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Short Communication

COVID-19 infection fatality rate: a new approach

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ABSTRACT

Infection fatality rate (IFR) in COVID 19 is a useful parameter for health-care planning during the current COVID-19 pandemic. The sensitivity of the reverse transcription polymerase chain reaction (RT-PCR) test, the rate of mortality reporting (MRR) in a country and the number of RT-PCR tests done per million population are the factors that influence the true infection fatality rate. In this article we present a ready reckoner for estimating the infection fatality rate for COVID-19, for a given RT-PCR test sensitivity and mortality reporting rate for use in middle and low-income countries with resource constraints. We further demonstrate the inverse relationship between infection fatality rate and the number of tests done.

Keywords: COVID-19, Infection fatality rate, Health care planning

INTRODUCTION

In the current context of the COVID-19 epidemic, middle and low-income countries need to Aly augment their health care facilities in order to control spread of the epidemic, take care of the large numbers of infected subjects and minimize mortality, so that their health care resources are not overwhelmed. One of the important indices that can help in this planning is the infection fatality rate (IFR). A rising IFR indicates a need to augment ICU and ventilator facilities, a progressive fall in IFR indicates that the epidemic is waning and the system is coping. An acute increase in IFR needs immediate action to prevent the system from being overwhelmed

Several online portals report daily number of new cases, daily deaths and updated cumulative numbers for both cases and deaths. With the available information in public domain, it is easy to calculate crude infection fatality rate (cumulative number of deaths expressed as a percentage of the cumulative cases with known outcome, recovery or death. However, this estimate does not give an accurate picture. Reverse transcription polymerase chain reaction (RT-PCR) tests, though specific, have significant false negatives leading to underestimation of number of infections.[1,2] This leads to artifactually high infection fatality rate. Mortality reporting is not 100% in middle and low-income countries such as India (particularly in rural areas) and may be as low as 22%.[3] This will obviously underestimate the fatality rate. A third factor, the number of PCR tests done per million population is also an important determinant of IFR. A progressive increase in the number of tests per million population, will detect more infections and so the denominator in the calculation of IFR increases and so the IFR will decline.

To summarize three major factors, influence the IFR are sensitivity of the PCR test (percentage of infected individuals identified by the test) which may vary with different kits, mortality reporting rate (MRR, proportion of deaths certified by a medical practitioner and may vary from country to country and may be lower in rural than in urban areas). The number of tests/million done in the population under consideration per week; the more the number of tests done, the greater the number of

asymptomatic subjects diagnosed with infection and the lower the IFR.

Infection fatality rate is defined as the percentage of infected subjects who die as a consequence. As deaths occur anywhere between 1-4 weeks after the infection is diagnosed, this lag time should be taken into account. The number of deaths reported on any particular day, should have occurred in the number of new patients diagnosed to have the infection approximately 1-4 weeks earlier. This fact is important to consider when calculating IFR.

METHODS

Source

Data from Worldometer coronavirus for India were collected from 20 April to 28 June 2020 and used in the calculations.[4] The number of tests done in India (in lakhs) on a weekly basis was obtained from 'Kaggle dataset'.[5]

We derived mathematical equations for applying correction factors for varying RT-PCR test sensitivity and varying mortality reporting (equations given in Appendix).

In the real-life situation, different infected subjects present at different points of time after their infection. Some are identified on routine screening of contacts, many are already past the incubation period and have developed some symptoms, some have clear-cut features and can be identified as a clinical syndrome and some present for the first time at an advanced stage of the disease with breathing difficulty and hypoxia. In order to allow for this variability in lag time between diagnosis and the terminal event, we assumed that 5 % of deaths occur in those found to be infected 1 week earlier, 10% 2 weeks earlier, 80% 3 weeks earlier and 5% 4 weeks earlier (this proportion can be altered for each country from actual figures obtained from hospitals). For deaths occurring in a particular week, for calculating the denominator for IFR we added 5% of new cases reported 1 week earlier, 10% reported 2 weeks earlier, 80% reported 3 weeks earlier and 5% reported 4 weeks earlier and this sum total was used as the denominator. Our observations are reported in this communication.

Statistical methods

Standard descriptive statistics and Pearson's correlation were performed using SPSS software. A 'p' value less than 0.05 was considered significant.

