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Delay-adjusted age- and sex-specific case fatality rates for COVID-19 in South Korea: Evolution in the estimated risk of mortality throughout the epidemic

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ABSTRACT

Objectives: The aim of this study was to estimate delay-adjusted case fatality rates (CFRs) for COVID-19 in South Korea, and evaluate how these estimates have evolved over time throughout the epidemic.
Methods: Public data from the Korea Centers for Disease Control and Prevention (KCDC) were used to estimate age- and sex-specific CFRs for COVID-19 in South Korea up to June 12, 2020. We applied statistical methods previously developed to adjust for the delay between diagnosis and death, and presented both delay-adjusted and crude (unadjusted) CFRs throughout the epidemic.
Results: The overall estimated delay-adjusted CFR was 2.39% (3.05% for males and 1.92% for females). Within each age strata where deaths were reported, males were found to have significantly higher CFRs than females. The estimated CFRs increased substantially from age 60 years in males and from 70 years in females. Both the delay-adjusted and crude CFRs were found to have evolved substantially, particularly early in the epidemic, converging only from mid-April 2020.
Conclusions: The CFRs for South Korea provide an estimate of mortality risk in a setting where case ascertainment is likely to be more complete. The evolution in CFRs throughout the epidemic highlights the need for caution when interpreting CFRs calculated at a given time point.

Introduction

Estimation of case fatality rates (CFRs) is an important element of infectious disease risk assessment. As the SARS-CoV-2 (COVID-19) pandemic has evolved, a number of studies have estimated CFRs from COVID-19 (Li et al., 2020). However, the lack of availability of widespread testing in many settings has meant that estimates are likely to have been affected by substantial ascertainment bias toward severe cases. Some studies have developed and applied approaches to adjust for underreporting of less severe cases (Verity et al., 2020), but an alternative approach is to estimate CFRs in settings where case ascertainment is more complete.

After the first case of COVID-19 in South Korea (Republic of Korea) was identified on January 20, 2020 (Korea Centers for Disease Control and Prevention, 2020c), a reverse transcription polymerase chain reaction (RT-PCR) test kit for COVID-19 was rapidly developed and approved on February 4, 2020 (Kim et al., 2020; Sung et al., 2020). Testing capacity then increased rapidly and by March 31, 2020 South Korea was able to conduct 20 000 COVID-19 tests per day (Sung et al., 2020). Due to this rapid deployment of high levels of testing and intensive contract tracing (Korea Centers for Disease Control and Prevention, 2020a) South Korea is likely to have captured a high proportion of symptomatic COVID-19 cases. In addition, a substantial proportion of asymptomatic cases may have been detected as part of clinical clusters and/or as close contacts of cases (approximately 20% of all confirmed cases were asymptomatic at discharge according to a report on March 16, 2020 (Chang-won, 2020)).

Another important factor to consider when estimating CFRs for COVID-19 is the substantial delay between the diagnosis (reporting) of a case and death from the disease (Lipsitch et al., 2015). While crude CFRs based on current reported cases and deaths are readily available, they are misleading because deaths from recently

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reported cases are yet to be observed. To address this complication when estimating CFRs various methods to adjust for the delay from diagnosis to reporting of death have been developed (Garske et al., 2009; Lee and Lim, 2019; Lipsitch et al., 2015; Nishiura et al., 2009).

Both age and sex have been identified as important risk factors in severe COVID-19 disease (Williamson et al., 2020) but, to date, many of the age- and sex-specific CFRs estimated for COVID-19 have been published in settings where case ascertainment is likely to be incomplete and/or not adjusted for delay to death. Despite the potential to provide important insights, we know of no published study that has estimated age- and sex-specific adjusted CFRs from COVID-19 for South Korea. One recent study has estimated adjusted CFR for South Korea (Shim et al., 2020), however this study did not stratify by age or sex and used data from China to estimate the delay to death for COVID-19.

This study aimed to estimate delay-adjusted age- and sex-specific case fatality rates for COVID-19 in South Korea, and evaluate how these estimates evolved over time throughout the epidemic. Estimation of age- and sex-specific CFRs from COVID-19 is critical to better understand mortality risk within the population, and to help inform planning for prevention and care of severe cases.

