Safety and effectiveness of COVID-19 vaccines in patients with IgA nephropathy: a retrospective cohort study from the TriNetX global collaborative networks

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Summary

Background This study aimed to evaluate the renal safety and effectiveness of COVID-19 vaccination in patients with immunoglobulin A nephropathy (IgAN).

Methods We conducted a global and retrospective collaborative network analysis using TriNetX data from September 11, 2018 to September 11, 2023, to address this question. The study recorded diagnoses of IgAN, COVID-19 vaccinations, and outcomes of effectiveness using International Classification of Diseases, Tenth Revision, Clinical Modification codes and procedure codes. Propensity score matching (PSM) created matched groups (1:1). Hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated for outcomes of effectiveness, and Kaplan–Meier method assessed survival probability. Safety outcomes regarding renal function were compared with estimated glomerular filtration rate (eGFR), proteinuria, and hematuria. Subgroup analyses were based on sex and age group. Sensitivity analysis was done before the outbreak of Omicron (from September 11, 2018 to October 31, 2021).

Findings The study involved 1010 vaccinated and 2776 unvaccinated patients with IgAN without COVID-19 infection at baseline. After PSM (1:1) with 25 variables, both groups consisted of well-matched 979 patients who were relatively young (around 55 years old) and in good health (eGFR: 78–80 ml/min/1.732 m^2). Compared to the non-vaccinated group, vaccinated patients had significantly lower risks of COVID-19 infection and complications, including COVID-19 infection (HR: 0.050, 95% CI: 0.026, 0.093), COVID-19 pneumonia (HR: 0), severe lung complication (0.647, 95% CI: 0.421, 0.994), acute respiratory failure (0.625, 95% CI: 0.400, 0.978), sepsis (0.545, 95% CI: 0.334, 0.890), emergency department visits (0.716, 95% CI: 0.615, 0.833), all hospitalizations (0.573, 95% CI: 0.459, 0.715), and mortality (0.595, 95% CI: 0.366, 0.969). However, one month after the follow-up, the vaccinated group exhibited a slightly, but statistically significantly, lower eGFR compared to the non-vaccinated group (73.58 vs. 83.05 ml/min/1.732 m^2, p = 0.047). Nine months after the follow-up, the difference in eGFR between the two groups disappeared. The lower risk of COVID-19 infection was observed across genders (male and female) and age groups (young and old). For the period before Omicron outbreak, results were also similar.

Interpretation In the largest TriNetX matched cohort study of IgAN, COVID-19 vaccination was associated with a reduced risk of COVID-19 infection and associated complications. However, careful monitoring of renal function, especially GFR, is advisable.

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Keywords: COVID-19 vaccine; Immunoglobulin A nephropathy (IgAN); Safety; Effectiveness; Renal function; TriNetX

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Research in context

Evidence before this study

We conducted an extensive search on PubMed for articles published up to September 30, 2023, using the keywords "COVID-19," "vaccine," and "IgA nephropathy," with no language restrictions. Recent studies have primarily focused on relapsing or de novo IgA nephropathy after vaccination. However, no large-scale, control-matched study has been undertaken to investigate the effectiveness and renal safety of COVID-19 vaccines in patients with IgA nephropathy. Therefore, we initiated this study to address this knowledge gap.

Added value of this study

In this study, we leveraged the TriNetx database and employed propensity score matching to compare renal function and the effectiveness of COVID-19 vaccines in patients with IgA nephropathy. Compared to the non-vaccinated group, vaccinated patients exhibited significantly lower risks of COVID-19 infection and related complications, including COVID-19 pneumonia, acute respiratory failure, sepsis, emergency department visits, all hospitalizations, and mortality. However, one month after the follow-up, the vaccinated group displayed a statistically significant, albeit slight, decrease in estimated glomerular filtration rate (eGFR) compared to the non-vaccinated group. Nevertheless, nine months after the follow-up, the difference in eGFR between the two groups had disappeared. The reduced risk of COVID-19 infection was consistently observed across genders (both male and female) and age groups (both young and old). These findings remained consistent during the period preceding the Omicron outbreak.

Implications of all the available evidence

Based on our findings, we strongly recommend that patients with IgA nephropathy receive the COVID-19 vaccination to reduce the risk of infection and its associated complications. However, it is advisable to closely monitor renal function, particularly the GFR, in these patients.

Introduction

Since December 2019, COVID-19 has caused a major health crisis with patients experiencing various complications including heart injury,[1] kidney injury,[2] septic shock,[3] respiratory tract injury[4] and pulmonary embolism.[5] In response, over 12.7 billion vaccine doses have been administered in 184 countries by October 5, 2022, according to the Bloomberg Vaccine Tracker. However, increasing data suggests a link between post-COVID-19 vaccination and kidney issues, encompassing acute kidney injury (AKI),[6–9] chronic kidney disease (CKD),[10,11] and glomerular diseases (GD).[12–16]

Of all the GD, immunoglobulin A nephropathy (IgAN) is the most commonly reported to be related to COVID-19 vaccines.[13,17,18] Until October 2022, there have been 52 reported cases of IgAN associated with COVID-19 vaccines.[18] Previous case series have reported renal function deterioration associated with COVID-19 vaccination in individuals with IgAN.[13,18] In another observational cohort study,[19] the estimated glomerular filtration rate (eGFR) showed a mild but statistically significant reduction ($p = 0.03$). Furthermore, a case series involving 42 patients[13] found that 39.4% of patients experienced AKI. A review article[9] also reported 53 cases of renal function deterioration in IgAN following COVID-19 vaccination. However, some case reports did not show any instances of AKI.[20–24] Furthermore, a nationwide retrospect cohort study from Swiss population showed that most temporal associations between SARS-CoV-2 vaccination and glomerulonephritis likely coincidental.[25] On the contrary, another retrospective population-level cohort study also concluded that second or third dose of COVID-19 vaccine was associated with higher relative risk but low absolute increased risk of relapse.[26] Until now, investigations into the outcomes of renal function after COVID-19 vaccination in patients with IgAN have been limited to case series and population studies, lacking matched cohort studies. It is imperative to clarify the safety of COVID-19 vaccines concerning renal function in individuals with IgAN.

Several potential hypotheses have been suspected of COVID-19 vaccine on IgAN, such as the triggering of immunity by the vaccine, but none have been confirmed.[13,27–31] This aspect should be further investigated in patients with IgAN since IgAN is frequently triggered by virus infections of the upper respiratory tract.[32] If the COVID-19 vaccine can reduce virus infections, it is reasonable to assume that it may also reduce the relapse of IgAN, given its potential link to viral infections. However, it's important to note that COVID-19 can also trigger immune responses,[13,27–31] which may contribute to the relapse of IgAN. To date, there has been no large-scale matched study conducted to definitively answer this question.

In addition to the concerns mentioned, widespread vaccine usage is strongly recommended to mitigate the impact of COVID-19 and significantly reduce the risks of severe illness and death. All vaccines appear to be safe and effective in preventing severe complications of COVID-19, including pneumonia, respiratory failure, and sepsis, as well as reducing the risk of hospitalization and death.[33] However, regarding IgAN, there have been no clinical trials assessing the efficacy of COVID-19

vaccines specifically in IgAN patients, and no real-world effectiveness studies have been conducted thus far. The impact of COVID-19 vaccines on infection rates in immunocompromised patients remains a subject of ongoing debate. The efficacy or effectiveness of COVID-19 vaccines in immunocompromised patients has been reported to be reduced.[34] This issue should also be given more attention because many IgAN patients are relatively immunocompromised due to their treatment regimens. Further research is needed to clarify the vaccine's effectiveness in this specific population.

Based on the aforementioned reasons, we are conducting this large-scale study with control groups to investigate the safety, with a particular focus on renal function, and effectiveness of COVID-19 vaccines in patients with IgAN.

Methods

Data sources

Our study utilized data from the Global Collaborative Network, consisting of 106 leading healthcare organizations (HCOs). Within the TriNetx network, we accessed data from over 124 million participants across 15 countries. This extensive dataset enabled us to comprehensively analyze different study aspects. The collaboration among these organizations was essential for deriving valuable insights and meaningful conclusions from this rich dataset. The TriNetx is a platform that amalgamates data from Electronic Health Records and insurance claims into a unified, longitudinal record for each of the 11.2 million patients represented in both sources. Details about this dataset's validation can be found in a published paper.[35] Up to this point, over 450 papers sourced from TriNetx have been published on PubMed.

The retrospective dataset we have at our disposal is comprehensive, encompassing a diverse range of crucial information, including demographics, diagnoses (coded of International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM), procedures (coded in International Classification of Diseases, Tenth Revision, Procedure Coding System, ICD-10-PCS, or Current Procedural Terminology, CPT), medication (coded in Veterans Affairs National Formulary), laboratory tests (coded in Logical Observation Identifiers Names and Codes, LOINC), and healthcare utilization. The richness and diversity of this dataset offer an exceptional opportunity to delve into various aspects of our study with precision and depth. All the data used in this study were sourced from TriNetx.

The HCOs involved in this collaborative network include hospitals, primary-care units, and specialists, and they contributed data from both uninsured and insured patients. HCOs contributing to TriNetX are primarily large academic centers, and the treatment of IgAN also predominantly occurs in such institutions. The TriNetX database served as the data source for this research, functioning as a global health-collaborative clinical-research platform that acquires real-time electronic medical data from a network of HCOs. For more details about TriNetx, please refer to the Appendix file.

Notably, TriNetX currently houses the most extensive global dataset concerning COVID-19. Numerous prior studies have leveraged TriNetX to explore the risk, trends, and outcomes associated with COVID-19 infection. For our study, we established a cohort spanning from September 18, 2018 to September 18, 2023, leveraging the global collaborative network within TriNetX. We defined inclusion and exclusion criteria, determined the index event and index date, and specified time windows for baseline data collection. Subsequently, we conducted a comparison of the two cohorts using the built-in propensity score matching (PSM) tool, selecting the variables for matching. We also have the capability to define follow-up conditions, including duration, time windows, and outcome settings.

