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Original Article



ORIGINAL ARTICLE

# The impact of mild and moderate COVID-19 infection on the progression of kidney dysfunction in patients with IgA nephropathy

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## ABSTRACT

**Background.** Previous research indicates that coronavirus disease 2019 (COVID-19) infection may have a role in triggering immunoglobulin A (IgA) nephropathy. However, limited research has explored the clinical implications of COVID-19 infection in individuals already diagnosed with IgA nephropathy. This study aimed to determine whether COVID-19 infection independently affects the subsequent trajectory of kidney function in IgA nephropathy patients.
**Methods.** This was a single-center cohort study. The study included 199 patients diagnosed with IgA nephropathy. The COVID-19 infection status was determined using a combined method: a questionnaire and the Health Code application, both administered at the end of 2022 in northern China. Kidney function trajectory was assessed by the estimated glomerular filtration rate (eGFR), calculated based on serum creatinine levels measured during follow-up outpatient visits. The primary endpoint of interest was the eGFR trajectory.
**Results.** Out of the 199 participants, 75% ($n = 181$) reported a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, determined through antigen or polymerase chain reaction tests, accounting for 79% ($n = 143$) of the infected patients. A significant majority (98%) experienced mild to moderate symptoms. Over a median follow-up period of 10.7 months post-COVID-19 infection, notable clinical events included gross hematuria in 30 patients (16.6%), which normalized within an average of 3 days. Additionally, a 2-fold increase in proteinuria or progression to the nephrotic range was observed in 10 individuals (5.5%). No cases of acute kidney injury were noted. COVID-19 exposure was associated with an absolute change in eGFR of 2.98 mL/min/1.73 $m^2$ per month (95% confidence interval 0.46 to 5.50). However, in a fully adjusted model, the estimated changes in eGFR slope post-COVID-19 were –0.39 mL/min/1.73 $m^2$ per month (95% confidence interval –0.83 to 0.06, $P = .088$) which included the possibility of no significant effect. Notably, a higher rate of kidney function decline was primarily observed in patients with a baseline eGFR <45 mL/min/1.73 $m^2$ [–0.56 mL/min/1.73 $m^2$ (–1.11 to –0.01), $P = .048$]. In the cohort, there were few instances of severe COVID-19 cases. The absence of long-term follow-up outcomes was observed.
**Conclusions.** Overall, mild to moderate COVID-19 infection does not appear to significantly exacerbate the subsequent decline in kidney function among IgA nephropathy patients, particularly in those with preserved baseline kidney function.

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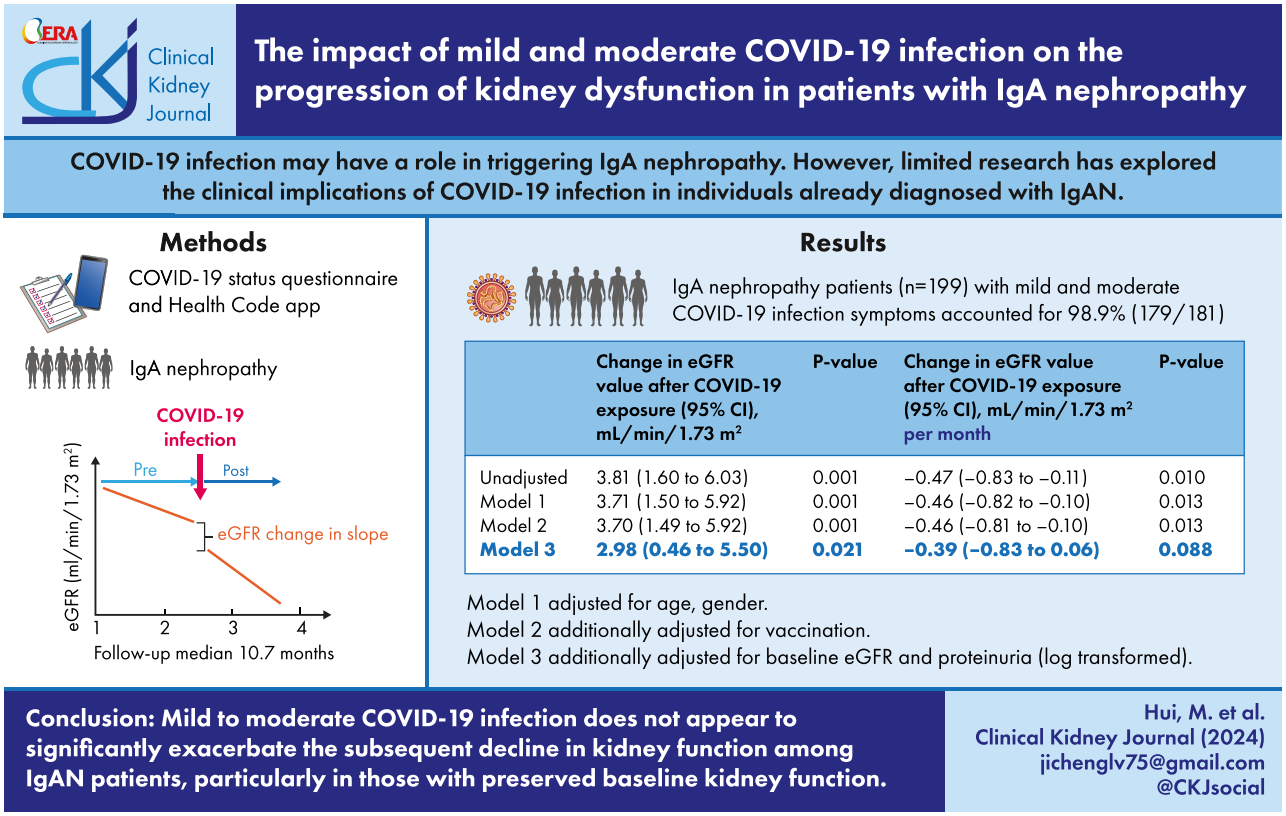
## GRAPHICAL ABSTRACT




