Supplementary Material

Supplementary Methods

Estimating the 30-day rate of disease relapse throughout follow-up

In our Cox regression model, COVID-19 vaccine exposure was considered as a time-dependent variable where a patient was considered exposed to the vaccine for 30 days after the vaccination date. As such, an individual could be at an altered risk of glomerular disease relapse attributable to the vaccine for a maximum of 30 days after each dose of vaccine. Based on this Cox regression model, we can derive at any given day (t_1) during the follow-up period, the relapse risk in the next 30 days in the following three scenarios, conditional on no relapse prior to time t_1:

(i) Scenario 1. Patient unexposed to vaccine up to time t_1 as well as in the next 30 days, i.e., unexposed from time t_1 to t_1+30

(ii) Scenario 2. Patient received the 1st dose of vaccine at t_1 and did not receive the 2nd dose within 30 days, therefore, was exposed to the 1st dose from time t_1 to t_1+30

(iii) Scenario 3. Patient received the 2nd dose of vaccine at t_1 and did not receive the 1st dose within 30 days prior and nor the 3rd dose within 30 days after, therefore, was exposed to the 2nd dose from time t_1 to t_1+30.

At time t_1, the difference in the 30-day relapse risk was calculated comparing the risk if the patient was exposed to the 1st dose of vaccine compared to remaining unexposed, and comparing the risk if the patient was exposed to the 2nd/3rd dose of vaccine compared to remaining unexposed. The calculations are as follows:

Absolute risk difference for scenario 2 vs scenario 1

$$= \left[\frac{S_0(t_1) - S(t_1+30|X_{t<t_1}=0,\ X_{t\geq t_1}=1,\ \beta_1)}{S_0(t_1)}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \left[\frac{e^{-\int_0^{t_1} h_0(s)ds} - e^{-\int_0^{t_1} h_0(s)ds - e^{\beta_1}\int_{t_1}^{t_1+30} h_0(s)ds}}{e^{-\int_0^{t_1} h_0(s)ds}}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \left[\frac{S_0(t_1) - S_0(t_1)e^{\left[\int_0^{t_1+30} h_0(s)ds - \int_0^{t_1} h_0(s)ds\right]e^{\beta_1}}}{S_0(t_1)}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \left[\frac{S_0(t_1) - S_0(t_1)\left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{e^{\beta_1}}}{S_0(t_1)}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= 1 - \left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{HR_1} - \left[1 - \frac{S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \frac{S_0(t_1+30)}{S_0(t_1)} - \left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{HR_1}, \qquad \text{…eq.1}$$

where $X_{t<t_1}$ is the exposure status to the 1st dose up to time t_1, $h_0(t)$ and $S_0(t)$ are the glomerular disease type specific hazard and survival function, respectively, if a patient was never exposed to a COVID-19 vaccine, and β_1 and HR_1 are the coefficient and hazard ratio, respectively, associated with exposure to the 1st dose of vaccine that were estimated from the extended Cox proportional hazards regression model in Table 3 stratified on type of glomerular disease and without interaction between disease and vaccine exposure.

Absolute risk difference for scenario 3 vs scenario 1

$$\left[\frac{S_1(t_1) - S(t_1+30|Z_{t<t_1}=0,\ Z_{t\geq t_1}=1,\ \beta_2)}{S_1(t_1)}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \left[\frac{S_1(t_1) - S_1(t_1)\left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{e^{\beta_2}}}{S_1(t_1)}\right] - \left[\frac{S_0(t_1)-S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= 1 - \left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{HR_2} - \left[1 - \frac{S_0(t_1+30)}{S_0(t_1)}\right]$$

$$= \frac{S_0(t_1+30)}{S_0(t_1)} - \left[\frac{S_0(t_1+30)}{S_0(t_1)}\right]^{HR_2}, \qquad \text{…eq.2}$$

where $Z_{t<t_1}$ is the exposure status to the 2nd dose, $S_1(t_1) = S_0(l)\left[\frac{S_0(l+30)}{S_0(l)}\right]^{e^{\beta_1}} \frac{S_0(t_1)}{S_0(l+30)}$ is the survival function for a patient who received the first dose at time l, $0 < l < t_1 - 30$. and β_2 and HR_2 are the coefficient and hazard ratio, respectively, associated with exposure to the 2nd/3rd dose of vaccine that were also estimated from the same model as above.

