



Comparison of the Causes of Death in Patients With Delta variant versus Omicron variant infections

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Revised Abstract

- ◆ **Background:** Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) variant strain B.1.1.529 (omicron) has been less virulent than SARS-CoV-2 B.1.617.2 variant (delta), but there are limited data on the comparison of the cause of death between delta variant and omicron variant infections. We thus compared the causes of death in COVID-19 patients with the delta variant and omicron variant.
- ◆ **Methods:** We retrospectively reviewed the medical records of adult patients with COVID-19 who were admitted at Asan Medical Center, Seoul, South Korea, between July 2021 and March 2022. We divided into delta-variant dominant period (from July 2021 to December 2021) and omicron-dominant period (from February 2022 to March 2022) with the exclusion of January 2022 because this period was overlapping of delta and omicron variant. The causes of death were classified into COVID-19-associated pneumonia, other causes, and indeterminate cause.
- ◆ **Results:** A total of 654 patients with COVID-19 were admitted and 42 (6.4%) died during the omicron dominant period (between February and March 2022), while a total of 366 patients with COVID-19 were hospitalized and 42 (11.5%) died during the delta dominant period (between July and December 2021). The primary cause of death was COVID-19-associated pneumonia in 64% (27/42) during the omicron era whereas that was COVID-19-associated pneumonia in 88% (37/42) during the delta era (p value=0.01).
- ◆ **Conclusion:** We found that about two thirds of patients with omicron variant infection died due to COVID-19, while the majority of patients with delta variant infection died due to COVID-19.

Introduction

- ◆ SARS-CoV-2 variant strain B.1.1.529 (Omicron) was first reported to the World Health Organization in South Africa on November 24, 2021.¹ The previous study confirmed that the severity of clinical infection is lower in association with the Omicron variant than the Delta variant.² The recent study reported that substantial excess mortality occurred during the Omicron-dominant era, although Omicron variant may cause milder COVID-19.³ Collateral damage due to the limitation of healthcare accessibility (especially intensive care service) or increase of COVID-19-associated deaths may explain this important public health questions. However, these data were based on the mortality statistics record, so the exact causes of deaths were not known. Therefore, uncertainty largely remains regarding the relative contribution of Omicron-variant infection to deaths. Nevertheless, there are limited comparative data available that account for the relative contributions of less-virulent variants, such as Omicron, compared with those of highly virulent strains, such as the Delta variant. Therefore, we investigated the causes of death among COVID-19 patients with Delta- and Omicron-variant infections.

