Can judgments according to case fatality rate be correct all the time during epidemics? Estimated cases based on CFR in different scenarios and some lessons from early case fatality rate of coronavirus disease 2019 in Iran

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Abstract

Background: The new Coronavirus disease (COVID-19) was first identified in China in 2019. Case fatality rate (CFR) indicator of the disease is one of the most important indices noticed by experts, policymakers, and managers, based on which daily evaluations and many judgments are made. CFR can change during epidemics. This study aimed to estimate the actual number of COVID-19 cases in Iran and to calculate the early CFR for the disease based on official statistics.

Methods: This was a descriptive study whose data were obtained from the website of the Ministry of Health and Medical Education of Iran from February 20, 2020 until March 26, 2020. CFR has been obtained by dividing the total number of deaths by the total number of confirmed cases at one point in time. In this study, the actual number of COVID-19 cases in Iran was estimated based on the mortality model in 4 scenarios. Excel 2013 software was used to analyze the data.

Results: According to the findings of this study, In Iran, until March 26, 2020, a total of 27 017 people have been infected by COVID-19 and 2077 died of it. However, CFR indicator had a descending trend in Iran: 100%, 18.6%, 8.8%, 3.3%, 6.9%, and 7.7% on days 1, 5, 10, 20, 30, and 35, respectively. The actual number of COVID-19 cases in Iran was estimated to be 4 789 454, 2 873 673, 1 436 836, and 718418 as of March 26, 2020 according to the 4 scenarios, respectively.

Conclusion: In emerging epidemics, CFR indicator must not be used as a basis to judge the performance of a health system unless that epidemic condition has been clarified. Moreover, it is suggested that in the outbreak of an epidemic, specifically emerging diseases, CFR must not be the base of judgment. Making judgments, specifically in the outbreak of emerging epidemics, based on fatality rate can lead to information bias. It is also possible to estimate the total number of patients based on the CFR in circumstances where little information is available on the disease.

Keywords: Coronavirus, COVID-19, Case fatality rates, Pandemic, Mortality estimated model, Iran

Introduction

Coronaviruses are a large family of viruses, and some of them cause diseases in humans and some others in animals

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↑*What is "already known" in this topic:*
The present study is the first study to investigate the case fatality rate (CFR) in Iranian Covid-19, and estimated case of this disease based on CFR in different scenarios.

→*What this article adds:*
The present study investigate trend of CFR based on reported Covid-19 in the Iran, and we notice that in emerging epidemics, CFR indicator must not be used as a basis to judge a health system's performance until that epidemics condition has not been clarified. Also in this study, the actual number of COVID-19 cases in Iran was estimated based on the mortality model.

such as bats and camels. Human coronaviruses typically cause mild diseases. Sometimes, animal coronaviruses evolve and spread among humans and cause severe diseases, such as severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 (1-3). A new species of this virus is 2019-Novel Coronavirus [severe acute respiratory syndrome co rona-virus (SARS-CoV)-2], COVID-19, which had not been previously identified in humans. This virus was first identified in city of Wuhan in China in December 2019. This virus had a more widespread outbreak in China and positive cases of this disease were reported in more than 160 countries until March 26, 2020 (1, 4). According to the published world statistics, the number of identified people infected with coronavirus was 460 611 until March 26, 2020, of whom 113 798 recovered and 20 842 died. The reported fatality rate of this disease has been 2.4% to date. According to the existing evidences, the emergence of this disease is mild in almost 96% of people and is serious or critical in 4% (5).

In Iran, the first positive case of COVID-19 was confirmed in February 20, 2020 in city of Qom and until March 26, 2020, the total number of cases in the country reached 27 017. Of the total number of patients, 9625 recovered and 2077 died (6). According to global statistics, to date, Iran has reported the most positive cases of coronavirus after China, Italy, USA, Spain, and Germany (5).

