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Assessing acute kidney injury risk after COVID vaccination and infection in a large cohort study

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Acute kidney injury (AKI) has been noticed after both COVID-19 vaccination and infection, affecting risk-benefit evaluations and vaccine hesitancy. We conducted a large-scale N3C cohort study to compare AKI incidence following COVID-19 vaccination and infection. Participants from December 2020 to August 2023 were divided into two groups based on their initially observed COVID-19 antigen exposure: COVID-19 vaccination group (n = 2,953,219) and COVID-19 infection group (n = 3,616,802). AKI was defined by diagnostic codes and serum creatinine changes within a 30 day follow-up window after exposure. The absolute risk of AKI was 0.66% in the vaccination group versus 4.88% in the infection group. After adjusting for various confounders, COVID-19 infection was associated with a significantly higher risk of AKI than COVID-19 vaccination (aHR = 10.31, $P < 0.001$). Our study reveals that COVID-19 vaccination is associated with a significant lower AKI risk compared to COVID-19 infection.

While vaccination continues to be considered as a critical and highly recommended strategy for preventing COVID-19 infection and its complications[1,2], as of December 2023, approximately 30% of the global population[3,4], representing over 2 billion of individuals, remains unvaccinated without at least one dose of the COVID-19 vaccines. A significant barrier to achieving widespread immunity through vaccination is the concerns about vaccine safety and adverse events (AEs), constituting an important subset of vaccine hesitancy characterized by reluctance to receive the vaccine among those eligible[5,6]. Some rare AEs may not have been adequately tested in limited-sized clinical trials or small-scale studies, especially considering the expedited process based on emergency use authorization (EUA)[7].

Given above concerns and the expanding portion of the population experiencing COVID-19 infection and its complications, it is crucial to thoroughly evaluate risk-benefit of vaccination during a pandemic context, especially when certain diseases can be both associated with vaccination and natural infection[8]. Notably, acute kidney injury (AKI) as a rare AE is detected through pharmacovigilance platforms like the Vaccine Adverse Event System (VAERS)[9,10], VigiBase since its introduction[11,12], as well as case reports and series of AKI after COVID-19 vaccination administration consistently appear[13–21]. Conversely, AKI is a recognized complication of natural COVID-19 infection, particularly in hospitalized patients with high mortality rates[22–24]. For now, vaccination is deemed acceptable under the hypothesis that an individual faces a higher risk of developing diseases, such as AKI, from COVID-19 infection compared to that from COVID-19 vaccination. However, this hypothesis has not been extensively tested on a large scale with accurate calculation.

In this study, we used the National COVID Cohort Collaborative (N3C)[25,26], the largest U.S. electronic health record (EHR) dataset of patients related to COVID-19. We conducted a retrospective cohort study focusing on AKI as an AE of interest, comparing its incidence following the COVID-19 vaccination and infection. We aimed to validate the hypothesis that the risk of AKI incidence is significantly lower in individuals exposed to COVID-19 vaccination compared to those exposed to COVID-19 infection.

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Furthermore, we considered both COVID-19 infection and COVID-19 vaccination as different forms of COVID-19 antigens that can induce immune responses[27], and explored the association between AKI incidence and two types of COVID-19 antigen and other predefined risk factors.

Methods

Dataset

The N3C dataset serves as a de-identified repository of EHR sourced from over 98 medical institutions across the United States. It aggregates demographic and clinical data from over 20 million individuals, incorporating a cohort of >7 million confirmed COVID-19 patients as of the latest update in November 2023. The dataset provides records of medical information dating back to January 1, 2018. Noteworthy features encompass a diverse range of variables, including diagnoses, laboratory results, medication history, demographics and comorbidities, etc. To ensure standardized integration, storage, and representation of data, the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM)[28] is employed by N3C enclave. Further details regarding the dataset's structure and methodology can be found in previous publications[25] and on the official N3C website[26].

Ethics approval

The N3C Data Enclave is managed under the authority of the NIH. Data transferred to the National Center for Advancing Translational Sciences (NCATS) from N3C is conducted under a Johns Hopkins University Reliance Protocol (IRB00249128) or individual site agreements with NIH. Data usage of this study was authorized by N3C (DUR-22361BD) and had been reviewed and approved by the Medical School Institutional Review Board (IRB) at the University of Michigan (HUM00192962).

Study design

Our study adopted a comparative retrospective observational cohort design[29], leveraging de-identified data of N3C from December 11, 2020, the time of COVID-19 vaccine introduction, to August 1, 2023 (Fig. 1). Two cohorts were defined as the vaccination group and the infection group based on patients' index events, either COVID-19 vaccination or infection, with specific inclusion and exclusion criteria. The follow-up periods started at the index date and extended for a duration of 30 days to capture outcomes, with secondary analyses conducted using follow-up periods of 60 days and 90 days.

