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Original article

# Inverse association with COVID-19 vaccination status of the incidence of pneumonia after SARS-CoV-2 infection: A nationwide retrospective cohort study

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ABSTRACT

*Background:* Although one of the characteristics of COVID-19 is accompanied by acute pneumonia immediately after infection, large-scale cohort studies focused on this issue are lacking. In addition, there is interest in how COVID-19 vaccinations reduce the incidence of acute pneumonia for people infected with different strains of SARS-CoV-2. Thus, we assess the short-term incidence of pneumonia after COVID-19 with the vaccination and SARS-CoV-2 variants.

*Methods:* As data for 2136,751 COVID-19 patients between January 01, 2020 and February 28, 2022 was collected, they were observed for one month from the day of infection. Patients in retrospective cohort study were classified according to doses of the received vaccine and the epidemic phase when SARS-CoV-2 variants prevailed. Multivariable logistic regression analysis calculated adjusted odds ratios (aOR) and 95% confidence intervals (CIs) for the pneumonia risk.

*Results:* In B.1.1.7-B.1.351, B.1.617.2, and B.1.617.2 variants, the aORs (95% CIs; *p*-value) for incidence of pneumonia were 0.93 (0.89–0.98; < 0.001), 0.74 (0.70–0.78; < 0.001), and 0.04 (0.038–0.043; < 0.001), respectively, compared to the original strain. More than 80% of patients have received the second and more doses of the vaccine (average age=44.67 years). The aORs (95% CIs; *p*-value) for pneumonia were 0.61 (0.58–0.64; < 0.001), 0.39 (0.38–0.40; < 0.001), and 0.18 (0.166–0.184; < 0.001) in patients who received the first (N = 68,216), second (N = 898,838), and ≥ third doses (N = 836,173), respectively, compared to unvaccinated patients. According to the received vaccine (second dose of mRNA or viral vector), those who received BNT162b2 and mRNA-1273 (N = 787,980) had lower risk of pneumonia, compared to that in those who received h ChAdOx1 nCov-19 and AD26. COV2-S (N = 89,024).

*Conclusions:* Our findings suggest that the second and ≥ third doses (61% and 82% of risk aversion effect increased, respectively) of the COVID-19 vaccine can prevent the COVID-19-related pneumonia, regardless of the variants.



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## Introduction

Those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) often experienced acute pneumonia. The incidence of acute respiratory distress syndrome, including pneumonia, is approximately 15–30% among hospitalized patients with coronavirus disease 2019 (COVID-19) [1]. Another study reported a crude ventilator-associated pneumonia incidence rate of 48.9% among inpatients [2]. Several recent studies have discussed the molecular and cellular mechanisms of COVID-19 pneumonia [3]. As the risk of severe COVID-19 symptoms is compounded by uncontrolled and unregulated immunity [4,5], suppression and control of excessive immune responses through the administration of COVID-19 vaccine are expected to reduce the risk of complications after developing COVID-19 [6]. The failure of immune responses to clearly remove SARS-CoV-2 and, conversely, the excessive immune responses both trigger the occurrence of severe pneumonia. Moreover, as vaccines and drugs for the treatment of COVID-19 were quickly developed [7,8] and several variants of SARS-CoV-2 had emerged (mainly alpha- [α; B.1.1.7], beta- [β; B.1.351], delta- [B.1.617.2], and omicron [B.1.1.529]) within the 3-years of the pandemic period (2020-early 2022), changes may have occurred in the incidence of pneumonia according to the mutation of SARS-CoV-2 and COVID-19 vaccination status [9]. Little is known about the effect of inoculation with the third dose of vaccine, usually called booster shoot, or the type of vaccine received (mRNA-based or virus vector vaccine) on the incidence of pneumonia [10,11]. Among 303 patients, not inoculated patients had a higher pneumonia score (computed tomography (CT)-based severity score) than both completely or boost vaccinated patients. Thus, the observation and investigation of the incidence of pneumonia and its risk factors among patients with COVID-19, particularly those with a history of vaccination, should be conducted.

Herein, using K-COV-N cohort (Korea Disease Control and Prevention Agency-COVID19-National Health Insurance Service cohort), we aimed to investigate the association of COVID-19 vaccine and SARS-CoV-2 mutations with the short-term incidence of pneumonia after infection among 2136,751 patients with COVID-19.

## Methods

### *Study population*

The retrospective cohort study used the K-COV-N cohort database, provided by the Korea Disease Control and Prevention Agency (KDCA) and the National Health Insurance Service (NHIS) [12,13]. The K-CoV-N database includes the medical history of almost all patients with COVID-19 in Korea, based on a daily COVID-19 report from the KDCA and an insurance claim from the NHIS. Thus, the sociodemographic information (age, sex, and income level), the record of medical service (treatment pattern, drug prescription, and received vaccine), and the official date of SARS-CoV-2 infection of all patients with COVID-19 (January 01, 2020 and March 31, 2022) were collected from the K-CoV-N database.