Methods

The public data obtained from the Korea Centers for Disease Control and Prevention (KCDC) (2020d) website were used to analyze age- and sex-specific delay-adjusted CFRs. The first case of COVID-19 in South Korea was identified on January 20, 2020 and the first death on February 19, 2020; however, the age- and sex-specific data we used did not begin to be reported publicly until March 10, 2020. To allow detailed analysis by age and sex, March 10, 2020 was used as our index date for the study; however, when estimating the overall (all ages) CFR, we used the index date of January 29, 2020. Data were analyzed up until June 12, 2020. The age groupings explored were 0–29, 30–49, 50–59, 60–69, 70–79, and 80+ years; these were further stratified by sex (male and female) to provide age- and sex-specific CFR estimates.

The statistical methods we used to estimate the delay-adjusted age- and sex-specific CFRs were based on Nishiura et al. (2009). For age group a and sex s on day t, given the daily number of new cases $c_{a,s}(t)$, the cumulative number of cases $C_{a,s}(t)$, the cumulative number of deaths $D_{a,s}(t)$, and the delay distribution F, the daily delay-adjusted $CFR_{a,s}(t)$ is computed as:

$$CFR_{a,s}(t) = \frac{D_{a,s}(t)}{u_{a,s}(t)\left(C_{a,s}(t) - D_{a,s}(t)\right) + D_{a,s}(t)} \quad (1)$$

where $u_{a,s}(t)$ is the adjustment factor to account for the expected delay until death among diagnosed cases whose outcome is not yet known. This is expressed as:

$$u_{a,s}(t) = \frac{\sum_{j=0}^{t} c_{a,s}(j)F(t-j)}{C_{a,s}(t)} \quad (2)$$

where j is the number of days since March 10, 2020—our index date when both age- and sex-stratified data were first made available—until day t so that $t-j$ is the time delay since a case was first confirmed. In principle, the CFR denominator by day t is the sum of cases with known outcomes (e.g. died, $D_{a,s}(t)$) and the expected number of other cases predicted to have a known outcome, based on the delay distribution F, among those still considered active $\left(u_{a,s}(t) \times \left(C_{a,s}(t) - D_{a,s}(t)\right)\right)$. For comparison, we also computed the crude daily CFRs given by $D_{a,s}(t)/C_{a,s}(t)$.

To generate 95% confidence intervals (CIs), we assumed that $D_{a,s}(t) \sim \text{Binomial}\left(N_{a,s}(t),\ CFR_{a,s}(t)\right)$, where $N_{a,s}(t)$ is the denominator used in computing the CFR: $C_{a,s}(t)$ for the crude rates or $u_{a,s}(t)\left(C_{a,s}(t) - D_{a,s}(t)\right) + D_{a,s}(t)$ for the delay-adjusted rates. Modified Jeffreys CIs were computed because $CFR(t)$ is very close to 0%, ensuring that the lower limit was bounded by 0%, and the upper limit was adjusted so that the resulting CI had a coverage probability of 95%.

To estimate the delay between diagnosis of a case and reporting of a death, we used a South Korean study that reported on the first 66 deaths from COVID-19 (Korea Centers for Disease Control and Prevention, 2020b). In the primary analysis we used the estimated delay between symptom onset and death (median 10 days; range 1–24) and as a sensitivity analysis we used the estimated delay between hospitalization and death (median 5 days; range 0–16) (Korea Centers for Disease Control and Prevention, 2020b). We fitted differing lognormal distributions to these two delay distributions, such that the medians of the distributions corresponded to the reported medians and the reported ranges corresponded to the 0th (minimum) and 95th percentiles to account for the right-skewness of the lognormal distributions (Appendix A, Figure A1). The choice of a lognormal distribution was based on a previous study that found that this distribution type was the best fit for delay until death data (Linton et al., 2020).

In addition to the primary methods used to estimate the delay-adjusted age- and sex-specific CFRs based on Nishiura et al. (2009), as a scenario analysis we also explored an alternative method using the approach outlined in Garske et al. (2009).

Appendix B provides an outline of the R code used to generate the results.

