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Vaccine Effectiveness Against Severe Disease and Death for Patients With COVID-19 During the Delta-Dominant and Omicron-Emerging Periods: A K-COVE Study

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ABSTRACT

National cohort data collected during the coronavirus disease 2019 (COVID-19) delta and omicron periods in Korea revealed a lower risk of severe infection in recipients of three doses of the COVID-19 vaccine (adjusted odds ratio [aOR], 0.05–0.08). The risk of death was reduced during the omicron period compared to the delta period (aOR, 0.75; 95% confidence interval, 0.67–0.84).

Keywords: Coronavirus; COVID-19; SARS-CoV-2; Vaccine; Booster

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is characterized by the serial emergence of variants, resulting in continued challenges to public health.¹ The major variants, delta and omicron, have different virulence, transmissibility, and vaccine-evasive properties.² Understanding the vaccine effectiveness of severe health outcomes during periods with different dominant SARS-CoV-2 variants is important to guide public health policies. In this study, the risk factors for severe disease and death in patients with coronavirus disease 2019 (COVID-19) in South Korea are investigated to determine the impact of the delta and omicron variants on population health outcomes.

This study is part of the Korea Covid-19 Vaccine Effectiveness (K-COVE) study, which was conducted by the Korea Disease Control and Prevention Agency (KDCA, **Supplementary Fig. 1**). National COVID-19 registry data were merged with the vaccine registry data to construct a cohort of patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infections reported between July 1, 2021 and January 31, 2022 (the last cases were followed until February 28, 2022), as described in a previous report.³ The merged database represents the country's entire population.

Individuals aged < 12 years, foreigners, those immunized with the Ad26.COV2.S vaccine, patients with imported COVID-19, individuals without documented vaccination status, and

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Disclosure

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency or the institutions with which the authors are affiliated.

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim YY, Choe YJ, Jang EJ, Park YJ. Data curation: Kim YY, Choe YJ, Park YJ. Formal analysis: Kim YY, Choe YJ, Kim RK, Yi S, Park YJ. Funding acquisition: Park YJ. Investigation: Kim YY, Choe YJ, Kim J, Jang EJ, Lee H, Park YJ. Methodology: Kim YY, Kim J, Yi S. Project administration: Park YJ. Resources: Kim J, Kim RK, Lee H, Lee S. Software: Kim J. Supervision: Yi S, Lee S, Park YJ. Validation: Kim RK, Lee H, Lee S, Park YJ. Visualization: Choe YJ. Writing - original draft: Kim YY, Choe YJ, Jang EJ, Park YJ. Writing - review & editing: Kim YY, Choe YJ, Lee S, Park YJ.

patients reinfected with COVID-19 were excluded. The monthly percentage of SARS-CoV-2 variants in the patients was determined. For import-related cases, targeted sequencing based on the risk of variant was conducted, whereas for domestic cases, random sampling was conducted to sequence the complete SARS-CoV-2 genome from the available specimens.⁴

Severe disease was defined as that in patients who required oxygen supplementation, mechanical ventilation, or intensive care within 28 days of the PCR-confirmed diagnosis. Death in all patients (with and without severe disease) was noted if it occurred within 28 days of the diagnosis based on the follow-up investigations in all reported cases. Unvaccinated individuals were defined as those without COVID-19 immunization history or those who were diagnosed with COVID-19 via PCR < 14 days since the first dose of the vaccine. The vaccine effectiveness was measured against SARS-CoV-2 severe disease or death 14 or more days after the second dose or the third dose.

Patients were stratified based on the interval between the last dose of vaccine and the PCR-confirmed diagnosis of COVID-19 (before 90 days and ≥ 90 days). The type of immunization received was classified as viral vector (ChAdOx1) or mRNA (BNT162b2 and mRNA-1273). A multivariable logistic regression model was constructed with the composite of sex, age (continuous [years] and categorical), area of residence, month of the PCR-confirmed diagnosis, and vaccination status to calculate the adjusted odds ratio (aOR) of severe disease or death.

Anonymized clustered data were shared with the investigators. R software (R Core Team) was used to prepare the data and perform the statistical analyses.

In total, 530,827 patients with PCR-confirmed SARS-CoV-2 infections were included in the analyses (**Supplementary Fig. 2**). The delta variant accounted for 59.6–100% of the COVID-19 infections between July and December 2021. In January 2022, 69.4% of the isolates were identified as the omicron variant (**Supplementary Fig. 3**). Among unvaccinated patients, 3.02% had severe disease and 1.39% died. Among patients who received three doses of vaccine 0.18–0.59% had severe disease and 0.03–0.57% died (**Table 1**).

