Kidney360

COVID-19 in Patients with Glomerular Disease: Follow-Up Results from the IRoc-GN International Registry

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Key Points

- Mortality and incidence of AKI do not differ between coronavirus disease 2019 (COVID-19) patients with or without glomerular diseases.
- The main predictor of AKI is pre-COVID-19 eGFR, independent of the presence of GN.
- Incomplete kidney function recovery after COVID-19-associated AKI is more common in GN patients than in controls.

Abstract

Background The acute and long-term effects of severe acute respiratory syndrome coronavirus 2 infection in individuals with GN are still unclear. To address this relevant issue, we created the International Registry of COVID-19 infection in GN.

Methods We collected serial information on kidney-related and -unrelated outcomes from 125 GN patients (63 hospitalized and 62 outpatients) and 83 non-GN hospitalized patients with coronavirus disease 2019 (COVID-19) and a median follow-up period of 6.4 (interquartile range 2.3–9.6) months after diagnosis. We used logistic regression for the analyses of clinical outcomes and linear mixed models for the longitudinal analyses of eGFR. All multiple regression models were adjusted for age, sex, ethnicity, and renin-angiotensin-aldosterone system inhibitor use.

Results After adjustment for pre-COVID-19 eGFR and other confounders, mortality and AKI did not differ between GN patients and controls (adjusted odds ratio for AKI=1.28; 95% confidence interval [CI], 0.46 to 3.60; P=0.64). The main predictor of AKI was pre-COVID-19 eGFR (adjusted odds ratio per 1 SD unit decrease in eGFR=3.04; 95% CI, 1.76 to 5.28; P<0.001). GN patients developing AKI were less likely to recover pre-COVID-19 eGFR compared with controls (adjusted 6-month post-COVID-19 eGFR=0.41; 95% CI, 0.25 to 0.56; times pre-COVID-19 eGFR). Shorter duration of GN diagnosis, higher pre-COVID-19 proteinuria, and diagnosis of focal segmental glomerulosclerosis or minimal change disease were associated with a lower post-COVID-19 eGFR.

Conclusions Pre-COVID-19 eGFR is the main risk factor for AKI regardless of GN diagnosis. However, GN patients are at higher risk of impaired eGFR recovery after COVID-19-associated AKI. These patients (especially those with high baseline proteinuria or a diagnosis of focal segmental glomerulosclerosis or minimal change disease) should be closely monitored not only during the acute phases of COVID-19 but also after its resolution.

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Introduction

The International Registry of COVID-19 infection in GN (IRoc-GN) was created shortly after the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic in March 2020 by the World Health Organization. The purpose of the registry was to examine the short- and long-term effect of

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coronavirus disease 2019 (COVID-19) in patients with underlying GN and identify risk factors for unfavorable outcomes.

Our initial report comparing 40 GN patients and 80 controls with SARS-CoV2 infection showed that the GN cohort had higher overall rates of mortality (15% versus 5%, respectively) and AKI (39% versus 14%, respectively) (1). Immunosuppressive therapy at presentation was not associated with greater mortality or AKI in the GN cohort, but more pronounced hypoalbuminemia at presentation and shorter duration of glomerular disease were associated with greater risk of AKI and need for kidney replacement therapy (KRT) in GN patients.

Enrollment of new patients in the IRoc-GN registry and collection of longitudinal data continued throughout the pandemic. Herein, we present the results of our follow-up study that was aimed to extend the findings of our initial report, describe the spectrum of COVID-19 in a larger GN cohort, and explore the interactions of underlying GN, immunosuppressive medications, and other determinants on susceptibility and outcomes of COVID-19 (AKI, need for KRT, or death). In addition, we aimed to characterize kidney recovery after COVID-19-associated AKI in GN patients and the longer-term consequences of COVID-19 on kidney prognosis.

Methods

Study Design and Participants

Details of this registry have been previously described (1). We used data collected from April 20, 2020, to April 20, 2021, *via* a secure public survey (https://redcapsurvey.niddk.nih.gov/surveys/?s=FPM87NK7T4) on REDCap (Research Electronic Data Capture) (2).

Briefly, we included patients with biopsy-proven GN diagnosed with COVID-19 managed as inpatients or outpatients from centers participating in the IRoc-GN registry. For each GN patient entered in the registry, reporters were asked to enter at least one age- and sex-matched control patient who was positive for SARS-CoV-2 but without GN and with an eGFR of >60 ml/min per 1.73 m^2. Controls were hospitalized within ±2 weeks of the GN patients to account for changes in treatment strategies over time that may influence outcomes. Patients on maintenance hemodialysis before infection and kidney transplant recipients were excluded.

Data Collection

The initial survey collected data on pre-COVID-19 renal parameters, glomerular disease diagnosis, immunosuppressive medications, COVID-19-related symptoms, COVID-19-directed therapies, management of immunosuppression during infection, outcomes, the maximum level of care, nonrenal complications, AKI, need for KRT, disposition (*i.e.*, recovery or death), and laboratory parameters. Links to follow-up surveys were automatically generated and sent by REDCap at predefined intervals (8 weeks) to collect longitudinal data on patient status and kidney outcomes after infection. With this combination of surveys, renal parameters were collected at various time points: (*1*) pre COVID-19 (latest available before infection onset), (*2*) at COVID-19 presentation, (*3*) peak, (*4*) post COVID-19 as defined by the absence of or marked improvement in original COVID-19-related symptoms or signs, and (*5*) during extended follow-up after recovery from acute infection. All data were checked for quality by three physicians (M.W., P.C., and U.M.).

Statistical Analyses

We compared baseline differences between groups in continuous variables using the Kruskal–Wallis test for three-group equality testing and the Mann–Whitney test for pairwise testing. We compared baseline differences between groups in categorical variables using Fisher's exact test. We used Wilcoxon matched-pairs signed-rank test to compare crude paired continuous measurements over follow-up.

