

# Risk factors affecting COVID-19 case fatality rate: A quantitative analysis of top 50 affected countries

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## Abstract:

**Background:** Latest clinical data on treatment on coronavirus disease 2019 (COVID-19) indicated that older patients and those with underlying history of smoking, hypertension or diabetes mellitus might have poorer prognosis of recovery from COVID-19. We aimed to examine the relationship of various prevailing population-based risk factors in comparison with mortality rate and case fatality rate (CFR) of COVID-19.

**Methods:** Demography and epidemiology data were used, which have been identified as verified or postulated risk factors for mortality of adult inpatients with COVID-19. The number of confirmed cases and the number of deaths until April 16, 2020 for all affected countries were extracted from Johns Hopkins University COVID-19 websites. Datasets for indicators that are prevailing or postulated factors of COVID-19 mortality were extracted from the World Bank database. Out of 185 affected countries, the top 50 countries were selected for analysis in this study. The following seven variables were included in the analysis, based on data availability and completeness: 1) proportion of people aged 65 and above, 2) proportion of male in the population, 3) smoking prevalence, and 4) number of hospital beds. Linear regression analysis was carried out to determine the relationship between CFR and the aforementioned risk factors.

**Results:** United States shows approximately 0.20% of confirmed cases and it has about 4.85% of CFR. Luxembourg shows the highest percentage of confirmed cases of 0.55% but a low 2.05% of CFR, showing that a high percentage of confirmed cases does not necessarily lead to high CFR. There is a significant association between CFR, people aged 65 and above ( $\beta=4.70$ ;  $p = 0.035$ ).

**Conclusion:** Countries with high proportion of older people above 65 years old have a significant risk of having high CFR from COVID-19. Nevertheless, gender differences and smoking prevalence failed to prove a significant relationship with COVID-19 mortality rate and CFR.

**Keywords:** COVID-19, risk, epidemiology, demography, fatality, age, diabetes

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## Introduction

On February 11, 2020, the World Health Organisation (WHO) renamed the highly contagious respiratory disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as coronavirus disease-19 (COVID-19) [1]. The unprecedented increase in COVID-19 cases has led WHO to call it as a pandemic on March 11, 2020 [2,3].

As this pandemic continues to evolve, researchers are learning more about SARS-CoV-2 every day, including the fact that it can be transmitted from symptomatic, pre-symptomatic and asymptomatic people infected with COVID-19 [4]. Studies have shown that COVID-19 is primarily transmitted from symptomatic people to people who are in close contact through respiratory droplets, by

direct contact with infected persons or by contact with contaminated objects and surfaces [5]. Fever, tiredness and dry cough are the most common symptoms in symptomatic COVID-19 patients [6,7].

Current evidence indicated that certain group of people are at a higher risk of suffering from severe illness from COVID-19 [8,9]. Such risk factors include gender, Bacillus Calmette-Guerin (BCG) vaccination, smoking and malaria prevalence [10,11]. Older people have a higher risk due to the decreasing function of the age-dependent lymphocytes, which resulting in their increased susceptibility to COVID-19 disease [7]. In addition, a study shows that there is a higher percentage of death among patients aged over 65 years (62%) than patients aged below 65 years old (37%) [12]. Furthermore, male gender is commonly observed in COVID-19 patients (73%) according to a retrospective study done on 113 deceased patients [13].

Another risk factor for COVID-19 mortality is existing comorbidities. A study by Guan et al. shows that COVID-19 are more commonly seen in patients with hypertension, diabetes, cardiovascular disease and a history of smoking [14]. Not only were these patients susceptible to the disease, they also had a higher chance of obtaining poor health outcomes after Immediate Care Unit (ICU) admission and may lead to death [12]. Moreover, a study on the correlation between COVID-19 mortality and BCG vaccination suggested that early BCG vaccination could help to decrease the mortality rate [10]. Other than that, malaria prevalence is also another risk factor of COVID-19 mortality. A higher number of COVID-19 cases were reported in countries with low malaria prevalence than countries that had higher malaria prevalence [15,16]. Apart from addressing risk factors, there are also parameters that may affect the COVID-19 mortality rate such as shortage of staff, lack of medical supply or equipment, insufficient hospital beds and the country's health expenditure.