Three doses of mRNA vaccines (aOR, 0.05; 95% confidence interval [CI], 0.04–0.07), two doses of viral vector vaccine followed by an additional dose of mRNA vaccine (aOR, 0.06; 95% CI, 0.05–0.07), and one dose of viral vector vaccine followed by two doses of mRNA vaccines (aOR, 0.08; 95% CI, 0.03–0.15) were associated with lower risks of severe disease (**Fig. 1**). The risk of death was lower in January 2022 (aOR, 0.75; 95% CI, 0.67–0.84) than in November 2021. Three doses of mRNA vaccines had the lowest risk of death (aOR, 0.02; 95% CI, 0.01–0.03). **Table 2** shows the multivariable logistic regression model with the composite of sex, age in years, area, month of diagnosis, and vaccination status, to estimate the risk factors for severe disease and death.

The emergence of the omicron variant in January 2022 may have resulted in a lower risk of severe disease and death in patients with COVID-19. Three doses of vaccine significantly protected individuals from critical health outcomes. Previous studies conducted in South Africa,² England,⁵ and Canada⁶ suggested that the clinical severity of the SARS-CoV-2 omicron variant was less than that of the delta variant, which is consistent with the results of the current study. A U.S. study reported a lower risk of severe disease in hospitalized patients with the omicron variant than in those with the delta variant (aOR, 0.61; 95% CI, 0.49–0.77).⁷ A Swedish study suggested that patients with the omicron variant had a lower risk of death,

Table 1. Severe disease and death in patients with PCR-confirmed COVID-19

Variable	Patients	Severe disease	Death
Sex			
Male	261,022	4,957 (1.90)	2,228 (0.85)
Female	269,805	3,640 (1.35)	2,141 (0.79)
Age, yr			
12–29	162,520	148 (0.09)	9 (0.01)
30–59	242,225	2,344 (0.97)	266 (0.11)
60–74	96,223	3,515 (3.65)	1,233 (1.28)
75+	29,859	2,590 (8.67)	2,861 (9.58)
Area of residence			
Non-metropolitan	155,446	2,322 (1.49)	1,346 (0.87)
Metropolitan	375,381	6,275 (1.67)	3,023 (0.81)
Month			
2021			
Jul	33,492	822 (2.45)	86 (0.26)
Aug	40,861	978 (2.39)	150 (0.37)
Sep	42,990	757 (1.76)	195 (0.45)
Oct	35,983	840 (2.33)	367 (1.02)
Nov	67,490	1,847 (2.74)	1,144 (1.70)
Dec	142,782	2,518 (1.76)	1,815 (1.27)
2022			
Jan	167,229	835 (0.50)	612 (0.37)
Vaccination status			
Unvaccinated	174,607	5,277 (3.02)	2,431 (1.39)
1 dose (viral)	10,800	396 (3.67)	126 (1.17)
1 dose (mRNA)	29,564	183 (0.62)	107 (0.36)
2 doses (viral < 90 days)	34,843	734 (2.11)	328 (0.94)
2 doses (viral ≥ 90 days)	39,395	871 (2.21)	639 (1.62)
2 doses (viral-mRNA < 90 days)	3,921	7 (0.18)	2 (0.05)
2 doses (viral-mRNA ≥ 90 days)	7,774	42 (0.54)	22 (0.28)
2 doses (mRNA < 90 days)	120,069	183 (0.15)	70 (0.06)
2 doses (mRNA ≥ 90 days)	67,639	752 (1.11)	530 (0.78)
3 doses (viral-viral-mRNA)	14,354	85 (0.59)	82 (0.57)
3 doses (viral-mRNA-mRNA)	3,955	7 (0.18)	1 (0.03)
3 doses (mRNA-mRNA-mRNA)	23,906	60 (0.25)	31 (0.13)

The ChAdOx1 vaccine is considered a viral vector vaccine. The BNT162b2 and mRNA-1273 S vaccines are considered mRNA vaccines. Values are presented as number of patients (%).

PCR = polymerase chain reaction, COVID-19 = coronavirus disease 2019.

though the risk remained high (> 5%) for older people with comorbidities.⁸ The results of the current study suggest that the vaccines remain the most important modifiable intervention to protect public health and are consistent with the results of a recent observational cohort study.⁹ The findings of the current study highlight the importance of vaccination against COVID-19, especially in people at risk for developing serious illness. The vaccine effectiveness against severe disease decreased as the time from immunization increased. However, any number of vaccine doses and both vaccine types were effective for the protection against death, highlighting the benefits of COVID-19 vaccines.

