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REVIEW ARTICLE

The disease severity of COVID-19 caused by Omicron variants: A brief review

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ABSTRACT

The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in November 2021 and spread worldwide. This review summarizes the reported mortality and morbidity rates of coronavirus disease (COVID-19) caused by Omicron variants. In 21 previous studies, the mortality of patients infected with Omicron variants ranged from 0.01 to 13.1%, whereas that of those infected with previous variants was from 0.08% to 29.1%. The proportions of intensive care unit admissions and mechanical ventilation were lower for Omicron variants than for the previous variants. Future studies should clarify the mechanisms of transmissibility and severity of COVID-19 caused by the Omicron variants.

KEY WORDS

Omicron variant, COVID-19

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INTRODUCTION

The Omicron variant is a new variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) that causes coronavirus disease (COVID-19). It was first identified in South Africa in November 2021 and has since spread to other parts of the world [1]. In early to mid-2022, the Omicron variants BA.1, BA.1.1, and BA.2 appeared. The Omicron sublineages BA.4, BA.5, and, more recently, BA.2.75, BA.4.6, BF.7, BQ.1, and XBB are still circulating [2]. The Omicron variant is characterized by many mutations in the spike protein of the virus, which are responsible for human cell infection. Some of these mutations may be associated with increased transmissibility and resistance to SARS-CoV-2 treatment and prevention [3–5]. Although antibody evasion by the Omicron variant has been well documented, the severity of COVID-19 caused by Omicron variants in comparison with previous variants remains uncertain. Here, we present a narrative review of the severity of COVID-19 caused by Omicron variants with a focus on mortality and other critical conditions.

LITERATURE SEARCH

We conducted literature searches on PubMed up to January 23, 2023, using keywords (**Supplemental Table 1**). We screened the titles and abstracts for relevance. Studies were required to either be associated with COVID-19 severity caused by the Omicron variants or to compare the outcomes of Omicron to previous variants. There were limited reports on Omicron variants from Asia and the high vaccination rate in Japan. Japanese studies were included in the analysis despite the lack of comparative evaluation of outcomes between Omicron and prior variants. We excluded studies that focused on excess mortality stratified by different circulating variants because excess mortality is affected not only by the severity of the disease but also by the transmissibility of the variants. For the selected studies, we recorded the authors, year, country, viral variants, outcome measures, study population, number of participants, number of severe COVID-19 cases, and effect measures for severe COVID-19.

RESULTS

We identified 21 relevant papers and presented their recorded data in **Table 1** [6–26]. Eight studies from the United States [6–13], five from South Africa [18–22], three from the United Kingdom [15–17], and three from other countries [14, 23–26] compared the severity of COVID-19 between the Omicron variants and previous variants. Two studies from Japan reported the proportion of severe COVID-19 cases without comparing different variants. No Japanese study has compared the severity of COVID-19 between the Omicron variants and previous variants. The mortality of patients infected with Omicron variants in studies involving a comparison of different variants ranged from 0.01 to 13.1%; from 0.01% to 4.1% in the non-hospitalized population; and from 2.7% to 13.1% in the hospitalized population, whereas the mortality of patients infected with previous variants ranged from 0.08% to 29.1% overall; from 0.08% to 9.5% in the non-hospitalized population; and from 8.3% to 29.1% in the hospitalized population. One study [10] was omitted because of the small number of patients and lack of in-hospital deaths observed for the previous variants. Effect measures (95% confidence interval) of mortality comparing Omicron sublineage B1.1.529 with Delta variants (reference) were adjusted hazard ratios, 0.33 (0.19–0.56) [7], 0.21 (0.10–0.44) [11], 0.31 (0.26–0.37) [15], and 0.34 (0.25–0.46) [16]; adjusted relative risk, 0.69 (0.68–0.70) [8]; adjusted odds ratio, 0.34 (0.16–0.79); and adjusted risk difference (%), −4.2 (−6.5, −2.0) [24]. They consistently showed that patients infected with Omicron variants had statistically significantly lower risk of death and in-hospital death than those infected with Delta variants. Similarly, the proportions of intensive care unit admissions and mechanical ventilation were 0.03–27.4% and 0.01–14.9% for Omicron variants, and 0.1–39.6% and 0.08–22.0% for previous variants. All 19 reports that compared different variants showed a lower severity of the Omicron variants than previous variants (mainly Delta variants). Regarding different sublineages of the Omicron variant, a study from South Africa suggested that the risk of severe disease with BA.4 and BA.5 is comparable to that of earlier Omicron BA.1 [18].