As of late April 2020, SARS-CoV-2 virus has resulted in more than 3.1 million infections and over 217,000 deaths globally [1]. As COVID-19 has become a global pandemic issue, implementation of suitable interventions will be needed for the public, healthcare professionals and patients and also to ensure all sectors to work together cohesively and efficiently [17]. Even though COVID-19 originate from the same family as other known coronaviruses, SARS-CoV-2 has very different severity and contagion characteristics and much still needs to be learned about it. Thus, it is imperative to evaluate the relationship of postulated or verified risk factors with COVID-19 mortality, as presented in a recent analysis based on United Kingdom [18] and Spain [19]. It is absolute crucial to evaluate the risk factors of mortality among patients infected with COVID-19 at population level. By validating the relationship, patients with COVID-19 can be treated more aggressively than those without the risk factor [20]. The findings of the current study provide a picture of COVID-19 case fatality rate (CFR) in top 50 affected countries.

We aimed to determine the association between specific risk factors and COVID-19 CFR. These findings consolidate the evidence of crucial risk factors that front liners need to prioritise to decrease the COVID-19 mortality globally.

This is an ecological study that examines indicators or variables that could be associated with COVID-19 mortality. The unit of observation in an ecological study is the population of the particular area or specific country in which the disease rates were measured. One of the advantages of an ecological study is it provides a snapshot of a transforming event, in addition to the fact that the disease rate and indicator statistics could be mined from existing databases thus saving time [21]. The compared populations and disease of interest are normally defined based on temporal and spatial variation. It is apparent that the reported cases of COVID-19 tend to fluctuate and the sudden spike could be linked to so local transmission cluster. In term of geographical comparisons, epidemiologists are also interested to determine the geographical associations between disease incidence or mortality and the prevalence of risk factors, as exemplified by recent COVID-19 study by Whittle and Diaz-Artiles [22].

## **Methods**

### **Data extraction**

Demography and epidemiology data which have been identified as verified or postulated risk factors for mortality among adult inpatients with COVID-19 were used. The data were collected from World Bank (<https://data.worldbank.org/>) and Johns Hopkins University COVID-19 (<https://coronavirus.jhu.edu/map.html>) websites. The number of confirmed cases and the number of deaths for all affected countries were extracted from the latter [23], while datasets for indicators that are prevailing or postulated as the risk factors of COVID-19 mortality were extracted from the World Bank database [24]. Data extracted for this study was up until April 16, 2020. All data acquired were exported in excel format and arranged according to country rankings with the top having the highest number of confirmed cases as of April 16, 2020 and the bottom having the least. To facilitate comparison, out of about 185 affected countries, only top 50 countries were selected to be analyzed in this study.

The following seven variables were included in the analysis, based on data availability and completeness: 1) proportion of people aged 65 above, 2) proportion of male in the population, 3) smoking prevalence, and 4) number of hospital beds.

### **Data analysis**

For each country, the percentage of confirmed COVID-19 case per country was calculated by dividing the number of confirmed COVID-19 cases by the total population for each country. Also, CFR was calculated by dividing the number of deaths related to COVID-19 by the confirmed COVID-19 cases.

Linear regression analysis was conducted to determine the risk factors of CFR for COVID-19. This method was

chosen so that the degree of association can be quantified and that this estimate can be adjusted with other potential risk factors. For this analysis, two variables (CFR and number of hospital beds) were standardized due to differences in scale and very large range. Standardization was done by subtracting each value by the mean and then dividing it with the standard deviation. However, data for four variables (diabetes prevalence, current health expenditure, and number of nurses and midwives) were not normally distributed. Transforming these variables to normality were performed but model over-fitting occurred, therefore further analysis was not pursued. All analyses were conducted using Microsoft Excel and R (ver. 3.6.0). A  $p$ -value  $< 0.05$  was considered as statistically significant.

## Results

Information of 2,017,444 confirmed COVID-19 cases and 137,166 deaths from each of the 50 top countries (Supplementary Information) were extracted. This constitutes about 93.3% and 92.8% of the global confirmed cases and

and deaths on the data collection date (April 16, 2020).

