**Understanding the highly variable death rate of COVID-19 across countries**

**Abstract:**

**Background/objectives**

The pandemic of COVID-19 caused 6.3 million cases with more than 377,881 deaths as of June 2nd, 2020. The death rate (no of reported death per million population) observed in different countries varies greatly. The objective of this study was to identify variable(s) explains such a large variation of death rates across 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 208 countries as of January 01 to May 31, 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), proportion of population age 65 and above for the national population. We used negative binomial regression models to investigate the association between the number of COVID-19 related deaths of each country per million population and other explanatory variables and reported incidence rate ratios (IRRs) adjusted for total cases per million. We adjusted the stage of 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, 31st May 2020.

**Results**

The global mean death rate per million population is 48.5 on June 2, 2020. The highest mortality rate recorded in Belgium at 820/M whereas the lowest at Nepal at 0.3/M (countries with more than 1 Million inhabitants and reported first case before 29 February 2020). We found the proportion of country’s people aged 65 years and above as the single most important explanatory variable (IRR: 1.11 [95% CI: 1.08-1.13]) for the variation of mortality rate across the countries. Against our expectation, WGI had opposite correlation (IRR: 0.78 [95% CI: 0.66-0.92]) for COVID-19 related deaths indicating that countries with good governance reported higher mortality rate. Similarly, countries with higher preparedness (GHSI) for pandemic disease reported higher mortality rate (IRR: 1.02 [95% CI:1.01-1.03]).

**Conclusions**

Countries with higher population of older people (≥65 years) had higher mortality rate. The findings of countries with higher GHSI and WGI and their positive correlation with higher mortality rate matches with observed death rates in wealthier countries however, we need a careful observation as countries are still ate different stages of epidemics where countries in Africa, South America, Pacific Islands and South Asia affected lately with COVID-19.

**Introduction**

In December 2019, a new flu-like virus that affected many people in the city of Wuhan was reports emerged from China. The virus has spread rapidly and efficiently in the city of Wuhan in China's Hubei Province, and confirmed a dramatic increase in a few weeks and subsequently around the world1–4. In January 2020, the World Health Organization named the virus SARS-CoV-2 and the disease designated as COVID-2019. SARS-CoV-2 is a relatively large virus (120 nm) and has a positive-sense single-stranded RNA5. In March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a pandemic6. According to the Worldometer, as of June 2nd, 2020, there are over 6.3 million identified cases and 377,881 deaths of COVID-19 worldwide in 213 countries and territories7. Of these 213 countries, South Korea and Iran (outside of China) have the largest epidemic of COVID-19 and Italy, France and Spain are the countries with a major epidemic of COVID-19 in Europe8.

**Literature review**

Excess deaths from the coronavirus disease 2019 (COVID-19) pandemic might arise both in those infected (direct effects), as well as those affected (indirectly, not infected) by altered access to health services; the physical, psychological, and social effects of distancing; and economic changes9. The virus and its clinical course are new, and we still have little information about them. Health care capacity and capability factors, including the availability of healthcare workers, resources, facilities, and preparedness, also affect outcomes.

For example, some countries are able to invest resources for contact tracing and containing the spread through quarantine and isolation in infected or suspected cases.

An increasing number of studies have suggested that people of all ages are susceptible to SARS-CoV-2 infection, which can result in severe and even fatal respiratory diseases

An increasing number of studies have suggested that people of all ages are susceptible to SARS-Cavi-2 infection, which can lead to severe and even fatal respiratory diseases10,11. The median aged people affected COVID-19 transmission in its early stages, but when millions of cases gradually reached a critical stage after a significant increase, these factors would no longer have a significant impact on pandemic transmission12. Recent studies on COVID-19 patients have also suggested that age may be a significant predictor for potential severity and mortality13,14. Age and gender are well-established risk factors, currently accounting for more than 90% of deaths in the UK over 60 years of age, with 60% of deaths in men.15. Older age with cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers were all associated with increased risk of death16. For lower income countries with lower life expectancy, the proportion of deaths among younger age strata may be larger. For example, in India, life expectancy is almost a decade less than in the USA and almost 15 years less than in Switzerland, making octogenarians and nonagenarians few in relative terms. Not surprisingly, preliminary data suggest that 14% of COVID- 19 deaths in India are in people below 45 years and another 34% in people 45-6017.

We must also acknowledge that we are focused on the risk of death, not hospitalization. Experience has shown that COVID-19 has the potential to overwhelm certain hospitals, especially in settings where hospitals move closer to maximum capacity even in regular situations and when they serve high-risk populations in cities with high population densities and major congregations in mass events. Thus, hospital preparation is absolutely essential regardless of whether the risk of death among the general population is very low. Similarly, work modelling hospital bed needs is useful18.

A certain demographic factor, such as population density, also affects the spread and spread of an outbreak. It is more difficult with higher population-densities to maintain a distance of more than one meter between people coughing and sneezing as recommended by the WHO19. Baddit et al., (2020) reported that, they found a significant correlation between spread rate and population density that could increase and cause of COVID-19 death20. Thus, avoiding situations with high population densities area would be necessary to limit the spread of COVID-19.