Exposure: COVID-19 vaccination and infection

We defined the index events as the first observed exposure to COVID-19 vaccination or COVID-19 infection. For the vaccination group, we defined the index date as the date of receiving the first dose of the vaccine. The selection of the first dose date as the index date allows us to capture the initial immune response to the COVID-19 antigen, which may result in AKI[13–15]. Additionally, this helps to avoid selection bias that may occur if patients who experienced adverse events after the first dose did not complete the vaccination schedule. This study includes COVID-19 vaccination recorded in the N3C database, encompassing two types of mRNA vaccines (i.e., BNT162b2 from Pfizer-BioNTech and mRNA-1273 from Moderna) and one recombinant viral vector vaccine (i.e., Ad26.COV2.S from Johnson & Johnson). The sources of N3C vaccination records included EHR, claims data, written prescriptions, and self-reported medication information. For the infection group, diagnosis codes and laboratory tests, including SARS-CoV-2 culture and nucleic acid amplification tests, were utilized to identify COVID-19 infections. Specific concept IDs are detailed in Supplementary Table 1.

Cohort building, inclusion and exclusion criteria

Two patient groups were identified based on their initially observed COVID-19 antigen exposure: the vaccination group, with the documented first vaccination preceding any infection, and the infection group, with the first documented infection occurring before any vaccination. For the vaccination group, the inclusion criteria included: (1) patients receiving the first dose of COVID-19 vaccines between December 11, 2020, and August 1, 2023. Only the first dose was considered for patients who received multiple doses, with the index date being the day of the first vaccination; (2) patients having never been diagnosed with COVID-19 infection or tested positive for COVID-19 before the index date or during the follow-up period. Accordingly, patients remained in the group if they experienced the first COVID-19 infection after the specific follow-up period. For the infection group, the inclusion criteria included: (1) patients who were first diagnosed with COVID-19 infection or testing positive for COVID-19 between December 11, 2020, and August 1, 2023; (2) patients who had never received COVID-19 vaccines before the first infection or during the follow-up period. Patients were classified as not vaccinated if no documented vaccination records were found in any of the N3C data sources. Similarly, patients remained in the group if their first COVID-19 vaccination was initiated after the specific follow-up period. Patients were censored at death or the end of the follow-up period. Patients who were (1) ≤18 years old, (2) diagnosed with end-stage kidney disease, and (3) with diagnostic AKI codes within the 30 days before the index date were excluded to eliminate suspected non-onset AKI. Figure 2 illustrates the patient selection process. All concept IDs used in this study are detailed in Supplementary Table 1.

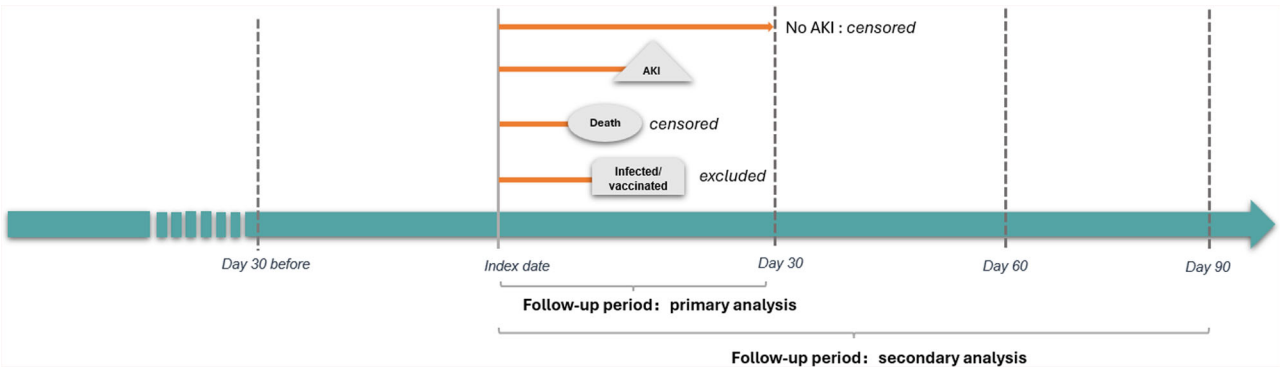

Fig. 1 | Study design for the vaccination group and the infection group (December 2020 to August 2023). Notes: Adults included in the study were categorized in two groups based on their initial exposure to COVID-19 antigens in the period over December 2020 – August 2023. The vaccination group: those whose first recorded COVID-19 vaccination preceded any infection formed the vaccine group; The infection group: those whose first documented COVID-19 infection occurred prior to any vaccination. The index event established as the initial instance of either vaccination or infection. Follow-up period: Patients were followed from the index date to 30 days (primary analysis) and 60/90 days (secondary analysis). Censored at the end of 30 days without AKI outcomes or death within 30 days (primary analysis). Selection period: 1 year before index date, assess for demographics and comorbidities. Patients who had AKI within 30 days before the index date were excluded to eliminate suspected non-onset events.Abbreviation: AKI acute kidney injury.