In an observation study for retrospective cohort, data on 2164,339 adults (≥ 20 years) diagnosed with COVID-19 from January 01, 2020 to February 28, 2022 and the general population, without COVID-19 from January 01, 2020 to March 31, 2022 were collected from the database. After a 1:3 age-sex-income-Charlson Comorbidity Index (CCI) exact matching, 6492,612 and 2164,204 uninfected and infected individuals were selected, respectively, with the exclusion of 135 unmated COVID-19 patients. In COVID-19 patients, the SARS-CoV-2 infection date, officially reported to the KDCA, was used as the index date (the starting point for observation). On the contrary, the index date of matched and uninfected participants was the same as the index date of the matched target; start to follow up with the matched. To evaluate the short-term incidence of pneumonia after COVID-19, 18,972 patients with COVID-19 and previous pneumonia prior to SARS-CoV-2 infection or deaths before follow-up were excluded; similarly, 58,480 uninfected participants with previous pneumonia or deaths before follow-up were excluded. In addition, 8481 and 2908 participants with and without COVID-19, respectively, who died within a month after follow-up were excluded. Finally, the analysis to evaluate the risk of COVID-19 pneumonia with 6431,224 SARS-CoV-2 uninfected participants, as the matched controls, was conducted. Furthermore, the history of vaccination form COVID-19 patients (N = 2136,751) was used to evaluate the risk of pneumonia according to vaccination status, (Supplementary Figure 1).

### *Diagnosis of COVID-19 and its severity*

An accurate and multiple-tested, positive polymerase chain reaction (PCR)-based clinical laboratory test for SARS-CoV-2 was used to confirm and diagnose the infection [14]. During this study period, the KDCA has found and managed COVID-19 patients in the whole nation through mandatory PCR tests for all people who were closely contact with infected people. The COVID-19 pandemic period in Korea was divided into four stages based on the epidemic pattern (COVID-19 outbreak, rapid increase in infected patients, and change in reproduction number) and dominant variants: 2020.01.01–2020.12.05; 2020.12.06–2021.07.01 (alpha/beta-variant); 2021.07.02–2022.01.20 (delta-variant); and 2022.01.21–2022.02.28 (omicron). The participants diagnosed with COVID-19 were assigned to each group based on the index date.

Within a month after the index date, any medical records related to the treatment pattern, including intensive care unit, oxygen supplementation (high-flow oxygen therapy and high-flow nasal cannula therapy), cardiopulmonary resuscitation, and extracorporeal membrane oxygenation, were collected from the K-COV-N cohort database. Information on the prescribed COVID-19 targeted drugs within a month after the index date, including regdanvimab, nirmatrelvir, and paxlovid, was collected. Moreover, participants who had chronic obstructive pulmonary disease (COPD), asthma, hypertension, diabetes, liver disease, all types of cancer, or sickle-cell anemia, and were prescribed with immunosuppressive drugs prior to the index date, were identified. Based on the World Health Organization (WHO) definition of mild or severe COVID-19, the COVID-19 severity was determined according to the treatment, drug prescription, underlying disease, obesity status (body mass index; BMI ≥ 30 kg/m$^2$), and age (≥ 60 years).

### *Vaccination status*

Using information on the vaccination history, collected from the K-COV-N cohort database, uninfected people and patients with COVID-19 were classified by vaccination status (the number of vaccine dose and the type of vaccine). If a participant received the vaccine for at least 14 days (2 weeks; the minimum period for SARS-CoV-2-antibody production) prior to the index date, this participant was considered vaccinated; meanwhile, no vaccine was classified as un-vaccinated, only received the first dose of vaccine as first vaccinated, received the second dose of vaccine as second vaccinated, and received the third or more dose of vaccine (booster shot) as third and more vaccinated. Participants who received the second or more vaccine doses were additionally classified according to the type of COVID-19 vaccine (mRNA-based vaccines, including Pfizer-BioNTech vaccine [Comirnaty; BNT162b2] [15] and Moderna vaccine [mRNA-1273] [16] and virus-derived vaccines, including AstraZeneca vaccine [AZD1222; ChAdOx1 nCov-19] [7] and Janssen vaccine [AD26. COV2-S] [8]).

*Outcome: hospitalized pneumonia*

Hospitalized pneumonia was defined as a diagnosis of pneumonia and ≥ 2 days of hospitalization for pneumonia. To evaluate the short-term incidence of pneumonia in uninfected and infected people, patients who were newly diagnosed with pneumonia within a month after infection and not diagnosed with pneumonia within 1-year prior to the index date were identified using the International Classification of Diseases, Tenth Revision (ICD-10 codes; J12-J18), and their data were collected.