Ethics statement

Given the anonymous nature of the data, the requirement for informed consent was waived. It is worth emphasizing that TriNetX adheres to the guidelines stipulated by the Health Insurance Portability & Accountability Act and the General Data Protection Regulation. Additionally, the Western Institutional Review Board has granted TriNetX an informed consent waiver, as the platform solely aggregates counts and statistical summaries of de-identified information. Moreover, our specific use of TriNetX for this study received approval from the institutional review board (IRB) committee of Taichung Veterans General Hospital (approval number: SE22220A-1, TCVGH).

Study design

The study design and recruitment algorithms are presented in Fig. 1A (vaccination group) and Fig. 1B (non-vaccination group). The entire study period spans from September 11, 2018 to September 11, 2023, for both groups. In the vaccination group (Fig. 1A), the index event is COVID-19 vaccination, and the vaccination date serves as the index date. In the non-vaccination group (Fig. 1B), patients in this group should not have received any COVID-19 vaccination throughout the study period. The index event for this group is a negative result for a COVID-19 PCR test. However, in both groups, only individuals diagnosed with IgAN (at least one day before the index event) and confirmed to be free of COVID-19 infection. Patients confirmed to be free of COVID-19 infection within the time frame from one month to one day before the index event.

For both groups, baseline data were collected within one year before the index date, with the most recent data also being collected. Regarding the collection of outcomes, to prevent reverse causality, we initiated data collection one week after the index event.

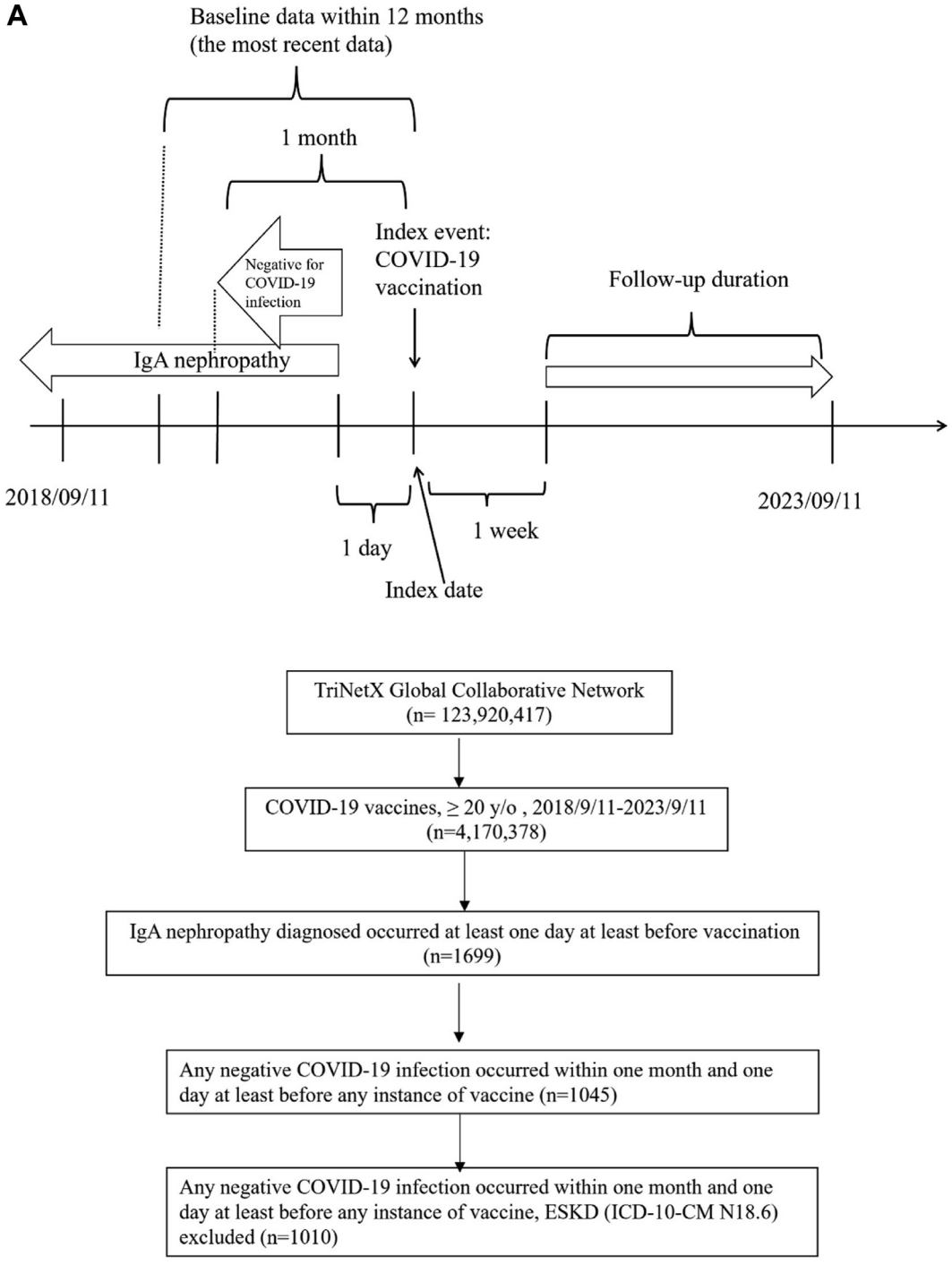


Fig. 1: Study design and flowchart of cohort construction. (A) Vaccinated group. (B) Non-vaccinated group.

Definition of population of IgAN: inclusion and exclusion criteria

The study population of IgAN was defined based on ICD-10 code D80.2, comprising individuals aged 20 years or older, in accordance with the IRB regulations at TCVGH. To conduct this search on the global collaborative network of TriNetX, we applied a time constraint within five years (from September 11, 2018 to September 11, 2023). We

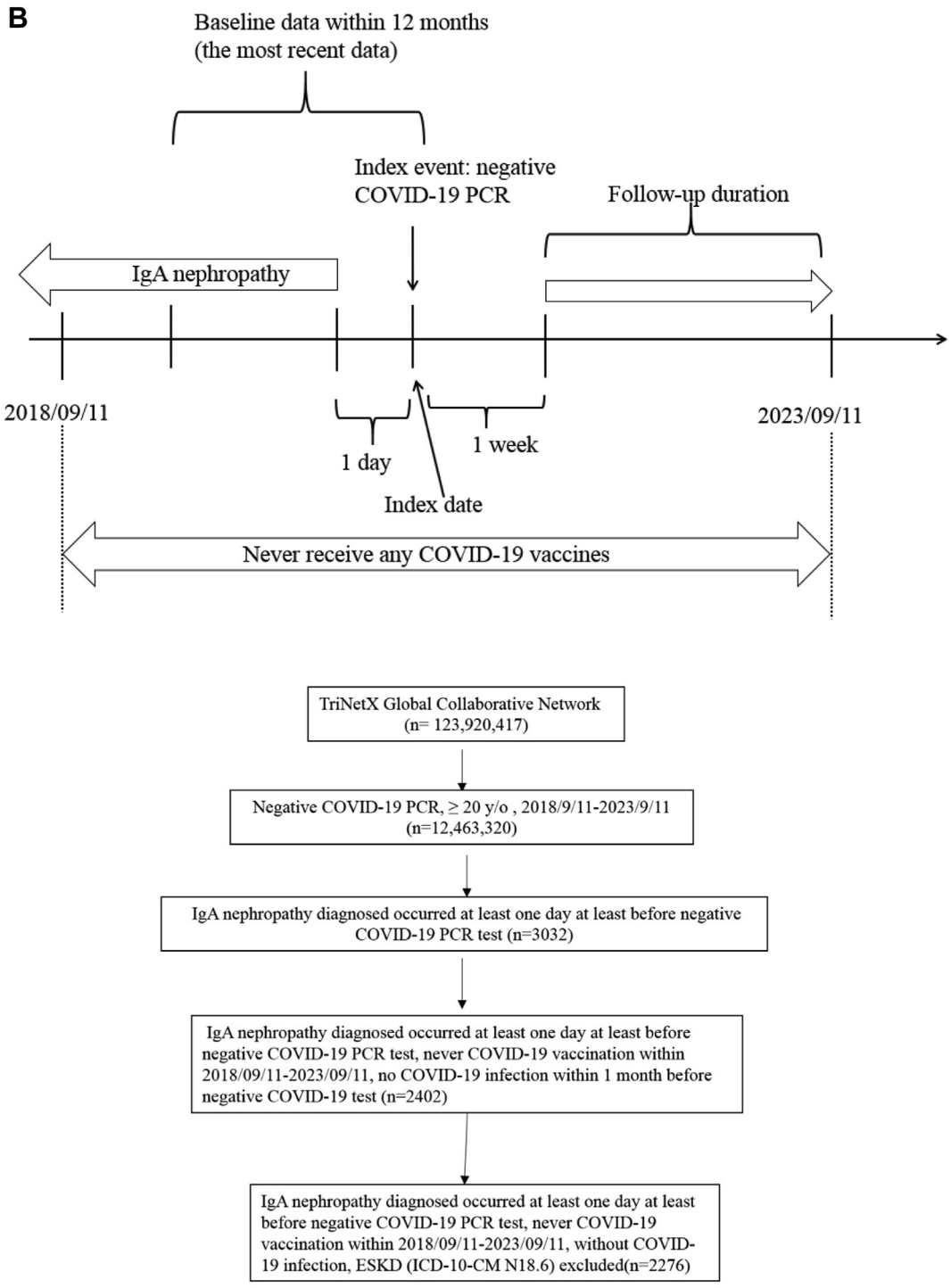


Fig. 1: (continued).

included only IgAN patients who tested definitely negative for COVID-19 infection. Patients without a test or those who tested positive were excluded. All the detailed selections for this cohort are presented in Fig. 1A and B. In both groups, patients with end-stage kidney disease (ESKD) (ICD-10-CM N18.6) were excluded from the study.

