

Global between-countries variance in SARS-CoV-2 mortality is driven by reported prevalence, age distribution, and case detection rate

Submitted: 28 May 2020

Haris Babačić, Janne Lehtiö, Maria Pernemalm¹

Objective: To explain the global between-countries variance in number of deaths per million citizens (nD_{pm}) and case fatality rate (CFR) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Design: Systematic analysis.

Data sources: Worldometer, European Centre for Disease Prevention and Control, United Nations

Main outcome measures: The explanators of nD_{pm} and CFR were mathematically hypothesised and tested on publicly-available data from 88 countries with linear regression models on May 1st 2020. The derived explanators - age-adjusted infection fatality rate (IFR_{adj}) and case detection rate (CDR) - were estimated for each country based on a SARS-CoV-2 model of China. The accuracy and agreement of the models with observed data was assessed with R^2 and Bland-Altman plots, respectively. Sensitivity analyses involved removal of outliers and testing the models at five retrospective and four prospective time points.

Results: Globally, IFR_{adj} estimates varied between countries, ranging from below 0.2% in the youngest nations, to above 1.3% in Portugal, Greece, Italy, and Japan. The median estimated global CDR of SARS-CoV-2 infections on April 16th 2020 was 12.9%, suggesting that most of the countries have a much higher number of cases than reported.

At least 93% and up to 99% of the variance in nD_{pm} was explained by reported prevalence expressed as cases per million citizens (nC_{pm}), IFR_{adj} , and CDR . IFR_{adj} and CDR accounted for up to 97% of the variance in CFR , but this model was less reliable than the nD_{pm} model, being sensitive to outliers (R^2 as low as 67.5%).

Conclusions: The current differences in SARS-CoV-2 mortality between countries are driven mainly by reported prevalence of infections, age distribution, and CDR . The nD_{pm} might be a more stable estimate than CFR in comparing mortality burden between countries.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has substantially affected the lives of billions of people.(1,2) An ongoing question in the public is how high is the direct mortality caused by SARS-CoV-2. Observations in the case fatality rate (CFR), i.e. the

proportion of individuals with a confirmed SARS-CoV-2 infection who die, has raised concerns due to the high variability between countries, ranging from below 0.1% in Qatar and Singapore to above 15% in Belgium and France, on May 27th 2020.(3,4)

The global average case detection rate

¹ Science for Life Laboratory; Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden; email: haris.babacic@ki.se

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

(*CDR*) on March 30th was estimated at 9%, suggesting that the true prevalence of infections is likely underestimated in most of the countries.(9) Studies suggest that the reported number of cases per million citizens (nC_{pm}) is probably lower than the true number of infected individuals, and that this contributes to the varying *CFR* between countries.(5,6) *CFR* appears higher than the true infection fatality rate (*IFR*), i.e. the true proportion of individuals with a SARS-CoV-2 infection who will die in the population regardless of whether they are confirmed or not.(7) This was observed in China where the crude *CFR* estimate was 3.67%, whereas the age-adjusted overall *IFR* (IFR_{adj}) was estimated at 0.66%.(8)

The number of confirmed deaths per million citizens (nD_{pm}) is a population-normalised measure of mortality used to compare countries. However, the varying nD_{pm} in countries with similar nC_{pm} , population size and similar mitigation strategies has also raised fears of potential varying virulence of the virus and different treatment capacity between countries. A recent multivariable model could explain only 62.5% of SARS-CoV-2 mortality variance between countries.(10) Explaining the remaining variance of the reported mortality as nD_{pm} and *CFR* is extremely relevant for both the medical community and the public, to address public concerns. Furthermore, it is important to assess whether the adjusted mortality differs substantially between countries, in order to track the success of different strategies.

The aim of this study was to test two mathematical hypotheses that explain the global between-countries variance in SARS-CoV-2 mortality expressed as nD_{pm} and *CFR* on real data.

