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Appendix

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

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## **Supplementary Materials**

### **Glomerulonephritis after SARS-CoV-2 infection**

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### **Supplementary Methods**

#### **Study design and data collection**

The methods of this study have already been reported.<sup>8</sup> Briefly, we used two interconnected study designs to investigate the association between SARS-CoV-2 infection and the development of glomerulonephritis.

For the first retrospective cohort study, we collected the numbers of kidney biopsies for adult ( $\geq 18$  years) patients showing IgAN, PIGN, MCD, or MN from January 1, 2015, through August 31, 2021, from all Swiss histology institutes analyzing kidney biopsies. Lupus nephritis was not included in the analysis, because repeat biopsies are often performed for this glomerular lesion, constituting a significant proportion of all lupus nephritis biopsies. Furthermore, we did not include focal segmental glomerulosclerosis (FSGS), since distinction of secondary (adaptive) FSGS from primary FSGS (as a podocytopathy) may be challenging by histology alone and structured clinical information was not available from the local histology databases.<sup>8</sup> Notably, by deciding not to include FSGS, we also did not include collapsing glomerulopathy, which is usually considered a variant of primary FSGS. This was in line with the aim of the analysis presented here to test for a possible association of glomerular diseases other than collapsing glomerulopathy (COVAN) with SARS-CoV-2 infection. The data were retrieved by nephrologists from their local databases or electronic health record searches and included biopsy date, age, sex, and histologic diagnosis. Using this information together with census data, we calculated incidence rates of each glomerular disease.

In the second study, using a case-cohort design, we included patients with a diagnosis of a de-novo glomerulonephritis between January 1, 2021, and August 31, 2021. For this aim,

nephrologists provided the referring nephrologists' names for all eligible patients. We then contacted the respective nephrology divisions and practices and asked them to contact their patients. For patients who gave written informed consent, a case report form containing clinical information and laboratory data was completed by the treating nephrologists and a questionnaire was completed by the patients. The latter included information on SARS-CoV-2 infection with the date of symptom onset and the date of a positive test result. Using these data, we were able to match all patients by age-decade and time point of the kidney biopsy with the general Swiss population. Data on the number of individuals tested positive for SARS-CoV-2 by calendar week and age decade were downloaded from the Swiss Federal Office of Public Health website (<https://www.covid19.admin.ch/de/epidemiologic/case>, accessed on July 20, 2023).

Ethical approval for both studies was obtained from the Ethics Committee of Eastern Switzerland. The retrospective cohort study was exempt from patient consent due to the minimal amount of data used. For the case-cohort study, written informed consent was obtained from all participants. We adhered to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. We followed the STROBE Guidelines for reporting observational studies.

### **Statistical Analysis**

To calculate the expected incidence of biopsy-proven glomerulonephritis cases for each month between 2020 and 2021, we used a Bayesian Poisson regression model based on data from the years 2015 – 2019. Incidence rate ratios were calculated by dividing the observed cases during the given time period by the expected cases and expressing the uncertainty using 95% credible intervals. We calculated the correlation between SARS-CoV-2 infection and histological glomerulonephritis cases in either the following month or the following three-month period using Spearman's rank correlation. For the case-cohort study, we matched controls from the general population to patients with a new histologic diagnosis of glomerulonephritis by age-decade and the calendar week of kidney biopsy. Due to the low

patient number with symptoms or signs of their glomerular disease before SARS-CoV-2 infection, we did not perform an analysis using onset of symptoms or signs as the reference time point. For each patient, we determined the percentage of the general population of the same age decade (using the decade 20–29 for cases aged 18 or 19 years) who had a documented SARS-CoV-2 infection in every one-week interval before their kidney biopsy. We calculated and reported risk ratios because the data from the Swiss Federal Office of Public Health included all SARS-CoV-2 infections in Switzerland, including patients with glomerulonephritis. Risk ratios were calculated using 1000 matched controls for every case and adjusted for age as the matching factor using the Mantel-Haenszel approach.

All statistical analyses were carried out using R software, version R 4.0.2 (R Core Team 2020).

R: a language and environment for statistical computing. R Foundation for Statistical Computing, <https://www.R-project.org>).