The above calculations were carried out for all days (t_1) during the follow-up period between day 43 (the first day a 2nd dose of vaccine was administered in the cohort) and day 210 (30 days after the median time to the 2nd dose of vaccine administration in the cohort from Table 1). The absolute risk difference was plotted against time using LOESS to generate a smoothed curve.

Self-controlled case series

To further interrogate the potential for confounding in the primary analysis (extended Cox regression model with vaccination as a time-varying exposure), we conducted a self-controlled case series (SCCS). The SCCS is an alternative method to estimate the risk of an outcome event from a transient exposure, and has been previously used to estimate the incidence of adverse events following vaccination[1]. As opposed to a cohort design where comparison of the outcome event is made between individuals (exposed versus unexposed), estimation of incidence in the SCCS is made only within individuals who experienced the outcome. Patient-level characteristics that remain constant over the observation period are therefore implicitly accounted for, with the result that the SCCS effectively removes all time-invariant confounding (measured and unmeasured)[2].

In the SCCS design, the analysis is conducted in the subgroup of patients who experienced a relapse. Each patient who experienced a relapse is followed from the index date until the end of the observation period (i.e. they are not censored at the time of disease relapse). Their observation time is divided into "exposed" time (a 30-day exposure window after each vaccine dose they receive) and "unexposed" time (all other times). Using a Poisson model, the rate of relapse in exposed person-time is compared to the rate of relapse in unexposed-person time to generate a rate ratio and associated 95% confidence interval. The SCCS Poisson model included a variable for calendar time intervals to account for changing background rate of relapse over time, as is typical in SCCS analyses[3]. The advantage of the SCCS is that by comparing risk within individuals, it effectively accounts for all measured and unmeasured time-invariant confounding. A disadvantage of the method is that it is conducted in a much smaller subgroup of patients who experienced a relapse, compared to the extended Cox regression analysis which is conducted in a much larger cohort that includes all patients and was therefore considered a priori as the primary analysis to assess a rare outcome event such as vaccine-induced relapse events.

Supplementary Table 1: Definitions used to ascertain a recent disease relapse at the index date.

Baseline laboratory value was the closest that preceded the index date. The window period used to define minimum or maximum values was 12 months prior to the index date. Definitions were chosen to be consistent with KDIGO guidelines on glomerular diseases and existing clinical trials[4, 5]. The index date was December 14th, 2020. eGFR, estimated glomerular filtration rate. ANCA-GN: ANCA-vasculitis associated glomerular disease. MMF, mycophenolate mofetil. N/a, not applicable.

Disease type	Kidney function-based definition	Proteinuria-based definition	Drug exposure-based definition
Focal segmental glomerulosclerosis	n/a	(i) Baseline value >3.5g/day	(i) On prednisone >10mg/day on index date (ii) On any other immunosuppressive medication newly initiated within 6 months prior to the index date
Membranous nephropathy	n/a	(i) Baseline value >3.5g/day	(i) On prednisone >10mg/day on index date (ii) On any other immunosuppressive medication newly initiated within 6 months prior to the index date
Minimal change disease	n/a	(i) Baseline value >3.5g/day	(i) On prednisone >10mg/day on index date (ii) On any other immunosuppressive medication newly initiated within 6 months prior to the index date
IgA nephropathy	(i) Baseline eGFR >25% lower than maximum value, and (ii) Baseline eGFR <90ml/min/1.73m^2	(i) Baseline value >50% higher than minimum value, and (ii) Baseline value >0.5g/day	(i) On prednisone at any dose on index date (ii) On cyclophosphamide within 2 months prior to index date (iii) On any other immunosuppressive medication newly initiated within 6 months prior to the index date
Lupus nephritis	(i) Baseline eGFR >25% lower than maximum value, and (ii) Baseline eGFR <90ml/min/1.73m^2	(i) Baseline value >50% higher than minimum value, and (ii) Baseline value >0.5g/day	(i) On prednisone >10mg/day on index date, or (ii) On cyclophosphamide within 2 months prior to index date, or (iii) On MMF >2g/day on index date
ANCA-GN	(i) Baseline eGFR >25% lower than maximum value, and (ii) Baseline eGFR <90ml/min/1.73m^2	(i) Baseline value >50% higher than minimum value, and (ii) Baseline value >0.5g/day	(i) On prednisone >10mg/day on index date, or (ii) On cyclophosphamide within 2 months prior to index date, or (iii) ≥3 doses of rituximab of any amount received within 3 months prior to the index date; or at least one dose of rituximab >500mg within 3 months prior to the index date
C3 glomerulonephritis	(i) Baseline eGFR >25% lower than maximum value, and (ii) Baseline eGFR <90ml/min/1.73m^2	(i) Baseline value >50% higher than minimum value, and (ii) Baseline value >0.5g/day	(i) On prednisone at any dose on index date (ii) On cyclophosphamide within 2 months prior to index date (iii) On any other immunosuppressive medication newly initiated within 6 months prior to the index date