COVID-19 continues to spread worldwide, and a second wave of COVID-19 appears21, so the effect of different parameters on the COVID-19 mortality needs to help to predict the development and preparation, although numerous factors can affect the progression of the COVID-19 epidemic that we cannot be included in this study. Therefore, the objective of this study was to identify variable(s) explains such a large variation of death rates across countries.

**Methods**

**Study design**

We designed a prospective cohort study of geopolitical areas with documented outbreaks of COVID-19 to determine the factors associated with the total deaths of this pandemic. Data, including daily new cases, daily new deaths, total deaths, and total cases, were collected from the “our world in data” of 208 countries as of January 01 to May 31, 2020, for this analysis22.

**Outcome variable**

In this study, total deaths of COVID-19 per million were taken as an outcome variable. COVID-19 death is defined for surveillance purposes as a death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery between the illness and death23.

**Predictor variables**

Six variables were included in the model as predictors: total case per million24, population density25, population ages 65 and above of the national population26, Global Health Security Index (GHSI)27, Gross Domestic Product (GDP)28 and worldwide governance indicators (WGI)29.

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 origin25,26. GHSI is the first comprehensive assessment of global health security capabilities to be employed in 195 countries; the 2019 GHSI report scored (out of 100) the country-level capacity for “early detection and reporting for epidemics of potential concern”27. 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 for depletion and degradation of natural resources. Data are in current U.S. dollars28. Governance 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 them29.

**Statistical analysis**

We used negative binomial regression models to investigate the association between the number of total deaths of a country and other explanatory variable. We adopted a negative binomial model instead of a Poisson regression model because the dispersion ratio is larger than one, which indicates, the variances were greater than the means in outcome variables (p<0·001) and suggesting that overdispersion was present in the outcome variables (Table S2). The negative binomial model allows for overdispersion by assuming that the individual error terms come from a particular probability distribution (the γ distribution)30.

For the negative binomial regression analysis, we report incidence rate ratios (IRRs) adjusted for total cases per million, population density (per square kilometre), population ages 65 and above (% of the total population), global health security index, gross domestic product (per million), and worldwide governance indicators, with 95% confidence intervals (CIs). ). All analyses were done using the R (statistical package) and SPSS (IBM SPSS 25).

**Variable selection**

Variables were selected in two stages. In the first stage, we used the variance inflation factor (VIF) value to examine multicollinearity in the dataset with a cut-off value of 10.00. As a rule of thumb, a VIF value for predictors that exceed 10 in a dataset and 5 in a model indicates a problematic amount of collinearity31. In our data, the VIF score for the predictor variable human development index (HDI), social progress index, and social mobility index is very high (VIF >10) and we are not considered these variables in the final model (Table S1). In the second stage, again we used VIF value in a negative binomial regression model with a cut-off value of 5.00 and in this stage, the VIF score for all the predictor variables is less than the cut-off value (Table S3).

**Results**

A total of 6.3 million cumulative confirmed cases and 377,881 deaths had been documented globally as of June 2nd, 2020. United States, United Kingdom, Italy, Brazil and France were the three countries with the most cases of COVID-19. Moreover, Belgium (815/M), United Kingdom (565/M), Italy (551/M), France (440/M), and Netherlands (347/M) had the most deaths of COVID-19. Distribution of worldwide total deaths (per million) of COVID-19 are presented in Fig. 1. Distribution of worldwide daily total deaths and cases (per million) of COVID-19 from January 1, 2020 to May 31, 2020 are presented in Fig. 2.

**Fig. 1: The death rate per million population due to COVID-19 in different countries of the world for the period January 1st to May 31st 2020.**



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| **Fig. 2. Worldwide distribution of daily deaths and cases of COVID-19 in 2020** | |

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| **2.1 Top 10 countries with total deaths** | **2.2 Mean Case-fatality rate in different continents** |

**Fig 2: Graphs for death rate per million population and different variables**

The estimates derived from negative binomial regression model are shown in Table 1 and indicate that, an increased incidence rate ratio was observed for total cases per million and population density per square kilometre. The incidence rate ratios (IRR) of 1.11 for population above 65 and above indicates a 11% increase of death rate for 1% increase of population ages 65 and above in total population (IRR: 1.11 [95% CI: 1.08-1.13]). A lower IRR was observed for worldwide governance indicators and had opposite correlation (IRR: 0.78 [95% CI: 0.66-0.92]) for COVID-19 related deaths. Similarly, countries with higher preparedness (GHSI) for pandemic disease reported higher mortality rate (IRR: 1.02 [95% CI:1.01-1.03]).