Results

There was a substantially higher proportion of females (57.8%) among cases of COVID-19 during the period of analysis for South Korea. However, male deaths were slightly more frequent, at 53.2% of total COVID-19 deaths recorded (Table 1). The age distribution of

Table 1
Cumulative reported COVID-19 cases and deaths by age and sex (up to June 12, 2020)[a].

Age group (in years)	Cumulative reported deaths			Cumulative confirmed cases		
	Male	Female	Total	Male	Female	Total
0–29	0 (0.0%)	0 (0.0%)	0 (0.0%)	2006 (39.6%)	2076 (29.9%)	4082 (34.0%)
30–49	4 (2.7%)	1 (0.8%)	5 (1.8%)	1182 (23.4%)	1746 (25.2%)	2928 (24.4%)
50–59	10 (6.8%)	5 (3.9%)	15 (5.4%)	731 (14.4%)	1423 (20.5%)	2154 (17.9%)
60–69	30 (20.4%)	9 (7.0%)	39 (14.1%)	634 (12.5%)	896 (12.9%)	1530 (12.7%)
70–79	48 (32.7%)	33 (25.6%)	81 (29.3%)	341 (6.7%)	448 (6.5%)	789 (6.6%)
80+	55 (37.4%)	81 (62.8%)	136 (49.3%)	167 (3.3%)	353 (5.1%)	520 (4.3%)
All ages	147	129	276	5061	6942	12003

[a] Note that in the public KCDC data which was not stratified by both age and sex there were 40 deaths in those aged 60–69 years recorded on June 12, 2020, however for consistency we used the age and sex specific data from the KCDC website.

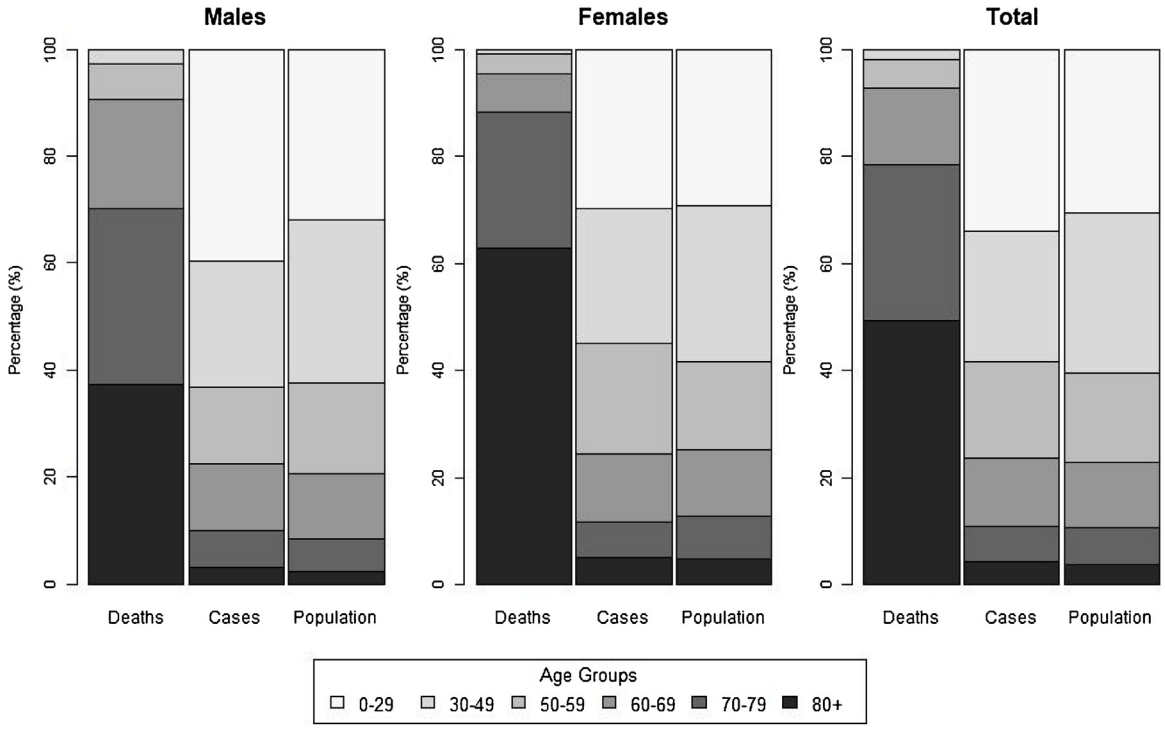

Figure 1. Percentages of COVID-19 deaths, cases, and overall population by age and sex (up to June 12, 2020). Shaded areas indicate the age groupings used. Population estimates for January 2020 obtained from public data (Korean Statistical Information Service (KOSIS), 2020).