Methods

Data sources

Global data on cumulative number of cases (nC), cumulative number of deaths (nD), cumulative number of tests (nT), number of tests per million citizens (nT_{pm}), number of cases per million citizens (nC_{pm}), and nD_{pm} per country were downloaded from

Worldometer.(3) Global data on number of new cases and deaths per day were downloaded from the European Centre for Disease Prevention and Control (ECDC).(4) Global data on age distribution and 2018 GDP per country were obtained from United Nations (UN) statistics.(11,12)

Derivation of hypotheses

The overall IFR_{adj} per country was estimated and weighed per nine age groups, following the equation:

$$IFR_{adj} = \frac{\sum_{i=1}^9 n_i \times IFR_i}{N}$$

where IFR_{adj} is the IFR_{adj} in percentages (%), N is the total population size, n_i is the number of susceptible individuals within an age group, IFR_i is the *IFR* for that age group in % as estimated by Verity and colleagues.(8) For the purposes of this study, the IFR_{adj} serves as an age-adjustment factor.

The *CDR* per country was estimated as the percentage of the estimated cases that have been confirmed cases, following the approach of Vollmer & Bommer (9):

$$CDR_i = \frac{nC_{\tau i}}{nD_{\tau j} \times \frac{100}{IFR_i}} \times 100\%,$$

where CDR_i is *CDR* in %, IFR_i is IFR_{adj} in %, $nC_{\tau i}$ is cumulative number of confirmed cases at time τi , and $nD_{\tau j}$ is cumulative number of confirmed deaths at time τj . Following the Verity model(8), τi is 14 days before τj in this approach, based on the estimate that on average 18.8 days pass from the onset of symptoms to death, holding a conservative assumption that on average 4.8 days pass from symptom onset to case detection.

From these equations, $nD_{\tau j}$ is implied to have an inverse relation with the CDR_i and will depend on the cumulative number of cases 14 days before the $nD_{\tau j}$ have occurred, and the age-adjusted IFR_i :

$$nD_{\tau j} = \frac{nC_{\tau i} \times IFR_i}{CDR_i}$$

Assuming that the number of cases at the time of $nD_{\tau j}$ ($nC_{\tau j}$) will have a constant dependence on the $nC_{\tau i}$, as observed repeatedly in epidemics, including SARS-CoV-2, $nC_{\tau j}$ can replace it in the equation. In order to explain the population-

normalised number of deaths - nD_{pm} , one has to normalise the $nC_{\tau j}$ per population size with nC_{pm} , deriving that:

$$nD_{pm,\tau j} = \frac{nC_{pm,\tau j} \times IFR_i}{CDR_i} \text{ [hypothesis 1]},$$

where nD_{pm} at time τj will be higher in countries with higher nC_{pm} at time τj and higher IFR_{adj} , whereas it will be lower in countries with the same nC_{pm} and IFR_{adj} that have higher CDR .

Following that the CFR is the proportion of $nD_{\tau j}$ from the $nC_{\tau j}$, the subsequent relationship between the CFR , the IFR_{adj} and CDR is implied as:

$$CFR_i = \frac{nC_{\tau i} \times IFR_i}{nC_{\tau j} \times CDR_i},$$

where CFR_i is the CFR of a country, IFR_i is the IFR_{adj} of a country, $nC_{\tau j}$ is the cumulative number of cases on the day of $nD_{\tau j}$, and $nC_{\tau i}$ is the cumulative number of cases two weeks before τj . Again, assuming that $nC_{\tau j}$ will have a constant dependence on the $nC_{\tau i}$, they can be omitted from the equation, deriving that:

$$CFR_i = \frac{IFR_i}{CDR_i} \text{ [hypothesis 2]},$$

where the CFR will be higher in countries with higher IFR_{adj} and will have an inverse relation with the CDR . Hypothesis 2 implies that older countries will have higher CFR and countries with higher CDR will have lower CFR , and predicts that the $nC_{\tau j}$ will not drive CFR .

Testing hypotheses on real data

To test hypothesis 1, we built linear regression model 1 (nD_{pm} model), to explain nD_{pm} with nC_{pm} , IFR_{adj} , and CDR . To test hypothesis 2, we built linear regression model 2 (CFR model), to explain CFR with IFR_{adj} and CDR . Only countries with more than 1,000 cases were included in the analyses. All variables were normalised by log transformation. We have additionally tested whether GDP, nT_{pm} , and duration of epidemic (as days from first case) could explain the mortality after being added to the models.(10) The accuracy was assessed with R^2 , and the agreement was analysed graphically with the Bland-Altman mean difference plot.(13)

Sensitivity analyses. To address uncertainty, we removed outliers outside of the 95% confidence intervals (95% CI) of the Bland-Altman plots, and reiterated the analyses retrospectively on April 4th, 8th, 12th, 21st, 24th, and prospectively on May 7th, 11th, 18th, and 27th 2020.