**Table 1: Factors associated with death rate per million population due to COVID-19 in different countries of the world.**

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| Variables | **incidence rate ratios (**IRR) | 95%CI | P-value |
| Total Cases per million | 1.01 | 1.01-1.02 | <0.001 |
| Population Density (per square Kilometre) | 1.01 | 0.99-1.01 | 0.631 |
| Population ages 65 and above (% of total population) | 1.11 | 1.08-1.13 | <0.001 |
| Global Health Security Index | 1.02 | 1.01-1.03 | <0.001 |
| Gross Domestic Product (per million) | 0.99 | 0.99-1.00 | <0.001 |
| Worldwide Governance Indicators | 0.78 | 0.66-0.92 | <0.001 |

**Discussion**

Our analyses indicate that the growing rate of total cases, GHSI, population over 65 years, GDP and WGI are the main factors that underlies the high mortality rate of COVID-19 patients worldwide. Among them, the proportion of people aged 65 or older in the country as the single most important explanatory variable in the variability of mortality across the country. As COVID-19 is a new disease whose pathophysiology remains to be defined. Data from China indicate that age is the strongest predictor of COVID-19 severity. In particular, the association with age is direct and linear, meaning that older people will present the most severe form of the disease, while younger subjects, including children and babies, will be either asymptomatic or present mild diseases32.

As of May 31, 2020, the Belgium (815/M), United Kingdom (565/M), Italy (551/M), France (440/M), and Netherlands (347/M) are the top most-affected counties in terms of mortality rate. According to world bank, among the highest mortality countries, Belgium has one of the highest (18.79%) percentage of older than 65 years aged living among the 28 EU Member States in 2015 with mean elderly age of 15.5% (Range:3.3%-22.4%) years33. In Italy, 22% of people were over 65 years of age34 and also increased the mortality rate. This observation was also consistent with higher observations of several clinical co-morbidities associated with aging. In this respect, 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 were over 65 years of age35. 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 individuals18, which conclude similar result to our study.

In our study we found an increasing rate of mortality due to population density. There are many determinants of the reproductive number of SARS-COV-2; including control measures such as social distancing and quarantine. Cruise ships are an example of a dense mixing of many people in a limited space over a relatively long period of time. A study in Yokohama, Japan, a cruise ship hosting 3,711 people underwent a 2-week quarantine after a former passenger was found earlier this year, was estimated around four times higher than that in Wuhan, as was also the reproduction number before the onset of countermeasures36.

Contrary to our expectations, the WGI had the opposite relationship with COVID-19 related deaths, 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 countries in the world37. This may be the reason we get the opposite relationship.

Similarly, countries with higher preparedness (GHSI) for pandemic diseases have reported higher mortality rates. 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 pandemic.

A country can reduce the potential gap of physical resources (higher GHSI), but there is a much wider gap in human resources (HR) which might be not enough to handle that resources or facing this situation. Most hospitals are staffed appropriately at their usual capacity utilization rate, and expanding even up to, but then potentially well beyond, licensed capacity will require finding substantial additional HR38. Most hospitals are adequately staffed at their normal capacity utilization rate, and it extends as far as possible but there is a need to find enough additional HR for licensed capacity beyond the possibility.

**Conclusion**

Countries with higher population of older people (≥65 years) had higher mortality rate. The findings of countries with higher GHSI and WGI and their positive correlation with higher mortality rate matches with observed death rates in wealthier countries however, we need a careful observation as countries are still ate different stages of epidemics where countries in Africa, South America, Pacific Islands and South Asia affected lately with COVID-19.

The mortality rate of COVID-19 is related to age and comorbid worldwide. Strategies need to be applied to high-risk groups, such as the elderly, especially in countries with the highest incidence and those with other underlying diseases such as diabetes and cancer that should receive adequate protection against COVD-19. In addition, a detailed and accurate treatment history can highlight the highest risk areas and instruct to intervene more efficiently to reduce the spread of the virus worldwide.

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**Table S1. Variance inflation factor (VIF) value to examine multicollinearity in the data set**

|  |  |
| --- | --- |
| Variables | VIF |
| Total deaths per million | 2.36 |
| Total Cases per million | 2.70 |
| Population Density (per square Kilometre) | 1.16 |
| Population ages 65 and above (% of total population) | 4.79 |
| Global Health Security Index | 3.38 |
| Gross Domestic Product (per million) | 1.46 |
| Human development Index | 15.63 |
| Social Progress index | 15.09 |
| Social Mobility Index | 19.56 |
| Worldwide Governance Indicators | 9.91 |
| Days | 1.58 |

**Table S2. Overdispersion Test of the Poisson model**

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| Dispersion ratio | 121.54 |
| Pearson's Chi-Squared | 20783.30 |
| p-value | < 0.001 |

**Table S3. Variance inflation factor (VIF) value to examine multicollinearity in the final model (NB)**

|  |  |
| --- | --- |
| Variables | VIF |
| Total Cases per million | 1.70 |
| Population Density (per square Kilometre) | 1.42 |
| Population ages 65 and above (% of total population) | 3.19 |
| Global Health Security Index | 3.78 |
| Gross Domestic Product (per million) | 1.58 |
| Worldwide Governance Indicators | 4.51 |