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Differences in case-fatality-rate of emerging SARS-CoV-2 variants

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ABSTRACT

Objects: Variants of Severe-Acute-Respiratory-Syndrome Coronavirus-2 (SARS-CoV-2) has caused tremendous impact globally. It has been widely reported that the Omicron (B.1.1.529) variant is less deadly than the Delta (B.1.617.2) variant, presumably due to immunity from vaccination and previous infection. When measuring the severity of a variant, Case-Fatality-Rate (CFR) is often estimated. The purpose of this work is to calculate the change in CFR of different variants over time from a large number of countries/regions since the start of the pandemic in 2020.
Study design: A Cross-sectional study.
Methods: We extend the comparison to all previous VOCs in 58 counties/regions. We use reported death divided by reported cases in 30-day sliding window with a two-week shift between reported death and reported cases.
Results: The drop from Delta variant to Omicron variant is substantial and the difference between subvariants of Omicron is not evident.
Conclusion: We showed that the CFR dropped over time, presumably due to vaccine-induced immune and infection induced immune. Population age structure and prevalence of comorbidity influence CFR.

1. Background

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), hit the humankind tremendously with 544,946,610 reported cases and 6,342,015 reported deaths by June,2022 [1,2]. The rapid evaluation of the viruses led to variants with high transmissibility and high immune evasion ability and posed challenges for prevention and control [3]. Among the new variants, the Delta variant (B.1.617.2) was first identified in December 2020 [4] and classified by the World Health Organization (WHO) as Variant of Concern (VOC) on June 2021, updated as Variant Being Monitored (VBM) on April 2022 [3]. The Omicron variant (B.1.1.529) was first detected in specimens collected on November 2021, and classified as a Variant of Concern (VOC) [5]. Several subvariants of Omicron variant has been reported so far. Previous studies on the case-fatality-rate (CFR) of different variants were conducted in individual countries. Large-scale comparison across multiple countries is missing. The CFR is an important indicator of disease severity. Many factors may affect the estimates. Infection attack rate (proportion of population being infected) with previous variants, vaccination coverage, age structure of the population and the medical system preparedness may affect the CFR in different population/locations. In this work, we combine the reported cases and deaths and variant proportion over time in 58 locations (see Appendix) to calculate the raw CFR for 8 variants (or subvariants), thus, to get a large-scale picture of the changing pattern of the severity of SARS-CoV-2.

The Omicron variant spreads faster than the Delta variant due to the combined effects of increased transmissibility and immune evasion ability. In South Africa, the proportion of patients with Omicron infection presenting to emergency departments has fallen to half its previous level, and the proportion of Omicron patients presenting with acute respiratory conditions and requiring oxygen therapy and mechanical ventilation has fallen dramatically [6].

In United States, the number of deaths in the Omicron wave (analyzed from December 15, 2021 to March 15, 2022) was very similar to that seen in the Delta wave (analyzed from July 15, 2021 to November 15, 2021). However, the number of confirmed cumulative cases during this period was twofold higher with Delta. The CFR of Omicron variant is about half that of Delta variant in the both US and South Africa [7].

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2. CFR of variants across 58 locations

2.1. Study design

A Cross-sectional study of Case-Fatality-Rate during the epidemic in each variant was conducted in 58 countries/regions, with controls for age group and vaccination status. We compared and calculated the relative difference in CFR between infection with Delta and Omicron variants under different age groups and the efficacy of vaccination in reducing CFR under Delta or Omicron variant prevalence time breaks.

2.2. Data collection

The data collected were incremental confirmations of different variants in 58 countries or regions on a two-week cycle. We selected the countries with relatively well-developed data among them to be collected in order of the total number of confirmed diagnoses, from most to least.

2.3. Method

Here we extend the comparison to all previous VOCs in 58 counties/regions. We use reported death divided by reported cases in 30-day sliding window with a two-week shift between reported death and reported cases.

$$Case\ Fatality\ Ratio(CFR\ in\%) = \frac{Number\ of\ deaths\ from\ disease\ in\ the\ past\ 30\ days}{Number\ of\ confirmed\ cases\ of\ disease\ in\ the\ past\ 15\ to\ 45\ days} \times 100\%$$

Based on the biweekly variant proportion data [8,9], we determine the dominant time interval for each variant in each location when the proportion of a variant is above 60% among all samples processed. Namely the raw CFR in a time interval when the proportion of variant is above 60% is assigned as the CFR for the variant in that location. We calculated the mean CFR values for each variant in its dominant time interval in each location. Fig. 1 summarized the mean CFR for each variant across 58 locations.

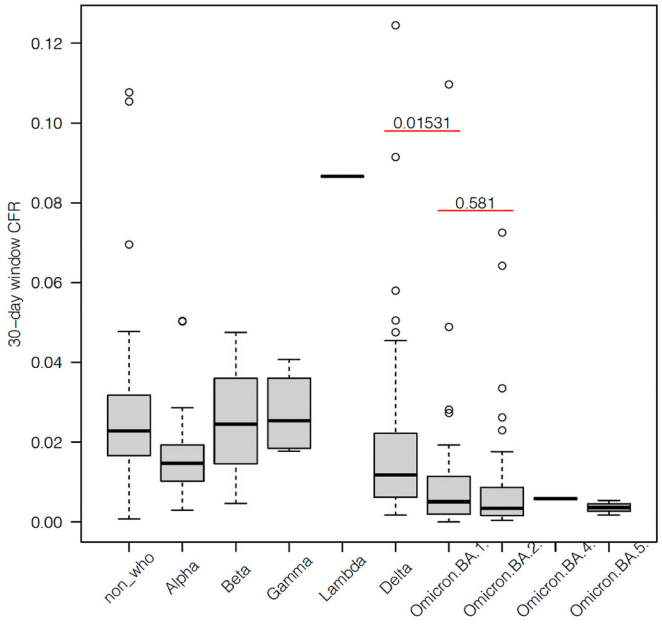

Fig. 1. The summary of the mean case-fatality rate (CFR) during its dominant time interval in 58 locations for ten variants or subvariants.