We used logistic regression to examine the association between glomerular disease status (indicator variable for patients with history of glomerular disease) and the clinical outcomes of AKI, KRT, and death (primary end points). This analysis was limited to hospitalized patients (*i.e.*, glomerular disease patients versus controls). We calculated crude odds ratios (OR), OR adjusted for pre-COVID-19 eGFR, and OR additionally adjusted for demographic characteristics (age, continuous variable; men, indicator variable for men; ethnicity, indicator variable for non-White ethnicity), and renin-angiotensin-aldosterone system inhibitor (RAASi) use (indicator variable for their use). We deemed that RAASi use is a potential confounder because it had different distribution between patients with glomerular disease and controls (and within glomerular disease patients, between patients with different disease severity), and may also be associated with increased risk of AKI and KRT. Models that additionally adjusted for diabetes, obesity, and hypertension provided similar results. However, to avoid having to report several regression models that included more variables than the data could support, we did not report them in the final results.

The analysis of recovery of kidney function was based on the multiple regression models examining the effect of each variable on post-COVID-19 eGFR analyzed as longitudinal (repeated measures) continuous variable. Because the longitudinal eGFR measurements were unbalanced between patients, and because there was inconsistency among subjects in timing of the eGFR assessment, we examined longitudinal eGFR using random effects regression models estimated *via* restricted maximum likelihood. These models estimated eGFR as a linear change over time, which provided a good fit to the data points (Supplemental Figures 1 and 2).

We performed all of the analyses using Stata v17 (StataCorp, College Station, TX). The Stata code for all of the analyses is freely available at https://github.com/UMaggiore/iROC-GN.

A two-sided P value of <0.05 was regarded as statistically significant. Unless otherwise stated, we reported nominal P values without adjustment for multiple testing.

Further details on statistical analyses are included in the Supplemental Methods.

Results

Study Population

The study population included 125 patients with a history of GN diagnosed with COVID-19 (63 requiring hospitalization

Table 1. Baseline characteristics of the study population

	Study Group									
	Control Hospitalized (*N*=83)			Glomerular Neuropathy Hospitalized (*N*=63)			Glomerular Neuropathy Outpatients (*N*=62)			*P* Value
Age, yr	80	60.0	14.4	60	62.4	15.9	60	45.4	12.9	<0.001[b,c]
Women		29	35%		28	44%		36	58%	0.02[b]
Race										
White		59	71%		38	60%		28	45%	0.05[b]
Black		5	6%		3	5%		4	7%	
Asian		0	0%		3	5%		3	5%	
Other		18	22%		19	30%		27	44%	
Unknown		1	1%		0	0%		0	0%	
Ethnicity										
Hispanic/Latino		20	24%		19	31%		26	42%	0.03[b]
BMI, kg/m^2	68	30.2	7.4	50	27.6	4.9	53	27.2	5.6	0.06
Comorbidities										
Hypertension		45	54%		43	68%		29	47%	0.05[c]
Diabetes		23	28%		14	22%		5	8%	0.009[b,c]
Cardiovascular disease		16	19%		12	19%		4	7%	0.06
Asthma		6	7%		3	5%		1	2%	0.34
COPD		4	5%		7	11%		2	3%	0.23
Liver disease		4	5%		3	5%		1	2%	0.66
Cancer[d]		4	5%		7	11%		0	0%	0.02[c]
HIV/AIDS		0	0%		0	0%		1	2%	0.3
Rheumatoid arthritis		0	0%		3	5%		0	0%	0.05
Smoking habit		5	6%		1	2%		1	2%	0.3
Use of RAASi		3	4%		17	27%		22	36%	<0.001[a,b,c]
Clinical presentation										
Fever		66	80%		46	73%		31	50%	0.001[b,c]
Dyspnea		53	64%		34	54%		8	13%	<0.001[b,c]
Cough		27	33%		32	51%		28	45%	0.07
GI symptoms		26	31%		13	21%		11	18%	0.14
Anosmia		15	18%		4	6%		12	19%	0.06
Fatigue		8	10%		19	30%		24	39%	<0.001[a,b]
Myalgia		8	10%		14	22%		20	32%	0.003[b]
Anorexia		4	5%		12	19%		7	11%	0.02[a]
Chills		4	5%		9	14%		5	8%	0.12
Sore throat		3	4%		2	3%		8	13%	0.05
Nasal congestion		2	2%		3	5%		8	13%	0.04[b]
Neurologic symptoms		0	0.0%		1	2%		0	0%	0.6

Table 1. (Continued)

	Study Group								
	Control Hospitalized (N=83)			Glomerular Neuropathy Hospitalized (N=63)			Glomerular Neuropathy Outpatients (N=62)		P Value
Pre-COVID-19 kidney parameters									
sCr, mg/dl	74	1.1	0.9	62	1.8	1.7	62	1.5	1.6	<0.001[a,c]
eGFR, ml/min per 1.73 m^2	71	80.0	25.8	59	52.9	28.7	60	73.0	31.0	<0.001[a,c]
Serum albumin, g/dl	42	3.9	0.6	55	3.7	0.6	59	4.1	0.7	0.002[a,c]
Proteinuria, g/d	13	0.1	0.3	52	2.6	3.9	56	1.4	2.3	<0.001[a,b,c]
Kidney parameters at presentation/ admission									
sCr, mg/dl	80	1.5	2.0	56	2.7	2.8	30	1.5	1.3	<0.001[a,c]
eGFR, ml/min per 1.73 m^2	77	76.2	32.0	53	46.1	32.4	30	72.0	35.8	<0.001[a,c]
Laboratory parameters during COVID-19									
Serum albumin, g/dl	64	3.5	0.8	47	3.0	0.9	24	4.0	0.6	<0.001[a,b,c]
Proteinuria, g/d	5	0.1	0.3	14	5.1	6.3	11	0.3	0.4	0.001[a,c]
White blood cells, $n/\mu l$	43	8208.8	3581.1	52	8476.9	5274.4	38	6510.3	2341.6	0.12
Lymphocytes, $n/\mu l$	65	1126.5	1705.5	57	1730.9	2510.1	37	1533.4	1856.5	0.13
Neutrophils, $n/\mu l$	43	7105.1	6144.9	51	6496.2	3884.9	36	4726.6	2836.2	0.02[b,c]
Hemoglobin, g/dl	43	13.1	2.6	52	11.5	2.4	39	12.8	1.6	0.002[a,c]
Platelets, $n/\mu l$	43	248,720.9	132,425.1	52	230,230.8	105,626.2	39	243,820.5	72,710.6	0.57
Ferritin, ng/ml	64	1128.8	1527.2	38	927.2	840.4	23	260.1	231.6	<0.001[b,c]
CRP, mg/l	79	111.0	121.4	57	81.6	77.4	24	11.7	21.6	<0.001[b,c]
D-Dimer, ng/ml	70	1382.2	1984.5	41	1721.2	1787.0	11	613.7	731.4	0.010[b,c]

