The protective effect of covid-19 vaccination on post-acute sequelae of covid-19 (pasc): a multicenter study from a large national health research network

Sokratis N. Zisis M.D. [1], Jared C. Durieux M.S., M.D.S., M.P.H. [2], Christian Mouchati M.D. [1], Jamie A. Perez Ph.D. [2], Grace A. McComsey M.D., FIDSA. [1,2,3]

[1]School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

[2]Clinical Research Center, University Hospitals Health System, Cleveland, Ohio, USA

[3]Department of Pediatrics and Medicine, Case Western Reserve University, Cleveland, Ohio, USA

[*]**Corresponding Author:**

Grace A McComsey, MD, FIDSA

Vice President of Research

Associate Chief Scientific Officer, University Hospitals Health System

Professor of Pediatrics and Medicine

Principal Investigator, Case CTSC

Case Western Reserve University

11100 Euclid Ave, Cleveland, OH 44106

Tel: +1 216-844-5936, Fax: 216-201-4607

Email: Grace.McComsey@UHhospitals.org

Alternate Author:

Sokratis N. Zisis, MD

UH Cleveland Medical Center

11100 Euclid Ave, Cleveland, OH 44106

Phone: 216-844-2739, Fax: 216-201-4607,

Email: Sokratis.Zisis@UHhospitals.org

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Abstract

Background

COVID-19 vaccines have been proven to decrease the severity of acute phase infection, however little is known about its effect on Post-Acute Sequelae of COVID-19 (PASC).

Methods

Patients with confirmed COVID-19 diagnosis, minimum age of 18 years with 3 month follow-up post-diagnosis between September 21, 2020 and December 14, 2021 were identified from 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 pre-existing comorbidities. At 28 days following COVID 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 diagnosis, the relative risk of hypertension was 0.33 (95% CI: 0.26, 0.42), diabetes was 0.28 (95% CI: 0.20, 0.38), heart disease was 0.35 (95% CI: 0.29, 0.44), and death was 0.21 (95% CI: 0.16, 0.27). 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.

Conclusion

Our data suggest that COVID-19 vaccine is protective against post-acute sequelae of SARS-CoV-2 (PASC) symptoms, new onset of health conditions, and mortality.

INTRODUCTION

With over 312 million infections and over 5 million deaths reported globally as of January 12, 2022, 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 now termed post-acute sequelae of COVID-19 (PASC)(2).

PASC is manifesting in a wide range of persistent or new symptoms that do not resolve for many months(3–5). Indeed, 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 system(2,6–11).

To face the pandemic, major international entities set vaccination as their top priority(12). Worldwide, more than 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 of America, we aimed to analyze the effect of immunization on post-acute 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 [PCR] who sought care in the United States from September 21, 2020 to December 14, 2021. The de-identified patients' data included in this analysis belong to the TriNetX Research Network platform, a network of electronic medical records (EMR) from 57 health care organizations currently involving over 70 million patients across the United States of America.

We collected patients' demographics, comorbidities, COVID vaccination, as well as symptoms and diagnoses prior to, at the time, and after 3 months of COVID infection. We stratified COVID- infected patients into two groups: vaccinated patients with breakthrough infection and unvaccinated patients. PASC was defined as new, continuing or recurrent symptoms that occur four or more weeks after the initial Covid -19 infection ; while it should be mentioned that 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 vaccine and no-vaccine groups. Data extraction and analysis were performed using a list of ICD-10 codes (detailed in 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 chi-square. 1:1 propensity score matching using greedy nearest-neighbor method was used to balance the two cohorts on age, gender, 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 diagnosis. Rates were presented per 1,000 and p-values less than alpha <.05 were considered statistically significant.