cases was (approximately) similar to population estimates for South Korea (Figure 1), but with some differences, such as a lower proportion of total cases aged 30–49 years (24.4% vs 29.8% of the population). When disaggregated by sex, we also noted an increased proportion of cases in males aged over 80 years (3.3%) compared with the population (2.4%). Deaths recorded for COVID-19 increased substantially with age, with 49.3% of total deaths occurring in those aged over 80 years. The number of deaths increased at an earlier age in males than in females, with 88.4% of deaths in females occurring in those aged 70 years and above, compared with 70.1% in males (Figure 1). There were no COVID-19 deaths recorded in those aged under 30 years in South Korea during the period of analysis.

The crude and delay-adjusted CFRs were very similar at the end of the analysis (Table 2). This was because enough time had elapsed from the peak in cases such that most cases were resolved by the endpoint of the analysis, either by recovery or death. The estimated CFRs increased substantially from age 60 years in males and from 70 years in females. We found substantial and consistent differences in sex-specific CFRs within age groups, with estimates in younger males several times higher than females, but based on small numbers of deaths. In persons of older age, the delay-adjusted CFR was approximately 90% higher in males aged 70–79 years (15.01% in males compared with 7.76% in females) and 45% higher in males aged over 80 years (34.20% in males compared with 23.48% in females). The overall delay-adjusted CFR was 2.39%, and when disaggregated by sex was 3.05% for males and 1.92% for females.

The delay-adjusted CFR was highly unstable in the initial period (Figure 2), increasing to very high levels shortly after the first death was reported on February 19, 2020 before declining rapidly. This early and rapid rise occurred because the number of deaths reported in late February increased at approximately the same time as cases started to increase (Appendix 1, Figures A2–A5) resulting in a period where the denominator—the number of cases predicted to have a

Table 2
Crude and delay-adjusted (symptom onset to death) case fatality rates by age and sex (up to June 12, 2020).

Age groups (in years)	Male (95% confidence intervals)		Female (95% confidence intervals)		Total (95% confidence intervals)	
	Crude	Delay-adjusted	Crude	Delay-adjusted	Crude	Delay adjusted
0–29	0.00% (0.00%, 0.18%)	0.00% (0.00%, 0.19%)	0.00% (0.00%, 0.18%)	0.00% (0.00%, 0.18%)	0.00% (0.00%, 0.09%)	0.00% (0.00%, 0.09%)
30–49	0.34% (0.11%, 0.80%)	0.36% (0.12%, 0.85%)	0.06% (0.00%, 0.27%)	0.06% (0.00%, 0.27%)	0.17% (0.07%, 0.37%)	0.18% (0.07%, 0.39%)
50–59	1.37% (0.71%, 2.41%)	1.44% (0.75%, 2.55%)	0.35% (0.13%, 0.77%)	0.37% (0.14%, 0.80%)	0.70% (0.41%, 1.12%)	0.73% (0.43%, 1.17%)
60–69	4.73% (3.28%, 6.59%)	5.07% (3.52%, 7.07%)	1.00% (0.50%, 1.83%)	1.07% (0.53%, 1.95%)	2.55% (1.85%, 3.43%)	2.73% (1.98%, 3.67%)
70–79	14.08% (10.69%, 8.07%)	15.01% (11.42%, 9.24%)	7.37% (5.22%, 10.06%)	7.76% (5.50%, 10.59%)	10.27% (8.29%, 12.53%)	10.88% (8.79%, 13.27%)
80+	32.93% (26.15%, 0.31%)	34.20% (27.20%, 1.76%)	22.95% (18.79%, 7.54%)	23.48% (19.24%, 28.16%)	26.15% (22.52%, 0.06%)	26.90% (23.18%, 0.89%)
All ages[a]	2.90% (2.47%, 3.39%)	3.05% (2.59%, 3.56%)	1.86% (1.56%, 2.20%)	1.92% (1.61%, 2.27%)	2.30% (2.05%, 2.58%)	2.39% (2.13%, 2.68%)

[a] The index date used for all ages was the January 29, 2020, while all other estimates used the index date of the March 10, 2020.