RESULTS

We have mathematically derived the factor (number) by which the reported IFR should be multiplied to arrive at the corrected IFR (CIFR) for a given RT-PCR test sensitivity and a given mortality rate reporting (mathematical equations are given in Appendix). The correction factor is presented in Table 1 and in Figure 1. Both can be used as ready reckoners for deriving CIFR. The method of using the table and graph are shown in the appropriate legends.

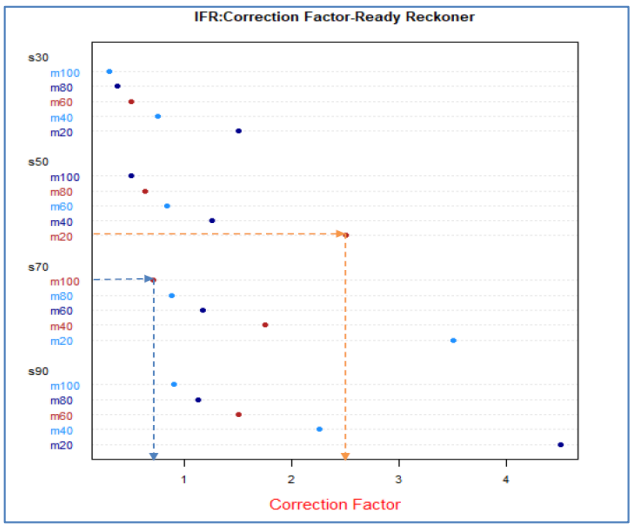

Figure 1: A graphic representation of the same information contained in the two-way (Table 1). In Figure 1, 's' denotes test sensitivity and 'm' denotes mortality reporting rate. The examples cited above are shown in the graph. The figure illustrates the relationship between s, m and the correction factor.

The number of deaths due to COVID-19 per week in India and the corresponding number of new cases 1-4 weeks earlier are tabulated (Table 2) and the calculated IFR shown in the 2nd last but two columns. The CIFR computed by this method was multiplied by the correction factor for 70% test sensitivity[3] (average reported sensitivity) and 40 % mortality reporting is shown in Table 2 (last but one column). The number of RT PCR tests (in lakhs) done per week is also presented in Table 2 in the last column.

Serial values for CIFR and the number of tests performed for the corresponding week are plotted in a line graph and presented in Figure 2. It is apparent that the serial CIFR values show a declining trend as serial values for the total tests done per week show a progressive increase.

The correlation (Pearson's correlation) between serial values for the number of RT-PCR tests done per week and serial values for CIFR per week, is shown in a scatter plot with the correlation coefficient and regression equation in Figure 3. There is a significant negative correlation ($p<0.01$) between these two parameters as anticipated.

For getting the correction factor for 70% RT-PCR test sensitivity and 40% mortality reporting, the corresponding column and row are chosen and the intersection are identified. In this example correction factor will be 1.75 (shown in bold characters).

Table 1: Infection fatality rate - correction factor.

Variables		Mortality reporting (%)				
		20	40	60	80	100
Test sensitivity (%)	30	1.500	0.750	0.500	0.375	0.3
	50	2.500	1.250	0.833	0.625	0.5
	70	3.500	1.750	1.167	0.875	0.7
	90	4.500	2.250	1.500	1.125	0.9

Table 2: Computation of weekly CIFR of COVID-19 for different lag times between case detection and death (1, 2, 3 and 4 weeks).

Week	Week no.	Total cases	0.05* cases	0.10* cases	0.80* cases	0.05* cases	Deaths	IFR (%)	CIFR (%)	Tests (in lakhs)
Apr 20-Apr 26	1	10275	514	1028	8220	514	322	9.1	15.8	2.64
Apr 27 - May 3	2	14615	731	1462	11692	731	510	9.4	16.4	4.41
May 4-May 10	3	24656	1233	2466	19725	1233	821	9.4	16.5	5.66
May 11-May 17	4	28537	1427	2854	22830	1427	813	7.2	12.6	6.29
May 18-May 24	5	42838	2142	4284	34270	2142	999	6.2	10.9	7.31
May 25-May 31	6	52073	2604	5207	41658	2604	1384	5.4	9.5	8.04
Jun 1 - Jun 7	**7**	66877	3344	6688	53502	3344	1799	5.8	10.2	9.37
Jun 8-Jun 14	8	75297	3765	7530	60238	3765	2313	5.2	9.1	10.00
Jun 15 - Jun 21	9	94127	4706	9413	75302	4706	4183	7.7	13.5	11.76
Jun22-Jun 28	10	122287	6114	12229	97830	6114	2784	4.1	7.1	14.48

Table 3: Inverse relationship between CIFR and tests.

