**Understanding the highly variable mortality rate of COVID-19 over time**

**Abstract:**

**Background/objectives**

The worldwide case-fatality rate (CFR) of COVID-19 varied in different countries, regions, and continents of the world.. The objective of this study was to understand the variation of CFR or IFR of COVID-19 globally over time and to identify variable(s) that explains such a large variety of fatality rates over time.

**Methods**

We collected COVID-19 related data from the WHO daily COVID-19 situation reports from January 01 to August 10, 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**

As of August 10, 2020, the global reported CFR is 3.7% while top-five countries are: Yemen (28.55%), France (15.32%), United Kingdom (14.98), Italy (14.05%) and Belgium (13.17%). The peak of weekly cumulative CFR reached peak to 17th Epidemiological week, i.e. April 22-28, 2020 (considering January 1st 2020 as the starting date of epidemiological week). Before CFR reached to the peak, the median age of the population of the country (IRR: 0.96, 95% CI: 0.89-1.03), the prevalence of diabetes in the country (IRR: 0.91, 95% CI: 0.87-0.94) and GHSI score of the the country (IRR: 0.98, 95% CI: 0.97-0.99) were the most important explanatory variables. After CFR passed the peak, WGI (IRR: 1.26 [95% CI: 1.07-1.50]) remained the only significant variable. .

**Conclusions**

Our study indicate that during beginning of the pandemic the age and other co-morbidity of the population played a key role in the CFR of COVID-19 while post-peak period countries governance showed a difference in reporting CFR.

. **Introduction**

On March 11, 2020, the WHO declared the COVID-19 outbreak as a global pandemic1. 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 territories2. Of these 213 countries, India, Iran, and Pakistan have the largest epidemic of COVID-19 in Asia, Russia, United Kingdom, Italy, and Spain are the countries with a major affected counties in Europe3 , Brazil, Peru, Chile, Ecuador are major victim in South America, the United States of America and Mexico are primary affected countreis in North America, South Africa, Egypt, Morocco and Nigeria are top reported countries in Africa. In terms of mortality, 4

An important question is why the mortality rate due to COVID-19 varies so greatly in different countries. For example, the mortality rate of COVID-19 varies from 26% in Yemen to 0.1% in Singapore. A recent study described possible drivers behind such national level variation 5. According to the study, the COVID-19 mortality rate is negatively associated with COVID-19 test number per 100 people, government effectiveness score, and number of hospital beds 5. The study further showed a positive correlation between the proportion of population aged 65 years and above, and transport infrastructure quality score 5. Individual patient-level data showed that mortality can be explained by age, obesity, and underlying diseases, such as hypertension, diabetes, and coronary heart disease 6. However, little is known how the case-fatality rate/mortality rate has changed over time.

As the Pandemic is progressing, the countries are gaining experience and building capacity to handle the severity of COVID-19. At least two drugs (dexamethasone 7 and Remdesivir 8) had shown some degree of effectiveness in reducing deaths or hospital stay of COVID-19 patients. Testing capacity has increased in most of the countries of the world over time that is being useful in detection of asymptomatic cases. The doctors and nurses gained experience in managing severely affected COVID-19 patients. Thus, this is important to quantify whether the mortality rate/ CFR of COVID-19 has changed over time. The objective of this study was to identify the variables affecting the CFR 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 210 countries as of January 01 to August 10, 202021. In this study, COVID-19 mortality rate was defined as the number of deaths per 100 Covid-19 cases.

**Predictor variables**

We used several predictors such as population density 22, latitude of the region, median ages of the national population (in percentage)23, Global Health Security Index (GHSI)24, Gross Domestic Product (GDP)25, Diabetes patients in total population (in percentage) and worldwide governance indicators (WGI)26 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 origin22,23. 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 Africa24. 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. dollars25. 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 performance26.

**Statistical analysis**

**The peak of mortality reached peak at 17th epidemiological week (22-28 April 2020) and then started to platued. We collected the the COVID-19 data from 1st January up until August 10th, 2020. We then divided the dataset into two half one until it reach peak (until 17th Week) and another with 18th week till 10th Ausgust (XXth week.). We ran our model separately for each dataset. Finally, we also ran our model for overall dataset (January 1st – August 10th). .**

As the outcome variable (CFR) was in interval of 0 or 1, we used beta regression models to investigate the association between possible explanatory variables and the CFR 27

For the beta regression, we reported incidence rate ratios (IRRs) adjusted for population density (per square kilometre), the median age of the total population, total test per thousand, 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, 10th August 2020. All analyses were done using the R (statistical package).

This study also conducted weekly cumulative 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**

A total of 19.87 million cumulative confirmed cases and 731,706 deaths had been documented globally as of August 10th, 2020. Yemen (28.55%), France (15.32%), United Kingdom (14.98), Italy (14.05%) and Belgium (13.17%) had the most CFR due to COVID-19 (Fig. 1). The overall mean weekly CFR of COVID-19 is 2.9% and during the peak week the CFR was 3.98%. The top-20 countries for CFR up until August 10, 2020, is presented in Fig. S2.