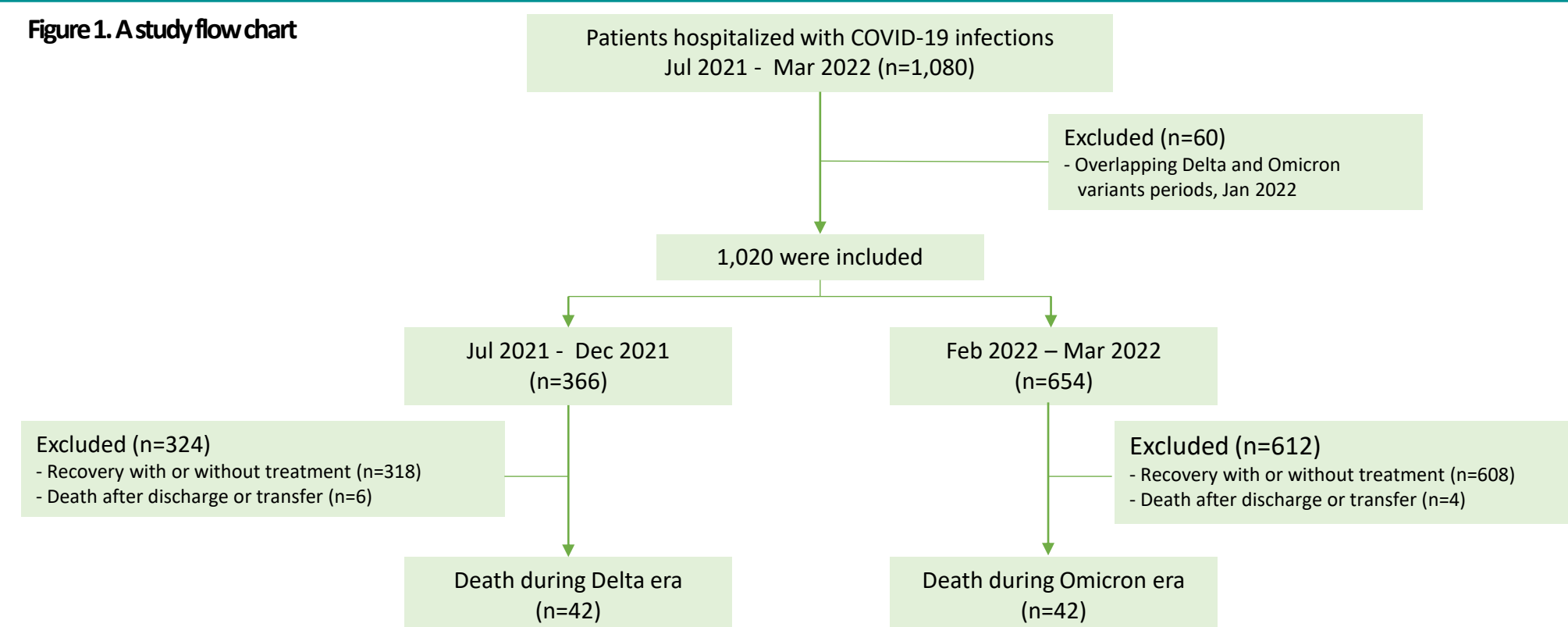
Methods

- ◆ We retrospectively reviewed the medical records of adult patients with COVID-19 who were admitted to Asan Medical Center, Seoul, South Korea, between July 2021 and March 2022
- ◆ We divided the study period in to Delta-dominant (July through December 2021) and Omicron-dominant (February through March 2022) periods. January 2022 was excluded because there was a relative balance in the frequency of Delta and Omicron infections during that month
- ◆ The causes of death were classified into 3 categories such as ;
 1) COVID-19 pneumonia was defined as death following imaging-confirmed (chest x-ray and computed tomography) pneumonia without any other plausible cause of death
 2) All deaths with other identified causes – in the presence or absence of COVID-19 pneumonia – were categorized as other

Results

- ◆ A total of 1,020 COVID-19 patients were hospitalized at our center between July 2021 and March 2022, among whom 366 were admitted during the Delta-dominant period (February through March 2022), and 654 were admitted during the Omicron-dominant period (July through December 2021). Of the 654 COVID-19 patients admitted during the Omicron-dominant period, 42 (6.4%) died during the Omicron-dominant period. There were also 42 deaths (11.5%) among the 366 patients admitted with COVID-19 during the Delta-dominant period. The primary cause of death was COVID-19-associated pneumonia in both the Omicron (64%, 27/42) and Delta (88%, 37/42) eras ($P = 0.01$).

Results



Characteristics	Delta (n=42)	Omicron (n=42)	Total (n=84)
Men	27 (64.3)	30 (71.4)	57 (67.9)
Age group, year			
≤49	2 (4.8)	4 (9.5)	6 (7.1)
50-59	1 (2.4)	5 (11.9)	6 (7.1)
60-69	11 (26.2)	8 (19.0)	19 (22.6)
70-79	13 (31.0)	13 (31.0)	26 (31.0)
80-89	12 (28.6)	10 (23.8)	22 (26.2)
≥90	3 (7.1)	2 (4.8)	5 (6.0)
Comorbidities			
Diabetes mellitus	9 (21.4)	13 (31.0)	22 (26.2)
Hypertension	22 (52.4)	18 (42.9)	40 (47.6)
Cardiovascular disease	10 (23.8)	13 (31.0)	23 (27.4)
Chronic respiratory disease	5 (11.9)	8 (19.0)	13 (15.5)
Chronic liver disease	3 (7.1)	7 (16.7)	10 (11.9)
Chronic kidney disease	9 (21.4)	6 (14.3)	15 (17.9)
Solid organ cancer	13 (31.0)	18 (42.9)	31 (36.9)
Hematologic malignancy	0	4 (9.5)	4 (4.8)
Rheumatic disease	4 (9.5)	0	4 (4.8)
Obesity (BMI >25)	12 (28.6)	9 (21.4)	21 (25.0)
Smoking	0	2 (4.8)	2 (2.4)
Symptoms			
Fever	11 (26.2)	7 (16.7)	18 (21.4)
Chills	3 (7.1)	1 (2.4)	4 (4.8)
Cough	15 (35.7)	5 (11.9)	20 (23.8)
Sputum	8 (19.0)	7 (16.7)	15 (17.9)
Sore throat	3 (7.1)	2 (4.8)	5 (6.0)
Dyspnea	22 (52.4)	28 (66.7)	50 (59.5)
Hemoptysis	0	1 (2.4)	1 (1.2)
Chest pain	0	4 (9.5)	4 (4.8)
Diarrhea	0	0	0
Headache	3 (7.1)	1 (2.4)	4 (4.8)
Myalgia	3 (7.1)	0	3 (3.6)
Hypogeusia	1 (2.4)	0	1 (1.2)
Pneumonia	40 (95.2)	34 (81.0)	74 (88.1)
Initial laboratory findings			
White blood cell, count/ μ l	8,800 (5,700 - 12,625)	8,400 (4,550 - 14,350)	8,500 (5,100 - 13,000)
Neutrophil, %	84.95 (77.98 - 89.73)	84.55 (75.70 - 88.30)	84.65 (77.98 - 89.00)
Lymphocyte, %	10.55 (4.75 - 15.03)	9.90 (6.60 - 14.95)	10.25 (6.18 - 14.93)
Hemoglobin, g/dL	12.30 (11.12 - 13.10)	10.20 (8.40 - 12.50)	11.50 (9.60 - 13.00)
Platelet, $\times 10^3/\mu$ l	162 (118 - 249)	135 (70 - 212)	150 (95 - 220)
C-reactive protein, mg/dL	9.71 (5.76 - 15.83)	10.56 (5.14 - 17.39)	9.94 (5.49 - 16.86)

