The confounded crude case-fatality rates for COVID-19 hide more than they reveal - a comparison of age-specific and age-adjusted rates between six countries

Manfred S Green MBChB,PhD¹, Victoria Peer MSc¹, Dorit Nitzan MD, MPH²

Affiliation
1. School of Public Health, University of Haifa, Israel
2. World Health Organization, European Region, Copenhagen, Denmark

Correspondence:
School of Public Health
University of Haifa,
Abba Khoushy 199,
Haifa 3498838,
Israel.
E-mail: manfred.s.green@gmail.com
Abstract

Background
The reported crude case-fatality rates (CFRs) vary widely between countries. The serious limitations of using crude rates for comparisons are sometimes overlooked. In this paper we examined to what extent the age distribution of the cases is responsible for the differences in CFRs between countries.

Methods
Data on COVID-19 were extracted from the reports of individual countries. Overall and age-specific CFRs were available for six countries. The CFRs by country were adjusted for age using the direct method, using the combined age-specific number of cases of all six countries as the standard population.

Findings
The age distribution of the cases varied widely between countries. The crude CFRs varied between 1.6% and 11%. The differences in the age-specific CFRs were much smaller and the age-adjusted rates were much closer than the crude rates. The ratio of the crude CFR for the country with the highest to that with the lowest, was reduced substantially from 7.4 to 2.3 for the age-adjusted rates.

Conclusions
The age structure of the cases dramatically impacts on the differences in the crude CFRs between countries. Adjusting for age substantially reduces this variation. Other factors such as the differences in the definition of the denominators, the definition of a case and the standard of healthcare are likely to account for much of the residual variation. It is misleading to compare the crude COVID-19 CFRs between countries and should be avoided. Comparisons should be based on age-specific and age-adjusted rates.

Key words: COVID-19, case-fatality rates, age-specific rates, age-adjusted rates, confounding

No funding was provided for this study. The authors declare no conflict of interests
Background

The novel coronavirus SARS-2-CoV 2019 was first identified in Wuhan in China in early December 2019. On January 30, 2020, when the total number of cases reached 7,711 in China and 83 in other countries, the World Health Organization declared it as a Public Health Emergency of International Concern (PHEIC) (1) and on March 11, 2020, it was declared as a pandemic. By May, 2020, almost all countries had been affected with more than three million cases reported. Early estimates indicated an average case-fatality rate (CFR) of around 2.0% (2, 3). However, subsequently, the reported CFRs varied widely between countries (3,4).

A number of factors could impact on the calculation of the CFRs. These include the lag time between diagnosis and death, possible misclassification of causes of death and the definition of cases to determine the denominator. A dominant factor could be the age structure of the cases (2-5). This may be due to the age structure of the population, the differential exposure by age group, and the testing strategy. In this paper, we examine the role of the age distribution of the cases on the crude CFRs. In order to assess the effect of age, we focused on six countries, with widely varying CFRs.

Methods

The study was a comparison of published crude and age-adjusted CFRs in cohorts of cases of COVID-19 in selected countries, with varying periods of follow-up. The countries chosen were based on the accessibility of the data at the beginning of May, 2020. The data for each country were not necessarily updated to the time of the study. Total and age-specific data on the cases and deaths were available for six countries: Italy (6), Spain (7), Sweden (8), China (9), S Korea (10) and Israel (unpublished data). They all provided data on cases and deaths by ten-year age groups (0-9, 10-19, …..80+). The outcome was the crude CFR defined as the number of deaths divided by the number of reported cases. The exposures were the countries. Age-group was considered as the major confounding variable. Age-adjustment was carried by the direct method, using the distribution of the combined cases of all six countries as the standard population. 95% confidence intervals were computed for each age-adjusted rate, using WinPepi (PEPI-for-Windows).
Ethical considerations
Open access aggregative and anonymous data were used and there was no need for ethics committee approval.

Results
The age-specific CFRs and crude CFRs by country are given in Table 1.
Table 1. Age-specific case-fatality rate (CFR) from COVID-19 for six countries