*Statistical analysis*

The study population was evaluated for adjusted odds ratio (aOR) and 95% confidence intervals (CIs) of the short-term incidence and risk of pneumonia after COVID-19, according to the epidemic phase and vaccination status. As doses of vaccine were mainly considered as exposure, un-vaccinated participants were used as the reference. To minimize the bias such as selection bias, the multivariable logistic regression (Event: the occurrence of pneumonia) was used after adjustments for several covariates (age, sex, income, CCI, and COVID-19-targeted drug prescription), after testing the suitability of the regression model, including the distribution of the number of events in the groups and interaction between the used covariates. Additionally, stratified analysis (subgroup of underlying disease) was performed. Data were expressed as mean ± standard deviation (SD) and number of participants (percentage [%]). The chi-square test for categorical variables and analysis of variance for continuous variables were used to compare differences in the distribution of covariates. A $p$–value of < 0.05 was considered significant. Data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

2136,751 COVID-19 patients were included in this study, together with 6431,224 uninfected participants (Non-infected) as matched controls (Table 1). The average ages ± SD of patients with COVID-19 who did not receive vaccine (No, N = 333,524), received the first dose (First, N = 68,216), the second dose (Second, N = 898,838), and the third or more doses of vaccine (≥ Third, N = 839,173) were 43.47 ± 15.87, 43.91 ± 14.71, 40.23 ± 14.69, and 49.11 ± 16.53 years, respectively. The percentage of high CCI score (≥ 3) in the third or more vaccine doses was 12.2%, which indicated the highest level of comorbidity. Within a month from the matched and infected dates, the aOR of pneumonia was 170 (157–184) among the participants with COVID-19, compared with that among uninfected participants (Table 2). The all-cause mortality within a month of follow-up also showed the same tendency: the aOR of death was 8.18 (7.84–8.54). Table 3 shows the difference in the incidence of pneumonia among inpatients within a month from the index date according to the SARS-CoV-2 variant and the epidemic phase of COVID-19. In alpha-/beta-, delta-variant, and omicron, the aORs (95% CIs) for incidence of pneumonia were 0.93 (0.89–0.98), 0.74 (0.70–0.78), and 0.04 (0.038–0.043), respectively, compared with that of the original SARS-CoV-2. When omicron was dominant, the incidence of pneumonia decreased significantly. This result was observed regardless of the number of vaccine doses. To evaluate the effect of the vaccine on the all-cause mortality, the aORs of death in the first, second, ≥ third dose groups were 0.46 (0.41–0.52), 0.31 (0.29–0.32), and 0.11 (0.10–0.12), respectively, compared to the no vaccine group (Supplementary Table 1). Among patients with COVID-19, the short-term risk of pneumonia was reduced as the COVID-19 vaccine doses increased (Table 4). The aORs of pneumonia throughout the overall COVID-19 pandemic period (January 1, 2020 to February 28, 2022) were 0.44 (0.42–0.46), 0.12 (0.122–0.129), and 0.02 (0.023–0.026) in the first, second, and ≥ third dose groups, respectively, compared with that in the no vaccine group (Model 1). The results were statistically significant ($p$ for trend < 0.001). Even in the omicron dominant phase (January 21, 2022 to February 28, 2022), the short-term risk of pneumonia was reduced in the second and ≥ third dose groups; the aORs of pneumonia were 0.30 (0.28–0.33) and 0.15 (0.14–0.17), respectively, and were statistically significant ($p$ for trend < 0.001). As shown in Model 2 (considering the COVID-19-targeted drug prescriptions), the results were the same. As regards the type of vaccine (mRNA-based or virus-derived vaccines) and the strategy for vaccination among those who were inoculated with the second or ≥ third dose of vaccine before infection, the aORs of pneumonia in participants who were vaccinated with only the mRNA-based vaccine (BNT162b2 and mRNA-1273) were lower than that in participants with the virus-derived vaccine (ChAdOx1 nCov-19 and AD26. COV2-S): 0.27 (0.26–0.28) and 0.59 (0.56–0.61) in the mRNA[2] and virus[2] group, respectively, compared to the no vaccine group (Table 5). Similarly, among those who received the third or more doses of vaccine, the aOR of pneumonia was lowest in participants who only received the mRNA-based vaccine, regardless of the epidemic period. In a stratified analysis of the subgroups classified by underlying disease, including COPD and asthma, the aORs of pneumonia decreased as the vaccine dose increased. In addition, the percentage of pneumonia events as the CCI levels increased (Supplementary Table 2). Patients with severe COVID-19 were classified according to the WHO criteria (Supplementary Table 3). Compared with the patients with mild COVID-19, the aOR of pneumonia in patients with severe COVID-19 was 470 (358–617) (Supplementary Table 4). Even if the risk is extremely higher in severe COVID-19 patients, the risk was gradually reduced in order of the number of vaccine doses, regardless of the epidemic period; 826 (No), 482 (First), 352 (Second), 138 times (≥ Third). The aORs of pneumonia in the first, second, and ≥ third dose groups were 0.58 (0.55–0.62), 0.43 (0.41–0.44), and 0.17 (0.16–0.18), respectively, compared with that in the no vaccine group, and were statistically significant ($p$ for trend < 0.001).

