Title

COVID-19 Vaccination and New Onset Glomerular Disease: Results from the IRocGN2 International Registry.

Journal

Kidney360, 4(3)

Authors

Waldman, Meryl
Sinaii, Ninet
Lerma, Edgar
et al.

Publication Date

2023-03-01

DOI

10.34067/KID.0006832022

Peer reviewed

Kidney360

COVID-19 Vaccination and New Onset Glomerular Disease: Results from the IRocGN2 International Registry

Meryl Waldman,[1] Ninet Sinaii,[2] Edgar V. Lerma,[3] Anila Abraham Kurien,[4] Kenar D. Jhaveri,[5] Nupur N. Uppal,[5] Rimda Wanchoo,[5] Rupali Avasare,[6] Jonathan E. Zuckerman,[7] Adrian Liew,[8] Alexander J. Gallan,[9] Ashraf El-Meanawy,[10] Yoram Yagil,[11,12] Larissa Lebedev,[11,12] Krishoban Baskaran,[13,14] Eswari Vilayur,[13] Adrienne Cohen,[13] Nethmi Weerasinghe,[13] Ioannis Petrakis,[15] Kostas Stylianou,[16] Hariklia Gakiopoulou,[17] Alexander J. Hamilton,[18] Naomi Edney,[18] Rachel Millner,[19] Smaragdi Marinaki,[20] Joshua L. Rein,[21] John Paul Killen,[22,23] Jose Manuel Rodríguez Chagolla,[24] Claude Bassil,[25,26] Ramon Lopez del Valle,[27] Jordan Evans,[28] Anatoly Urisman,[29] Mona Zawaideh,[30] Pravir V. Baxi,[31] Roger Rodby,[31] Mahesha Vankalakunti,[32] Juan M. Mejia Vilet,[33] Silvia E. Ramirez Andrade,[34] Mal P. Homan,[35] Enzo Vásquez Jiménez,[36] Natasha Perinpanayagam,[37] Juan Carlos Q. Velez,[38,39] Muner M.B. Mohamed,[38,39] Khalid M.G. Mohammed,[40] Arjun Sekar,[41] Laura Ollila,[42] Abraham W. Aron,[43] Kevin Javier Arellano Arteaga,[44] Mahmud Islam,[45] Esperanza Moral Berrio,[46] Omar Maoujoud,[47] Rebecca Ruf Morales,[48] Regan Seipp,[49] Carl E. Schulze,[50] Robert H. Yenchek,[51] Irina Vancea,[52] Muhammad Muneeb,[53] Lilian Howard,[1] and Tiffany N. Caza[54]

Key Points

- IgAN and MCD are the most common *de novo* glomerular diseases reported after COVID-19 vaccination, particularly after mRNA vaccination.
- Membranous nephropathy, pauci-immune GN, and collapsing GN have also been attributed to COVID-19 vaccination, some with dual histologies.
- Recovery of kidney function and proteinuria remission is more likely in IgAN and MCD by 4–6 months compared with the other glomerular diseases.

Abstract

Background Patients with *de novo* glomerular disease (GD) with various renal histologies have been reported after vaccination against SARS-CoV-2. Causality has not been established, and the long-term outcomes are not known. To better characterize the GDs and clinical courses/outcomes, we created the International Registry of COVID-19 vaccination and Glomerulonephritis to study in aggregate patients with *de novo* GN suspected after COVID-19 vaccine exposure.

Methods A REDCap survey was used for anonymized data collection. Detailed information on vaccination type and timing and GD histology were recorded in the registry. We collected serial information on laboratory values (before and after vaccination and during follow-up), treatments, and kidney-related outcomes.

Results Ninety-eight patients with GD were entered into the registry over 11 months from 44 centers throughout the world. Median follow-up was 89 days after diagnosis. IgA nephropathy (IgAN) and minimal change disease (MCD) were the most common kidney diseases reported. Recovery of kidney function and remission of proteinuria were more likely in IgAN and MCD at 4–6 months than with pauci-immune GN/vasculitis and membranous nephropathy.

Conclusions The development of GD after vaccination against SARS-CoV-2 may be a very rare adverse event. Temporal association is present for IgAN and MCD, but causality is not firmly established. Kidney outcomes for IgAN and MCD are favorable. No changes in vaccination risk-benefit assessment are recommended based on these findings.

KIDNEY360 4: 349–362, 2023. doi: https://doi.org/10.34067/KID.0006832022

Introduction

The swift development, clinical trial testing, manufacturing, and global distribution of COVID-19 vaccines less than a year since the World Health Organization (WHO) declaration of a pandemic was an unprecedented achievement. According to the COVID-19 vaccine tracker, as of September 2022, more than five billion people received at least one vaccine dose.[1] Various COVID-19 vaccine platforms are currently available, but the most widely distributed

Correspondence: Dr. Meryl Waldman, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Clinical Center Dr., Bethesda, Maryland. Email: waldmanm@niddk.nih.gov

vaccines are the two mRNA-based vaccines, Pfizer-BioNTech and Moderna mRNA-1273, and viral vector vaccines, Oxford-AstraZeneca and Johnson & Johnson/Janssen. These vaccines have shown to be highly effective in preventing severe COVID-19 with excellent safety profiles.

The mRNA vaccines received emergency use authorization in December 2020, followed by authorization of the vector-based vaccines. Reports of *de novo* and relapses of glomerular disease (GD) temporally associated with COVID-19 vaccination (termed CVAGD for COVID-19 vaccine–associated GD) began to emerge by mid-2021 with an increasing number of reports published.[2-27] To date, a cause-effect relationship has not been established. Given the relative rarity of these events and limited follow-up, we created an International Registry of COVID-19 vaccination and Glomerulonephritis to collect consistent data on potential cases of CVAGD to analyze in aggregate. The aim of the study was to describe the range of kidney histologies, vaccine types and timing of administration relative to the onset of kidney disease manifestations, clinical features at presentation, and kidney outcomes.

Methods

Study Design and Participants

This retrospective cohort study included subjects of any age with *de novo* GN presenting within 3 months after vaccination against SARS-CoV-2. Inclusion criteria were (*1*) new-onset biopsy-proven GN and (*2*) received at least one vaccine dose within 3 months before biopsy. Exception to biopsy requirement was a positive serum test for phospholipase A2 receptor (PLA2R) antibody consistent with membranous nephropathy (MN). Exclusion criteria include active COVID-19 or other infection at GN diagnosis or preexisitng GN. Owing to pandemic-related biopsy delays, we included patients outside the 3-month window if compatible kidney-related symptoms (*i.e.,* edema, hematuria) were evident within 2 weeks of vaccination. Data were deidentified, and a computer-generated code was assigned to allow for editing as data became available.

Data Collection

The registry was launched on June 8, 2021. Information regarding the registry with a link to the secure public survey (https://redcapsurvey.niddk.nih.gov/surveys/?s=LCDAMFD9JA) was posted on various social media platforms, newsletters, networks, and international professional societies for nephrologists and pathologists. Practicing providers were able to voluntarily report on patients with new-onset GN suspected after COVID-19 vaccination based on timing of symptoms and clinical presentation. REDCap (Research Electronic Data Capture),[28,29] a secure web-based electronic data capture tool hosted by National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), was used to manage data. A separate comprehensive survey was completed for each patient using the same web address, but a unique code was generated for each case submission. This code allowed the reporter to return to the survey at any time to modify and add follow-up data related to changes in patient clinical status, new laboratory values, boosters, outcomes, *etc*. The survey allowed for both retrospective and prospective data collection. Emails generated from the REDCAP system were periodically sent to reporters to prompt them to update records after the initial survey was submitted. Before closing the registry for analysis, additional email notifications were sent out prompting all reporters to add the most recent clinical information relevant to outcomes.

Registry data elements include sociodemographics, comorbidities, COVID-19 vaccine(s), kidney and nonkidney symptoms, histology, treatment, and outcomes. Complete remission was defined as proteinuria <0.3 g/g (and negative serologies if relevant), and partial remission as <3.5 g/g and 50% proteinuria reduction. Other vaccines administered simultaneously were recorded in addition to other potential triggers. Laboratory parameters collected were serum creatinine (SCr), serum albumin, proteinuria, serologies (*i.e.,* ANCA, antiglomerular basement membrane [anti GBM], PLA2R). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021[30] equation. Parameters were collected at (*1*) baseline prevaccination (most proximate before vaccination), (*2*) biopsy (after vaccination, at the time of kidney biopsy$\pm$2 weeks), and (*3*) follow-up. Data were checked for quality by MW and NS.

Ethical Considerations The project was reviewed by the NIH Office of Institutional Review Board Operations and determined that storage and analysis of anonymous, deidentified data collected by the registry did not qualify as human subjects research defined under federal regulations (45 Code of Federal Regulations 46.102) and did not require institutional review board approval.

Statistical Analysis Data are described using frequencies (percentages) and simple descriptive statistics (mean$\pm$SD or median [interquartile range]), as appropriate. Data were exported from REDCap, and variables were created for analysis. Data were assessed for distributional assumptions, and appropriate statistical tests were performed. Repeated measures analyses were performed using mixed models, with compound symmetry correlations between intervals. In situations where models would not converge, proc Generalized Linear Models-Mixed (GLIMMIX) was used. *Post hoc* comparisons among histologies or time intervals were corrected for multiplicity using the Bonferroni method, and corrected *P*-values are reported. Repeated measures analyses could not be computed for less common histologies because of limited follow-up and/or sample sizes. Categorical data were compared using the Fisher exact test. Statistical evidence was based on effect sizes, data variability, and P-values. Data were analyzed using SAS v9.4 (SAS Institute, Inc, Cary, NC).

Results

Demographics

Data from a total of 104 patients were entered into the International Registry of COVID-19 vaccination and Glomerulonephritis from June 8, 2021, to April 29, 2022. Six were excluded due to relapse of primary GN or insufficient data. In total, 98 patients with *de novo* GN attributed to vaccines were included in the analysis from 44 centers in 13 countries.

