

## Letter To Editor

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## Case fatality rate of coronavirus disease 2019 (COVID–19) in Iran—a term of caution

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Coronavirus disease 2019 (COVID-19) has spread to 72 countries by the time of writing this report on 4th March 2020[1]. On 20th February 2020, the first two confirmed deaths from COVID-19 were reported in Iran. Till 4<sup>th</sup> March 2020, 2 922 confirmed and 92 death cases have also been reported till 4th March 2020 in Iran (Figure 1)[1].

A key question that remains unanswered or controversial among the public, media, and researchers is the exact COVID-19 case fatality rate (CFR) in Iran. Why does the CFR in Iran appear to be higher compared to the rest of the world until now? Or why the fatality rate is high at the beginning of the epidemic in Iran?

For an epidemic of an emerging disease such as COVID-19, CFR is one of the most important epidemiological values. Little knowledge regarding various methods to estimate the CFR and their limitations can lead to misleading and misinterpretations and eventually may lead the decision-makers to make the wrong decisions.

In general, the fatality rate is calculated as follows[2]:

Case fatality (%)=(No. of deaths of individuals during a specific period of time after disease onset or diagnosis)/(No. of individuals with the specified disease)×100

At the beginning of the COVID-19 epidemic in Iran, it is tempting to calculate the CFR by the above formula. However, a simple statistical analysis of the mortality rate obtained from these reports would be misleading if, at the time of analysis, the outcome of a negligible proportion of patients is unknown (detection bias). Generally, this bias can happen as a result of a systematic error during screening, evaluation, diagnosis and outcome confirmation[3].

This means that COVID-19 patients with mild symptom or asymptomatic cases are not diagnosed. The current situation is like an iceberg which its tip is only visible and just the clinical symptoms are apparent. But infections without clinical symptoms are also important,

particularly in the network of disease transmission[2]. Therefore, the simple calculation at the onset of the epidemic does not represent the true CFR and might be overestimated[4].

Time interval between detection and death/recovery and the degree of underreporting will vary over time as well as between cities and countries. It is currently impossible to estimate precisely the CFR in Iran. Figure 2 illustrates this uncertainty.

At the beginning, the CFR may also be overestimated. For instance, in a study using the database of Jin Yin-tan Hospital and Tongji Hospital in Wuhan, they conducted a retrospective multi-center study of 68 death cases (68/150, 45%) with laboratory-confirmed infection of COVID-19[5]. In the other studies by Huang *et al.* and Chen *et al.* in Wuhan, CFR was estimated to be 15% up to 2nd February and 11% up to 20th February, respectively[6,7]. In a report of 72 314 cases from the Chinese Center for Disease Control and Prevention updated on 11th February, the overall CFR was reported to be 2.3%[8]. Variations in mortality in the current epidemic in China supports our analysis and inference.

The comparison of CFR between different countries and regions is questionable[4] because the number of cases screened by the surveillance systems can affect the denominator of the fatality fraction (see the above equation). In an area where the active

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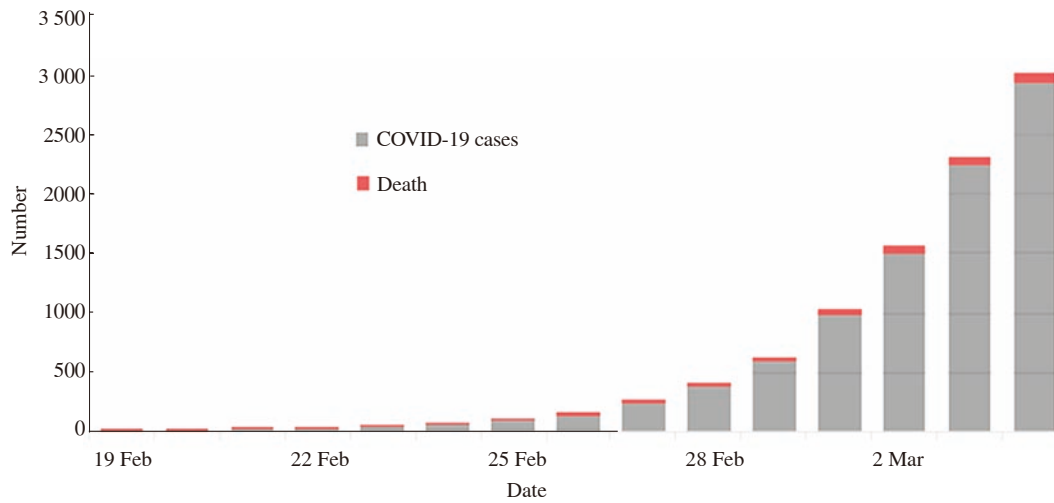
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Date	19 Feb	20 Feb	21 Feb	22 Feb	23 Feb	24 Feb	25 Feb	26 Feb	27 Feb	28 Feb	29 Feb	1 Mar	2 Mar	3 Mar	4 Mar
COVID-19 cases	2	2	4	5	8	12	15	22	26	34	43	54	66	77	92
Death2	2	5	18	28	43	61	95	141	245	388	593	978	1 501	2 236	2 922

