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MAJOR ARTICLE

The Protective Effect of Coronavirus Disease 2019 (COVID-19) Vaccination on Postacute Sequelae of COVID-19: A Multicenter Study From a Large National Health Research Network

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Background. Coronavirus disease 2019 (COVID-19) vaccines have been proven to decrease the severity of acute-phase infection; however, little is known about their effect on postacute sequelae of COVID-19 (PASC).

Methods. Patients with confirmed COVID-19 diagnosis and minimum age of 18 years with 3-month follow-up postdiagnosis between 21 September 2020 and 14 December 2021 were identified from the TriNetX Research Network platform. The primary outcomes consisted of new-onset or persistent symptoms, new-onset diagnoses, and death and were compared between vaccine and no-vaccine groups.

Results. At baseline, 1 578 719 patients with confirmed COVID-19 were identified and 1.6% (n = 25 225) completed vaccination. After matching, there were no differences ($P > .05$) in demographics or preexisting comorbidities. At 28 days following COVID-19 diagnosis, the incidence of hypertension was 13.52 per 1000, diabetes was 5.98 per 1000, thyroid disease was 3.80 per 1000, heart disease was 15.41 per 1000, and mental disorders was 14.77 per 1000 in the vaccine cohort. At 90 days following COVID-19 diagnosis, the relative risk of hypertension was 0.33 (95% confidence interval [CI], .26–.42), diabetes was 0.28 (95% CI, .20–.38), heart disease was 0.35 (95% CI, .29–.44), and death was 0.21 (95% CI, .16–.27). Differences in both 28- and 90-day risk between the vaccine and no-vaccine cohorts were observed for each outcome, and there was enough evidence ($P < .05$) to suggest that these differences were attributed to the vaccine.

Conclusions. Our data suggest that COVID-19 vaccine is protective against PASC symptoms, new onset of health conditions, and mortality.

Keywords. COVID-19 vaccination; long COVID; PASC; postacute sequelae of COVID–19.

With >312 million infections and >5 million deaths reported globally as of 12 January 2022, the coronavirus disease 2019 (COVID-19) pandemic is still an unresolved crisis that is affecting the healthcare system worldwide [1]. Despite mitigation efforts, COVID-19 is affecting the health of patients suffering from the persistence or emergence of new symptoms and multiple complications after recovery, termed postacute sequelae of COVID-19 (PASC) [2].

PASC manifests in a wide range of persistent or new symptoms that do not resolve for many months [3–5]. Up to 70% of recovered patients report fatigue, persistent loss of taste or smell, shortness of breath, cough, headache, pain, and a wide array of serious complications affecting the cardiovascular, pulmonary, renal, endocrinological, and neurological systems [2, 6–11].

To face the pandemic, major international entities have set vaccination as their top priority [12]. Worldwide, >9 billion vaccines doses have been administered as of 12 January 2022 [1]. Immunization is effective in preventing infection [13] and decreasing its severity [14]. However, there are only a few studies that have assessed the effect of COVID-19 vaccination on the long-term sequelae of the disease [15].

In this study, using TriNetX, a large national health research network that relies on data from multiple centers across the United States, we aimed to analyze the effect of immunization on postacute sequelae of COVID-19.

METHODS

Data Collection and Definitions

We used the TriNetX database to conduct a retrospective study of adult patients aged ≥18 years with SARS-CoV-2 infection (confirmed by polymerase chain reaction) who sought care in the United States from 21 September 2020 to 14 December 2021.

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The de-identified patients' data included in this analysis belong to the TriNetX Research Network platform, a network of electronic medical records (EMRs) from 57 healthcare organizations currently involving >70 million patients across the United States.

We collected patients' demographics, comorbidities, and COVID-19 vaccination, as well as symptoms and diagnoses prior to, at the time of, and after 3 months of SARS-CoV-2 infection. We stratified COVID-19 patients into 2 groups: (1) vaccinated patients with breakthrough infection and (2) unvaccinated patients. PASC was defined as new, continuing, or recurrent symptoms that occur 4 or more weeks after the initial SARS-CoV-2 infection; baseline comorbidities were used for matching. For the vaccinated cohort, patients diagnosed with COVID-19 after at least a week of administration of the complete vaccine were included. The primary outcomes consisted of new-onset or persistent symptoms, new-onset diagnoses, and death and were compared between the vaccine and no-vaccine groups. Data extraction and analysis were performed using a list of *International Classification of Diseases, 10th Revision* codes (detailed in the Supplementary Materials).