DISCUSSION

This review presented the current evidence and understanding of COVID-19 severity caused by Omicron variants. The evidence suggests that COVID-19 caused by Omicron variants is less severe than that caused by other variants, even when vaccination status is considered.

The mechanism underlying the less severity of COVID-19 caused by Omicron variants has not yet been elucidated. Several studies have noted that Omicron

Table 1 **Summary of studies that compared the severity of Omicron variants with previous variants**

Author	Year	Country	Population	Outcome	Omicron			Previous variants*		Effect measures (95%CI)†/p-value
					Sublineage	No of participants	No of cases with outcome	No of participants	No of cases with outcome	
Iuliano [6]	2022	United States of America	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation In-hospital death	B.1.1.529	128,000	1,658 (13.0%) 358 (3.5%) 533 (7.1%)	10,440	1,824(17.5%) 503(6.6%) 803(12.3%)	RR, 0.74 RR, 0.54 RR, 0.58
Ulloa [7]	2022	United States of America	Individuals diagnosed with COVID-19	Hospitalization or death ICU admission or death Death	BA.1	9,087 (Matched)	53 (0.6%) 8 (0.1%) 3 (0.03%)	9,087	129 (1.4%) 42 (0.5%) 26 (0.3%)	aHR, 0.41 (0.30–0.55) aHR, 0.19 (0.09–0.39) aHR, 0.33 (0.19–0.56)
Adjei [8]	2022	United States of America	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation In-hospital death	Early, B.1.1.529 Later, BA.2/ BA.2.12.1	20,655 104,395	**Early Omicron** 22,320 (21.4%); 14,049 (13.5%); 13,701 (13.1%) **Later Omicron** 2,747 (13.3%); 1,260 (6.1%); 1,004 (4.9%)	163,094	40,818 (25.0%) 28,367 (17.4%) 24,658 (15.1%)	**aRR (95%CI) for in-hospital death** **Early Omicron** 0.69 (0.68–0.70) **Later Omicron** 0.24 (0.22–0.25)
Esper [9]	2022	United States of America	Individuals diagnosed with COVID-19	Hospitalization ICU admission Mechanical ventilation Death	B.1.1.529/BA	696	41 (5.9%) 7 (1.0%) 5 (0.7%) 3 (0.4%)	808	103(12.7%) 29(3.6%) 11(1.4%) 8(1.0%)	—
Hamid [10]	2022	United States of America	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation In-hospital death	BA.2/BA.5	473	87 (18.0%) 15 (3.2%) 3 (0.6%)	321	72(22.5%) 17 (5.4%) 0(–)	p = 0.08 p < 0.01 NA
Lewnard [11]	2022	United States of America	Individuals diagnosed with COVID-19	Any hospitalization ICU admission Mechanical ventilation Death	B.1.1.529	222,688	1,642 (0.7%) 57 (0.03%) 26 (0.01%) 19 (0.01%)	23,305	369 (1.6%) 29 (0.1%) 19 (0.08%) 19 (0.08%)	aHR, 0.61 (0.54–0.68) aHR, 0.48 (0.29–0.81) aHR, 0.32 (0.17–0.62) aHR, 0.21 (0.10–0.44)
Lauring [12]	2022	United States of America	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation Death or mechanical ventilation In-hospital death	B.1.1.529/BA	565	155 (27.4%) 84 (14.9%) 96 (17.0%) 40 (7.1%)	3788	1,500 (39.6%) 833 (22.0%) 958 (25.3%) 461 (12.2%)	—
Modes [13]	2022	United States of America	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation In-hospital death	B.1.1.529	737	124 (16.8%) 68 (9.2%) 22 (4.0%)	339	79 (23.3%) 46 (13.6%) 28 (8.3%)	—
Pinato [14]	2022	United Kingdom, Italy, Spain, France, Belgium, Germany	Individuals with cancer, who were diagnosed with COVID-19	Complications from Covid-19 Hospitalization Death in 14 days Death in 28 days	B.1.1.529		56 (15.3%) 86 (24.4%) 31 (9.0%) 45 (13.1%)	2,033 (Pre-vaccination phase) 535 (Alpha-Delta transition)	801 (39.4%); 1,142 (56.6%); 466 (23.1%); 584 (29.0%) 361 (33.6%); 437 (41.4%); 148 (13.9%); 250 (23.5%)	**aOR, Omicron vs. Pre-vaccination phase (Reference)** 0.26 (0.17–0.46); 0.17 (0.09–0.32); 0.32 (0.19–0.61); 0.34 (0.16–0.79) **aOR, Alpha-Delta transition vs. Pre-vaccination phase (Reference)** 0.76 (0.54–1.07); 0.56 (0.39–0.80); 0.49 (0.29–0.82); 0.70 (0.44–1.11)

