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EDITORIAL

Delpino MV, Quarleri J. Perilipin 2 inhibits replication of hepatitis B virus deoxyribonucleic acid by regulating autophagy under high-fat conditions. *World J Virol* 2024; 13(1): 90384 [DOI: [10.5501/wjv.v13.i1.90384](https://doi.org/10.5501/wjv.v13.i1.90384)]

REVIEW

Musa M, Enaholo E, Aluyi-Osa G, Atuanya GN, Spadea L, Salati C, Zeppieri M. Herpes simplex keratitis: A brief clinical overview. *World J Virol* 2024; 13(1): 89934 [DOI: [10.5501/wjv.v13.i1.89934](https://doi.org/10.5501/wjv.v13.i1.89934)]

MINIREVIEWS

De Pauli S, Grando M, Miotti G, Zeppieri M. Hepatitis B virus reactivation in patients treated with monoclonal antibodies. *World J Virol* 2024; 13(1): 88487 [DOI: [10.5501/wjv.v13.i1.88487](https://doi.org/10.5501/wjv.v13.i1.88487)]

Bhide M, Singh O, Nasa P, Juneja D. Cytomegalovirus infection in non-immunocompromised critically ill patients: A management perspective. *World J Virol* 2024; 13(1): 89135 [DOI: [10.5501/wjv.v13.i1.89135](https://doi.org/10.5501/wjv.v13.i1.89135)]

ORIGINAL ARTICLE**Retrospective Study**

Sohail A, Ali H, Patel P, Subramaniam S, Dahiya DS, Sohail AH, Gangwani MK, Satapathy SK. Impact of metabolic dysfunction-associated steatotic liver disease on COVID-19 hospitalizations: A propensity-matched analysis of the United States. *World J Virol* 2024; 13(1): 91149 [DOI: [10.5501/wjv.v13.i1.91149](https://doi.org/10.5501/wjv.v13.i1.91149)]

Observational Study

Sudevan N, Manrai M, Tilak TVSVGK, Khurana H, Premdeep H. Chronic hepatitis B and occult infection in chemotherapy patients - evaluation in oncology and hemato-oncology settings: The CHOICE study. *World J Virol* 2024; 13(1): 89104 [DOI: [10.5501/wjv.v13.i1.89104](https://doi.org/10.5501/wjv.v13.i1.89104)]

Ali H, Vikash F, Moond V, Khalid F, Jamil AR, Dahiya DS, Sohail AH, Gangwani MK, Patel P, Satapathy SK. Global trends in hepatitis C-related hepatocellular carcinoma mortality: A public database analysis (1999-2019). *World J Virol* 2024; 13(1): 89469 [DOI: [10.5501/wjv.v13.i1.89469](https://doi.org/10.5501/wjv.v13.i1.89469)]

Basic Study

Sagheb S, Gholamrezanezhad A, Pavlovic E, Karami M, Fakhrzadegan M. Country-based modelling of COVID-19 case fatality rate: A multiple regression analysis. *World J Virol* 2024; 13(1): 87881 [DOI: [10.5501/wjv.v13.i1.87881](https://doi.org/10.5501/wjv.v13.i1.87881)]

Nemr WA, Nashwa RK. Development of a multiplex polymerase chain reaction assay for detection of hepatitis C virus, hepatitis B virus, and human immunodeficiency virus 1. *World J Virol* 2024; 13(1): 88164 [DOI: [10.5501/wjv.v13.i1.88164](https://doi.org/10.5501/wjv.v13.i1.88164)]

SYSTEMATIC REVIEWS

Cheo FY, Chan KS, Shelat VG. Outcomes of liver resection in hepatitis C virus-related intrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *World J Virol* 2024; 13(1): 88946 [DOI: [10.5501/wjv.v13.i1.88946](https://doi.org/10.5501/wjv.v13.i1.88946)]

META-ANALYSIS

Amani B, Khodavirdilou L, Rajabkhah K, Kardan Moghaddam V, Akbarzadeh A, Amani B. Efficacy and safety of bamlanivimab in patients with COVID-19: A systematic review and meta-analysis. *World J Virol* 2024; 13(1): 88660 [DOI: [10.5501/wjv.v13.i1.88660](https://doi.org/10.5501/wjv.v13.i1.88660)]

Juneja D, Jain R, Nasa P. Dengue induced acute liver failure: A meta summary of case reports. *World J Virol* 2024; 13(1): 91457 [DOI: [10.5501/wjv.v13.i1.91457](https://doi.org/10.5501/wjv.v13.i1.91457)]

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The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

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Basic Study

Country-based modelling of COVID-19 case fatality rate: A multiple regression analysis

Soodeh Sagheb, Ali Gholamrezanezhad, Elizabeth Pavlovic, Mohsen Karami, Mina Fakhrzadegan

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Abstract

BACKGROUND

The spread of the severe acute respiratory syndrome coronavirus 2 outbreak worldwide has caused concern regarding the mortality rate caused by the infection. The determinants of mortality on a global scale cannot be fully understood due to lack of information.

