**Understanding the highly variable of Case Fatality Rate (CFR) over the time**

**Abstract:**

**Background/objectives**

The pandemic of COVID-19 caused 10.25 million cases with more than 505,322 deaths as of June 30th, 2020. The worldwide case-fatality rate (CFR) was 4.90% and this rate observed in different countries varies greatly over time. The objective of this study was to identify variable(s) that explains such a large variety of fatality rates over time across the countries.

**Methods**

We collected COVID-19 related data from the WHO daily COVID-19 situation reports from January 01 to June 30, 2020. Further, we collected exploratory variables for each country from United Nations or other reliable sources including population density, gross domestic product (GDP), worldwide governance indicator (WGI), Global Health Security Index (GHSI), the median age for the national population. We used beta regression models to investigate the association between the CFR of each country with reported incidence rate ratios (IRRs).

**Results**

Out of 4.90% worldwide CFR, Yemen (26.95%), France (18.15%), Belgium (15.84%), Italy (14.45%), and Hungary (14.11%) had the most CFR due to COVID-19. Distribution of worldwide weekly CFR shows that after 17 epidemiological weeks of the pandemic, the fatality rate was decreased. We found that the median age, diabetes and GHSI were the most important explanatory variables (IRR: 1.05, 95% CI: 1.02-1.07), (IRR: 0.91, 95% CI: 0.87-0.94) and (IRR: 0.98, 95% CI: 0.97-0.99) for the variation of fatality rate across the countries before peak. Surprisingly, when CFR decreasing WGI was observed only significant factor (IRR: 1.26 [95% CI: 1.07-1.50]).

**Conclusions**

The CFR can play a great role in establishing the public health threat of a given disease. Many factors associated with and vary at the various stage of CFR over time. An accurate assessment of CFR over country and time is important to inform and determine appropriate control and mitigation interventions such as social constraints and mobility restrictions. **Introduction**

In December 2019, some cases of pneumonia of unknown causes have been detected in the city of Wuhan, China and it spread rapidly in the Hubei Province of China1. In a few weeks, the number of cases was dramatically increased and subsequently spread around the world2–5. In January 2020, the World Health Organization (WHO) named the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and designated as Coronavirus Disease 2019 (COVID-19). On March 11, 2020, the WHO declared the COVID-19 outbreak a global pandemic6. According to the Worldometer, as of June 30th, 2020, there are over 10.25 million identified cases and 505,318 deaths of COVID-19 worldwide in 213 countries and territories7. Of these 213 countries, India, Iran (outside of China), and Pakistan have the largest epidemic of COVID-19 in Asia. Russia, Italy, and Spain are the countries with a major epidemic of COVID-19 in Europe8.

As the virus and its clinical course are still investigating, we have little information about the transmission and control of the disease9. Health care capacity and capability factors, including the availability of healthcare workers, resources, facilities, and preparedness, also affect outcomes of disease10. For example, some countries (e.g. Canada, South Korea, France, etc) can invest resources for contact tracing and containing the spread through quarantine and isolation in infected or suspected cases11.

The case fatality rate (CFR) is a degree of the capability of a virus to infect a host in infectious disease and is described as the ratio of deaths within the percentage of cases that result in deaths12. CFRs provide the extent and need for disease severity to prioritize public health in interventions aimed at reducing the severity of risks13. A wide-ranging body of literature that emerged since the outset of the epidemic in China has examined the rate of severe and critically severe illnesses, as well as the death rate case fatality associated with COVID-1914.

The mortality varies greatly reported by various countries over time. As of June 30, 2020, worldwide with a case-fatality rate of 4.90%. The United States of America (2.59 million cases), Brazil (1.37 million cases), Russia (641,156 cases), Spain (249,271 cases), and the United Kingdom (UK) (283,541 cases) are the top most-affected counties in terms of confirmed cases. France (29,813 deaths, 18.1%), Italy (34,744 deaths, 14.5%) and Spain (28,355 deaths, 11.4%) and UK (43,575 deaths, 15.4%) are leading the list in terms of case- fatality rates15.

Some study indicated that variation in prevalence could be due to differences in transmission, migration rates, social habits, a greater susceptibility of the population, the presence of “super-spreaders”, delayed implementation of measures intended to stop the spread of infectious disease such as social distancing and closure of public areas16–18. Very few published studies have assessed the epidemiological status of COVID-19 infection over time19–22. However, the variation of this fatality and associated risk factors of COVID-19 over time at the global level remain unanswered. Therefore, our objective was to identify variable(s) that explains such a large variation of CFRs across countries over different stages of the pandemic.

**Methods**

**COVID-19 Data**

We collected COVID-19 related data, including daily new cases, daily new deaths, total deaths, death per million, and total cases, from the WHO daily COVID-19 situation reports of 209 countries as of January 01 to June 30, 202023.