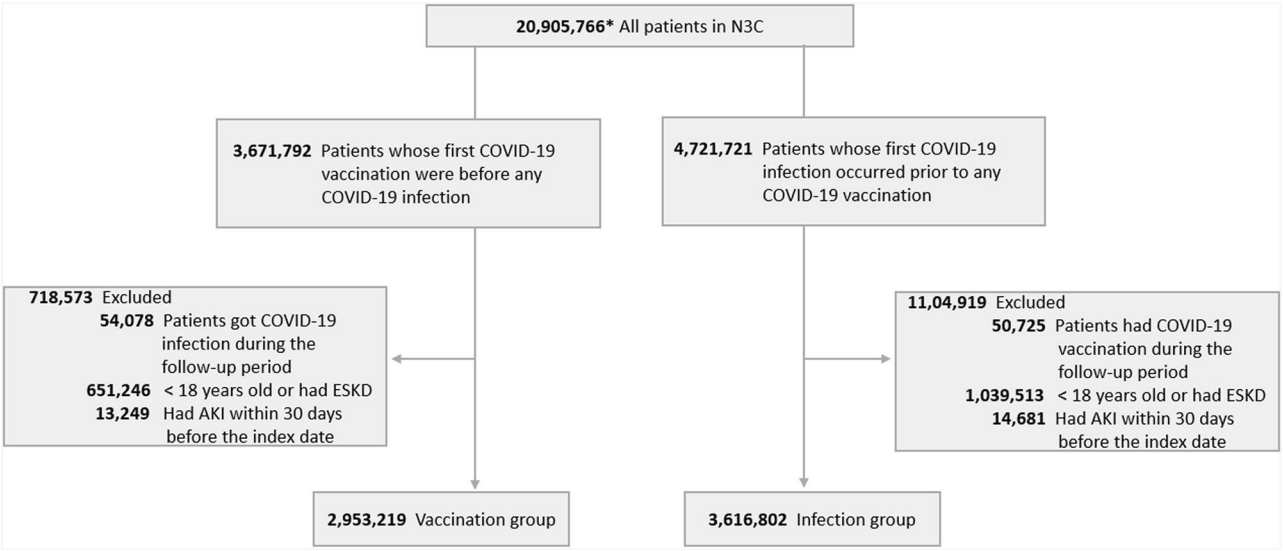

Fig. 2 | Flowchart of patient selection for the vaccination group and the infection group in N3C. Notes: Adults included in the study were categorized into two groups based on their initial exposure to COVID-19 antigens (vaccines or pathogens) over December 2020 – August 2023. The vaccine group: Firstly those who received COVID-19 vaccines were included, after excluding any preceded infection or follow-up period infection, people younger than 18 years old or had ESKD history, the vaccine group formed; The infection group: Those who were confirmed withCOVID-19 infection after 2020-12-11 were included, after excluding any preceded vaccination or follow-up period vaccination, people younger than 18 years old or had ESKD history, the infection group formed. Abbreviation: ESKD end stage kidney disease, AKI acute kidney injury.

Outcome

The primary outcome was the incidence of AKI within 30 days after the index date. AKI was defined by both diagnostic codes and/or serum creatinine changes, according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria[23,30], which include: (1) A serum creatinine change of >0.3 mg/dL within any 48-h period during the follow-up; (2) The lowest serum creatinine value rising by >1.5 times within any 7 day period during the follow-up. (3) The maximum serum creatinine during the follow-up period being at least 1.5 times higher than the patient's baseline creatinine value. A patient's baseline serum creatinine was determined by the following criteria[30,31]: (1) the average serum creatinine value within 2 years prior to the index date; (2) If no records were available within the 2 year period, the lowest serum creatinine value during the follow-up period was considered as the baseline value.

Primary analysis

We assessed each patient's history of previous AKI and other comorbidities within 1 year prior to the index date using the N3C data. The demographic characteristics and AKI incidence in both groups were compared using Chi-square tests for categorical variables and *t*-tests for continuous variables. Absolute risk and relative risk of AKI, along with their 95% confidence intervals, were calculated. Time-to-event data were analyzed using the Kaplan-Meier (KM) method and Cox proportional hazards model. The Cox model, adjusted for demographic factors and comorbidity status, was utilized to evaluate the hazard ratio of AKI incidence following COVID-19 infection compared to COVID-19 vaccination.

Secondary analysis

We conducted a secondary analysis encompassing three dimensions:(1) Temporal phases: We divided the study period into three phases corresponding to the predominant strains during the pandemic era: Alpha (Phase 1, P1) from December 11, 2020, to April 1, 2021; Delta (Phase 2, P2) from April 1, 2021, to November 30, 2021; and Omicron and its subvariants (Phase 3, P3) from December 1, 2021, until the study's end date[32]. (2) Extended follow-up period: We extended the follow-up period from 30 days to 60 and 90 days after the index date. (3) AKI measurement methods: We included different AKI measurements, defined by either diagnostic codes only, changes in serum creatinine only, or both. These dimensions aimed to assess the consistency of results between two groups across different temporal phases, extended time-to-event periods and AKI measurement methods. We further assessed AKI incidence by different strains (Alpha, Delta and Omicron) in the infection group and by different types of vaccines (mRNA vaccines and viral vector vaccines) in the vaccination group.