### Case Fatality Rate (CFR) and mortality rate of COVID-19 in the top 50 countries

From data extracted up until April 16, 2020, the United States (US) reported to have the highest number of total confirmed cases and the highest total number of deaths of 639,733 cases and 31,002 cases respectively. Despite that, the US accounted about 0.20% (Table 1) of confirmed cases and it had about 4.85% of CFR (Table 1), indicating a moderate mortality rate of COVID-19 in comparison to other countries. Luxembourg, ranked 47<sup>th</sup> in the list of top 50 COVID-19 countries, had the highest percentage of confirmed cases of 0.55% but a low 2.05% of CFR (Table 1), indicating that a high percentage of confirmed cases does not necessarily lead to a high CFR. This is due to variations in number, transmission rate and severity of the disease regardless of the rankings<sup>[25]</sup>. Hence, it is important to evaluate the possible factors that can affect the increase of COVID-19 mortality rate globally.

**Table 1:** Percentage of confirmed CFR and COVID-19 cases (In sequence of the highest to lowest CFR%)

No.	Countries	Confirmed COVID-19 cases (%)	Case Fatality Rate (%)
1	Belgium	0.3	13.95
2	United Kingdom	0.15	13.82
3	Italy	0.27	13.11
4	France	0.2	12.77
5	Netherlands	0.17	11.32
6	Sweden	0.12	10.63
7	Spain	0.39	10.46
8	Indonesia	0.002	8.99
9	Mexico	0.005	7.68
10	Philippines	0.01	6.4
11	Iran	0.1	6.24
12	Brazil	0.01	6.07
13	Dominican Republic	0.03	5.23
14	Romania	0.04	5.09
15	Ecuador	0.05	4.94
16	United States	0.2	4.85
17	Switzerland	0.31	4.8
18	Denmark	0.12	4.54
19	Colombia	0.01	4.22
20	China	0.01	4.01
21	Poland	0.02	3.76
22	Canada	0.08	3.56
23	Ireland	0.26	3.54
24	India	0.001	3.4
25	Portugal	0.18	3.33
26	Germany	0.1	2.86
27	Ukraine	0.01	2.79

Table 1: Percentage of confirmed CFR and COVID-19 cases (In sequence of the highest to lowest CFR%) (Continued)

28	Panama	0.09	2.75
29	Austria	0.16	2.73
30	Czech Republic	0.06	2.63
31	Finland	0.06	2.23
32	Norway	0.13	2.21
33	Peru	0.04	2.21
34	Turkey	0.08	2.19
35	Korea, Rep	0.02	2.16
36	Japan	0.01	2.06
37	Luxembourg	0.56	2.05
38	Serbia	0.07	2.03
39	Pakistan	0.003	1.85
40	Thailand	0.004	1.72
41	Malaysia	0.02	1.62
42	Saudi Arabia	0.02	1.3
43	Chile	0.04	1.14
44	Israel	0.14	1.11
45	Australia	0.03	0.97
46	Belarus	0.04	0.95
47	Russian Federation	0.02	0.83
48	United Arab Emirates	0.06	0.62
49	Singapore	0.07	0.27
50	Qatar	0.15	0.17

**Relationship between the different risk factors and COVID-19 CFR**

The proportion of people aged 65 and above had a significant association with CFR (4.70 [95% CI: 0.34,

9.06],  $p = 0.04$ , Table 2). For every 1-unit increase in the proportion of people aged 65 years, the CFR increased by 4.7 units. This relationship is illustrated in Figure 1, where CFR sharply increases when the proportion of people aged 65 years is 0.18 and above.