## Discussion

In this retrospective cohort study of more than 2.1 million COVID-19 patients aged 20 years or older who were inoculated with the COVID-19 vaccine (the first, second, and ≥ third doses), SARS-CoV-2 infection was significantly associated with a higher risk of pneumonia within a month after infection. However, the risk of pneumonia was relatively low during the omicron-dominant outbreak. Regardless of the epidemic phases and severity of COVID-19, a higher number of dose of vaccine decreases the risk of pneumonia. To our knowledge, this study is the first to investigate the risk of pneumonia according to the SARS-CoV-2 variant and vaccination status.

An increased incidence of COVID-19 pneumonia has been reported in previous studies [1, 17, 18]. A recent study revealed that SARS-CoV-2 infected people suffered an upper respiratory tract disease (40% of patients) and pneumonia (20% of patients: sum of non-hypoxemic-moderate type (10%) and hypoxemic type (10%)), thus requiring hospitalization for oxygen therapy. The percentage (10%: hypoxemic type) was almost consistent with that of hospitalized pneumonia events reported in this study (8.04%). Additionally, the patients with COVID-19 caused by the omicron had a lower prevalence of COVID-19-induced pneumonia than those with COVID-19 caused by other variants after analyzing the characteristic CT images [19–21]. Despite of safety issues of vaccination [22], vaccination against COVID-19 reduced the risk of severe COVID-19 and hospitalized pneumonia after infection. Similar to our findings, a previous study reported a reduced risk of pneumonia in patients who received vaccination following SARS-CoV-2 infection [23].

**Table 1**
Descriptive characteristics of the study population.

| | Non-infected (Matched group) | COVID-19 (SARS-CoV-2 infected) | | | | |
|---|---|---|---|---|---|---|
| | | Overall | Vaccination status [dose] | | | |
| | | | No | First | Second | ≥ Third |
| **Study population, N** | 6431,224 | 2136,751 | 333,524 | 68,216 | 898,838 | 836,173 |
| **Sex, N (%)** | | | | | | |
| Men | 3004,633 (46.7) | 1000,184 (46.8) | 162,300 (56.7) | 38,680 (56.7) | 419,367 (46.7) | 379,837 (45.4) |
| Women | 3426,591 (53.3) | 1136,567 (53.2) | 171,224 (51.3) | 29,536 (43.3) | 479,471 (53.3) | 456,336 (54.6) |
| **Age [years], mean ± SD** | 44.44 ± 16.14 | 44.33 ± 16.13 | 43.47 ± 15.87 | 43.91 ± 14.71 | 40.23 ± 14.69 | 49.11 ± 16.53 |
| **Age [years], N (%)** | | | | | | |
| 20-39 | 2720,208 (42.3) | 909,205 (42.6) | 153,989 (46.2) | 31,404 (46.0) | 468,356 (52.1) | 255,456 (30.6) |
| 40-59 | 2451,706 (38.1) | 815,121 (38.1) | 123,728 (37.1) | 24,526 (36.0) | 325,534 (36.2) | 341,333 (40.8) |
| ≥ 60 | 1259,310 (19.6) | 412,425 (19.3) | 55,807 (16.7) | 12,286 (18.0) | 104,948 (11.7) | 239,384 (28.6) |
| **Income level, quartiles, N (%)** | | | | | | |
| 1st (highest) | 2004,131 (31.2) | 669,491 (31.3) | 91,457 (27.4) | 19,111 (28.0) | 281,683 (31.3) | 227,240 (33.2) |
| 2nd | 1586,845 (24.7) | 529,109 (24.8) | 83,810 (25.1) | 18,589 (27.2) | 226,417 (25.2) | 200,293 (24.0) |
| 3rd | 1426,573 (22.2) | 475,248 (22.2) | 79,270 (23.8) | 15,951 (23.4) | 204,425 (22.7) | 175,602 (21.0) |
| 4th (lowest) | 1413,675 (22.0) | 462,903 (21.7) | 78,987 (23.7) | 14,565 (21.4) | 186,313 (20.7) | 183,038 (21.9) |
| **Charlson comorbidity index, N (%)** | | | | | | |
| ≤ 2 | 5849,055 (91.0) | 1930,386 (90.3) | 295,888 (88.7) | 60,524 (88.7) | 839,590 (93.4) | 734,384 (87.8) |
| 3-4 | 408,616 (6.4) | 141,986 (6.6) | 24,287 (7.3) | 5026 (7.4) | 41,653 (4.6) | 71,020 (8.5) |
| ≥ 5 | 173,553 (2.7) | 64,379 (3.0) | 13,348 (4.0) | 2666 (3.9) | 17,595 (2.0) | 30,769 (3.7) |
| **COVID-19 Vaccination, N (%)**[a] | | | | | | |
| No | 1091,638 (17.0) | 333,524 (15.6) | - | - | - | - |
| Yes (1st vaccination) | 217,652 (3.4) | 68,216 (3.2) | - | - | - | - |
| Yes (2nd vaccination) | 2406,272 (37.4) | 898,838 (42.1) | - | - | - | - |
| Yes (3rd and more vaccination) | 2715,662 (42.2) | 836,173 (39.1) | - | - | - | - |
| **Drug prescription, N (%)** | | | | | | |
| **COVID-19-targeted drugs**[b] | 11 (0.0) | 119,435 (5.6) | 65,916 (19.8) | 8272 (12.1) | 30,874 (3.4) | 14,373 (1.7) |
| 2020.01.01-2020.12.05 | 2 (0.0) | 8023 (6.7) | 8023 (12.2) | - | - | - |
| 2020.12.06-2021.07.01 | 1 (0.0) | 20,316 (17.0) | 20,057 (30.4) | 246 (3.0) | 13 (0.04) | - |
| 2021.07.02-2022.01.20 | 2 (0.0) | 65,933 (55.2) | 33,907 (51.4) | 7333 (88.6) | 23,173 (75.1) | 1520 (10.6) |
| 2022.01.21-2022.02.28 | 6 (0.0) | 25,163 (21.1) | 3929 (6.0) | 693 (8.4) | 7688 (24.9) | 12,853 (89.4) |