All analyses were conducted within the N3C enclave using SQL, Python, and R programming languages. Various packages, including ggplot2, survival, and survminer, were employed for analysis.

Results

Of the 6,570,021 adults included in the study, 2,953,219 individuals received COVID-19 vaccines (mean age 52.60 [SD 18.19], 60.3% female, 66.4% white), while 3,616,802 individuals contracted COVID-19 infection (mean age 47.99 [SD 17.79], 56.3% female, 68.6% white). Vaccination distribution peaked in P2 (54.8%), then P1 (34.0%). Conversely, most initial infections occurred in P3 (44.9%), followed by P2 (35.4%) (Table 1).

The absolute 30 day risk of AKI in the vaccination group was 0.66% (95% CI, 0.64% – 0.68%), contrasting with 4.88% (95% CI, 4.81% – 4.95%) in the infection group, resulting in a relative risk of 7.35 (95% CI, 7.25 – 7.46, $P < 0.001$). Among the 19,621 patients experiencing AKI in the vaccination group (mean age 63.91 [SD 15.22] years, 48.9% female, and 62.8% white), the onset occurred after a mean of 13.16 [SD 9.50] days. In comparison, the 176,731 patients with AKI in the infection group (mean age 63.95 [SD 15.87] years, 42.7% female, and 64.0% white) had an onset after a mean of 3.46 [SD 6.09] days. Overall, serum creatinine changes were the predominant indicators of AKI events, capturing 57.9% for the vaccination group and 48.3% for the infection group. Diagnostic codes accounted for the smallest proportion, at 17.9% and 13.0%, respectively. Our study found that 3.1% of AKI patients ($n = 610$) of the vaccination group and 14.3% of AKI patients ($n = 25,366$) of the infection group deceased within the 30 day observed period (Supplementary Table 2).

The time-to-event analysis revealed that the probability of developing AKI in the infection group was significantly higher than that in the vaccination group from day 0 to day 30(Log-Rank test, $P < 0.001$)(Fig. 3). Notably, the KM curve for the infection group exhibited a substantial drop from day 0 to day 3, followed by a smoothing out of the curve after 10 days.

Table 1 | Baseline Characteristics of Patients Included in COVID-19 Vaccination Group and Infection Group

	Total (*N* = 6,570,021) no.(%)	Vaccination Group (*N* = 2,953,219) no.(%)	Infection Group (*N* = 3,616,802) no.(%)	*P*-value[b]
Age, mean(SD), y	50.06 (18.22)	52.60 (18.19)	47.99 (17.97)	<0.001
Age category, y				
<30	1,072,333 (16.3)	390,224 (13.2)	682,109 (18.9)	<0.001
30-49	2,183,346 (33.2)	894,977 (30.3)	1,288,369 (35.6)	
50-64	1,651,881 (25.1)	774,464 (26.2)	877,417 (24.3)	
65-90	1,662,461 (25.3)	893,554 (30.3)	768,907 (21.3)	
Race				
White	4,442,098 (67.6)	1,961,718 (66.4)	2,480,380 (68.6)	<0.001
Black	895,130 (13.6)	424,031 (14.4)	471,099 (13.0)	
Asian	212,645 (3.2)	126,783 (4.3)	85,862 (2.4)	
Other	289,348 (4.4)	92,820 (3.1)	196,528 (5.4)	
Unknown	730,800 (11.1)	347,867 (11.8)	382,933 (10.6)	
Gender				
Female	3,820,272 (58.1)	1,781,799 (60.3)	2,035,693 (56.3)	<0.001
Male	2,756,048 (41.9)	1,171,420 (39.7)	1,581,109 (43.7)	
Ethnicity				
Hispanic or Latino	693,295 (10.6)	326,377 (11.1)	366,918 (10.1)	<0.001
Not Hispanic or Latino	5,265,056 (80.1)	2,444,651 (82.8)	2,820,405 (78.0)	
Unknown	611,670 (9.3)	182,191 (6.2)	429,479 (11.9)	
AKI defined by				
Only diagnostic codes	26,466 (0.4)	3,518 (0.1)	22,948 (0.6)	<0.001
Only Scr[a] changes	96,724 (1.5)	11,351 (0.4)	85,373 (2.4)	
Both methods	73,162 (1.1)	4,752 (0.2)	68,410 (1.9)	
Previous AKI history	91,699 (1.4)	48,000 (1.6)	43,699 (1.2)	<0.001
Hypertension	1,297,616 (19.8)	707,056 (23.9)	590,560 (16.3)	<0.001
Diabetes mellitus	271,745 (4.1)	144,695 (4.9)	127,050 (3.5)	<0.001
Heart failure	189,004 (2.9)	102,316 (3.5)	86,688 (2.4)	<0.001
Cardiovascular disease	711,533 (10.8)	379,434 (12.8)	332,099 (9.2)	<0.001
Obesity	574,859 (8.7)	300,759 (10.2)	274,100 (7.6)	<0.001
Period of strains				
P1: Alpha	-	-	713,347 (19.7)	<0.001
P2: Delta	-	-	1,280,905 (35.4)	<0.001
P3: Omicron	-	-	1,622,550 (44.9)	<0.001
Vaccine type				
mRNA	-	2,645,093 (89.6)	-	<0.001
Viral vector	-	172,269 (5.8)	-	<0.001
Unknown[c]	-	135,857 (4)	-	<0.001