Continuous data are reported as number of nonmissing variables, mean (SD); categorical data are reported as number of nonmissing variables and percentages. Due to the distribution of serum creatinine, which, unlike eGFR, is highly skewed on the right, and due to missing values in eGFR, mean serum creatinine and mean eGFR may erroneously appear inconsistent with each other. For continuous data, P values refer to Kruskal–Wallis test for any difference between the three groups, and Mann–Whitney for pairwise two-sample comparisons, for categorical data, to Fisher's exact test. GN, history of glomerular disease; BMI, body mass index; sCr, serum creatinine; SLE, systemic lupus erythematosus; RAASi, renin-angiotensin-aldosterone system inhibitors; GI, gastrointestinal; COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

The test for pairwise differences between the groups are indicated by superscripts as follows:.

[a]P<0.05 Ctrl hospitalized versus GN hospitalized.

[b]P<0.05 Ctrl hospitalized versus GN outpatients.

[c]P<0.05 GN hospitalized versus GN outpatients.

[d]None of the patients with cancer were on active chemotherapy treatment.

Table 2. Baseline characteristics of glomerular neuropathy patients: diagnosis, treatment, and disease duration

	Admission Status				*P* Value
	Outpatients		Hospitalized		
SLE GN or vasculitis (systemic GN)	26	42%	26	41%	>0.99
Lupus nephritis	19	31%	11	18%	0.1
Vasculitis	7	11%	15	24%	0.1
IgA nephropathy	13	21%	5	8%	0.04
FSGS or MCD	11	18%	9	14%	0.63
Membranous nephropathy	8	13%	5	8%	0.4
Amyloidosis/fibrillary GN	2	3%	2	3%	>0.99
Thrombotic microangiopathy	1	2%	0	0%	0.5
Membranoproliferative GN	0	0%	4	6%	0.12
Post-infectious GN	0	0%	2	3%	0.5
Not specified	1	2%	10	16%	0.009
Immunosuppression at time of COVID-19	38	61%	35	56%	0.59
Prednisone	23	37%	23	37%	>0.99
Prednisone dose, mg/d		8.6 (7.4)		15.7 (22.0)	0.21
MMF	15	24%	11	18%	0.39
AZA	1	2%	4	6%	0.37
RTX	1	2%	11	18%	0.004
CNI	2	3%	15	24%	0.001
Therapy reduction/withdrawal during COVID-19[a]					
Prednisone	0	0%	1	4%	>0.99
MMF	3	20%	8	73%	0.007
AZA	0	0%	3	75%	0.24
CNI	1	50%	1	7%	0.47
Duration of GN disease					
1–6 mo	5	8%	13	27%	0.004
6–12 mo	0	0%	6	12%	
12–24 mo	9	15%	5	10%	
2–5 yr	17	28%	6	12%	
>5 yr	29	48%	19	39%	
Active GN disease at COVID-19 onset	5	8%	8	18%	0.23

Continuous data are reported as number of non-missing variables, mean (SD); categorical data are reported as number of nonmissing variables and percentages. Active GN disease was defined based on reporter assessment of patient's clinical and laboratory features. *P* values refer to Fisher's exact and to Cochran–Armitage test for trend (with exact *P* values) for GN disease. GN, history of glomerular disease; MCD, minimal change disease; SLE, systemic lupus erythematosus; MMF, mycophenolate mofetil; AZA, azathioprine; CNI, calcineurin inhibitor; RTX, rituximab.
[a]Out of patients on immunosuppression at time of COVID-19.

and 62 managed as outpatients) and 83 patients without GN who developed COVID-19 requiring hospitalization (Ctrl hospitalized). Baseline kidney function (pre-COVID-19 eGFR) was assessed at a median of 3.7 months (interquartile range 1.8–6.2 months) before infection. After COVID-19, the median follow-up of kidney function was 6.4 months (interquartile range 2.3–9.6).

The characteristics of the study population are reported in Table 1. Compared with Ctrl hospitalized patients, GN hospitalized patients had lower eGFR, serum albumin, and hemoglobin pre-COVID-19 and at time of admission (Table 1 and Supplemental Table 1). GN hospitalized patients also had lower eGFR, lower serum albumin, and higher proteinuria levels pre-COVID-19 and at COVID-19 diagnosis than GN outpatients (Table 1).

GN hospitalized patients and GN outpatients had similar distributions in the type of glomerular disease (Table 2). However, compared with GN outpatients, GN hospitalized patients were more likely to have received rituximab before COVID-19 diagnosis, to be on calcineurin inhibitors at the time of COVID-19, and to have a shorter duration of GN disease (<6 months; Table 2), whereas RAASi therapy was less common (Table 1). The percentage of patients with active GN disease at COVID-19 onset was similar between the two groups (Table 2). Tapering or withdrawal of immunosuppression during COVID-19 was uncommon and did not statistically differ between GN outpatients and GN hospitalized patients, with the exception of mycophenolate mofetil, which was more frequently reduced or discontinued in GN hospitalized patients (Table 2).