**Keywords:** albuminuria, chronic renal insufficiency, CKD, glomerulonephritis, IgA nephropathy

## KEY LEARNING POINTS

**What was known:**

- COVID-19 may trigger IgA nephropathy (IgAN), but its impact on IgAN progression is unclear.
- Existing studies show inconsistent findings on COVID-19's effect on IgAN progression.
- Pre-existing kidney conditions' progression during COVID-19 has been underexplored.

**This study adds:**

- Mild to moderate COVID-19 infection doesn't significantly worsen kidney function in IgAN patients overall.
- Patients with pre-existing reduced kidney function may experience accelerated decline post-COVID-19.
- Tailored management based on kidney function status is crucial for IgAN patients.

**Potential impact:**

- Supports ongoing monitoring for IgAN patients, particularly those with compromised kidney function.
- Emphasizes the need for larger, diverse studies to validate findings.
- Guides future research and informs tailored management approaches for IgAN patients.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has manifested in a variety of clinical ways, extending beyond the commonly recognized respiratory symptoms. Importantly, accumulating evidence suggests that the chronic kidney diseases may experience worsened progression during the pandemic [1]. Furthermore, several reports have highlighted the onset and relapse of various glomerulonephritis (GN) conditions in the context of COVID-19 infection and vaccination [1–7].

The pathophysiological mechanisms underlying these kidney manifestations are complex, potentially involving direct viral damage, endothelial injury, immune system dysregulation

and alterations in the renin–angiotensin–aldosterone system (RAAS) [8]. Immunoglobulin A (IgA), a prevalent immunoglobulin in the early stages of COVID-19, has been identified as a marker of clinical severity [9, 10]. While the precise causative pathways remain elusive, it is noteworthy that COVID-19 infection has been linked to the triggering or revealing of autoimmune processes, such as anti-neutrophil cytoplasmic antibody–associated GN, anti-glomerular basement membrane disease, IgA nephropathy and lupus nephritis [1].

Given these considerations, it is imperative to explore the impact of COVID-19 on pre-existing kidney conditions like IgA nephropathy, which previously demonstrated a correlation with visible hematuria following upper respiratory tract infections. However, the clinical outcomes for IgA nephropathy post-COVID-19 infection remain uncertain. Moreover, the modification in the Chinese government's zero-COVID-19 prevention policy and the emergence of the Omicron variant in late 2022 have introduced new challenges for nephrologists in China, tasked with managing COVID-19 infections in patients with IgA nephropathy.

This study seeks to address a lack of understanding by investigating whether COVID-19 infection exacerbates kidney dysfunction in individuals with pre-existing IgA nephropathy. Utilizing a longitudinal cohort study design, we endeavor to assess the kidney function of IgA nephropathy patients before and after COVID-19 exposure, shedding light on this clinically relevant and evolving scenario.

## MATERIALS AND METHODS

### Study population

This investigation delineated a retrospective cohort analysis of adult patients (aged >18 years) with established diagnoses of IgA nephropathy based on native kidney biopsy. These patients were ascertained at a prominent kidney disease facility situated in northern China and available MEST-C scores from the cohorts as previously described [11]. Cohort members were scheduled for regular in-person consultations at intervals spanning from 1 to 6 months, during which estimated glomerular filtration rate (eGFR) based on serum creatinine and 24-h proteinuria levels were measured with comprehensive updates to their records. Exclusion criteria included individuals who had undergone renal replacement therapy or transplantation, those who discontinued their participation in our cohort, and cases of newly diagnosed IgA nephropathy concomitant with COVID-19 or following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.