One of the most important indices noticed by health care experts, policymakers, and managers in epidemics, specifically in emerging epidemics, is CFR indicator, which is obtained by dividing the total number of deaths by the total number of confirmed cases at one point in time. In most cases, this indicator is utilized for specific epidemics of acute diseases such as cholera during which all patients are under treatment in a specific period of time and this makes it possible to calculate the death toll caused by a disease. The CFR indicates the fatality potential of a disease and it just includes the proportion of death toll to the number of patients. This indicator can be used for the following purposes: to describe fatality trend and its general changes; (1) to make decisions for health care priorities, resource allocation, planning intervention programs, and evaluation; and (2) to refine plans to improve public health; however, CFR can terrify a society in case of emerging epidemics when it is reported high (7, 8). The exact value of CFR in the early stages of the epidemic is unknown and its precise estimation is impossible. At the beginning of epidemics, the number of actual cases exposed is largely underestimated (9). Therefore, current estimates of CFR for COVID-19 should also be interpreted with caution as the disease is currently unknown. In Iran and in many other countries, some interpretations were made based on CFR during or in the middle of COVID-19 outbreak. These interpretations were sometimes published on social news networks and caused fear among people and put pressure on countries' health system. In Iran, given the fact that in this outbreak, CFR was high, there were different interpretations on the fatality rate of this disease, based on which different judgments were made concerning the health system. This study

aimed to estimate the actual number of COVID-19 cases in Iran and to calculate the early CFR (not the actual CFR value) based on published official statistics. This study also aimed to answer the question of whether epidemics are best judged by the CFR indicator at each stage.

Methods
This was a descriptive study whose required data were obtained from the website of the Ministry of Health and Medical Education of Iran and that of Worldmeter from February 20, 2020 until March 26, 2020 (6, 5). Data were published daily. CFR was obtained by dividing the total number of deaths by the total number of confirmed cases at one point in time (8) (Formula 1).

Equation (1):
Case Fatality Rate= $\frac{Total\ confirmed\ death\ from\ COVID-19}{Total\ confirmed\ cases\ of\ COVID-19}$

In this study, the actual number of COVID-19 cases in Iran was estimated based on the mortality model, details of which are provided in Tomas Pueyo's article (10). This estimate was based on the following assumptions:
1. In 4 scenarios, CFR was considered to be 0.3%, 0.5%, 1%, and 2%.
2. The mean interval between the person being infected with the virus and the person's death was 17.3 days on average.
3. The average doubling time of infected cases was 6.2 days.

For example, under the third scenario, 1 death in one day means almost 692 actual cases in that day.

Given that the number of deaths is considered to be the peak of the disease, which is not usually underestimated, we think that it is better to calculate CFR based on different scenarios of best estimates of asymptomatic cases not referring to hospitals. Thus, based on the number of deaths, we estimated the total number of patients in several scenarios. Excel 2013 was used to analyze the data.

Results
As demonstrated in Table 1, until March 26, 2020, the total number of the identified infected patients was 27 017 in Iran, of whom 9625 recovered and 2077 died. This table shows the number of the identified cases since the outbreak and the number of perished people on different days. The indicator of CFR has had a descending trend such that the amount of this indicator on day 1, 5, 10, 20, 30, and 35 was 100%, 18.6%, 8.8%, 3.3%, 6.9% and 7.7%, respectively.

Based on the first, second, third, and fourth scenarios, the actual number of COVID-19 cases on March 26, 2020 in Iran was estimated to be 4 789 454, 2 873 673, 1 436 836, and 718 418, respectively (Table 1).

Figure 1 presents the time course of the number of people infected by COVID-19 its CFR based on confirmed cases in Iran.

Figure 2 shows the time course of official and definitive number of COVID-19 cases in Iran based on 4 scenarios.