In TriNetX collaborative network, the entire case number of IgAN (≥20 y/o) is 11760 according to ICD-10 code D80.2. For renal biopsy-proved IgAN (codes for renal biopsy were CPT 1008085, 50200, 50205, 1027857, 77012, 88305, 88348, 88346, and 88313; and SNOMED: 769246001, 274326000, 175967008, 175962002, and 1727790008), the case number is 4688 (39.9%). In our cohort, case number of renal biopsy-proved IgAN is 479 in vaccinated group, and 1113 in non-vaccinated group, respectively. Therefore, the proportion of renal biopsy-proved IgAN is 47.4% and 48.9%, respectively. In the sensitivity analysis (before outbreak of Omicron, October 31 2021), the proportional for renal-biopsy proved IgAN is 51.1% for vaccinated group and 59.7% for non-vaccinated group, respectively.

The treatment group, which received at least one dose of the COVID-19 vaccine, was identified using the COVID-19 related vaccination code (Supplementary Table S1). The COIVD-19 infection status (Supplementary Table S1) was confirmed by COVID-19 PCR test, other COVID-19 related test other than PCR, and ICD-10-CM U70.1.

Pre-specified outcomes

All the desired outcomes are pre-specified as follows, based on the following codes:

(1) Renal function: baseline and followed eGFR based on Modification of Diet in Renal Disease equation (eGFR-MDRD) (TNX: 8001), proteinuria (urine protein creatinine ratio) (UPCR) (TNX: LG34791-0), and hematuria (erythrocyte count per high power field microscopy) (UMLS: LNC: 13945-1). We also defined ESKD or dialysis according to ICD-10-CM N18.6, and CPT codes (90935, 90937, 90945, 90947, 90989, 90999, 90960, 90961, 90962, 90965, 90966, 90957, 90958, 90959, 90969 or 90970).
(2) COVID-19 Infection related outcomes: all COVID-19 infection (ICD-10-CM: J12.82, U07.1, B34.2, U09, U09.9; TNX: 9088; LOINC: 94531-1, 94306-8, and 41458-1), and COVID-19 related pneumonia (ICD-10-CM: J12.82).
(3) Lung conditions: acute respiratory failure (ICD-10-CM: J96.0), intubation and mechanical ventilator support (CPT: 1015098), acute respiratory distress syndrome (ICD-10-CM: J80), and composite outcome (all of the above).
(4) Sepsis cascade: sepsis (ICD-10-CM: A41.9), severe sepsis without shock (ICD-10-CM: R65.20), septic shock (ICD-10-CM: R65.21), and composite outcome (all of the above).
(5) Outcomes related to hospital visit: emergency department visit (CPT: 99281, 99282, 99283, 99284, 99285, and 1013711) and all hospitalization (CPT: 1013659, 1013660, 1013699, 1013729, 99221, 99222, 99223, 99231, 99232, 99233, 99234, 99235, 99236, 99251, 99252, 99253, 99254, and 99255).
(6) Outcomes related to heart: ischemic heart disease (ICD-10-CM: I20–I25, I21.3, I21.4, and I21.9), and heart failure (ICD-10-CM: I50 and I50.9).
(7) All-cause mortality: deceased code.

Statistical analyses

In this study, PSM (utilizing the built-in TriNetX tool) was employed to create matched groups with similar baseline characteristics on a 1:1 basis. The PSM is only done for covariates that are not missing and it is done separately for subgroup analysis and only includes enough covariates. The variables used for matching encompassed demographic data (age at index, sex, and race), comorbidities (diabetes mellitus, asthma, chronic obstructive pulmonary disease, and ischemic heart diseases), medications (glucocorticoids), angiotensin-converting enzyme inhibitors (ACEis), angiotensin II inhibitors (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, and mycophenolic acid), renal function (eGFR-MDRD, proteinuria (UPCR), and hematuria (erythrocyte in urine per high power field (HPF) microscopy), and blood C-reactive protein (CRP).

The PSM was integrated into the TriNetX system. This method generated 1:1 matched group with similar baseline characteristics by utilizing greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations (SDs), where a value of Standardized Mean Difference (SMD) <0.1 indicates a small difference, signifying successful matching.

Subsequently, the hazard ratio (HR) was calculated with a 95% confidence interval (95% CI) for outcomes of effectiveness in both the vaccinated and unvaccinated groups. The assumption of proportional hazards was tested using the generalized Schoenfeld approach, which is integrated into the TriNetX platform.

In our Kaplan–Meier analyses, patients are censored when they no longer provide additional information for the analysis. When the last clinical fact in the patient's record falls within the time window for analysis, they are censored on the day following the last fact in their record. The data for followed hematuria, proteinuria, and eGFR between the vaccinated and non-vaccinated groups were analyzed using the built-in Student's t-test in TriNetX.

Subgroup analyses were performed to examine how the risks for all outcomes varied based on sex (male and female) and age group (20–<64 years old vs. ≥65 years old). Importantly, to avoid confounding by unreported and underestimated COVID-19 infection, we also performed sensitivity analysis in the different time period (from September 11 2018 to October 31 2021), which indicated before outbreak of Omicron variants.

The TriNetX platform is a custom developed solution purpose built for the clinical research domain. As such,

the underlying technology proprietary and much of it is protected by trade secrets. The list of software languages and packages were Java 11.0.16 (Apache Commons Math 3.6.1), R 4.0.2 (Hmisc1-1, and Survival 3.2-3), and Python 3.7 (lifelines 0.22.4, matplolib 3.5.1, numpy 1.21.5, pandas 1.3.5, scipy 1.7.3, and statsmodels 0.13.2).

Roles of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Baseline characteristics of this cohort before and after matching

Prior to PSM, the vaccinated group consisted of 1010 individuals, while the non-vaccinated group included 2770 individuals. As shown in Table 1, after PSM, both groups were reduced to 979 patients each for further analysis. There were only 27 (2.8%) patients loss of follow-up in the vaccinated group and 38 (3.9%) patients loss of follow-up in the non-vaccinated group. The median duration of follow-up was 1.9 and 2.1 years for the vaccinated and non-vaccinated groups, respectively.

Overall, the patients in this cohort were young, with an average age of around 55 years, and predominantly female (n = 686, 70%). Baseline renal function was fair, with an eGFR-MDRD of 78–80 ml/min/1.732 m^2, UPCR of 111–112 mg/g, and 3–4 red blood cells per HPF of hematuria. In terms of race, the majority were white (n = 842, 88%). Non-United States patients comprised less than 1% in both groups, as shown in Supplementary Figure S1.

Regarding comorbidities, approximately 14–15% of patients had diabetes mellitus (n = 148 and 140 for each group, respectively), 11% had ischemic heart disease (n = 104 and 102 for each groups, respectively), 16–18% had asthma (n = 180 and 159 for each groups, respectively), and 1% had bronchitis (n = 13 and 10 for each groups, respectively). Approximately 8% and 10% of patients were taking ACEi (n = 82 and 77 for each group) and ARBs (n = 98 and 88 for each group), respectively. Around 25% patient ever took NSAID (n = 237 and 218 for each group) and 40% had previously taken glucocorticoids (n = 396 and 395 for each group). Other immunosuppressants were seldom used in both groups (1%). Overall, this population exhibited relatively good health conditions. The 1:1 PSM was successful, as evidenced by all SMDs being less than 0.1, as shown in Table 1 and Supplementary Figure S3.

The types of COVID-19 vaccines administered to this cohort are listed in Supplementary Table S2. As the majority (>99%) of patients in this cohort resided in the United States, the most administered vaccines were mRNA vaccines, with Pfizer-BioNTech being the most prevalent, followed by Moderna. These vaccine types align with the summary of COVID-19 vaccine types reported by the Centers for Disease Control and Prevention (CDC), as depicted in Supplementary Figure S2.

Effectiveness outcome: incidence of outcomes between vaccinated and non-vaccinated groups

The HR for all relevant effectiveness outcomes between the vaccinated and non-vaccinated groups was analyzed (Table 2). Compared to the non-vaccinated group, vaccinated patients exhibited a lower HR (95% CI) for COVID-19 infection and related complications, including all COVID-19 infection (HR: 0.050, 95% CI: 0.026, 0.093), COVID-19 pneumonia (HR: 0), severe lung complication (0.647, 95% CI: 0.421, 0.994), acute respiratory failure (0.625, 95% CI: 0.400, 0.978), sepsis (0.545, 95% CI: 0.334, 0.890), emergency department visits (0.716, 95% CI: 0.615, 0.833), all hospitalizations (0.573, 95% CI: 0.459, 0.715), and mortality (0.595, 95% CI: 0.366, 0.969). The most significant risk reduction (up to 95%) was observed for COVID-19 infection, followed by sepsis (45.5%), the composite outcome of sepsis (44.4%), all hospitalization (42.7%), acute respiratory failure (37.5%), the composite outcome of lung complications (35.2%), and emergency department visits (28.4%). Furthermore, after COVID-19 vaccination, no patients developed COVID-19 pneumonia, whereas the non-vaccinated group still had 19 cases.

In Fig. 2, Kaplan–Meier curves illustrating significant differences in the above outcomes also demonstrate a significant survival benefit in the vaccinated groups. Significantly, the vaccinated group experienced a notably lower incidence of COVID-19 infection very early in the follow-up period (Fig. 2A). Similarly, significant differences in emergency department visits (Fig. 2G) and all hospitalization outcomes (Fig. 2H) can be observed during the early follow-up period.