AIM

To identify key factors that may explain the variability in case lethality across countries.

METHODS

We identified 21 Potential risk factors for coronavirus disease 2019 (COVID-19) case fatality rate for all the countries with available data. We examined univariate relationships of each variable with case fatality rate (CFR), and all independent variables to identify candidate variables for our final multiple model. Multiple regression analysis technique was used to assess the strength of relationship.

RESULTS

The mean of COVID-19 mortality was $1.52 \pm 1.72\%$. There was a statistically significant inverse correlation between health expenditure, and number of computed tomography scanners per 1 million with CFR, and significant direct

correlation was found between literacy, and air pollution with CFR. This final model can predict approximately 97% of the changes in CFR.

CONCLUSION

The current study recommends some new predictors explaining affect mortality rate. Thus, it could help decision-makers develop health policies to fight COVID-19.

Key Words: COVID-19; SARS-CoV-2; Case fatality rate; Predictive model; Multiple regression

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Core Tip: The current study recommends some new predictors explaining affect mortality rate. Thus, it could help decision-makers develop health policies to fight coronavirus disease 2019.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to tremendous worldwide effects on the lives of people around the world, including large-scale morbidity and mortality and limited access to healthcare services (covid19.who.int)[1]. The worldwide case fatality rate (CFR) of COVID-19 has been estimated to be around 1.5% as of now[2]. Different variants of the SARS-CoV-2 virus have been discovered to cause the disease. The clinical presentation of the disease ranges from asymptomatic status to upper respiratory tract symptoms, mild pneumonia, severe respiratory symptoms, acute respiratory distress syndrome, extrapulmonary manifestations, and death[1,3].

Various risk factors for COVID-19 mortality have been named in the literature, including age, male gender, comorbidities (such as chronic kidney disease (CKD), cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, malignancy, underlying autoimmune disease, and hypertension), ethnicity, vaccination status, smoking history, obesity, and socioeconomic status[4-12]. On the other hand, some factors have been proven to be protective, which may reduce the severity or mortality of COVID-19 infection, as among which vaccination[13], efficiently staffed facilities, particularly by registered nurses[14,15] corticosteroid treatment[16], and healthy diet[17] are the most notable. Gathering updated information from international data sources could throw light on the protective or potential risk factors to avoid COVID's severe morbidities and mortality.

This study aims to assess the correlation between different known risk factors or protective measures and the COVID-19 CFR, described by the number of deaths relative to number of confirmed cases. A similar study was performed in 2020 on 39 countries[18]. Our study is an update to the former one.

MATERIALS AND METHODS

Data collection

In this modeling publicly available register-based ecological study, we started with a literature review focused on the potential risk factors of COVID-19 mortality through Our World in Data, and COVID-related mortality risk factors through World Bank, Our World in Data, Statistica, OECD Database, and World Population Review. Our approach was consistent with a study done by Jennifer Pan, a Modelling study of factors causing death variation estimation by country.

We included all the countries with available COVID-19 CFR data, which enclosed 188 countries. There were 17 countries that had not reported any mortality data until the last date of our data collection (June 24, 2022); therefore, they were not included in the study. We did not have any exclusion criteria. We determined 21 risk factors for the worthwhile COVID-19 deaths, including GDP per capita, Population density, health expenditure per capita, Age, Obesity, Diabetes, human immunodeficiency viruses (HIV), Tobacco Users, Life expectancy, General death rate per 1000, Hospital beds per 1000, Physicians per 1000, Radiologist per 100 K, computed tomography (CT) scanners per million, Air pollution, Literacy rate, Human development index, case fatality rate, Tests per 1 million, Doses per 100 people, Given 1+ dose, Percent Fully vaccinated. In calculating the CFR, we used the total number of confirmed cases and fatalities for a particular country from Our World in Data[19]. Therefore, the CFR formula would be as follows: $CFR \text{ in } \% = \frac{\text{Number of deaths from Corona}}{\text{Number of confirmed cases of Corona}} * 100$ [20].