Statistical Analysis

Characteristics of patients were described using mean ± standard deviation for continuous variables and frequency and percentage for categorical variables (Table 1). Differences between vaccine and no-vaccine groups were calculated using independent *t* test or χ^2 test. Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities. Incidence, relative risk (RR), and attributable risk (risk difference) estimates along with 95% confidence intervals (CIs) were used as measures of risk at 28 days (Table 2) and 90 days (Table 3) following COVID-19 diagnosis. Rates were presented per 1000 and *P* values (α) < .05 were considered statistically significant.

RESULTS

At baseline, 1 578 719 patients with confirmed COVID-19 were identified and 1.6% (n = 25 225) had documented COVID-19 vaccination. Among the vaccine cohort, the average age was 54.82 ± 17.77 years, 59.84% (n = 15 094) were female, and 68.45% (n = 17 266) were white. The average body mass index (BMI) was 30.20 ± 7.33 kg/m^2; 47.36% (n = 11 947) had

Table 1. Baseline Characteristics of Coronavirus Disease 2019 Patients and Vaccine Status Before and After Propensity Score Matching

	Before Matching			After Matching		
Characteristic	Vaccine + COVID-19 (n = 25 225)	No-Vaccine + COVID-19 (n = 1 553 494)	*P* Value	Vaccine + COVID-19 (n = 25 225)	No-Vaccine + COVID-19 (n = 25 225)	*P* Value
Age, y, mean ± SD	54.82 ± 17.77	42.91 ± 21.84	<.0001	54.82 ± 17.77	55.06 ± 17.96	.13
Sex						
Female	15 094 (59.84)	870 301 (56.02)	<.0001	15 094 (59.84)	15 129 (59.98)	.75
Male	10 130 (40.16)	682 700 (43.95)	<.0001	10 130 (40.16)	10 095 (40.02)	.75
Unknown	10 (0.04)	493 (0.03)	.49	10 (0.04)	10 (0.04)	1.00
Race						
Black/African American	4907 (19.45)	287 241 (18.49)	<.0001	4907 (19.45)	4853 (19.24)	.54
White	17 266 (68.45)	965 166 (62.13)	<.0001	17 266 (68.45)	17 381 (68.90)	.27
Asian	860 (3.41)	31 290 (2.01)	<.0001	860 (3.41)	874 (3.47)	.73
American Indian/Alaska Native	159 (0.63)	6163 (0.4)	<.0001	159 (0.63)	126 (0.50)	.05
Native Hawaiian/Pacific Islander	41 (0.16)	2357 (0.15)	.66	41 (0.16)	47 (0.19)	.52
Unknown	1992 (7.90)	261 277 (16.82)	<.0001	1992 (7.90)	1944 (7.71)	.43
Comorbidities						
Hypertension	11 947 (47.36)	435 700 (28.16)	<.0001	11 947 (47.36)	11 963 (47.43)	.89
Neoplasm	9487 (37.61)	298 980 (19.25)	<.0001	9487 (37.61)	9533 (37.79)	.67
Diabetes mellitus	5774 (22.89)	214 891 (13.83)	<.0001	5774 (22.89)	5698 (22.59)	.42
Asthma	3818 (15.14)	181 145 (11.66)	<.0001	3818 (15.14)	3678 (14.58)	.08
Atherosclerosis	3464 (13.73)	106 882 (6.88)	<.0001	3464 (13.73)	3314 (13.14)	.05
CKD	3210 (12.73)	98 199 (6.32)	<.0001	3210 (12.73)	3097 (12.18)	.13
COPD	1981 (7.85)	70 746 (4.55)	<.0001	1981 (7.85)	1879 (7.45)	.09
Transplanted organ and tissue status	1218 (4.83)	20 323 (1.31)	<.0001	1218 (4.83)	1051 (4.17)	.0003
HIV	209 (0.83)	6063 (0.39)	<.0001	209 (0.83)	152 (0.60)	.003
BMI, kg/m^2, mean ± SD	30.20 ± 7.33	29.16 ± 8.12	<.0001	30.20 ± 7.33	30.68 ± 7.40	.98

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; SD, standard deviation.