RESULTS

At baseline, 1,578,719 patients with confirmed COVID-19 were identified and 1.6% (n=25225) had documented COVID vaccination. Among the vaccine cohort, the average age 54.82 ± 17.77 years, 59.84% (n=15094) were female, and 68.45% (n=17266) were white. The average body mass index (BMI) was 30.20 ± 7.33 kg/m^2, 47.36% (n=11947) had hypertension (HTN), 22.89% (n=5774) had diabetes (DM), and 12.73% (n=3210) had chronic kidney disease (CKD). Among the no-vaccine cohort, the average age was 42.91 ± 21.84, 56.02% (n=870301) were female, and 62.13% (n=965166) were white. The average BMI was 29.16 ± 8.12 kg/m^2, 28.16% (n=435700) had HTN, 19.25% (n=298980) had DM, and 6.32% (n=98199) had CKD. After matching, there were no differences in age (p=0.13), gender (p=0.75), race or ethnicity (p>.05), BMI (p=0.98), HTN (p=0.89), DM (p=0.42), or CKD (p=0.13).

At 28 days following COVID 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 (relative risk) of HTN was 0.45 (95% CI: 0.38, 0.54), DM was 0.43 (95% CI: 0.35, 0.54), heart disease was 0.49 (95% CI: 0.43, 0.57), and death was 0.33 (95% CI: 0.28, 0.39). The RR for respiratory symptoms [0.70 (95% CI: 0.74)], headache [0.56 (95% CI: 0.50, 0.63)], fatigue [0.65 (95% CI: 0.61, 0.70)], body ache [0.50 (95% CI: 0.42, 0.57)], and diarrhea or constipation [0.60 (95% CI: 0.55, 0.65)] was also less than 1.0.

At 90 days following COVID 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: 0.26, 0.42), DM was 0.28 (95% CI: 0.20, 0.38), heart disease was 0.35 (95% CI: 0.29, 0.44), and death was 0.21 (95% CI: 0.16, 0.27). Decreases in RR were also observed in respiratory symptoms [0.54 (95% CI: 0.50, 0.57)], headache [0.39 (95% CI: 0.34, 0.45)], fatigue [0.48 (95% CI: 0.43, 0.52)], body ache [0.34 (95% CI: 0.28, 0.42)], and diarrhea or constipation [0.44 (95% CI: 0.40, 0.49)]. 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 (i.e., 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 post-infection. In this study with data from a large-scale electronic health records network, we showed that individuals with COVID breakthrough infections after vaccination have lower rates of PASC or long-COVID symptoms/outcomes compared with propensity-matched unvaccinated COVID-infected people. As such, our work extends the current data on the efficacy of COVID vaccination in acute COVID infection, to show that vaccination is associated with faster and better COVID 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 like headaches, fatigue, body aches, and respiratory and gastrointestinal symptoms. We also found significant differences in post-acute COVID-19 mortality rates between vaccinated and unvaccinated COVID-infected patients. These findings are in line with previously published data, suggesting a potential implication of immunizations in preventing the development of chronic-COVID 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 like 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 post-acute 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. Hypertension, cardiovascular disease, diabetes) that occurred after COVID infection and not any pre-existing medical conditions. On that, COVID-19 has been associated with new-onset hyperglycemia and acute decompensation of diabetes(20). 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 beta-cell function (20, 21). However, it is unclear whether new-onset diabetes following hospitalization for COVID-19 is permanent (20). 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(23). Nonetheless, we cannot rule out that these individuals were already predisposed to these conditions and that COVID-19 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 required ICU admissions, and those with higher symptom load in the acute phase(23, 24). Furthermore, findings of another study suggest that moderate and severe obesity (BMI ≥ 35 kg/m2) 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 co-morbidities, but also the higher health care utilization by this portion of population which increases the chances of detecting and reporting any long-term complaints(26–33). Moreover, it should be mentioned that we included post COVID follow up results no later than December 14, 2021 to avoid the new SARS-CoV-2 variants like Omicron, which might affect the protective effect of vaccines; since there is evidence that variants of concerns are overrepresented in breakthrough infections(34). Last but not least, it is possible that vaccination status was under-reported 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 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, the use of electronic medical records to capture data. Second, the true prevalence of PASC among COVID-19 patients is still unknown since 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 some of the vaccinated individuals. Another potential limitation is that capturing the location that patients were seen and the difference between health care utilization among the two groups based on their concurrent comorbidities; which might provide another potential explanation for the post-covid 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 post-acute 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.