Most of the patients were White; 53% were female; and the mean ($\pm$SD) age at diagnosis was 48.3$\pm$18.4 years (range: 15–79) (Supplemental Table 1 and Table 1). Most (64%) were from the United States. Hypertension was present in 35%, and 16% had preexisting chronic kidney

Table 1. Study population baseline characteristics

Characteristic	*n*	%
No. of patients	98	100.0
Age, in yr		
Mean±SD	48.3±18.4	
Median (IQR)	49.5 (33.0–66.0)	
Range	15–79	
Female	52	53.1
Race		
White	48	49.0
Asian	26	26.5
Black	8	8.2
American Indian/Alaska Native	1	1.0
Other/unknown	15	15.3
Ethnicity		
Not Hispanic/Latino	63	64.3
Hispanic/Latino	12	12.2
Unknown	23	23.5
Countries		
Australia	3	3.1
Finland	1	1.0
Greece	3	3.0
India	13	13.3
Israel	1	1.0
Mexico	5	5.1
Morocco	1	1.0
New Zealand	1	1.0
Singapore	3	3.1
Spain	2	2.0
Turkey	1	1.0
United Kingdom	1	1.0
United States	63	64.3
Vaccination name[a]		
Pfizer-BioNTech BNT162b2	53	54.1
Moderna mRNA-1273	19	19.4
Johnson & Johnson/Jansen	3	3.1
Oxford-AstraZeneca ChAdOx1 nCoV-19 (AZD1222)	9	9.2
Sinovac/Coronavac	3	3.1
Bharat Biotech BBV152 Covaxin	7	7.1
Other[b]	6	6.1
GN after vaccine dose		
Primary vaccination	89	90.8
First dose	36	40.5
Second dose	53	59.6
Booster[c]	9	9.2
First booster	7	87.5
Second booster	1	12.5
GD diagnosis		
MCD	28	28.6
IgAN	24	24.5
Pauci-immune crescentic GN/Vasculitis	16	16.3
MN[d]	10	10.2
CG	3	3.1
FSGS	1	1.0
Anti-GBM disease	5	5.1
Lupus nephritis (class V)[e]	2	2.0
Immune complex GN NOS[f]	2	2.0
Light chain (AL) amyloidosis	1	1.0
Global glomerulosclerosis	1	1.0
Mixed glomerular histologies[g]	5	5.1
Pauci immune GN+anti-GBM disease	1	1.0
IgAN+FSGS	1	1.0
IgAN+CG	1	1.0
IgAN+MCD	1	1.0
MN+CG	1	1.0
Elapsed time from vaccine to kidney-related symptoms		
Within hours	2	2.0
Within 1–2 d	15	15.3
3–4 d	6	6.1
5–7 d	26	26.5
2 wk	28	28.6
3 wk	4	4.1
4 wk	9	9.2
5 wk	2	2.0
6 wk	1	1.0
7 wk	1	1.0
8 wk	2	2.0
3 mo	2	2.0
Kidney-related symptoms		
New-onset swelling (edema)	53	54.1
Macroscopic hematuria	29	33.7
Microscopic hematuria	36	36.7
Hypertension (new onset or worsening)	40	40.8
Foamy urine	33	33.6
Non–kidney-related symptoms		
Fatigue	37	37.8
Fever	15	15.3
Rash	11	11.2
Muscle aches	27	27.6
Weakness	14	14.3
Joint pain	8	8.2
Neuropathy	2	2.0
Shortness of breath	10	10.2
History of COVID-19 infection before vaccine	5	5.1
Comorbidities		
Hypertension	34	34.7
Chronic kidney disease[h]	16	16.3
Diabetes	13	13.3
Obesity	13	13.3
Asthma, chronic obstructive pulmonary disease	8	8.2
Cancer	6	6.1
Hepatitis C	2	2.0
HIV	1	1.0
Rheumatoid arthritis	3	3.1
Psoriatic arthritis	1	1.0
Deep venous thrombosis	2	2.0
Stroke	1	1.0
Guillain-Barre syndrome	1	1.0
Lupus (without kidney disease)	2	2.0
Neurofibromatososis 1	1	1.0
Nephrectomy	1	1.0
Smoker (current)	3	3.1
Total follow-up for cohort, in d	(*n*=86)	
Mean±SD	115±101	
Median (IQR)	89 (27–177)	
Range	5–448	

Data are presented in frequency and percentage. Total percentages may not equal to 100% due to rounding. IQR, interquartile range (25th–75th percentiles); GD, glomerular disease; NOS, not otherwise specified; MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; CG, collapsing glomerulopathy; PLA2R, phospholipase A2 receptor.

[a]The number of total vaccines is greater than the number of patients because of heterologous administration of vaccines in two patients (Moderna+J&J, Pfizer+AstraZeneca).

[b]Other vaccine: Indicated mRNA but did not specify which one.

[c]First or second booster specified in eight of nine subjects and serves as the denominator.

[d]One MN diagnosis was based exclusively on positive anti-PLA2R antibody.

[e]Occurred in patients with known SLE without prior renal manifestations/nephritis.

[f]Morphologic patterns include (*1*) a membranoproliferative pattern with subendothelial and subepithelial glomerular deposits and IgG dominance and (2) mesangial proliferation and mesangial deposits and negative IgA staining on immunofluorescence.

[g]For all subsequent analyses, the five cases of mixed histologies were classified under one subgroup; therefore, the higher "n" in each subgroup beyond Table 1 reflects this reclassification: pauci-immune GN+anti-GBM was classified as pauci-immune crescentic GN; IgAN+MCD and IgAN+FSGS were classified as IgAN; and IgAN+CG and MN+CG were classified as collapsing GN.

[h]Unrelated to GN, attributed to various causes including kidney donation, nephrectomy for renal cell cancer, medication toxicity related to treatment of other conditions, and hypertension.

disease, which was attributed to causes unrelated to GD (*e.g.*, kidney donation, nephrectomy for renal cell cancer, medication toxicity for treatment of other conditions, long-standing hypertension). Most (73%) received mRNA vaccines, with fewer patients (12%) receiving the vector vaccines or inactivated whole-virus vaccines (10%). Eleven (11%) received additional vaccine(s) (*i.e.*, influenza, zoster) before the onset of GN. Nonsteroidal anti-inflammatory drug (NSAID) use was reported in 4% before or around the time of vaccination.

Biopsy Findings

Diagnoses included minimal change disease (MCD, $n=28$), IgA nephropathy (IgAN, $n=24$), pauci-immune crescentic GN/vasculitis ($n=16$), MN ($n=10$), collapsing glomerulopathy (CG, $n=3$), FSGS ($n=1$), anti-GBM disease ($n=5$), lupus nephritis ($n=2$), immune complex GN ($n=2$), AL amyloidosis ($n=1$), and global glomerulosclerosis ($n=1$) (Table 1). One patient with MN was diagnosed based on a positive anti-PLA2R antibody test (ELISA) and did not undergo kidney biopsy. MCD (29%) and IgAN (27%) were the most common histologies, followed by pauci-immune GN (17%) and MN (10%). Five patients showed dual glomerulopathy: pauci-immune GN with anti-GBM; IgAN mixed with CG, MCD, and FSGS; and MN mixed with CG (Table 1). For subsequent analyses, the classification of pauci-immune GN+anti-GBM was "pauci-immune," IgAN+MCD and IgAN+FSGS were "IgAN," and CG+IgAN and CG+MN were "CG."

Onset of Disease and Clinical Presentation

The onset of GN was suspected after the second vaccine dose in more than half of patients (Table 1), but there was significant heterogeneity based on vaccine type and GN (Table 2). Minimal change disease (MCD) was more frequently reported after the first vaccine dose, whereas the second dose was more frequently implicated in IgAN ($P=0.033$) and other histologies. Kidney-related symptoms developed within 2 weeks of the suspected vaccine dose in 75% of patients (Tables 1 and 2), but onset varied between GN and vaccines, with a trend toward earlier symptom onset for MCD, IgAN, and MN and with the Pfizer vaccine (Table 2). Most common kidney-related symptoms were edema (54%), hypertension (41%), foamy urine (34%), and macroscopic hematuria (34%). Macroscopic hematuria occurred most frequently in IgAN (54%) but was also reported in anti-GBM (60%), pauci-immune (47%), and MCD (7%).

Clinical presentation included nephrotic syndrome in 55%, subnephrotic range proteinuria in 35%, microscopic

Table 2. Timing of onset of kidney-related symptoms based on vaccine type, dose, and glomerular disease

Patient Cohort Based on Glomerular Disease	*n* (%)	Vaccine	Timing from Vaccine to Kidney-Related Symptoms	Culprit Vaccine Dose	Timing from Culprit Vaccine to Biopsy, Days[a]
All patients	98 (100%)	Pfizer-BioNTech (54.1%)	Within 5–7 d (34.5%)	Dose 2: 54 (55.7%)	(*n*=97)
		Moderna (19.4%)	2 wk (31.0%)	Dose 1: 36 (37.1%)	35±35
		AstraZeneca (9.2%)	Within 1–2 d (6.9%)	Booster: 7 (7.2%)	21 (13–44)
			4 wk (6.9%)		2–177
MCD	28 (28.6%)	Pfizer-BioNTech (67.9%)	Within 5–7 d (35.7%)	Dose 1: 15 (53.6%)	27±23
		AstraZeneca (14.3%)	2 wk (28.6%)	Dose 2: 12 (42.9%)	20 (13–38)
		Moderna (7.1%)	Within 1–2 d (7.1%)	Booster: 1 (3.6%)	2–88
		Covaxin (7.1%)	4 wk (7.1%)		
IgAN	26 (26.5%)	Pfizer-BioNTech (57.7%)	Within 1–2 d (38.5%)	(*n*=25)	39±46
		Moderna (15.4%)	2 wk (23.1%)	Dose 2: 17 (68.0%)	22 (5–47)
		Other (11.5%)	Within 5–7 d (15.4%)	Dose 1: 6 (24.0%)	2–177
				Booster: 2 (8.0%)	
Pauci-immune crescentic GN/Vasculitis	17 (17.3%)	Pfizer-BioNTech (52.9%)	2 wk (35.3%)	Dose 2: 12 (70.6%)	36±34
		Moderna (41.2%)	Within 5–7 d (29.4%)	Dose 1: 3 (17.7%)	19 (7–58)
		AstraZeneca (5.9%)	4 wk (11.8%)	Booster: 2 (11.8%)	4–105
MN	10 (10.2%)	Pfizer-BioNTech (50.0%)	Within 5–7 d (30.0%)	Dose 2: 6 (60.0%)	33±23
		Moderna (30.0%)	4 wk (30.0%)	Dose 1: 3 (30.0%)	33 (13–38)
		J&J (10.0%)	Within 3–4 d (20.0%)	Booster: 1 (10.0%)	5–75
		AstraZeneca (10.0%)			
Anti-GBM disease	5 (5.1%)	Pfizer-BioNTech (40.0%)	2 wk (60.0%)	Dose 2: 3 (60.0%)	38±29
		Covaxin (40.0%)	3 wk (20.0%)	Dose 1: 2 (40.0%)	28 (19–42)
		Sinovac (20.0%)	3 mo (20.0%)		15–86
CG	5 (5.1%)	Moderna (60.0%)	Within 5–7 d (60.0%)	Dose 2: 3 (60.0%)	42±61
		Pfizer-BioNTech (20.0%)	2 wk (20.0%)	Dose 1: 2 (40.0%)	18 (14–20)
		AstraZeneca (20.0%)	6 wk (20.0%)		7–150