The present analysis focused on individuals from the cohort who maintained attendance at in-person outpatient sessions subsequent to the alterations in COVID-19 policy within China. Through collaborative efforts with visiting medical practitioners, we conducted a survey employing a paper-based questionnaire and cross-referenced with the Health Code application, which is linked to each person's COVID-19 status under a real-name system, to ascertain COVID-19 infection statuses. This was done for a patient group under continuous monitoring during two distinct time periods at our institution: from 1 January 2023 to 1 February 2023 (herein referred to as Follow-up 3), and from April to July 2023 (designated as Follow-up 4). In addition to the primary data collection, we expanded our analysis to include a retrospective review of data from two preliminary follow-up phases, designated as Follow-up 1 and Follow-up 2. The term "baseline" refers to the initial in-person visit

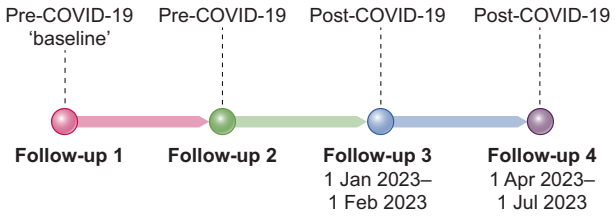



**Figure 1:** Chronological timeline of follow-up phases in the study of IgA nephropathy and COVID-19 infection.

(Follow-up 1) when eGFR measurements were taken. The chronological design of this study is illustrated in Fig. 1.

Participants in the research provided verbal informed consent. The inquiry was conducted in strict compliance with the ethical guidelines delineated in the Declaration of Helsinki. Preliminary authorization for this investigation was granted by the Ethics Committee Board of Peking University First Hospital, with the assigned reference number 2023-117.

### Data collection

The questionnaire primarily comprises inquiries related to the following aspects:

(i) Patient's demographic profile.

(ii) Review of SARS-CoV-2 vaccine background: this included documenting the type and dates of vaccine doses administered, verified using digital records in the Health Code application.

(iii) Determination of COVID-19 diagnosis: this was confirmed using the Health Code application and established using polymerase chain reaction tests, antigen self-tests or clinical symptom manifestation. The severity of the disease was classified according to Ninth edition of the diagnostic and treatment standards outlined from the Chinese National Health Commission, released on 14 March 2022. Definitions ranged from asymptomatic cases, mild symptoms, severe illness to critical illness, each with specific criteria:

Asymptomatic: defined as the absence of clinical symptoms of COVID-19 but with recent close contact with symptomatic cases. A condition or disease. (Without signs and symptoms but recent strict contact with symptomatic cases.)
Mild symptoms: including fever, cough, sore throat, malaise, headache or muscle pain, in the absence of any abnormal findings on chest imaging.
Severe illness: characterized by a respiratory rate exceeding 30 breaths per minute, oxygen saturation level of 93% or below while breathing room air, or a diagnosis of pneumonia with pulmonary infiltrates exceeding 50% on imaging. Additionally, an oxygenation index of 300 mmHg or lower was observed in these cases.
Critical illness: indicating the need for mechanical ventilation, septic shock or multiple organ dysfunction.
The duration of the disease course was defined as the period from the onset of fever or upper respiratory tract infection symptoms to symptoms resolution. The survey was terminated if the participant answered negatively (i.e. "no"), which confirmed with Health Code application to the third question.

(iv) Occurrence and duration of gross hematuria: investigating the presence and duration of gross hematuria as an

indicator of kidney disease flare-up. Blood pressure evaluation in COVID-19 infected patients, including stabilization, increase, decline and recording specific values.

(v) Comprehensive medication record. Documenting the use of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antivirals and traditional Chinese medicine (TCM).

(vi) Discontinuation of medications. Specifically, immunosuppressants, steroids, RAAS inhibitors (RAASi), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and other pharmaceutical agents used in IgA nephropathy management.

The complete questionnaire is available in English in the Supplementary document titled "Questionnaire.

Among all consented patients, information on laboratory tests including eGFR, proteinuria and microhematuria before and after infection, was extracted from four different follow-up visits cohort database or clinic electronic health records as previously described. The Chronic Kidney Disease Epidemiology Collaboration 2012 equation was used to calculate eGFR, and proteinuria was measured in grams per day from 24-h urine specimens. All data underwent rigorous assessment by the study investigators. Records from 7 days before and after disease onset were excluded to eliminate potential unstable factors during the acute phase of infection.