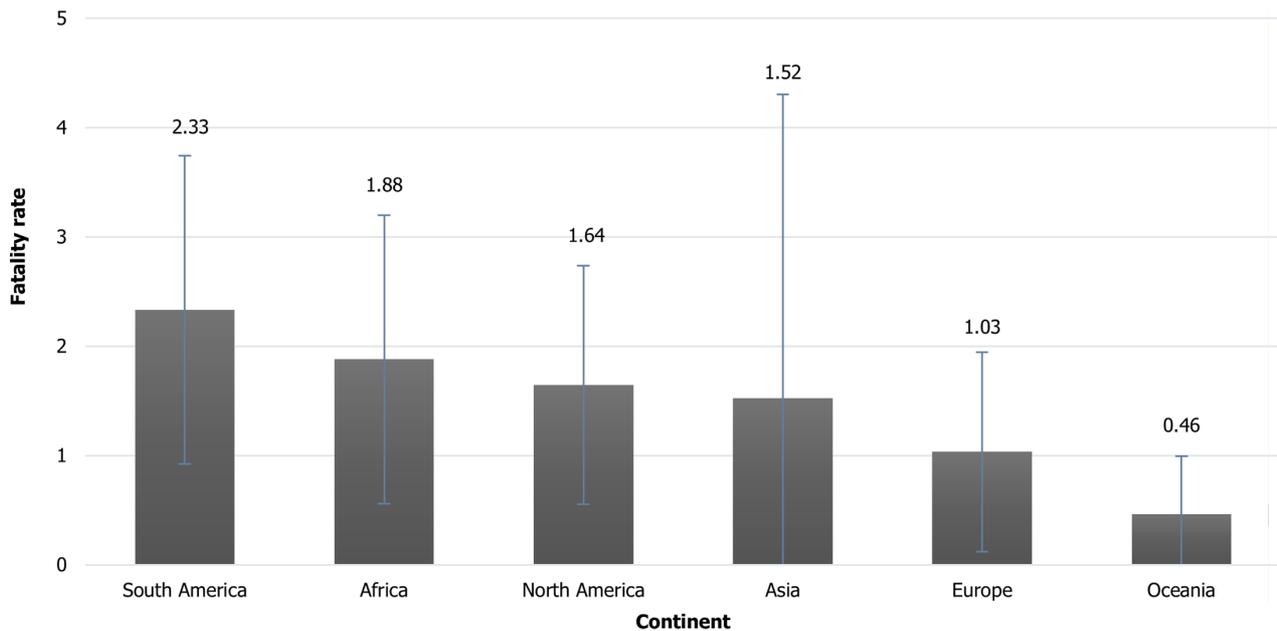


Figure 1 Coronavirus disease 2019 fatality rate by continent.

In regard to vaccination, people are placed in fully vaccination group two weeks after a second dose of mRNA COVID-19 vaccine, two weeks after receiving a second dose of the Novavax COVID-19 vaccine, or two weeks after they get a single dose of the Janssen/Johnson & Johnson COVID-19 vaccine. They are considered in given 1+ group if they have received at least one dose of COVID-19 vaccine, including fully vaccinated people[21]. Therefore, fully vaccinated people are those who have received two doses for most vaccines, or one or three doses for a few manufacturers[22].

Statistical analysis

A descriptive analysis of variables has been carried out. Data were presented as mean \pm standard deviation for quantitative variables, and numbers (percentage) for qualitative data. We found that GDP, Health Expenditure per capita, Percent HIV, Air pollution, and tests per 1 million were highly positively skewed. In order to reduce the influence of extreme observations, we processed these variables at the logarithm scale.

As our dependent variable, we looked at the univariable relationships between case fatality rates in the next step, and all independent variables to identify candidate variables for our final multiple model.

Multiple regression analysis technique was used to assess the strength of the relationship between an outcome (the dependent variable) and several predictor variables as well as the importance of each of the predictors to the relationship, often with the effect of other predictors statistically eliminated by using the ordinary least squares[23], and the ability to identify outliers we found the multiple models for case fatality rate to be appropriate.

We pointed out the significance of each variable in these univariable models and finally selected variables for our multiple model at P value < 0.05 . To detect the severity of multicollinearity, we focused on variance inflation factor (VIF) [24,25]. The model was designed by including all univariable candidate predictors and further developed by adding all significant interaction terms. Our preliminary final model included all 16 variable predictors significant at P values < 0.05 . All reported P values were 2-sided with a 0.05 significance level. All variables screening in multiple regression methods led to choosing the most important variables that contribute to the response variable. Statistical analyses were conducted using SPSS version 28 and GraphPad Prism 8.

RESULTS

All 188 countries were included in the analysis. The total number of registered COVID-19 cases was 541937600 with a total mortality number of 6317644 patients. The mean of COVID-19 mortality was $1.52 \pm 1.72\%$, with a range between a minimum of 0.03% (Bhutan country) to a maximum of 18.2% (Yemen country). Evaluation of CFR based on the continents, revealed the minimum fatality rate which was in Oceania continent (0.46%) and the maximum which was in South America (2.33%). It was mentioned that 50% of the studied countries had the case fatality rate $> 1.15\%$ (median) (Figure 1).