Data are presented in frequency and percentage, unless otherwise specified. Histologies with $n<3$ are not included. Columns 3–5 represent the top three common responses; thus, the total percentages will not equal to 100%. Available *n* is provided if data were missing. MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; CG, collapsing glomerulopathy; IQR, interquartile range (25th–75th percentiles).
[a]Timing data are mean±SD, median (IQR), and range.

hematuria in 37%, and isolated hematuria in 2.4%. Thromboses (renal vein or inferior vena cava) were diagnosed in three. Other contemporaneous diagnoses included autoimmune hepatitis (n=1) and hemophagocytic lymphohistiocytosis (n=1). Among pauci-immune GN, concurrent complications included pulmonary hemorrhage (n=3), pericarditis (n=1), and leukocytoclastic vasculitis rash (n=1).

Laboratory Parameters and Histopathology

At biopsy, mean (±SD) SCr was highest in anti-GBM (8.4±6.2 mg/dl) and lowest in MN (1.4±1.1 mg/dl) (Supplemental Table 2). Proteinuria was highest in MCD and CG.

Crescents were present in 29% of patients, including all pauci-immune and anti-GBM, and in 23% of patients with IgAN (Table 3). Endocapillary proliferation was predominant in IgAN (26%). Tubulointerstitial nephritis (TIN) was a coexisting finding in 25% of patients, as was acute tubular injury.

Five (50%) patients with MN were PLA2R-positive by tissue staining (Table 3) and/or anti-PLA2R serology (Supplemental Table 3). The others were of an unknown antigen type. Among pauci-immune patients, 76% were ANCA-positive, without a consistent autoantibody pattern. Rather, there was a mixture of C- and P-ANCAs, double seropositive (n=1) and copositivity with anti-GBM (n=1). ANCAs were rare in IgAN. Antinuclear antibodies (ANA) were present in various GNs, but anti-double stranded DNA (anti-dsDNA) and hypocomplementemia were uncommon in nonlupus patients (Supplemental Table 3). Among three CG with available apolipoprotein L1 (APOL1) genotyping, two Black patients had two APOL1 risk alleles.

Management and Outcomes

Renin-angiotensin-aldosterone system inhibitors were initiated in 30% (Table 4); 60% received immunosuppressive therapy, with corticosteroids alone or in combination with anti CD20 therapy, cyclophosphamide, mycophenolate, or calcineurin inhibitors. The kidney disease was self-limiting in 11%. Complete or partial remission (spontaneous or with immunosuppression) was achieved in 60% of patients overall, in 86% of patients with MCD and 61% of patients with IgAN, but fewer remissions among other subgroups (Table 5); 14% did not achieve remission and 9% required dialysis, the majority with pauci-immune or anti-GBM disease. Five patients died, one of whom required hemodialysis. The histologies associated with these patients are summarized in Table 5.

Among 36 patients with GN onset attributed to the first vaccine dose, 44% did not receive subsequent vaccine doses and 25% received the second dose. Details of vaccine rechallenges and relapses are limited. A different vaccine platform was used in two of the vaccine rechallenges (changing from the mRNA platform to the viral vector) (Table 5). Two patients with MCD experienced disease relapses despite no additional vaccine doses.

Longitudinal Outcomes

Median duration of follow-up was 89 (27–177) days. Overall, when histologies were combined, there was a substantial increase in median SCr (mg/dl) from baseline (0.9 [0.8–1.1]) to biopsy (1.7 [1.0–3.7], P<0.001) with improvement at follow-up (1.2 [0.9–1.7] P = 0.043) (Figure 1A). eGFR (ml/min per 1.73 m^2) decreased from 90 (67–109) (mean 88±26) at baseline to 42 (15–81) (mean 51±39) at biopsy (P<0.001) with some improvement at follow-up (70 [43–92], mean 67±32; P = 0.052). Although there was no statistical difference in SCr between baseline and follow-up (P = 0.38), overall eGFR remained significantly lower at follow-up compared with baseline (P = 0.001), suggesting incomplete or lack of renal recovery (Figure 1C).

In MCD and IgAN, kidney function tended to decline from baseline to biopsy (Figure 1, B and D, Supplemental Table 2), but there were no statistical differences in eGFR between baseline and follow-up (P = 1.0 and P = 0.12, respectively), suggesting recovery. By contrast, in pauci-immune GN and MN, eGFR at follow-up was lower compared with that at baseline (P = 0.009 and P = 0.035, respectively).

Most did not have proteinuria at baseline (Supplemental Table 2). At biopsy, overall median proteinuria (g/g) was 4 (2–9), which decreased to 1 (0–4), (P<0.001) by follow-up (Figure 2A). Persistent proteinuria was reported in 16% of patients (Table 5) after a mean follow-up of 120±109 days. Changes in proteinuria based on histology are presented in Figure 2B and Supplemental Table 2. Substantial improvements in proteinuria were seen over time with MCD and IgAN, for whom the majority achieved remission (Table 5). Specifically, in MCD, median proteinuria (g/g) decreased from 10 (7–15) at biopsy to 0 (0–3) at follow-up (P<0.001). For IgAN, proteinuria decreased from 2 (0.3–2) at biopsy to 1 (0–2) at follow-up, although statistical evidence was not strong (P = 0.081). By contrast, there were no statistical differences in proteinuria from biopsy to follow-up for pauci-immune GN (2 [1–4] versus 3 [1–4]; P = 0.18) and MN (6 [4–11] versus 10 [3–13]; P = 1.0).

Overall, median serum albumin (g/dl) decreased from 4.2 at baseline (4.0–4.5) to 2.7 (2.1–3.4) (P<0.001) at biopsy with recovery to 3.8 (3.1–4.3) at follow-up (P<0.001) but lower compared with baseline (P = 0.047) (Figure 3, A and B and Supplemental Table 2). There were no substantial changes in albumin in patients with IgAN (P = 0.17). In MCD, albumin decreased expectedly from baseline to biopsy (P<0.001) with a trend toward recovery at follow-up (P = 0.048), whereas in MN, albumin was lower at follow-up versus baseline (P<0.001).

Discussion

To the best of our knowledge, this represents the largest series to date of *de novo* GN temporally related to COVID-19 vaccination or any vaccine, in general. IgAN and MCD were the dominant kidney diseases and more common after mRNA-based vaccines. The dominance of these GNs is consistent with published reports and an analysis of the WHO's pharmacovigilance database, Vigibase.[31] Of 143 patients with nephrotic syndrome in Vigibase after COVID-19 vaccination, 72% received Pfizer. Minimal lesion GN was predominantly associated with the Pfizer vaccine, whereas IgAN was modestly associated with Moderna. In our cohort, the onset of symptoms was more frequent after the second dose, with the exception of MCD, which was slightly more common after the first dose.

The age distribution for the GN subtypes is similar to primary GN. Patients with pauci-immune GN, anti-GBM, and MN tended to be older than those with MCD, IgAN,

Table 3. Selected histologic features on kidney biopsies among patients with glomerular disease

Feature	Frequency of Finding (All Patients) (*n*=98)	MCD (*n*=28)	IgAN (*n*=26)	Pauci-Immune Crescentic GN/Vasculitis (*n*=17)	MN[a] (*n*=10)	Anti-GBM Disease (*n*=5)	CG (*n*=5)
Collapsing features	6 (6.1%)	0	0	1 (5.9%)	0	0	5 (100.0%)
Crescents	28 (28.6%)	0	6 (23.1%)	17 (100%)	0	5 (100%)	0
TRI	1 (1.0%)	0	0	0	0	0	1 (20.0%)
Focal acute tubular injury	9 (9.2%)	2 (7.1%)	3 (11.5%)	1 (5.9%)	1 (10.0%)	1 (20.0%)	1 (20.0%)
Diffuse acute tubular injury	24 (24.5%)	4 (13.3%)	6 (23.1%)	6 (35.3%)	2 (20.0%)	3 (60.0%)	2 (40.0%)
Acute tubular necrosis	7 (7.1%)	2 (7.1%)	1 (3.9%)	2 (11.8%)	0	0	2 (40.0%)
TIN/inflammatory infiltrate	25 (25.5%)	6 (21.4%)	6 (23.1%)	7 (41.2%)	1 (10.0%)	3 (60.0%)	1 (20.0%)
Endocapillary proliferation	11 (11.2%)	0	7 (26.9%)	2 (11.8%)	0	0	0
Electron microscopy deposits							
Subepithelial	10 (10.2%)	[b]1 (3.6%)	0	0	[c]6 (60.0%)	0	1 (20.0%)
Subepithelial humps	2 (2.0%)	0	1 (3.9%)	0	1 (10.0%)	0	0
Subendothelial	3 (3.1%)	0	1 (3.9%)	1 (5.9%)	0	0	0
Mesangial	33 (33.7%)	2 (7.1%)	22 (84.6%)	3 (17.7%)	1 (10.0%)	1 (20.0%)	1 (20.0%)
Global sclerosis	1 (1.0%)	0	0	0	0	0	0
Other					PLA2R+: 4/9 (44%)		
Immunostaining[d]					THSD7A: 3/3: neg NELL1: 3/3: neg EXT1/2: 3/3: neg		

Data are presented in frequency and percentage. Total percentages may not equal to 100% due to rounding. Histologies with $n<3$ are not included. MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; CG, collapsing glomerulopathy; TRI, tubuloreticular inclusions; TIN, tubulointerstitial nephritis; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A; NELL1, neural epidermal growth factor-like 1; EXT1/2, exostosin.
[a]One patient did not undergo kidney biopsy but was diagnosed with MN based on a positive serum anti-PLA2R antibody test.
[b]Rare deposit insufficient to explain diffuse process effacement, thus classified as MCD rather than MN by the pathologist.
[c]Not all patients examined by electron microscopy.
[d]MN antigen immunostaining not performed in all patients; denominator represents the number of patients tested.

or CG. There were few pediatric patients in our registry (n=4), which may reflect the timing of vaccine approval in this population or lower vaccine doses. Published pediatric patients with GN are predominantly IgAN and MCD.[26,32-35] Racial distribution was noteworthy, in that AA represented a minority of patients in our registry and 38% developed CG. This distribution should be interpreted with caution in light of vaccine access issues and hesitancy among underrepresented minorities, particularly early in the vaccination rollout. Nevertheless, this contrasts with the AA predominance observed with COVID-19–associated nephropathy.