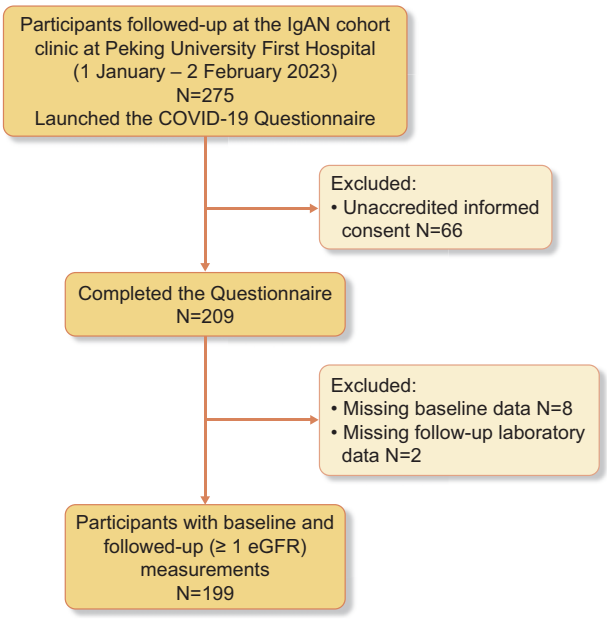



**Figure 2:** Study flowchart of the COVID-19 infection questionnaire in IgA nephropathy patients.

### Outcome and estimates

The primary outcome of interest was the trajectory of eGFR. The parameters of interest were change in the absolute eGFR value and change in eGFR slope before and after a time-updated cumulative primary exposure to COVID-19. Measurement commenced from baseline, was established during the initial in-person study visit prior to any COVID-19 infection and incremented by 1 at each follow-up visit post-exposure (refer to Supplementary data, Fig. S1 for visual depiction).

### Covariates

The covariates included age, gender and coronavirus vaccination history. Additionally, 24-h proteinuria was incorporated as a time-updated variable.

### Statistical analysis

Data presentation followed the convention of expressing categorical variables as percentages and continuous variables as mean ± standard deviation (SD) or medians with interquartile ranges (IQR). Linear mixed-effects regression models were employed to investigate the association between COVID-19 exposure and changes in eGFR. These models included the following fixed effects: time-updated cumulative exposures of COVID-19 infection, months of follow-up and an interaction term between time-updated cumulative exposures of COVID-19 and follow-up duration. Random effects were introduced to account for individual variability and the follow-up period's slope. Furthermore, statistical models were sequentially adjusted for covariates: first, demographic variables (age and gender); secondly, vaccination history; and thirdly, the interaction between baseline eGFR and COVID-19 exposure, along with the log-transformed 24-h proteinuria. Exploratory analyses further stratified the data based on whether baseline eGFR was above or below 45 mL/min/1.73 $m^2$, in accordance with the KDIGO guidelines for distinguishing between CKD stages 3a and 3b.

Statistical analyses were performed using R software (version 4.2.2; R Foundation, Vienna, Austria), and statistical significance was defined as a two-tailed $P$-value of $<.05$.

## RESULTS

### Baseline characteristics

The study's flowchart is depicted in Fig. 2. A total of 275 patients were followed at the IgA nephropathy clinic from December 2022 to July 2023. Of these, 209 individuals over 18 years old with a diagnosis of IgA nephropathy completed the questionnaire. Sixty-six patients declined to complete the questionnaire during follow-up clinic visits for various reasons (details in Supplementary data, Table S1). Ten participants were excluded from the final analysis due to incomplete baseline data. During a median follow-up of 10.7 months, a total of 199 participants were included in the present investigation. Among them, 181 individuals (75%) reported positive for COVID-19, with 143 (79%) of these confirmed through testing. The remaining 18 participants (25%) were confirmed to be negative for COVID-19 during the study period through testing. The baseline clinical characteristics of the study population are presented in Table 1. Participants had a median age of 38 years, with males accounting for 45.23% of the cohort. The average duration of disease among the participants was 5.8 years (SD 5.4) and the Oxford pathology score (MEST-C) was applied to evaluate the biopsy samples of 171 patients with IgA nephropathy, representing 85.93% of the study population. The mean eGFR was 64.57 mL/min/1.73 $m^2$ (SD 28.52), and the median proteinuria level was 0.66 g/day (IQR 0.36, 1.15 g/day). Among the participants, 116 individuals (58.29%) received non-activated vaccines for SARS-CoV-2.

Among the 181 reported positive cases, the majority (98.9%) experienced mild to moderate symptoms, with only 2 (1.1%) of them requiring hospitalization due to lung infection, and no severe or critical cases were observed. The median interval from the onset of COVID-19 symptoms to the first outpatient visit was 28 days, with a range of 23–35 days. A total of 64.6% of the

