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RESEARCH LETTER

Incidence of Common Glomerular Diseases Other Than Collapsing Glomerulopathy is Not Increased After SARS-CoV-2 Infection

Matthias Diebold[1], Annette Enzler-Tschudy[2], Birgit M. Helmchen[3], Helmut Hopfer[4], Min Jeong Kim[5], Solange Moll[6], Giliane Nanchen[7], Samuel Rotman[8], Harald Seeger[9,10] and Andreas D. Kistler[11,12]

[1]Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, University of Basel, Basel, Switzerland; [2]Institute of Pathology, Cantonal Hospital St. Gallen, Switzerland; [3]Institute of Pathology and Molecular Pathology, University of Zurich, Zurich, Switzerland; [4]Department of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, Switzerland; [5]Division of Nephrology, Cantonal Hospital Aarau, Aarau, Switzerland; [6]Service of clinical Pathology, University Hospital Geneva, University of Geneva, Geneva, Switzerland; [7]Service of Nephrology, Department of Medicine, Lausanne University Hospital and University of Lausanne, Switzerland; [8]Service of Clinical Pathology, Lausanne University Hospital and University of Lausanne, Switzerland; [9]Division of Nephrology, University Hospital Zurich, Zurich, Switzerland; [10]Institute for Nephrology and Dialysis, Cantonal Hospital Baden, Baden, Switzerland; [11]Department of Medicine, Cantonal Hospital Frauenfeld, Spital Thurgau AG, Frauenfeld, Switzerland; and [12]Faculty of Medicine, University of Zurich, Zurich, Switzerland

Correspondence: Andreas D. Kistler, Department of Medicine, Cantonal Hospital Frauenfeld, Pfaffenholzstrasse 4, 8501 Frauenfeld, Switzerland. E-mail: andreas.kistler@stgag.ch

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INTRODUCTION

Acute kidney injury has been recognized as a frequent complication of severe COVID-19 early in the pandemic[1] with histology mostly revealing acute tubular injury.[2] Later, collapsing glomerulopathy was identified as a peculiar manifestation of SARS-CoV-2 and termed COVID-19 associated nephropathy (COVAN).[3–5] COVAN is morphologically indistinguishable from HIV-associated nephropathy and affects, with few exceptions, persons of African ancestry with high-risk *APOL1* genotype.[6] In addition to these 2 well-recognized renal manifestations of COVID-19, numerous case reports and case series have described a variety of other renal diseases, mostly glomerulopathies, manifesting in temporal association with SARS-CoV-2 infection.[7]

Although a causal relationship between COVID-19 and COVAN appears very likely, given the high number of reported cases and a plausible pathophysiological mechanism, causality remains questionable for other glomerular diseases manifesting in temporal association with COVID-19. To the best of our knowledge, this question has not yet been rigorously addressed using a population-based analysis or a case-control/cohort-design. Here, we analyzed the incidence of biopsy-proven IgA nephropathy (IgAN), pauci-immune necrotizing glomerulonephritis (PINGN), membranous nephropathy (MN), and minimal change disease (MCD) among the adult Swiss population before and during the COVID-19 pandemic and tested for correlation of their incidence to SARS-CoV-2 infection incidence in the preceding month. In a case-cohort analysis, we further compared the history of SARS-CoV-2 infection in patients with a new histological diagnosis of one of the mentioned glomerular diseases to matched controls. Methodological details are given in the Supplementary Methods.

RESULTS

Incidence of Specific Glomerular Diseases Before and During the COVID-19 Pandemic

During the baseline period (2015 to 2019), the incidences of IgAN, PINGN, MCD, and MN were 23.8, 11.9, 5.1, and 9.3 cases/million population/yr and remained stable over time.[8] During the first infection wave with public lockdown measures, the incidence of biopsy-proven IgAN decreased temporarily, resulting in a reduced overall incidence of the 4 glomerular diseases studied (Figure 1). After May