This study is limited by the retrospective study design. The nature of SARS-CoV-2 outbreaks and public health measures evolved during the study period, especially during January 2022 when the COVID-19 outbreak peaked. The healthcare capacity to care for patients may have differed between July 2021 and January 2022. In addition, severe disease and death data are subject to reporting delays. While a multivariable logistic regression model stratified by vaccinated date, test date, and observation period was used, if the probability to get tested differed between the delta and omicron period, a residual bias may remain. Moreover, other factors, including underlying disease, clinical details, socioeconomic status, and laboratory

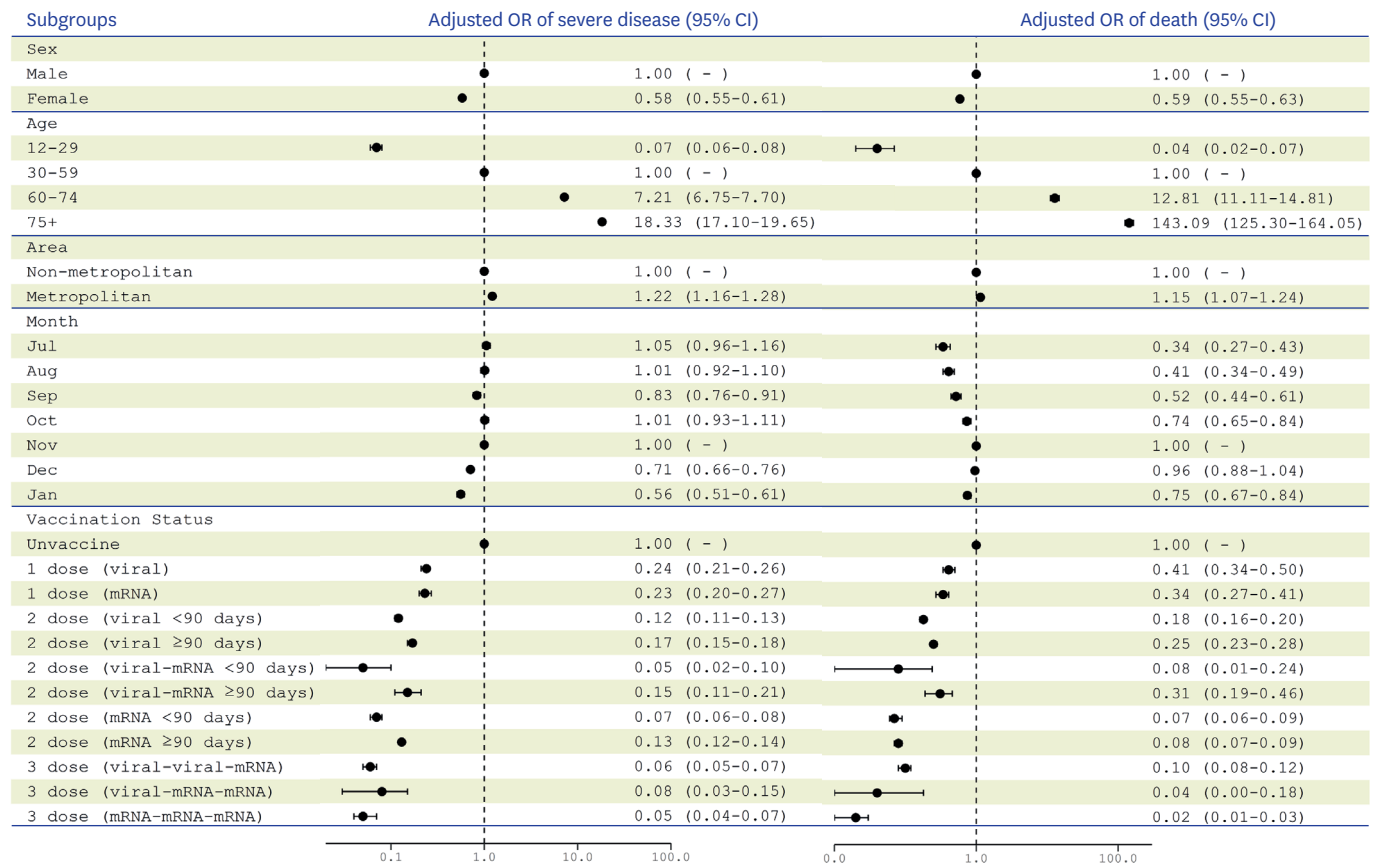


Fig. 1. Multivariable logistic regression model with the composite of sex, age categories, area of residence, month of diagnosis, and vaccination status to estimate risk factors for severe disease and death in patients with PCR-confirmed COVID-19 in South Korea, July 2021–January 2022. PCR = polymerase chain reaction, COVID-19 = coronavirus disease 2019, CI = confidence interval.