*p*-values calculated via Chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables.
[a] First, second, and third or more dose of COVID-19 vaccine prior to SARS-CoV-2 infection between 2020.01.01 and 2022.02.28.
[b] Including regdanvimab, nirmatrelvir, paxlovid, and remdesivir.

**Table 2**
Association of SARS-CoV-2 infection with pneumonia and all-cause mortality within a month among non-infected and infected participants.

| | Non-infected | COVID-19 |
|---|---|---|
| **All-cause mortality** | | |
| Study population, N | 6434,132 | 2145,232 |
| Event, N (%) | 2908 (0.05) | 8481 (0.40) |
| aOR (95% CIs) | 1.00 (Reference) | 8.18 (7.84, 8.54)# |
| **Pneumonia** | | |
| Study population[a], N | 6431,224 | 2136,751 |
| Event, N (%) | 646 (0.01) | 35,775 (1.67) |
| aOR (95% CIs) | 1.00 (Reference) | 170 (157, 184)# |

Adjusted odds ratios and 95% confidence intervals were calculated by multivariable logistic regression analysis after adjustments for the following covariates: age, sex, income, and Charlson comorbidity index.
Acronyms: adjusted odds ratio (aOR); confidence interval (CIs).
* *p*-value < 0.05,
* * *p*-value < 0.01 and
#*p*-value < 0.001.
[a] Excluded due to events of death.

Similar studies focusing on the higher risk of pneumonia in patients who developed respiratory infections showed that other respiratory infections, such as influenza, were associated with pneumonia [24,25].

The association between variants and vaccination status with the risk of pneumonia can be interpreted as the following mechanisms. The omicron is less virulent, with a lower rate of hospitalization and mortality, than alpha-/beta-/delta-variants, although the omicron can infect more people than the delta-variant [26]. The typical infection pattern of the omicron reduces the incidence of pneumonia [27–29]. Furthermore, as the COVID-19 vaccine is known to reduce severity after infection, it prevents the risk of pneumonia after infection by preventing infection and damage to the respiratory system. When vaccinated individuals are infected, an appropriate amount of antibodies is produced early and the activation of CD4 + / 8 + T-cells provides an effective defense, which eventually prevents severe COVID-19 and pneumonia outbreaks, as a result of a trained adaptive immune response [30]. Since the released cytokines prevent the reproduction and spread of SARS-CoV-2, cytokines such as interferon-gamma (INF-γ), tumor necrosis factor-alpha (TNF-α), interleukin (IL)− 1, IL-6, and IL-12 with immune cell responses (macrophages and T-/B-cells) effectively protect the host from infection when they are secreted at appropriate levels [31]. However, an uncontrolled immune response against SARS-CoV-2 infection causes an overexpression of released cytokines, known as a cytokine storm. As the unregulated immune response is associated with mortality and severity of COVID-19, the cytokine storm in patients with COVID-19 induces damage to the respiratory system [32]. Thus, severe lung injury, pulmonary tissue fibrosis, and inflammation may progress to hospitalized pneumonia through an unregulated immune response [30,33]. In vaccinated individuals, damage to the respiratory system caused by an unregulated immune response is prevented by trained immunity [34]. With regard to the relationship between trained immunity and the severity of COVID-19, the mRNA-based vaccine shows a higher efficacy in the prevention of pneumonia than the virus-derived vaccine because the mRNA-based vaccine further alleviates the occurrence of critical events related to COVID-19: the vaccine efficacy rates and 95% CIs of Pfizer-BioNTech, Moderna, and AstraZeneca vaccines were 95.0% (90.3–97.6), 94.1% (89.3–96.8), and 74.0% (65.3–80.5), respectively [7, 15, 16].