| Age   | China                  | Israel                | Italy                  | S Korea                | Spain                  | Sweden                |
|-------|------------------------|-----------------------|------------------------|------------------------|------------------------|-----------------------|
|       | Cases/died             | CFR%                  | Cases/died             | CFR%                   | Cases/died             | CFR%                  | Cases/died | CFR% |
| 0-9   | 416/0                  | 0.00                  | 838/0                  | 0.00                   | 589/0                  | 0.00                   | 112/0       | 0.00 |
| 10-19 | 549/1                  | 0.20                  | 2028/0                 | 0.20                   | 766/0                  | 0.20                   | 513/0       | 0.20 |
| 20-29 | 3619/7                 | 0.20                  | 3299/0                 | 0.20                   | 3830/2                 | 0.10                   | 2630/0      | 0.20 |
| 30-39 | 7600/18                | 1.20                  | 1952/2                 | 0.10                   | 6523/2                 | 0.30                   | 1002/1      | 0.20 |
| 40-49 | 8571/38                | 0.40                  | 1792/1                 | 0.00                   | 12084/89               | 0.70                   | 1297/1      | 0.10 |
| 50-59 | 10008/130              | 1.30                  | 1752/3                 | 0.20                   | 18678/369              | 2.00                   | 1812/10     | 0.60 |
| 60-69 | 8583/309               | 3.60                  | 1364/14                | 1.10                   | 16395/1162             | 7.10                   | 1218/21     | 1.70 |
| 70-79 | 3918/312               | 8.00                  | 761/41                 | 4.00                   | 17464/3456             | 19.80                  | 640/45      | 7.00 |
| 80+   | 1408/208               | 14.80                 | 541/110                | 13.50                  | 17759/4923             | 27.70                  | 437/80      | 18.30 |
| Total | 44672/1023             | 2.30                  | 14327/230              | 1.60                   | 124352/14589           | 11.90                  | 10728/242   | 2.30 |
| Age-adj | 4.8/4.4 – 5.2         | 6.4/5.6-7.1           | 10.8/10.6-11.0         | 6.5/5.7-7.3            | 6.9/6.8-7.0            | 10.6/10.2-11.0        |  


In general, the crude CFR’s varied widely, whereas the age-specific CFRs were more similar. The age distribution of the cases is shown in Figure 1.

**Figure 1. Cases distribution by age for six countries (China, Italy, S Korea, Spain, Israel and Sweden)**

They distributions vary markedly. The distribution of the cases for Israel and South Korea are heavily weighted in the 20-39 age group, China has a more balanced distribution and Italy and Sweden are heavily weighted in the over 70 age groups. The age-specific CFRs are shown in Figure 2.
Figure 2. Age specific case-fatality rates for six countries – China, Italy, S Korea, Spain, Israel and Sweden

While there are still marked differences in the age-specific CFRs, the trend of steeply increasing CFRs in the oldest age groups is evident. The crude and age-adjusted CFRs are compared in Table 2.

Table 2. Crude and age standardized case-fatality rates (CFR) for COVID-19 in six countries

| Country       | Crude CFR % | Age-adjusted CFR rate % (95% CI) | Ratio to lowest crude CFR | Ratio to lowest age-adjusted CFR |
|---------------|-------------|----------------------------------|---------------------------|---------------------------------|
| Israel        | 1.6         | 6.4 (5.6-7.1)                    | 1.0                       | 1.3                             |
| Korea         | 2.3         | 6.5 (5.7-7.3)                    | 1.4                       | 1.4                             |
| China         | 2.3         | 4.8 (4.4-5.2)                    | 1.4                       | 1.0                             |
| Spain         | 7.7         | 6.9 (6.8-7.0)                    | 4.8                       | 1.4                             |
| Sweden        | 11.8        | 10.6 (10.2-11.0)                 | 7.4                       | 2.2                             |
| Italy         | 11.9        | 10.8 (10.6-11.0)                 | 7.4                       | 2.3                             |
The crude CFRs varied from 1.6% for Israel to 11.9% for Italy and the ratios of the crude CFRs compared with lowest CFR, varied between 1.4 and 7.4. The age-adjusted CFRs varied between 4.8% for China to 10.8% for Italy and the ratios of the age-adjusted CFRs for each country compared with the lowest CFR adjusted varied between 1.2 to 2.3. For example, the ratio of the CFR for Italy to Israel dropped from 7.4 to 1.7. Figure 3 shows the marked reduction in the differences between the crude and age-adjusted CFRs for the six countries.

**Figure 3. Crude and age-adjusted case-fatality rates by country for six countries**

![Crude and age-adjusted case-fatality rates by country](image)

**Discussion**

In our study, we examined crude, age-specific and age-adjusted CFRs for COVID-19 in six countries, with widely varying crude CFRs. The trends in the age-specific CFRs were remarkably similar in the six countries, with the CFR’s increasing steeply in those over 70. After adjusting for age, the marked differences in the CFRs were substantially reduced. These results demonstrate the importance of accounting for age when comparing rates in general and CFRs in particular. The results of this study are strengthened by the use of national data or large datasets from a number of countries, with considerable differences in the extent of the pandemic in each country. It should be stressed that the age distribution of the cases and not the age distribution of the total population in each country cases that was used to compute the age-adjusted CFRs.
This study may have several potential limitations. The number of cases and deaths depends on the testing strategy of each country. The deaths that are reported may vary according whether these include only hospitalized cases with definite diagnoses, whereas others may also count deaths occurring at home. There is a lag time between the reporting of the case and the death which can occur up to weeks later. In the country reports, cases and deaths are usually reported at the same time, so the cases in the denominator are usually an overestimate of the true denominator which should be the number of cases reported sometime earlier. This will have a more dramatic effect when the number of cases are rising rapidly. There may be misclassification of cases, depending on the sensitivity and the specificity of the methods used to diagnose a case. The cause of death could be wrongly coded particularly in elderly people with multiple co-morbidities. However, while these factors will affect the calculation of the true CFR, they should not have an important impact on demonstrating the serious limitations in using crude CFRs for country comparisons. This is the main purpose of this paper.