Abbreviations: ICU, intensive care unit; CI, confidence interval; RR, relative risk; aRR, adjusted relative risk; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRD, adjusted risk difference

* Delta variants unless otherwise indicated.

† Delta variants were used as a reference category, otherwise indicated

Table 1-2 Summary of studies that compared the severity of Omicron variants with previous variants

Author	Year	Country	Population	Outcome	Omicron			Previous variants*		Effect measures (95%CI)†/p-value
					Sublineage	No of participants	No of cases with outcome	No of participants	No of cases with outcome	
Nyberg [15]	2022	United Kingdom	Individuals diagnosed with COVID-19	Hospitalization in 14 days Death in 28 days	B.1.1.529	1,067,859	9,624 (0.90%) 1,225 (0.11%)	448,843	7,358 (1.64%) 1,205 (0.27%)	aHR, 0.41 (0.39–0.43) aHR, 0.31 (0.26–0.37)
Ward [16]	2022	United Kingdom	Individuals diagnosed with COVID-19	Death	BA.1	814,003	160 (0.02%)	221,146	204 (0.09%)	aHR, 0.34 (0.25–0.46)
Menni [17]	2022	United Kingdom	Individuals diagnosed with COVID-19	Hospitalization	Unspecified (data were collected between June 2021and Jan 2022)	4,990 (Matched)	94 (1.9%)	4,990	130 (2.6%)	aOR, 0.75 (0.57–0.98)
Davies [18]	2022	South Africa	Individuals diagnosed with COVID-19	Critical condition (ICU admission/ mechanical ventilation/steroid use) Death in 21 days	BA.4/BA.5 Omicron BA.1	3,793 27,614	61 (1.6%); 70 (1.9%) 481 (1.7%); 699 (2.5%)	40,204 (Ancestral) 19,083 (Beta) 68,750 (Delta)	**Critical condition; Death** NA; 2,147 (5.3%) 1,916 (3.5%); 3,717 (6.9%) 2,066 (3.0%); 4368 (6.4%)	**aHR (95%CI) for Critical condition; aHR (95%CI) for death** NA; 1.30 (1.17–1.44)—Ancestral 1.28 (1.20–1.38); 1.47 (1.34–1.62)—Beta 1.44 (1.35–1.54); 1.75 (1.59–1.92)—Delta 1.12 (0.93–1.34); 1.16 (0.90–1.50)—Omicron BA.4/BA.5 Reference—Omicron BA.1
Wolter [19]	2022	South Africa	Individuals diagnosed with or hospitalized for COVID-19	Hospitalization (Diagnosed) Severe disease (Hospitalized)	B.1.1.529	10,547 204	256 (2.4%) 42 (21%)	948 113	121 (12.8%) 45 (40%)	aOR, 0.2 (0.1–0.3) aOR, 0.7 (0.3–1.4)
Jassat [20]	2022	South Africa	Individuals diagnosed with or hospitalized for COVID-19	Hospitalization (Diagnosed) ICU admission (Hospitalized) In-hospital death (Hospitalized)	B.1.1.529	629,617 45,927 45,927	52,038 (8.3%) 2,872 (6.3%) 4,907 (10.7%)	1,306,260 128,558 128,558	131,083 (10.0%) 18,812 (14.6%) 33,947 (26.4%)	p < 0.0001 p < 0.0001 p < 0.0001
Abdullah [21]	2022	South Africa	Individuals hospitalized for COVID-19	ICU admission In-hospital death	Unspecified (data were collected between Nov 2021and Dec 2021)	466	5 (1%) 21 (4.5%)	3,962	172 (4.3%) 847 (21.3%)	p = 0.0007 p < 0.00001
Maslo [22]	2022	South Africa	Individuals hospitalized for COVID-19	ICU admission Mechanical ventilation In-hospital death	Unspecified (data were collected between Nov 2021and Dec 2021)	971	180 (18.5%) 16 (1.6%) 27 (2.7%)	4,400	1,318 (29.9%) 548 (12.4%) 1,284 (29.1%)	p < .001 p < .001 p < .001
Mndala [23]	2022	Malawi	Pregnant women hospitalized for COVID-19	In-hospital maternal death	B.1.1.529	57	3 (5%)	128	23 (18%)	Delta vs. Omicron (reference) aOR, 3.52 (0.98–12.60)
Bouzid [24]	2022	France	Individuals diagnosed with COVID-19	ICU admission Mechanical ventilation In-hospital death	B.1.1.529	898	41.1 (4.6%) 17.1 (1.9%) 36.8 (4.1%)	818	150.8 (18.4%) 55.8 (6.8%) 77.3 (9.5%)	aRD(%), −11.4 (−14.4, −8.4) aRD(%), −3.6 (−5.6, −1.7) aRD(%), −4.2 (−6.5, −2.0)
Suzuki [25]	2022	Japan	Individuals hospitalized for COVID-19	Mechanical ventilation In-hospital death	Unspecified (data were collected between Jan 2022 and Apr 2022)	920	5 (0.5%) 1 (0.1%)	—	—	—
Matsumura [26]	2022	Japan	Fully vaccinated nursing home residents	Death within 90 days of the outbreak	BA.1	31	8 (25.8%)	—	—	—