Data and code availability

The study is conducted according to the Guidelines for Accurate and Transparent Health Estimates Reporting.(14) The code, data, and results are publicly available at https://github.com/harbab/covid_19_mortality. All analyses were performed in R V.3.6.1.

Results

Descriptive statistics

As of May 1st 2020, a total of 214 countries in the world have reported SARS-CoV-2 infections. Of these, 88 countries have reported more than 1,000 SARS-CoV-2 infections. The estimated IFR_{adj} varied from below 0.2% in the youngest nations of Ivory Coast, Guinea, Nigeria, UAE, Cameroon, and Afghanistan, up to above 1.3% in the world's oldest nations of Germany, Portugal, Greece, Italy, and highest in Japan with 1.6%. The global average CDR on April 16th 2020 was 22.12% (median: 12.9%, SD: 32.47), suggesting that most of the cases were undetected. Only two countries detected more than 100% of expected cases – Iceland (154.50%) and Singapore (234.95%). Estimates for each country are shown in Table S1, supplementary information.

Model 1 – nD_{pm}

Univariate analyses showed that nC_{pm} , IFR_{adj} , and nT_{pm} could explain 65.57%, 40.29%, and 25.91% of the variance in nD_{pm} , respectively ($p < 3.922 \cdot 10^{-7}$). The CDR was not univariately associated with nD_{pm} ($p = 0.738$). However, combined together nC_{pm} , IFR_{adj} and CDR could explain 97.18% of the variance in nD_{pm} ($p < 2.2 \cdot 10^{-16}$). Introducing nT_{pm} to the model only slightly improved the R^2 to 0.9728 ($p < 2.2 \cdot 10^{-16}$). All four variables were included in the final model 1 (Table 1). The relationship

Table 1. Linear model 1 – explaining the log-transformed citizens nD_{pm} . The model had a residual standard error of 0.3073 on 79 degrees of freedom (4 observations with missing data). Multiple $R^2 = 0.9741$, adjusted $R^2 = 0.9728$. F-statistic: 743.8 on 4 and 79 DF, p-value: $< 2.2 \cdot 10^{-16}$.

Coefficient	Estimate	95% CI	Std. error	t-value	p-value	significance
Intercept	-0.9277	-1.3786, -0.4769	0.227	-4.096	0.0001	***
$\log (IFR_{adj})$	1.2951	1.1656, 1.4246	0.065	19.907	$1.61 \cdot 10^{-32}$	***
$\log (nC_{pm})$	0.9432	0.8647, 1.0216	0.039	23.931	$6.03 \cdot 10^{-38}$	***
$\log (CDR)$	-0.9899	-1.0785, -0.9012	0.045	-22.218	$1.01 \cdot 10^{-35}$	***
$\log (nT_{pm})$	0.0922	0.0071, 0.1774	0.043	2.156	0.0341	*

***, statistically highly significant; *, statistically low significance.

between the variables was as hypothesised mathematically. The model showed almost perfect accuracy (Figure 1A) and high agreement (Figure 1B) in explaining nD_{pm} . Some countries were outliers (Figure 1C).

Univariately, nD_{pm} had a positive association with GDP ($p = 8.213 \cdot 10^{-11}$) and the duration of the epidemic (0.0227). However, neither variable had an association with nD_{pm} when added to model 1 ($p = 0.308$ and 0.196 , respectively). GDP had a positive correlation with all four explanators of model 1 ($p < 9.341 \cdot 10^{-6}$), most evidently with nT_{pm} ($R^2 = 0.592$), and was thus redundant in the model. GDP and duration of epidemic are possibly unstable explanators that can be useful in stratified analyses per continents and regions.

Model 2 – CFR

Univariately, IFR_{adj} and CDR explained 17.68% and 40.35% of the variance in CFR , respectively. When combined together, IFR_{adj} and CDR accounted for 91.84% of the variance in CFR (Table 2). The predicted CFR also had high accuracy and high agreement with observed CFR (Figure 2). Both nC_{pm} and nC_{τ_j} were not associated with the CFR when added to model 2 independently, confirming the assumption on which hypothesis 2 relies. None of the additional variables (nT_{pm} ,

GDP, or duration of epidemic) was associated with CFR univariately or when added to model 2. nT_{pm} and GDP were also not associated with CFR in a previous report (10).

