Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Comparison of the causes of death associated with delta and Omicron SARS-CoV-2 variants infection

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Dear Editor.

The recent study reported that substantial excess mortality occurred during the Omicron-dominant era, although Omicron variant may cause milder COVID-19 [1]. However, these data were based on the mortality statistics record, so the exact causes of deaths were not known and uncertainty largely remains regarding the relative contribution of Omicron-variant infection to deaths. Therefore, we investigated the causes of death among COVID-19 patients with Delta- and Omicron-variant infections. 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. The causes of death were classified into COVID-19 pneumonia, other causes, and indeterminate cause. The study was approved by the institutional review board of Asan Medical Center (IRB No 2022-1431), and informed consent was waived because of the retrospective nature of this study.

A total of 1020 COVID-19 patients were hospitalized at our center between July 2021 and March 2022, among whom 366 were admitted during the Delta-dominant period (Jul 2021- Dec 2021), and 654 were admitted during the Omicron-dominant period (Feb 2022-Mar 2022). The demographic and clinical characteristics, along with the causes of death of the COVID-19 patients, are shown in Table 1. During the Delta-dominant period, 42 (11%) of 366 patient with COVID-19 were admitted died. During the Omicron-dominant period, 42 (6%) of 654 patients with COVID-19 were admitted died (Supplemental Figure 1). 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). Univariable analysis revealed that old age, COVID-19 severity, variant types, and solid cancer were associated with COVID-19-pneumonia-associated deaths. Multivariable analysis exhibited that old age and underlying solid cancer were independently associated with COVID-19-pneumonia-associated deaths (Supplemental Table 1). Unadjusted odds ratio (OR) for COVID-19-pneumonia-associated deaths in Delta group compared with those in Omicron group was 4.11 (95% CI 1.33–12.69, p value=0.01). However, after adjustment of potential confounders, there was a trend toward being higher COVID-19-pneumonia-associated deaths in Delta variant infection than in Omicron variant infection (OR=3.84, 95% CI 0.95–18.65, p value=0.07) (Supplemental Table 1).

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 [2]. 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 [3], so the overestimations are inevitable. 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. Overwhelming number of patients with Omicron infections can cause collateral damage of healthcare system. For example, inaccessibility of intensive care service or emergency service due to overwhelming COVID-19 patients may result in excess deaths during the large community outbreaks. Further studies are urgently

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Table 1
Baseline clinical characteristics and causes of deaths between patients during delta variant dominant period and omicron variant dominant period.

Characteristics	Total (n = 84)	Delta (n = 42)	Omicron (n = 42)	*P* value
Age, years, median (IQR)	72.5 (65.0–81.0)	74.0 (66.8–82.0)	71.5 (60.8–81.0)	0.282
Male gender	57 (67.9)	27 (64.3)	30 (71.4)	0.483
Comorbidities				
Diabetes mellitus	22 (26.2)	9 (21.4)	13 (31.0)	0.321
Hypertension	40 (47.6)	22 (52.4)	18 (42.9)	0.382
Cardiovascular disease	23 (27.4)	10 (23.8)	13 (31.0)	0.463
Chronic lung disease	13 (15.5)	5 (11.9)	8 (19.0)	0.365
Liver disease	10 (11.9)	3 (7.1)	7 (16.7)	0.178
Renal disease	15 (17.9)	9 (21.4)	6 (14.3)	0.393
Solid cancer	31 (36.9)	13 (31.0)	18 (42.9)	0.258
Hematologic malignancy	4 (4.8)	0	4 (9.5)	0.116
Rheumatic disease	4 (4.8)	4 (9.5)	0	0.116
Obesity (BMI > 25)	21 (25.0)	12 (28.6)	9 (21.4)	0.450
Smoking	2 (2.4)	0	2 (4.8)	0.494
Symptoms at diagnosis				
Fever	18 (21.4)	11 (26.2)	7 (16.7)	0.287
Chill	4 (4.8)	3 (7.1)	1 (2.4)	0.616
Cough	20 (23.8)	15 (35.7)	5 (11.9)	0.010
Sputum	15 (17.9)	8 (19.0)	7 (16.7)	0.776
Sore throat	5 (6.0)	3 (7.1)	2 (4.8)	> 0.999
Dyspnea	50 (59.5)	22 (52.4)	28 (66.7)	0.182
Rhinorrhea	0	0	0	NA
Hemoptysis	1 (1.2)	0	1 (2.4)	> 0.999
Chest pain	4 (4.8)	0	4 (9.5)	0.116
Diarrhea	0	0	0	NA
Headache	4 (4.8)	3 (7.1)	1 (2.4)	0.616
Myalgia	3 (3.6)	3 (7.1)	0	0.241
Hypogeusia	1 (1.2)	1 (2.4)	0	> 0.999
Pneumonia at admission	74 (88.1)	40 (95.2)	34 (81.0)	0.043
Severity				0.175
Mild to moderate	19	7	12	
Severe	34	21	13	
Critical	31	14	17	
Deaths	84/1020 (8.2)	42/366 (11.5)	42/654 (6.4)	
COVID-19 pneumonia	64/84 (76.2)	37/42 (88.1)	27/42 (64.3)	0.010
Other causes	19/84 (22.6)	5/42 (11.9)	14/42 (33.3)	0.019
Underlying disease	5	1	4	
Cardiovascular disease	6	1	5	
Bleeding	3	1	2	
Sepsis	5	2	3	
Indeterminate cause	1/84 (1.2)	0	1/42 (2.4)	> 0.999

Data are presented as number (%) unless otherwise indicated. Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019, IQR, interquartile range

needed on the collateral damage of COVID-19 to healthcare system in SARS-CoV-2-uninfected patients. Although there are several retrospective studies [4–10] on the severity and risk factor of COVID-19 infection according to variant types, there are few prospective studies on this area. And data directly comparing the causes of death between Omicron variant and Delta variant infection are also limited. The small number of deaths and the analysis solely of patients admitted to a tertiary care hospital may limit the generalizability of our findings. Assuming that in-hospital mortality of COVID-19 patients was 15.1% during Delta period and 4.9% during later Omicron period [10], 135 participants were needed for each group for 80% power of the study and 5% margin of error. Therefore, our findings of Delta variant infection having marginal statistical significance on COVID-19-pneumonia-associated mortality after adjustment of potential confounders might be due to low study power. Taken together, our data clearly demonstrated that 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. Although we could not access the collateral damage of COVID-19 in SARS-CoV-2-uninfected dead patients, our data provide important insight for us to figure out the mortality of SARS-CoV-2-infected patients with the relative contribution to excess mortality during the Omicron outbreaks.

Despite some 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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Conflicts of Interest Disclosure

All authors have no potential conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.11.030.

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