Table 1. Confirmed cases, confirmed deaths, and estimated cases by Covid-19 in Iran as of March 26, 2020

ID	Date	Confirmed Cases	Confirmed Deaths	Recovered	Case Fatality Rate: Confirmed Deaths/ Confirmed Cases (Reported cases)	Scenario 1. Estimated Cases based on first scenario (CFR=0.3%)	Scenario 2. Estimated Cases based on second scenario (CFR=0.5%)	Scenario 3. Estimated Cases based on third scenario (CFR=1%)	Scenario 4. Estimated Cases based on fourth scenario (CFR=2%)
1	Feb 20, 2020	2	2	0	100.0	4612	2767	1384	692
2	Feb 21, 2020	5	2	0	40.0	4612	2767	1384	692
3	Feb 22, 2020	18	4	0	22.2	9224	5534	2767	1384
4	Feb 23, 2020	28	5	0	17.9	11530	6918	3459	1729
5	Feb 24, 2020	43	8	0	18.6	18448	11069	5534	2767
6	Feb 25, 2020	61	12	0	19.7	27671	16603	8301	4151
7	Feb 26, 2020	95	15	25	15.8	34589	20754	10377	5188
8	Feb 27, 2020	141	22	54	15.6	50731	30439	15219	7610
9	Feb 28, 2020	245	26	64	10.6	59955	35973	17986	8993
10	Feb 29, 2020	388	34	73	8.8	78402	47041	23521	11760
11	Mar 1, 2020	593	43	123	7.3	99156	59493	29747	14873
12	Mar 2, 2020	978	54	175	5.5	124521	74713	37356	18678
13	Mar 3, 2020	1501	66	291	4.4	152193	91316	45658	22829
14	Ma 4, 2020	2339	77	144	3.3	177558	106535	53267	26634
15	Mar 05, 2020	2922	92	408	3.1	212147	127288	63644	31822
16	Mar 06, 2020	3513	107	331	3.0	246736	148042	74021	37010
17	Mar 07, 2020	4747	124	913	2.6	285938	171563	85781	42891
18	Mar 08, 2020	5823	145	1669	2.5	334362	200618	100309	50154
19	Mar 09, 2020	6566	194	2134	2.9	447354	268412	134206	67103
20	Mar 10, 2020	7161	237	2394	3.3	546510	327906	163953	81976
21	Mar 11, 2020	8042	291	2731	3.6	671031	402619	201309	100655
22	Mar 12, 2020	9000	354	2959	3.9	816306	489783	244892	122446
23	Mar 13, 2020	10075	429	3276	4.2	989252	593551	296776	148388
24	Mar 14, 2020	11364	514	3529	4.5	1185257	711154	355577	177788
25	Mar 15, 2020	12729	611	4339	4.8	1408934	845361	422680	211340
26	Mar 16, 2020	13938	724	4590	5.1	1669506	1001704	500852	250426
27	Mar 17, 2020	14991	853	4996	5.6	1966974	1180184	590092	295046
28	Mar 18, 2020	16169	988	5389	6.1	2278277	1366966	683483	341741
29	Mar 19, 2020	17361	1135	5710	6.5	2617251	1570351	785175	392587
30	Mar 20, 2020	18407	1284	5979	6.9	2960837	1776503	888251	444125
31	Mar 21, 2020	19644	1433	6745	7.2	3304423	1982654	991327	495663
32	Mar 22, 2020	20610	1556	7635	7.5	3588055	2152833	1076417	538208
33	Mar 23, 2020	21638	1685	8525	7.7	3885522	2331314	1165657	582828
34	Mar 24, 2020	23049	1812	8625	7.8	4178378	2507027	1253513	626756
35	Mar 25, 2020	24811	1934	9088	7.7	4459703	2675822	1337911	668955
36	Mar 26, 2020	27017	2077	9625	7.6	4789454	2873673	1436836	718418