Sensitivity analyses

Reiterating the analysis at five retrospective and four prospective time-points showed that model 1 could robustly explain at least 93% of the variance in nD_{pm} (at least 95% after removing outliers), but model 2 had lower accuracy at earlier stages of the pandemic (Figure 3). Less countries had $>1,000$ cases at earlier time-points (range: 56 on April 4th – 110 on May 27th). The nT_{pm} was an unreliable explainer of nD_{pm} that accounted for a very small proportion of variance that can be omitted; the effect of nT_{pm} is possibly underestimated due to its association with nC_{pm} .

The CFR model was more sensitive to outliers compared to the nD_{pm} model, with a higher average decrease in R^2 of 5.53% (range: 1.4-9.6%, median: 5.85%) compared to an average decrease of 1.59% for the nD_{pm} model (range: 0.5-3.4%, median: 1.2%) when including outliers ($p = 0.0035$). The assumption of no effect of nC_{τ_j} on CFR was violated at some time-points.

Table 2. Linear model 2 – explaining the log-transformed CFR . The model had a residual standard error of 0.3126 on 84 degrees of freedom (1 missing data). Multiple $R^2 = 0.9203$, adjusted $R^2 = 0.9184$. F-statistic: 485 on 2 and 84 DF, p-value: $< 2.2 \cdot 10^{-16}$.

Coefficient	Estimate	95% CI	Std. error	t-value	p-value	significance
Intercept	4.0300	3.8188, 4.2412	0.1062	37.9440	$1.22 \cdot 10^{-54}$	***
$\log (CDR)$	-0.9366	-1.0048, -0.8685	0.0343	-27.3358	$1.42 \cdot 10^{-43}$	***
$\log (IFR_{adj})$	1.3290	1.2150, 1.4430	0.0573	23.1818	$2.93 \cdot 10^{-38}$	***