**Table 1: Baseline characteristics of IgA nephropathy study participants, overall and by COVID-19 infection status.**

| Characteristics | Overall (N = 199) | Non-COVID-19 (N = 18) | COVID-19 (N = 181) |
|---|---|---|---|
| Age, years | 40.66 (10.94) | 38.22 (8.47) | 40.90 (11.13) |
| <45 years | 144 (72.36) | 14 (77.78) | 130 (71.82) |
| 45–59 years | 40 (20.10) | 4 (22.22) | 36 (19.89) |
| >60 years | 15 (7.54) | 0 (0.00) | 15 (8.29) |
| Male, *n* (%) | 90 (45.23) | 9 (50.00) | 81 (44.75) |
| Vaccination, *n* (%) | 116 (58.29) | 11 (61.11) | 105 (58.01) |
| First | 8 (4.02) | 0 (0.00) | 8 (4.42) |
| Second | 39 (19.60) | 6 (33.33) | 33 (18.23) |
| Third | 68 (34.17) | 5 (27.78) | 63 (34.81) |
| Fourth | 1 (0.50) | 0 (0.00) | 1 (0.55) |
| Gross hematuria, *n* (%) | | | |
| Yes | | | 30 (16.57) |
| Gross hematuria days | | | 2.97 (1.39) |
| COVID-19 testing status, *n* (%) | | | |
| No | 38 (19.10) | 0 (0.00) | 38 (20.99) |
| Yes | 161 (80.90) | 18 (100.00) | 143 (79.01) |
| Testing method, *n* (%) | | | |
| Antigen test | 147(91.30) | 18 (100.00) | 129 (90.21) |
| RT-PCR | 14 (8.70) | 0 (0.00) | 14 (9.79) |
| COVID-19 severity, *n* (%) | | | |
| Asymptomatic | | | 3 (1.66) |
| Mild | | | 167 (92.27) |
| Moderate | | | 9 (4.97) |
| Hospitalization | | | 2 (1.10) |
| COVID-19 symptom days | | | 5.00 (3.00, 7.00) |
| Blood pressure change, *n* (%) | | | |
| Stabilize | | | 148 (81.77) |
| Increase | | | 21 (11.60) |
| Decrease | | | 12 (6.63) |
| | | | |
| Systolic BP, mmHg | | 110.40 (7.80) | 116.03 (15.77) |
| Diastolic BP, mmHg | | 76.00 (5.48) | 76.11 (10.22) |
| Medicine, *n* (%) | | | 151 (83.43) |
| NSAIDs | | | 117 (64.64) |
| Antibiotics | | | 17 (9.39) |
| Antiviral | | | 1 (0.55) |
| TCM | | | 57 (31.49) |
| Medication, days | | | 2.00 (1.00, 3.00) |
| Nephrology medication ceased, *n* (%) | | | |
| Yes | | | 46 (25.41) |
| Immunosuppressor | | | 21 (11.60) |
| Corticosteroid | | | 3 (1.66) |
| RAASi | | | 30 (16.57) |
| SGLT2i | | | 3 (1.66) |
| Others | | | 1 (0.55) |
| Medication ceased, days | | | 7.00 (3.00, 14.25) |
| Follow-up, months | 10.73 (8.9, 12.17) | 10.25 (9.33, 11.16) | 10.73 (8.8, 12.37) |
| Baseline kidney measurements | | | |
| IgAN course, years | 5.80 (5.37) | 8.17 (7.98) | 5.53 (4.94) |
| MEST-C score, *n* (%) | 171 (85.93) | 17 (94.44) | 154 (81.91) |
| M1 | 92 (53.80) | 9 (52.94) | 83 (53.90) |
| E1 | 75 (43.86) | 7 (41.18) | 68 (44.16) |
| S1 | 119 (69.59) | 12 (70.59) | 107 (69.48) |
| T1 | 45 (26.32) | 8 (47.06) | 37 (24.03) |
| T2 | 10 (5.85) | 1 (5.88) | 9 (5.84) |
| Crescents | 120 (70.18) | 9 (52.94) | 111 (72.08) |
| Creatine, $\mu$mol/L | 132.69 (65.77) | 144.37 (59.94) | 131.53 (66.41) |
| eGFR, mL/min/1.73 $m^2$ | 64.57 (28.52) | 60.44 (26.98) | 64.98 (28.65) |
| Mean eGFRcr slope before COVID exposure (SD), mL/min/1.73 $m^2$ per month | –0.44(0.16) | | |
| eGFR ≥45 mL/min/1.73 $m^2$, *n* (%) | 143 (71.86) | 12 (66.67) | 131 (72.38) |
| eGFR <45 mL/min/1.73 $m^2$, *n* (%) | 56 (28.14) | 6 (33.33) | 50 (27.62) |
| Proteinuria, g/day | 0.66 (0.36, 1.15) | 0.74 (0.43, 1.10) | 0.65 (0.35, 1.17) |

**Table 1: Continued**

| Characteristics | Overall (N = 199) | Non-COVID-19 (N = 18) | COVID-19 (N = 181) |
|---|---|---|---|
| Proteinuria <1 g/day, *n* (%) | 137 (68.84) | 13 (72.22) | 124 (68.51) |
| Proteinuria ≥1 g/day, *n* (%) | 62 (31.16) | 5 (27.78) | 57 (31.49) |
| Hematuria, $\mu$L | 19.30 (5.30, 52.83) | 17.20 (3.10, 31.40) | 20.40 (5.80, 56.10) |

Values for continuous variables given as mean ± SD or median (IQR) according to their distribution and frequency (percentage) for categorical variables. Proteinuria, 24-h total urine protein excretion.
RT-PCR, reverse transcriptase–polymerase chain reaction; BP, blood pressure; IgAN, IgA nephropathy.

