 mL/min.

Demographics included the patient’s age, sex, and ethnicity. Relevant past medical history included presence or absence of co-morbidities including pre-existing chronic kidney disease, hypertension, diabetes mellitus, and obesity. Laboratory parameters included serum creatinine, quantitative proteinuria, and urinalysis for presence/absence of hematuria (microscopic or macroscopic). Quantitative proteinuria included urine protein-to-creatinine ratio, albumin-to-creatinine ratio, or 24 hour urinary protein measurements. Hematuria was defined as positivity for blood on a dipstick urinalysis, or ≥ 5 RBC/high power field on urine microscopy. Sub-nephrotic proteinuria included
300 mg to <3.5 grams of urinary protein and nephrotic range proteinuria ≥3.5 grams/day.

**Genetic testing for APOL1 risk alleles.**

Genetic testing for APOL1 G1 and G2 risk alleles was performed on all African American and Hispanic patient samples with sufficient tissue available for DNA extraction. PCR was used to amplify the regions of the APOL1 gene carrying one of the two G1 risk allele pair (rs73885319 / c.1024A>G), the G2 6-bp insertion/deletion risk allele (rs71785313 / c.1164_1169delATAATT), and wild type alleles at these two loci. The G1 and G2 loci are in near perfect linkage disequilibrium. Taqman PCR was performed on a ViiA 7 Real-Time PCR system, as previously described. Genotyping data were evaluated using ViiA7 sequence detection software and allelic discrimination plots were used to assess the call results. Genotypes of G0/G0, G0/G1, or G0/G2 were combined as ‘low risk’ status, while G1/G1, G1/G2, or G2/G2 were grouped as ‘high risk’.

**Literature review.**

All case reports and clinical case series describing manifestations of COVID-19 within kidney biopsies or autopsies were included in a comprehensive review of the literature in the English language. Articles were identified through PubMed and Google Scholar, using various search terms including COVID-19, COVID19, SARS-CoV-2 AND kidney, renal biopsy, kidney biopsy, and autopsy. Conference abstracts from the American Society of Nephrology and United States and Canadian Society of Pathology meetings were also included.

**Results.**

**Demographics of the study population.**

A total of 284 kidney biopsies from patients with COVID-19 were evaluated, collected from March 2020 through March 2021 and including 240 native and 44 allograft biopsies. The mean time interval between COVID-19 diagnosis and kidney biopsy was 22.3 ± 26.8 days for native biopsies and 21.9 ± 23.5 days for allografts. Patients undergoing native biopsy (43.3%) and 40.9% transplant recipients had a biopsy in the same week of COVID-19 diagnosis. There was a slight male dominance in native biopsies (57.1% native biopsies, 50.0% allograft biopsies). African American patients were disproportionately impacted, comprising 44.6% of native COVID-19 kidney biopsies, compared to an estimated 15.4% of patients in the biopsy database (Table 1).

All demographic and clinical parameters were compared to five years of biopsies prior to the pandemic (January 1, 2015 to January 1, 2020), comprising 63,575 native and 13,955 allograft biopsies. To provide estimates from the general biopsy database, the data are from a random sampling of 100 cases per year over 5 years (500 cases total, with 429 native and 71 allograft cases) through use of a random number generator. As
a control for systemic viral infection, 100 cases from HIV-positive individuals were also compared.

The mean age of COVID-19 patients undergoing native kidney biopsy was similar to the biopsy database (53.7 years versus 56.3 years), however the HIV comparison cohort was younger (mean age = 43.5 years). Co-morbid conditions, including CKD, hypertension, diabetes mellitus, and obesity, were common in COVID-19 patients and in controls, with at least one co-morbidity in 85.4% of patients with COVID-19 and 76.0% from the biopsy database (Table 1). A majority of patients had moderate to severe disease at the time of kidney biopsy (70.5% of patients), with moderate disease defined as requiring hospitalization and/or supplemental oxygen and severe disease involving intensive care unit admission with mechanical ventilation and/or dialysis (Table 1).

The leading indication for native biopsy was AKI (30.8% patients, mean creatinine=5.69 mg/dL), followed by AKI on CKD (14.6%), and proteinuria (8.8%). For all patients with COVID-19 with COVAN, all had AKI. For transplant biopsies, the most common indication was a rise in serum creatinine (86.4%), followed by delayed graft function, hematuria, and protocol surveillance biopsy. Concurrent proteinuria and/or hematuria was seen in a high proportion of patients for both native and transplant biopsies (Table 1).