Safety outcome: renal function

In Table 3, renal function, including eGFR, proteinuria, and hematuria, is presented based on different follow-up time points. Throughout the entire follow-up period, there were no significant differences in proteinuria and hematuria between the vaccinated and non-vaccinated groups (all $p > 0.05$). However, concerning eGFR, the vaccinated group exhibited lower eGFR levels than the non-vaccinated group at 1-month, 3-month, 6-month, and at the end of the follow-up period. Notably, the disparity in eGFR gradually decreased over the duration of follow-up, with differences of 1.94 (baseline, not statistically significant), 9.47 (1-month), 6.33 (3-month), 5.54 (6-month), 2.71 (9-month, not statistically significant), and 2.36 ml/min/1.732 m^2 (12-month, not statistically significant). At the time point for end of follow-up, the eGFR difference is 3.56 ml/min/1.732 m^2. However, it is worth mentioning that in both groups, the final eGFR did not

	Before matching				After matching			
	Vaccination group (n = 1010)	Non-vaccination group (n = 2776)	p-value	SMD	Vaccination group (n = 979)	Non-vaccination group (n = 979)	p-value	SMD
	n (%) or mean ± SD	n (%) or mean ± SD			n (%) or mean ± SD	n (%) or mean ± SD		
Demographic data								
Age at index (y/o)	55.6 ± 17.2	49.2 ± 18.0	<0.001	0.366	55.21 ± 17.14	55.04 ± 17.44	0.832	0.010
Male	298 (29.5%)	610 (26.8%)	0.108	0.061	284 (29.0%)	277 (28.3%)	0.726	0.016
Race or ethnicity								
White	858 (85.0%)	1929 (84.8%)	0.857	0.007	842 (86.0%)	846 (86.4%)	0.793	0.012
Hispanic	29 (2.9%)	67 (3.0%)	0.911	0.004	29 (3.0%)	33 (3.4%)	0.606	0.023
Black or African American	39 (3.9%)	105 (4.6%)	0.333	0.037	39 (4.0%)	33 (3.4%)	0.471	0.033
Asian	25 (2.5%)	17 (0.8%)	<0.001	0.138	13 (1.3%)	15 (1.5%)	0.703	0.017
Unknown ethnicity	92 (9.1%)	445 (19.6%)	<0.001	0.301	92 (9.4%)	88 (9.0%)	0.754	0.014
Diagnosis								
Diabetes mellitus	152 (15.1%)	292 (12.8%)	0.085	0.064	148 (15.1%)	140 (14.3%)	0.610	0.023
Ischemic heart diseases	107 (10.6%)	190 (8.4%)	0.038	0.077	104 (10.6%)	102 (10.4%)	0.883	0.007
Asthma	183 (18.1%)	445 (19.6%)	0.339	0.036	180 (18.4%)	159 (16.2%)	0.210	0.057
Other chronic obstructive pulmonary disease	65 (6.4%)	143 (6.3%)	0.865	0.006	65 (6.6%)	58 (5.9%)	0.514	0.029
Chronic bronchitis	13 (1.3%)	58 (2.6%)	0.022	0.092	13 (1.3%)	10 (1.0%)	0.529	0.028
Laboratory data of blood								
Hemoglobin A1c (%)	6.09 ± 1.39	6.24 ± 1.77	0.204	0.094	6.104 ± 1.42	6.16 ± 1.56	0.687	0.034
CRP (mg/dl)	12.26 ± 23.92	15.14 ± 37.32	0.406	0.092	11.59 ± 22.47	12.41 ± 32.19	0.811	0.030
Renal function								
eGFR-MDRD (ml/min/1.732 m^2)	78.07 ± 23.33	83.48 ± 29.00	<0.001	0.206	78.09 ± 23.36	80.03 ± 27.86	0.182	0.075
UPCR (mg/g)	117.74 ± 290.03	89.32 ± 248.45	0.645	0.105	122.99 ± 295.73	111.87 ± 308.05	0.902	0.037
Erythrocytes in urine sediment by microscopy high power field	4.0 ± 8.0	5.4 ± 12.3	0.500	0.134	4.0 ± 8.0	3.4 ± 6.9	0.728	0.077
Medication								
ACEi	82 (8.1%)	151 (6.6%)	0.125	0.057	82 (8.4%)	77 (7.9%)	0.679	0.019
ARB	101 (10.0%)	189 (8.3%)	0.113	0.059	98 (10.0%)	88 (9.0%)	0.441	0.035
Glucocorticoids	409 (40.5%)	916 (40.3%)	0.884	0.006	396 (40.5%)	395 (40.4%)	0.963	0.003
NSAID	240 (23.8%)	574 (25.2%)	0.376	0.034	237 (24.2%)	218 (22.3%)	0.309	0.046
Cyclosporine	16 (1.6%)	26 (1.1%)	0.297	0.038	16 (1.6%)	16 (1.6%)	1	0
Tacrolimus	16 (1.6%)	26 (1.1%)	0.297	0.038	13 (1.3%)	15 (1.5%)	0.703	0.017
Mycophenolate mofetil	10 (1.0%)	30 (1.3%)	0.430	0.030	10 (1.0%)	10 (1.0%)	1	0
Azathioprine	12 (1.2%)	22 (1.0%)	0.562	0.022	10 (1.0%)	12 (1.2%)	0.668	0.019

SMD: standardized mean difference; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor II blocker; NSAID: non-steroidal anti-inflammatory drugs; eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio; CRP: C-reactive protein.

Table 1: **Baseline characteristics of study subjects before and after propensity score matching.**

exhibit significant changes compared to the baseline eGFR in each group, with values of 77.14 vs. 78.09 ml/min/1.732 m^2 in the vaccinated group and 80.70 vs. 80.03 ml/min/1.732 m^2 in the non-vaccinated group.

In both groups, there were 10 patients diagnosed with ESKD or undergoing dialysis. The risks in both groups were 1%, and there was no statistical significance.

Subgroup analysis by gender and age

Baseline characteristics of study subjects in the male, female, young, and old groups are presented in Supplementary Tables S3–S6, respectively. After PSM, the case numbers for both vaccinated and non-vaccinated groups were 282, 654, 595, and 391 for the male, female, young, and old subgroups, respectively.

The HR for outcomes of effectiveness is summarized in Table 4. A reduced HR for all COVID-19 infections can be observed in the vaccinated group across all four subgroups. Furthermore, there were no reported cases of COVID-19 pneumonia in the vaccinated groups across all four subgroups. Reduced HRs for severe lung complications (composite outcome), composite outcome of sepsis, sepsis, emergency department visits, and all hospitalizations can be observed in the female, young, and old subgroups of the vaccinated group.

When assessing renal safety outcomes for the four subgroups (Table 5 for male, Table 6 for female, Table 7 for young, and Table 8 for old cohort), there were no differences in proteinuria and hematuria between the vaccinated and non-vaccinated groups in all four

	Patients with outcome		Hazard ratio (95% CI)	Risk difference (95% CI)	p-value
	Vaccination	Non-vaccination			
1. COVID-19 infection related					
1.1 All COVID-19 infection	10	202	0.050 (0.026, 0.093)	−0.196 (−0.222, −0.170)	<0.001
1.2 COVID-19 pneumonia	0	19	0 (–, –)	−0.019 (−0.028, −0.011)	<0.001
2. Severe lung complication (composite outcome)	33	51	0.647 (0.421, 0.994)	−0.018 (−0.036, −0.000)	0.045
2.1 Acute respiratory failure	30	48	0.625 (0.400, 0.978)	−0.018 (−0.036, −0.001)	0.038
2.2 Intubation and ventilator support	10	10	1 (0.418, 2.392)	0 (−0.009, 0.009)	1
2.3 Acute respiratory distress syndrome	10	10	1 (0.418, 2.392)	0 (−0.009, 0.009)	1
3. Sepsis cascade (composite outcome)	25	45	0.556 (0.343, 0.899)	−0.020 (−0.037, −0.004)	0.015
3.1 Sepsis	24	44	0.545 (0.334, 0.890)	−0.020 (−0.037, −0.004)	0.014
3.2 Severe sepsis without shock	10	11	0.909 (0.388, 2.131)	−0.001 (−0.010, 0.008)	0.826
3.3 Septic shock	10	10	1 (0.418, 2.392)	0 (−0.009, 0.009)	1
4. Hospital visit					
4.1 Emergency department visit	214	299	0.716 (0.615, 0.833)	−0.087 (−0.126, −0.048)	<0.001
4.2 All hospitalization	106	185	0.573 (0.459, 0.715)	−0.081 (−0.112, −0.049)	<0.001
5. Cardiovascular outcome					
5.1 Ischemic heart disease	134	139	0.964 (0.774, 1.201)	−0.005 (−0.036, 0.026)	0.744
5.2 Heart failure	68	78	0.872 (0.638, 1.192)	−0.010 (−0.033, 0.013)	0.390
6. All-cause mortality	25	42	0.595 (0.366, 0.969)	−0.017 (−0.033, −0.001)	0.035

eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio.

Table 2: **Incidence of outcomes for effectiveness in the vaccinated and non-vaccinated groups (after propensity score matching).**

subgroups. Similarly, at 3-month of follow-up, there is also temporary eGFR difference between vaccinated and non-vaccinated group in 3 subgroups (female, young and old cohort). Then the decreased eGFR in vaccinated group all nearly increased to baseline eGFR after longer follow-up. The final eGFR was still lower in vaccinated groups than non-vaccinated group in the female subgroup (77.08 ± 23.85 vs. 82.05 ± 29.05, p = 0.004) and the old subgroup (66.41 ± 20.90 vs. 71.75 ± 26.58, p = 0.005).

Sensitivity analysis in different time period (before the outbreak of Omicron variant)

Baseline characteristics of subjects from September 11, 2018 to October 31, 2021, are presented in Supplementary Table S7, demonstrating good PSM with SMD less than 0.1. The outcomes observed were similar to those in the study population over the entire time frame from September 11, 2018 to September 11, 2023. The incidence of outcomes is summarized in Supplementary Table S8. Significantly lower risks were observed for various outcomes, including all COVID-19 infections (HR: 0.052, 95% CI: 0.027–0.099), COVID-19 pneumonia (HR: 0, no cases), severe lung complications (HR: 0.524, 95% CI: 0.300–0.914), acute respiratory failure (HR: 0, no cases), ARDS (HR: 0, no cases), ER visits (HR: 0.768, 95% CI: 0.595–0.993), all hospitalizations (HR: 0.568, 95% CI: 0.417–0.773), heart failure (HR: 0.659, 95% CI: 0.444–0.978), and all-cause mortality (HR: 0.426, 95% CI: 0.230–0.791). Kaplan–Meier curves for all the aforementioned outcomes are displayed in Supplementary Figure S4.