When all histologies were combined, eGFR was significantly lower at follow-up compared with prevaccination baseline. Among the different histologies, patients with IgAN and MCD tended to have more favorable kidney prognosis, with improvement in GFR and proteinuria, and were more likely to show remission by 4–6 months. By contrast, MN and pauci-immune GN were less likely to achieve remission or renal recovery during the short-term follow-up. However, the kinetics of proteinuria reduction in MN is often delayed, lagging behind immunologic responses. The less favorable clinical course of pauci-immune GN is likely influenced by the nature of the disease, lower GFR before vaccination and at presentation, older age, and comorbidities. Longer term follow-up is needed to assess the potential for kidney recovery among all the histologies.

Among histological subgroups in which serology is the basis for classification, autoantibody (AB) profiles were mixed. For the MN subgroup, 50% were PLA2R-positive, but the AB profile was undefined in PLA2R-negative patients. There are rare reports of neural epidermal growth factor-like 1[36] and thrombospondin type 1 domain-containing 7A-positive MN after COVID-19 vaccination.[37] Our limited data set precludes meaningful interpretation of whether suspected postvaccine MN is "secondary" to the vaccine (possibly with unique AB profiles) or "unmasked" subclinical MN. Indeed, PLA2R

Table 4. Management of the common glomerular diseases reported after vaccination

Treatment	All Patients (n=98)	MCD (n=28)	IgAN (n=26)	Pauci-Immune GN (n=17)	MN (n=10)	Anti-GBM Disease (n=5)	CG (n=5)
Observation only	14 (14.3%)	1 (3.6%)	6 (23.1%)	1 (5.9%)	4 (40.0%)	0	0
RAAS inhibition	29 (29.6%)	5 (17.9%)	14 (53.9%)	3 (17.7%)	6 (60.0%)	0	1 (20.0%)
Immunosuppression	70 (71.4%)	26 (92.9%)	10 (38.5%)	16 (94.1%)	5 (50.0%)	0	4 (80.0%)
Corticosteroids	59 (60.2%)	26 (92.9%)	8 (30.8%)	13 (76.5%)	2 (2.0%)	3 (60.0%)	3 (60.0%)
Rituximab	14 (14.3%)	2 (7.1%)	0	6 (35.3%)	3 (30.0%)	2 (40.0%)	0
Cyclophosphamide	13 (13.3%)	0	2 (7.7%)[a]	8 (47.1%)	0	3 (60.0%)	0
Plasma exchange	10 (10.2%)	0	0	5 (29.4%)	0	5 (100.0%)	0
Mycophenolate mofetil	8 (8.2%)	0	2 (7.7%)	0	0	0	2 (40.0%)
Tacrolimus	4 (4.1%)	1 (3.6%)	1 (3.9%)	0	1 (10.0%)	0	0
Cyclosporine	1 (1.0%)	1 (3.6%)	0	0	0	0	0
Azathioprine	1 (1.0%)	0	0	1 (5.9%)	0	0	0
Other	2 (2.0%)	0	0	1 (5.9%)	0	0	0

Data are presented as frequency and percentage. Total percentage may not equal to 100% due to rounding.
Histologies with n<3 are not included. MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; CG, collapsing glomerulopathy; RAAS, renin-angiotensin-aldosterone system.
[a]Cyclophosphamide used in these patients because of acute kidney injury in the setting of crescents on kidney biopsy.

AB may develop years before MN diagnosis.[38] Similarly, in pauci-immune patients, there was no consistent AB pattern. Thus, the serologies do not provide insight into potential distinct mechanisms in vaccine-associated GN.

Co-occurrence of histolopathologies, mainly podocytopathy mixed with IgAN or MN, was observed in a subset of cases. Whether these findings are fortuitous, directly pathogenically linked to vaccination or whether one glomerular

Table 5. Outcomes based on selected glomerular disease subgroup

Outcome	All Patients (n=98)	MCD (n=28)	IgAN (n=26)	Pauci-Immune GN (n=17)	MN (n=10)	Anti-GBM Disease (n=5)	CG (n=5)
Spontaneous remission	4 (4.1%)	1 (3.6%)	3 (11.5%)	0	0	0	0
PR without treatment	7 (7.1%)	1 (3.6%)	4 (15.4%)	0	2 (2.0%)	0	0
PR after treatment	23 (23.5%)	7 (25.0%)	7 (26.9%)	4 (23.5%)	1 (10.0%)	1 (20.0%)	2 (40.0%)
CR after treatment	24 (24.5%)	15 (53.6%)	2 (7.7%)	4 (23.5%)	0	1 (20.0%)	0
No response to treatment/no remission	14 (14.3%)	1 (3.6%)	3 (11.5%)	3 (17.7%)	3 (30.0%)	1 (20.0%)	2 (40.0%)
Progression of disease with decline in GFR	4 (4.1%)	0	1 (3.9%)	0	1 (10.0%)	0	1 (20.0%)
Persistent proteinuria	16 (16.3%)	1 (3.6%)	5 (19.2%)	2 (11.8%)	5 (50.0%)	0	2 (40.0%)
Relapsed after achieving remission	2 (2.0%)	2 (7.1%)	0	0	0	0	0
Relapsed after vaccine rechallenge[a]	6	3[b]	3[c]				
Required RRT	9 (9.2%)	0	2 (7.7%)	4 (23.5%)	0	2 (40.0%)	1 (20.0%)
Died[d]	5 (5.1%)	1 (3.6%)	0	2 (11.7%)	0	1 (20.0%)	1 (20.0%)

Data are presented as frequency and percentage. Total percentages may not equal to 100% due to rounding. Histologies with n<3 are not included. MCD, minimal change disease; IgAN, IgA nephropathy; MN, membranous nephropathy; CG, collapsing glomerulopathy; PR, partial remission; CR, complete remission.
[a]Limited data on vaccine rechallenges available, thus denominator not known.
[b]One patient with MCD developed nephrotic syndrome within 6 days of the first vaccine dose, spontaneously remitted, and then relapsed after the second vaccine dose requiring immunosuppression. Two patients with MCD treated with immunosuppression after diagnosis (achieved remission) relapsed after additional doses. In one of these patients, two additional vaccine doses were tolerated well, but another relapse occurred after the fourth dose.
[c]Two patients who developed gross hematuria within days of the first vaccine dose had recurrence of hematuria within hours of the second vaccine dose leading to diagnostic renal biopsy of IgAN. One patient with onset of IgAN during pregnancy after the second vaccine dose had recurrence of gross hematuria after the third dose that resolved spontaneously.
[d]One patient with CG required RRT. Comorbidities in deceased included chronic kidney disease (3), cancer (2), viral hepatitis (1), rheumatoid arthritis (2), and chronic obstructive lung disease (1). The cause of death was unknown in two. Withdrawal of care due to cancer progression, cardiogenic shock, and respiratory failure/pulmonary hemorrhage contributed to death in three patients.