The mean population density was 447.6 ± 2113 person/Km². The percentage of population > 70 years old was $5.42 \pm 4.22\%$ (min: 0.53, United Arab Emirates, max: 18.5, Japan). The mean GDP per capita in 2020 was 15389.61 ± 23441.43 . The lowest life expectancy rate was in Central African Republic (53.6 years) and the highest was in Hong Kong (85.39 years). There were 2.35 ± 1.93 physicians per 1000, and hospital beds per 1000, with the highest for Cuba (8.3) and Japan (13.05) respectively. The lowest number of conducted tests per one million population was in Algeria (5083) and the highest was

Table 1 Descriptive statistics (mean \pm SD) for candidate predictor variables, R square, coefficient (SE) for univariate regression between predictors and case

| Variable | Mean (SD) | R ² | Beta (SD) | P value |
|--|-------------------------|----------------|----------------|---------|
| Population density ¹ | 300.96 (1539.00) | 0.027 | -0.116 (0.051) | 0.025 |
| GDP per capita in 2020 ¹ | 15389.61 (23441.43) | 0.000 | 0.013 (0.053) | 0.812 |
| Health Expenditure per capita ¹ | 1161.25 (1865.17) | 0.176 | -0.251 (0.041) | < 0.001 |
| Population ages \geq 70 yr | 5.42 (4.22) | 0.062 | -0.059 (0.017) | < 0.001 |
| Percent Obese | 18.93 (9.93) | 0.042 | -0.021 (0.007) | 0.006 |
| Percent Diabetes | 7.92 (4.09) | 0.030 | -0.042 (0.018) | 0.018 |
| Percent HIV ¹ | 1.91 (4.33) | 0.001 | 0.022 (0.066) | 0.743 |
| Percent Tobacco Users | 20.05 (9.55) | 0.016 | -0.013 (0.008) | 0.116 |
| Life expectancy at birth | 72.53 (7.31) | 0.157 | -0.054 (0.009) | < 0.001 |
| General death rate per 1000 | 7.87 (2.97) | 0.017 | 0.044 (0.025) | 0.075 |
| Hospital beds per 1000 | 3.29 (2.44) | 0.115 | -0.145 (0.041) | < 0.001 |
| Physicians per 1000 | 2.35 (1.93) | 0.064 | -0.197 (0.074) | 0.009 |
| Radiologist per 100 K | 13.56 (5.52) | 0.005 | 0.008 (0.026) | 0.759 |
| CT scanners per million | 29.05 (20.02) | 0.353 | -0.932 (0.213) | < 0.001 |
| Air pollution ¹ | 22.31 (14.73) | 0.066 | 0.416 (0.165) | 0.014 |
| Literacy rate | 82.25 (17.33) | 0.067 | 0.013 (0.006) | 0.023 |
| Human development index | 0.72 (0.15) | 0.178 | -2.787 (0.445) | < 0.001 |
| Tests per 1 million ¹ | 1654560.98 (2994282.33) | 0.234 | -0.266 (0.036) | < 0.001 |
| Doses per 100 people | 133.56 (79.68) | 0.356 | -0.007 (0.001) | < 0.001 |
| Given 1+ dose | 57.71 (26.97) | 0.319 | -0.020 (0.002) | < 0.001 |
| Percent Fully vaccinated | 52.49 (26.82) | 0.341 | -0.021 (0.002) | < 0.001 |

¹Ln Transformed.

HIV: Human immunodeficiency viruses; CT scanner: Computed tomography scanner GPD: Gross Domestic Product.

in Denmark (21880771). Regarding the vaccination rate, the lowest percentage of fully vaccinated rate was in Algeria (5083) and the highest was in Denmark (21880771). It was mentioned that 50.8% of the studied countries given 1+ dose vaccination rate < 65.4 (median), and 50.5% given full vaccinated rate < 60.7 (median).

With regards to the number of confirmed cases and performed COVID tests, the minimum and maximum rates were from Africa and Europe, respectively. The minimum and maximum vaccination rates associated with Africa and South America, respectively.

Means and standard deviations of candidate predictors along with the univariate regression coefficient for each individual predictor are shown in **Table 1**. In these univariate regression models, our analysis demonstrated a statistically significant inverse correlation between CFR and logarithm of population density ($P = 0.025$), logarithm of health expenditure per capita ($P < 0.001$), Population ages \geq 70 Years ($P < 0.001$), percent obese ($P = 0.006$), percent diabetes ($P = 0.018$), life expectancy at birth and hospital beds per 1000 ($P < 0.001$), physicians per 1000 ($P = 0.009$), CT scanners per 1 million, Human Development Index (HDI), logarithm of tests per 1 million, given greater than one vaccination, and percent of fully vaccinated people ($P < 0.001$). Conversely, it revealed a statistically significant direct correlation between logarithm of air pollution ($P = 0.014$) and literacy rate ($P = 0.023$) with CFR (**Table 1**).