Renal function data before outbreak of Omicron are presented in Supplementary Table S9. There were no significant differences in proteinuria and hematuria between the vaccinated and non-vaccinated groups throughout the entire follow-up period (all p > 0.05). The eGFR did not differ between the two groups at baseline and at the end of the follow-up. However, in the vaccination group, a significant decline in eGFR was observed at 3 months (73.91 ± 21.93 vs. 78.50 ± 27.31, p = 0.028), but this decrease gradually diminished by the 6-month mark.

In summary, during the period before the outbreak of Omicron, both effectiveness and safety outcomes exhibited consistent results throughout the entire time frame.

Discussion

Until now, there have only been case reports or case series regarding the safety and effectiveness of post-COVID-19 vaccines in IgAN. Our study represents the first controlled and matched investigation into the effectiveness and safety of COVID-19 vaccination in IgAN. This study involved 979 IgAN patients in the vaccinated group and 979 matched individuals in the non-vaccinated group. Our findings indicate that COVID-19 vaccination offers direct benefits in reducing both COVID-19 infection and COVID-19 pneumonia, and these benefits were observed across four subgroups. Furthermore, we observed fewer complications in the vaccinated group, including lung issues, sepsis, hospital visits, and mortality. While these reductions of complications may not

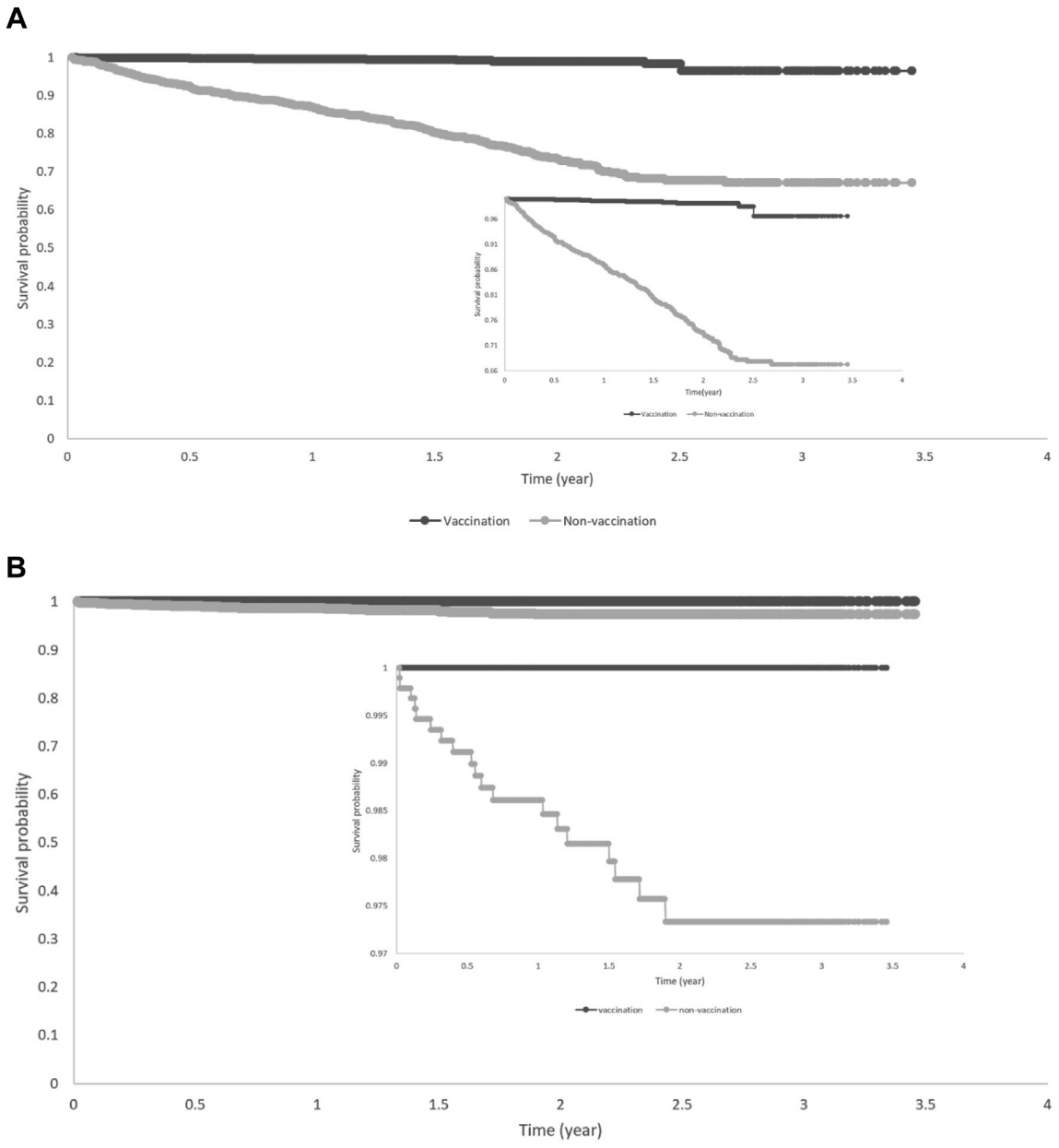
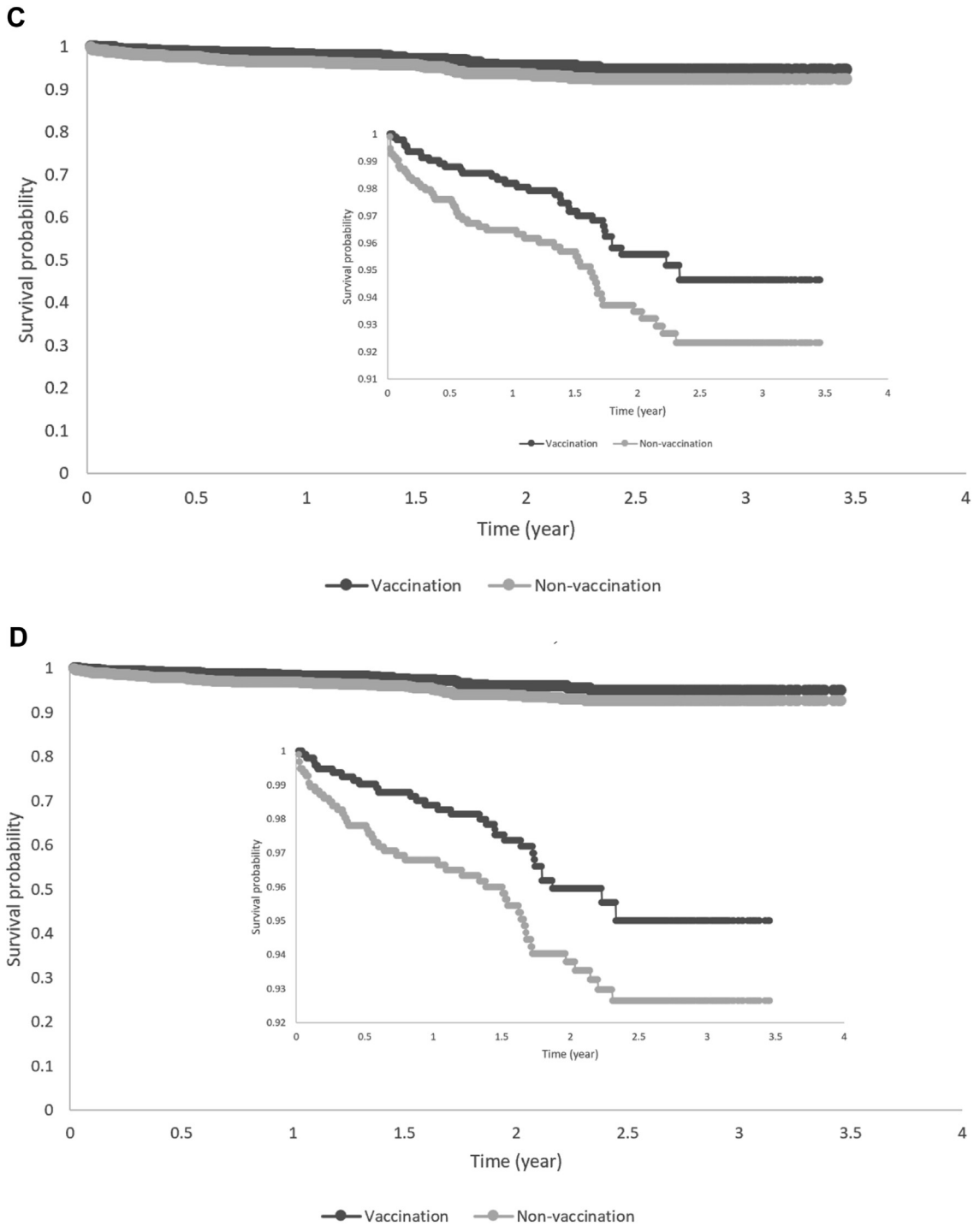


Fig. 2: Kaplan–Meier curves for all outcomes of effectiveness in patients with IgA nephropathy, stratified by vaccination status (Two Kaplan–Meier curves were presented per outcome with different scales to highlight the differences). (A) All COVID-19 infection (log-rank test, $p < 0.001$). (B) COVID-19 related pneumonia (log-rank test, $p < 0.001$). (C) Severe lung complication (composite outcome) (log-rank test, $p = 0.028$). (D) Acute respiratory failure (log-rank test, $p = 0.023$). (E) Systemic manifestation of infection (composite outcome of sepsis) (log-rank test, $p = 0.015$). (F) Sepsis (log-rank test, $p = 0.022$). (G) Emergency department visit (log-rank test, $p < 0.001$). (H) All hospitalization (log-rank test, $p < 0.001$). (I) All-cause mortality (log-rank test, $p = 0.029$).

be fully explained by COVID-19 vaccination alone, they could at least partially be attributed to it. During the follow-up period, despite similar levels of proteinuria and hematuria, we observed a reduced eGFR compared to the non-vaccinated group initially. However, this reduced eGFR gradually improved over time. We believe that renal function still necessitates regular follow-up.