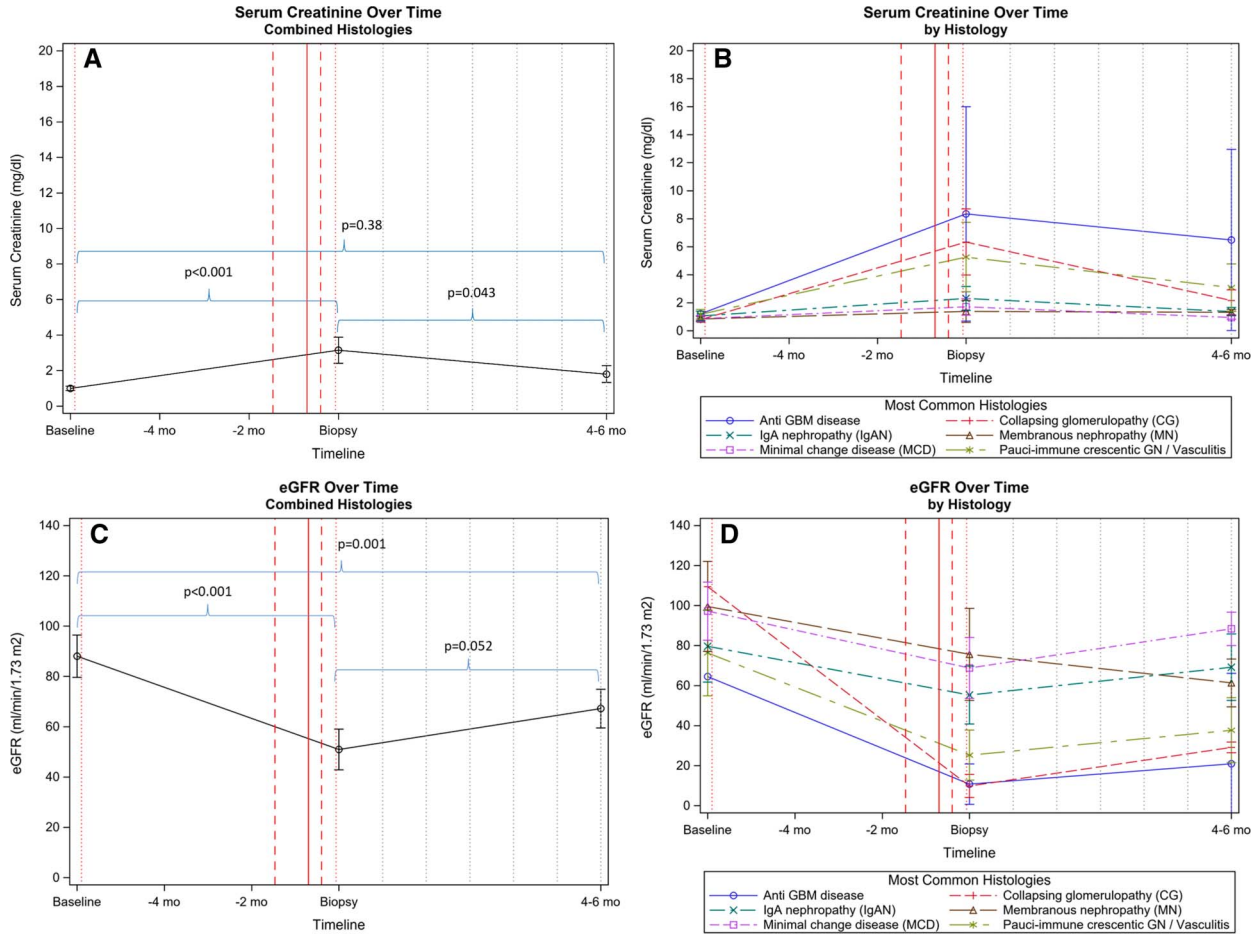

Figure 1. Longitudinal changes in serum creatinine and eGFR show decline in renal function, and subsequent recovery varies based on glomerular disease histology after vaccination. All histologies combined (A, C) and based on histology (B, D), at baseline (prevaccination), and at/around the time of kidney biopsy and follow-up (approximately 4–6 months). Data are presented as mean ±95% confidence interval. Data were assessed for statistical assumptions, and longitudinal data were analyzed using mixed models. *Post hoc* comparisons were corrected for multiplicity using the Bonferroni method, and corrected *P*-values are reported along the brackets. The timing of the culprit vaccine dose relative to the timing of renal biopsy is represented by the vertical red lines (solid=median; dash=interquartile range; dot=range). Combined histologies include those most commonly observed ($n>3$).

lesion enhances susceptibility after vaccination is uncertain. This may be a potential unmasking mechanism. In addition, TIN was superimposed on glomerular pathologies in 25% of patients. Patients with isolated TIN after COVID-19 vaccination have been reported[20,39-42] and may be another unmasking mechanism by exacerbating an unrecognized GN.

According to WHO guidelines, adverse events (AE) following immunization can be defined as any untoward, unfavorable, or unintended medical occurrence after vaccination, not necessarily exhibiting a consistent, causal relationship with the vaccine product. WHO recommends a four-step algorithm for assessing causality of AE after vaccination,[43] but Bradford Hill criteria may also be used[44] and considers criteria of temporality, consistency, strength of association, specificity, and biological plausibility. Using these criteria to assess causality for GN is not straightforward: (*1*) **Temporality and consistency:** Kidney-related symptoms (with exception of gross hematuria) tend to be subtle and nonspecific making it challenging to define a temporal relationship between vaccination and GN. However, among GNs, temporality is more consistent for IgAN and MCD. Although temporality does not prove causation, lack of temporality does not disprove causation because autoimmune responses may evolve slowly and clinical manifestations may lag. (*2*) **Strength of association:** Relapses of MCD and IgAN shortly after vaccine rechallenge adds strength to this association. (*3*) **Specificity:** There is lack of specificity to one COVID-19 vaccine. Non–COVID-19 vaccines are also implicated in *de novo* GN. While the proportion of events related to mRNA vaccines is higher than other platforms, this may reflect more widespread global distribution and a much larger denominator. (*4*) **Biologic plausibility:** A unique biological mechanism by which the COVID-19 vaccine(s) potentially triggers GN is yet to be clarified. The mRNA technology promotes more potent immune responses than inactivated viral vaccines or adjuvanted protein vaccines, but given the heterogeneity and spectrum of GN observed, multiple mechanisms as part of a multihit process in a susceptible host is likely and hypothesized elsewhere.[11,45-47]

It is possible that some GN cases are coincidental and unrelated to vaccination. In this regard, we identified

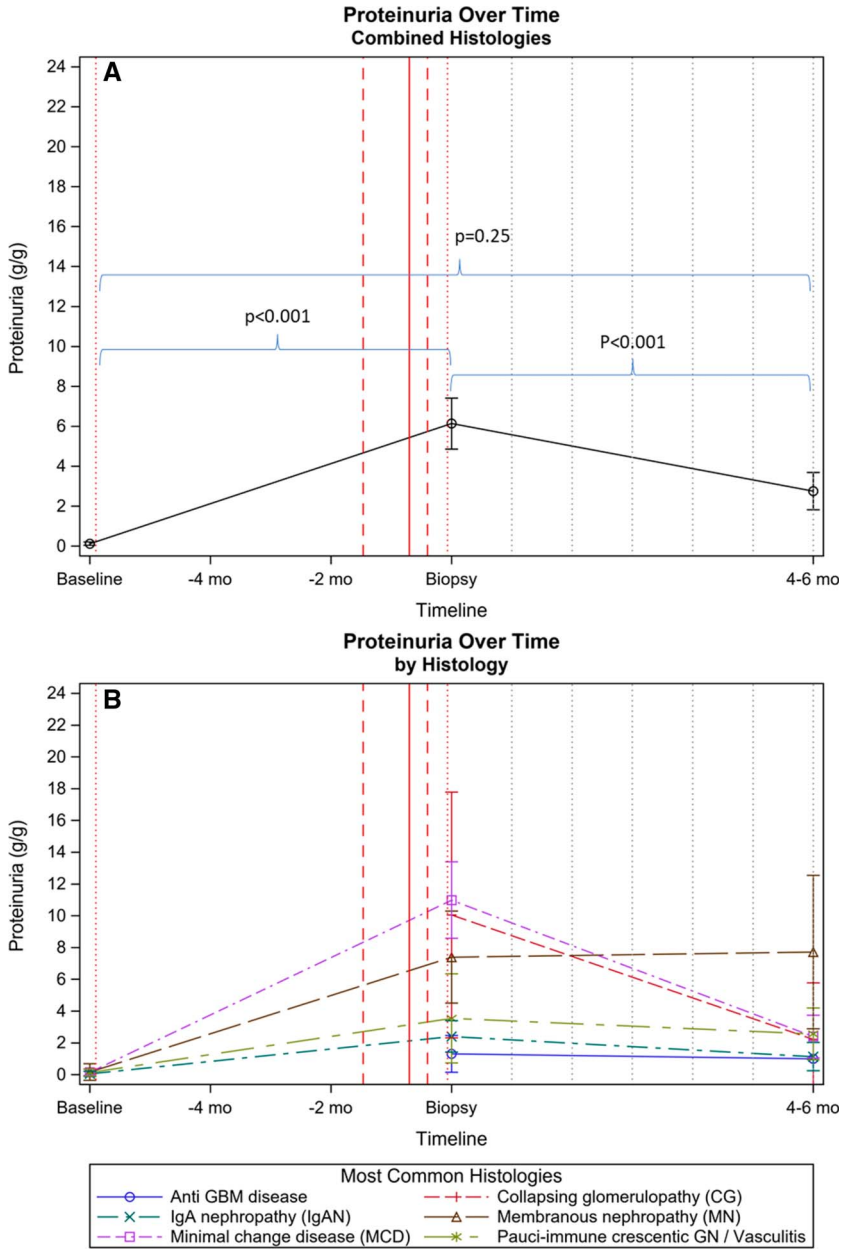

Figure 2. Longitudinal changes in proteinuria show significant proteinuria at time of kidney biopsy, and remission at follow-up varied based on glomerular disease histology after vaccination. All histologies combined (A) and based on histology (B), at baseline (prevaccination), and at/around the time of kidney biopsy and follow-up.

comorbidities and medications that may be alternative contributors to GN in some patients, *i.e.,* HIV and psoriatic arthritis in IgAN, NSAID use and Guillian-Barre syndrome in MCD, hepatitis C/colon cancer/NSAIDs in PLA2R-negative MN, lymphoma in CG, and hydralazine use in pauci-immune GN. In other cases, histology patterns such as global glomerulosclerosis and amyloid are more suggestive of long-standing disease that preceded vaccination. Three patients with IgAN had documented hematuria (single-episode gross hematuria or intermittent microscopic) before vaccination. This hematuria had been attributed to other reasons (cystitis, nephrolithiasis, urinary tract infection) but may have reflected preexisting GD. Similarly, it is also possible that patients with preexisting CKD (attributed to other causes) had underlying GD. However, they did not have documented hematuria or significant proteinuria at baseline. Contributions from coadministered vaccines or prior COVID-19 infection cannot be excluded. Finally, increased health care utilization after vaccination compared with the height of the pandemic may be a nonimmunologic factor unmasking preexisting GN.

Optimal management is not defined, but standard immunosuppressive treatments have led to responses. It is unknown whether the molecular and immunologic mechanisms of CVAGD are similar to non-CVAGD. An improved