There were also several cases of collinearity. For instance, there were strong positive correlations between the general death rate and Prevalence of current tobacco use ($r = 0.333$, $P < 0.001$), Hospital beds per 1000 ($r = 0.598$, $P < 0.001$), Physicians per 1000 ($r = 0.467$, $P < 0.001$), HDI ($r = 0.176$, $P = 0.018$), Current health expenditure per capita ($r = 0.154$, $P = 0.042$), and inverse correlation with Diabetes prevalence ($r = -0.299$, $P < 0.001$), and Air pollution ($r = -0.317$, $P = 0.002$). Also we find a significant positive correlation between CT scanners per 1M and Current health expenditure per capita ($r = 0.337$, $P = 0.041$), Hospital beds per 1000 ($r = 0.479$, $P = 0.003$), Human development index ($r = 0.358$, $P = 0.029$), and inverse correlation with obesity rate ($r = -0.422$, $P = 0.009$), and there was a significant direct correlation between HDI and Obesity Rates ($r = 0.533$, $P < 0.001$) and Diabetes ($r = 0.224$, $P = 0.002$).

In the following, we have multiple predictors without a statistically significant association with the response (all variable with $P > 0.05$ in **Table 1**). VIF values were < 5 which represents a medium level of collinearity, therefore we decided to keep all variables, thus we used model reduction (reduce the model by removing terms one at a time) to

Table 2 Multiple regression results with forward method for all candidate statistically significant correlated independent variables

| Model | Variable | Beta (SD) | Standardized beta | P value | R square (P value) |
|-------|--|--------------|-------------------|---------|--------------------|
| 1 | (Constant) | 7.80 (1.30) | | < 0.001 | 0.799 (< 0.001) |
| | Health expenditure per capita | -1.06 (0.17) | -0.894 | < 0.001 | |
| 2 | (Constant) | 3.42 (1.82) | | 0.093 | 0.895 (< 0.001) |
| | Health expenditure per capita | -0.79 (0.16) | -0.667 | < 0.001 | |
| | Air pollution | 0.93 (0.32) | 0.384 | 0.018 | |
| 3 | (Constant) | 4.29 (1.40) | | 0.016 | 0.947 (< 0.001) |
| | health Expenditure per capita | -0.69 (0.12) | -0.580 | < 0.001 | |
| | Air pollution | 0.91 (0.24) | 0.377 | 0.006 | |
| | Number of CT scanners (1 million people) | -0.51 (0.18) | -0.246 | 0.023 | |
| 4 | (Constant) | 3.10 (1.14) | | 0.030 | 0.974 (< 0.001) |
| | Health expenditure per capita | -0.58 (0.10) | -0.486 | < 0.001 | |
| | Air pollution | 1.01 (0.19) | 0.415 | < 0.001 | |
| | Number of CT scanners (per 1 million people) | -0.74 (0.16) | -0.357 | 0.002 | |
| | Literacy rate | 0.01 (0.00) | 0.199 | 0.031 | |

CT scanner: Computed tomography scanner.

increases the precision of predictions from the model. To use the statistical significance criterion, after set the significance level on 0.05 we tried different variables to find a model with as many statistically significant terms as possible but with no statistically insignificant terms. We applied the statistical significance criterion manually, with stepwise regression algorithm.

It has been observed that first "Current Health expenditure per capita "with $P < 0.001$ was entered into the model (model 1), then the variable "Air pollution" has been added to the model with level of significance of 0.018 (model 2), in the third model, "number of CT scanners per 1000 people" has been added to the model and it has been observed that the entry of these changes the Air pollution level of significance from 0.018 (model 2) to 0.006 (model 3). In the fourth model, after entering the "Literacy rate" variable, the regression coefficients and P values of all three previous variables have changed in the model, but the direction of their relationship has not changed. After entering the last variable (literacy rate) into the other model, none of the candidate predictors had the criteria to enter the model, therefore the final model will be the fourth model, with the final multiple regression equation: $Y = 3.1 - 0.58$ (Health Expenditure per capita) + 1.01 (Air pollution) - 0.74 (Number of CT scanners) + 0.01 (Literacy rate).

Base on this model, we could claim that this final model can predict approximately 97% of the changes in CFR. Therefore, it suggested an optimal model (Table 2, Figure 2). In this model, there was a statistically significant inverse correlation between health expenditure ($P < 0.001$) and number of CT scanners per 1 million ($P = 0.002$) with CFR. In addition, a statistically significant direct correlation was found between literacy rate ($P = 0.038$) and air pollution ($P < 0.001$) with CFR.

The correlation between estimated model and CFR is shown in Figure 2. As mentioned before, despite the fact that the model has shown an appropriate fit, due to the lack of data in some variables, including the CT variable, we have lost a lot of data.

DISCUSSION

Our study provides new population-based insights regarding the risk factors of COVID-19 mortality. This is an update on our previous efforts to identify indices and predictors of fatal outcomes in different populations based on their socioeconomic status and healthcare system resources.