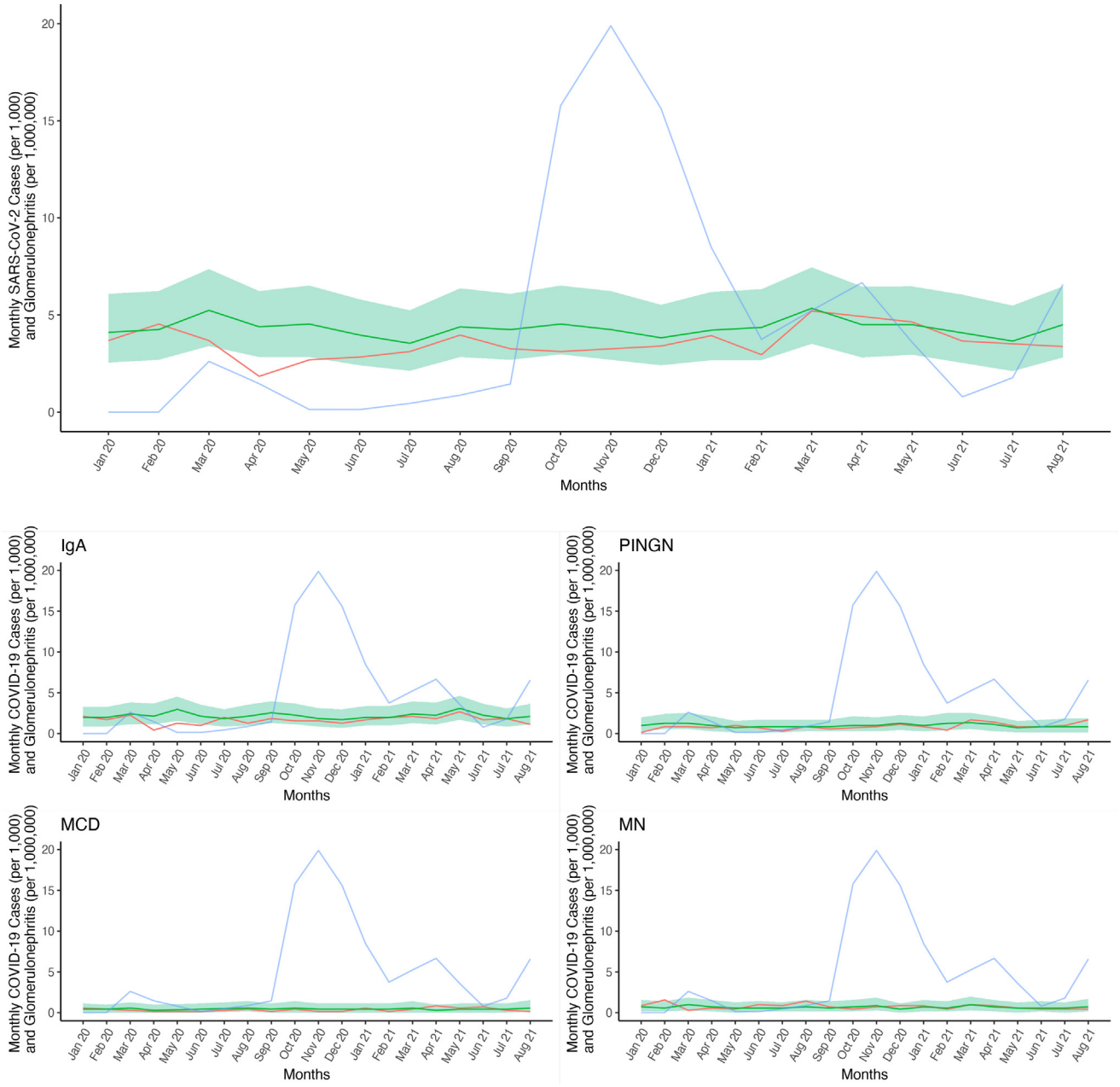

Figure 1. Expected and observed incidence of glomerulonephritis between January 2020 and August 2021 (upper panel: all 4 glomerular diseases together; lower panels: individual glomerular diseases). IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; PINGN, pauci-immune necrotizing glomerulonephritis. The observed incidence of glomerulonephritis in patients aged ≥18 years per million persons is shown in red. The expected incidence with a 95% credible interval is shown in green and green shading. The monthly incidence of SARS-CoV-2 infections per 1000 persons is shown in blue.

2020, monthly incidences returned to expected numbers and the observed incidence was compatible with the expected incidence for each of the following months of the study period (overall incidence rate ratio, 0.87; 95% credible interval, 0.60–1.38). We found no correlation between the monthly incidence of SARS-CoV-2 infections and the histologically proven incidence of the 4 studied glomerular diseases in the following 1-month or 3-month-period (Spearman's ρ 0.09; $P = 0.710$ and 0.12; $P = 0.627$, respectively).