**Kidney biopsy diagnoses in patients with COVID-19.**

Kidney biopsies from patients with COVID-19 had a wide range of histopathologic diagnoses (Table 2). For native biopsies (n=240), COVAN was the most common (25.8%), with 27 other diagnoses represented (Table 2A). There was evidence of ATI within the majority of biopsies (78.3% of native and 88.6% of allografts), although it was the sole or predominant finding within only 13.3% of cases. Within COVAN cases, a higher proportion of cases had concomitant ATI (96.8%). Within allografts, the most common diagnosis was allograft rejection (61.4%), followed by acute tubular injury (27.3%, Table 2B).

Seven children were included in the above analysis, three who had native biopsies and four allograft cases. They ranged from 11-17 years old, five were female, and two were male. Two were Caucasian, two were Hispanic, one was African American, and two were of unknown race. Native biopsy diagnoses included membranous nephropathy (NELL1 positive), crescentic IgA nephropathy, and acute tubular injury. The transplant diagnoses were antibody-mediated rejection (n=2), antibody-mediated rejection with concurrent collapsing glomerulopathy, and acute T-cell mediated rejection.

**Frequencies of COVID-19 kidney biopsy diagnoses to the total population undergoing kidney biopsy.**

To determine whether there was enrichment in any biopsy diagnosis within patients with COVID-19 compared to the general biopsied populations, the frequencies of each diagnosis were compared to the frequency of diagnosis within the 5-year biopsy
database, as well as the cohort of 100 HIV-positive patients (Tables 2A + 2B). A comparison of each COVID-19 kidney biopsy diagnosis to disease severity is included in Supplemental Tables 3A + 3B (for native and allograft biopsies, respectively).

Kidney diseases enriched in COVID-19 native biopsies included collapsing glomerulopathy, myoglobin cast nephropathy, and proliferative glomerulonephritis with monoclonal IgG deposits (Figure 1). For patients with myoglobin case nephropathy, four patients had an elevated creatinine kinase level at the time of biopsy (with the remainder of cases not having data available). A total of 4 patients had proliferative glomerulonephritis with monoclonal IgG deposits (PGMID), of which all contained kappa restricted immune deposits. The patients with PGMID were older adults (mean age = 65.8 years), and two had follow-up serum and urine electrophoresis (SPEP/UPEP) and were negative for a monoclonal paraprotein.

Kidney diseases with reduced frequency in the setting of COVID-19 included chronic conditions, such as diabetic nephropathy, arterionephrosclerosis, and IgA nephropathy. Despite reduced diabetic nephropathy and arterionephrosclerosis in COVID-19 kidney biopsies, the frequency of diabetes mellitus and hypertension as clinical co-morbidities was increased in patients with COVID-19 (40.4% versus 29.6% diabetes; 72.5% versus 63.6% with hypertension). This finding is likely due to differences in biopsy indication, as there was an increased frequency of patients with COVID-19 presenting with AKI compared to the biopsy database (45.4% versus 31.2%). An additional 21 diagnoses showed no differences from the biopsy database (Table 2A).

When comparing diagnostic frequencies with HIV-positive patients, there was an increased frequency of infection-associated glomerulonephritis and of acute interstitial nephritis in HIV patients compared to patients with COVID-19 (Table 2A). Of note, there was a similar proportion of collapsing glomerulopathy cases (25.8% of patients with COVID-19 and 27.7% in HIV-positive patients), which may suggest similarities between COVAN and HIV-associated nephropathy (HIVAN).

Among allograft biopsies, there were increased frequencies of transplant rejection in patients with COVID-19 as compared to pre-pandemic biopsies, and fewer biopsies with a diagnosis of ‘negative for rejection’. Other diagnoses were not significantly different between groups (Tables 2A + B, Figure 1).

**Histopathology of COVID-19 kidney biopsies.**

Histopathologic parameters assessed for all kidney biopsies in patients with COVID-19 included light, immunofluorescence, and electron microscopic features as detailed within the Materials and Methods section. A majority of the histopathologic findings was as expected for each pathologic diagnosis and was not unique within the setting of COVID-19 (detailed in Supplemental Tables 4-9), with a few interesting observations.

For biopsies with membranous glomerulopathy, although not increased compared to the biopsy database, there was an enrichment of cases of unknown antigen type. Four of
11 cases were PLA2R-positive, 2 were NELL1 positive, and 5 were negative for PLA2R, NELL1, EXT1 or 2, and THSD7A.

All PGMID biopsies were kappa-light chain restricted, with one case being IgG1 kappa, 2 cases IgG3 kappa, and 1 case being kappa-light chain only (light chain only variant of PGMID). There was an additional case of membranous-like glomerulopathy with masked IgG kappa deposits was identified. There is one biopsy with a membranous glomerulopathy with IgG1 kappa-restricted immune deposits, yielding a total of six patients with an immune complex-mediated glomerulonephritis with kappa light chain restricted deposits. Other types of paraprotein-associated diseases were not increased in patients with COVID-19. There were two cases of light chain cast nephropathy and a single case of light chain deposition disease, all of which were kappa light chain restricted. AL amyloidosis cases (n=3) all were lambda light chain type.