Supplementary Table 2: Definitions used to ascertain disease relapse after the index date to generate the primary outcome.

Baseline laboratory value was the closest that preceded the index date. The index date was December 14th, 2020. Acute dialysis was that used for acute kidney injury, not dialysis started for end-stage kidney disease. Definitions were chosen to be consistent with KDIGO guidelines on glomerular diseases and acute kidney injury, and existing clinical trials[4-6]. ANCA-GN: ANCA-vasculitis associated glomerular disease. N/a, not applicable.

Disease type	Kidney function-based definition	Proteinuria-based definition
Focal segmental glomerulosclerosis	n/a	(i) Value >50% higher than baseline value, and (ii) Value >3.5g/day
Membranous nephropathy	n/a	(i) Value >50% higher than baseline value, and (ii) Value >3.5g/day
Minimal change disease	n/a	(i) Value >50% higher than baseline value, and (ii) Value >3.5g/day
IgA nephropathy	(i) Creatinine >1.5x higher than baseline value, or (ii) Acute dialysis	(i) Value >50% higher than baseline value, and (ii) Value >1.0g/day
Lupus nephritis	(i) Creatinine >1.5x higher than baseline value, or (ii) Acute dialysis	(i) Value >50% higher than baseline value, and (ii) Value >0.5g/day
ANCA-GN	(i) Creatinine >1.5x higher than baseline value, or (ii) Acute dialysis	(i) Value >50% higher than baseline value, and (ii) Value >0.5g/day
C3 glomerulonephritis	(i) Creatinine >1.5x higher than baseline value, or (ii) Acute dialysis	(i) Value >50% higher than baseline value, and (ii) Value >1.0g/day

Supplementary Table 3: Patient characteristics on the index date associated with the occurrence of glomerular disease relapse during the follow-up period based on the primary outcome definition.

Data reported as count (frequency) or median (interquartile range). FSGS, focal segmental glomerulosclerosis; ANCA-GN, ANCA-vasculitis associated glomerular disease; eGFR, estimated glomerular filtration rate. *Intravenous cyclophosphamide and rituximab use includes administration within 6 months prior to index date. **Based on applying the criteria from Supplementary Table 1 on December 14th, 2019 (one year prior to the index date), which use a one-year prior window period from December 14th, 2018 to December 14th, 2019 to ascertain worsening disease activity. Note that inclusion criteria for this analysis were based on the criteria in Supplementary Table 1 to exclude patients with worsening disease activity in the one-year period prior to the index date.

Characteristics	Did not experience disease relapse	Experienced disease relapse	P-value
Number of patients	971	134	
Age (years)	60.3 (46.6, 70,8)	58.2 (46.7, 66.5)	0.12
Female sex	502 (52%)	81 (60%)	0.06
eGFR(ml/min/1.73m^2)	51.0 (32.0, 78.0)	50.5 (32.0, 79.0)	0.99
Glomerular disease type:			0.002
IgA nephropathy	256 (26%)	45 (34%)	
Minimal change disease	75 (8%)	7 (5%)	
FSGS	220 (23%)	19 (14%)	
Membranous nephropathy	164 (17%)	18 (13%)	
ANCA-GN	140 (14%)	14 (10%)	
Lupus nephritis	112 (12%)	30 (22%)	
Proteinuria (g/day)	0.3 (0.1, 1.0)	0.6 (0.3, 1.7)	<0.01
Albumin (g/L)	42.0 (40.0, 44.0)	41.0 (39.0, 43.0)	<0.01
Immunosuppression use:			
Any (n, %)	276 (28%)	52 (39%)	0.01
Mycophenolate mofetil or azathioprine	163 (17%)	31 (23%)	0.07
Tacrolimus or cyclosporine	86 (9%)	23 (17%)	<0.01
Cyclophosphamide*	9 (1%)	1 (1%)	0.99
Prednisone	95 (10%)	16 (12%)	0.44
Rituximab*	26 (3%)	2 (1%)	0.57
Time from biopsy to index date (years)	5.2 (2.5, 10.9)	5.7 (2.9, 10.9)	0.34
Worsening disease activity between 1-2 years prior to index date**	43 (4%)	15 (11%)	<0.01