SARS-CoV-2 Infection History in Patients With New-Onset glomerular Disease and Matched Controls

Two-hundred twenty-nine adult patients had a native kidney biopsy showing IgAN ($n = 106$), PINGN ($n = 62$), MCD ($n = 26$), or MN ($n = 35$) between January and August 2021. The majority of them ($n = 125$; 54.6%) were included in a case-cohort study and completed a questionnaire reporting their SARS-CoV-2 infection history. Reasons for noninclusion have been previously reported[8] and primarily included lack of study

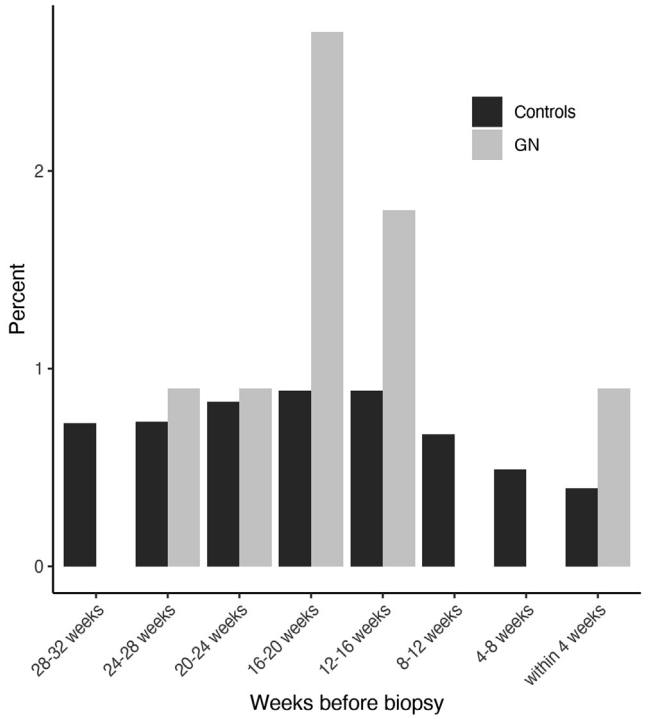

Figure 2. Frequency and timing of SARS-CoV-2 infection in patients with glomerulonephritis (GN) compared with matched controls. Grey bars represent the percentage of patients with a new diagnosis of IgA nephropathy, pauci-immune necrotizing glomerulonephritis, minimal change disease, or membranous nephropathy during the first 8 months of 2021, who reported a SARS-CoV-2 infection for each 4-week interval before the date of their kidney biopsy. Black bars represent the percentages of the controls from the general population matched for age and biopsy date with SARA-CoV-2 infection in the corresponding time interval.

participation of their treating center and inability to contact the patients or loss to follow-up. We excluded 14 patients (11.2%) with glomerular diseases previously established by biopsy, resulting in 111 patients with a new histological diagnosis of IgAN, PINGN, MCD, or MN. Eight of these patients (7.2%) reported a history of SARS-CoV-2 infection prior to the date of kidney biopsy. Demographic and clinical characteristics of these patients were similar to those without prior SARS-CoV-2 infection (Supplementary Table S1). Their patient-level data are shown in Supplementary Table S2. Of the general population matched for age (by decade) and calendar date of kidney biopsy, 5.2% had a history of SARS-CoV-2 infection. The estimated risk ratio for the development of new-onset biopsy-proven IgAN, PINGN, MCD or MN was 1.28 (95% confidence interval, 0.62 to 2.65; $P = 0.63$) in patients with a history of SARS-CoV-2 infection, compared to uninfected persons matched for age and calendar date of biopsy. The percentage of patients testing positive in each 4-week period prior to the day of kidney biopsy, compared to their matched controls, is shown in Figure 2. Notably, of the 8 patients with a history of COVID-19 before kidney biopsy, 4 had symptoms or signs clearly attributable to their glomerular disease prior to SARS-CoV-2 infection (Supplementary Table S2). Thus, SARS-CoV-2 infection preceded manifestations of glomerular disease in only 4 patients.

DISCUSSION

In this study, by combining 3 complementary approaches, we found no evidence for a causal relationship between SARS-CoV-2 infection and *de novo* development of any of the 4 glomerular diseases studied. First, in an epidemiological analysis including the entire adult Swiss population, we did not observe an increase in cases during the initial 20 months of the pandemic. Second, the monthly incidence of SARS-CoV-2 infections did not correlate with the incidence of glomerular disease in the following 1-month or 3-month periods. Third, in a case-cohort study, the history of prior COVID-19 was similar in patients with a newly established diagnosis of glomerular disease compared to the matched general population.