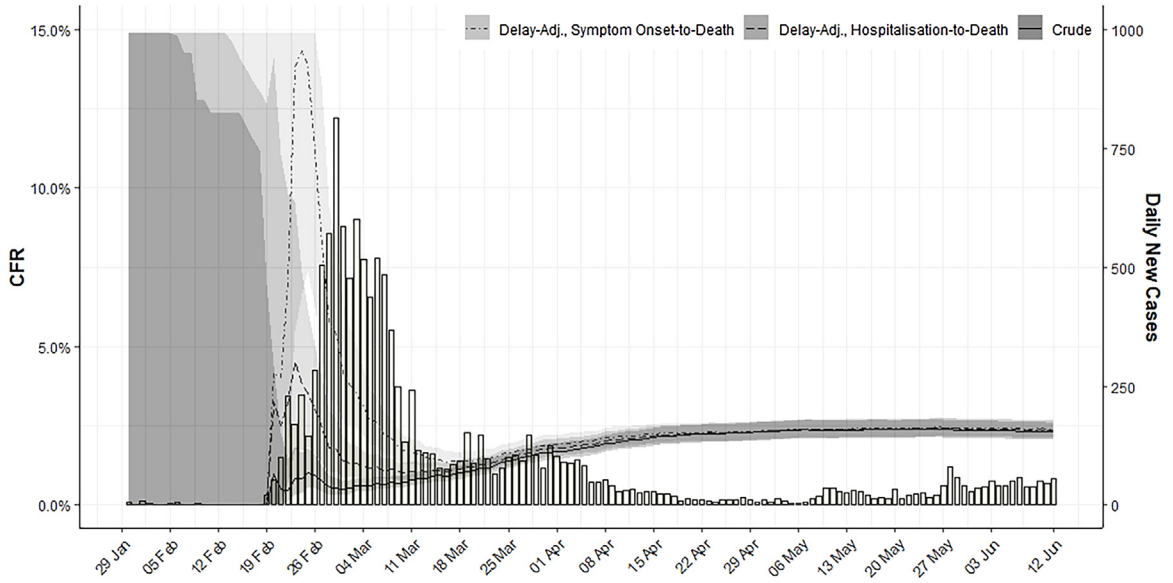

Figure 2. Crude and delay-adjusted case fatality rates for all ages and both sexes combined (up to June 12, 2020). Shaded areas indicate the 95% confidence intervals for each case -fatality rate estimated. Note that the figure is capped at 15%, but that the confidence intervals extend beyond this in the initial period (not shown). The index date for these estimates was the January 29, 2020.

known outcome (survived or died)—was relatively low. The delay-adjusted CFR then declined as the number of daily cases increased rapidly and adequate time had elapsed for more of the early cases to have a known outcome predicted and form part of the denominator. Both delay-adjusted CFRs declined to a relatively stable level from approximately mid-March before starting to converge with the crude CFR and gradually increasing, with all methods settling on a similar final value from mid-April.

The crude CFR followed a similar pattern (Figure 2) but the initial increase was much less pronounced as all cases that had occurred were included in the denominator rather than only those with, and the proportion predicted to have, a known outcome at a given time point. However, there were changes in the crude CFR as it increased from early March as the number of new daily cases declined and deaths in earlier cases continued. From early March (when data became available), CFRs stratified into those aged above and below 70 years (Appendix 1, Figure A6) and by sex (Appendix 1, Figure A7) also started at a very high level and declined rapidly. In these analyses, the CFR adjusted for the delay from symptom onset to death converged earlier on a value closer to the CFR at the end of the period of analysis, than either the CFR adjusted for the delay from hospitalization to death or the crude CFR.