Discussion

According to statistics released in Iran, as of March 26, 2020, a total of 27 017 people were infected with COVID-19, while this number was estimated to be 1 436 836 (based on CFR = 1%) in the mortality model. According to studies, cases reported in official statistics at the begin-ning of the epidemics are likely to have a severe underestimation of the total of actual cases, so estimating the actual CFR for COVID-19 is currently impossible (9, 10). The actual CFR of COVID-19 varies across different regions of the world due to differences in the quality of medical care, socioeconomic factors, immunologic factors, and readiness for the disease (9, 11).
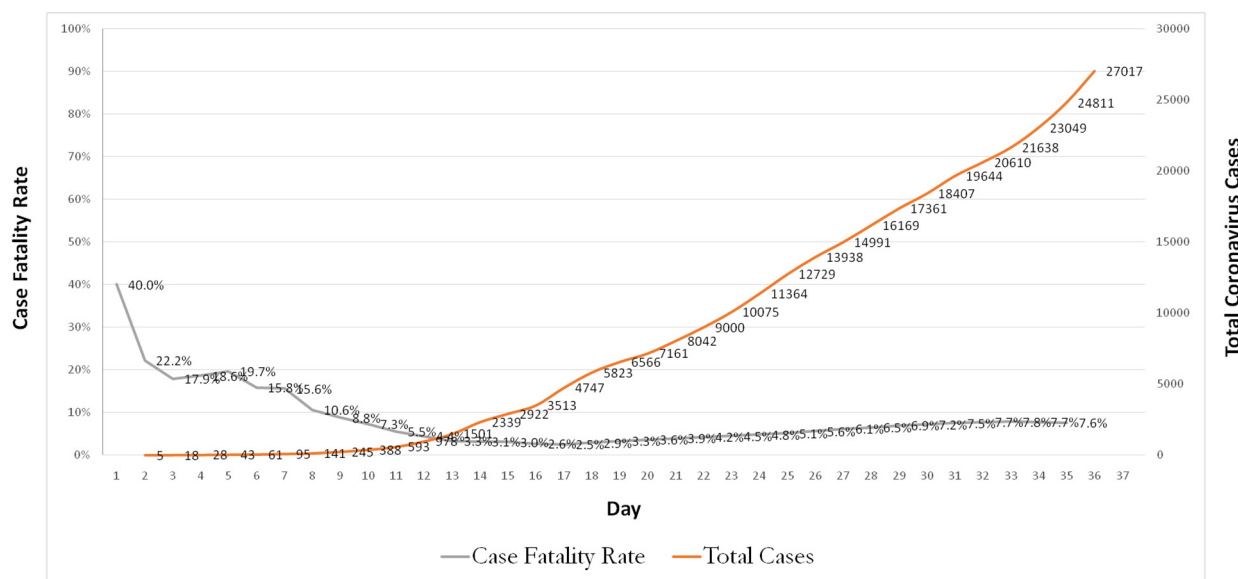

Fig. 1. Confirmed cases and early case fatality rate of COVID-19 in Iran as of March 26, 2020
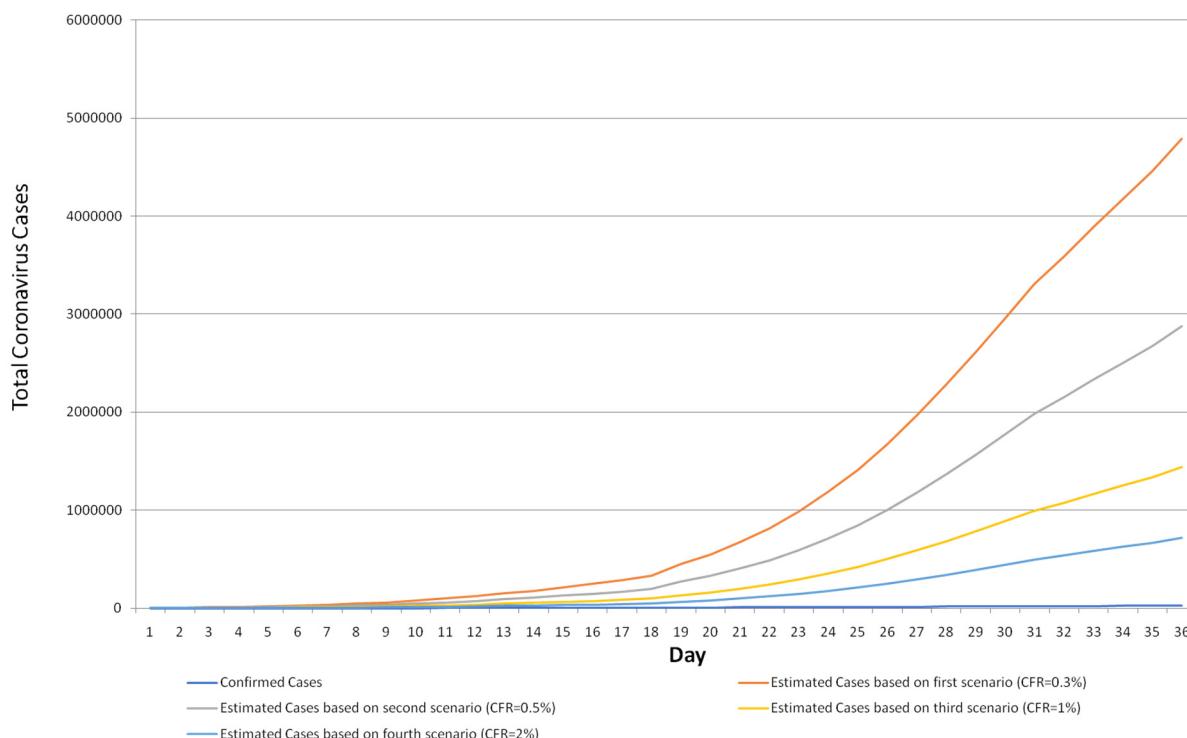
Fig. 2. Confirmed and estimated cases of COVID-19 in Iran as of March 26, 2020