Variables	Coefficient	SE	t-ratio	P value	Sig
Constant	17.922	1.835	9.769	<0.0001	**
Tests (in lakhs)	-0.721	0.212	-3.409	0.0092	**

**Significant at 1% level.

Example (Table 1)

If the number of deaths reported in a week is 10 and the number of proportionate new cases reported in the preceding 4 weeks is 100, the uncorrected IFR=10/100=10%.

If test sensitivity is 70% and mortality reporting is 40%, from the table, the correction factor is 1.75. Corrected IFR (CIFR)=1.75X10%=17.5%.

Example (Table 2)

Deaths during 7th week=1799 (high-lighted in the Table). The denominator for calculating IFR will be 0.05*cases at 6th week+0.10*cases at 5th week+0.80*cases at 4th week+0.05*cases at 3rd week=2604+4284+22830+1233=30951 (numbers high-lighted in the Table).

So IFR for the 7th week=1799/((30951)=0.05812≈5.81% (formula given in Appendix).

Using the correction factor (1.75) from Table 1, CIFR in this example would be 5.8X1.75=10.15%. CIFR for all the weeks in the table were computed in the same way.

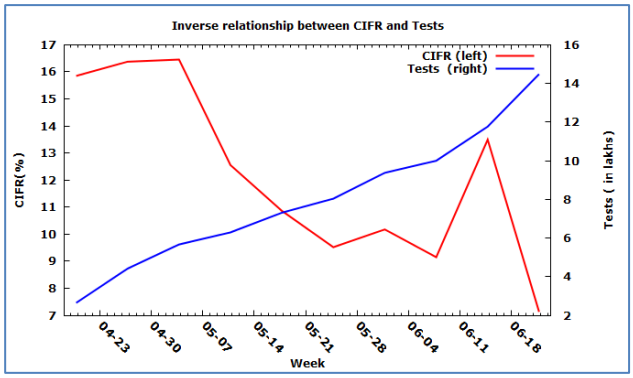

Figure 2: Trends in CIFR and tests (per week).

CIFR (left) and the number of tests in lakhs per week (right) are plotted with time in weeks on the X-axis. It is evident that in the first 6 weeks when the number of tests were progressively increasing the CIFR came down. The relative plateau in number of tests in week 7 (last week of May, arrow) was associated with a spike in the CIFR in week 8. When the testing rate accelerated from week 8 onwards, the CIFR markedly declined.

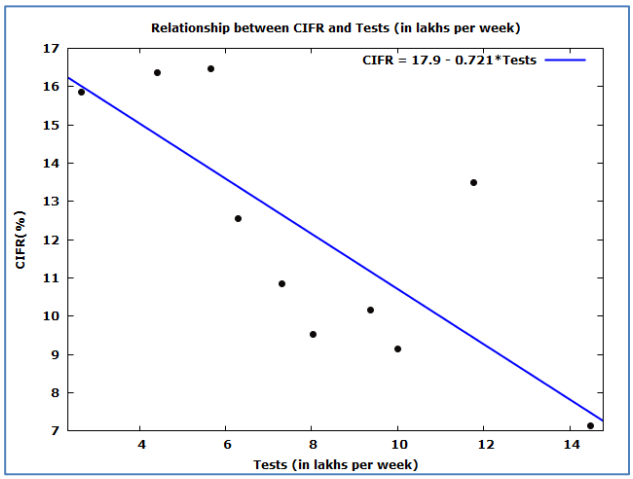

Figure 3: Shows the inverse correlation between the tests per week in lakhs (X-axis) and the CIFR %(Y-axis). There is a statistically significant inverse correlation (R= -0.77, p< 0.01). The regression equation is shown in the top right corner.

DISCUSSION

In this communication we present a simple method of estimating a corrected infection fatality rate (CIFR) which corrects for the RT-PCR test sensitivity and the mortality reporting rate. These corrections are important to get a truer estimate of the actual IFR. We have made available a ready reckoner which can be used by middle and low-income countries for deriving a corrected estimate of infection fatality rate.