Table 2. Postacute Sequelae of Coronavirus Disease 2019 Mortality and Morbidity Risk at 28 Days: Vaccine Versus No Vaccine

		28-Day Risk (Rates per 1000)			
Outcomes	Total, No.	Vaccine + COVID-19 No. (Incident Rate)	No-Vaccine + COVID-19	Relative Risk (95% CI)	Attributable Risk (95% CI)
Mortality	50 450	171 (6.78)	522 (20.69)	0.33 (.28–.39)	−13.91 (−15.94 to −11.89)
New conditions since COVID-19					
Hypertension	25 862	176 (13.52)	384 (29.90)	0.45 (.38–.54)	−16.38 (−19.93 to −12.83)
Diabetes mellitus	38 762	116 (5.98)	269 (13.88)	0.43 (.35–.54)	−7.90 (−9.87 to −5.93)
Thyroid disease	43 481	82 (3.80)	193 (8.80)	0.43 (.33–.56)	−5.00 (−6.48 to −3.51)
Heart disease	33 836	253 (15.41)	543 (31.17)	0.49 (.43–.57)	−15.76 (−18.96 to 12.57)
Malignant neoplasm	42 705	84 (3.95)	260 (12.14)	0.32 (.25–.42)	−8.20 (−9.89 to −6.50)
Thrombosis	43 486	137 (6.36)	332 (15.14)	0.42 (.34–.51)	−8.78 (−10.72 to −6.85)
Rheumatoid arthritis	49 289	16 (0.65)	32 (1.30)	0.50 (.28–.91)	−0.65 (−1.20 to −.09)
Mental disorders	32 307	231 (14.77)	604 (36.23)	0.41 (.35–.47)	−21.45 (−24.86 to −18.05)
New symptoms since COVID-19					
Respiratory symptoms	50 450	2263 (89.71)	3219 (127.61)	0.70 (.67–.74)	−37.90 (−43.32 to −32.48)
Headache	50 450	450 (17.84)	804 (31.87)	0.56 (.50–.63)	−14.03 (−16.75 to −11.32)
Fatigue	50 450	1138 (45.14)	1750 (69.38)	0.65 (.61–.70)	−24.26 (−28.31 to −20.21)
Body ache	50 450	235 (9.32)	480 (19.03)	0.50 (.42–.57)	−9.71 (−11.77 to −7.65)
Diarrhea or constipation	50 450	857 (33.97)	1424 (56.45)	0.60 (.55–.65)	−22.48 (−26.10 to −18.86)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

hypertension (HTN), 22.89% (n = 5774) had diabetes mellitus (DM), and 12.73% (n = 3210) had chronic kidney disease (CKD). Among the no-vaccine cohort, the average age was 42.91 ± 21.84 years, 56.02% (n = 870 301) were female, and 62.13% (n = 965 166) were white. The average BMI was 29.16 ± 8.12 kg/m^2; 28.16% (n = 435 700) had HTN, 19.25% (n = 298 980) had DM, and 6.32% (n = 98 199) had CKD. After matching, there were no differences in age ($P = .13$), sex ($P = .75$), race or ethnicity ($P > .05$), BMI ($P = .98$), HTN ($P = .89$), DM ($P = .42$), or CKD ($P = .13$).

At 28 days following COVID-19 diagnosis (Table 2), the risk of new or persistent outcomes in the vaccine cohort was less than the risk in the no-vaccine cohort for each outcome. In the vaccine cohort, the incidence of HTN was 13.52 per 1000, DM was 5.98 per 1000, thyroid disease was 3.80 per 1000, heart disease was 15.41 per 1000, and mental disorders was 14.77 per 1000. The estimated probability (RR) of HTN was 0.45 (95% CI, .38–.54), DM was 0.43 (95% CI, .35–.54), heart disease was 0.49 (95% CI, .43–.57), and death was 0.33 (95% CI, .28–.39). The RR for respiratory symptoms (0.70 [95% CI, .67–.74]),

Table 3. Postacute Sequelae of Coronavirus Disease 2019 Mortality and Morbidity Risk at 90 Days: Vaccine Versus No Vaccine