When interpreting the results of this study, several limitations should be considered. Despite the question of whether vaccination

**Table 3**
Overall events of pneumonia according to phase (mutants) and vaccination status within a month after SARS-CoV-2 infection.

| | COVID-19 | | | | |
|---|---|---|---|---|---|
| | Overall | Vaccination status [dose] | | | |
| | | No | First | Second | ≥ Third |
| **Phase (variants)** | | | | | |
| **2020.01.01-2020.12.05** | | | | | |
| Study population, N | 27,685 | 27,685 | - | - | - |
| Events of pneumonia, N (%) | 2227 (8.04) | 2227 (8.04) | - | - | - |
| aOR (95% CIs) | 1.00 (Reference) | 1.00 (Reference) | - | - | - |
| **2020.12.06-2021.07.01 (alpha-/beta-)** | | | | | |
| Study population, N | 89,596 | 88,416 | 1113 | 67 | - |
| Events of pneumonia, N (%) | 6745 (7.53) | 6689 (7.57) | 52 (4.67) | 4 (5.97) | - |
| aOR (95% CIs) | 0.93 (0.89, 0.98)* * | 0.94 (0.89, 0.99)* | 1.00 (Reference) | - | - |
| **2021.07.02-2021.01.20 (delta-)** | | | | | |
| Study population, N | 378,223 | 130,944 | 46,171 | 187,446 | 13,662 |
| Events of pneumonia, N (%) | 22,066 (5.83) | 13,528 (10.33) | 2124 (4.60) | 6171 (3.29) | 243 (1.78) |
| aOR (95% CIs) | 0.74 (0.71, 0.78)* | 1.92 (1.83, 2.02)# | 2.22(1.66, 2.97)# | 1.00 (Reference) | 1.00 (Reference) |
| **2022.01.21-2022.02.28 (omicron)** | | | | | |
| Study population, N | 1641,247 | 86,479 | 20,932 | 711,325 | 822,511 |
| Events of pneumonia, N (%) | 4737 (0.29) | 1475 (1.71) | 150 (0.72) | 1176 (0.17) | 1936 (0.24) |
| aOR (95% CIs) | 0.04 (0.038, 0.043)# | 0.25 (0.23, 0.26)# | 0.40 (0.28, 0.55)# | 0.18 (0.17, 0.19)# | 0.24 (0.21, 0.27)# |

Adjusted odds ratios and 95% confidence intervals were calculated by multivariable logistic regression analysis after adjustments for the following covariates: age, sex, income, and Charlson comorbidity index.
Acronyms: adjusted odds ratio (aOR); confidence interval (CIs).
* $p$-value < 0.05,
* * $p$-value < 0.01 and
#$p$-value < 0.001.