Post-COVID vaccine-related renal function deterioration, including AKI and ESKD, has been discussed in the general population. Clinical trials[36,37] did not report any



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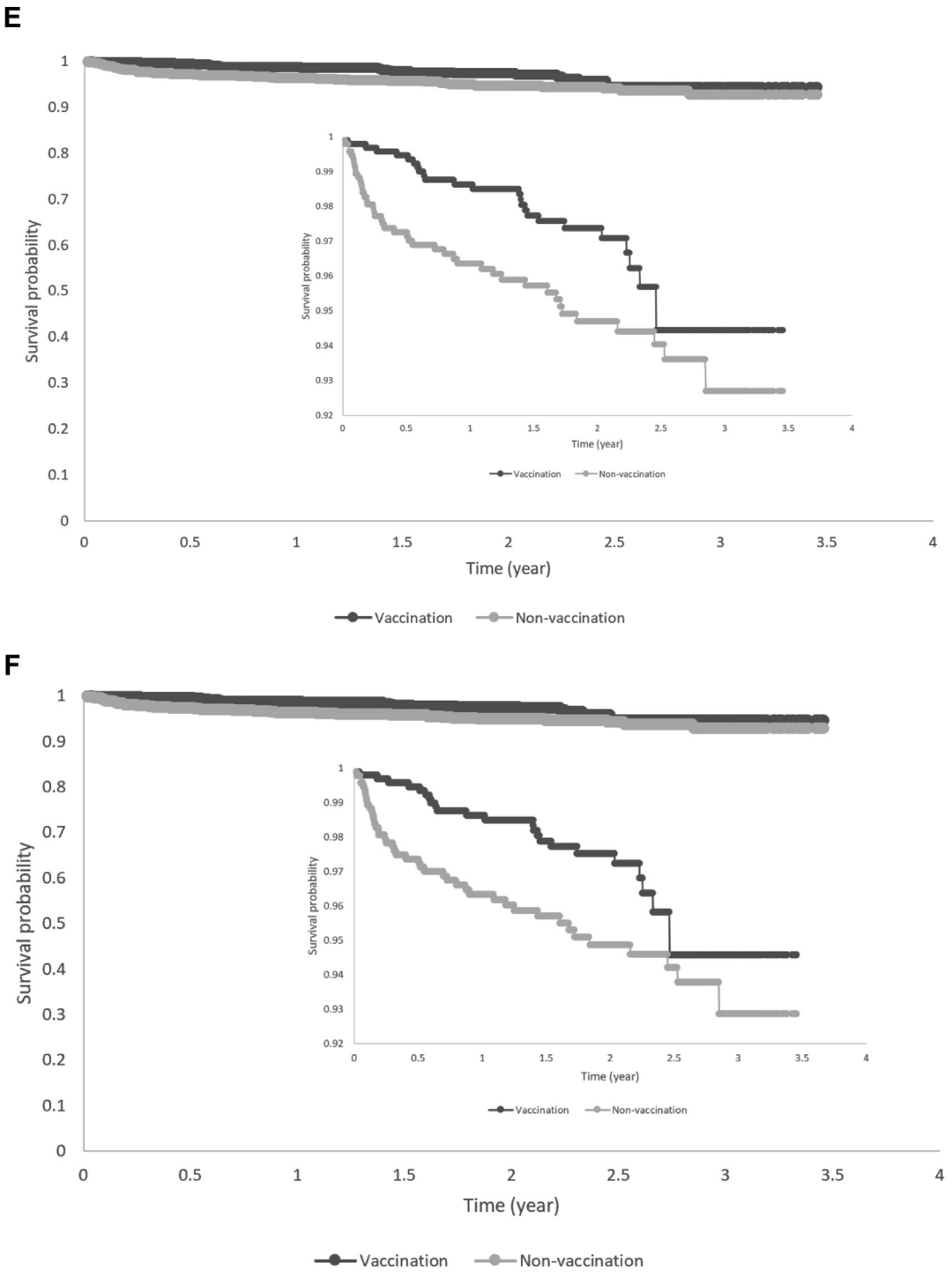
cases of AKI, and it has been considered rare in some case reports only.[15,38–45] A study from post-marketing surveillance reported to the Vaccine Adverse Event Reporting System between December 2020 and June 2021[46] revealed 1133 cases of AKI after vaccination, which accounted for only 0.006% among more than 493 million



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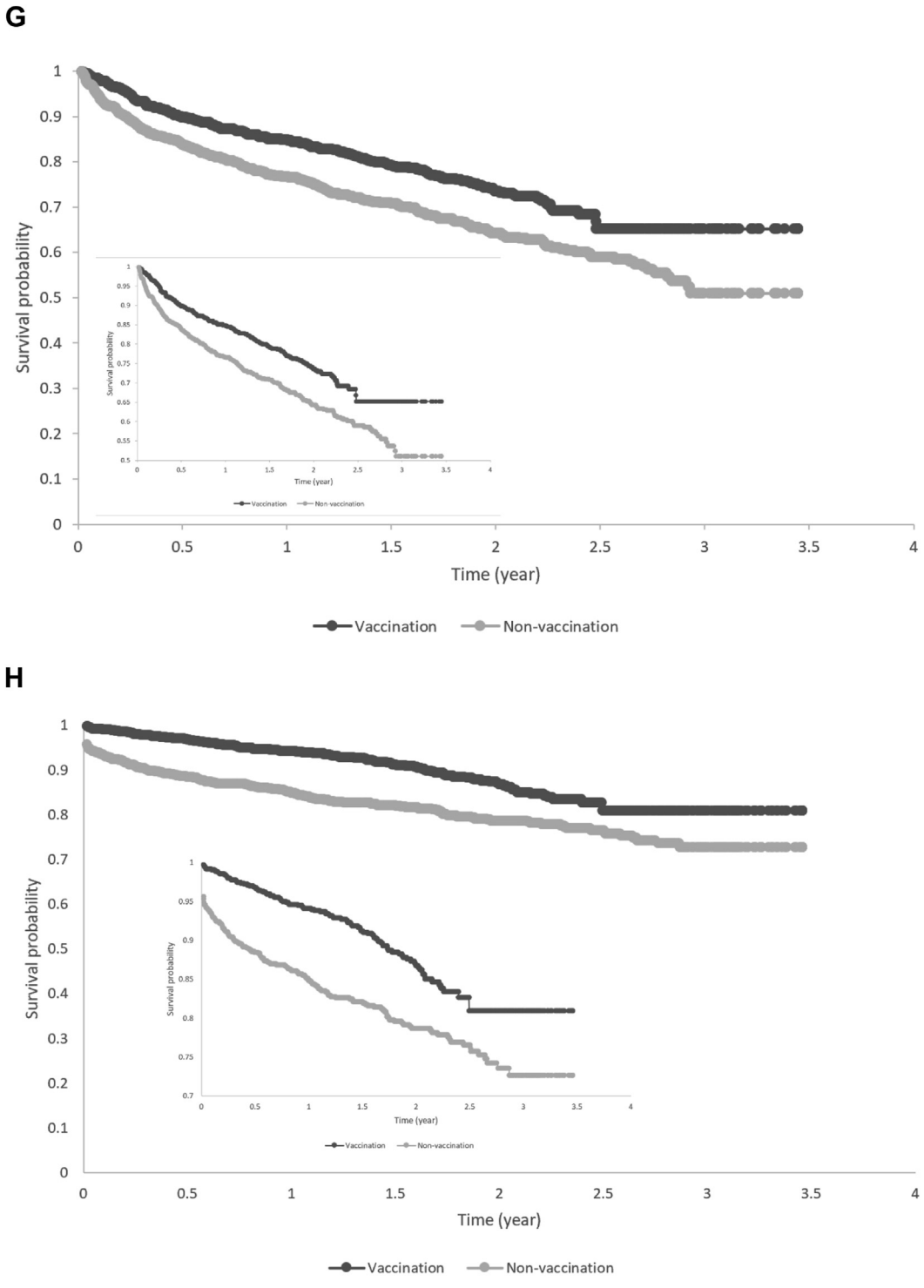
vaccine doses administered, indicating a very low occurrence rate. We believe that, particularly in the case of IgAN, this issue deserves greater attention.

Our study demonstrated that in both groups of IgAN, there were no significant changes in the final eGFR compared to the baseline eGFR, with values of 77.14 vs.