In previous studies there was a direct association between CFR and increasing age with or without comorbidities[7-9, 16-18,26,27]; however, in this study, age 70 and above showed a negative correlation with CFR. This finding can be explained by variance factors such as priority in receiving jabs, strict isolation and social distancing for seniors and lower threshold of intensive care unit (ICU) admission. A higher development index in the countries with a higher median age was also reported as another explanation[19].

With regard to the association between CFR and smoking, there have been discrepant results in the literature. A meta-analysis by Hou *et al*[28] revealed that smoking was independently associated with increased mortality rate in COVID-19 patients, particularly in former smokers. A review article by World Health Organization (WHO) in 2020 demonstrated an increased severity and mortality of COVID-19 in hospitalized smoking patients[29]. Conversely, in a review article in

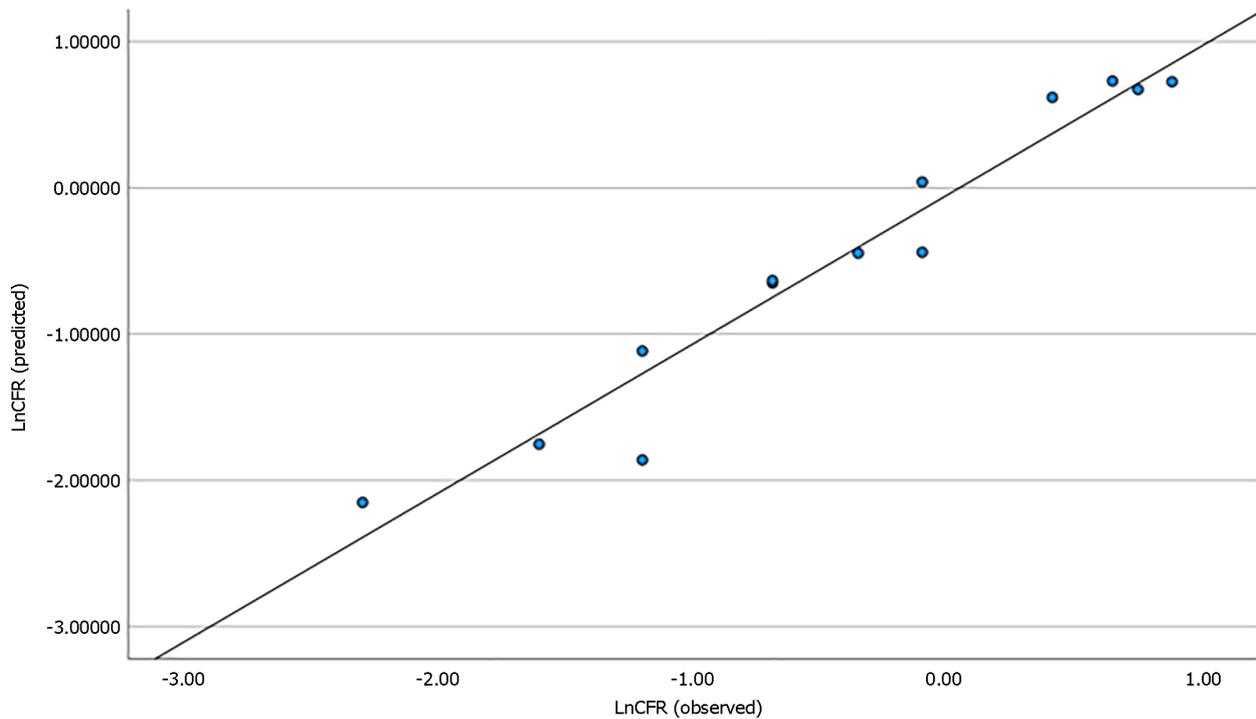


Figure 2 In this scatter plot, the relationship between the observed case fatality rate values and the estimated values obtained by the model can be seen. Despite the fact that the model has shown a favorable fit, but due to the small number of data related to some variables, including the computed tomography scanners variable, we have lost a lot of data regarding case fatality rate. CFR: Case fatality rate.

Alberta, there was no significant increase in severity of COVID-19 in smokers[12]. Comparably, smoking did not have statistically significant correlation with CFR in our study. The reasonable explanation for this controversy could be a lower threshold to use antivirals in these patients or admit them to an ICU.

Life expectancy at birth is described by the average number of years that a newborn is expected to live, considering the age- and sex-specific rates at the time of birth[30]. It is an indicator of the overall mortality level of a population which summarizes the mortality pattern including all age groups - children and adolescents, adults, and the elderly. In our study, countries with a higher COVID-19 CFR had a lower life expectancy at birth which have a latitude of explanations such as better health service coverage and higher health literacy rate in those countries with longer life expectancy. This finding was in agreement of the results of life expectancy evaluation in several countries, including United States and Canada, during the COVID-19 pandemic[31-35].

