Understanding of COVID-19 from infection–fatality ratio

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Since the emergence of the COVID-19 pandemic, confirmed cases and cumulative deaths have been the most important numbers released by WHO and raised worldwide attention.[1] The two numbers can help to roughly estimate the COVID-19 mortality rate (COVID-19 deaths to population numbers at risk) and case-fatality ratio (COVID-19 deaths to confirmed COVID-19 cases) of a population, although using reported COVID-19 deaths could underestimate the death toll related to the COVID-19 pandemic.[2] Another important concept, the infection–fatality ratio (IFR), has been rarely mentioned. The IFR is crucial for risk perception, policy making for epidemic control, and estimation of COVID-19 burden. The IFR is calculated as COVID-19 deaths divided by the number of people infected with SARS-CoV-2, the denominator of which cannot be directly obtained and could be estimated with data from seroprevalence surveys.

By combining seroprevalence surveys (2073 all-age surveys and 718 age-specific surveys) with estimates of total COVID-19 mortality, the COVID-19 Forecasting Team[3] provide important data for IFR with adjustment for antibody-test sensitivity in *The Lancet*. They focused on IFR estimation during the prevaccination era (from April, 2020, to January, 2021) because COVID-19 epidemiological patterns were more stable before delivery of vaccination and emergence of new SARS-CoV-2 variants. The authors explored the IFR variation from three dimensions including age, geography, and time, which all have important and specific public health implications.

When analysing IFR variation by age, the team found J-shaped patterns with the lowest level of IFR detected at age 7 years. IFR was higher among younger children and increased with age among people older than 7 years. The increased IFR for infants and children younger than 7 years indicates the importance of vaccination delivery and policy recommendation for this population. Regarding IFR variation by geography, the majority of variation across different countries and territories was attributable to population age distribution, and was estimated to be 74% among countries with seroprevalence data and 87% when out-of-sample countries were additionally included. After age standardisation, locations in American continents and a few European countries with good access to health-care resources had the highest IFR. During outbreaks of infectious disease, access to health-care resources is crucially important, but might not be the only determinant for lowering IFR or success of pandemic control. Other factors including comorbidities, which potentially worsen COVID-19 severity, and management of care home epidemics could also be important in explaining IFR variation. These factors provide clues for responding to future outbreaks. Regarding IFR variation in time, median country-specific all-age IFR and age-standardised IFR decreased from 0·47% (IQR 0·22–0·84) to 0·31% (0·14–0·55), and from 0·54% (0·45–0·66) to 0·35% (0·29–0·43) during the prevaccination era. This positive sign brought by IFR reduction could strengthen the confidence of clinicians in providing medical care for patients with COVID-19 and our confidence in dealing with this COVID-19 pandemic. IFR reduction over time could be attributable to several reasons, including more experienced clinicians treating patients with COVID-19, better access to COVID-19-related health resources, deeper understanding of risk factors of COVID-19 death,[4] and demonstration of dexamethasone for lowering 28-day mortality among patients hospitalised with COVID-19 receiving either invasive mechanical ventilation or oxygen alone.[5]

By delineating IFR variation during the prevaccination era from different aspects, this study provided abundant

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data for a more comprehensive understanding of the burden of COVID-19. However, attention should be paid when interpretating findings from this study. First, seroprevalence data, which is important for estimation of IFR, was absent in most locations in Asia, Australia, and South America. This situation was more obvious for age-stratified seroprevalence data. Although several models were constructed to obtain age-standardised IFRs, the effect of incompleteness of data on seroprevalence and mortality across countries and territories on model constructions might not be avoided. Second, the clinical predictors selected and effect sizes for these clinical predictors used as priors for modelling age-standardised IFRs were all based on data from the USA. Whether the model performance for other countries and territories, especially low-income countries, can be affected is not known.

Although IFR after the prevaccination era is not sufficiently delineated for now, the fight against COVID-19 still continues. The emergence of the SARS-CoV-2 variant, omicron (B.1.1.529), has raised global concern and led to resurgence of COVID-19 waves in many countries. For now, vaccination is the most important intervention to reduce resurgence and transmission of COVID-19 epidemics and lower the number of new fatalities.[6,7] Other promising SARS-CoV-2 antivirals are extending pandemic control to pharmaceutical intervention. With more promising weapons to fight against COVID-19, whether IFR will continue to reduce after the prevaccination era needs to be answered by future studies. As the COVID-19 pandemic continues, society has to be prepared for and adapt to the potential for living with SARS-CoV-2 in the coming years.

We declare no competing interests.

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