***, statistically highly significant.

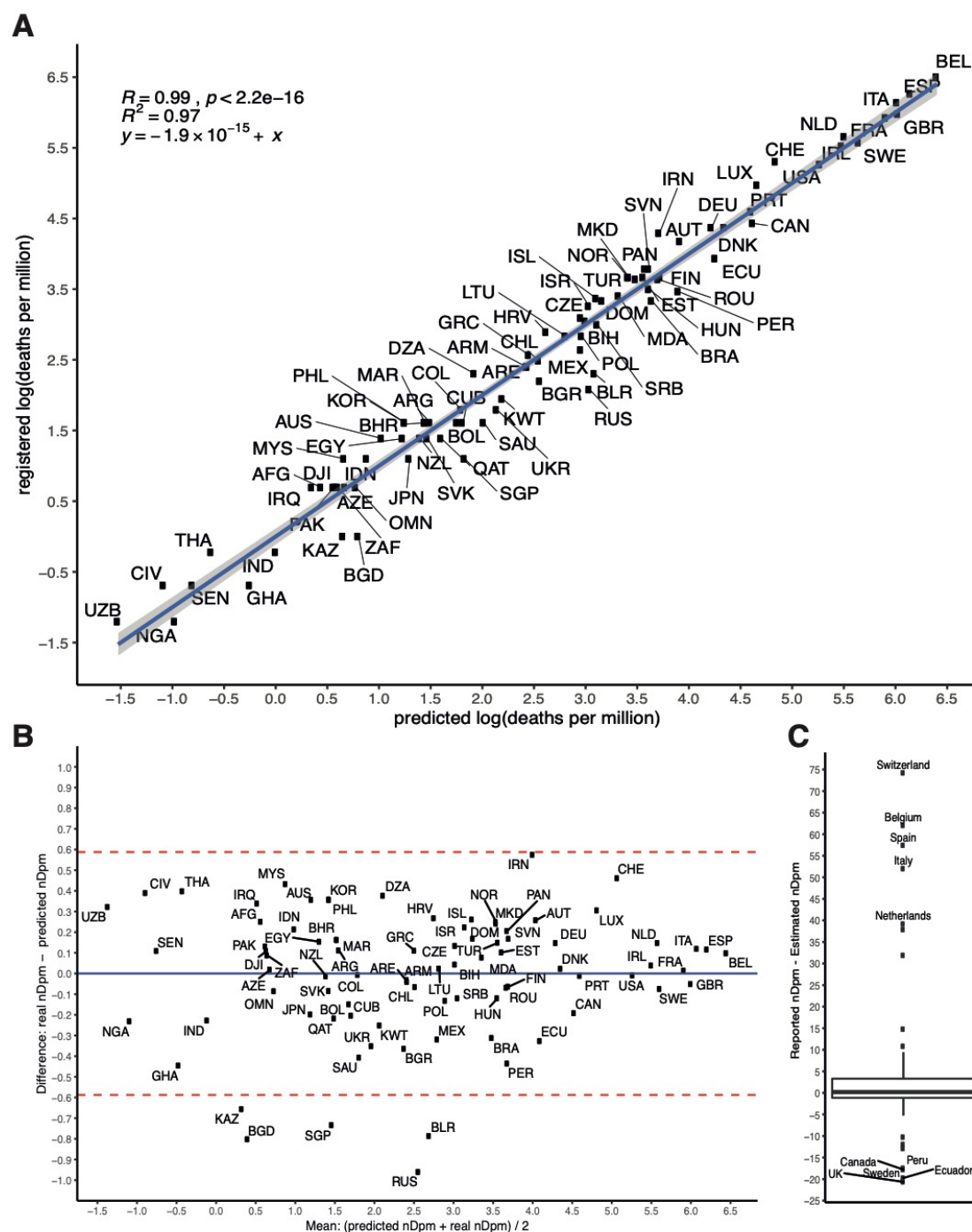


Figure 1. Agreement between predicted and observed deaths per million citizens (nD_{pm}). The countries are annotated with their country code. **A.** Predicted log-normalised nD_{pm} (x axis) vs log-normalised observed nD_{pm} (y axis). The model could almost perfectly predict the nD_{pm} in a linear fashion. The blue line is model fit and the shades are 95% CI; **B.** Bland-Altman plot. The mean of the predicted log-normalised nD_{pm} and observed log-normalised nD_{pm} is plotted on the x axis, whereas the difference on a log scale between the observed nD_{pm} and predicted nD_{pm} is plotted on the y axis. The mean difference between the observed nD_{pm} and predicted nD_{pm} was 0 (blue, full line), with the 95% confidence intervals (red, dashed lines) containing most of the values. Five countries were outliers in this model, having less nD_{pm} than predicted: Russia, Belarus, Singapore, Bangladesh, and Kazakhstan; **C.** Countries outliers. Actual difference between observed nD_{pm} and predicted nD_{pm} in numbers. The labelled countries in the upper part of boxplot ($>95^{th}$ quantile) had much more observed nD_{pm} than predicted, whereas the labelled countries in the lower part had much less nD_{pm} than predicted by the model.

