**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 across all over the countries.

**Methods**

We collected COVID-19 related data, including daily new cases, daily new deaths, total deaths, and total cases, from the WHO daily COVID-19 situation reports of 209 countries as of 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 negative beta regression models to investigate the association between the CFR of each country and other explanatory variables and reported incidence rate ratios (IRRs) adjusted with 95% confidence intervals (CIs). We 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 May 2020.

**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, in comparison with previous epidemiological week, the fatality rate was decreased. In WHO regions, the Western Pacific Region (WPRO) indicating the early spread of the virus before others. Almost all-region declines about to 15 – 20 weeks. When the EURO region started to decline their CFR rate, the world CFR also started to decline sharply. We found the median age, diabetes and GHSI the most important explanatory variable (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 week. Surprisingly, when CFR decreasing WGI was observed significantly correlate after peak week (IRR: 1.26 [95% CI: 1.07-1.50]) for COVID-19 CFR.

**Conclusions**

The CFR can play a great role in establishing the public health threat of a given disease. Many factors associated with these CFR and the factor vary at the various stage to explained CFR. In our findings, all countries CFR increases overtime 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 a fatality. 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. **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 measure of the ability of a pathogen or virus to infect or damage a host in infectious disease. 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 low published studies have assessed the epidemiological status of COVID-19 infection over time. However, the variation of this fatality and associated risk factors of COVID-19 overtime at the global level remain unanswered. In this study, we tried to figure out the reason for the high variability of CFRs and its association between various factors over different stages of the pandemic, which may help to intervene to control the disease and reduce the death. Therefore, our objective was to identify variable(s) that explains such a large variation of CFRs across countries over time.

**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, 202019.

**Outcome variable**

In this study, CFR was taken as the main outcome variable. As a definition, the formulas below were used to measure CFR in this study.

**Predictor variables**

Seven variables were included in the model as predictors: population density20, latitude of the region, median ages of the national population (in percentage)21, Global Health Security Index (GHSI)22, Gross Domestic Product (GDP)23, Diabetes patients in total population (in percentage) and worldwide governance indicators (WGI)24.

Population density is midyear population divided by land area in square kilometres and the population ages 65 and above as a percentage of the total population. 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 origin20,21. 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 Africa22. 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. dollars23. 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 performance24.

**Statistical analysis**

As the outcome variable was in the interval of (0,1), we used beta regression models to investigate the association between CFR and the possible explanatory variables of a country. The term beta regression was first introduced by Ferrari and Cribari–Neto25 . It refers to regression models in which the dependent variable is assumed to have a beta distribution. 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 structure26.

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).

**Results**

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 worldwide CFR due to COVID-19 is presented in Fig. 1. Distribution of highest CFR by the first 20 countries on June 30, 2020, is presented in Fig. S2.

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

Distribution of worldwide weekly CFR from January 1, 2020, to June 30, 2020, is presented in Fig. 3. The Figure shows (with arrow sign) that after 17 epidemiological weeks of the pandemic, in comparison with previous epidemiological week, the fatality rate was decreased.

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

Figure 3 shows the overall pandemic CFR overtime for the COVID-19 spread in the WHO region and included world CFR in the same graph for comparison. 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. This data could be skewed 15 epidemiological weeks than almost all regions declines about 15 – 20 weeks. When the EURO region started to decline their CFR rate, the world CFR also started to decline sharply. This might be due to a lack of testing in other countries. A similar comparison was shown between EU countries and world CFR in Figure S2.

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

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.