In scenario analysis, based on the alternative approach to adjust for delay, outlined by Garske et al. (2009), the results (not shown) were very similar to those generated using our primary approach based on Nishiura et al. (2009). Minor differences were observed during the early part of the series. For example, at its peak, our main result estimated an approximate 14.2% delay-adjusted CFR on February 24, 2020, while the alternative method estimated approximately 15.1%. This difference was due to a larger denominator in our primary approach, which considered both estimated and actual cases with known outcomes (Nishiura et al., 2009), whereas the alternative method (Garske et al., 2009), considered only cases predicted to have known outcomes according to the assumed delay distribution.

Discussion

We found that both crude and delay-adjusted CFRs for South Korea increased rapidly in older age, with males at a substantially higher risk of death in all age strata where deaths were reported. This highlights the importance of presenting age- and sex-specific CFRs when assessing the risk of mortality from COVID-19, rather than reporting the overall CFR, which if given without appropriate context may result in a misleading assessment of the risk of mortality. We found that both the estimated delay-adjusted and crude CFRs evolved substantially throughout the epidemic in South Korea. Similar changes over time were also observed for the delay-adjusted CFRs when we applied an alternative methodological approach to estimating the delay-adjusted CFRs (Garske et al., 2009). Our results highlight the need for caution when interpreting CFRs calculated at a given point in time (particularly earlier in the epidemic), even when attempts have been made to adjust for the delay between diagnosis and death. The substantial variation in the delay-adjusted CFRs by time until late into the epidemic, and the failure to predict (earlier in the epidemic) a delay-adjusted CFR similar to the rate found at the end of the analysis period, may relate to the evolving nature of the delay between diagnosis of cases and reporting of COVID-19 deaths. The sensitivity of the methods we applied to the delay to death estimate has been noted previously (Lee and Lim, 2019).

While we used South Korean data for the delay adjustment distributions, these were by necessity based on imperfect data on the delay from symptom onset to death (or hospitalization to death) rather than the data on the specific delay between reporting/diagnosis of a case and reporting of death. The median delay from symptom onset to death in Europe and the UK has been estimated at 11 days (European Centre for Disease Prevention and Control, 2020), which is similar to the 10-day median delay used in our primary analysis (Korea Centers for Disease Control and Prevention, 2020b). The ECDC weekly surveillance report provides estimates of delays for European countries; however, while delay from symptom onset and/or hospitalization to death is available for many countries, delays from diagnosis to death are rarely reported (European Centre for Disease Prevention and Control, 2020). While these proxies for delay to death have been used in many studies to date (e.g. Shim et al., 2020), caution is needed as these delays may differ from the delay from diagnosis of a case to reporting of death.

The delay estimates used in our and other studies have also typically been calculated at a fixed point in time. However, it is likely that the delay varies substantially throughout an epidemic. Firstly, there are likely to be changes in the time it takes for cases and deaths from COVID-19 to be reported, due to changes in surveillance and reporting practices during a rapidly evolving health crisis. For example, there may be changes in the time between symptom onset and testing results being reported, and in the time between a death and the recording of the death. Secondly, there are likely to be changes in the actual time from onset of symptoms to death—for example, due to changes in the availability of healthcare resources and in treatment practices for cases as the epidemic continues. In addition, the demographic distribution of cases may evolve throughout the epidemic, and changes in factors such as the ages of cases may impact on the delay. For example, the South Korean epidemic moved from an initial specific population cluster to cases more widely distributed in the community. Finally, by virtue of the fact that they are reported early in the epidemic, early estimates of the time between diagnosis of a case and reporting of death will not include those cases that may take many weeks or months to die as a result of COVID-19 infection.