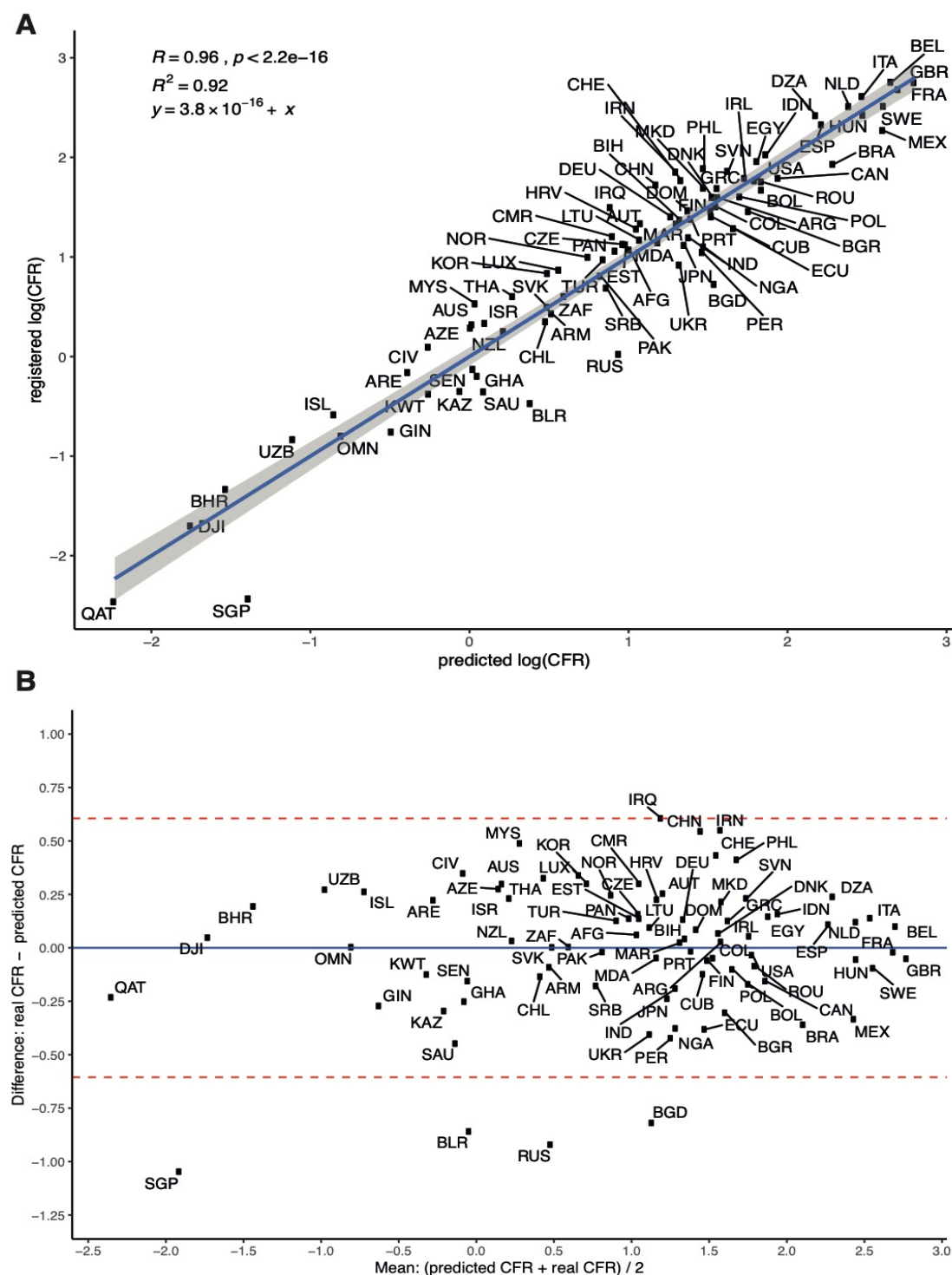


Figure 2. Agreement between observed and predicted case fatality rate (CFR). The countries are annotated with their country code. **A.** Predicted log-normalised CFR (x axis) vs log-normalised observed CFR (y axis). The model could predict almost perfectly the CFR in a linear fashion. The blue line is model fit and the shades are 95% CI; **B.** Bland-Altman plot. The mean of the predicted log-normalised CFR and observed log-normalised CFR is plotted on the x axis, whereas the difference on a log scale between the observed CFR and predicted CFR is plotted on the y axis. The mean difference between the observed CFR and predicted CFR was 0 (blue, full line), with the 95% confidence intervals (red, dashed lines) containing most of the values. Four countries were outliers in this model, having lower CFR than predicted: Russia, Belarus, Singapore, and Bangladesh.

On average, several countries had > 25 more nD_{pm} than expected - Italy, Belgium, Switzerland, Spain, the Netherlands, and Iran, whereas others had on average > 5 less nD_{pm} than expected - UK, Peru, Brazil, Belarus, Russia, Canada, Chile and Kuwait. Likewise, Italy, Algeria, Iran, the Netherlands, China, Belgium, Iraq, Indonesia, Spain, Switzerland, and the Philippines had on average $> 1.5\%$ higher CFR than expected according to the model, whereas Bangladesh, Ukraine, Brazil, Bolivia, Mexico, Belarus, Russia, Peru, and Honduras had on average $> 1\%$ lower CFR than expected.

At prospective time-points in May, three countries had consistently higher than 100% CDR , reporting more cases than expected: Singapore (range: 404-854%), Iceland (range: 159-160%), and Qatar (range: 121-210%). Detailed results from the sensitivity analyses are available in supplementary information.