Eleven patients had pauci-immune crescentic glomerulonephritis, including eight with a known positive ANCA serology at the time of biopsy. The ANCA serologies were MPO-ANCA (n=4), PR3-ANCA (n=2), one with a positive ANCA by indirect immunofluorescence without MPO or PR3 testing, and one with dual ANCA and anti-GBM disease. 'Secondary' focal segmental glomerulosclerosis cases (n=8) also had varied features, with two cases with APOL1-risk alleles (APOL1 nephropathy), two had concurrent glomerulomegaly (hyperfiltration), one had concurrent arteriosclerosis (ischemia), one had atypical segmental sclerosis with fibrous crescents (sclerosing glomerulopathy), and two were of unknown etiology. For patients with amyloidosis, three were AL amyloidosis and one was LECT2 amyloidosis. For lupus nephritis biopsies (n=6), there were no cases showing activity, with three cases of sclerosing lupus nephritis (two ISN/RPS class IV-C and one advanced sclerosing lupus nephritis ISN/RPS class VI), two cases of membranous lupus nephritis (ISN/RPS class V), and one case of minimal mesangial lupus nephritis (ISN/RPS class I). In cryoglobulinemic glomerulonephritis biopsies (n=3), one had associated Hepatitis C, one is favored to be autoimmune in nature (positive ANA at 1:1280) and one had concurrent vasculitis of unknown etiology.

Histopathologic parameters are documented in supplemental tables for podocytopathies (Supplemental Table 4), other glomerular diseases (Supplemental Table 5A + B), tubulointerstitial diseases (Supplemental Table 6), vascular diseases (Supplemental Table 7), chronic kidney diseases (Supplemental Table 8), and transplants (Supplemental Table 9).

Evaluation of SARS-CoV-2 within biopsy tissue.

Immunohistochemistry for SARS-CoV-2 was used to evaluate for direct viral infection within kidney parenchyma. SARS-CoV-2 IHC was focally positive within <1% of tubular epithelial cells in 10 of 235 native kidney biopsies and 1 of 38 allograft biopsies. Most likely, these 3.7% of cases were false positives. However, SARS-CoV-2 in situ hybridization was negative within these positive biopsies. There is equivalent sensitivity
and increased specificity of *in situ* hybridization compared to immunohistochemistry, and therefore, is no definite evidence of direct viral infection within the samples.

**APOL1 genotyping and distribution of low-risk and high-risk genotype to biopsy diagnosis.**

**APOL1** genotyping for G1 and G2 alleles was performed for all patients with collapsing morphology with residual tissue available for testing (n=48), as well as non-collapsing FSGS biopsies from all patients of African American or Hispanic descent that had tissue available for testing (n=59 patients, for a total of 107 patients). Of collapsing glomerulopathy cases, 38 were from African Americans, 2 were from Hispanics, and 8 were of unknown race. Data with additional cases and corresponding genotypes are included in Supplemental Table 10.

The majority of native biopsies from African Americans and Hispanics had a high-risk **APOL1** genotype (60.7%). A majority of patients with COVAN had a high-risk genotype (91.7%). Of note, there were only four COVAN patients without a high-risk genotype, all of which carried zero APOL1-risk alleles (Table 3).

In native non-COVAN biopsies, 35.6% carried a high-risk **APOL1** genotype, with an additional 20.3% with one risk allele. Of non-COVAN cases with segmental sclerosis with or without another concurrent diagnosis (n=36), 13 had 2 **APOL1** risk alleles (36.1%, Supplemental Table 10). A high risk APOL1 genotype had a trend towards increased FSGS lesions, compared to patients with a low risk genotype (p=0.03). Additionally, there was an increased degree of podocyte foot process effacement in patients with two APOL1 risk alleles (median 90% versus 30% without risk alleles, p<0.001).

**Review of COVID-19 kidney biopsies reported in the literature.**

A total of 38 kidney biopsy case studies or case series were reported in the literature, including manuscripts and conference abstracts. Combined, these accounted for 165 cases, of which included 158 native biopsies and seven transplant biopsies. The kidney diseases included COVAN (36.4%), ATI (28.9%), non-collapsing FSGS (5.0%), TMA (4.4%), and crescentic glomerulonephritis (4.4%), with 15 other diagnoses reported within native cases (Table 4 and Supplemental Table 1). Seven allograft biopsies were reported, three of which showed rejection (Table 4 and Supplemental Table 1). Comparison of diagnostic frequencies compared to COVID-19 patients in this cohort, as well as the 5-year biopsy database, is depicted in Figure 2.