In a study by Sen-Crowe *et al*[36] on 183 countries, there was a weakly positive significant association between the number of ICU beds per 100000 population and COVID-19 mortality. Though, there was no significant association between the number of hospital beds or acute care beds per 100000 populations and COVID-19 mortality. In other studies, a negative association between hospital capacity, especially hospital beds, and COVID-19 mortality has been confirmed[18,37,38]. Similarly, our study revealed lower COVID-19 CFR in the countries with a higher number of hospital beds per 1000 population, which potentially can be explained by the higher level of care for COVID-19 patients in these countries. Similar findings were noted in association of COVID-19 CFR and the number of physicians per 1000 population, which was in line with the cross-sectional study by Tchicaya *et al*[39] in France in 2020. Increased staffing, particularly with Registered Nurses, has been reported as a protective factor leading to decreased mortality[15]. In another study by Stephen Rocks in 2020 on the effects of hospital capacity on COVID-19 mortality in 33 countries, a negative association between hospital capacity, especially hospital beds, and COVID-19 mortality rate was found. However, they realized that the main determinants in these countries were mostly variables other than treatment capacity per se, including earlier lock-down restrictive measures, which limited the number of new cases. Moreover, they found that low hospital capacity can affect mortality by detracting other sources from non-health sections leading to indirect effects on COVID-19 mortality rather than a direct effect[37].

With regards to COVID-19 testing, the more COVID tests were performed, the lower was the CFR. This finding was in agreement with the previous studies in which a negative association between COVID-19 testing and mortality was demonstrated[40-42], particularly among low-income countries and those with fewer hospital beds[41]. Timely testing can lead to earlier isolation and effectively limit the disease spread, as well as appropriate treatment interventions, if required[43,44].

HDI is defined by having a standard living with a healthy and long life and access to education (Our World in Data). Studies on the association between HDI and COVID-19 CFR, found a negative correlation[45-48]. However, there have been a few studies that have reported positive correlation which was explained by a higher infection rate as a result of higher rate of chronic disease, higher number of performed COVID-19 tests and older population in these high HDI countries[14,49,50]. Our study demonstrated less CFR in countries with a higher HDI worldwide. This also could be due

to more access to education in these countries.

Several types of COVID vaccines have been produced from inactivated or weakened virus vaccines to RNA and DNA vaccines[51]. To date, based on the WHO vaccine tracker, 169 and 198 vaccines have been under clinical and pre-clinical development, respectively. Vaccination by COVID-19 vaccine has been mentioned as a protective factor against the disease severity and mortality in the literature[9,17]. In a meta-analysis by Huang *et al*[13] in 2021, it was found that all types of vaccines, compared with no vaccine status, were effective to decrease the frequency of severe cases and consequently, to decrease the mortality rate. In a longitudinal study on 90 countries, 10% increase in vaccine coverage led to 7.6% decrease in CFR[52]. Our study also revealed a negative association between the number of COVID-19 vaccine doses, receiving at least one dose vaccine and fully vaccination with CFR.

With regard to the correlation between comorbidities such as diabetes and obesity with CFR, there have been various results in the literature. In a meta-analysis of 87 studies on the association between COVID-19 mortality and the comorbidities, diabetes mellitus was one of the most important factors associated with mortality[53]. Similar findings have been reported in the literature[54,55]. Comparably, there has been an increased COVID-19 mortality in obese patients (body mass index over 30 kg/m²), both in adults and pediatrics[17,56,57]; however, in an evidence-based review in Alberta, there has not been a consistent association between obesity and mortality. Moreover, there was not a high strength association between diabetes and COVID-19 mortality[12]. Our study revealed a negative correlation between diabetes and obesity with CFR indicating decreased CFR in diabetics or obese patients (Table 1). The higher prevalence of obesity and diabetes in countries with higher HDI[11,14,45,47,48] which can explain the lower CFR in this population.

Our regression analysis modeling was able to define the effects of the above given variables on the CFR, when considering them together. Our subsequent modeling and regression analysis revealed that the following variables have the highest connection with CFR: Health expenditure per capita, CT scanner per 1 million, air pollution, and literacy rate.

Health expenditure means all expenditures required for the planning of health services, family planning activities, nutrition activities and emergency aid designated for health, except for the provision of drinking water and sanitation (WHO). There has been a negative correlation between health expenditure and rigorous policies regarding COVID-19, including closure of the schools, universities and working places, home confinement, as well as internal and international travel restrictions[58]. Despite the thought that higher health expenses should decrease mortality due to better patient care, a positive correlation between health expenditure and COVID-19 mortality is reported in the literature[59]. This finding is in agreement with our study. It could be the result of lower efficacy of the health care in regions with higher health expenses.

In a literature review by Pan *et al*[18] on 39 countries in 2020, the number of CT scanners per one million was associated with decreased CFR. We also found statistically significant association between the number of CT scanners per one million and COVID-19 CFR. This can be explained by earlier detection of lung involvement through CT scan which leads to timely treatment[60,61], particularly in low- to mid-income countries with less availability of COVID-19 tests, earlier in the course of pandemic[62] which can prevent more severe disease and subsequently decreases mortality.