Discussion

Most of the global variance in nD_{pm} between countries was explained by reported prevalence of SARS-CoV-2

infections (nC_{pm}) and age distribution as expressed with the IFR_{adj} . This has to be further adjusted for the CDR , which has an inverse relation with the nD_{pm} , but only in the context of using nC_{pm} and IFR_{adj} to explain nD_{pm} . As expected, the richer countries were better at testing and detecting cases, but were also older and had a higher infection mortality burden. The CFR is also dependent on the IFR_{adj} and the CDR , but does not depend on the prevalence or the total number of SARS-CoV-2 confirmed cases.

Some countries remain outliers, having consistently higher or lower mortality than expected according to the models. This is possibly due to consistent misreporting (10), differences in reporting deaths, diagnostic bias, sex distribution and average age of individuals who died - countries with on average higher mortality than expected possibly had more older people and more men infected and dying.(15)

The observation that several countries have detected a higher number of cases than expected and had lower observed CFR than IFR_{adj} (see supplementary

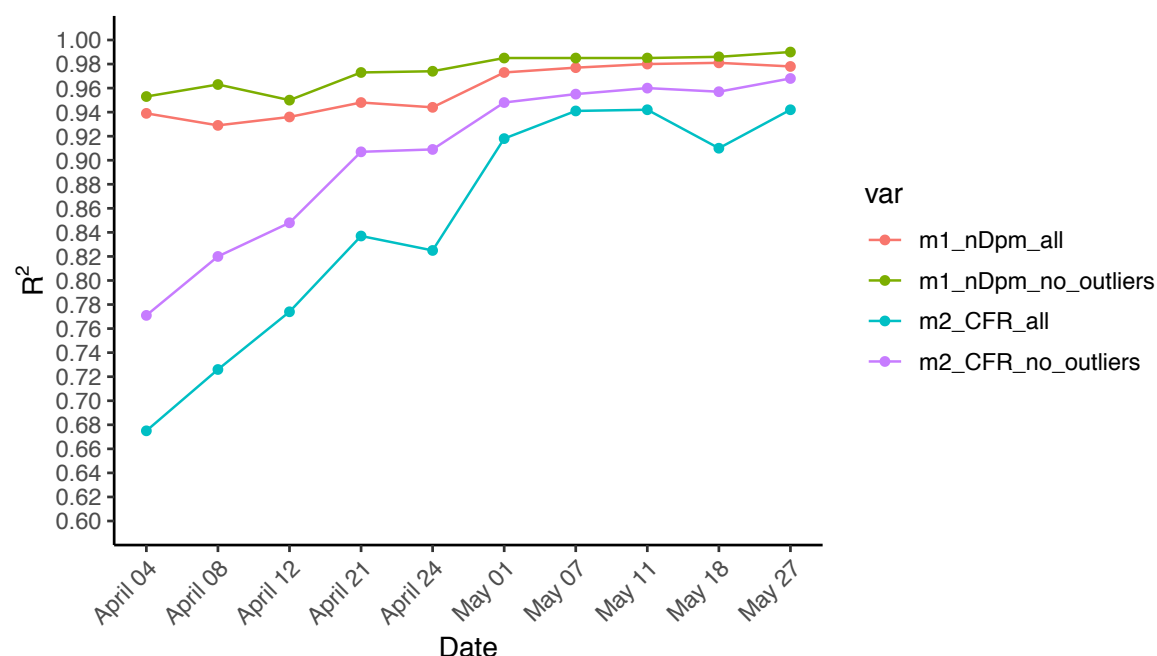


Figure 3. R^2 at ten time points of linear model 1 (explaining nD_{pm}) and linear model 2 (explaining CFR). m1_nDpm_all, model 1 with all countries included; m1_nDpm_no outliers, model 1 after excluding outliers; m2_CFR_all, model 2 with all countries included; m2_CFR_no_outliers, model 2 after excluding outliers.

information), supports the notion that the current *IFR* is overestimated and that the actual mortality is lower than estimated. To confirm these observations, serological surveys of populations will be essential in correctly estimating the true prevalence and mortality of SARS-CoV-2.