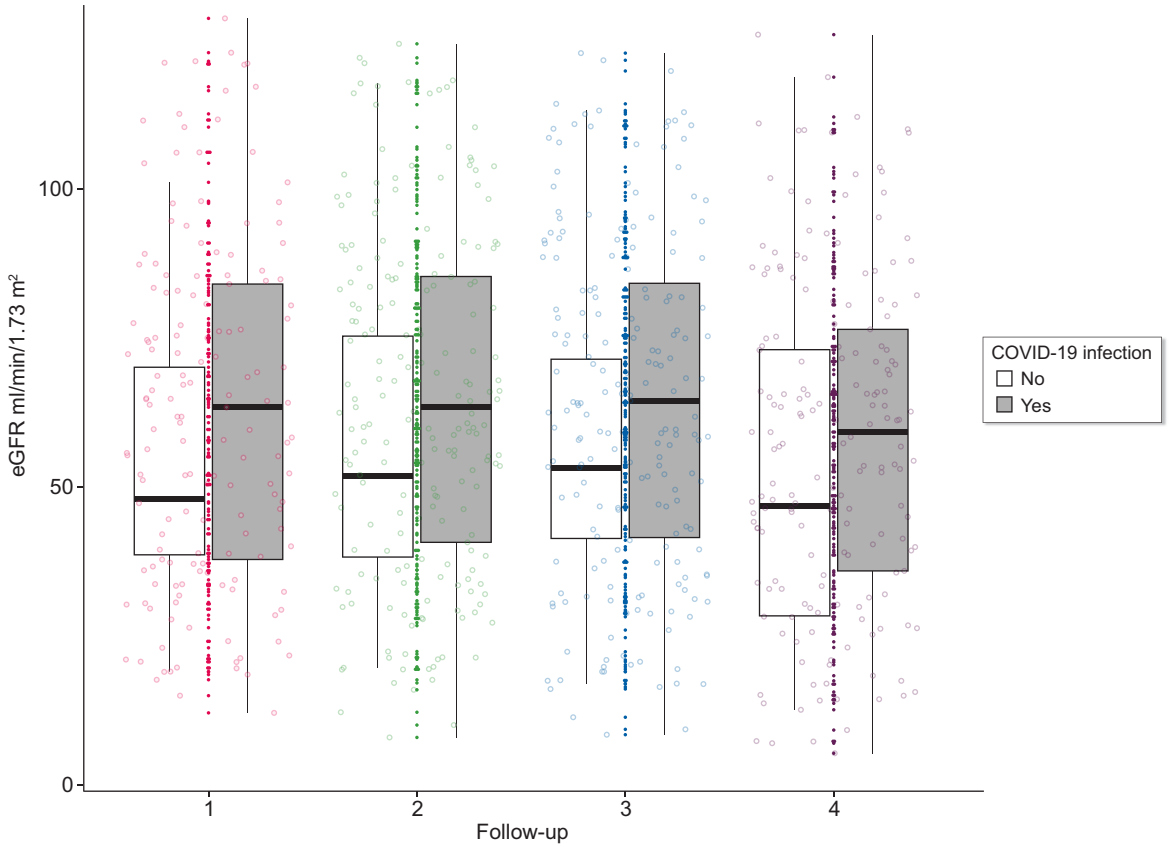



**Figure 3:** Longitudinal participant data pre- and post-COVID-19 exposure across four follow-up phases

infected population received treatment with NSAIDs for fever reduction, and 31.49% opted for TCM, with the median duration of the therapy course was 2 days (range 1–3 days). Regarding the treatment of IgA nephropathy, during a span of 7 days (range 3–14 days), 25.4% of patients discontinued their prescribed medications, 16.6% stopped taking RAASi and 11.6% discontinued their immunosuppressants.

Approximately 16.6% of patients reported experiencing gross hematuria, with the condition typically resolving spontaneously within an average duration of 3 days without the need for medical intervention. Two individuals (1.1%) had proteinuria levels increase to the nephrotic range (>3.5 g/day), and eight individuals (4.4%) exhibited at least a 2-fold increase in proteinuria, exceeding 1.0 g/day. Notably, there were no cases of acute kidney damage. Home-based blood pressure measurement showed that 81.7% of patients maintained stable readings, while the remaining participants showed either increases or decreases in blood pressure.

## Kidney characteristics

To elucidate the impact of COVID-19 infection on the trajectory of kidney function among patients with IgA nephropathy, we present the aggregated individual data of eGFR in Fig. 3. In the analysis of kidney characteristics using unadjusted linear mixed-effects regression models, the COVID-19 infection was found to be associated with an absolute change in eGFR of 3.81 mL/min/1.73 $m^2$ [95% confidence interval (CI) 1.60 to 6.03] (refer to Table 2, unadjusted model). This estimated change experienced some attenuation following adjustments for demographic characteristics and remained consistent upon further controlling for vaccination status (refer to Table 2, Models 1 and 2). Further adjustments were made for baseline eGFR and proteinuria, resulting in the absolute change in eGFR of 2.98 mL/min/1.73 $m^2$ (95% CI 0.46 to 5.50) (refer to Table 2, Model 3).