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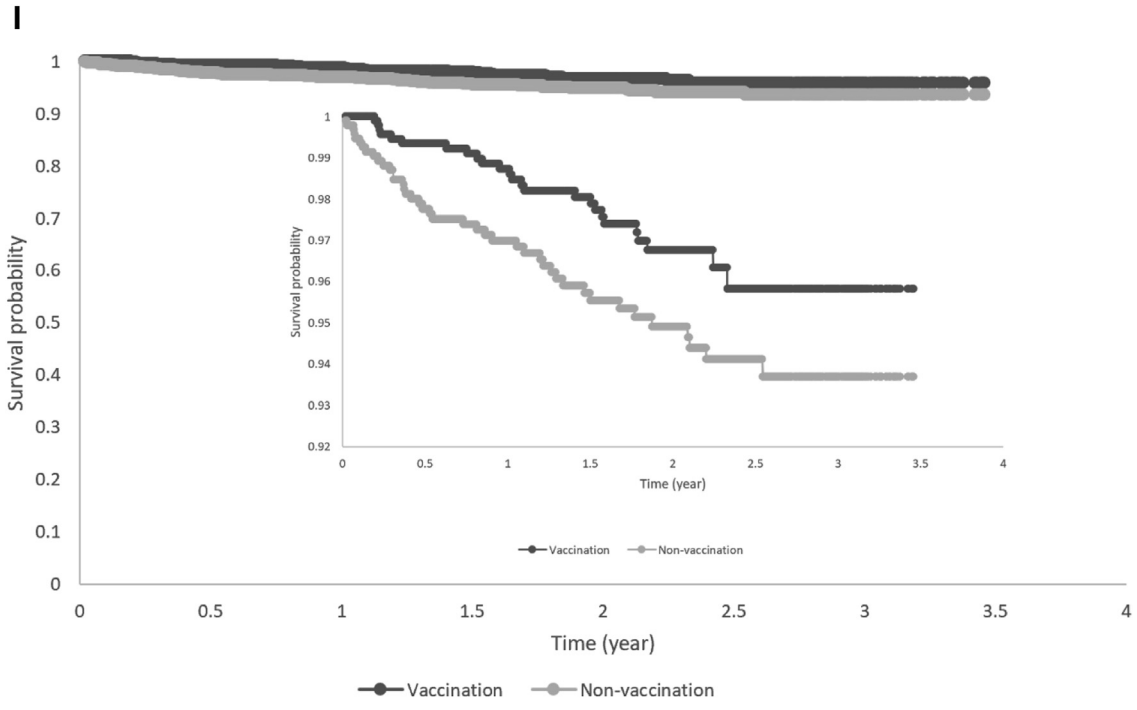
78.09 ml/min/1.732 m^2 in the vaccinated group and 80.70 vs. 80.03 ml/min/1.732 m^2 in the non-vaccinated group. It appears to be very safe without any eGFR concerns. However, during the first month of eGFR assessment, the vaccinated group exhibited a significant decrease in eGFR compared to the non-vaccinated group



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(73.58 ± 27.8 vs. 83.05 ± 35.37, p = 0.047, difference in eGFR: 9.47 ml/min/1.732 m^2) or compared to their baseline eGFR (73.58 ± 27.84 vs. 78.09 ± 23.36, difference in eGFR: 4.51 ml/min/1.732 m^2). Nevertheless, the reduced eGFR gradually improved during the follow-up period, and after 9 months, no difference in eGFR could be observed. There is a temporal change in eGFR difference between the vaccinated and non-vaccinated groups. In addition, there is also a temporal change in eGFR in vaccinated group (baseline: 78.09, 1-month: 73.58 (lowest), and final: 77.14 ml/min/1.732 m^2), not for non-vaccinated group (all around 80 ml/min/1.732 m^2). This temporal change in eGFR can be also observed in the time period before outbreak of Omicron. Our study is the first to follow a matched population at different time points to observe renal function in individuals with IgAN after COVID-19 vaccination.

In previous case series,[13,18] patients with IgAN experienced AKI. In another observational cohort study from China,[19] they followed up 202 patients within 3 months before and after vaccination. The eGFR showed a mild but statistically significant difference (68.39 vs. 67.33 ml/min/1.732 m^2, p = 0.03). In the latest and largest case series with 42 patients,[13] 39.4% of patients experienced AKI, but only 3 patients did not respond to treatment. Based on the findings from the above-mentioned case series, it appears that AKI may occur in some patients. However, the following case reports

	eGFR-MDRD (ml/min/1.732 m^2)			Proteinuria (UPCR) (mg/g)			Hematuria (erythrocyte/HPF)		
	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value
Baseline	78.1 ± 23.4	80.0 ± 27.9	0.182	123.0 ± 295.7	111.9 ± 308.1	0.902	4.0 ± 8.0	3.4 ± 6.9	0.728
1-month	73.6 ± 27.8	83.1 ± 35.4	0.047	148.5 ± 277.3	923.1 ± 1300.4	0.225	8.8 ± 7.8	0.8 ± 0.5	0.087
3-month	74.3 ± 25.8	80.6 ± 29.7	0.015	104.0 ± 214.2	305.8 ± 736.4	0.396	7.5 ± 11.3	3.6 ± 3.5	0.373
6-month	73.8 ± 24.9	79.4 ± 28.3	0.030	164.3 ± 310.9	439.5 ± 905.9	0.500	5.5 ± 8.8	13.8 ± 23.5	0.359
9-month	77.1 ± 25.3	79.9 ± 27.9	0.319	155.5 ± 363.4	612.4 ± 1082.4	0.347	1.5 ± 2.1	5.3 ± 10.5	0.632
12-month	75.4 ± 24.2	77.8 ± 29.3	0.387	102.6 ± 204.3	781.7 ± 1353.8	0.354	7.8 ± 9.5	2.4 ± 2.5	0.100
End of follow-up	77.1 ± 24.5	80.7 ± 28.2	0.012	53.6 ± 102.7	233.3 ± 643.6	0.136	9.5 ± 23.3	8.3 ± 22.1	0.799

eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio; HPF: high power field of microscopy.

***Table 3:* Follow-up renal function at different time periods among vaccinated and non-vaccinated groups.**

Incidence of outcome	Hazard ratio (95% CI)			
	Male	Female	Young	Old
1. COVID-19 infection related				
1.1 All COVID-19 infection	0.213 (0.110, 0.413)	0.075 (0.040, 0.142)	0.083 (0.044, 0.156)	0.149 (0.078, 0.286)
1.2 COVID-19 pneumonia	0	0	0	0
2. Severe lung complication (composite outcome)	0.813 (0.398, 1.658)	0.515 (0.290, 0.916)	0.440 (0.218, 0.886)	0.579 (0.349, 0.960)
2.1 Acute respiratory failure	0.846 (0.386, 1.857)	0.500 (0.277, 0.902)	0.476 (0.226, 1.002)	0.583 (0.347, 0.981)
2.2 Intubation and ventilator support	1 (0.423, 2.365)	1 (0.419, 2.386)	1 (0.419, 2.385)	1 (0.421, 2.376)
2.3 Acute respiratory distress syndrome	0	– (–, –)	0	1 (0.421, 2.376)
3. Sepsis cascade (composite outcome)	1.083 (0.503, 2.333)	0.375 (0.195, 0.722)	0.385 (0.187, 0.790)	0.514 (0.296, 0.892)
3.1 Sepsis	1.182 (0.539, 2.593)	0.344 (0.175, 0.676)	0.400 (0.194, 0.825)	0.500 (0.284, 0.880)
3.2 Severe sepsis without shock	1 (0.423, 2.365)	1 (0.419, 2.386)	1 (0.419, 2.385)	1 (0.421, 2.376)
3.3 Septic shock	1 (0.423, 2.365)	1 (0.419, 2.386)	1 (0.419, 2.385)	1 (0.421, 2.376)
4. Hospital visit				
4.1 Emergency department visit	0.765 (0.579, 1.009)	0.719 (0.597, 0.865)	0.694 (0.566, 0.850)	0.696 (0.557, 0.870)
4.2 All hospitalization	0.685 (0.467, 1.006)	0.459 (0.346, 0.609)	0.522 (0.374, 0.729)	0.696 (0.557, 0.870)
5. Cardiovascular outcome				
5.1 Ischemic heart disease	0.906 (0.636, 1.290)	1.130 (0.833, 1.534)	1 (0.643, 1.555)	0.925 (0.732, 1.170)
5.2 Heart failure	0.839 (0.512, 1.375)	0.854 (0.571, 1.277)	0.923 (0.536, 1.589)	0.797 (0.558, 1.138)
6. All-cause mortality	0.556 (0.261, 1.182)	0.452 (0.243, 0.841)	0.769 (0.340, 1.741)	0.531 (0.300, 0.941)

Table 4: **Subgroup analysis of effectiveness by gender (Male and Female) and age (Young: 20–<65 y/o, Old: ≥65 y/o).**

	eGFR-MDRD (ml/min/1.732 m^2)			Proteinuria (UPCR) (mg/g)			Hematuria (erythrocyte/HPF)		
	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value
Baseline	79.0 ± 25.0	77.9 ± 27.5	0.703	2.2 ± 3.8	0.7 ± 1.0	0.251	6.8 ± 15.1	6.9 ± 11.7	0.987
1-month	72.7 ± 30.2	80.5 ± 36.9	0.411	312.1 ± 36.2	211.5 ± 211.4	0.302	5.5 ± 3.5	3.0 ± 2.8	0.517
3-month	77.1 ± 29.7	80.9 ± 28.1	0.303	102.1 ± 323.2	123.4 ± 123.2	0.456	8.5 ± 12.5	2.5 ± 1.7	0.385
6-month	79.6 ± 29.2	78.8 ± 30.0	0.881	143.2 ± 362.4	4.0 ± 2.3	0.425	4.7 ± 6.4	16.8 ± 29.5	0.526
9-month	82.5 ± 30.8	76.1 ± 29.1	0.277	311.2 ± 122.5	219.5 ± 437.7	0.560	5.2 ± 6.5	6.4 ± 6.2	0.639
12-month	74.9 ± 24.3	75.4 ± 24.4	0.922	433.1 ± 747.3	325.6 ± 326.9	0.369	1.0 ± 2.3	2.7 ± 2.9	0.326
End of follow-up	77.5 ± 26.1	79.5 ± 30.1	0.479	5.1 ± 10.0	211.5 ± 454.2	0.391	4.4 ± 7.2	7.1 ± 15.9	0.525

eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio; HPF: high power field of microscopy.