		90-Day Risk (Rates per 1000)			
Outcome	Total, No.	Vaccine + COVID-19 No. (Incident Rate)	No-Vaccine + COVID-19	Relative Risk (95% CI)	Attributable Risk (95% CI)
Mortality	50 450	60 (2.38)	293 (11.62)	0.21 (.16–.27)	−9.24 (−10.69 to −7.78)
New conditions since COVID					
Hypertension	25 634	83 (6.42)	249 (19.59)	0.33 (.26–.42)	−13.17 (−15.95 to −10.40)
Diabetes mellitus	38 616	52 (2.69)	187 (9.69)	0.28 (.20–.38)	7.00 (−8.56 to −5.44)
Thyroid disease	43 391	33 (1.53)	152 (6.95)	0.22 (.15–.32)	−5.41 (−6.63 to −4.19)
Heart disease	33 506	117 (7.19)	349 (20.26)	0.35 (.29–.44)	−13.07 (−15.55 to −10.60)
Malignant neoplasm	42 599	45 (2.12)	193 (9.04)	0.23 (.17–.32)	−6.92 (−8.34 to −5.51)
Thrombosis	43 312	62 (2.89)	233 (10.67)	0.27 (.20–.36)	−7.79 (−9.32 to −6.25)
Rheumatoid arthritis	49 275	10 (0.41)	24 (0.97)	0.42 (.20–.87)	−0.57 (−1.03 to −.10)
Mental disorders	31 993	100 (6.45)	421 (25.53)	0.25 (.20–.31)	−19.08 (−21.80 to −16.37)
New symptoms since COVID-19					
Respiratory symptoms	50 450	1251 (49.59)	2344 (92.92)	0.54 (.50–.57)	−43.33 (−47.80 to −38.86)
Headache	50 450	247 (9.79)	635 (25.17)	0.39 (.34–.45)	−15.38 (−17.66 to −13.10)
Fatigue	50 450	605 (23.98)	1268 (50.27)	0.48 (.43–.52)	−26.28 (−29.58 to −22.99)
Body ache	50 450	124 (4.92)	361 (14.31)	0.34 (.28–.42)	−9.40 (−11.10 to −7.70)
Diarrhea or constipation	50 450	480 (19.03)	1083 (42.93)	0.44 (.40–.49)	−23.90 (−26.92 to −20.89)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

headache (0.56 [95% CI, .50–.63]), fatigue (0.65 [95% CI, .61–.70]), body ache (0.50 [95% CI, .42–.57]), and diarrhea or constipation (0.60 [95% CI, .55–.65]) was also <1.0.

At 90 days following COVID-19 diagnosis (Table 3), the incidence of HTN was 6.42 per 1000, DM was 2.69 per 1000, thyroid disease was 1.53 per 1000, heart disease was 7.19 per 1000, and mental disorders was 6.45 per 1000. The RR of HTN was 0.33 (95% CI, .26–.42), DM was 0.28 (95% CI, .20–.38), heart disease was 0.35 (95% CI, .29–.44), and death was 0.21 (95% CI, .16–.27). Decreases in RR were also observed in respiratory symptoms (0.54 [95% CI, .50–.57]), headache (0.39 [95% CI, .34–.45]), fatigue (0.48 [95% CI, .43–.52]), body ache (0.34 [95% CI, .28–.42]), and diarrhea or constipation (0.44 [95% CI, .40–.49]). Differences in both 28- and 90-day risk between the vaccine and no-vaccine cohorts were observed for each outcome and there was enough evidence ($P < .05$) to suggest that these differences were attributed to the vaccine.

DISCUSSION

In our study using real-time EMR data from a large national health network, we demonstrated that the vaccine was protective (ie, RR <1.0) against mortality and each incident PASC outcome and that having the vaccine is associated with a significantly lower likelihood of experiencing new or persistent PASC symptoms. This suggests that patients with COVID-19 who are not vaccinated are at greater risk of death and incident morbidity during the 90 days postinfection. In this study with data from a large-scale EHR network, we showed that individuals with COVID-19 breakthrough infections after vaccination have lower rates of PASC (or "long COVID") symptoms/outcomes compared with propensity-matched unvaccinated COVID-19–infected people. As such, our work extends the current data on the efficacy of COVID-19 vaccination in acute COVID-19, to show that vaccination is associated with faster and better COVID-19 recovery.

In our study, vaccination against COVID-19 is associated with a lower risk of outcomes that have not been assessed in previous studies—namely, new-onset diseases including hypertension, diabetes, malignant neoplasms, heart and thyroid diseases, hypercoagulopathy or venous thromboembolism, and mental disorders, or new-onset symptoms known to be part of long COVID syndrome such as headaches, fatigue, body aches, and respiratory and gastrointestinal symptoms. We also found significant differences in postacute COVID-19 mortality rates between vaccinated and unvaccinated SARS-CoV-2–infected patients. These findings are in line with previously published data, suggesting a potential implication of immunizations in preventing the development of chronic COVID-19 symptoms [15].