At disease presentation, GN outpatients had less severe inflammatory indexes compared with GN hospitalized patients (C-reactive protein, serum ferritin, and D-dimer levels), whereas the same characteristics were similar between GN hospitalized patients and Ctrl hospitalized patients (Table 1). The rates of in-hospital complications (*i.e.*, need for intubation or inotropes/vasopressors, superimposed bacterial infections, or thrombotic and cardiovascular complications) were similar between GN hospitalized patients and Ctrl hospitalized patients, but the duration of hospitalization was slightly longer in GN patients (mean 16.3 versus 14.4 days, respectively; $P=0.03$; Supplemental

Table 3. Association between presence of glomerular disease and clinical outcomes AKI, KRT, and death

	AKI			KRT			Death		
	Crude	eGFR Adjusted	Fully Adjusted	Crude	eGFR Adjusted	Fully Adjusted	Crude	eGFR Adjusted	Fully Adjusted
Preexisting GN	3.44[a]	1.62	1.28	1.43	0.68	0.60	1.80	0.90	0.80
	(1.58 to 7.47)	(0.66 to 4.00)	(0.46 to 3.60)	(0.49 to 4.22)	(0.19 to 2.36)	(0.15 to 2.38)	(0.67 to 4.83)	(0.29 to 2.79)	(0.23 to 2.81)
	0.002	0.29	0.64	0.51	0.54	0.46	0.24	0.85	0.73
Prior eGFR (per 1 SD unit decrease)		2.68[a]	3.04		2.31[b]	2.39[b]		2.21[a]	1.76
		(1.64 to 4.37)	(1.76 to 5.28)		(1.21 to 4.44)	(1.20 to 4.78)		(1.22 to 3.99)	(0.91 to 3.37)
		<0.001	<0.001		0.01	0.01		0.009	0.09
Age (per 1 SD unit increase)			0.84			0.90			2.33[b]
			(0.48 to 1.47)			(0.46 to 1.76)			(1.10 to 4.94)
			0.54			0.75			0.03
Sex			1.81			1.04			0.77
			(0.68 to 4.79)			(0.31 to 3.50)			(0.25 to 2.35)
			0.23			0.95			0.65
Non-White ethnicity			3.06[b]			1.50			4.62[b]
			(1.12 to 8.34)			(0.41 to 5.57)			(1.30 to 16.44)
			0.03			0.54			0.02
RAASi use			1.55			1.08			0.87
			(0.44 to 5.51)			(0.19 to 6.21)			(0.15 to 4.99)
			0.5			0.93			0.88

Data shown are odds ratios from logistic regression models examining the association between history of glomerular disease and the clinical outcomes AKI, KRT, and death, comparing GN hospitalized patients with Ctrl hospitalized patients. For each outcome, three regression models are reported: crude model (no adjustment), eGFR adj. (adjusted for pre-COVID-19 eGFR), and fully adj. (additionally adjusted for age, sex, non-White ethnicity, and RAASi use). Odds ratios associated with eGFR are expressed per 1 SD unit (approximately 30 ml/min per 1.73 m^2) decrease. Therefore, an odds ratio for AKI associated with prior eGFR (*i.e.*, pre-COVID-19 eGFR) of 3.04 means that the odds of AKI increases by 3.04 times every 30 ml/min per 1.73 m^2 decrease of pre-COVID-19 eGFR; the odds ratio for age is expressed per 1 SD (approximately 15 years) increase in age. Numbers in brackets represent 95% confidence intervals; the numbers below the brackets are the associated *P* values. Ctrl, control; KRT, kidney replacement therapy; RAASi, renin-angiotensin-aldosterone system inhibitors.

[a]$P<0.01$.

[b]$P<0.05$.

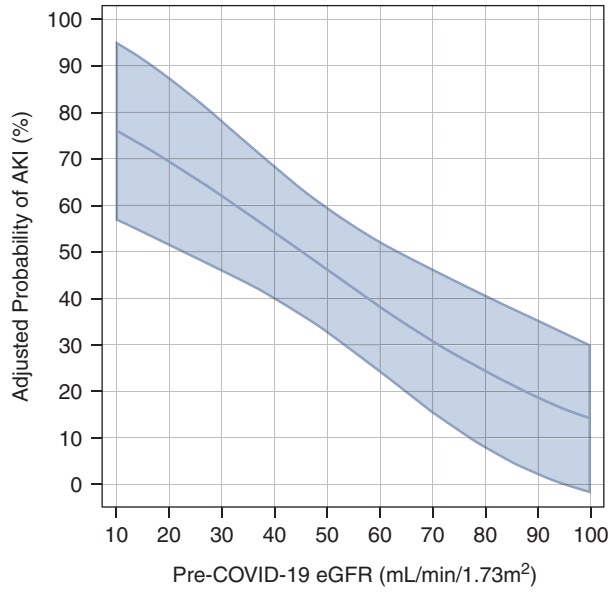

Figure 1. | Probability of developing AKI as a function of eGFR before coronavirus disease 2019 (COVID-19). The probability is based on a regression model, which is adjusted for age, sex, non-White ethnicity, and use of renin-angiotensin-aldosterone system inhibitors. The model is estimated only in hospitalized patients with glomerular disease. The shadowed area represents the 95% confidence interval (CI). The adjusted odds ratio of AKI per 1 SD unit decreases in eGFR (approximately 15 ml/min per 1.73 m^2) was 2.88 (95% CI, 1.38 to 6.02; P=0.005).

Table 1). As predicted on the basis of lower disease severity, fewer GN outpatients received any COVID-19 treatment compared with GN hospitalized patients and Ctrl hospitalized patients (Supplemental Table 2). Within hospitalized patients, fewer GN hospitalized patients received hydroxychloroquine and azithromycin than Ctrl hospitalized patients (Supplemental Table 2).

Clinical Outcomes in Patients with Glomerular Disease

We assessed the effect of glomerular disease on COVID-19 outcomes by comparing GN hospitalized with Ctrl hospitalized patients before and after adjusting for potential confounders (Table 3). Primary end points were incidence of AKI, initiation of KRT, and death. Incidence of AKI, KRT, and death were 46% versus 19%, 13% versus 10%, and 19% versus 10% in GN hospitalized patients versus Ctrl hospitalized patients, respectively. In crude analyses, GN hospitalized patients had increased odds of AKI (OR=3.44; 95% confidence interval [CI], 1.58 to 7.47; P=0.002) but not of KRT or death (Table 3). However, after adjusting for pre-COVID-19 eGFR and additional confounders (age, sex, non-White ethnicity, and RAASi use), the odds of AKI were similar between groups (OR=1.28; 95% CI, 0.43 to 3.60; P=0.64; Table 3). The adjusted analyses confirmed that OR for KRT and death were similar between GN hospitalized patients and Ctrl hospitalized patients (Table 3).