**Outcome variable**

In this study, CFR was taken as the main outcome variable and the following the formula was used to measure CFR.

**Predictor variables**

We used several predictors such as population density24, latitude of the region, median ages of the national population (in percentage)25, Global Health Security Index (GHSI)26, Gross Domestic Product (GDP)27, Diabetes patients in total population (in percentage) and worldwide governance indicators (WGI)28 in our analyses.

Population density is midyear population divided by land area in square kilometres and the population median age of the countries. The population is based on the de facto definition of population, which counts all residents regardless of legal status or citizenship--except for refugees not permanently settled in the country of asylum, who are generally considered part of the population of their country of origin24,25. GHSI is the first comprehensive assessment of global health security capabilities to be employed in 195 countries; the GHSI index scored (out of 100), if a country scored near 100 then the country has the capacity for early detection and reporting for epidemics and if a country scored lowest, the country categorised as "least prepared". According to GHSI, The United States was ranked first with an index value of 83.5 out of 100. The largest number of countries in the category "least prepared" was in Western and Central Africa26. GDP at purchaser's prices is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products. It is calculated without making deductions for depreciation of fabricated assets or depletion and degradation of natural resources. Data are in current U.S. dollars27. Governance index consists of the traditions and institutions by which authority in a country is exercised. This includes the process by which governments are selected, monitored and replaced; the capacity of the government to effectively formulate and implement sound policies; and the respect of citizens and the state for the institutions that govern economic and social interactions among them. The WGI scored -2.5 to 2.5, ranges from approximately -2.5 (weak) to 2.5 (strong) governance performance28.

**Statistical analysis**

In this study, we used COVID-19 data at two different stage of time. We gathered all data from 1st week (January) to before peak week of CFR and apply in our first model. We consider, peak week by the date when CFR is high in overall period. We find this date in 17 epidemiological weeks. After that date, we count all case, deaths and CFR newly and gathered data from 18 weeks to 26 weeks then apply to our second model. In addition, we also apply our third model with overall data (from January to July). We partition our data to check out the variation and associated factor that contribute on COVID-19 CFR. As the outcome variable (CFR) was in the interval of (0,1), we used beta regression models to investigate the association between possible explanatory variables and the CFR. Beta regression models are used in situations where the variable of interest is continuous and restricted to the interval (0, 1) and is related to other variables through a regression structure29.

For the beta regression, we reported incidence rate ratios (IRRs) adjusted for population density (per square kilometre), the median age of the total population, global health security index, gross domestic product (per million), and worldwide governance indicators, with 95% confidence intervals (CIs). We also adjusted the stage of the epidemic in each country by including a variable of interval (in days) between detection of first COVID-19 case in the country and last date of data collection, 30th June 2020. All analyses were done using the R (statistical package).

This study also conducted weekly trend comparison of different CFRs: the regional CFRs of WHO regions and EU with world CFR. WHO Member States are grouped into 6 WHO regions: African Region (AFRO), Region of the Americas (PAHO), South-East Asia Region (SEARO), European Region (EURO), Eastern Mediterranean Region (EMRO), and Western Pacific Region (WPRO), indicating the early spread of the virus in WPRO before others. The EU countries consists with Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

**Results**

The basic COVID-19 characteristics of the 206 countries are presented in Table 1. The mean (SD) total COVID-19 cases, total deaths and CFR was 13770.5 (71024.8), 999.0 (5003.2), and 3.98 (4.26), respectively, before the CFR became as peak point (before 17 weeks). After peak point, when CFR decline (after 17 weeks), the mean (SD) total COVID-19 cases, total deaths, and CFR was 36068.0 (159063.8), 1453.6 (6863.8) and 4.3 (8.4), respectively. However, though the CFR declined after 17 epidemiological weeks the mean CFR still high.

A total of 10.25 million cumulative confirmed cases and 505,322 deaths had been documented globally as of June 30th, 2020. Yemen (26.95%), France (18.15%), Belgium (15.84%), Italy (14.45%), and Hungary (14.11%) had the most CFR due to COVID-19. The distribution of CFR is presented in Fig. 1. Distribution of highest CFR by the first 20 countries on June 30, 2020, is presented in Fig. S2.

[Table 1 here]

[Figure 1 here]

Fig. 2 shows the variation of CFR in worldwide over time (weekly) . The Figure shows (with arrow sign) that after 17 epidemiological weeks, the fatality rate was gradually decreasing.

[Figure 2 here]

Figure 3 shows the variation of CFR over time by WHO region including world CFR. This data show that except EURO region, there is no unique trend before 17 weeks and after that almost all regions the CFR were gradually decreasing. A similar comparison was shown between EU countries and world CFR in Figure S2.