The etiologic and pathophysiologic mechanisms behind PASC are not clear and the effects of vaccination status on it, in particular, are totally unclear. It is thought that factors from the acute phase such as endotheliopathy, antigen-antibody reactions, and the ability of the virus to initiate an immense inflammatory response may trigger the secondary responses in the body [16, 17]. Although previous studies have shown that immunizations are highly effective at preventing severe acute COVID-19–associated outcomes; little is known about the effect of vaccination on postacute outcomes of COVID-19 [17, 18]. However, we hypothesize that its effect on reducing the inflammatory responses during the acute phase does also explain the lower rates of all PASC outcomes observed in our study among the vaccinated group.

Moreover, it should be noted that we very carefully captured new outcomes (eg, HTN, cardiovascular disease, DM) that occurred after SARS-CoV-2 infection and not any preexisting medical conditions. On that, COVID-19 has been associated with new-onset hyperglycemia and acute decompensation of diabetes [19]. Besides drug-induced hyperglycemia from steroid use, proposed mechanisms for hyperglycemia after infection include insulin resistance as a result of the inflammatory state and insulin secretory deficits from impaired β-cell function [19, 20]. However, it is unclear whether new-onset diabetes following hospitalization for COVID-19 is permanent [19]. Markedly, even new-onset hypertension has been suggested by a study as a possible sequela of COVID-19. In particular, an enhanced angiotensin II signaling, driven by SARS-CoV-2 infection, is thought to play an important role in the renin-angiotensin system, leading to the development of hypertension in COVID-19 [21]. Nonetheless, we cannot rule out that these individuals were already predisposed to these conditions and that SARS-CoV-2 infection somehow accelerated the development of these conditions.

Apart from the above-mentioned lack of understanding in the pathophysiology of PASC, detailing the predictors of it is also essential but still unknown. Only a few studies have previously tackled the subject, with most of them revealing that long-term unfavorable outcomes (ie, PASC symptoms) were significantly more frequent in women, those with longer hospital stays, those who required intensive care unit admissions, and those with higher symptom load in the acute phase [21, 22]. Furthermore, findings of another study suggest that moderate and severe obesity (BMI $\geq$35 kg/m^2) is associated with a greater risk of PASC. This observation can be explained not only by the underlying mechanisms of obesity, including obesity-related hyperinflammation, immune dysfunction, and comorbidities, but also the higher healthcare utilization by this portion of the population, which increases the chances of detecting and reporting any long-term complaints [23–30]. Moreover, it should be mentioned that we included post–COVID-19 follow-up results no later than 14 December 2021 to avoid the new SARS-CoV-2 variants such as Omicron, which might affect the protective effect of vaccines, since there is evidence that

variants of concerns are overrepresented in breakthrough infections [31]. Last but not least, it is possible that vaccination status was underreported in TriNetX and that a proportion of patients in the no-vaccine group may have been vaccinated. This observation would suggest that the protective effects of COVID-19 vaccine on PASC in our study may be underestimated and the true estimated decreased risk among vaccinated patients is greater than what we reported.

Despite the novelty of our findings, our study has several limitations. First, there are some inherent limitations when EHRs are used to capture data. For instance, since the data are presented as they are recorded, we cannot be sure that there has not been mis-recording of information . Second, the true prevalence of PASC among COVID-19 patients is still unknown as many asymptomatic patients have never been tested. Third, we cannot rule out the possibility that immunization status affects the probability to seek or receive medical attention, particularly for less severe outcomes. Fourth, this study is not informative on outcomes in patients infected with SARS-CoV-2 but who did not get tested nor diagnosed with COVID-19. Additionally, our vaccination rate is low and we cannot rule out that EMR documentation of vaccination may have been missed in some of the vaccinated individuals. Another potential limitation is that capturing the location where patients were seen and the difference between healthcare utilization among the 2 groups based on their concurrent comorbidities, which might provide another potential explanation for the post–COVID-19 outcomes that we have described, is beyond the capacity of this database. Finally, being an observational study, causation cannot be inferred.

In summary, the present data show that prior vaccination against COVID-19 is associated with significantly lower risk of postacute COVID-19 symptoms or new onset of health conditions, referred to collectively as PASC or long COVID. These findings may raise awareness to public health on the importance of vaccination programs, by highlighting the urgent need for vaccination to prevent the long-term sequelae of COVID-19.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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