[a] Abbreviation for Serum Creatinine.
[b] Comparisons are made between the COVID-19 group and COVID-19 vaccination group using *t*-tests for continuous variables and Chi-square tests for categorical variables.
[c] Types of COVID-19 vaccine were not reported.

In contrast, the curve for the vaccination group showed a consistently smooth trend throughout the entire follow-up period.

In the univariate analysis of AKI incidence using the Cox proportional hazards model(Table 2), COVID-19 infection demonstrated a 7.55-fold higher hazard of AKI incidence compared to COVID-19 vaccination (HR, 7.55; 95% CI, 7.43-7.66, $P < 0.001$). In the multivariable analysis adjusting for demographics, previous AKI history, and comorbidities, the COVID-19 infection remained a significantly higher risk factor with an adjusted hazard ratio (aHR) of 10.31 (95% CI, 10.16–10.47, $P < 0.001$) compared to the COVID-19 vaccination.

The multivariable analysis also demonstrated significantly higher risks of AKI in older age groups (age group of 65-90: aHR, 11.43; 95% CI, 11.14–11.72, $P < 0.001$) and among individuals with a previous AKI history (aHR, 3.17; 95% CI, 3.12-3.23, $P < 0.001$) (Table 2). Additionally, male gender (aHR, 1.59; 95% CI, 1.58–1.60, $P < 0.001$), diabetes mellitus (aHR, 1.67; 95% CI, 1.65–1.70, $P < 0.001$), a history of heart failure (aHR, 1.70; 95% CI, 1.67–1.72, $P < 0.001$) and cardiovascular disease (aHR, 1.38; 95% CI, 1.36–1.40, $P < 0.001$) were associated with an increased hazard of developing AKI. Individuals of black race (aHR, 2.09; 95% CI, 2.06–2.11, $P < 0.001$), asian race (aHR, 1.10; 95% CI, 1.06–1.13, $P < 0.001$), other races (aHR, 1.17; 95% CI, 1.14–1.20, $P < 0.001$) and unknown race (aHR, 1.28; 95% CI, 1.25–1.30, $P < 0.001$) exhibited higher hazards of AKI. Individuals who did not identify themselves as Hispanic or Latino had a lower hazard (aHR, 0.93; 95% CI, 0.91–0.95, $P < 0.001$), as did those with no ethnicity