The relatively low overall (all ages) CFR estimated for South Korea (2.39%) compared with estimates from some other settings may partly be explained by differences in population demographics between countries (Dowd et al., 2020; Dudel et al., 2020). The proportion of the South Korean population aged over 80 years (3.7%) (Korean Statistical Information Service (KOSIS), 2020)—the age group with the highest CFR—is relatively low compared with other high-income settings. For example, many European countries have substantially higher proportions of their population aged over 80 years (2015 estimates: Italy = 6.5%, Spain = 5.9%, France = 5.8%) (Eurostat, 2016). This may partly explain, for example, the higher all-age crude CFR in Italy of 13.9% reported on June 16, 2020 (Epicentro, 2020). However, although population age structure is clearly important, even when comparing within the same age groups, there were substantial differences in CFRs between countries. For example, in Italy those aged 60–69 years had a crude CFR of 10.6% (Epicentro, 2020), substantially higher than the CFR of 2.73% we estimated for the same age group in South Korea. In Italy, the crude CFR of approximately 30% for persons aged over 70 years (Epicentro, 2020) was closer to estimates for those aged over 80 in South Korea. These large differences in age-specific CFR results are likely to reflect differences in the comprehensiveness of testing, with many milder cases potentially missed in some settings.

Alongside population demographics, differences in case demographics among settings may also help explain differences in CFRs (Sudharsanan et al., 2020). For example, a relatively higher proportion of the recorded total cases of COVID-19 in South Korea was in younger adults compared with other countries, such as China and some other high-income countries (Natale et al., 2020). However, the extent to which this reflects differences in the true numbers of infections by age, or differences in testing practices between settings, is difficult to ascertain. Healthcare system differences and accessibility to these services may also help explain differences between settings. In South Korea, the healthcare system has generally not been overwhelmed by COVID-19 cases and there is universal national health insurance and patients are not charged the cost of diagnosis and treatment for COVID-19 (Korean Ministry of Health and Welfare, 2020).

The higher CFR estimated for males in South Korea was in line with other countries, such as Italy, which found rates to be approximately 75–100% higher in males than in females for those aged over 70 years, and larger differences in younger age groups (Epicentro, 2020). There are several potential explanations for these sex differences. One important difference between the sexes in South Korea is the rate of smoking, with the prevalence of smoking in men (39.7% in 2016) approximately 10 times that of women (3.3%) (Chang et al., 2019). However, the impact of smoking on risk of severe COVID-19 remains uncertain at this time, with a large UK study not finding it to be a risk factor after adjusting for other factors (Williamson et al., 2020). Due to the large differences in CFR by sex, the relatively high proportion of female cases in South Korea may also have contributed to a relatively lower overall CFR in South Korea, when compared with settings with more equal distributions of cases by sex.

While case ascertainment in South Korean data is likely to be more complete than in many settings, it does have limitations. A recent small seroprevalence study in Daegu has provided some evidence to support substantial numbers of undiagnosed cases in South Korea (Song et al., 2020). However, the successful control of the epidemic during our period of analysis in South Korea suggests a relatively high degree of case capture. One complication with the South Korean data we used is that it includes a proportion of, but not all asymptomatic cases, which means it does not represent purely an estimate of symptomatic CFR but also does not reflect a CFR for all infections. Furthermore, the aggregated public data from the KCDC did not provide daily data by age and sex over the entire period, although this limitation did not impact on our estimates of CFR at the end of the period of analysis because the cumulative numbers of cases and deaths were still available. However, there appear to have been occasional delays between the reporting of deaths and their classification into the age- and sex-specific data used in our study.

Finally, although we found substantial and important differences by age and sex, further investigation is needed to better understand the independent predictors of mortality risk for COVID-19. A number of pre-existing conditions are thought to play an important role in mediating the severity of COVID-19 infection, such as hypertension, diabetes, cardiovascular disease, and body mass index (Pigoga et al., 2020). The extent to which sex and age may be proxies for increased rates of other risk conditions requires further study. While there were no COVID-19 deaths recorded in those aged under 30 years in South Korea during the period of analysis, deaths in this age group have occurred in other settings.

This study presents crude and delay-adjusted age- and sex-specific CFRs using data from South Korea, which is one of the most completely ascertained epidemics of COVID-19. The variation in the crude and delay-adjusted CFRs throughout the epidemic (to date) highlight the need for caution when interpreting these estimates, particularly earlier in the epidemic.

Conflicts of interest

All authors declare that they have no known conflicts of interest.

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Ethical approval

Ethical approval was provided by the UNSW Human Research Advisory Panel Executive (HC200222).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.09.1478.

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