Figure 1. Frequency distribution of confirmed cases and deaths of COVID-19 in Iran on 4th March 2020.

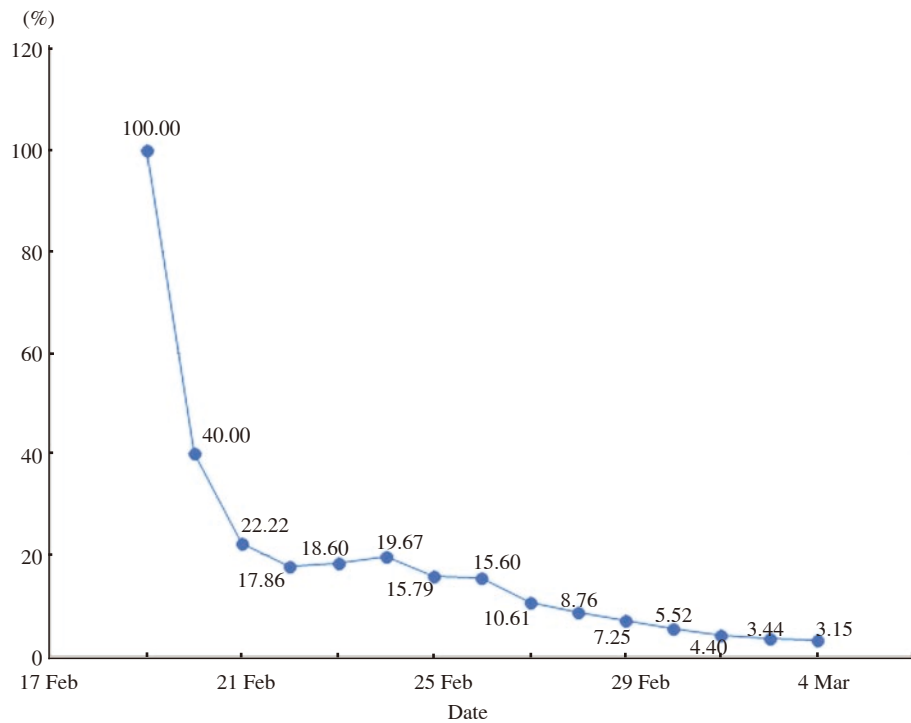


Figure 2. Frequency distribution of CFR of COVID-19 in Iran on 4th March 2020.

surveillance system with mass screening could be performed, the CFR could be lower. But due to economic, cultural and other factors, it is impossible to implement an active surveillance system in some areas and resultantly CFR could be overestimated.

The sensitivity of diagnostic tests may vary along with the development of the disease[3,9]. Depending on the stage of the disease and the disease course, different diagnostic test should be performed. In addition, considering the heterogeneous population such as age, underlying disease, etc. in different countries and

regions, it is recommended to calculate and interpret CFR for various subgroups. As the study of China with 72 314 cases, the overall fatality rate was reported to be 2.3%, 14.8% in patients aged 80 years, 8.0% in patients aged 70-79 years and 49.0% of critical cases[8]. Accurate estimate and analysis of the trends in the proportion of deaths can be used to evaluate the effectiveness of new treatments. In conclusion, number of undiagnosed mild or asymptomatic cases, type of surveillance system, the sensitivity of diagnostic tests and population heterogeneity can affect the fatality

rate. Therefore, the interpretation of the fatality rate at the beginning of an epidemic should be cautious, and the estimates will be close to actual at the end of the epidemic.

Eventually, it is highly recommended to use various methods and compare them with the current methods. For example, prediction of the fatality rate using the modified Kaplan-Meier estimator enables us to consider censored data and thus be able to detect changes more rapidly at the beginning of the epidemic.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

### Authors' contributions

VR, and MR conceived and designed the study. VR, and MR were responsible for literature search and screening. MR were responsible for data collection and analyses. VR, MR, contributed to data interpretation. VR and MR drafted the manuscript and HSH, critically revised the manuscript.

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