Table 5: **Subgroup analysis of safety concerning renal function at different time periods in male gender.**

	eGFR-MDRD (ml/min/1.732 m^2)			Proteinuria (UPCR) (mg/g)			Hematuria (erythrocyte/HPF)		
	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value
Baseline	78.3 ± 22.4	79.4 ± 25.4	0.479	158.5 ± 330.0	74.2 ± 170.5	0.345	3.2 ± 3.9	5.1 ± 9.8	0.313
1-month	74.5 ± 24.6	83.3 ± 36.7	0.110	185.6 ± 305.6	179.8 ± 252.9	0.983	12.0 ± 11.3	4.0 ± 5.2	0.342
3-month	73.2 ± 20.9	81.3 ± 30.4	<0.001	104.1 ± 214.2	393.8 ± 902.7	0.315	29.5 ± 54.5	1.3 ± 0.5	0.195
6-month	72.1 ± 22.9	77.0 ± 27.5	0.095	197.1 ± 335.7	34.7 ± 68.9	0.379	5.2 ± 9.7	13.4 ± 30.3	0.538
9-month	75.3 ± 22.3	79.6 ± 32.1	0.216	182.6 ± 399.4	243.2 ± 430.4	0.816	1.5 ± 2.1	1.6 ± 1.1	0.948
12-month	75.6 ± 24.0	78.5 ± 30.8	0.394	136.6 ± 236.0	236.7 ± 330.0	0.498	7.7 ± 9.6	4.1 ± 6.8	0.388
End of follow-up	77.0 ± 23.9	82.1 ± 29.1	0.004	87.6 ± 143.6	83.2 ± 271.2	0.947	12.6 ± 28.6	8.0 ± 21.5	0.426

eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio; HPF: high power field of microscopy.

Table 6: **Subgroup analysis of safety concerning renal function at different time periods in female gender.**

	eGFR-MDRD (ml/min/1.732 m^2)			Proteinuria (UPCR) (mg/g)			Hematuria (erythrocyte/HPF)		
	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value
Baseline	85.8 ± 22.8	87.0 ± 27.2	0.559	163.6 ± 395.8	327.2 ± 514.1	0.422	5.0 ± 9.8	1.6 ± 2.2	0.087
1-month	85.0 ± 28.1	91.6 ± 37.1	0.316	234.8 ± 620.0	1384.5 ± 1450.8	0.176	3.5 ± 0.7	16.2 ± 3.2	0.629
3-month	83.7 ± 24.7	89.0 ± 26.6	0.031	217.4 ± 422.4	473.1 ± 1270.2	0.401	27.1 ± 50.7	60.3 ± 171.7	0.631
6-month	85.3 ± 26.1	85.5 ± 27.7	0.944	221.1 ± 382.9	1097.3 ± 1356.6	0.251	7.3 ± 11.9	1.2 ± 0.5	0.284
9-month	88.7 ± 27.1	84.1 ± 29.5	0.279	218.6 ± 100.0	919.0 ± 1175.4	0.171	6.2 ± 3.2	16.0 ± 21.0	0.636
12-month	84.8 ± 22.7	86.0 ± 33.0	0.744	302.2 ± 123.0	782.6 ± 1353.0	0.326	10.0 ± 10.8	2.0 ± 1.6	0.135
End of follow-up	85.1 ± 24.5	87.1 ± 28.1	0.275	25.1 ± 45.7	413.5 ± 864.8	0.065	12.4 ± 28.7	10.0 ± 25.7	0.734

eGFR-MDRD: estimated glomerular filtration rate-modification of diet in renal disease; UPCR: urine protein creatinine ratio; HPF: high power field of microscopy.

Table 7: **Subgroup analysis of safety concerning renal function at different time periods in young cohort.**

did not show any AKI. In a case report[21] proteinuria showed remission within 2 weeks, and serum creatinine remained unchanged. In another three cases with relapsing IgAN with hematuria,[22–24] they were treated with supportive therapy, resulting in rapid resolution of hematuria, and no AKI was reported. Two other cases of relapsing IgAN showed only mildly increased serum creatinine.[20] In summary, it is difficult to reach a consensus based solely on case reports or case series studies. However, with our study involving a well-matched control population and continuous monitoring of eGFR, we have concluded that there is a significant temporal change in eGFR, particularly at the 1-month mark (with an eGFR difference of 9.47 ml/min/1.732 m^2 compared to the non-vaccinated group and an eGFR difference of 4.15 ml/min/1.732 m^2 compared to baseline). Besides, the final eGFR in the vaccinated group was significantly lower than in the non-vaccinated group (77.14 ± 24.53 vs. 80.70 ± 28.16, p = 0.012). Even though the difference could be due to the baseline difference in eGFR (78.09 ± 23.36 vs. 80.03 ± 27.86, p = 0.182), we still recommend continued monitoring of eGFR in the vaccinated group.

In our study, we did not observe any statistical differences in proteinuria and hematuria between the two groups at different follow-up time points. Additionally, there were no statistically significant changes in proteinuria and hematuria among the four subgroups. At most, there may be a numerical reduction in proteinuria between the two groups at different follow-up time points, but this did not reach statistical significance. However, this could be attributed to the limited number of cases and large standard deviation with proteinuria or hematuria. Therefore, we believe that our database is insufficient for a comprehensive investigation of relapsed IgAN. Further evaluations with a larger dataset of proteinuria and hematuria are needed.

This is the first large-scale controlled matched study to evaluate the effectiveness of COVID-19 vaccines in patients with IgAN. Our findings demonstrate that the vaccine has a significant impact on lowering the overall risk of COVID-19 infection and related pneumonia, even among the 44% of patients who had previously received immunosuppressants. A report[34] concerning the efficacy or effectiveness of COVID-19 vaccines in immunocompromised patients highlighted that the most evident cases of reduced effectiveness were observed in patients infected with the human immunodeficiency virus, followed by those who had undergone solid organ transplantation, had inflammatory bowel disease, or had rheumatoid arthritis. Many transplant organizations have acknowledged the diminished antibody response to COVID-19 vaccines among these groups, which can result in reduced clinical effectiveness.[34] A systematic review and meta-analysis (involving 26 studies and 3207 immunocompromised patients)[47] revealed that the risk of positive seroconversion in immunocompromised patients was 48% lower than in healthy controls. This

	eGFR-MDRD (ml/min/1.732 m^2)			Proteinuria (UPCR) (mg/g)			Hematuria (erythrocyte/HPF)		
	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value	Vaccination	Non-vaccination	p-value
Baseline	67.9 ± 20.0	69.6 ± 22.3	0.356	75.7 ± 147.6	131.5 ± 359.8	0.618	2.1 ± 1.6	5.6 ± 9.3	0.159
1-month	60.9 ± 20.0	69.5 ± 29.1	0.096	319.1 ± 451.0	263.0 ± 162.0	0.456	14.0 ± 8.5	6.3 ± 6.2	0.163
3-month	63.7 ± 19.6	69.1 ± 24.3	0.014	130.3 ± 248.2	469.3 ± 970.3	0.356	5.3 ± 7.7	1.1 ± 0.4	0.144
6-month	62.0 ± 19.2	67.9 ± 26.3	0.060	51.0 ± 69.3	21.6 ± 20.9	0.169	3.0 ± 5.1	16.3 ± 29.8	0.354
9-month	66.7 ± 19.3	73.2 ± 28.3	0.678	449.3 ± 633.1	236.3 ± 427.6	0.640	2.3 ± 3.2	1.8 ± 1.9	0.463
12-month	63.9 ± 20.8	69.4 ± 26.1	0.120	204.8 ± 288.8	648.1 ± 916.3	0.581	2.0 ± 2.7	3.6 ± 2.9	0.450
End of follow-up	66.4 ± 20.9	71.7 ± 26.6	0.005	139.5 ± 185.4	139.7 ± 351.5	0.999	5.4 ± 14.6	5.3 ± 10.8	0.979

Table 8: **Subgroup analysis of safety concerning renal function at different time periods in old cohort.**

substantially lower risk of positive seroconversion in transplant recipients may explain the reduced effectiveness of COVID-19 vaccines in this population. In terms of immunosuppressants, within our IgAN patient cohort, only 40% had ever taken glucocorticoids, and very few had received other immunosuppressants. It should be noted that the proportion of patients receiving immunosuppressants, which was 44%, was lower than that observed in other IgAN cohort studies, such as the 80% reported in a Chinese cohort study.[48] Similarly, organ transplant recipients are generally more immunocompromised due to the lifelong use of multiple immunosuppressants. Therefore, among our IgAN patients (with lower rate of immunosuppressants), the immunocompromised status is unlikely to significantly reduce the effectiveness of COVID-19 vaccines.

This study has several limitations. Firstly, we were unable to analyze IgAN cases in patients who had previously experienced COVID-19 infection. Secondly, there is a lack of investigation into doses of COVID-19 vaccine. Thirdly, the major racial groups in our study do not include Asians, who are more prone to IgAN. Fourthly, our study population consists of individuals with IgAN, and we cannot investigate the de novo IgAN related to the COVID-19 vaccine. Fifthly, the number of patients with monitored proteinuria and hematuria remained limited, which means that changes in proteinuria and hematuria may not have been detectable. We suggest that the issue of relapsed IgAN still needs further investigation. Sixthly, our diagnosis of IgAN was based on ICD 10 code D80.2. The renal biopsy proved IgA was around 50% in our study. Seventhly, the results were obtained from a database, and there may be some unadjusted confounding factors. Finally, only less than 20% IgAN took ACEi or ARB and nearly 25% took NSAID, Therefore, the results of this population must be taken cautiously. Nevertheless, our study still stands as the largest cohort investigating the safety and effectiveness of COVID-19 vaccines in individuals with IgAN.

In the largest TriNetx matched cohort study of IgAN, COVID-19 vaccination was associated with a reduced risk of COVID-19 infection and associated complications. However, careful monitoring of renal function, especially GFR, is advisable.

Contributors

SFT, MJW, and CHC: study design; SFT and CHC: data acquisition and analysis; SFT and CHC: data interpretation; SFT: manuscript drafting; SFT, MJW, and CHC: approving the submitted version.

Data sharing statement

De-identified participant data will be made available upon request to the corresponding author according to the regulation of Taichung Veterans General Hospital.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102306.

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