Additionally, 13 autopsy case studies and series were reported in the literature, which together included 176 decedents. ATI was the predominant finding within autopsies (55.1%), with 16 other diseases reported (Supplemental Table 2). Unlike in kidney biopsies, COVAN was only reported in 1.1% of cases, however there was a lower frequency of patients of African descent.

**Discussion.**
We formed a multi-institutional collaboration to compare demographics and determine the frequency of kidney diseases in patients with COVID-19 and compared these frequencies to the general population biopsied to find those individuals most at risk and identify diseases increased among patients with COVID-19. COVAN, myoglobin cast nephropathy, and proliferative glomerulonephritis with monoclonal immunoglobulin deposits are increased in native kidney biopsies in our COVID-19 cohort, and allograft rejection was over-represented in transplant biopsies.

Within the literature, there was a predominance of COVAN and ATI reported. The high number of COVAN cases is consistent with our cohort and we did not identify an enrichment in ATI, TMA, or crescentic glomerulonephritis in our biopsy series, although several cases are reported in the literature. The reported cases of TMA may denote a selection bias in light of coagulopathy described in this population. Only six transplant biopsies were previously reported, three of which had allograft rejection, which is consistent with our study in which 61.3% of transplant biopsies had rejection. There was a lower frequency of diabetic nephropathy, IgA nephropathy, and arterionephrosclerosis as the primary diagnosis in kidney biopsies from patients with COVID-19 in our study and within the literature, likely due to an increased proportion of patients with COVID-19 being biopsied due to AKI, rather than CKD.

The most common reported finding in autopsy studies was ATI (55.1%), markedly increased from native kidney biopsies (13.3%). A high prevalence of ATI within autopsies could indicate multi-organ system dysfunction in severe illness rather than a primary manifestation, and could be over-represented due to post-mortem autolysis. Additionally, the demographic distribution of the autopsied population varied from that of COVID-19 kidney biopsies (both reported and in this case series), with only 7.4% of decedents (for which ethnicity data are available) being African American.

We observed a 2.9-fold increase of African Americans biopsied compared to their representation in the general population within the United States (44.6% versus 15.4%) African Americans have a disproportionate burden of COVID-19 infection and development of AKI compared to other ethnic populations, even aside from COVAN, the reasons of which are multi-factorial. The incidence of SARS-CoV-2 infection in African Americans is nearly three times that of Caucasians. Geographic location is a contributing factor, with urban living and 96% of ‘hot spots’ for SARS-CoV-2 infection having an increased proportion of African Americans. African Americans also have a 1.5-to 2.4-fold increased incidence of co-morbidities contributing to kidney dysfunction, including diabetes mellitus and obesity. Yet, the most important factor contributing to disproportionate acute kidney injury is likely related to APOL1 genomic risk alleles. Genotyping was selected for African Americans and Hispanics because 14% of all African Americans and 1% of Hispanics carry a high-risk APOL1 genotype. A staggering 60.7% of kidney biopsies from African Americans with COVID-19 were from patients with a high-risk APOL1 genotype, greater than four times that of the general African American population.
While a diagnosis of collapsing glomerulopathy was markedly increased from the general population undergoing kidney biopsy, the frequency was similar to that of HIV patients. COVAN and HIVAN are thought to have similar pathophysiology, with a ‘second hit’ to APOL1 risk alleles driven by increased circulating interferon generated as an immune response to viral infection. Supporting this, tubuloreticular inclusions serving as ‘interferon footprints’ have been identified ultrastructurally. Although the ‘second hit’ for collapsing glomerulopathy may be short-lived due to viral clearance, it is uncertain whether outcomes in COVAN differ than those with a more persistent trigger, such as HIVAN, systemic lupus erythematosus, or malignancy.

With regards to the increase in myoglobin cast nephropathy within patients with COVID-19, there are reports of rhabdomyolysis associated with COVID-19, supporting this finding. Other viral infections have been reported to cause AKI due to rhabdomyolysis. Rhabdomyolysis is often a late complication of SARS-CoV-2 infection, can present prior to AKI and carries a high mortality rate. Rhabdomyolysis in the setting of COVID-19 can be due to a necrotizing myopathy, which has been reported. A representative case from our muscle biopsy service is shown in Supplemental Figure 1. Early recognition of rhabdomyolysis through measuring a creatine kinase level on admission could lead to early recognition to initiate hydration therapy.

Transient paraproteinemia has been reported in the setting of various infectious and autoimmune diseases. While not previously described, it is possible that SARS-CoV-2 can induce transient paraproteinemia due to hyperactivity of the immune system in response to infection. Transient paraproteinemia has also been associated with kidney dysfunction. It is unknown whether this accounts for the increased frequency of proliferative glomerulonephritis with monoclonal IgG deposits in COVID-19 patients.