Table 2. Multivariable logistic regression model with the composite of sex, age in years, area, month of the PCR-confirmation, and vaccination status, to estimate risk factors for severe disease and death in PCR-confirmed COVID-19 case-patients within specified subgroups, South Korea, July 2021–January 2022

Variable	Severe disease		Death	
	OR	95% CI	OR	95% CI
Female	0.50	0.46–0.53	0.53	0.51–0.56
Age	1.13	1.13–1.14	1.08	1.08–1.08
Metropolitan	1.17	1.09–1.26	1.26	1.19–1.32
Jul	0.30	0.23–0.37	0.93	0.84–1.02
Aug	0.38	0.31–0.46	0.93	0.85–1.02
Sep	0.55	0.46–0.65	0.88	0.80–0.96
Oct	0.75	0.66–0.85	1.02	0.93–1.12
Dec	0.97	0.89–1.05	0.75	0.70–0.80
Jan	0.70	0.62–0.78	0.55	0.50–0.60
1 dose (viral)	0.39	0.32–0.47	0.32	0.29–0.36
1 dose (mRNA)	0.33	0.26–0.40	0.20	0.17–0.23
2 doses (viral < 90 days)	0.15	0.13–0.17	0.15	0.14–0.16
2 doses (viral ≥ 90 days)	0.20	0.19–0.22	0.18	0.16–0.19
2 doses (viral-mRNA < 90 days)	0.08	0.06–0.10	0.06	0.05–0.07
2 doses (viral-mRNA ≥ 90 days)	0.11	0.10–0.13	0.13	0.12–0.14
2 doses (mRNA < 90 days)	0.07	0.01–0.23	0.06	0.03–0.12
2 doses (mRNA ≥ 90 days)	0.29	0.18–0.44	0.17	0.12–0.23
3 doses (viral-viral-mRNA)	0.09	0.07–0.11	0.07	0.05–0.08
3 doses (viral-mRNA-mRNA)	0.03	0.02–0.04	0.05	0.04–0.06
3 doses (mRNA-mRNA-mRNA)	0.04	0.00–0.18	0.09	0.04–0.17

PCR = polymerase chain reaction, COVID-19 = coronavirus disease 2019, OR = odds ratio, CI = confidence interval.

findings were not included in the analyses, thus posing residual confounding effect to the result. Despite these limitations, this study includes a large population of patients with PCR-confirmed COVID-19 infections in a country that has universal health coverage and relatively equitable access to care. This study includes vaccination health outcome data collected on a national scale, allowing for precise characterization of time periods dominated by specific variants of SARS-CoV-2.

The use of a national cohort allows for a robust analysis to describe the risk factors associated with severe disease and death from COVID-19 in South Korea, and the importance of vaccinations was revealed in this study. The COVID-19 vaccine has been available to children aged 5–11 years in South Korea since March 31, 2022. Based on the disease burden of COVID-19 in this population, the evaluation of the vaccine effectiveness should be expanded to include children in future studies. Understanding the public health benefits of vaccination provides vital information required to emphasize patient awareness among those at risk for severe clinical outcomes.

Ethics statement

This study was conducted as a legally mandated public health investigation under the authority of the Korean Infectious Diseases Control and Prevention Act (No. 12,444 and No. 13,392) and was reviewed by the Korea Disease Control and Prevention Agency Institutional Board Review (IRB No. 2021-12-03-PE-A).

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SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Description of immunization registry linked with epidemiological database to form K-COVE data. K-COVE = Korea Covid-19 Vaccine Effectiveness, COVID-19 = coronavirus disease 2019, NIP = National Immunization Programme, SSN = Social Security Number, NNIDSS = National Notified Infectious Disease Surveillance System.

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Supplementary Fig. 2

Patient selection criteria.

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Supplementary Fig. 3

Percentage of SARS-CoV-2 variants of concerns detected in South Korea, April 2021–January 2022.

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