Pre-COVID-19 eGFR was the major determinant of clinical outcomes in adjusted analyses: for every 1 SD unit decrease in eGFR (approximately 30 ml/min per 1.73 m^2 decrease), the adjusted OR was 3.04 (95% CI, 1.76 to 5.28; P<0.001) for AKI, 2.39 (95% CI, 1.20 to 4.78; P=0.014) for KRT, and 1.76 (95% CI, 0.91 to 3.37; P=0.09; Table 3) for death.

The multivariable adjusted relationship between pre-COVID-19 eGFR and the probability of AKI is reported in Figure 1: patients with pre-COVID-19 eGFR <30 ml/min per 1.73 m^2 had a probability of developing AKI during their hospital stay of >50%. In the adjusted analyses, the rate of death increased with age (OR per 1 SD unit increase, which is approximately 15 years=2.33; 95% CI, 1.10 to 4.94; P=0.03) and in patients with non-White ethnicity (OR=4.62; 95% CI, 1.30 to 16.44; P=0.02; Table 3).

Determinants of Clinical Outcomes in Patients with Glomerular Disease

We assessed the effect of determinants of clinical outcomes (AKI, KRT, or death) in patients with glomerular disease by performing analyses on GN hospitalized patients and GN outpatients pooled, after adjusting for potential confounders, including hospitalization status. Similar to the results above, pre-COVID-19 eGFR was the only significant determinant of AKI, KRT, and death (OR for death associated with 1 SD unit decrease in eGFR=3.00; 95% CI, 1.15 to 7.85; P=0.03), the latter being also associated with older age (OR for death associated with 1 SD increase in age=3.97; 95% CI, 1.47 to 10.74; P=0.007). In the crude analysis, only serum albumin was associated with AKI, and the presence of SLE was associated with the need for KRT (Supplemental Table 3). However, in the adjusted analyses, serum albumin, urinary protein excretion, and immunosuppressive drugs (azathioprine, calcineurin inhibitors, mycophenolate, rituximab, or steroids) were not significantly associated with the main clinical outcomes (Supplemental Table 3). In addition, the duration of glomerular disease diagnosis and type of GN (including a comparison of systemic GN versus renal limited GN) were not significantly associated with the main clinical outcomes (Supplemental Table 3).

Effect of Presence of Glomerular Disease on Recovery of Kidney Function Post-COVID-19

We assessed the effect of presence of glomerular disease on post-COVID-19 kidney function by comparing GN hospitalized patients with Ctrl hospitalized patients after adjusting for potential confounders. Kidney function recovery was assessed as a categorical outcome (*i.e.*, any post-COVID-19 eGFR within –10% of pre-COVID-19 eGFR [baseline]). Overall, the rate of kidney function recovery was similar in GN hospitalized patients and Ctrl hospitalized patients (OR=1.47; 95% CI, 0.57 to 3.77; P=0.43; Table 4). In adjusted models, the only borderline statistically significant determinant of kidney function recovery was pre-COVID-19 eGFR (OR of kidney function recovery per 1 SD unit eGFR decrease=0.55; 95% CI, 0.33 to 0.90; P=0.02; Table 4).

We next analyzed data using kidney function as a continuous outcome (by comparing pre- and post-COVID-19 eGFR). Overall, there was no significant difference in the correlation between pre- and post-COVID-19 eGFR between GN hospitalized patients and Ctrl hospitalized

Table 4. Association between history of glomerular disease with kidney function recovery, and determinants of kidney function recovery in patients with history of glomerular disease

	Glomerular Neuropathy Hospitalized versus Control Hospitalized			Glomerular Neuropathy Hospitalized and Glomerular Neuropathy Outpatients Pooled	
	Crude	eGFR Adjusted	Fully Adjusted	eGFR	Full Model
Preexisting GN	1.23	1.60	1.47		
	(0.62 to 2.43)	(0.66 to 3.86)	(0.57 to 3.77)		
	0.55	0.3	0.43		
Prior eGFR (per 1 SD unit decrease)		0.57[b]	0.55[b]	0.55[a]	0.59[b]
		(0.36 to 0.90)	(0.33 to 0.90)	(0.35 to 0.86)	(0.36 to 0.95)
		0.02	0.02	0.009	0.03
Age (per 1 SD unit increase)			1.10		1.02
			(0.66 to 1.82)		(0.61 to 1.73)
			0.73		0.93
Sex			0.93		1.25
			(0.40 to 2.15)		(0.49 to 3.18)
			0.86		0.64
Non-White ethnicity			1.78		2.73[b]
			(0.69 to 4.60)		(1.03 to 7.28)
			0.24		0.04
RAASi use			1.07		1.24
			(0.31 to 3.67)		(0.44 to 3.46)
			0.92		0.69

Data shown are odds ratios from logistic regression models examining the association between history of glomerular disease and recovery of kidney disease (*i.e.*, at least one eGFR values with –10% of pre-COVID-19 eGFR [baseline]), comparing GN hospitalized patients with Ctrl hospitalized patients. For each outcome, three regression models are reported: crude model (no adjustment), eGFR adj. (adjusted for pre-COVID-19 eGFR), and fully adj. (additionally adjusted for age, sex, non-White ethnicity, and RAASi use). On the right, the same logistic model is fitted in GN hospitalized patients and GN outpatients (pooled) for examining prior eGFR (*i.e.*, pre-COVID-19). The model is fitted before (eGFR model), and after (full model) adjusting for the other covariates. Odds ratios associated with eGFR are expressed per 1 SD unit (approximately 30 ml/min per 1.73 m^2) decrease. Therefore, an odds ratio associated with a prior eGFR of 0.55 means that the odds of recovery decreases by 0.55 times every 30 ml/min per 1.73 m^2 decrease of pre-COVID-19 eGFR; the odds ratio for age is expressed per 1 SD (approximately 15 years) increase in age. Numbers in brackets represent 95% confidence intervals; the numbers below the brackets are the associated *P* values. Crtl, control; GN, history of glomerular disease; RAASi, renin–angiotensin–aldosterone system inhibitors.