Supplementary Table 4: The relative hazard of disease flare that is associated with COVID-19 vaccine exposure using the primary outcome and a 45-day window period after vaccine administration to define exposure status.

Vaccine exposure was modeled as a time-varying variable with exposure continuing until 45 days after vaccine administration. All models were stratified on glomerular disease (GN) type, and exclude 5 patients with C3 glomerulonephritis because of too few patients to allow stratification.

Exposure	Type of GN	Hazard Ratio (95% Confidence Interval)	P-value
Any vaccine exposure	All GN	1.11 (0.69, 1.79)	0.66
Dose of vaccine	All GN		
	1st dose	0.73 (0.39, 1.35)	0.32
	2nd or 3rd dose	2.18 (1.09, 4.37)	0.03

Supplementary Table 5: The relative hazard of disease flare that is associated with COVID-19 vaccine exposure using the secondary outcome.

Vaccine exposure was modelled as a time-varying variable with exposure continuing until 30 days after vaccine administration. All models were stratified on glomerular disease (GN) type, and exclude 5 patients with C3 glomerulonephritis because of too few patients to allow stratification.

Exposure	Type of GN	Hazard Ratio (95% Confidence Interval)	P-value
Any vaccine exposure	All GN	1.38 (0.79, 2.44)	0.26
Dose of vaccine	All GN		
	1^{st} dose	0.85 (0.39, 1.88)	0.69
	2^{nd} or 3^{rd} dose	2.72 (1.20, 6.18)	0.02

Supplementary Table 6: The relative hazard of disease flare that is associated with COVID-19 vaccine exposure among patients who received at least one vaccine dose during follow-up (n=1011).

Vaccine exposure was modelled as a time-varying variable with exposure continuing until 30 days after vaccine administration. All models were stratified on glomerular disease (GN) type, and exclude 5 patients with C3 glomerulonephritis because of too few patients to allow stratification.

Exposure	Type of GN	Hazard Ratio (95% Confidence Interval)	P-value
Any vaccine exposure	All GN	1.05 (0.62, 1.76)	0.86
Dose of vaccine	All GN		
	1st dose	0.65 (0.32, 1.32)	0.23
	2nd or 3rd dose	2.25 (1.04, 4.88)	0.04

Supplementary Table 7: The relative hazard of disease flare that is associated with COVID-19 vaccine exposure among patients who received at least two vaccine doses during follow-up (n=982).

Vaccine exposure was modelled as a time-varying variable with exposure continuing until 30 days after vaccine administration. All models were stratified on glomerular disease (GN) type, and exclude 5 patients with C3 glomerulonephritis because of too few patients to allow stratification.

Exposure	Type of GN	Hazard Ratio (95% Confidence Interval)	P-value
Any vaccine exposure	All GN	0.99 (0.58, 1.67)	0.95
Dose of vaccine	All GN		
	1st dose	0.58 (0.28, 1.22)	0.15
	2nd or 3rd dose	2.18 (1.0, 4.74)	0.05

Supplementary Table 8. Comparison of results from the primary analysis (extended Cox regression model) and a self-controlled case series (SCCS).

	Hazard ratio (95% CI) from Cox regression model	**Rate ratio (95% CI) from SCCS**
Any vaccine exposure	1.08 (0.65, 1.80)	1.09 (0.66, 1.78)
Vaccine #1 vs unexposed	0.67 (0.33, 1.36)	0.73 (0.37, 1.43)
Vaccine #2/3 vs unexposed	2.23 (1.06, 4.71)	1.92 (0.94, 3.90)

References

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