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Table 1. Baseline characteristics of COVID-19 patients and vaccine status before and after propensity score matching

	Before Matching			After Matching		
	Vaccine + COVID (n=25225)	NO-Vaccine + COVID (n=1553494)	p-value	Vaccine + COVID (n=25225)	NO-Vaccine + COVID (n=25225)	p-value
Characteristics	mean ± SD / n (%)			mean ± SD / n (%)		
Age (years)	54.82 ± 17.77	42.91 ± 21.84	<.0001	54.82 ± 17.77	55.06 ± 17.96	0.13
Gender						
Female	15094 (59.84)	870301 (56.02)	<.0001	15094 (59.84)	15129 (59.98)	0.75
Male	10130 (40.16)	682700 (43.95)	<.0001	10130 (40.16)	10095 (40.02)	0.75
Unknown Gender	10 (0.04)	493 (0.03)	0.49	10 (0.04)	10 (0.04)	1.00
Race						
Black or African American	4907 (19.45)	287241 (18.49)	<.0001	4907 (19.45)	4853 (19.24)	0.54
White	17266 (68.45)	965166 (62.13)	<.0001	17266 (68.45)	17381 (68.90)	0.27
Asian	860 (3.41)	31290 (2.01)	<.0001	860 (3.41)	874 (3.47)	0.73
American Indian or Alaska Native	159 (0.63)	6163 (0.4)	<.0001	159 (0.63)	126 (0.50)	0.05
Native Hawaiian or Pacific Islander	41 (0.16)	2357 (0.15)	0.66	41 (0.16)	47 (0.19)	0.52
Unknown Race	1992 (7.90)	261277 (16.82)	<.0001	1992 (7.90)	1944 (7.71)	0.43
Comorbidities						
Hypertension	11947 (47.36)	435700 (28.16)	<.0001	11947 (47.36)	11963 (47.43)	0.89
Neoplasms	9487 (37.61)	298980 (19.25)	<.0001	9487 (37.61)	9533 (37.79)	0.67
Diabetes mellitus	5774 (22.89)	214891 (13.83)	<.0001	5774 (22.89)	5698 (22.59)	0.42
Asthma	3818 (15.14)	181145 (11.66)	<.0001	3818 (15.14)	3678 (14.58)	0.08
Atherosclerosis	3464 (13.73)	106882 (6.88)	<.0001	3464 (13.73)	3314 (13.14)	0.05
Chronic kidney disease	3210 (12.73)	98199 (6.32)	<.0001	3210 (12.73)	3097 (12.18)	0.13
Chronic obstructive pulmonary disease	1981 (7.85)	70746 (4.55)	<.0001	1981 (7.85)	1879 (7.45)	0.09
Transplanted organ and tissue status	1218 (4.83)	20323 (1.31)	<.0001	1218 (4.83)	1051 (4.17)	0.0003
Human immunodeficiency virus	209 (0.83)	6063 (0.39)	<.0001	209 (0.83)	152 (0.60)	0.003
Body mass index (kg/m2)	30.20 ± 7.33	29.16 ± 8.12	<.0001	30.20 ± 7.33	30.68 ± 7.40	0.98

Table 2. Post-Acute Sequelae of Sars-Cov-2 (PASC) Mortality and Morbidity Risk at 28 days: vaccine vs. no-vaccine.