It has been postulated that SARS-CoV-2 may induce AKI through direct viral infection since angiotensin 2 (ACE2), a membrane-bound peptidase that acts as receptor for SARS-CoV-2, is expressed within kidney tubular epithelial cells. While this is possible, we were unable to demonstrate SARS-CoV-2 expression within tubular epithelial cells of COVID-19 kidney biopsies. While there have been reports of viral-like particles seen ultrastructurally, similar ubiquitous intracellular structures were identified within biopsies of non-COVID-19 patients prior to the pandemic. Morphologic mimics of virions include secretory vesicles, multivesicular bodies, exosomes, coatomer-coated vesicles, and clathrin-coated vesicles. Therefore, detailed high power electron microscopy to ultrastructurally evaluate for viral-like particles within podocytes was not performed in this study.

Limitations.

Our study includes the clinical and histopathologic data from kidney biopsies collected during the COVID-19 pandemic from March 2020 to March 2021, however, it is lacking in longitudinal clinical follow-up. Therefore, we are unable to make comparisons of diagnostic data to patient outcomes. In the HIV-positive patient cohort, data on anti-
retroviral drug use, CD4+ T cell count, or progression to acquired immunodeficiency syndrome (AIDS) is not available. Random sampling was used to estimate demographic data and biopsy indications for a 5-year cohort from the biopsy database, as these data could not be easily queried. Evaluation for direct viral infection included only SARS-CoV-2 immunohistochemistry, with SARS-CoV-2 in situ hybridization only performed as a reflex test for positive cases and not for the entire cohort. Additionally, detailed ultrastructural evaluation was not performed to examine for virions or tubuloreticular inclusions within COVID-19 patient biopsies, although routine electron microscopy was done on most cases.

Conclusion.

In summary, we present the largest cohort of kidney biopsies from patients with COVID-19 to date, showing an increased frequency of COVAN, PGMID, and myoglobin cast nephropathy. Further studies are required to determine long-term clinical outcomes of patients with kidney disease in the setting of COVID-19, particularly in the setting of COVAN. As pulmonary manifestations have been found to persist long after viral clearance, it is uncertain if this is also true for kidney manifestations and is a subject for further investigation.

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|                      | Native                  | Pre-pandemic native | Transplant             | Pre-Pandemic Transplant |
|----------------------|-------------------------|---------------------|------------------------|-------------------------|
| **Number of Biopsies**| 240                     | 429                 | 44                     | 71                      |
| **Age**              | 53.7 years (11-84)      | 56.3 years (2-94)   | 36.8 years (12-66)     | 52.6 years (4-79)       |
| **Sex**              | F 103 M 137             | F 192 M 237         | F 22 M 22              | F 21 M 50              |
|                      | 42.9 57.1               | 44.8 55.2           | 50.0 50.0              | 29.6 70.4              |
| **Days between diagnosis and biopsy** | 22.3 days (0-90) | n/a | 21.9 days (0-85) | n/a |
| **Severity of Infection** | Mild | n/a | 10 | 22.7 |
|                      | Moderate                | 39                  | 16.3                   | 14                      |
|                      | Severe                  | 87                  | 36.3                   | 33                      |
|                      | Unknown                 | 82                  | 34.2                   | 76.0                    |
|                      | 32                      | 13.3                | 15                     | 19                      |
| **Race**             | African American        | 107                 | 44.6                   | 14                      |
|                      | Caucasian               | 45                  | 18.8                   | 19                      |
|                      | Native American         | 5                   | 2.1                    | 1.4                     |
|                      | Hispanic                | 15                  | 6.3                    | 5.6                     |
|                      | Asian/Indian            | 11                  | 4.6                    | 0.0                     |
|                      | Unknown                 | 57                  | 23.8                   | 26.8                    |
| **Comorbidities (≥1)** | Obesity               | 89                  | 37.1                   | 40.0                    |
|                      | DM                      | 97                  | 40.4                   | 32.8                    |
|                      | HTN                     | 174                 | 72.5                   | 40.9                    |
|                      | CKD                     | 89                  | 37.1                   | 37.0                    |
| **Biopsy Indication**| AKI: 74                 | 30.8                | 8.8                    | 10.0                    |
|                      | AKI on CKD: 35          | 14.6                | 2.9                    | 10.0                    |
|                      | Proteinuria: 21         | 8.8                 | 2.5                    | 2.0                     |
|                      | AKI and Proteinuria: 81 | 33.8                | 5.0                    | 3.8                     |
|                      | Hematuria and Proteinuria: 7 | 2.9             | 1.7                    | 1.7                     |
|                      | Hematuria: 6            | 2.5                 | 1.7                    | 1.7                     |
|                      | CKD: 12                 | 5.0                 | 1.7                    | 1.7                     |
|                      | Unknown: 4              | 1.7                 | 1.7                    | 1.7                     |
| **Creatinine (mg/dL)** | 5.69 (0.32-30.74) | 3.24 (104-20.6)    | 4.21 (0.73-23.0)       | 2.80 (0.6-11.5)         |
|                      | Unknown 9               | 44                  | 23                     | 18                      |
|                      | 3.24 (104-20.6)         | 63                  | 155                    | 36.1                    |
|                      | Unknown 83              | 1.3                 | 5.1                    | 6.8                     |
|                      | 20.8                    | 158                 | 36.8                   | 14                      |
|                      | 22.6                    | 61                  | 14.2                   | 15.9                    |
|                      | 23                      | 210                 | 49.0                   | 52.2                    |
|                      | 7.5                     | 3                   | 6.8                    | 10                      |
|                      | 38.7                    | 18                  | 40.9                   | 25                      |
|                      | 53.8                    | 23                  | 52.4                   | 45                      |
| **Need for RRT**     | Yes                     | 71                  | 29.6                   | 6.8                     |
|                      | No                      | 55                  | 22.9                   | 36.8                    |
|                      | Unknown                 | 114                 | 47.5                   | 35.2                    |