However, when examining alterations in the eGFR slope, it was observed that the estimation of the fully adjusted model,

**Table 2: Multivariable mixed-effects model showing association of COVID-19 with IgA nephropathy patients kidney function progression.**

| Model | Change in eGFR value after COVID-19 exposure (95% CI), mL/min/1.73 $m^2$ | *P*-value | Change in eGFR slope after COVID-19 exposure (95% CI), mL/min/1.73 $m^2$ per month | *P*-value |
|---|---|---|---|---|
| Unadjusted | 3.81 (1.60 to 6.03) | .001 | −0.47 (−0.83 to −0.11) | .010 |
| Model 1 | 3.71 (1.50 to 5.92) | .001 | −0.46 (−0.82 to −0.10) | .013 |
| Model 2 | 3.70 (1.49 to 5.92) | .001 | −0.46 (−0.81 to −0.10) | .013 |
| Model 3 | 2.98 (0.46 to 5.50) | .021 | −0.39 (−0.83 to 0.06) | .088 |

Model 1: adjusted for age, gender.
Model 2: additionally adjusted for vaccination.
Model 3: additionally adjusted for baseline eGFR and proteinuria (log transformed).

**Table 3: Multivariable mixed effects model showing association of COVID-19 infection with IgA nephropathy patients kidney function progression, by eGFR.**

| | Change in eGFR value after COVID-19 exposure (95% CI) | P[a]-value | Change in eGFR slope after COVID-19 exposure (95% CI) per month | P[a]-value |
|---|---|---|---|---|
| eGFR ≥45 mL/min/1.73 $m^2$ | 2.08 (−1.24 to 5.40) | .223 | −0.01 (−0.57 to 0.59) | .973 |
| eGFR <45 mL/min/1.73 $m^2$ | 3.45 (0.30 to 6.61) | .033 | −0.56 (−1.11 to −0.01) | .048 |
| P[a] for interaction | | .035 | | |

[a]The *P*-values for estimate of the change in eGFR after COVID-19 infection adjusted for baseline age, gender, the status of vaccination, baseline eGFR and (log transformed) 24-h urine total protein.

along with their respective CIs [–0.39 (95% CI –0.83 to 0.06) mL/min/1.73 $m^2$], included the possibility of no effect. The interactions analysis for eGFR change, particularly between baseline eGFR and COVID-19 exposure status, revealed statistically significant multiplicative effects (completely adjusted *P* for interaction = .035) (refer to Table 3).

Furthermore, we conducted a stratified analysis of IgA nephropathy patients based on their baseline eGFR levels (refer to Table 3). The finding indicated that a higher rate of kidney function decline among patients with eGFR <45 mL/min/1.73 $m^2$, with a rate of decline measured at –0.56 mL/min/1.73 $m^2$ per month (95% CI –1.11 to –0.01, $P = .048$). However, in patients with eGFR ≥45 mL/min/1.73 $m^2$, the presence of COVID-19 infection had no apparent affect the rate of kidney function decline, as indicated by an estimated change of –0.01 mL/min/1.73 $m^2$ per month (95% CI –0.57 to 0.59, $P = .973$).

## DISCUSSION

In this study, we sought to investigate the impact of SARS-CoV-2 infection on kidney disease progression among patients with IgA nephropathy, utilizing data from a cohort database and detailed questionnaires. While some patients experienced an acute exacerbation of their condition during SARS-CoV-2 infection, our analysis, after adjusting for baseline clinical characteristics, did not demonstrate a significant overall worsening of the subsequent trajectory of kidney function in the short-term following infection. However, for patients with pre-existing reduced kidney function, specifically those classified as having CKD stage 3b or lower, SARS-CoV-2 infection was associated with an accelerated rate of kidney function decline. These findings highlight the critical need for ongoing monitoring and vigilant care for individuals with reduced kidney function. Our study provides valuable insights into the interplay between COVID-19 and IgA nephropathy, emphasizing the necessity for tailored management approaches based on the patient's kidney function status.

The emergence of the COVID-19 pandemic has witnessed a proliferation of studies focusing on kidney pathology, predominantly concentrating on the *de novo* glomerular disorders, while the progression of pre-existing kidney conditions has been neglected. The precise pathophysiological mechanisms underlying the development of IgA nephropathy in the context of COVID-19 remain elusive. Until now, several studies have shown an association between COVID-19 infection or vaccination [12] and the subsequent worsening of GN disease activity, primarily evidenced by increased proteinuria [13]. However, case reports and before-and-after studies have yielded inconsistent findings regarding the association between COVID-19 infection and worsening of IgA nephropathy. Consequently, the true impact of COVID-19 on the progression of IgA nephropathy remains largely unexplored [4, 8, 14–18].