[a]$P<0.01$.

[b]$P<0.05$.

patients. However, when we stratified patients on the basis of development of AKI, the correlation between pre- and post-COVID-19 eGFR significantly differed between GN hospitalized patients and Ctrl hospitalized patients. In particular, we found that Ctrl hospitalized patients who developed AKI had a full recovery of eGFR (to pre-COVID-19 levels) by 6 months after COVID-19. In contrast, kidney recovery was only partial in GN hospitalized patients who developed AKI during hospitalization. This is demonstrated by the four-way interaction term between GN versus Ctrl, time, AKI, and pre-COVID-19 eGFR, which was statistically significant ($P=0.03$). To have a visual appraisal of the interaction term, we estimated the adjusted coefficient of the relationship between pre-COVID-19 eGFR and 6-month post-COVID-19 eGFR according to the history of glomerular disease and AKI, and plotted the results predicted by the multiple regression model (Supplemental Table 4 and Figure 2). For all of the groups, except GN hospitalized patients who had AKI, the coefficient between pre-COVID-19 and 6-month post-COVID-19 was close to one (Supplemental Table 4) and the line close to the line of identity (the line of identity between pre-COVID-19 and 6-month post-COVID-19 eGFR is the dotted line in Figure 2): Ctrl hospitalized patients without AKI: 0.90 (95% CI, 0.75 to 1.04); GN hospitalized patients without AKI: 0.87 (95% CI, 0.70 to 1.04); Ctrl hospitalized patients with AKI: 0.98 (95% CI, 0.82 to 1.14); and GN hospitalized patients with AKI: 0.41 (95% CI, 0.25 to 0.56). The intercept was not statistically significantly different from zero in all four groups (data not shown). The visual representation of how the four-way interaction in terms of changes in eGFR over time is shown in Supplemental Figure 3.

In the multivariable regression models, determinants that were significantly associated with lower post-COVID-19 eGFR were older age (–3.5 ml/min per 1.73 m^2 per 1 SD unit increase) and non-White ethnicity (–5.4 ml/min per 1.73 m^2).

Determinants of Kidney Function Recovery in Patients with Glomerular Disease

Among infected GN patients, pre-COVID-19 eGFR and serum albumin decreased only in those who were hospitalized (Supplemental Table 5). The only borderline significant determinant of kidney function recovery was pre-COVID-19 eGFR (OR of kidney function recovery per 1 SD unit decrease of eGFR=0.62 (95% CI, 0.38 to 1.01; $P=0.06$;

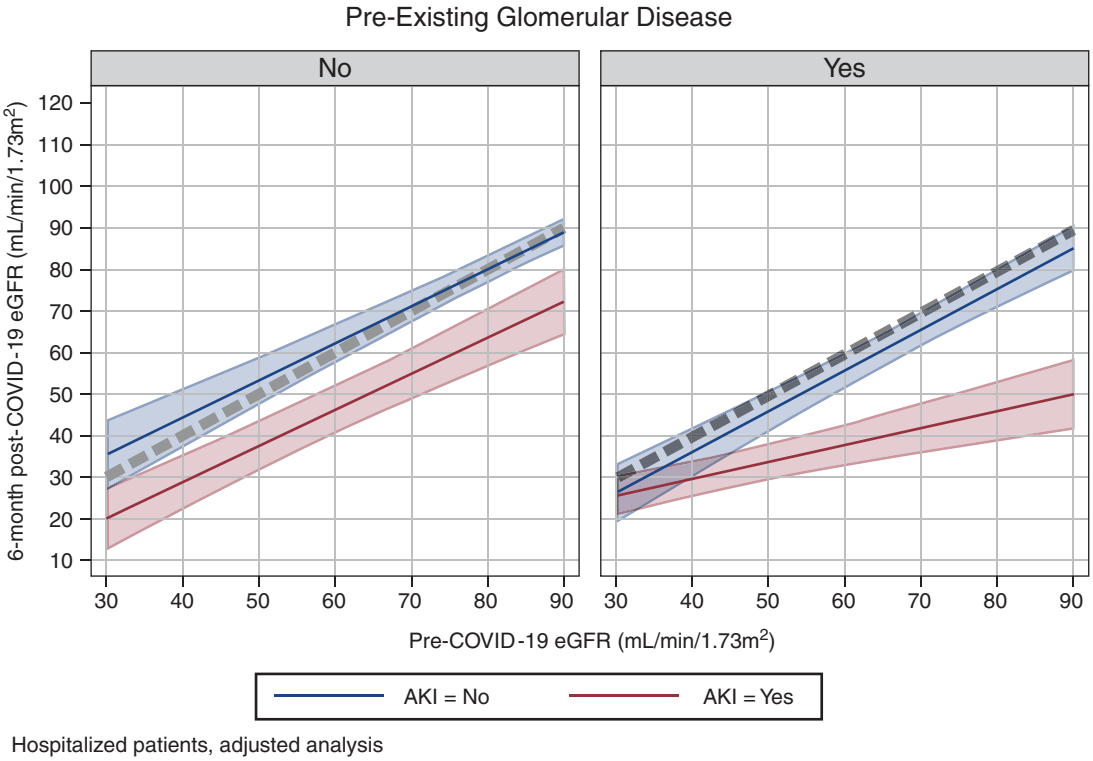

Figure 2. | Visual representation of the results of the four-way interaction term from the longitudinal mixed model on eGFR between GN and Ctrl hospitalized patients, time, AKI, and pre-COVID-19 eGFR (P=0.02). The figure represents the predicted relationship between pre- and post-COVID-19 eGFR after stratification of hospitalized patients according to the absence (left panel) and presence (right panel) of a history of glomerular disease (Ctrl hospitalized and GN hospitalized, respectively, throughout the text). Patients are additionally stratified on the basis of those who did not develop (blue) or who developed (red) AKI during their hospital stay. The dotted gray line represents the line of identity between pre- and post-COVID-19 eGFR (*i.e.*, full recovery of kidney function). Although Ctrl hospitalized patients had a full recovery of eGFR at 6 months after COVID-19, the recovery was only partial in GN hospitalized patients who developed AKI during their hospital stay. For all of the groups, except GN hospitalized patients who had AKI, the coefficient between pre-COVID-19 and 6-month post-COVID-19 was close to one and the line close to the line of identity: Ctrl hospitalized patients without AKI: 0.90 (95% CI, 0.75 to 1.04); GN hospitalized patients without AKI: 0.87 (95% CI, 0.70 to 1.04); Ctrl hospitalized patients with AKI: 0.98 (95% CI, 0.82 to 1.14); GN hospitalized patients with AKI: 0.41 (95% CI, 0.25 to 0.56; see Supplemental Table 4). The visual representation of the four-way interaction term as eGFR change over time is reported in Supplemental Figure 3.