## Supplementary Tables

**Supplementary Table 1. Characteristics of patients with a new histologic diagnosis of glomerular disease with vs. without prior SARS-CoV-2 infection**

Variable	No prior SARS-CoV-2 infection n=103	Prior SARS-CoV-2 infection n=8	All Patients n=111
Median age (IQR), yr	57 (43 to 72)	51 (42 to 67)	55 (43 to 72)
Female Sex	39 (38)	3 (38)	42 (38)
Histologic diagnosis			
AAV	27 (26)	2 (25)	29 (26)
IgAN	54 (52)	4 (50)	58 (52)
MCD	8 (8)	1 (12)	9 (8)
MN	14 (14)	1 (12)	15 (14)
Comorbidities			
Diabetes	14 (15)	0 (0)	14 (14)
Hypertension	43 (47)	2 (25)	45 (45)
Clinical syndrome / indication for biopsy			
Nephrotic syndrome	27 (26)	2 (25)	29 (26)
Nephritic syndrome	58 (56)	2 (25)	60 (54)
Acute GN	20 (19)	1 (12)	21 (19)
Chronic GN	24 (23)	0 (0)	24 (22)
RPGN	14 (14)	1 (12)	15 (14)
Asymptomatic microhematuria	20 (19)	3 (38)	23 (21)
Asymptomatic proteinuria	18 (17)	4 (50)	22 (20)
Isolated macrohematuria	2 (2)	0 (0)	2 (2)
Laboratory parameters at the time of biopsy, median (IQR)			
Creatinine, $\mu\text{mol/l}$	128 (85 to 186)	100 (89 to 250)	128 (85 to 190)
eGFR median (IQR)	48 (29 to 70)	68 (24 to 81)	48 (29 to 72)
Serum albumin, g/l	35 (28 to 40)	33 (27 to 40)	34 (28 to 40)
Proteinuria, g/d	2.0 (0.8 to 5.5)	1.5 (0.8 to 4.3)	1.9 (0.8 to 5.4)

eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; IgAN, IgA nephropathy; IQR, interquartile range; MCD, minimal change disease; MN, membranous nephropathy; RPGN, rapidly progressive GN. To convert the creatinine values from  $\mu\text{mol/l}$  to  $\text{mg/dl}$ , divide by 88.4. Values are n (%) if not otherwise stated. Note that information was unavailable for some patients and, hence, the denominator is not equal to the total n for all variables given as percentages.

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

age	sex	Histological diagnosis	Glomerular disease manifestations and temporal relation to COVID	Comorbidities
82	m	AAV	<ul style="list-style-type: none"> <li>• Patient-reported polyarthralgia / arthritis with unclear onset date</li> <li>• Hematuria first detected 47 days after COVID symptom onset (45 days after positive test)</li> <li>• Worsening kidney function 94 days after COVID symptom onset</li> <li>• Kidney biopsy performed 115 days after COVID symptom onset because of nephritic syndrome</li> </ul>	None
65	m	MCD	<ul style="list-style-type: none"> <li>• COVID symptom onset 7 days after a first dose of Moderna SARS-CoV-2 vaccine</li> <li>• Self-reported ankle swelling one day after COVID symptom onset, foamy urine 5 days after COVID symptom onset.</li> <li>• Positive SARS-CoV-2 test 5 days after symptom onset</li> <li>• Proteinuria and hypoalbuminemia first documented 6 days after COVID symptom onset</li> <li>• Kidney biopsy performed 12 days after COVID symptom onset because of nephrotic syndrome</li> </ul>	Hypertension Colitis ulcerosa
72	m	AAV	<ul style="list-style-type: none"> <li>• Patient presented with RPGN and advanced renal failure 176 days after COVID symptom onset and 27 days after a single Moderna vaccine dose</li> <li>• No self-reported symptoms of glomerular disease</li> <li>• Kidney biopsy 178 days after COVID symptom onset (2 days after presentation with RPGN)</li> </ul>	Preexisting CKD stage G3b
47	m	IgAN	<ul style="list-style-type: none"> <li>• Hematuria first detected 66 days after COVID symptom onset</li> <li>• Kidney biopsy performed 112 days after COVID symptom onset because of asymptomatic microhematuria and proteinuria</li> </ul>	None
46	f	IgAN	<ul style="list-style-type: none"> <li>• Microhematuria and proteinuria first documented 16 months prior to SARS-CoV-2 infection</li> <li>• Self-reported ankle swelling and paresthesias of the feet and hands since 6 months prior to SARS-CoV-2 infection</li> <li>• Kidney biopsy performed 130 days after COVID symptom onset because of asymptomatic microhematuria and proteinuria</li> </ul>	Obesity Hypertension Coronary artery disease
30	f	IgAN (as renal manifestation of PSH)	<ul style="list-style-type: none"> <li>• Self-reported arthralgia / arthritis, skin rash, bloody diarrhea and stomach pain ca. 9 months before SARS-CoV-2 infection</li> <li>• Documented microhematuria ca. 1 month and histologically confirmed cutaneous vasculitis 2 months after SARS-CoV-2 infection</li> <li>• Kidney biopsy performed 155 days after COVID symptom onset because of persistent asymptomatic microhematuria and proteinuria</li> </ul>	None (except for renal hypertension since diagnosis of IgAN)