**Table 1.** Demographics and clinical features of native and allograft COVID-19 kidney biopsies, compared to pre-pandemic native and allograft kidney biopsies.
Table 2A. Final diagnosis in kidney biopsies of from patients with COVID-19 (n=240) compared biopsies from HIV positive patients (n=64), from 5 years of total biopsies prior to the COVID-19 pandemic (1/1/2015 to 1/1/2020, n=63,575). P-values represent comparisons to the COVID-19 patient cohort. Abbreviations: HIV, Human Immunodeficiency Virus; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; PGMID, proliferative glomerulonephritis with monoclonal IgG deposits; MGMID, membranous-like glomerulopathy with monoclonal IgG kappa deposits.

| Final Diagnosis | COVID-19 (N= 240) | HIV (N= 94) | Biopsy database (N= 63,575) |
|-----------------|-------------------|-------------|-----------------------------|
|                 |                   |             |                             |

Table 2A. Final diagnosis in kidney biopsies of from patients with COVID-19 (n=240) compared biopsies from HIV positive patients (n=64), from 5 years of total biopsies prior to the COVID-19 pandemic (1/1/2015 to 1/1/2020, n=63,575). P-values represent comparisons to the COVID-19 patient cohort. Abbreviations: HIV, Human Immunodeficiency Virus; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; PGMID, proliferative glomerulonephritis with monoclonal IgG deposits; MGMID, membranous-like glomerulopathy with monoclonal IgG kappa deposits.
| Diagnosis                          | N  | %   | N  | %   | P-value | N  | %   | P-value |
|-----------------------------------|----|-----|----|-----|---------|----|-----|---------|
| Collapsing Glomerulopathy         | 62 | 25.8| 26 | 27.7| 0.73    | 1,177| 1.8 | <.001   |
| Acute Tubular Injury              | 32 | 13.3| 20 | 21.3| 0.07    | 7,613| 11.9| 0.52    |
| Diabetic Nephropathy              | 29 | 12.1| 18 | 19.2| 0.09    | 13,549| 21.3| <.001   |
| Podocytopathies                   |    |     |    |     |         |      |      |         |
| Minimal change disease            | 18 | 7.5 | 2  | 2.1 | 0.07    | 3,877| 6.1 | 0.34    |
| Primary, non-collapsing FSGS      | 11 | 4.6 | 2  | 2.1 | 0.07    | 1,606| 2.5 | 0.34    |
| Pauci-Immune Crescentic Glomerulonephritis | 7  | 2.9 | 0  | 0   | 0.09    | 2,271| 3.6 | <.001   |
| Membranous Nephropathy            | 11 | 4.6 | 4  | 4.3 | 1.0     | 3,999| 6.2 | 0.35    |
| Myoglobin Cast Nephropathy        | 8  | 3.3 | 1  | 1.1 | 0.45    | 89   | 0.1 | <.001   |
| Infection-Associated GN           | 8  | 3.3 | 10 | 10.6| 0.01    | 2,289| 3.6 | 1.0     |
| Arterionephrosclerosis            | 8  | 3.3 | 5  | 5.3 | 0.53    | 10,441| 16.4| <.001   |
| FSGS, secondary                   | 8  | 3.3 | 9  | 9.6 | 0.03    | 2,144| 3.3 | 1.0     |