**Table 4**
Association of vaccination status with pneumonia within a month after SARS-CoV-2 infection.

| | Vaccination status [dose] in patients with COVID-19 | | | | $P_{\text{for trend}}$ |
|---|---|---|---|---|---|
| | No | First | Second | ≥ Third | |
| **Overall** | | | | | |
| Study population, N | 333,524 | 68,216 | 898,838 | 836,173 | |
| Event, N (%) | 23,919 (7.17) | 2326 (3.41) | 7351 (0.82) | 2179 (0.26) | |
| aOR (95% CIs) | | | | | |
| Model 1 | 1.00 (Reference) | 0.44 (0.42, 0.46)# | 0.12 (0.122, 0.129)# | 0.02 (0.023, 0.026)# | < 0.001 |
| | - | - | 1.00 (Reference) | 0.20 (0.185, 0.204)# | |
| Model 2 | 1.00 (Reference) | 0.61 (0.58, 0.64)# | 0.39 (0.38, 0.40)# | 0.18 (0.166, 0.184)# | < 0.001 |
| | - | - | 1.00 (Reference) | 0.45 (0.43, 0.47)# | |
| **2021.07.02-2022.01.20** | | | | | |
| Study population, N | 130,944 | 46,171 | 187,446 | 13,662 | |
| Event, N (%) | 13,528 (10.33) | 2124 (4.60) | 6171 (3.29) | 243 (1.78) | |
| aOR (95% CIs) | | | | | |
| Model 1 | 1.00 (Reference) | 0.31 (0.30, 0.33)# | 0.15 (0.148, 0.159) | 0.07 (0.06, 0.08)# | < 0.001 |
| | - | - | 1.00 (Reference) | 0.43 (0.38, 0.49)# | |
| Model 2 | 1.00 (Reference) | 0.50 (0.47, 0.53)# | 0.36 (0.34, 0.38)# | 0.18 (0.16, 0.38)# | < 0.001 |
| | - | - | 1.00 (Reference) | 0.50 (0.43, 0.57)# | |
| **2022.01.21-2022.02.28** | | | | | |
| Study population, N | 86,479 | 20,932 | 711,325 | 822,511 | |
| Event, N (%) | 1475 (1.71) | 150 (0.72) | 1176 (0.17) | 1936 (0.24) | |
| aOR (95% CIs) | | | | | |
| Model 1 | 1.00 (Reference) | 0.51 (0.43, 0.60)# | 0.21 (0.19, 0.23)# | 0.10 (0.089, 0.103)# | < 0.001 |
| | - | - | 1.00 (Reference) | 0.45 (0.42, 0.49)# | |
| Model 2 | 1.00 (Reference) | 0.46 (0.38, 0.56)# | 0.30 (0.28, 0.33)# | 0.15 (0.14, 0.17)# | 0.002 |
| | - | - | 1.00 (Reference) | 0.50 (0.46, 0.55)# | |

Adjusted odds ratios and 95% confidence intervals were calculated by multivariable logistic regression analysis after adjustments for the following covariates:
Model 1: age, sex, income, and Charlson comorbidity index.
Model 2: Model 1 + COVID-19-targeted drug prescription.
Acronyms: adjusted odds ratio (aOR); confidence interval (CIs).
* $p$-value < 0.05,
* * $p$-value < 0.01 and
#$p$-value < 0.001.

can fundamentally prevent SARS-CoV-2 infection, the risk of pneumonia might reduce, due to not only protection against severe COVID-19 but also prevention from the infection itself. Thus, the episode (Inoculation-Infection-Pneumonia) based study design is necessary to consider the combination of protection and prevention. Re-infection with SARS-CoV-2 was not considered. Although re-infection could occur with SARS-CoV-2 variants, a very small number of re-infected individuals existed in this study. Since the officially reported date for SARS-CoV-2 infection was used in this study, there may be a difference of 1–3 days between the index date and the actual infection date. The level of activated antibodies against SARS-CoV-2 was not fully considered. Similarly, as only the number of vaccine doses received within 14 days prior to infection was reflected, the time series effect of vaccination was not completely considered.

**Table 5**
Stratified analysis on the association of SARS-CoV-2 infection with pneumonia according to vaccine type within a month.

| | COVID-19 | | | | | | |
|---|---|---|---|---|---|---|---|
| | No vaccination | First and second dose of vaccine | | First, second, and third dose of vaccine | | | |
| | | mRNA[2] | Virus[2] | mRNA-mRNA[3] | mRNA-Virus[3] | Virus-mRNA[3] | Virus-Virus[3] |
| **Overall** | | | | | | | |
| Study population, N | 333,524 | 787,980 | 89,024 | 470,007 | 3 | 232,062 | 8 |
| Event, N (%) | 23,919 (7.17) | 2723 (0.35) | 4451 (5.00) | 810 (0.17) | 0 | 1186 (0.51) | 0 |
| aOR (95% CIs) | 1.00 (Reference) | 0.27 (0.26, 0.28)# | 0.59 (0.56, 0.61)# | - | - | - | - |
| | - | 1.00 (Reference) | 2.20 (2.08, 2.32)# | - | - | - | - |
| | 1.00 (Reference) | - | - | 0.15 (0.14, 0.16)# | - | 0.22 (0.21, 0.24)# | - |
| | - | - | - | 1.00 (Reference) | - | 1.51 (1.38, 1.66)# | - |
| **2021.07.02-2022.01.20** | | | | | | | |
| Study population, N | 130,944 | 108,386 | 69,311 | 4460 | 0 | 5607 | 0 |
| Event, N (%) | 13,528 (10.33) | 1899 (1.75) | 4126 (5.95) | 87 (1.95) | 0 | 128 (2.28) | 0 |
| aOR (95% CIs) | 1.00 (Reference) | 0.27 (0.25, 0.28)# | 0.45 (0.43, 0.48)# | - | - | - | - |
| | - | 1.00 (Reference) | 1.71 (1.61, 1.82)# | - | - | - | - |
| | 1.00 (Reference) | - | - | 0.16 (0.12, 0.20)# | - | 0.20 (0.16, 0.24)# | - |
| | - | - | - | 1.00 (Reference) | - | 1.28 (0.95, 1.71) | - |
| **2022.01.21-2022.02.28** | | | | | | | |
| Study population, N | 86,479 | 679,555 | 19,685 | 465,547 | 3 | 226,455 | 8 |
| Event, N (%) | 1475 (1.71) | 821 (0.12) | 324 (1.65) | 723 (0.16) | 0 | 1058 (0.47) | 0 |
| aOR (95% CIs) | 1.00 (Reference) | 0.27 (0.24, 0.29)# | 0.48 (0.42, 0.55)# | - | - | - | - |
| | - | 1.00 (Reference) | 1.80 (1.56, 2.10)# | - | - | - | - |
| | 1.00 (Reference) | - | - | 0.12 (0.11, 0.14)# | - | 0.18 (0.16, 0.19)# | - |
| | - | - | - | 1.00 (Reference) | - | 1.44 (1.30, 1.59)# | - |