In our study, we observed that only a subset of patients experienced adverse events, including 16.6% who experienced visible hematuria, 1.1% developed nephrotic syndrome–range proteinuria, and notably, there were no cases of acute kidney injury. Our regression analysis revealed no significant effect of COVID-19 on the rate of kidney function decline among patients with preserved kidney function. However, a more detailed subgroup analysis indicated that patients with an initial eGFR <45 mL/min per 1.73 $m^2$ might experience an accelerated decline in eGFR following SARS-CoV-2 infection. These results underscore the importance of continued monitoring in patients with compromised kidney function.

Furthermore, our review of existing literature revealed that COVID-19 has the potential to unmask and induce IgA nephropathy, particularly in an older demographic (median age 64.5 years), where a significant majority experienced hematuria and had notably elevated proteinuria levels , with a median proteinuria 3.7 g/day (IQR 1.3, 4.9) [1]. In contrast, our study cohort reflects a more general IgA nephropathy population, with an average age of 38 years, over half in early-stage kidney function, and the majority presenting a mild level of proteinuria at baseline (median proteinuria 0.66 g/day). This discrepancy may

suggest that the impact of the Omicron variant, which remained relatively stable during our limited study period [19], possibly explaining the absence of severe cases. Adaptive immunity, bolstered by vaccination and herd immunity strategies, likely played a significant role in mitigating the severity of COVID-19 infections and, by extension, the progression of kidney function [20]. Furthermore, it is crucial for patients with kidney disease to exercise caution when taking medications known to potentially induce kidney impairment, such as NSAIDs.

The utilization of linear mixed-effect models in our cohort study for the analysis of longitudinal data offers several distinct advantages. Primarily, it allows us to assess the impact of exposure events at various time points throughout the study period. Moreover, this methodological approach enables a thorough evaluation and comparison of individual-level changes, focusing on both the absolute change and the rate of change (as a random effect) in the eGFR before and after exposure to COVID-19. Importantly, by incorporating within-individual variations, we achieve a more nuanced and detailed understanding of the underlying dynamics of kidney function over time. In contrast to our findings, an investigation led by Diamantidis *et al.* [1], utilizing a similar analytical method and comparing cohorts from pre- and post-pandemic periods, reported that over three-quarters of their study population experienced a decline in kidney function during pandemic. However, it is important to note that this approach may not effectively capture before-and-after comparisons across distinct populations.

The study conducted during the post-pandemic period, from mid-to-late 2021, revealed the virus's high level of pathogenicity, resulting in significant morbidity and mortality. Notably, the population studied, with an average age of 74.3 years and a high comorbidity score within the Medicare Advantage insurance plan, presented unique characteristics that could introduce potential confounding and bias, complicating the interpretation of subsequent changes in eGFR slopes. The authors suggested that the impact of the pandemic on kidney function might extend beyond the immediate effects of the virus, implicating indirect factors such as disruptions in social and mental health care. These considerations underscore the importance of carefully interpreting and contextualizing the results of different studies, particularly when comparing diverse populations and study periods. Such careful consideration ensures a more accurate understanding of the research findings in the broader spectrum of public health knowledge.

### Limitations

Our study, as the largest of its kind exploring the association between COVID-19 and subsequent kidney progression in IgA nephropathy, presents significant insights. However, it is essential to acknowledge the limitations that may restrict the generalizability of our findings to a broader population.

First, a portion of our data collection relied on subjective reporting, introducing the potential memory and reporting biases. As a result, the weight of infection may have been underestimated within our study.

Secondly, our investigation primarily included mildly infected participants seen during clinic visits in the short term, excluding hospitalized patients. Consequently, our study may have had limited statistical power to assess the impact of more severe COVID-19 infections, which are known to carry a higher risk of kidney injury.

Thirdly, we were unable to account for other hemodynamic factors that could influence eGFR levels over time, such as the subsequent use of RAAS blockers or more intensive blood pressure control. These factors could potentially lead to increased eGFR within the follow-up period.

These limitations underscore the need for further research in larger and more diverse populations to validate and expand upon our findings. Additionally, future studies should consider more objective measures of COVID-19 infection and its severity to provide a more comprehensive understanding of its impact on kidney function in individuals with IgA nephropathy.

## CONCLUSION

In summary, our study rigorously examines the association between mild to moderate COVID-19 infections and the subsequent kidney function trajectory in individuals with IgA nephropathy. Our findings suggest that mild to moderate COVID-19 infection does not appear to significantly exacerbate subsequent kidney function decline in IgA nephropathy patients, particularly those with preserved baseline kidney function.

To provide a more comprehensive assessment of the prognostic effect of COVID-19 in individuals with IgA nephropathy, future research with an extended duration of follow-up periods is imperative. Such studies will allow for a more nuanced understanding of the long-term implications of COVID-19 on kidney health within this specific patient population.

## SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

## CONFLICT OF INTEREST STATEMENT

All the authors declared no competing interests.

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