| IgA Nephropathy                   | 7  | 2.9 | 6  | 6.4 | 0.20    | 4,729| 7.4 | 0.004   |
| Lupus Nephritis                   | 6  | 2.5 | 0  | 0   | 0.19    | 3,160| 5.0 | 0.10    |
| Thrombotic Microangiopathy        | 5  | 2.1 | 3  | 3.2 | 0.69    | 1,096| 1.7 | 0.61    |
| Amyloidosis                       | 4  | 1.7 | 0  | 0   | 0.58    | 2,187| 3.4 | 0.13    |
| Acute Interstitial Nephritis      | 4  | 1.7 | 10 | 10.6| <.001   | 1,429| 2.2 | 0.54    |
| PGMID                             | 4  | 1.7 | 0  | 0   | 0.12    | 115  | 0.2 | 0.001   |
| Cryoglobulinemic Glomerulonephritis| 3  | 1.3 | 0  | 0   | 0.56    | 308  | 0.5 | 0.11    |
| Acute Pyelonephritis              | 2  | 0.8 | 0  | 0   | 1.0     | 972  | 1.5 | 0.59    |
| Light Chain Cast Nephropathy      | 2  | 0.8 | 0  | 0   | 1.0     | 1,109| 1.7 | 0.45    |
| MGMID                             | 1  | 0.4 | 0  | 0   | 1.0     | 132  | 0.2 | 0.39    |
| Cortical Infarct                  | 1  | 0.4 | 0  | 0   | 1.0     | 107  | 0.2 | 0.33    |
| Anti-Glomerular Basement Membrane Antibody Disease | 1  | 0.4 | 0  | 0   | 1.0     | 150  | 0.2 | 0.43    |
| Fibrillar Glomerulopathy          | 1  | 0.4 | 0  | 0   | 1.0     | 507  | 0.8 | 1.0     |
| Light Chain Deposition Disease    | 1  | 0.4 | 0  | 0   | 1.0     | 525  | 0.8 | 1.0     |
| Hemoglobin Cast Nephropathy       | 1  | 0.4 | 0  | 0   | 1.0     | 7    | 0.001| 0.03    |
| Thin Glomerular Basement Membrane Disease | 1  | 0.4 | 0  | 0   | 1.0     | 737  | 1.2 | 0.54    |
| Sickle Cell Nephropathy           | 1  | 0.4 | 0  | 0   | 1.0     | 371  | 0.6 | 1.0     |
| Final Diagnosis                        | COVID (N= 44) | HIV (N= 6) | Biopsy database (N= 13,955) |
|---------------------------------------|---------------|------------|-----------------------------|
|                                       | N   | %     | N   | %    | P-value | N   | %    | P-value |
| Allograft rejection                   |     |       |     |      |         | 3788| 27.1 | <.001   |
| Antibody-mediated rejection           | 27  | 61.4  | 5   | 83.3 | 0.39    |     |       |         |
| Acute T-cell mediated rejection       | 17  | 38.6  | 3   | 50   |         |     |       |         |
| Antibody + T-cell mediated rejection  | 6   | 13.6  | 2   | 33.3 |         |     |       |         |
|                                       | 4   | 9.1   | 0   |      |         |     |       |         |
| Acute tubular injury                  | 12  | 27.3  | 1   | 16.7 | 1.0     | 2472| 17.7 | 0.09    |
| Negative for rejection                | 2   | 4.5   | 0   | 0    | 1.0     | 5315| 38.1 | <.001   |
| Collapsing Glomerulopathy             | 2   | 4.5   | 0   | 0    | 1.0     | 187 | 1.3  | 0.12    |
| IgA Nephropathy                       | 1   | 2.3   | 0   | 0    | 1.0     | 371 | 2.7  | 1.0     |