Since early in the pandemic, multiple case reports have reported glomerular diseases in temporal relation to COVID-19. A recent review[7] summarizes published data on 511 native and 85 transplant kidney biopsies performed after SARS-CoV-2 infection, of which the vast majority were cases of collapsing glomerulopathy (i.e. COVAN), followed by podocytopathy (primary FSGS and MCD), diabetic nephropathy, and a variety of other histological diagnoses. The largest published case-series compared relative frequencies of kidney biopsy diagnoses obtained within 3 months after SARS-CoV-2 infection to a historical control biopsy database and found a significant difference for only the following 3 glomerular diseases: collapsing glomerulopathy (increased after COVID-19), diabetic nephropathy (decreased), and proliferative glomerulonephritis with monoclonal IgG deposits (increased but with a very low overall frequency).[9] However, the historical control database differed from post-COVID-19 cases by contributing centers and geography. In order to establish causality by observational studies, rigorous study designs are required to minimize bias.

Our study was originally designed to investigate the association between SARS-CoV-2 vaccination and glomerulonephritis.[8] Inclusion of SARS-CoV-2 infection history in the questionnaire enabled the secondary analysis reported here. Strengths of our study are as follows: (i) the combination of complementary study designs to address the research question; (ii) the availability of nationwide data, allowing a comparison of population-level incidence numbers over time; and (iii) availability of reliable COVID-19 incidence levels

due to near-universal testing of symptomatic patients. Importantly, we aimed to study a possible connection between SARS-CoV-2 infection and glomerular diseases other than COVAN. The incidence of the latter would have been expected to be low in Switzerland with its predominantly Caucasian population. Given that we did not include FSGS in our analysis, COVAN cases were not included, and our results do not extend to collapsing glomerulopathy or to other forms of FSGS.

Our study has several limitations. Because it was originally designed to address the effect of vaccination, the case-cohort study was limited to the period after approval of vaccines, when COVID-19 incidence was comparably low. However, by the end of the study period, 9.7% of the adult general Swiss population were infected with SARS-CoV-2 and infection occurred between October 2020 and February 2021 in 6.4% of the population. This high rate of infections over a relatively short period of time would be expected to affect glomerular disease incidence if there was a true association of relevant magnitude. Second, due to the small population size of Switzerland, the overall number of patients with glomerular diseases is relatively low, which may also result in a type 2 error. Third, we were not able to include all patients with *de novo* glomerulonephritis in the case-cohort study and cannot exclude selection bias with certainty. Fourth, SARS-CoV-2 infection history was self-reported and may be subject to reporting bias, and some patients may have forgone SARS-CoV-2 testing. However, universal testing of symptomatic individuals was still enforced at that time and positive tests were reported in immunity certificates, making these data readily available to patients completing their questionnaire. Finally, detection bias could theoretically be an issue if kidney biopsy rates were different during the pandemic. This was the case during the first infection wave with public lockdown measures, resulting in a lower incidence of IgAN, which is often asymptomatic and usually does not require urgent biopsy. However, for the remainder of the study period, biopsy rates were comparable to the baseline period (Supplementary Table S3). Given these limitations, we cannot exclude with certainty that SARS-CoV-2 infection might precipitate one of the 4 glomerular diseases studied in rare cases or that a preexisting glomerular disease might be worsened by COVID-19 and thereby unmasked. However, such an effect would be rather small, and our data are clearly in line with the null hypothesis that any temporal association of IgAN, PINGN, MCD, and MN to SARS-CoV-2 infection is solely attributable to chance.

In summary, we did not find an association between SARS-CoV-2 infection and 4 types of new-onset glomerular disease other than collapsing glomerulopathy.

DISCLOSURE

All the authors declared no competing interests.

AUTHORS CONTRIBUTIONS

ADK conceived the study. All authors contributed to the acquisition of data. ADK and MD had full access to all the data in the study, performed the statistical analyses and take responsibility for the integrity of the data and the accuracy of the data analysis. ADK and MD wrote the manuscript. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Characteristics of patients with a new histologic diagnosis of glomerular disease with vs. without prior SARS-CoV-2 infection.

Table S2. Clinical details on patients with a new histologic diagnosis of glomerular disease and prior SARS-CoV-2 infection.

Table S3. Total number of kidney biopsies analyzed per year by center and native vs. transplant biopsies.

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