2.4. Statistical analysis

We conduct a two-sample *t*-test to determine whether the mean CFR values of one variant is different to that of another variant (subvariant). The null hypothesis H_0: $\mu_1 = \mu_2$, the alternative hypothesis H_1: $\mu_1 \neq \mu_2$ (μ_i is the mean CFR value of different variants).

The mean CFR values for Delta variant was higher than that of Omicron variant (p-value = 0.01531, rejected the null hypothesis.) (Fig. 1). The mean CFR values was similar between subvariants of Omicron (p-value = 0.581, accept the null hypothesis.) (Fig. 1).

3. Age stratified CFR

In South Africa, the CFR during Omicron variant dominant time interval (November 21, 2021, to January 22, 2022) was substantially lower than that during Delta variant dominant time interval (May 9 to September 18, 2021), for 20+ age groups (see Table 1) [10]. This could be due to implementation of vaccination among adults and infection induced immunity across all ages.

In Table 1, the relative difference is defined as $\left(1 - \frac{CFR\_omicron}{CFR\_delta}\right)\%$. For all ages, the CFR of Delta variant is more than three-fold of the CFR of Omicron for overall age group and 40+ ages groups. The 5–19 age group has the lowest CFR for both variants.

Italy has a high proportion of elderly people (>65 age accounting 23% of the population) in 2019, which could have led to a higher CFR compared to other countries. Among 70–79 age group, the CFR is about 12.8% in Italy and 8.0% in China; among 80+ age group, the CFR is about 20.2% in Italy and 14.8% in China, in early 2020 [11]. 86% of patients in the Washington ICU have underlying chronic conditions such as kidney disease and heart failure [12]. Population age structure and prevalence of comorbidity influence CFR.

4. Impact of vaccination

Zhao et al. showed that, in the United Kingdom during May and June 2021, Delta variant had a smaller CFR than pre-variant and the CFR of pre-Delta variant dropped substantially while the vaccine coverage increased and the drop of the CFR of Delta variant is less evident (probably due to short study period) [13]. In the United States, Johnson et al. compared the CFR among unvaccinated and fully vaccinated individuals in 25 US jurisdictions and the vaccine efficacy substantially dropped over time (see Table 2) [14].

The vaccine efficacy (VE) is defined as $\left(1 - \frac{CFR\_vaccinated}{CFR\_unvaccinated}\right)\%$. The VE

Table 1
The summary of case-fatality rate (CFR) of Delta variant and Omicron variant among different age groups in South Africa.

CFR	Delta	Omicron	Relative difference
All ages	2.60%	0.78%	70%
Age 20–39 years	0.45%	0.24%	46.7%
Age 40–59 years	2.54%	0.64%	74.4%
Age ≥60 years	11.71%	2.38%	79.7%

Table 2
The summary of case-fatality rate (CFR) of Delta variant and Omicron variant in unvaccinated people and fully vaccinated people in United States.

Time	CFR among Unvaccinated	CFR among Fully vaccinated	Vaccine Efficacy in reduction CFR
Pre-Delta (2021, 4–5)	1.05%	0.10%	90.5%
Delta emergence (2021, 6)	1.37%	0.24%	82.5%
Delta predominance (2021, 7–11)	1.22%	0.32%	73.8%
Omicron emergence (2021, 12)	0.11%	0.03%	72.7%

drop substantially over time, due to a combined effect of natural waning of immune protection and immune evasion of Delta and Omicron variant.

5. Limitation

The work utilized bi-weekly variant sequencing data and reported deaths and cases. The under reporting of COVID-19 deaths and cases will impact the estimate of CFR. The CFR is an overestimate of the true infection-fatality-rate. If the reporting is consistent, the CFR across variants should be a fair comparison.

6. Conclusion

In this work, we compared the CFR for ten variants (including ancestral strain and Omicron subvariants) across 58 locations. We showed that the CFR dropped over time, presumably due to vaccine-induced immune and infection induced immune. The drop from Delta variant to Omicron variant is substantial while the difference between subvariants of Omicron is not evident.

Ethical approval statement and consent to participate

The data used in this study were collected originally via the public domains, and thus neither ethical approval nor individual consent was applicable.

Availability of materials

Data are publicly available online.

Consent for publication

Not applicable.

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Disclaimer

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author's contributions

DH and JL conceived the study, carried out the analysis and drafted the manuscript. All authors discussed the results, and revised the manuscript, and approved it for publishing.

Declaration of competing interest

All authors have no conflict of interest.

Acknowledgments

None.

Appendix

List of countries/regions used in the study

Argentina	Australia	Bangladesh	Belgium
Brazil	Bulgaria	Cambodia	Canada
Chile	Colombia	Costa Rica	Croatia
Czechia	Denmark	Ecuador	France
Georgia	Germany	Greece	Hong Kong, China
India	Indonesia	Ireland	Israel
Italy	Japan	Jordan	Lithuania
Luxembourg	Malaysia	Mexico	Netherlands
Norway	Pakistan	Peru	Poland
Portugal	Qatar	Russia	Singapore
Slovakia	Slovenia	South Africa	South Korea
Spain	Sweden	Switzerland	Turkey
Ukraine	United Kingdom	United States	Philippines
Romania	Thailand	Egypt	Austria
Latvia	Paraguay		

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