30	f	IgAN	<ul style="list-style-type: none"> <li>• The indication for kidney biopsy was persistent proteinuria post pre-eclampsia</li> <li>• Proteinuria was first detected 10 months before kidney biopsy</li> <li>• The patient had asymptomatic SARS-CoV-2 infection 101 days before kidney biopsy</li> </ul>	None
55	m	MN	<ul style="list-style-type: none"> <li>• The patient had self-reported and physician-confirmed edema since 1 month prior to SARS-CoV-2 infection</li> <li>• Proteinuria was first measured and detected 2½ months after SARS-CoV-2 infection</li> <li>• Kidney biopsy was performed 99 days after COVID symptom onset because of nephrotic syndrome</li> <li>• MN was negative for PLA2R by serology but positive by immune histochemistry</li> </ul>	Hypertension Asthma

**Supplementary Table 3. Total number of kidney biopsies analyzed per year by center and native vs. transplant biopsies.**

<b>Pathology center</b>	<b>2015</b>	<b>2016</b>	<b>2017</b>	<b>2018</b>	<b>2019</b>	<b>2020</b>	<b>2021</b>
<b>Number of native kidney biopsies analyzed per year</b>							
Lausanne	179	177	191	165	186	163	201
Basel	309	263	290	278	263	245	270
St. Gallen	53	77	57	87	73	64	77
Geneva	134	106	102	98	115	91	111
Aarau	21	27	41	29	36	34	46
Zurich	323	340	373	356	383	333	443
Bern	123	188	153	173	169	154	209
<b>Total of all centers</b>	<b>1142</b>	<b>1178</b>	<b>1207</b>	<b>1186</b>	<b>1225</b>	<b>1084</b>	<b>1357</b>
<b>Number of transplant kidney biopsies analyzed per year</b>							
Lausanne	45	52	39	22	36	39	36
Basel	214	223	256	259	245	214	218
St. Gallen	62	66	85	45	58	49	65
Geneva	129	171	147	167	158	94	130
Aarau	17	19	9	15	4	4	4
Zurich	161	147	149	185	171	204	192
Bern	83	91	93	77	109	70	78
<b>Total of all centers</b>	<b>711</b>	<b>769</b>	<b>778</b>	<b>770</b>	<b>781</b>	<b>674</b>	<b>723</b>
<b>Total number of kidney biopsies analyzed per year (transplant and native kidney biopsies)</b>							
Lausanne	224	229	230	187	222	202	237
Basel	523	486	546	537	508	459	488
St. Gallen	115	143	142	132	131	113	142
Geneva	263	277	249	265	273	185	241
Aarau	38	46	50	44	40	38	50
Zurich	484	487	522	541	554	537	635
Bern	206	279	246	250	278	224	287
<b>Total of all centers</b>	<b>1853</b>	<b>1947</b>	<b>1985</b>	<b>1956</b>	<b>2006</b>	<b>1758</b>	<b>2080</b>