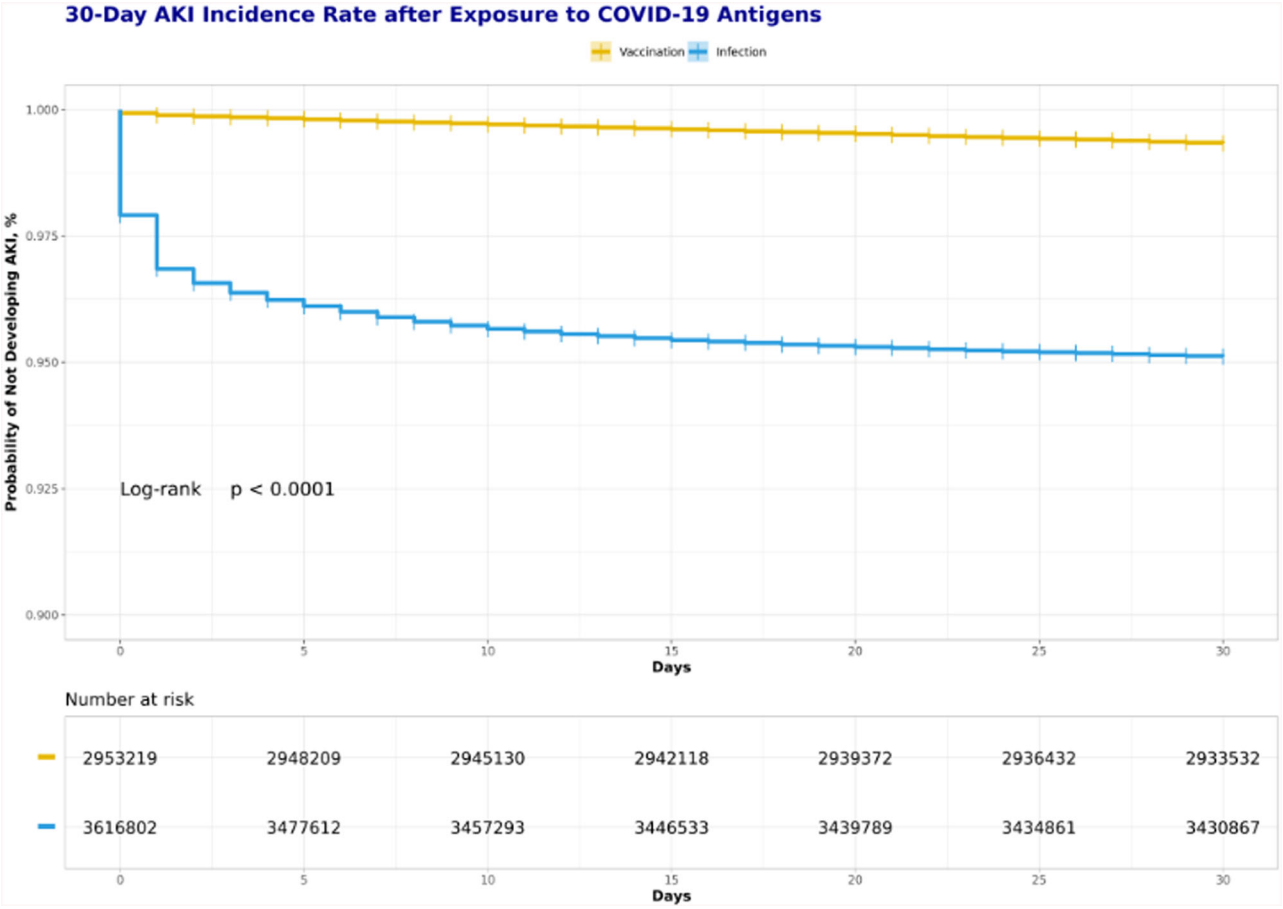

Fig. 3 | Comparative Kaplan-Meier analysis of AKI incidence within 30 days after exposure to COVID-19 antigens. Notes: Adults included in the study were categorized in two groups based on their initial exposure to COVID-19 antigens in the period over December 2020 to August 2023. The vaccination group: those whose first recorded COVID-19 vaccination preceded any infection formed the vaccination group; The infection group: those whose first documented COVID-19 infection occurred prior to any vaccination. Patients were followed from the index date to 30 days to observe AKI incidence. The probability of developing AKI in the infection group was significantly higher than that in the vaccination group from day 0 to day 30(Log-Rank test, $P < 0.001$). Abbreviation: AKI acute kidney injury.

information (aHR, 0.59; 95% CI, 0.57-0.60, $P < 0.001$), compared to individuals who identified themselves as Hispanic or Latino.

The secondary analysis results were consistent with primary analysis results. The risk of AKI was lower in the vaccination group compared to the infection group across all pandemic periods (Supplementary Fig. 1). Extending the observation period to 60 and 90 days showed a similar trend of the K-M curve to the initial 30 day period (Supplementary Fig. 2). Different methods of measuring AKI consistently showed lower risk with vaccination compared to infection. In all outcomes, COVID-19 infection posed a higher hazard of AKI than COVID-19 vaccination (Supplementary Fig. 3).

In the vaccination group, 2,645,093 patients received mRNA vaccines, with 16,455 (0.6%) experiencing AKI events, and 172,269 patients received recombinant viral vector vaccines, with 1,533 (0.9%) experiencing AKI events ($p < 0.001$). In the infection group, 1,622,550 patients were infected in the Omicron phase, with 77,635 (4.8%) developing AKI, compared to 1,280,905 patients in the Delta phase, with 65,215 (5.1%) developing AKI, and 713,347 patients in the Alpha phase, with 33,881 (4.7%) developing AKI ($p < 0.001$) (Supplementary Table 2).

Discussion

In a retrospective observational cohort study with a large-scale population, we observed a substantial disparity in AKI incidence between the COVID-19 vaccination group and the COVID-19 infection group. The infection group exhibited a significantly higher risk of AKI compared to the vaccination group.

Our findings contribute to addressing vaccine hesitancy arising from concerns about vaccine safety, particularly underscoring a significantly lower risk of AKI following COVID-19 vaccination. With the ongoing emergence of variants and a growing population affected by COVID-19, regular vaccination stands as a crucial preventive measure against the disease. Consequently, our results offer insights for the risk-benefit evaluation of vaccination in a post-pandemic context, where patients face over 10 times higher risk of AKI after COVID-19 infection compared to vaccination after adjustment. Another important aspect of the risk-benefit evaluation is to examine the natural background rate of the specific AE. Previous studies on the background rate of AKI generally varied considerably due to differences in the targeted population, diagnostic criteria, and whether the AKI is hospital or community-acquired, ranging from 1% to 60%[33]; our finding of the AKI incidence rate after COVID-19 vaccination is 0.66%, but direct comparisons cannot be made. Further investigation into this aspect is crucial.