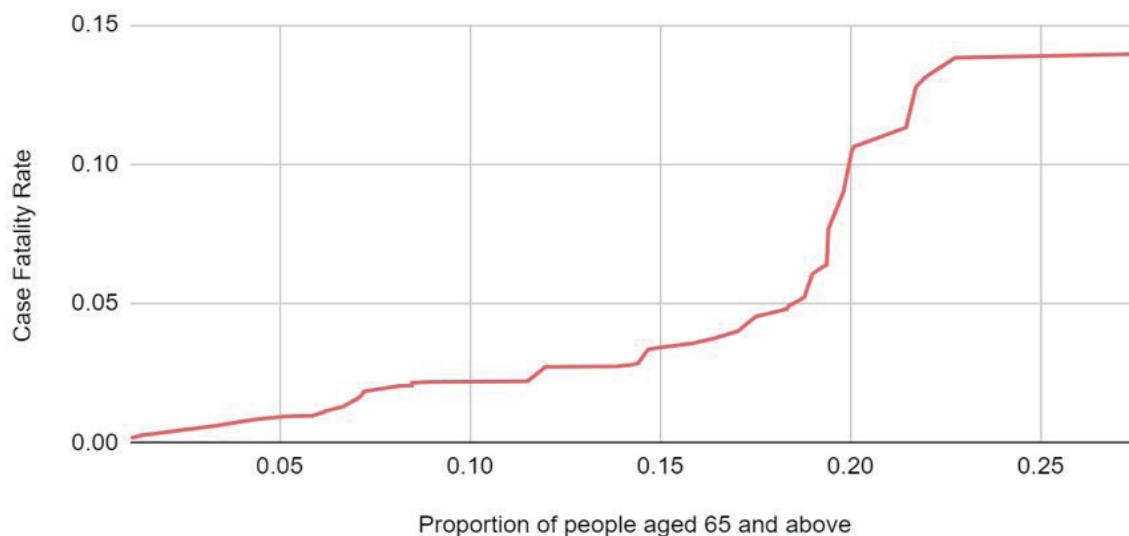
Table 2: Linear regression analysis for different risk factors (independent variable) and COVID-19 CFR (dependent variable)

Independent variable	$\beta$ estimate (95% CI)	Standard Errors	$p$ -value
Age (above 65 years)	4.70 (0.34, 9.06)	2.17	<b>0.035</b>
Gender - Male	-0.33 (-0.92, 0.26)	0.29	0.26
Smoking Prevalence (total % of people aged 15 and above)	0.009(-0.03, 0.04)	0.02	0.60
Hospital Beds (per 1,000 people)	-0.097 (-0.39, 0.19)	0.14	0.50

**Discussion**

There are still a lot of unknown regarding COVID-19 disease. However, good clinical findings are made available now to understand the risk factors that could affect its treatment outcomes.

Studies have shown that age is a clear risk factor for severe COVID-19 disease. This has been confirmed by our study where the proportion of people aged 65 and above has shown a significant association with CFR. This indicates that countries with a higher proportion of people aged 65 and above may result in higher COVID-19 mortality



**Figure 1:** Association between case fatality rate and proportion of people aged 65 and above.

rate (Figure 1). Bhatraju *et al.* (2020) has shown that in Seattle, the US reported more than 60% of COVID-19 deaths in patients aged 65 years and above than those who are younger than 65 years old [12]. Verity *et al.* (2020) has shown that there is a stark difference in the CFR between those aged below and above 60 years (1.4% versus 4.5%, respectively) [9]. This suggests that the older the country population, the higher the CFR. For those 80 years old and above, COVID-19 appears to have a 13.4% fatality rate [9]. Notably, the average age of deceased and recovered patients were found to be 68 and 51 years, respectively [13]. These studies show that COVID-19 disproportionately impacts certain groups, and that older people [26] and pregnant women [27] are among the vulnerable groups. This could be due to the weakening effects of ageing on the immune system. As age increases, there is an increase of deficiency in T-cell and B-cell function and overproduction of type 2 cytokines [7]. This may promote viral replication and extend the duration of pro-inflammatory responses, leading to poor prognosis [7]. Furthermore, older people tend to have more underlying conditions that may also be risk factors for severe COVID-19 [9,14].

Studies have shown that many of the severe COVID-19 patients also have underlying medical conditions, such as diabetes and cardiovascular diseases [13,28]. Patients with existing comorbidities, including hypertension, diabetes, cardiovascular disease and history of smoking, seems to be associated with COVID-19 more severely [14]. With reference to a retrospective study of 113 deceased patients from COVID-19, 48% of the patients had chronic hypertension and 14% of them had cardiovascular diseases [13]. In addition to that, COVID-19 patients who have hypertension were closely associated with poor health outcomes after hospital admission. This may be due to factors such as vascular aging, reduced renal function and medication interactions [29]. Although smoking prevalence has shown no significant association with COVID-19 ( $p=0.60$ ), it cannot be assumed that there is no association between other comorbidities and COVID-19 CFR since not all factors were considered in this study, such as hypertension and cardiovascular diseases [6].