According to the results of this study, by the passage of time since the identification of the first case infected by COVID-19 and increase in the number of positive cases, the indicator of CFR decreases and as the time passes, the amount of this indicator approaches its real amount. To calculate the real amount of CFR indicator, it is necessary to identify all the cases infected by Covid-19 and the total death caused by it. However, currently, only the statistics belonging to those infected patients who refer to medical centers are recorded. The evidences indicate that more than 80% of people infected by COVID-19 show mild symptoms of the disease (5) and a fraction of this population may not refer to medical centers and, consequently, their data are not recorded. The findings of some studies reveal that the CFR of some emerging diseases such as Ebola decreases over time and this can be the result of creating and increasing the required facilities and infrastructures like laboratories and hospital beds and personnel's enhanced experience (12). On the first days of diagnosis, given the identification of cases most of which led to death, much pressure were on Iran's Health System and different interpretations were put forward regarding this issue. During the outbreak of this epidemic, the main criticism Iran faced was the probability of its inability to identify this virus. One of the other interpretations was that this virus species may be different from the basic species and may be more fatal. These interpretations caused much fear among people and put a great deal of pressure on managers and experts of the Health System for decision-making.

Therefore, making decisions just based on the CFR indicator during the outbreak of epidemics may not be the right choice and may result in overestimation and could threaten the mental health of a society. Therefore, more accurate calculation of this indicator requires the passage of time; also, determining CFR needs identification of its natural history. The definition of an appropriate indicator in epidemics is of great significance. In emerging diseases, CFR indicator must be interpreted carefully and its hasty calculation and interpretation can put great pressure on health systems and may lead to making wrong and unprofessional decisions by health care policymakers.

One limitation of this study may be the calculation of the number of patients based on CFR, as it may vary across countries due to differences in hospital services and health infrastructure in each country. Nonetheless, considering that there is no definitive cure for the disease and that the life expectancy of Iranians is near that of the most developed countries, this limitation may not have much impact on the estimations in this study.

Conclusion

At present, CFR is calculated by dividing the number of known deaths by the number of confirmed cases. The results did not indicate the actual number of deaths. The exact value of CFR in this stage of the epidemic is unknown and its precise estimation is currently impossible. Current estimates of CFR for COVID-19 should also be interpreted with caution as the disease is still unknown. In addition, CFR can be used to estimate the actual number of patients in such situations. Moreover, during the outbreak of epidemics, specifically emerging diseases, judgments should not be based on CFR. It is expected to identify the most emerging epidemics during their outbreak when they are severe and could lead to death. Making judgments based on CFR, specifically in the outbreak of

emerging epidemics, can lead to information bias. In addition, it seems that CFR decreases after the identification of the first cases and while health systems' ability and awareness gradually increases.

Conflict of Interests
The authors declare that they have no competing interests.

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