**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** |  |  |  |
| Minimum | 1.0 | 0.0 | 0.0 |
| Mean (SD) | 13770.5 (71024.8) | 999.0 (5003.2) | 3.98 (4.26) |
| Maximum | 939053.0 | 53189.0 | 25.0 |
| **After peak** |  |  |  |
| Minimum | 0.0 | 0.0 | 0.0 |
| Mean (SD) | 36068.0 (159063.8) | 1453.6 (6863.8) | 4.3 (8.4) |
| Maximum | 1651499.0 | 72951.0 | 75.0 |

The effect of selected predictors derived from the beta regression model is shown in Table 2. The results showed that a higher IRR (IRR: 1.05, 95% CI: 1.02-1.07) was observed for the factor of population median ages before peak data and the IRR is lowest in after peak (IRR: 1.02, 95% CI: 0.99-1.04). But, the association between CFR and the median age isn’t significant after peak data. Similar results found in the diabetes factor, the IRR for both before and after peak information was (IRR: 0.91, 95% CI: 0.87-0.94) and (IRR: 0.97, 95% CI: 0.93-1.01), respectively. The IRR greater than 1 for this factor indicates the CFR increased with that factor. In this study, CFR increased 2% - 6% by the increase of median age in total population, which is similar in all stages of the pandemic. A lower insignificant IRR was observed for worldwide governance indicators and had the opposite correlation before the peak (IRR: 0.86 [95% CI: 0.70-1.05]) for COVID-19 CFR. Surprisingly, when CFR decreasing WGI was observed significantly correlate after peak week (IRR: 1.26 [95% CI: 1.07-1.50]) for COVID-19 CFR. 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 & GHSI are given in Table S1. Before peak, the number of low governance country test lower than those countries that have high WGI. The mean value of test per thousand for low WGI was 53.71 where the mean value of test per thousand for high WGI was 59.10. After peak week the mean test value was much lower (44.48) for high governance countries but it was almost similar (50.58) for low governance countries.

**Table 2. Influence of factors associated with CFR using beta regression analysis**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **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)*

**Discussion**

The CFR can play a great role in establishing the public health threat of a given disease. Case fatality rates are not constant; they can vary between populations and over time because countries case totals and death tolls are constantly changing as the coronavirus outbreak evolves, their death rates are not static. Accurate estimates of the relative CFR can help determine the optimal allocation of resources for surveillance, prevention, and treatment of disease27. CFRs associated with COVID-19 vary strongly across countries and over time within countries. Although the virus spread most of the country, the rate of CFR is decreasing sharply over time.

Many factors associated with these CFR and the factor vary at the various stage to explained CFR. In our findings, all countries CFR increases overtime 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. At the beginning of the peak period, the data shows, age was a significant factor but with time it was not explained that much of variations. However, it is also plausible that the extensive testing itself in these countries prevented undetected community spread to older population groups.

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 WHO28. 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 hospital29,30. 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%)31.

CFRs are influenced by the combination of demographic and comorbidities of the population, the availability and preparedness of the healthcare system, and the differences between diagnostic, treatment, prevention, and control policies applied in different countries. Our findings show 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. Data from China indicate that the median age is the strongest predictor of COVID-19 severity. 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 people32. Wu et al 33 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 age34. A study conducted with US states reported that the risk of death is 13- to 73-fold lower in non-elderly people <65 years old than in older individuals35, which conclude similar result to our study.

Contrary to our expectations, the WGI had the opposite relationship with COVID-19 related to CFR before the peak, indicating that well-governed countries reported higher mortality rates. There were some nations like Italy and America which did not take the threat of coronavirus seriously so both countries are now the most affected in the world36. This may be the reason we get the opposite relationship. But, after peak week, data shows a positive higher IRR and explained that the percent change in the incident rate of CFR is a 26% increase for every unit increase in WGI. 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. Many low governance countries show low test rates and high governance shows a huge test rate.

**Conclusion**

The differences between countries with low and high CFRs may be driven significantly by age, WGI, GHSI, and diabetes. Reducing differences in case of fatality rates over time or between countries reveals important insights for monitoring the spread of COVID-19.The findings of countries with higher GHSI and WGI and their positive correlation with higher fatality rate matches with observed death rates in wealthier countries, however, we need a careful observation as countries are still at different stages of epidemics where countries in Africa, South America, Pacific Islands, and South Asia affected lately with 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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**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**

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| --- | --- | --- | --- | --- |
| **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*