# Letters

RESEARCH LETTER

## Association Between Vaccination and Acute Myocardial Infarction and Ischemic Stroke After COVID-19 Infection

Studies have suggested an increased incidence of acute myocardial infarction (AMI) and ischemic stroke after COVID-19 infection related to an increased risk of thrombosis.[1,2] Vaccines against SARS-CoV-2 are effective against COVID-19 and its progression to severe disease.[3] However, it is unclear if vaccines also prevent secondary complications. We examined the association between vaccination and AMI and ischemic stroke after COVID-19 infection.

Supplemental content

**Methods** | We conducted a retrospective cohort study to compare the incidence of AMI and ischemic stroke after COVID-19 infection between patients who were never vaccinated and those who were fully vaccinated (2 doses of mRNA vaccines or viral vector vaccine) against SARS-CoV-2. The Korean nationwide COVID-19 registry (on infection and vaccination) and the Korean National Health Insurance Service database were used. COVID-19 reporting is mandated, and Korea has universal health care coverage. Adults aged 18 years or older who were diagnosed with COVID-19, including asymptomatic infections, between July 2020 and December 2021 were included. Exclusion criteria included (1) outcome events less than 3 months before COVID-19 diagnosis; (2) reinfection; (3) hospitalization for COVID-19 for 30 or more days and, among vaccinated patients, (4) single dose of vaccine; and (5) COVID-19 diagnosis before or within 7 days after the second vaccination. Patients were observed until March 31, 2022.

The primary outcome was a composite of hospitalizations for AMI and ischemic stroke that occurred 31 to 120

Table 1. Baseline Characteristics of Study Population by Vaccination Status[a]

| | Unweighted population, No. (%)[b] | | | Weighted population, %[b] | | |
|---|---|---|---|---|---|---|
| | Not vaccinated (n = 62 727) | Fully vaccinated (n = 168 310) | Absolute standardized difference[c] | Not vaccinated | Fully vaccinated | Absolute standardized difference[c] |
| Sex[d] | | | 0.029 | | | 0.042 |
| Male | 30 407 (48.48) | 79 176 (47.04) | | 45.11 | 47.21 | |
| Female | 32 320 (51.52) | 89 134 (52.96) | | 54.89 | 52.79 | |
| Age, median (IQR), y[d] | 42 (31 to 58) | 57 (42 to 66) | 0.504 | 52 (37-68) | 54 (38-65) | 0.087 |
| 18-39 | 28 467 (45.38) | 36 444 (21.65) | | 30.39 | 26.80 | |
| 40-64 | 24 183 (38.55) | 80 647 (47.92) | | 39.71 | 46.66 | |
| ≥65 | 10 077 (16.06) | 51 219 (30.43) | | 29.90 | 26.54 | |
| Insurance plan for low income[d] | 3308 (5.27) | 6310 (3.75) | 0.074 | 4.47 | 4.24 | 0.011 |
| Comorbidities | | | | | | |
| Charlson Comorbidity Index, median (IQR)[e] | 0 (0 to 2) | 1 (0 to 2) | | | | |
| Charlson Comorbidity Index ≥5[d] | 4001 (6.38) | 11 792 (7.01) | 0.025 | 7.26 | 6.87 | 0.015 |
| Diabetes | 4479 (7.14) | 19 929 (11.84) | 0.161 | 9.17 | 11.06 | 0.063 |
| Hypertension[d] | 6782 (10.81) | 37 166 (22.08) | 0.308 | 20.07 | 19.03 | 0.029 |
| Dyslipidemia | 2254 (3.59) | 13 618 (8.09) | 0.193 | 4.25 | 7.57 | 0.141 |
| Previous history of outcome events | 909 (1.45) | 2704 (1.61) | 0.013 | 2.29 | 1.46 | 0.062 |
| Severity of COVID-19[f] | | | | | | |
| Severe | 6136 (9.78) | 5298 (3.15) | 0.289 | 12.45 | 2.84 | 0.399 |
| Critical | 3514 (5.60) | 1772 (1.05) | 0.276 | 8.52 | 0.95 | 0.397 |

[a] The Cox proportional hazard model was constructed for the outcome events with sex, age, previous history of outcome events, diabetes, hypertension, hyperlipidemia, CCI, and the severity of COVID-19 as covariates, weighted by the inverse probability of full vaccination.

[b] Data are presented as No. (%) or percentage of patients unless stated otherwise.

[c] Standardized mean difference <0.1 was considered a good balance between groups

[d] Variables included in the calculation of propensity score.

[e] Charlson Comorbidity Index (CCI) is calculated by the addition of points designated to each comorbid condition, identified from the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*) codes entered within 3 years. One point is given for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective disease, ulcer disease, mild liver disease, and diabetes. Two points for hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, any tumor, leukemia, and lymphoma. Three points for moderate or severe liver disease. Six points for metastatic solid tumor and AIDS.

[f] Severe COVID-19 was identified using electronic data interchange (EDI) procedure codes for supplementary oxygen. Critical COVID-19 was identified by the EDI codes for high-flow nasal cannula, intubation, tracheostomy, mechanical ventilation, and extracorporeal membrane oxygenation.