Table 4). In the adjusted analyses, serum albumin, urinary protein, type of immunosuppressive drugs (azathioprine, mycophenolate, calcineurin inhibitors, rituximab, or steroids), and duration and type of glomerular disease were not significantly associated with the rate of kidney function recovery (categorical variable; Supplemental Table 6). At variance, when we examined the effect of the same determinants of post-COVID-19 eGFR (continuous variable), we found that higher baseline proteinuria (–2.1 ml/min per 1.73 m^2 per 1 SD unit increase) and, more importantly, preexisting FSGS or minimal change disease (MCD) diagnosis (–7.7 ml/min per 1.73 m^2) were associated with significantly lower post-COVID-19 eGFR (Supplemental Table 7).

Discussion

To our knowledge, this is the first analysis of both the short- and long-term outcomes of COVID-19 infection among GN patients. On the basis of a meta-analysis from 2020, the pooled incidence of COVID-19-associated AKI among hospitalized patients was 29% (95% CI, 19.8 to 39.5) in the United States and Europe, although the reported ranges are quite broad (3). In our study, nearly half of the hospitalized GN patients experienced AKI, suggesting that the incidence of COVID-19-associated AKI in GN patients is at the higher range of estimates of AKI reported among hospitalized patients (4–8). However, our data indicate that the presence of underlying GN does not confer an independent risk for COVID-19-associated AKI. In line with the well-established association between preexisting CKD and risk of in-hospital AKI in general (9–11), and in the setting of COVID-19 (4,12–14), we showed that pre-COVID-19 eGFR is the main determinant of AKI and of need for KRT.

There was no difference in mortality between GN and control patients. Both in-hospital AKI and the presence of CKD have been consistently associated with higher COVID-19-associated mortality (5,15–20). The similar adjusted rates of AKI between the GN and control cohorts may partly explain the observed lack of difference in mortality in this study. AKI and death were almost entirely confined to hospitalized patients. Although we do not have information on COVID-19 severity scores, these data suggest that milder cases of

COVID-19 in GN patients managed in the outpatient setting have a more benign outcome than hospitalized patients.

Importantly, our results indicate that whereas controls with COVID-19-associated AKI tend to show recovery of kidney function by 6 months, GN patients with AKI have slower, incomplete kidney recovery and persistently lower eGFR at longer-term follow-up. Longitudinal outcome and recovery data on patients with COVID-19-associated AKI are still limited (4,21,22). One recent cohort study reported accelerated eGFR decline and lower rates of kidney recovery after hospitalization in patients with COVID-19-associated AKI compared with AKI for other reasons, independent of comorbidities or AKI severity (21). The etiology of the observed slower and incomplete kidney recovery in GN patients compared with control patients after COVID-19-associated AKI is likely multifactorial (20). It is noteworthy that a shorter duration of GN diagnosis was associated with both a greater risk of AKI and slower kidney recovery. In addition, a higher degree of pre-COVID-19 proteinuria and a history of FSGS/MCD were associated with decreased kidney recovery and lower eGFR post-COVID-19 at follow-up. These interesting observations set the basis for future studies aimed to better define GN subgroups that are particularly vulnerable to CKD progression after COVID-19-associated AKI.

Several pathophysiological pathways are believed to be activated in the context of SARS-CoV-2 infection leading to kidney injury, and a spectrum of histologic changes in the glomerular, tubulointerstitial, and vascular compartments of the kidney have been described. The extent to which baseline patient characteristics (*i.e.*, type, duration, or immunologic activity of underlying GN, proteinuria, and kidney gene expression profiles) contribute to the type of AKI or subsequent recovery warrants further study. The lack of kidney biopsies in the GN and control cohorts with COVID-19-associated AKI precludes comparisons. However, it is conceivable that GN patients with underlying immune dysregulation, kidney immune cell infiltration, and prothrombotic tendencies are more prone to endothelial dysfunction, coagulopathy, and complement activation or have greater sensitivity of podocytes and tubules to the effects of SARS-CoV-2, which may affect renal prognosis compared with those without GN. Superimposed on limited renal reserve, persistence of proteinuria, hematuria, and maladaptive repair mechanisms in GN patients after AKI may also promote renal fibrosis, leading to incomplete kidney recovery (23,24). Limited serial proteinuria values and relevant serological data in our study preclude meaningful conclusions regarding the contribution of changes in GN activity or GN relapses (possibly related to reduction of immunosuppression during infection or to the infection itself) in delayed kidney recovery.

Our data do not indicate an association between immunosuppressive treatment before COVID-19, level of pre-COVID-19 proteinuria, or the type of GN (systemic versus kidney limited) on the primary outcomes of mortality and AKI. However, hospitalized GN patients had higher pre-COVID-19 proteinuria and lower serum albumin than those managed as outpatients. In addition, a greater proportion of hospitalized patients were on calcineurin inhibitors at the time of COVID-19 or received rituximab within 6 months preceding infection. The published data regarding the influence of longitudinal immunosuppression on COVID-19 susceptibility and outcomes has been changing and contradictory. Although our data regarding calcineurin inhibitors and rituximab are too limited to draw firm conclusions, these observations deserve further study, particularly in light of the importance of B cell depleting therapy for GN. Some early reports suggested no effect of rituximab or a slightly increased risk of hospitalization from COVID-19 (25–29). More recently studies have reported unfavorable prognosis particularly in those with shorter duration between last rituximab infusion and infection (30–33). These conflicting results may reflect heterogeneity in the diseases treated with rituximab, intensity of B cell depletion and IgG levels at infection onset, and number of previous treatments. Similarly, the data regarding calcineurin inhibitors has been mixed. In a large Danish cohort study, treatment with cyclosporine or tacrolimus was associated with a significantly increased risk of hospitalization (34). In contrast, a retrospective study from Spain indicated beneficial effects of cyclosporine in COVID-19 (76% reduction in mortality) (35). This preliminary evidence has boosted interest in these drugs for treatment of COVID-19, and there are several ongoing clinical trials (36). Results of such trials may influence treatment decisions of underlying GN during the ongoing pandemic (37).