To our knowledge, our study is the first to use EHR data to investigate the risk of AKI after COVID-19 vaccination and compare it with the risk of AKI after COVID-19 infection in a large-scale general population. Previous case studies documenting AKI following COVID-19 vaccination lacked generalizability due to limited population sizes; Other studies relied data from pharmacovigilance databases: one study identified 1,113 AKI cases after COVID-19 vaccination from VAERS, however the fundamental incidence rate could not be calculated due to a lack of data on the total vaccinated population[10]. Another study reported an AKI incidence rate of 3.03 per million administered COVID-19 vaccine doses using

Table 2 | Association Between COVID-19 Vaccine and Infection and AKI Incidence: Results from Univariable and Multivariable-Adjusted Cox Models

	HR	Adjusted HR
COVID-19 vaccination	Reference	Reference
COVID-19 infection	7.55 (7.43-7.66)[a]	10.31 (10.16-10.47)[a]
Previous AKI history	8.90 (8.77-9.03)[a]	3.17 (3.12-3.23)[a]
Age <30	Reference	Reference
Age:30-49	2.17 (2.11-2.22)[a]	2.26 (2.20-2.32)[a]
Age:50-64	5.26 (5.13-5.40)[a]	5.55 (5.41-5.69)[a]
Age:65-90	10.78 (10.52-11.06)[a]	11.43 (11.14-11.72)[a]
White race	Reference	Reference
Black race	1.62 (1.60-1.64)[a]	2.09 (2.06-2.11)[a]
Asian race	0.73 (0.71-0.76)[a]	1.10 (1.06-1.13)[a]
Other race	0.91 (0.89-0.93)[a]	1.17 (1.14-1.20)[a]
No race info	0.90 (0.89-0.92)[a]	1.28 (1.25-1.30)[a]
Female	Reference	Reference
Male	1.83 (1.80-1.85)[a]	1.59 (1.58-1.60)[a]
Hispanic or Latino	Reference	Reference
Not Hispanic or Latino	1.27 (1.25-1.29)[a]	0.93 (0.91-0.95)[a]
Unknown ethnicity	0.89 (0.87-0.91)[a]	0.59 (0.57-0.60)[a]
Hypertension	2.55 (2.53-2.57)[a]	0.98 (0.97-0.99)[a]
Diabetes mellitus	4.02 (3.97-4.07)[a]	1.67 (1.65-1.70)[a]
Heart failure	5.79 (5.71-5.86)[a]	1.70 (1.67-1.72)[a]
Cardiovascular disease	3.58 (3.54-3.61)[a]	1.38 (1.36-1.40)[a]
Obesity	1.57 (1.52-1.56)[a]	0.97 (0.96-0.98) [a]

Abbreviation: *HR* hazard ratio, *CI* confidence interval.
[a]$p < 0.001$.

EudraVigilance and VAERS[11]. This rate was much lower than our finding, as they considered the number of administered COVID-19 vaccine doses across countries instead of analyzing the number of vaccinated patients individually, and data from pharmacovigilance may be subject to reporting bias[34]. While our study leveraged over 70 multi-center integrated EHR datasets, ensuring a representative and comprehensive population for robust results. We positively identified AKI cases through clinical diagnosis and laboratory results, rather than relying on self-reporting. So our findings offer a supplementary and positive method for vaccine safety surveillance[35], further helping to address vaccine hesitancy.

Given the established benefits of COVID-19 vaccination[36–38], comprehensive comparisons of AE risks between infection and vaccination facilitates the risk-benefit balance of COVID immunization strategies. Previous studies have highlighted substantially higher risks of thrombotic events after COVID-19 infection compared to COVID-19 vaccination in both self-controlled and cohort studies[39–41]. Similarly, a self-controlled study revealed the increased risk of immune-mediated neurological events after infection, whereas no such increase was found after vaccination[41]. In addition to the aforementioned AEs, AKI incidence following vaccination warrants investigation, considering the theoretical possibility of vaccine-induced podocyte injury leading to kidney injury[42,43]. Therefore, our study contributes to a comprehensive safety profile of COVID-19 vaccines.

Two aforementioned studies utilized a self-controlled study design, which might introduce time-varying confounders[44]. While our study adopted an observational cohort study for comparison. Furthermore, our research included secondary analysis and time-to-event analysis. We observed a consistently stable time-to-event curve within 30 days after COVID-19 vaccination, indicating a low risk of AKI. It is possible for events to occur beyond the 30 day follow-up period or vary with different strains and AKI measurement methods. However, extended studies over 60 and 90 days follow-up periods, various strains and AKI measurement consistently demonstrated this low-risk pattern in line with our primary findings.

We calculated the crude rates and found statistical differences between vaccine types, suggesting that the viral vector vaccine has a higher crude incidence rate of AKI than the mRNA vaccine. Our results are consistent with a previous study that found higher AKI reporting rates for viral vector vaccines compared to mRNA vaccines after COVID-19 vaccination11. However, our findings show associations instead of causality. Further studies are needed to investigate the biological link between AKI and vaccine types.