		28 day risk (Rates per 1,000)			
	Total (n)	Vaccine + COVID	No-Vaccine + COVID	Relative Risk (95% CIs)	Attributable Risk (95% CIs)
Outcomes		n (incident rate)			
Mortality	50450	171 (6.78)	522 (20.69)	0.33 (0.28, 0.39)	-13.91 (-15.94, -11.89)
New Conditions since COVID					
Hypertension	25862	176 (13.52)	384 (29.90)	0.45 (0.38, 0.54)	-16.38 (-19.93, -12.83)
Diabetes mellitus	38762	116 (5.98)	269 (13.88)	0.43 (0.35, 0.54)	-7.90 (-9.87, -5.93)
Thyroid Disease	43481	82 (3.80)	193 (8.80)	0.43 (0.33, 0.56)	-5.00 (-6.48, -3.51)
Heart Disease	33836	253 (15.41)	543 (31.17)	0.49 (0.43, 0.57)	-15.76 (-18.96, 12.57)
Malignant Neoplasms	42705	84 (3.95)	260 (12.14)	0.32 (0.25, 0.42)	-8.20 (-9.89, -6.50)
Thrombosis	43486	137 (6.36)	332 (15.14)	0.42 (0.34, 0.51)	-8.78 (-10.72, -6.85)
Rheumatoid Arthritis	49289	16 (0.65)	32 (1.30)	0.50 (0.28, 0.91)	-0.65 (-1.20, -0.09)
Mental Disorders	32307	231 (14.77)	604 (36.23)	0.41 (0.35, 0.47)	-21.45 (-24.86, -18.05)
New Symptoms since COVID					
Respiratory Symptoms	50450	2263 (89.71)	3219 (127.61)	0.70 (0.67, 0.74)	-37.90 (-43.32, -32.48)
Headache	50450	450 (17.84)	804 (31.87)	0.56 (0.50, 0.63)	-14.03 (-16.75, -11.32)
Fatigue	50450	1138 (45.14)	1750 (69.38)	0.65 (0.61, 0.70)	-24.26 (-28.31, -20.21)
Body Ache	50450	235 (9.32)	480 (19.03)	0.50 (0.42, 0.57)	-9.71 (-11.77, -7.65)
Diarrhea or constipation	50450	857 (33.97)	1424 (56.45)	0.60 (0.55, 0.65)	-22.48 (-26.10, -18.86)

Table 3. Post-Acute Sequelae of Sars-Cov-2 (PASC) Mortality and Morbidity Risk a 90 days: vaccine vs. no-vaccine.

	90 day risk (Rates per 1,000)				
	Total (n)	Vaccine + COVID	No-Vaccine + COVID	Relative Risk (95% CIs)	Attributable Risk (95% CIs)
Outcomes		n (incident rate)			
Mortality	50450	60 (2.38)	293 (11.62)	0.21 (0.16, 0.27)	-9.24 (-10.69, -7.78)
New Conditions since COVID					
Hypertension	25634	83 (6.42)	249 (19.59)	0.33 (0.26, 0.42)	-13.17 (-15.95, -10.40)
Diabetes mellitus	38616	52 (2.69)	187 (9.69)	0.28 (0.20, 0.38)	-7.00 (-8.56, -5.44)
Thyroid Disease	43391	33 (1.53)	152 (6.95)	0.22 (0.15, 0.32)	-5.41 (-6.63, -4.19)
Heart Disease	33506	117 (7.19)	349 (20.26)	0.35 (0.29, 0.44)	-13.07 (-15.55, -10.60)
Malignant Neoplasms	42599	45 (2.12)	193 (9.04)	0.23 (0.17, 0.32)	-6.92 (-8.34, -5.51)
Thrombosis	43312	62 (2.89)	233 (10.67)	0.27 (0.20, 0.36)	-7.79 (-9.32, -6.25)
Rheumatoid Arthritis	49275	10 (0.41)	24 (0.97)	0.42 (0.20, 0.87)	-0.57 (-1.03, -0.10)
Mental Disorders	31993	100 (6.45)	421 (25.53)	0.25 (0.20, 0.31)	-19.08 (-21.80, -16.37)
New Symptoms since COVID					
Respiratory Symptoms	50450	1251 (49.59)	2344 (92.92)	0.54 (0.50, 0.57)	-43.33 (-47.80, -38.86)
Headache	50450	247 (9.79)	635 (25.17)	0.39 (0.34, 0.45)	-15.38 (-17.66, -13.10)
Fatigue	50450	605 (23.98)	1268 (50.27)	0.48 (0.43, 0.52)	-26.28 (-29.58, -22.99)
Body Ache	50450	124 (4.92)	361 (14.31)	0.34 (0.28, 0.42)	-9.40 (-11.10, -7.70)
Diarrhea or constipation	50450	480 (19.03)	1083 (42.93)	0.44 (0.40, 0.49)	-23.90 (-26.92, -20.89)