Among GN patients, those of non-White ethnicity had a higher adjusted mortality risk—a finding consistent with many published reports that have highlighted race/ethnicity-related differences in COVID-19 rates and outcomes. Research to disentangle the various complex factors that contribute to ethnic variability is ongoing, although socioeconomic and sociodemographic factors appear to play important roles (19,33,38–40).

Our study has many strengths. There is global representation with a diverse population. It focuses on a subpopulation of CKD patients with unique (and potentially dynamic) baseline clinical characteristics and treatment challenges for which little data is currently available. The study is reflective of the various presentations of COVID-19 in GN patients managed as inpatients and outpatients. We also analyzed longitudinal laboratory data extending from pre-COVID-19 through recovery. This is particularly relevant because the 25th Consensus Conference of the Acute Disease Quality Initiative highlighted the natural history of kidney sequelae after COVID-19-associated AKI as major research recommendations (41,42). Importantly, inclusion of a control group of non-GN patients strengthened the validity of the findings. However, there are some caveats that should be considered. The sample size remains relatively small despite our large network. There were missing data at various time points, particularly for GN patients managed as outpatients. Serial laboratory tests (*i.e.*, proteinuria) that would provide a better understanding of GN relapses or changes in disease activity post-COVID-19 were not consistently performed. Also, the control and GN groups were not perfectly matched, and we chose to include only hospitalized controls due to limitations in data collection in outpatients. Adjustments for confounders allowed us to minimize the bias of the unbalanced control characteristics, but it is possible that differences between the two groups persist that cannot be fully accounted for.

In conclusion, in a diverse international cohort of patients with COVID-19, mortality and AKI did not differ between GN patients and controls. The main predictor of AKI was pre-COVID-19 eGFR. Incomplete kidney recovery after COVID-19-associated AKI was more common in GN patients compared with controls. Shorter duration of GN diagnosis, higher grade proteinuria, and FSGS/MCD diagnosis were associated with impaired kidney recovery during longer-term follow-up. These findings remain highly relevant despite the availability of COVID-19 vaccines in light of the rising rates of COVID-19 spread of the delta variant and other variants of concern, impaired vaccine response among immunocompromised patients (43–47), breakthrough infections among vaccinated (48,49), and waning vaccine immunity over time.

Disclosures

O. Bestard reports patents and inventions with Oxford Immunotec and is associate editor of *Transplant International* and *Frontiers in Immunology*. A. Bruchfeld reports consultancy agreements with AstraZeneca, Chemocentryx, Fresenius, and Merck; a research grant from AstraZeneca; honoraria from Bayer, Chemocentryx, Fresenius, Merck, and Vifor; and is a member of the ERA-EDTA scientific advisory board 2018–2024, chair of the ERA-EDTA Immunonephrology Working Group, and vice-chair of the Swedish Renal Fund. G. Comai reports honoraria from Alexion, Astellas, and Novartis. P. Cravedi reports honoraria as an advisor for Chinook Therapeutics and is associate editor for the *Journal of Nephrology* and the *American Journal of Transplantation*. G. Fernandez Juarez reports research funding from Instituto Salud Calos III and honoraria from Alexion and GSK. E. 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Author Contributions

P. Cravedi and M. Waldman conceived and oversaw the project; I. Agraz, A. Avello, O. Bestard, C. Bini, A. Bruchfeld, K.L. Budge,

C. Cantarelli, C. Chrysochou, G. Comai, M. Delsante, G. Fernández Juárez, R. Fernandez-Prado, E. Fiaccadori, O. Flossman, R. García-Agudo, C. Garcia-Carro, C. Geddes, M. Griffith, A.J. Hamilton, L. Howard, G. La Manna, T. Leach, L. Lightstone, J. Manrique, S. Marinaki, A.J. Martinez-Rueda, C. Martin Vasa, L. Martinez Valenzuela, E. Morales, J.A. Niño-Cruz, A. Ortiz, C. Rabasco Ruiz, M. Sierra-Carpio, S. Sinha, M.F. Slon, M.J. Soler, J. Torras, and T. Turner-Stokes collected the data; U. Maggiore performed all of the statistical analyses; P. Cravedi, U. Maggiore, and M. Waldman analyzed the data and wrote the initial draft of the manuscript; all of the authors reviewed and approved the final version of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0006612021/-/DCSupplemental.

Supplemental Methods

Supplemental Reference

Supplemental Figure 1. Analysis on the goodness of fit of the linear random-coefficient mixed model on eGFR.

Supplemental Figure 2. Data used for longitudinal analyses.

Supplemental Figure 3. Visual representation of the results of the four-way interaction term from the longitudinal mixed model on eGFR between GN patients and Ctrl hospitalized patients, time, AKI, and pre-COVID-19 eGFR.

Supplemental Table 1. Complications during hospital stay.

Supplemental Table 2. Treatments for COVID-19.

Supplemental Table 3. Association of various determinants with clinical outcomes AKI, kidney replacement therapy, and death in the overall cohort of GN patients.

Supplemental Table 4. Estimated relationship between pre- and post-COVID-19 eGFR at 6 months after COVID-19 admission.

Supplemental Table 5. Serial kidney parameters in patients with glomerular disease based on admission status.

Supplemental Table 6. Analysis on determinants of kidney function recovery (categorical variable) in GN patients.

Supplemental Table 7. Analysis on the determinants of post-COVID-19 eGFR (continuous variables).

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