* Data are presented as the median (interquartile range) or number (percentage) of patients.

Characteristics	Delta (n=42)	Omicron (n=42)	Total (n=84)
Deaths	42/366 (11.5)	42/654 (6.4)	84/1,020 (8.2)
Due to COVID-19 pneumonia	37/42 (88.1)	27/42 (64.3)	64/84 (76.2)
Due to other causes	5/42 (11.9)	14/42 (33.3)	19/84 (22.6)
Underlying disease	1	4	5
Cardiovascular disease	1	5	6
Bleeding	1	2	3
Sepsis	2	3	5
Due to indeterminate cause	0	1/42 (2.4)	1/84 (1.2)

* Data are presented as number (%) unless otherwise indicated.

Table 1. Baseline clinical characteristics and causes of death among patients hospitalized with COVID-19 during Delta-dominant and Omicron-dominant periods

Discussion

- ◆ A matched case-control study conducted in Canada demonstrated a 60% reduction in the composite outcome hospitalization or death associated with the Omicron variant compared with the Delta variant, along with an 80% reduction in intensive care hospitalization or death associated with Omicron compared with Delta.⁴ Investigators in France, studying emergency department visits, found the Omicron variant to be associated with fewer intensive care unit admissions and in-hospital deaths than the Delta variant.⁵ However, overall, there are limited data on specific causes of death among patients with COVID-19. In particular, the rate of “incidental” Omicron cases has sharply increased during recent pandemic waves, so public health officers naturally wonder about the relative contributions of this less-virulent Omicron variant to mortality figures. One study revealed that COVID-19 was documented as the direct cause of death in more than 90% of hospitalized patients with COVID-19 who eventually died.⁶ On the other hand, the government’s COVID-19 death figures are based on total deaths from any cause in patients recently diagnosed with COVID-19,⁷ so the overestimations are inevitable.
- ◆ Extensive medical records reviews can answer this important question. Our data showed that about two-thirds of the deaths among hospitalized patients with COVID-19 during the Omicron era were attributed directly to COVID-19, as were the majority of deaths among patients with COVID-19 during the Delta era. Therefore, the excess mortality during the Omicron-dominant period in highly vaccinated area like South Korea could be explained by about one-third indirect contribution of COVID-19 in SARS-CoV-2-infected dead patients as well as by about two-third direct contribution of COVID-19 in SARS-CoV-2-infected dead patients, in addition to the collateral damage of COVID-19 in SARS-CoV-2-uninfected dead patients. Further studies are urgently needed on the collateral damage of COVID-19 to healthcare system in SARS-CoV-2-uninfected patients (i.e. inaccessibility of intensive care service or emergency service due to overwhelming COVID-19 patients).
- ◆ The small number of deaths and the analysis solely of patients admitted to a tertiary care hospital may limit the generalizability of our findings. Despite these limitations, our data suggest that the Omicron variant has a relatively lower contribution to deaths than the Delta variant. However, during Omicron-dominant waves, large numbers of hospitalized patients still overwhelm health systems, and absolute mortality figures remain high despite relatively lower mortality rates compared with pandemic waves in which more virulent variants predominate. Therefore, our findings provide valuable and timely insight to facilitate preparedness for the emergence of less-virulent and more-transmissible variants.

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