Note that the etiology of AKI following COVID-19 vaccination was not investigated in this study. While the etiology has not not been determined yet, recent studies hypothesize that tissue antigens like transglutaminase, antiextraction nuclear antigen, and thyroid peroxidase can react with SARS-CoV-2 antibodies from vaccination[45,46]. The process of COVID-19 vaccines may activate antigen-presenting cells (APCs), leading to strong CD4+ and CD8 + T-cell responses and significant inflammatory cytokine release. This may trigger a cytokine storm and future lead to AKI.

We observed that the crude incidence of AKI was the highest in the Delta phase, followed by the Omicron and Alpha phases. A study with smaller sample size found a statistically significant difference of AKI incidence, indicating a higher incidence rate in the Omicron group compared to the Delta group[47], but the conclusion was made among critically ill patients, which was a totally different study population from ours. Therefore, further studies are needed in this regard.

The possible pathophysiology of COVID-19 infection-related AKI involves several complex mechanisms[48]. These include the potential direct viral infection of renal cells, which can damage the kidney tissue directly. Additionally, the inflammatory and immune responses triggered by the virus can lead to further renal injury through cytokine release and immune cell infiltration[49]. Activation of the coagulation system can result in microthrombi formation, impairing renal blood flow and causing ischemic damage. Moreover, the renin-angiotensin system may become dysregulated, exacerbating renal injury through altered blood pressure regulation and inflammatory pathways. Together, these factors contribute to the multifaceted pathogenesis of COVID-19 related AKI.

Our results identified many predefined risk factors that contributed to AKI incidence after exposure to COVID-19 antigens. We found that age was highly associated with the risk of AKI, which was consistent with recent reports on AKI after COVID-19 vaccination and infection10,11. This susceptibility might be attributed to physiological alterations associated with aging, a gradual decline in renal function, compromised immune responses, comorbidities and undiagnosed chronic diseases among the elderly[50]. We also found that the factor of previous AKI history increased the risk of AKI. This could be attributed to potential lingering effects on renal resilience, the persistence or progression of underlying conditions, and the sensitization to subsequent insults. We observed that minority races and ethnicities had lower risk of AKI. But this might be underestimated by residual confounding factors such as socioeconomic factors, cultural influences, lifestyle differences, or healthcare-seeking behaviors, et al. To draw more robust conclusions, further investigations are imperative.

Our study has some limitations. Firstly, the inherent weaknesses of EHR data pose challenges, such as potential inaccuracies, missing or incomplete records about COVID-19 vaccination and infection in N3C, and variations in data quality. Despite the extensive data available in N3C, it represents only a portion of the country rather than its entirety, limiting the generalizability of our findings. Our study design is retrospective and observational, introducing potential biases due to unmeasured confounders and lacking the ability to establish causal relationships between outcomes and exposures. Given these limitations, our findings need to be interpreted with caution. Meanwhile, the novelty of our research is also embedded in the above limitations. The N3C dataset provides the largest ever EHR dataset related to COVID-19 for an unparalleled opportunity to investigate the

vaccine adverse events and compare them with the occurrences of the diseases or symptoms following infections. COVID-19 pandemic made the majority of people worldwide infected; however, the massive COVID-19 vaccination campaign significantly reduced the severity of the disease. The simultaneous comparison of an adverse event such as the AKI provides us a unique angle to investigate the risk of a health outcome such as AKI following vaccination or natural infection. This work significantly supports our addressing of the vaccine hesitancy issue, promoting the wider usage of vaccination for the benefit of public health.

In conclusion, our retrospective cohort study reveals a significant difference in AKI incidence between individuals who received the COVID-19 vaccination and those who had COVID-19 infection. Specifically, individuals who received the COVID-19 vaccination experienced a significantly lower risk of AKI incidence compared to those who had COVID-19 infection.

Disclaimer

The N3C Publication committee confirmed that this manuscript msid:1834.309 is in accordance with N3C data use and attribution policies; however, this content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the N3C program.

Data availability

All data of this study is available in the N3C Data Enclave for researchers with an approved protocol and data use request from an institutional review board. Data access is governed by the National Institutes of Health. More information on the enclave and instructions for data access can be found at https://covid.cd2h.org/for-researchers.

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Author contributions

Y.P. was responsible for cohort data generation. Y.P. and Y.Han were responsible for data analysis and writing the first version of the manuscript. Y.P., X.Y., and Y.He initiated the project and provided the original project design. Y.P., Y.Han, C.Z., J.Z., Y.He, X.Y. played roles in developing research questions and ways to address the questions. C.Z. and L.Z. served as statistics experts. YHe served as the vaccine adverse event domain expert. X.Y. served as clinical domain expert. All authors participated in result interpretation, discussion, and paper editing. The corresponding authors are X.Y. and Y.He.

Competing interests
The authors declare no competing interests.

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