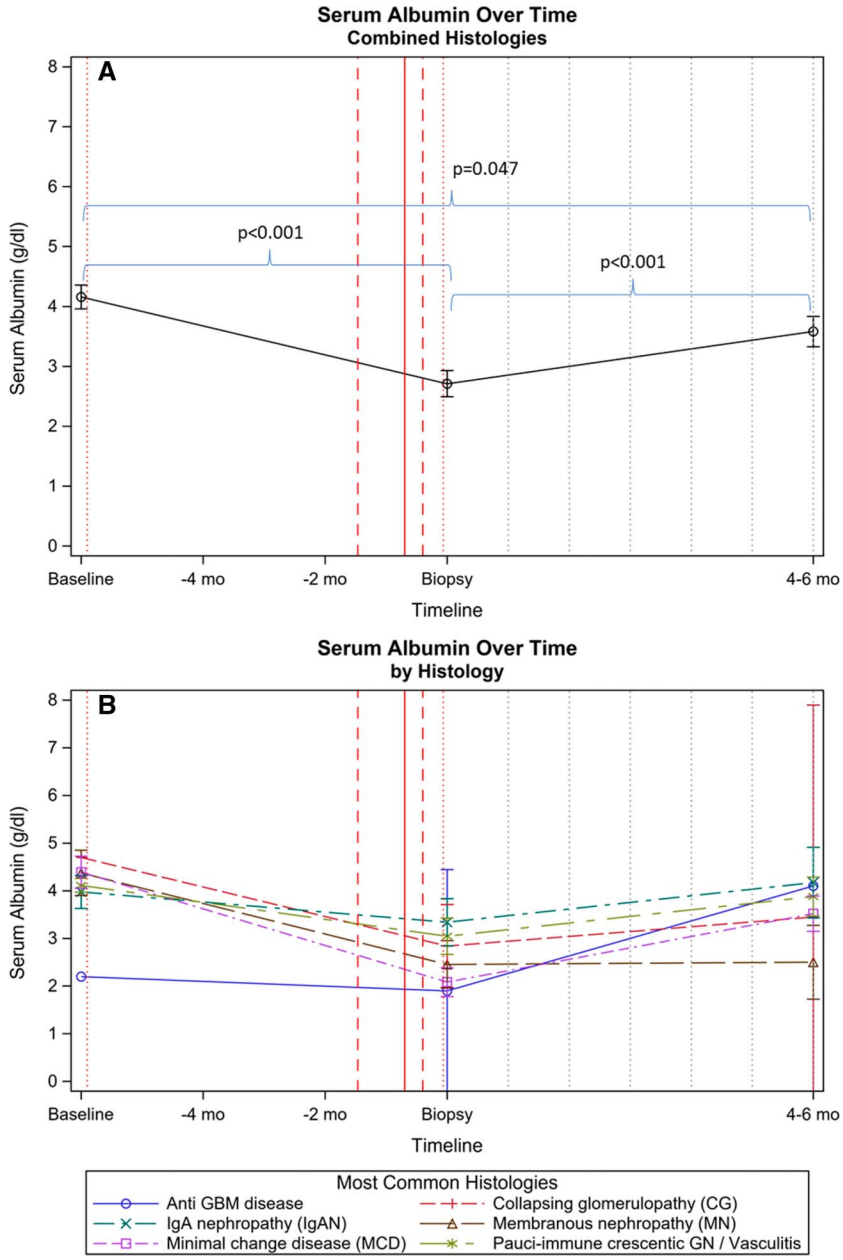

Figure 3. Longitudinal changes in serum albumin. Degree of hypoalbuminemia at time of kidney biopsy and potential for recovery at follow-up varies based on glomerular disease histology after vaccination. All histologies combined (A), and based on histology (B) at baseline (prevaccination), and at/around the time of kidney biopsy and follow-up.

understanding of immune responses and kinetics in CVAGD (and between GNs) and potential for spontaneous recovery versus relapse is needed to inform management.

The issue and safety of rechallenging with future boosters (using the same or different vaccine platform) needs clarification because some subjects relapsed after additional doses. Such decisions will need to be individualized, factoring in histologic diagnosis, previous recovery, comorbidities, and consideration that patients with GN are at higher risk of severe COVID-19.[48,49]

Our study has several limitations. The statistical power of analyses was limited, especially for the less frequent outcomes. The nature of the data set does not allow firm causal conclusions or estimate GN frequency. As with all passive reporting systems, our registry is subject to under/incomplete reporting. The registry relies on patient identification based on clinical judgment and voluntary submission, leading to possible selection bias toward more overt, earlier AEs, which may affect result generalizability. We purposefully did not apply a case-level clinical review to assess causality (or exclude cases). This allowed us to report an unbiased range of GN suspected after vaccination. Thus, misattribution is possible. We did not include control spontaneous GN patients for comparison. However, a study from Switzerland using data from all Swiss pathology institutes did not find any differences in

the incidence of the four common GNs before or after initiation of the COVID-19 vaccination campaign.[50] Finally, the risk of GN may be underestimated if the real risk interval was longer than the time window defined in inclusion criteria. However, there is lack of precise references on plausible time frames for appearance of AEs after vaccination, particularly for autoimmune diseases. Despite these limitations, the strengths of this study are international representation, comparisons between histologic subgroups and vaccines, and longitudinal data.

In conclusion, the exchange of information provided in this report, although preliminary, is important for transparency, awareness, and avoidance of misinformation. Any concerns regarding the safety of SARS-CoV-2 vaccines need to be taken seriously and warrant thorough investigation. Importantly, this report highlights the many challenges and complexity of assessing causality between AEs and vaccination. The true incidence of GN conferred by COVID-19 vaccines cannot be calculated, but risk appears low, likely close to the background incidence of these conditions in large populations[50] and represents a very small percentage of vaccinated individuals. Importantly, most patients with MCD and IgAN improved with conventional therapies. These outcomes are reassuring, particularly considering the prevalence of acute and chronic kidney injury and GN with less favorable outcomes linked to COVID-19. Given the well-established benefits of vaccination in prevention of severe COVID-19, no change in the current vaccination guidelines is suggested.

Collaborative research efforts, centralized repositories, and longitudinal data are needed to understand the potential role of COVID-19 vaccines in the development of GN. This is relevant in light of authorization of the bivalent COVID-19 boosters based on mRNA platforms, which will likely continue to be adapted in the future to target new SARS-CoV-2 variants.

Disclosures

R. Avasare reports the following: Employer: Oregon Health & Science University; Advisory or Leadership Role: editorial board of the Glomerular Disease Journal (Karger); and Other Interests or Relationships: member of ASN and NKF; Site PI for the NEFIGARD study and TRIDENT study; and Nephrology consultant for the LAPMS clinical trial (NCT03161028). K. Baskaran reports the following: Ownership Interest: Qantas. P. Baxi reports the following: Honoraria: Aurinia (voclosporin). A. Gallan reports the following: Consultancy: Vector Surgical LLC. A. Hamilton reports the following: Advisory or Leadership Role: Journal of Kidney Care Editorial Board; and Other Interests or Relationships: SONG-Kids Life Participation Expert Working Group member. K. Jhaveri reports the following: Consultancy: George Clinicals, PMV Pharmaceuticals, Calliditas, and Secretome; Honoraria: Uptodate.com, American Society of Nephrology, and International Society of Nephrology; Advisory or Leadership Role: American Journal of Kidney Diseases, CJASN, Clinical Kidney Journal, EIC-ASN Kidney News, Journal of Onconephrology, Kidney International, and NDT; and Other Interests or Relationships: President of American Nephrologists of Indian Origin and co-President and Founder of the American Society of Onconephrology. E. Lerma reports the following: Consultancy: Akebia, AstraZeneca, Bayer, Boehringer-Ingelheim, Glaxo Smith Kline, Otsuka, Travere, and Vifor; Ownership Interest: Fresenius Joint Venture; Honoraria: Honoraria for advisory board/speaker bureau: Akebia, AstraZeneca, Bayer, Boehringer-Ingelheim, Glaxo Smith Kline, Otsuka, Travere, and Vifor; Patents or Royalties: Elsevier Publishing, McGraw-Hill Publishing, Springer, UpToDate, and Wolters Kluwer Publishing; Advisory or Leadership Role: Editorial board member: American Journal of Kidney Diseases, ASN Kidney News, Clinical Journal of the American Society of Nephrology, International Urology and Nephrology Journal, Journal of Clinical Lipidology, Journal of Vascular Access, Prescribers Letter, Renal and Urology News, and Reviews in Endocrinology and Metabolic Disorders; and Speakers Bureau: Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Glaxo Smith Kline, Otsuka, Travere, and Vifor. A. Liew reports the following: Consultancy: Alnylam Pharmaceuticals, Baxter Healthcare, Bayer, Boehringer-Ingelheim, Chinook Therapeutics, DaVita Inc, Eledon Pharmaceuticals, George Clinical, Kira Pharmaceuticals, Otsuka Pharmaceuticals, and ProKidney; Honoraria: Alnylam Pharmaceuticals, AstraZeneca, Baxter Healthcare, Bayer, Boehringer-Ingelheim, Chinook Therapeutics, and Otsuka Pharmaceuticals; Advisory or Leadership Role: Alnylam, AstraZeneca, Bayer, Boehringer-Ingelheim, Chinook Therapeutics, Eledon Pharmaceuticals, Kidney International (editorial board), Kira Pharmaceuticals, Nephrology Journal (Associate Editor), Otsuka, Peritoneal Dialysis International (editorial board), and ProKidney; Speakers Bureau: Baxter Healthcare, Chinook Therapeutics, and Otsuka Pharmaceuticals; and Other Interests or Relationships: Secretary and Executive, ISPD; Chair, ISN Renal Disaster Preparedness Working Group; Working Group Member, KDIGO Guideline on Diabetes Management in CKD; Working Group Member, KDIGO Guideline Update on Glomerular Diseases; and Chair, Asian-Pacific Society of Nephrology Guideline on Diabetic Kidney Disease. O. Maoujoud reports the following: Consultancy: Baxter and Nipro; Research Funding: R2S; Honoraria: Nipro and Novo Nordisk; and Speakers Bureau: ORANGE and AWB. S. Marinaki reports the following: Honoraria: Alexion, AstraZeneca, Gilead, and GSK; Only for invited lectures as a speaker during 2022; and Advisory or Leadership Role: advisory for GSK (lupus nephritis) during 2022 and advisory for AstraZeneca (aHUS) during 2022. J. Mejia-Vilet reports the following: Consultancy: GlaxoSmithKline and Kezar Pharmaceuticals; and Honoraria: AstraZeneca, Boehringer-Ingelheim, and Roche. R. Morales reports the following: Ownership Interest: Meta. I. Petrakis reports the following: Honoraria: Vifor Pharma CH. R. Rodby reports the following: Advisory or Leadership Role: NXStage Scientific Advisory Board. C. Schulze reports the following: Other Interests or Relationships: Medical director, Davita Century City Home hemodialysis, January to June 2022. Resigned January 7, 2022. R. Seipp reports the following: Ownership Interest: Duly Health and Care; and Honoraria: M3 Global Research and Spherix Global Insights. K. Stylianou reports the following: Research Funding: AstraZeneca, Bayer, GSK, and Novartis; and Advisory or Leadership Role: AstraZeneca, Bayer, Baxter, Chiesi, GSK, and Menarini. A. Urisman reports the following: Consultancy: PLIANT Therapeutics. J. Velez reports the following: Consultancy: Bayer, Calliditas, Mallinckrodt Pharmaceuticals, and Travere; Honoraria: Bayer, Calliditas, Mallinckrodt Pharmaceuticals, and Travere; and Advisory or Leadership Role: Bayer, Calliditas, Mallinckrodt Pharmaceuticals, and Travere. R. Wanchoo reports the following: Advisory or Leadership Role: Associate Editor of the Journal of Onconephrology, editorial board of CKJ, and the founding member of ASON. J. Zuckerman reports the following: Consultancy: Leica Biosystems and PAthai; Honoraria: ApotheCom; and Advisory or Leadership Role: Pathologyoutlines.com. All remaining authors have nothing to disclose.