Table 2. Risk for Cardiovascular Events by Vaccination Status

| | No. of events | | Incidence per 1 000 000 person-days | | | |
|---|---|---|---|---|---|---|
| | Not vaccinated (n = 62 727) | Fully vaccinated (n = 168 310) | Not vaccinated | Fully vaccinated | Adjusted HR (95% CI) | *P* value |
| Composite outcome | 31 | 74 | 6.18 | 5.49 | 0.42 (0.29-0.62) | <.001 |
| Acute myocardial infarction | 8 | 24 | 1.60 | 1.78 | 0.48 (0.25-0.94) | .03 |
| Ischemic stroke | 23 | 50 | 4.59 | 3.71 | 0.40 (0.26-0.63) | <.001 |
| Subgroups | | | | | | |
| Male | 17 | 48 | 6.98 | 7.59 | 0.41 (0.26-0.66) | <.001 |
| Female | 14 | 26 | 5.44 | 3.63 | 0.42 (0.23-0.76) | .004 |
| Age, y | | | | | | |
| 40-64 | 11 | 22 | 5.48 | 3.39 | 0.38 (0.20-0.74) | .004 |
| ≥65 | 20 | 51 | 33.99 | 12.42 | 0.41 (0.26-0.66) | <.001 |
| Charlson Comorbidity Index | | | | | | |
| <5 | 25 | 56 | 5.22 | 4.45 | 0.40 (0.26-0.60) | <.001 |
| ≥5 | 6 | 18 | 25.04 | 19.79 | 0.54 (0.24-1.22) | .14 |
| Diabetes | | | | | | |
| No | 23 | 46 | 4.89 | 3.87 | 0.38 (0.24-0.61) | <.001 |
| Yes | 8 | 28 | 26.29 | 17.58 | 0.47 (0.25-0.91) | .03 |
| Hypertension | | | | | | |
| No | 20 | 46 | 4.41 | 4.39 | 0.50 (0.31-0.80) | .004 |
| Yes | 11 | 28 | 23.11 | 10.90 | 0.34 (0.18-0.62) | <.001 |
| Dyslipidemia | | | | | | |
| No | 27 | 70 | 5.58 | 5.65 | 0.54 (0.37-0.80) | .002 |
| Yes | 4 | 4 | 22.50 | 3.62 | 0.09 (0.03-0.34)[a] | <.001 |
| Previous history of outcome events | | | | | | |
| No | 26 | 67 | 5.24 | 5.05 | 0.44 (0.29-0.65) | <.001 |
| Yes | 5 | 7 | 97.55 | 33.26 | 0.33 (0.10-1.07) | .06 |
| Severe or critical COVID-19 | | | | | | |
| No | 22 | 65 | 5.02 | 5.00 | 0.37 (0.25-0.55) | <.001 |
| Yes | 9 | 9 | 14.38 | 18.51 | 0.66 (0.20-2.23) | .51 |

Abbreviation: HR, hazard ratio.

[a] The following covariates were excluded from this model due to separation: severity of COVID-19 and previous history of outcome events.

days after COVID-19 diagnosis; these were identified by the diagnosis codes and relevant imaging (eMethods in the Supplement). The first 30 days were excluded because of the difficulty of differentiating cardiovascular events occurring as complications of COVID-19 vs acute phase treatment. Secondary outcomes included the components of the composite outcome. Inverse probability of treatment weighting (IPTW) was used to control for differences in patient characteristics between the 2 groups,[4] with standardized differences used to assess the balance of covariates. Logistic regression was performed for IPTW with full vaccination as an independent variable and age, sex, Charlson Comorbidity Index, hypertension, and insurance type as covariates. A Cox proportional hazards model with IPTW was constructed for the outcome events, with sex, age, comorbidities, previous history of outcome events, and the severity of COVID-19 (need for supplementary oxygen [severe], high-flow nasal cannula or higher respiratory support [critical] vs no respiratory support needed) as covariates. The proportionality assumption was tested (zph tests) and met. SAS Enterprise Guide 7.1 (SAS Institute) was used for statistical analysis. A 2-tailed $P < .05$ was considered significant. This study was approved by the institutional review board of the Gil Medical Center with a waiver of informed consent.

**Results** | Of 592 719 patients with COVID-19 during the study period, 231 037 patients were included, of whom 62 727 were never vaccinated and 168 310 were fully vaccinated. Patients who were fully vaccinated were older and had more comorbidities (**Table 1**). In contrast, severe or critical COVID-19 was less common in the fully vaccinated group. The differences in age and comorbidities were reduced after weighting, while the severity of COVID-19 became less balanced. The median follow-up duration starting 30 days after COVID-19 was 90 days in the unvaccinated group and 84 days in the fully vaccinated group.

The composite outcome occurred in 31 unvaccinated patients and 74 fully vaccinated patients, with an incidence of 6.18 vs 5.49 per 1 000 000 person-days (**Table 2**). The adjusted risk was significantly lower in the fully vaccinated group (adjusted hazard ratio [aHR], 0.42; 95% CI, 0.29-0.62). The adjusted risk was significantly lower in fully vaccinated patients for both AMI (aHR, 0.48; 95% CI, 0.25-0.94) and ischemic stroke (aHR, 0.40; 95% CI, 0.26-0.63). A lower risk for

outcome events in fully vaccinated patients was observed in all subgroups, although some did not reach statistical significance, including those with severe or critical infection (Table 2).

**Discussion** | This study found that full vaccination against COVID-19 was associated with a reduced risk of AMI and ischemic stroke after COVID-19. The findings support vaccination, especially for those with risk factors for cardiovascular diseases. Study limitations include that diagnosis codes for reimbursement were used to capture outcome events. Although the operational definition in this study has been widely used, some diagnostic inaccuracies may exist. Also, there were imbalances in patient characteristics by vaccination status. The decision to be vaccinated is affected by multiple factors that may also be associated with cardiovascular risk. A robust model was applied to mitigate the effect of such imbalances, but the possibility of unobserved bias remains.

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