Several studies have considered air pollution as a risk factor which increases morbidity and mortality of COVID-19[43, 44,63]. This was in agreement with our study, both in univariate regression and multiple regression analysis. This could be because of the detrimental cardiovascular effects of air pollution, both short- and long-term, through oxidative stress and inflammation in lungs and heart vessels, leading to reduced lung function, atherosclerosis, and acute thrombotic complications[64].

There are many studies indicating negative correlation of health literacy with COVID-19 morbidity and mortality[65, 66]. To the best of our knowledge, the correlation between COVID-19 CFR and literacy rate has not been reviewed in the literature. This study revealed a negative correlation between CFR and literacy rate, based on the WHO's definition of literacy rate. High health literacy rate may originate from a better literacy rate leading to lower mortality due to healthier behavior.

CONCLUSION

This study revealed controversial findings pertaining to the different variables analysis per se. However, adding multiple variables in a model increased the accuracy of the evaluation of those risk factors. Our multiple-model regression analysis explained a higher percentage of changes in CFR in relation with health expenditure, number of CT scanners per one million, air pollution, as well as literacy rate.

Limitations

There were some limitations to this study. Firstly, source of the analysed data in our study was based on the reports from different countries; therefore, the true CFR could be more than the reported one. Moreover, in this study, we could not include all countries due to inadequate recording of data on CFR. Secondly, we could not evaluate or achieve statistically significant correlation between CFR and some variables due to incomplete data on some variables that have been already mentioned in some isolated reports.

ARTICLE HIGHLIGHTS

Research background

The worldwide case fatality rate (CFR) of coronavirus disease 2019 (COVID-19) has been estimated to be around 1.5% as of now. Different variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus have been discovered to cause the disease. The clinical presentation of the disease ranges from asymptomatic status to upper respiratory tract symptoms, mild pneumonia, severe respiratory symptoms, acute respiratory distress syndrome, extrapulmonary manifestations, and death. Various risk factors for COVID-19 mortality including age, male gender, comorbidities (such as chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease), diabetes mellitus, malignancy, underlying autoimmune disease, and hypertension), ethnicity, vaccination status, smoking history, obesity, and socioeconomic status. On the other hand, some factors have been proven to be protective, which may reduce the severity or mortality of COVID-19 infection, as among which vaccination, efficiently staffed facilities, particularly by registered nurses corticosteroid treatment, and healthy diet are the most notable. Gathering updated information from international data sources could throw light on the protective or potential risk factors to avoid COVID's severe morbidities and mortality.

Research motivation

We find it interesting the topic trend analysis in the COVID-19 literature, and the success of modeling studies in the field of predicting disease behavior was a turning point for us.

Research objectives

The objective motivation for doing this study is to assess the correlation between different known risk factors or protective measures and the COVID-19 case fatality rate and we decided to design and conduct a new study based on modeling.

Research methods

Twenty-one potential risk factors were identified for COVID-19 case fatality rate for all the countries with available data. Univariate relationships of each variable with case fatality rate, and all independent variables to identify candidate variables for our final multiple model were examined. Finally multiple regression analysis technique was used to assess the strength of relationship between case fatality rate and several predictors' variables as well as the importance of each predictor to the relationship.

Research results

There was a statistically significant inverse correlation between health expenditure, and number of computed tomography scanners per 1 million with case fatality rate, and a significant direct correlation was found between literacy, and air pollution with case fatality rate, this final model can predict approximately 97% of the changes in case fatality rate, conclusion: The current study recommends some new predictors explaining affect mortality rate. Thus, it could help decision-makers develop health policies to fight COVID-19.

Research conclusions

I suggest to do the same study with the updated data and compare the results. Multiple regression analysis technique is used as the most wrong and reliable method.

Research perspectives

Considering that global vaccination has been carried out, it is suggested that the approach of future realizations is to investigate the effectiveness of vaccines and compare the performance of vaccines with each other.

FOOTNOTES

Author contributions: Gholamrezanezhad A and Sagheb S conceived of the presented idea, and set the first draft of manuscript; Karami M and Pavlovic E developed the theory and worked out almost all of the technical details, and data extraction; Sagheb S and Fakhrazadegan M designed the model and the computational framework and analysed the data; language editing and revising the manuscript has done by Pavlovic E; All authors discussed the results and contributed to the final manuscript.

Institutional review board statement: In this modeling publicly available register-based ecological study as a population study, all data are available on open data sources like Our World in Data, World Bank, Statistics, OECD Database, and World Population Review. We included no private patients and no private data, and everything is clear in the references. As the research involves information freely available in the public domain, this study doesn't need to ethics code or institute approval.

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