Funding

This research was supported in part by the Intramural Research Program of the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Acknowledgments

The authors thank Matthew Breymaier (NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development) for his assistance with creation of the registry using REDCap. The authors thank Dr. Nabeel Ahmed (Sunshine Hospital, India) for his contributions of collection and reporting of subject data.

Author Contributions

Conceptualization: Tiffany N. Caza, Edgar V. Lerma, Ninet Sinaii, Meryl Waldman.
Data curation: Kevin Javier Arellano Arteaga, Abraham W. Aron, Rupali Avasare, Krishoban Baskaran, Claude Bassil, Pravir V. Baxi, Esperanza Moral Berrio, Tiffany N. Caza, Naomi Edney, Ashraf El-Meanawy, Jordan Evans, Harikleia Gakiopoulou, Alexander J. Gallan, Alexander J. Hamilton, Mal Homan, Mahmud Islam, Kenar D. Jhaveri, John Paul Killen, Anila Abraham Kurien, Larissa Lebedev, Adrian Liew, Ramon Lopez del Valle, Omar Maoujoud, Smaragdi Marinaki, Juan M. Mejia Vilet, Rachel Millner, Muner M.B. Mohamed, Khalid M.G Mohammed, Rebecca Ruf Morales, Muhammad Muneeb. Laura Ollila, Natasha Perinpanayagam, Ioannis Petrakis, Silvia E. Ramirez Andrade, Roger Rodby, Jose Manuel Rodríguez Chagolla, Joshua L. Rein, Carl E. Schulze, Arjun Sekar, Regan Seipp, Ninet Sinaii, Kostas Stylianou, Nupur N. Uppal, Anatoly Urisman, Irina Vancea, Mahesha Vankalakunti, Enzo Vásquez Jiménez, Juan Carlos Q. Velez, Eswari Vilayur, Adrienne Wai Seung, Meryl Waldman, Rimda Wanchoo, Nethmi Weerasinghe, Yoram Yagil, Robert H. Yenchek, Mona Zawaideh, Jonathan E. Zuckerman.
Formal analysis: Ninet Sinaii, Meryl Waldman.
Funding acquisition: Meryl Waldman.
Investigation: Lilian Howard, Meryl Waldman.
Methodology: Lilian Howard, Ninet Sinaii, Meryl Waldman.
Project administration: Lilian Howard, Meryl Waldman.
Resources: Meryl Waldman.
Software: Meryl Waldman.
Supervision: Meryl Waldman.
Validation: Meryl Waldman.
Visualization: Meryl Waldman.
Writing – original draft: Ninet Sinaii, Meryl Waldman.
Writing – review & editing: Abraham W. Aron, Rupali Avasare, Krishoban Baskaran, Claude Bassil, Pravir V. Baxi, Tiffany N. Caza, Alexander J. Gallan, Alexander J. Hamilton, Lilian Howard, Kenar D. Jhaveri, John Paul Killen, Anila Abraham Kurien, Edgar V. Lerma, Adrian Liew, Ramon Lopez del Valle, Smaragdi Marinaki, Rachel Millner, Ioannis Petrakis, Joshua L. Rein, Jose Manuel Rodríguez Chagolla, Ninet Sinaii, Kostas Stylianou, Nupur N. Uppal, Anatoly Urisman, Enzo Vásquez Jiménez, Meryl Waldman, Rimda Wanchoo, Yoram Yagil, Jonathan E. Zuckerman.

Data Sharing Statement

All data are included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A250.

Supplemental Table 1. Comparison of patient baseline characteristics based on glomerular disease.

Supplemental Table 2. Serial laboratory parameters for selected glomerular diseases.

Supplemental Table 3. Selected relevant serologies and genotyping based on glomerular disease.

References

1. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav.* 2021;5(7):947–953. doi:10.1038/s41562-021-01122-8
2. Bomback AS, Kudose S, D'Agati VD. De novo and relapsing glomerular diseases after COVID-19 vaccination: what do we know so far? *Am J Kidney Dis.* 2021;78(4):477–480. doi:10.1053/j.ajkd.2021.06.004
3. Salem F, Rein JL, Yu SMW, Abramson M, Cravedi P, Chung M. Report of three cases of minimal change disease following the second dose of mRNA SARS-CoV-2 COVID-19 vaccine. *Kidney Int Rep.* 2021;6(9):2523–2524. doi:10.1016/j.ekir.2021.07.017
4. Nakatani S, Mori K, Morioka F, et al. New-onset kidney biopsy-proven IgA vasculitis after receiving mRNA-1273 COVID-19 vaccine: case report. *CEN Case Rep.* 2022;11(3):358–362. doi:10.1007/s13730-021-00677-9
5. Marinaki S, Kolovou K, Liapis G, Skalioti C, Tsiakas S, Boletis I. De novo minimal change disease following vaccination with the Pfizer/BioNTech SARS-CoV-2 vaccine in a living kidney donor. *Medicina (Kaunas).* 2021;58(1):37. doi:10.3390/medicina58010037
6. Thappy S, Thalappil SR, Abbarh S, Al-Mashdali A, Akhtar M, Alkadi MM. Minimal change disease following the Moderna COVID-19 vaccine: first case report. *BMC Nephrol.* 2021;22(1):376. doi:10.1186/s12882-021-02583-9
7. Okada M, Kikuchi E, Nagasawa M, Oshiba A, Shimoda M. An adolescent girl diagnosed with IgA nephropathy following the first dose of the COVID-19 vaccine. *CEN Case Rep.* 2022;11(3):376–379. doi:10.1007/s13730-021-00679-7
8. Vornicu A, Berechet A, Frăţilă G, Obrisca B, Jurcut C, Ismail G. Relapse of cryoglobulinemic vasculitis with new-onset severe renal involvement in two patients following mRNA COVID-19 vaccination: a case report. *Medicine (Baltimore).* 2022;101(23):e29431. doi:10.1097/md.0000000000029431
9. Pella E, Sarafidis PA, Alexandrou ME, et al. De novo minimal change disease in an adolescent after Pfizer-BioNTech COVID-19 vaccination: a case report. *Case Rep Nephrol Dial.* 2022;12(1):44–49. doi:10.1159/000521981
10. Nakagawa N, Maruyama S, Kashihara N, Narita I, Isaka Y. New-onset and relapse of nephrotic syndrome following COVID-19 vaccination: a questionnaire survey in Japan. *Clin Exp Nephrol.* 2022;26(9):909–916. doi:10.1007/s10157-022-02231-y
11. Li NL, Coates PT, Rovin BH. COVID-19 vaccination followed by activation of glomerular diseases: does association equal causation? *Kidney Int.* 2021;100(5):959–965. doi:10.1016/j.kint.2021.09.002
12. Izzedine H, Bonilla M, Jhaveri KD. Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial? *Nephrol Dial Transplant.* 2021;36(9):1565–1569. doi:10.1093/ndt/gfab215
13. Abramson M, Mon-Wei Yu S, Campbell KN, Chung M, Salem F. IgA nephropathy after SARS-CoV-2 vaccination. *Kidney Med.* 2021;3(5):860–863. doi:10.1016/j.xkme.2021.05.002
14. Caza TN, Cassol CA, Messias N, et al. Glomerular disease in temporal association with SARS-CoV-2 vaccination: a series of 29 cases. *Kidney360.* 2021;2(11):1770–1780. doi:10.34067/KID.0005372021
15. Lebedev L, Sapojnikov M, Wechsler A, et al. Minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis.* 2021;78(1):142–145. doi:10.1053/j.ajkd.2021.03.010
16. D'Agati VD, Kudose S, Bomback AS, Adamidis A, Tartini A. Minimal change disease and acute kidney injury following the Pfizer-BioNTech COVID-19 vaccine. *Kidney Int.* 2021;100(2):461–463. doi:10.1016/j.kint.2021.04.035