We demonstrate that the CIFR in India show a gradual decrease with time, partly because of the linear increase in the number of PCR tests done per week which augments the denominator in the calculation of IFR. The falling trend of IFR is also indicative of a health care system that is responding well to the epidemic.

We have avoided using the term case fatality rate. In many viral infections a large proportion of infected subjects are asymptomatic or have mild transitory symptoms for which they do not seek medical help. Therefore a 'case of COVID-19' should be an infected person with symptoms. Case fatality rate therefore should refer to fatality in patients with COVID-19 clinical syndrome who present with symptoms and signs. Unfortunately, the number of symptomatic COVID-19 cases is not available in the public domain. Many countries report that asymptomatic infected subjects account for upto 40% of infected individuals and only about 60% were symptomatic. The first study from India during the first 100 days of the epidemic showed that 28% of the infections detected were asymptomatic and 72% symptomatic.[7] If we know the exact proportion of symptomatic subjects from public data bases, it will be easy to derive the case fatality rate from CIFR. For example, if this proportion is 60% then case fatality rate=CIFRX100 divided by 60.

A reliable estimate of IFR is important for individual countries, to anticipate and plan adequate medical facilities. The IFR may vary within each country as the epidemic advances and serial estimates are valuable. A falling IFR may indicate improved management of the sick patients (better healthcare delivery planning or better treatment). A steep rise in IFR may indicate a health care system that is getting overwhelmed by the epidemic. Further if case fatality rate can be computed it will aid in planning for the requirement of intensive care beds and ventilators.

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APPENDIX

Mathematical derivation of the formula for correction factor

We use the following notations:

C_t = Number of new cases reported by testing on day *t*

TC_t = Total number of cases in the population pool on day *t*

d_t = number of deaths recorded on day *t*

Td_t = Total number of deaths in the population pool on day *t*

p = proportion cases missed for testing COVID 19

m = mortality rate reported

s = sensitivity of the test = 1-*p*

Basic equations

The infection fatality rate (IFR) for any date, denoted by $\boldsymbol{IFR_t}$ is defined by the formula;

$$IFR_t = \frac{\text{Number of deaths on a particular day t}}{\text{Number of new cases on day (t} - \text{i)}} X\ 100$$

This formula will correctly estimate the IFR provided the numerator and denominator are correctly specified. As already stated, the number of new cases per day depends on how accurately the test identifies the cases and the denominator is influenced by the percentage of mortality reported. Hence in order to obtain a correct estimate of IFR, the above stated formula must be modified to take into account these variables.

Since the test misses a proportion p of the cases in the population, the proportion correctly reported is 1-p.

So, $$C_t = (1-p)TC_t = sTC_t$$

So, $$TC_t = \frac{C_t}{s}$$

Similarly, since mortality rate reported is *m*, actual number of deaths on any day *t* is given by

$$TD_t = \frac{d_t}{m}$$

Substituting these values in the above stated formula for IFR, we get

$$IFR_t = \left(\frac{s}{m}\right)\left(\frac{d_t}{C_{(t-i)}}\right)$$

This formula takes into account the sensitivity of the test and deaths lost due to lower mortality reporting. It can be easily seen that when 100% mortality is reported, i.e. m=1,

$$IFR_t = (s)\left(\frac{d_t}{C_{(t-i)}}\right)$$

When sensitivity is 100%, that is, when s=1,

$$IFR_t = \left(\frac{1}{m}\right)\left(\frac{d_t}{C_{(t-i)}}\right)$$

And finally, when 100% mortality (m=1) is reported and test sensitivity is also 100% (s=1) the above formula simplifies to

$$IFR_t = \frac{d_t}{C_{(t-i)}}$$

It is clear that in the above formula, the ratio, (s/m) is a correction factor. Both s and m range from 0% to 100%.

Mathematical formula for computing IFR with different lag times between detection of infection and death

The mathematical formula for computing IFR with different lag times between detection of infection and death can be written as

$$IFR_t = \frac{d_t}{(0.05)C_{(t-1)} + (0.10)C_{(t-2)} + (0.80)C_{(t-3)} + (0.05)C_{(t-4)}} X100$$

Where $\boldsymbol{d_t}$ is the number of deaths at t[th] week and $\boldsymbol{C_{(t-i)}}$ are the number of cases reported at week t-i, i = 1, 2, 3, and 4.