COVID-19 is a rapid spreading communicable disease and general public are responsible in controlling this COVID-19 pandemic. Various levels of well-preparedness plans are needed to tackle this pandemic situation [30]. These include availability of medicines or medical supplies to treat COVID-19 patients, availability of suitable places to quarantine or self-isolate these patients, number of healthcare professionals and a strategized interventions, such as social distancing, quarantine, isolation actions and proper management, for the patients and public to flatten the curve and to reduce healthcare burden. It is necessary for some countries which may need more supplies than others to cater all sick patients, and thus increasing the health expenditure of the country [2]. Some of the medical supplies include personal protective equipment, mechanical ventilators, COVID-19 testing kits and extracorporeal membrane oxygenation. Due to surge of demand on healthcare system, countries with low income and poor healthcare infrastructure suffer the most [14]. However, in our study, current health expenditure of the top 50 countries was not tested due to aforementioned reason.

Sufficient hospital capacity in term of hospital bed is necessary to accommodate unforeseen pandemic situations [31]. Despite the insignificant association to COVID-19 CFR ( $p=0.50$ ), accessibility to adequate hospital beds for COVID-19 patients can potentially affect the CFR as the number of beds required depends on the number of confirmed cases in each country. Apart from hospital beds, other medical supplies such as medical grade face mask and mechanical ventilators must be sufficient as they are the key equipment for frontline healthcare workers [32-34].

Evidence of high numbers of infections and deaths among healthcare workers due to lack of face mask and medical gowns were reported in Italy [32]. In the US, recent estimates have suggested that the estimated ventilators needed is ranging from several hundred thousand to a million, far more than what are currently available [32]. It is difficult to estimate the exact number of ventilators needed as it depends on the number, transmission rate and severity of the disease in each country.

There are a number of limitations in this study. The nature of the study design (ecological study) and type of analysis used (linear regression analysis) allowed us to use country-level aggregated data to determine the relationship between CFR and specific risk factors. Since aggregated data were used, this means that the results are only applicable at a country-level, instead of individual-level. Some factors had to be excluded due to incomplete data such as malaria prevalence and BCG vaccination. Even if the data were available, the data may come from different years. The years from which the data were retrieved were not consistent for all indicators. The data collected were also limited by unavailability of certain data to sufficiently make an overall conclusion for several factors, including comorbidities. There were four other proposed comorbidities to be analyzed but only two indicators' datasets were available in World Bank Data, which are diabetes and smoking prevalence. Of note, our study did not able to test the association between diabetes prevalence and CFR. Therefore, more research should be conducted to further understand the relationship between comorbidities and CFR. This would help to identify and to better understand other possible factors that may also affect CFR. However, even with these limitations, it is important to note that the aim of our report is to determine the association between specific risk factors and COVID-19 case fatality rate globally. Also, our analysis is limited by data derived from confirmed COVID-19 cases as of April 16, 2020, yet the number of global cases continues to increase. It is also important to note that transmissibility rate and various periods of the pandemic were not taken into account, as it may differ at different countries or even area within the same country [6,35,36].

## Conclusion

As COVID-19 is such a new disease, much still needs to be learned about it. Age is a clear risk factor for severe COVID-19 and death. COVID-19 is an illness that disproportionately impacts older people. However, other risk factor such as smoking should not be neglected. Prediction alone is not efficient, but well-planned and suitable interventions should also be carried out. In addition to that, potential risk factors need a lot more research in order to understand the risks for the worst forms of COVID-19 and what we ought to learn to best protect the people with higher risk. Participation and involvement of every individual, including patients, public and healthcare professionals, is necessary and everyone should work together towards combating COVID-19 disease.

## Conflict of interest

None declared.

## Funding

None.

## Author contributions

LCM conceived the project. HPG, WIM, NIA, LLC, LCM analyzed results and interpreted the data

and wrote the manuscript draft. NK, BHG, KWG, SFY revised the manuscript. All authors read and approved the final manuscript.

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