Abbreviations: ICU, intensive care unit; CI, confidence interval; RR, relative risk; aRR, adjusted relative risk; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRD, adjusted risk difference

* Delta variants unless otherwise indicated.

† Delta variants were used as a reference category, otherwise indicated

variants replicate more readily in the upper airways than in the lungs and appear to enter human cells via a different route than other variants [27, 28]. The difference in the replication area and infection route of the Omicron variants potentially reduces the risk of death from COVID-19 without causing critical conditions or multiorgan failure [29–31]. Indeed, Menni et al. reported that the symptoms of COVID-19 caused by Omicron variants were more localized and resolved sooner than those caused by the Delta variants [17].

Another explanation, based on factors other than the virus itself, for the less severe illness in individuals infected with the Omicron variant, may be attributed to partial immunity conferred by a previous infection or vaccination. Lauring et al. reported that the risk of severe illness and death was lower for the Omicron variants than that for previous strains in both vaccinated and unvaccinated populations [12], and the results adjusted for vaccination status were consistent [18, 19]. Furthermore, regarding immunological and external factors other than vaccination, Delta and Omicron variants that circulated in the same period were compared, and consistent results were confirmed [15, 16, 24]. Taken together, we believe that the milder virulence of the Omicron strain itselfis certainly suggested.

Further studies are required to clarify the mechanisms of transmissibility and the severity of COVID-19 caused by Omicron variants. Nonetheless, identifying Omicron variants in patients with COVID-19 implies a good prognosis. Variant identification can be used for the risk stratification of patients with COVID-19 at diagnosis or hospital admission. Because Omicron variants and their sublineages are still circulating worldwide, policymakers and healthcare professionals should consider the severity of COVID-19 caused by Omicron variants to predict prognosis and allocate medical resources adequately.

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