The age structures of the population of the countries varied markedly. The percentage of the population 65 and over is 11% in Israel, in Italy 23% in Italy, S Korea 14%, in Spain 19%, in Sweden 20% and in China 11%. However, the differences in the age structure of the of cases was often due to specific circumstances of exposure. For example, most of the cases in Italy occurred in an area of a particularly old population (4, 5). In some countries, many of the cases were medical personnel, a large number of whom were relatively young women (11). In South Korea, a large percentage of the cases were young women associated with a specific religious group (12). In Germany, many of the cases were relatively young people returning from skiing holidays in Austria and Italy (13). Other factors affecting the age were the number of outbreaks in homes for the elderly (14).

The results once again demonstrate the fallacy of comparing unadjusted rates. The assumption that differences in testing policies or standard of treatment accounted for the wide discrepancies in CFRs are not well-founded. This does not mean that there are no differences. For example, it is possible that where the health services were overloaded, younger patients were more likely to be admitted to intensive care units with better chances of survival. Clearly, the data are incomplete and other factors affecting CFRs such as case definitions, use of different denominators, underlying health conditions and the standard of health services
are likely to play important roles. In order to assess the impact of these factors, age-specific and age-adjusted CFRs must be used.

**Conclusions**

The age structure of the cases dramatically impacts on the differences in the crude CFRs between countries. The marked reduction in the differences in the age-adjusted CFRs suggest that differences in the standard of healthcare between these countries may not play as important a role in affecting the death rates, as some have hypothesized. Crude COVID-19 CFRs have no real use for between country comparisons and should be avoided. In general, foe comparisons, both age-adjusted and age-specific COVID-19 CFRs are far more meaningful.
Acknowledgements

We express our appreciation to the official institutions of all countries for the providing their data on Covid-19.

Funding

No funding was provided for the study.

Conflicts of interests

The authors declare that they have no conflicts of interests.
References

1. WHO: Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed on 1 May 2020.

2. Coronavirus disease 2019 (COVID-19): situation report - 36. Geneva: World Health Organization, February 25, 2020. Available at: https://www.who.int/docs/default-source/coronavirus/situation-reports/20200225-sitrep-36-covid-19.pdf?sfvrsn=2791b4e0_2. Accessed on 20 April 2020.

3. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious Diseases. 2020.

4. Mahase E. Covid-19: death rate is 0.66% and increases with age, study estimates. BMJ 2020;369:m1327.

5. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020.

6. Epidemia COVID-19. Aggiornamento nazionale. 6 aprile 2020. Available at: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_6-aprile-2020.pdf. Accessed on 25 April 2020.

7. Centro de Coordinación de Alertas y Emergencias Sanitarias. Available at: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_88_COVID-19.pdf. Accessed on 1 May 2020.

8. Statista. Available at: https://www.statista.com/topics/6267/coronavirus-covid-19-in-sweden/. Accessed on 20 April 2020.

9. Zhonghua Liu Xing Bing Xue Za Zhi. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. 2020;41:145-151.

10. Korea Centers for Disease Control (CDC). Available at: https://www.cdc.go.kr/board/board.es?mid=a30501000000&bid=0031&list_no=367045&act=view. Accessed on 20 April 2020.
11. Haozheng Cai, Baoren Tu, Jing Ma, et al. Psychological Impact and Coping Strategies of Frontline Medical Staff in Hunan Between January and March 2020 During the Outbreak of Coronavirus Disease 2019 (COVID-19) in Hubei, China. Med Sci Monit. 2020; 26: e924171-1–e924171-16.

12. Korean Society of Infectious Diseases; Korean Society of Pediatric Infectious Diseases; Korean Society of Epidemiology; Korean Society for Antimicrobial Therapy; Korean Society for Healthcare-associated Infection Control and Prevention; Korea Centers for Disease Control and Prevention. Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. J Korean Med Sci. 2020;35(10):e112.

13. A German Exception? Why the Country’s Coronavirus Death Rate Is Low. New York Times, Published April 4, 2020, updated April 6, 2020.

14. Available at: https://www.euronews.com/2020/04/20/coronavirus-and-the-elderly-what-s-life-inside-a-french-retirement-home-amid-covid-19-pand.