17. Maas RJ, Gianotten S, van der Meijden WAG. An additional case of minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis.* 2021;78(2):312. doi:10.1053/j.ajkd.2021.05.003
18. Tanaka F, Katayama K, Joh K, et al. Minimal change disease with thrombotic microangiopathy following the Pfizer-BioNTech COVID-19 vaccine. *Clin Kidney J.* 2022;15(3):567–568. doi:10.1093/ckj/sfab234
19. Schaubschlager T, Rajora N, Diep S, et al. De novo or recurrent glomerulonephritis and acute tubulointerstitial nephritis after COVID-19 vaccination: a report of six cases from a single center. *Clin Nephrol.* 2022;97(5):289–297. doi:10.5414/CN110794
20. Fenoglio R, Lalloni S, Marchisio M, et al. New onset biopsy-proven nephropathies after COVID vaccination. *Am J Nephrol.* 2022;53(4):325–330. doi:10.1159/000523962
21. Unver S, Haholu A, Yildirim S. Nephrotic syndrome and acute kidney injury following CoronaVac anti-SARS-CoV-2 vaccine. *Clin Kidney J.* 2021;14(12):2608–2611. doi:10.1093/ckj/sfab155
22. Zavala-Miranda MF, González-Ibarra SG, Pérez-Arias AA, Uribe-Uribe NO, Mejia-Vilet JM. New-onset systemic lupus erythematosus beginning as class V lupus nephritis after COVID-19 vaccination. *Kidney Int.* 2021;100(6):1340–1341. doi:10.1016/j.kint.2021.09.009
23. Aydın MF, Yıldız A, Oruç A, et al. Relapse of primary membranous nephropathy after inactivated SARS-CoV-2 virus vaccination. *Kidney Int.* 2021;100(2):464–465. doi:10.1016/j.kint.2021.05.001
24. Sekar A, Campbell R, Tabbara J, Rastogi P. ANCA glomerulonephritis after the Moderna COVID-19 vaccination. *Kidney Int.* 2021;100(2):473–474. doi:10.1016/j.kint.2021.05.017
25. Psyllaki A, Stavrakaki I, Androvitsanea A, Gakiopoulou H, Petrakis I, Stylianou K. Two cases of glomerular involvement after vaccination against COVID-19: epiphenomenon or causality? *Clin Kidney J.* 2022;15(3):574–575. doi:10.1093/ckj/sfab252
26. Hanna C, Herrera Hernandez LP, Bu L, et al. IgA nephropathy presenting as macroscopic hematuria in 2 pediatric patients after receiving the Pfizer COVID-19 vaccine. *Kidney Int.* 2021;100(3):705–706. doi:10.1016/j.kint.2021.06.032
27. Timmermans SA, Busch MH, Abdul-Hamid MA, Frenken LAM, Aarnoudse AJ, van Paassen P. Primary podocytopathies after COVID-19 vaccination. *Kidney Int Rep.* 2022;7(4):892–894. doi:10.1016/j.ekir.2021.12.023
28. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform.* 2019;95:103208. doi:10.1016/j.jbi.2019.103208
29. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–381. doi:10.1016/j.jbi.2008.08.010
30. Inker LA, Eneanya ND, Coresh J, et al. Chronic kidney disease epidemiology C: new creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med.* 2021;385(19):1737–1749. doi:10.1056/NEJMoa2102953
31. Kronbichler A, Jung SY, Kim MS, Shin JI. Distinct glomerular disease association after vaccination with BNT162b2 and mRNA-1273: a VigiBase analysis. *Kidney Int.* 2022;101(2):415–416. doi:10.1016/j.kint.2021.11.013
32. Niel O, Florescu C. IgA nephropathy presenting as rapidly progressive glomerulonephritis following first dose of COVID-19 vaccine. *Pediatr Nephrol (Berlin, Germany).* 2022;37(2):461–462. doi:10.1007/s00467-021-05351-x
33. Ota K, Yonekura Y, Saigan M, Goto K, Nishi S. Comparison of renal histopathology in three patients with gross hematuria after SARS-CoV-2 vaccination [published online ahead of print]. *CEN Case Rep.* 2022:1–8. doi:10.1007/s13730-022-00743-w
34. Jongvilaikasem P, Rianthavorn P. Minimal change disease and acute interstitial nephritis following SARS-CoV-2 BNT162b2 vaccination. *Pediatr Nephrol (Berlin, Germany).* 2022;37(6):1419–1421. doi:10.1007/s00467-022-05470-z
35. Nakazawa E, Uchimura T, Hirai Y, et al. New-onset pediatric nephrotic syndrome following Pfizer-BioNTech SARS-CoV-2 vaccination: a case report and literature review. *CEN Case Rep.* 2022;11(2):242–246. doi:10.1007/s13730-021-00656-0
36. Klomjit N, Alexander MP, Fervenza FC, et al. COVID-19 vaccination and glomerulonephritis. *Kidney Int Rep.* 2021;6(12):2969–2978. doi:10.1016/j.ekir.2021.09.008
37. Da Y, Goh GH, Khatri P. A case of membranous nephropathy following Pfizer-BioNTech mRNA vaccination against COVID-19. *Kidney Int.* 2021;100(4):938–939. doi:10.1016/j.kint.2021.07.016
38. Burbelo PD, Joshi M, Chaturvedi A, et al. Detection of PLA2R autoantibodies before the diagnosis of membranous nephropathy. *J Am Soc Nephrol.* 2020;31(1):208–217. doi:10.1681/ASN.2019050538
39. de la Flor J, Linares T, Alonso-Riaño M, et al. A case of acute interstitial nephritis following the Pfizer-BioNTech COVID-19 vaccine [in Spanish]. *Nefrologia (Engl Ed).* 2021;42(5):617–620. doi:10.1016/j.nefro.2021.05.004
40. Dheir H, Sipahi S, Cakar GC, Yaylaci S, Hacibekiroglu T, Karabay O. Acute tubulointerstitial nephritis after COVID-19 m-RNA BNT162b2 vaccine. *Eur Rev Med Pharmacol Sci.* 2021;25(20):6171–6173. doi:10.26355/eurrev_202110_26985
41. Tan FS, Kabir ME, Bhandari S. Acute interstitial nephritis after COVID-19 vaccination. *BMJ Case Rep.* 2022;15(5):e246841. doi:10.1136/bcr-2021-246841
42. Liew SK, Nair B, So B, Ponnusamy A, Bow A, Woywodt A. Acute interstitial nephritis following SARS-CoV-2 virus vaccination. *Clin Nephrol.* 2022;97(4):242–245. doi:10.5414/cn110753
43. Bellavite P. Causality assessment of adverse events following immunization: the problem of multifactorial pathology. *F1000Res.* 2020;9:170. doi:10.12688/f1000research.22600.2
44. Shimonovich M, Pearce A, Thomson H, Keyes K, Katikireddi SV. Assessing causality in epidemiology: revisiting Bradford Hill to incorporate developments in causal thinking. *Eur J Epidemiol.* 2021;36(9):873–887. doi:10.1007/s10654-020-00703-7
45. Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". *Clin Immunol.* 2021;224:108665. doi:10.1016/j.clim.2021.108665
46. Chen Y, Xu Z, Wang P, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. *Immunology.* 2022;165(4):386–401. doi:10.1111/imm.13443
47. Rodríguez Y, Rojas M, Beltrán S, et al. Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. *J Autoimmun.* 2022;132:102898. doi:10.1016/j.jaut.2022.102898
48. Waldman M, Soler MJ, García-Carro C, et al. COVID-19 in patients with glomerular disease: follow-up results from the IRoc-GN international registry. *Kidney360.* 2022;3(2):293–306. doi:10.34067/KID.0006612021
49. Waldman M, Soler MJ, García-Carro C, et al. Results from the IRoc-GN international registry of patients with COVID-19 and glomerular disease suggest close monitoring. *Kidney Int.* 2021;99(1):227–237. doi:10.1016/j.kint.2020.10.032
50. Diebold M, Locher E, Boide P, et al. Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased. *Kidney Int.* 2022;102(6):1409–1419. doi:10.1016/j.kint.2022.08.021

Received: October 27, 2022 **Accepted:** December 9, 2022

See related editorial, "New Onset Glomerular Disease Post–COVID-19 Vaccination: Is There a Link?" on pages 294-296.

AFFILIATIONS

[1]Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland
[2]Biostatistics and Clinical Epidemiology Service, National Institutes of Health Clinical Center, Bethesda, Maryland
[3]University of Illinois at Chicago/Advocate Christ Medical Center, Oak Lawn, Illinois
[4]Center for Renal and Urological Pathology, Chennai, Tamil Nadu, India
[5]Division of Kidney Diseases and Hypertension, Glomerular Center at Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Great Neck, New York
[6]Division of Nephrology and Hypertension, Department of Medicine, Oregon Health & Science University, Portland, Oregon
[7]Department of Pathology and Laboratory Medicine, University of California Los Angeles, Los Angeles, California
[8]The Kidney and Transplant Practice, Mount Elizabeth Novena Hospital, Singapore
[9]Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin
[10]Division of Nephrology, Medical College of Wisconsin, Milwaukee, Wisconsin
[11]Department of Nephrology and Hypertension, Barzilai University Medical Center, Ashkelon, Israel
[12]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheba, Israel
[13]Department of Nephrology, John Hunter Hospital, New Lambton Heights, New South Wales, Australia
[14]School of Medicine and Public Health, The University of Newcastle, Callaghan,New South Wales, Australia
[15]Department of Nephrology, General University Hospital of Heraklion, Crete, Greece
[16]Department of Nephrology, University of Crete, Greece
[17]Department of Pathology, Hellenic and Kapodistrian University of Athens, Greece
[18]Exeter Kidney Unit, Royal Devon University Healthcare NHS Foundation Trust, United Kingdom
[19]Department of Pediatrics, Pediatric Nephrology, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, Arkansas
[20]Clinic of Nephrology and Renal Transplantation, NKUA, Medical School, Laiko General Hospital, Athens, Greece
[21]Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York
[22]Department of Nephrology, Northern Beaches Hospital, Frenchs Forest, New South Wales, Australia
[23]Faculty of Medicine, Health and Human Sciences, Macquarie University, New South Wales, Australia
[24]Department of Nephrology, Centro Medico ISSEMYM Toluca, Mexico
[25]Division of Nephrology and Hypertension, University of South Florida, Tampa, Florida
[26]Renal Service, H. Lee Moffitt Cancer Center, Tampa, Florida
[27]Division of Nephrology, University of South Florida, Morsani College of Medicine
[28]Department of Nephrology, David Grant Medical Center, Travis Air Force Base, California
[29]Department of Pathology, University of California San Francisco, San Francisco, California
[30]Division of Pediatric Nephrology, Peyton Manning Children's Hospital, Indianapolis, Indiana
[31]Division of Nephrology, Rush University Medical Center, Chicago, Illinois
[32]Department of Pathology, Manipal Hospital, Bengaluru, India
[33]Department of Nephrology, Instituto Nacional de Ciencas Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico
[34]Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico
[35]Division of Nephrology, Department of Medicine, Lehigh Valley Health Network, Allentown, Pennsylvania
[36]Department of Nephrology; Hospital Juárez de México, Mexico City, Mexico
[37]Capital and Coast District Health Board, New Zealand
[38]Department of Nephrology, Ochsner Health, New Orleans, Louisiana
[39]Ochsner Clinical School, The University of Queensland, Brisbane, Queensland, Australia
[40]Faculty of Medicine, Tanta University, Tanta, Egypt
[41]Rochester General Hospital, Rochester, New York
[42]Helsinki University Central Hospital, Helsinki, Finland
[43]Department of Internal Medicine, Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut
[44]Internal Medicine Department, Nuevo Hospital Civil De Guadalajara Dr. Juan I Menchaca, Guadalajara, Mexico; Department of Clinical Medicine, University Center for Health Science, University of Guadalajara
[45]Division of Nephrology, Zonguldak Ataturk State Hospital, Zonguldak, Turkey
[46]Department of Nephrology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
[47]Faculty of Medicine, Cadi Ayyad University, Marrakech, Morocco
[48]Polyclinic, Seattle, Washington
[49]Duly Health and Care, Winfield, Illinois
[50]Division of Nephrology, Department of Medicine, University of California, Los Angeles, California
[51]Division of Nephrology, Department of Medicine, University of Utah, Salt Lake City, Utah
[52]Southern Colorado Nephrology Associates, Pueblo, Colorado
[53]Freeman Health System, Joplin, Missouri
[54]Arkana Laboratories, Little Rock, Arkansas