Adjusted odds ratios and 95% confidence intervals were calculated by multivariable logistic regression analysis after adjustments for the following covariates: age, sex, income, Charlson comorbidity index and COVID-19-targeted drug prescription.
mRNA-based vaccine includes Pfizer-BioNTech (Comirnaty; BNT162b2) and Moderna (mRNA-1273) vaccine.
Virus-derived vaccine includes AstraZeneca (adenovirus; ChAdOx1 nCov-19) and Janssen (AD26. COV2-S) vaccine.
1) mRNA[2] group with participants who were inoculated with an mRNA-based vaccine for both the first and second vaccinations; 2) virus[2] group, virus-derived vaccine for both the first and second vaccinations; 3) mRNA-mRNA[3] group, mRNA-based vaccine for the first, second, and third vaccinations; 4) mRNA-virus[3] group, mRNA-based vaccine for the first and second vaccinations and a virus-derived vaccine for the third vaccination; 5) virus-mRNA[3] group, virus-derived vaccine for the first and second vaccinations and an mRNA-based vaccine for the third vaccination; and 6) virus-virus[3] group, virus-derived vaccine for the first, second, and third vaccinations.
Acronyms: adjusted odds ratio (aOR); confidence interval (CIs).

For further study, research on the emerging omicron sub-variants, known as BA.2/4/5 and XBB, and enhanced vaccine is also needed [35]. Since other pathogens can invade and escape from the disturbed immune system after COVID-19 infection and develop secondary pneumonia as complication, future studies investigating the development and occurrence of pneumonia after infection from a long-term perspective (more than 2 years) are needed.

## Conclusion

In conclusion, the short-term incidence of pneumonia in those who were infected by SARS-CoV-2 increased compared to the uninfected and matched controls. However, the risk of COVID-19 pneumonia decreased by 61% in the second doses and by 82% in the third and more doses. Such results (the protective effect of vaccine against severe disease) may be useful for making decision in people who hesitates to be vaccinated with the delusion that vaccine would have no advantage. In addition, the results highlight the importance of managing COVID-19 patients who were not vaccinated or only received the first dose of the vaccine as the precautionary strategy for public health.

Acronyms: number of participants (N); standard deviation (SD).

## Ethical approval, informed consent, and Guideline

This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB no: 2204–126-1319), which complies with the principles of the Declaration of Helsinki. Access to the K-COV-N cohort database for research purposes was obtained through legal procedures following deliberation (KDCA-NHIS-2022–1-526). In addition, it was impossible to confirm the patient's personal information as it had been encrypted.

The methods, including flow diagram for study population and follow-up design for observation, and results in retrospective cohort study were followed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and checklist.

## Author Contributions

**Conceptualization:** Song J, Choi S, and Park SM. **Methodology:** Song J, Jeong S, and Chang JY. **Analysis:** Song J, and Jeong S. **Writing and Advice:** Song J, Oh YH, Park SJ, Cho Y, Byeon K, Choi JY, and Lee S. **Supervision:** Jeong J, Choi JY, and Park SM.

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## Declaration of Competing Interest

Sang Min Park is a member of the vaccination committee of the Korea Disease Control and Prevention Agency. Kyeonghyang Byeon is a researcher at the National Health Insurance Service. The remaining authors have nothing to disclose.

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## Code availability

Unless it deviates from the national and organizational regulations, access to the code used in this study is available from the authors upon request for noncommercial and academic purposes only.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2024.02.005.

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