Fig. 2 shows the variation of CFR in worldwide and WHO region overtime. 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.

In the regression model for the period before COVID-19 reached it’s peak (1-17th week), median age of the population of the country (IRR: 1.05, 95% CI: 1.02-1.07) and population density of the country (IRR, 95% CI:) were positively associated. The other factors, including GDP (IRR, 95% CI:), Latitude (IRR: YY, 95% CI:), GHSI (IRR: XX, 95% CI:) were negatively associated. After the CFR pass the peak week, only WGI showed significant impact on COVID-19 CRF.

For the entire pandemic period up until 10th August 2020, the CFR were significantly associated with median age of the population of the country (IRR: 1.06, 95% CI: 1.04-1.08) and prevenace of diabetes of the population (IRR: 0.96, 95% CI: 0.93-0.99) (Table 2).

**Discussion**

This study aimed to observe the Global CFR of COVID-19 using country level data and

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 people28. Data from China indicate that the median age is the strongest predictor of COVID-19 severity. Wu et al 29 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 age30.

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 rates5. 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 critical5,31,32. Thus, before peak WGI was opposite associated with CFR. Quick implementation of effective quarantine, lockdown and screening policies 5, as well as provision of good public health services in managing and treating Covid-19 patients, also require an effective government31. 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 pandemic33. 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 WHO34. 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 hospital35,36. 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%)37.

**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** | **Mortality (%)** |
| **Before peak (before 17 weeks)** |  |  |  |
| Minimum | 1.0 | 0.0 | 0.0 |
| Maximum | 939053.0 | 53189.0 | 25.0 |
| Mean (SD) | 13779.1 (71045.0) | 999.1 (5003.5) | 3.98 (4.25) |
| **After peak (after 17 weeks)** |  |  |  |
| Minimum | 0.0 | 0.0 | 0.0 |
| Maximum | 4105811 | 109749.0 | 50.0 |
| Mean (SD) | 82624 (391024.7) | 2552.4 (11462.7) | 3.04 (5.03) |
|  |  |  |  |
| **Overall (1st week to 32nd weeks)** |  |  |  |
| Minimum | 3.0 | 0.0 | 0.0 |
| Maximum | 5044864.0 | 162938.0 | 28.5 |
| Mean (SD) | 95062.0 (441662.2) | 3501.0 (14886.16) | 2.9 (3.3) |

**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 | 0.91 | 0.85-0.99 | 0.028 | 0.96 | 0.89-1.03 | 0.254 | 1.02 | 0.97-1.08 | 0.431 |
| GDP | 0.99 | 0.98-0.99 | <0.001 | 0.99 | 0.98-0.99 | <0.001 | 0.99 | 0.99-1.01 | 0.545 |
| Population Density | 0.99 | 0.98-1.01 | 0.868 | 1.01 | 1.01-1.02 | <0.001 | 0.99 | 0.99-1.01 | 0.859 |
| Latitude | 1.01 | 1.01-1.02 | <0.001 | 1.01 | 1.01-1.02 | <0.001 | 1.01 | 0.99-1.01 | 0.134 |
| Total tests (/1000) | 1.01 | 0.99-1.01 | 0.112 | 0.96 | 0.95-0.97 | <0.001 | 0.99 | 0.99-1.02 | 0.226 |
| Diabetes | 1.11 | 1.05-1.08 | <0.001 | 1.01 | 0.97-1.05 | 0.686 | 0.97 | 0.91-1.03 | 0.424 |
| CVD | 1.11 | 0.94-1.30 | 0.221 | 1.12 | 0.96-1.31 | 0.164 | 0.97 | 0.85-1.11 | 0.673 |
| GHSI | 1.07 | 1.05-1.08 | <0.001 | 1.01 | 0.99-1.02 | 0.106 | 1.02 | 1.01-1.03 | 0.033 |
| WGI | 1.46 | 1.16-1.81 | <0.001 | 2.40 | 1.77-3.14 | <0.001 | 1.15 | 0.86-1.55 | 0.353 |

*\*Overall = COVID-19 data from 1st January (1st week) to 10th August (32nd 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 32nd week (present)*

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| **Fig. 1: Mortality rates in different countries of the world for the period January 1st to August 10th 2020** |



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| **Fig. 2: Variation of mortality rate over time (weekly)** |

**Supporting information**

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| **Fig. S1: Top 20 countries with highest mortality rate (August 10th 2020)** |

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| **Fig. S2: Variation of mortality rate 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 | 0.28 | 0.21 | 0.28 | 0.21 |
| Mean (SD) | 12.23 (24.34) | 19.63 (23.71) | 6.99 (15.53) | 20.72 (25.44) |
| Maximum | 103.99 | 135.78 | 66.40 | 135.78 |
| **After peak** |  |  |  |  |
| Minimum | 3.84 | 0.95 | 3.84 | 3.39 |
| Mean (SD) | 83.73 (133.65) | 92.14 (110.96) | 39.35 (69.43) | 107.97 (125.84) |
| Maximum | 463.07 | 656.95 | 262.59 | 656.95 |

*\*Low = below median value*

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