[Figure 3]

Table 2 shows the association of several factors with CFR using a beta regression model. Before peak, all factors except WGI had been significantly associated with CFR. However, only the WGI was significantly and positively associated with the CFR after peak (IRR 1.26, 95% CI [1.07-1.50], P=0.006). We observed that for overall analyses, population median age (1.06 [1.04-1.08], p<0.001), GDP (0.98 [0.98-0.99], P=0.039), and diabetes (0.96 [0.93-0.99], p=0.040) were significantly associated with the CFR. We also observed that for after peak, population median age), GDP, population density, latitude, diabetes and GHSI were significantly associated with the CFR. The estimated IRRs for the selected factors decreased slightly after peak for median age, except for WGI. CFR increased by 2 per cent-6 per cent due to an increase in the median age of the total population and 1 per cent- 26 per cent due to WGI.

[Table 2 here]**Discussion**

**First paragraph**

1. Start with in one sentence your main goal (main objective of the papers)

2. Key findings in two/three sentences in three analyses models

Then explain all factors, particularly, your significant factors in the following paragraph.

Refer if you get any similar or dissimilar results from previous articles

This study aimed to observe the CFR of different WHO region using recent country level data, showing that alongside this study was also work to identify variable(s) that explains such a large variety of fatality rates on different stages of pandemic over time. Regional comparisons of CFR, as important indicators of disease characteristics are vital for national and international priority setting and recognizing health system performance. However, many factors associated with these CFR and the factor vary at the various stage of pandemic. In our findings, all countries CFR increases over time at the beginning of the pandemic and it begins to decreasing when most of the developed countries conduct extensive early testing of contacts to known cases (most of the countries of PAHO and EURO regions) are largely driven by differences in fatality and not by differences in the age distribution, suggesting that those countries might be more successful at catching the mild and asymptomatic cases among the younger population groups. Our findings also showed that there is substantial variation in which factor explains the differences in CFRs. Results indicate that before peak week, median age and diabetes are the important factors that explained the large variation of CFR across the countries, and after peak week, only WGI are the only important factors that explained the large variation of CFR worldwide.

In both periods, the median age explained high variation in both stages of the pandemic. A higher IRR explained that CFR increased as the median age also increased. WHO chief Tedros Adhanom Ghebreyesus state that spikes in cases in some countries are being driven in part by younger people30. Data from China indicate that the median age is the strongest predictor of COVID-19 severity. Wu et al 31 published that in 44672 patients with confirmed COVID-19 the overall case-fatality rate was 2.3% and 7.3% for diabetes. This observation was also consistent with higher observations of several clinical comorbidities associated with aging. The Italian Society for Hypertension reported that more than a third of Italians suffer from hypertension and that about 5% of Italians had diabetes, this percentage rising to 16.5% for those who were over 65 years of age32.

Surprisingly, after peak CFR was observed significantly correlate with WGI (IRR: 1.26 [95% CI: 1.07-1.50]). The number of COVID-19 tests may be played a role in this variation. Descriptive statistics of the total number of tests (per thousand) by WGI and GHSI are given in Table S1. High governance was found to be associated with lower Covid-19 mortality rates33. Good governance is essential to long-term development outcomes. Several studies demonstrated that for short-term crises such as the Covid-19 outbreak, government effectiveness remains critical33–35. Thus, before peak WGI was opposite associated with CFR. Quick implementation of effective quarantine, lockdown and screening policies 33, as well as provision of good public health services in managing and treating Covid-19 patients, also require an effective government34. Similarly, countries with higher preparedness (GHSI) for pandemic diseases have reported higher mortality rates in recent data. The severity of the disease among those infected has overwhelmed healthcare systems and frontline healthcare providers and has exhausted resources, revealing how ill-equipped the world was to manage the pandemic37. However, outbreak settings often generate incomplete data, where both recovered and fatal cases go unreported.

The World Health Organization (WHO) welcomes the results of preliminary clinical trials from the United Kingdom that show dexamethasone, a corticosteroid, may save lives for patients with the COVD-19 crisis. In the case of ventilator patients, the treatment was found to reduce the mortality rate by about one-third, and for patients who needed oxygen, the mortality rate was reduced by about one-fifth, according to preliminary studies shared with the WHO38. Furthermore, On May 1, 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) of remdesivir for serious COVID-19 (confirmed or suspected) patients in adults and children admitted to hospital39,40. In this cohort of patient’s patients admitted to the hospital for severe COVD-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 out of 53 patients (68%)41.

**Conclusion**

In conclusion, we have found that world CFR driven significantly by median age, GDP, population density, latitude, WGI, GHSI, and diabetes. The findings of countries with low WGI showed high fatality rate in early period of pandemic, however, in recent period of the pandemic, the result showed completely opposite than before and all of the countries now overcome this situation gradually.