**Table 2B.** Final diagnosis in kidney allograft biopsies of from patients with COVID-19 (n=44) compared to HIV positive patients (n=6), from 5 years of total biopsies prior to the COVID-19 pandemic (1/1/2015 to 1/1/2020, n=13,955). P-values represent comparisons to the COVID-19 patient cohort.
| Diagnosis                        | Total Number | 0 alleles | 1 allele | High Risk 2 alleles | % High Risk |
|---------------------------------|--------------|-----------|----------|---------------------|-------------|
| Collapsing                      | 48           | 4         | 0        | 44                  | 91.7        |
| Acute Tubular Injury            | 10           | 3         | 0        | 7                   | 70.0        |
| Diabetic nephropathy            | 13           | 5         | 4        | 4                   | 30.8        |
| Primary Podocytopathies         | 7            | 1         | 0        | 6                   | 85.7        |
| Membranous                      | 5            | 3         | 2        | 0                   | 0           |
| FSGS, Favor Secondary           | 4            | 2         | 0        | 2                   | 50          |
| ANCA-associated GN              | 2            | 2         | 0        | 0                   | 0           |
| Arterionephrosclerosis          | 3            | 1         | 1        | 1                   | 33.3        |
| Myoglobin Casts                 | 3            | 1         | 2        | 0                   | 0           |
| Thrombotic microangiopathy      | 1            | 1         | 0        | 0                   | 0           |
| Lupus nephritis                 | 1            | 1         | 0        | 0                   | 0           |
| Light Chain Cast Nephropathy    | 2            | 1         | 1        | 0                   | 0           |
| Amyloidosis                     | 1            | 1         | 0        | 0                   | 0           |
| Cortical infarct                | 1            | 1         | 0        | 0                   | 0           |
| Acute interstitial nephritis    | 1            | 0         | 0        | 1                   | 100         |
| Hemoglobin Casts                | 1            | 1         | 0        | 0                   | 0           |
| Cryoglobulinic GN               | 1            | 1         | 0        | 0                   | 0           |
| Sickle Cell Nephropathy         | 1            | 0         | 1        | 0                   | 0           |
| C3 Glomerulonephritis           | 1            | 0         | 1        | 0                   | 0           |
| Light Chain Deposition Disease  | 1            | 1         | 0        | 0                   | 0           |
| Total Low-Risk                  |              |           |          |                     | 39.3        |
| Total High-Risk                 |              |           |          |                     | 60.7        |

**Table 3.** *APOL1* TaqMan PCR genotyping results from African American and Hispanic patients with COVID-19 (n=107). A comparison of biopsy diagnosis to genomic risk allele status of low risk (G0/G0, G1/G0, or G2/G0) or high risk (G1/G1, G1/G2, or G2/G2) is shown.
| Diagnosis                                                                 | Number of cases | Frequency of cases in literature | Published references |
|--------------------------------------------------------------------------|-----------------|----------------------------------|----------------------|
| Collapsing glomerulopathy                                                | 58              | 36.7%                            | 7-9, 15, 20, 21, 29-43 |
| Acute tubular injury                                                     | 46              | 29.1%                            | 7-24                 |
| FSGS, non-collapsing                                                    | 8               | 5.1%                             | 9, 19-20, 29         |
| Thrombotic microangiopathy                                               | 7               | 4.4%                             | 9, 16, 20, 25-27     |
| Crescentic GN, pauci-immune                                              | 7               | 4.4%                             | 20, 51, 52           |
| IgA nephropathy                                                          | 6               | 3.8%                             | 20, 42, 48-50        |
| Minimal change disease                                                   | 5               | 3.2%                             | 8-9, 21              |
| Membranous glomerulopathy                                                | 5               | 3.2%                             | 8, 20, 42            |
| Diabetic glomerulopathy                                                  | 4               | 2.5%                             | 9, 11, 14, 16, 27, 42 |
| Oxalate nephropathy                                                      | 2               | 1.3%                             | 14, 44               |
| Anti-GBM antibody disease                                                | 2               | 1.3%                             | 46-47                |
| Granulomatous tubulointerstitial nephritis                               | 1               | 0.6%                             | 28                   |
| Acute interstitial nephritis                                             | 1               | 0.6%                             | 14                   |
| Lupus nephritis                                                          | 1               | 0.6%                             | 8                    |
| MPGN, immune complex type (COVIC)                                       | 1               | 0.6%                             | 45                   |
| Infection-associated glomerulonephritis                                  | 1               | 0.6%                             | 9                    |
| Cortical infarct                                                         | 1               | 0.6%                             | 8                    |
| Arteritis                                                                | 1               | 0.6%                             | 20                   |
| Amyloidosis                                                              | 1               | 0.6%                             | 11, 20               |
| Light chain cast nephropathy                                             | 1               | 0.6%                             | 20                   |

| Transplant Kidney Biopsies (n=7)                                          |                 |                                  |                      |
|--------------------------------------------------------------------------|-----------------|----------------------------------|----------------------|
| Antibody-mediated rejection                                              | 2               | 28.6%                            | 9                    |
| T-cell mediated rejection                                                | 1               | 14.3%                            | 8                    |
| Acute tubular injury                                                     | 1               | 14.3%                            | 22                   |
| Calcineurin inhibitor nephrotoxicity                                     | 1               | 14.3%                            | 20                   |
| Collapsing glomerulopathy                                                | 1               | 14.3%                            | 43                   |
| Severe IF/TA                                                             | 1               | 14.3%                            | 20                   |

**Table 4.** Diagnoses reported within the literature of reported COVID-19 kidney biopsies (n=158 native and 7 allograft biopsies). Abbreviations: GBM, glomerular basement membrane; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; COVIC, COVID-19-associated immune complex disease.
Reported COVID-19 biopsies (n=159) COVID-19 biopsies (n=240) Control biopsy database (n=63,575)