Reducing differences in case of fatality rates over time across the countries reveals important insights for monitoring the spread of COVID-19. An accurate assessment of these differences in the CFR over country and time is important to inform and determine appropriate control and mitigation interventions such as social constraints and mobility restrictions. In addition, a detailed and accurate treatment history can highlight the highest risk areas and instruct them to intervene more efficiently to reduce the spread of the virus worldwide.

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**Tables and figures**

**Table 1. Descriptive statistics of the characteristics at different stage of pandemic**

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| **Stage of pandemic** | **Characteristics** | | |
| **Total Cases** | **Total Deaths** | **CFR (%)** |
| **Before peak (before 17 weeks)** |  |  |  |
| Minimum | 1.0 | 0.0 | 0.0 |
| Maximum | 939053.0 | 53189.0 | 25.0 |
| Mean (SD) | 13770.5 (71024.8) | 999.0 (5003.2) | 3.98 (4.3) |
| **After peak (after 17 weeks)** |  |  |  |
| Minimum | 0.0 | 0.0 | 0.0 |
| Maximum | 1651499.0 | 72951.0 | 75.0 |
| Mean (SD) | 36068.0 (159063.8) | 1453.6 (6863.8) | 4.3 (8.4) |
|  |  |  |  |
| **Overall (1st week to 26th weels)** |  |  |  |
| Minimum | 3.0 | 0.0 | 0.0 |
| Maximum | 2590552.0 | 126140.0 | 27.0 |
| Mean (SD) | 49152.0 (214860.5) | 2418.0 (10897.0) | 3.3 (3.8) |

**Table 2. Factors associated with CFR using beta regression analysis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall\*** | | | **Before peak\*\*** | | | **After peak\*\*\*** | | |
| **Variables** | **IRR** | **95%CI** | **P-value** | **IRR** | **95%CI** | **P-value** | **IRR** | **95%CI** | **P-value** |
| Median age | 1.06 | 1.04-1.08 | <0.001 | 1.05 | 1.02-1.07 | <0.001 | 1.02 | 0.99-1.04 | 0.096 |
| GDP | 0.98 | 0.98-0.99 | 0.039 | 0.99 | 0.98-0.99 | 0.018 | 0.99 | 0.98-1.01 | 0.581 |
| Population Density | 0.99 | 0.98-1.01 | 0.373 | 1.01 | 1.01-1.02 | 0.040 | 0.99 | 0.99-1.02 | 0.063 |
| Latitude | 0.99 | 0.98-1.01 | 0.349 | 0.99 | 0.98-0.99 | 0.007 | 1.01 | 0.98-1.01 | 0.151 |
| Diabetes | 0.96 | 0.93-0.99 | 0.040 | 0.91 | 0.87-0.94 | <0.001 | 0.97 | 0.93-1.01 | 0.074 |
| GHSI | 0.99 | 0.98-1.01 | 0.072 | 0.98 | 0.97-0.99 | 0.021 | 1.01 | 0.99-1.01 | 0.224 |
| WGI | 1.01 | 0.83-1.23 | 0.897 | 0.86 | 0.70-1.05 | 0.140 | 1.26 | 1.07-1.50 | 0.006 |

*\*Overall = COVID-19 data from 1st January (1st week) to 30th June (26th week), 2020*

*\*\*Before peak = COVID-19 data from 1st week to 17th week (peak week)*

*\*\*\*After peak = COVID-19 data from 18th week (after peak week) to 26th week (present)*

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| **Fig. 1: Case fatality rates in different countries of the world for the period January 1st to June 30th 2020** |

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| **Fig. 2: Variation of death rate (CFR) over time (weekly) in world** |

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| **Fig. 3: Variation of death rate (CFR) over time (weekly) by WHO regions** |

**Supporting information**

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| **Fig. S1: Top 20 countries with highest CFR (June 30st 2020)** |

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| **Fig. S2: Variation of death rate (CFR) over time (weekly) in EU countries** |

**Table S1: Descriptive statistics of total number of tests (per thousand) by WGI & GHSI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Stage of pandemic** | **Number of Test Cases (per thousand)** | | | |
| **Low WGI** | **High WGI** | **Low GHSI** | **High GHSI** |
| **Before peak** |  |  |  |  |
| Minimum | 0.65 | 1.75 | 0.65 | 1.43 |
| Mean (SD) | 53.71 (92.00) | 59.10 (62.77) | 25.89 (56.84) | 66.34 (75.45) |
| Maximum | 363.26 | 296.05 | 222.64 | 363.26 |
| **After peak** |  |  |  |  |
| Minimum | 1.81 | 0.67 | 1.81 | 1.54 |
| Mean (SD) | 50.58 (78.28) | 44.48 (46.39) | 22.63 (43.54) | 53.65 (58.81) |
| Maximum | 259.28 | 233.75 | 156.24 | 259.28 |

*\*Low = below median value*

*\*High = above or equal to median value*