Strengths and limitations

These models use very few explanators while maintaining high accuracy in explaining mortality. The sensitivity analyses demonstrated the robustness of the mathematical models when tested on real data. There is a remaining small proportion of variance that cannot be explained by the models, and this can be due to data mishandling or estimation errors, which limit the study. Independent of these limitations, the nD_{pm} model remained robust. The *CFR* model was more sensitive to outliers than the nD_{pm} model, and might be a less stable mortality outcome to follow SARS-CoV-2 mortality burden over time and across countries. The models were somewhat less accurate at earlier stages, which can be due to the amount of data (number of countries) used to build the models.

Conclusions and policy implications

Overall, this study demonstrates that most countries are on a similar SARS-CoV-2 mortality trajectory as the number of cases increases, after adjusting for age distribution and *CDR*. These models should be used for less biased comparisons of mortality between countries. The nD_{pm} model appears as a more stable indicator of SARS-CoV-2 infection mortality burden and should be favoured in following and comparing mortality within and between countries.

Evidence before this study

- Verity and colleagues (Lancet Inf Dis 2020) have estimated the SARS-CoV-2 infection fatality rates (*IFR*) per age groups, and Vollmer & Bommer (2020) have estimated that the average case detection rate (*CDR*) of SARS-CoV-2 infections in 40 countries was below 10% end of March.
- No studies have been published explaining the global SARS-CoV-2 variance in mortality. A medRxiv preprint by Shagam (2020) reports that approximately 60% of SARS-CoV-2 mortality variance can be explained by gross domestic product per capita in United States dollars (GDP), latitude, hemisphere, press freedom, population density, fraction of citizens over 65 years old, and outbreak duration.

Added value of this study

- The models in this study demonstrate that most of the between-countries variance in SARS-CoV-2 mortality can be explained with two to three explanators, maintaining high accuracy. This can help to alleviate public concerns of potential varying virulence of the virus, and provide a less biased, standardised comparison of mortality burden between countries.
- In the setting of lacking an effective and safe treatment and/or vaccine against SARS-CoV-2, most of the countries will be on a similar SARS-CoV-2 mortality trajectory as the number of cases increases, after adjusting for the age distribution of the population and the case detection rate.

References

1. Studdert DM, Hall MA. Disease Control, Civil Liberties, and Mass Testing - Calibrating Restrictions during the Covid-19 Pandemic. *N Engl J Med*. 2020 Apr;
2. McKee M, Stuckler D. If the world fails to protect the economy, COVID-19 will damage health not just now but also in the future. *Nat Med*. 2020 Apr;
3. Worldometer. COVID-19 Coronavirus Pandemic [Internet]. 2020 [cited 2020 May 27]. Available from: <https://www.worldometers.info/coronavirus/>
4. European Centre for Disease Prevention and Control ECDC. Geographic distribution of COVID-19 cases worldwide [Internet]. [cited 2020 May 27]. Available from: <https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide>

5. Bendavid E, Mulaney B, Sood N, Shah S, Ling E, Bromley-Dulfano R, et al. COVID-19 Antibody Seroprevalence in Santa Clara County, California. medRxiv [Internet]. 2020 Jan 1;2020.04.14.20062463. Available from: <http://medrxiv.org/content/early/2020/04/30/2020.04.14.20062463.abstract>
6. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020 May;368(6490):489–93.
7. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. The Lancet. Infectious diseases. United States; 2020.
8. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Mar;
9. Vollmer S, Bommer C. Average detection rate of SARS-CoV-2 infections is estimated around nine percent [Internet]. 2020 [cited 2020 May 12]. Available from: <https://www.uni-goettingen.de/en/606540.html>
10. Shagam L. Untangling factors associated with country-specific COVID-19 incidence, mortality and case fatality rates during the first quarter of 2020. medRxiv [Internet]. 2020 Jan 1;2020.04.22.20075580. Available from: <http://medrxiv.org/content/early/2020/04/27/2020.04.22.20075580.abstract>
11. United Nations, Department of Economic and Social Affairs, Population Dynamics UN. World Population Prospects 2019, Online Edition. [Internet]. 2020 [cited 2020 Apr 12]. Available from: <https://population.un.org/wpp/Download/Standard/Population/>
12. UN Data, United Nations Statistics Division UN. Per capita GDP at current prices - US dollars [Internet]. 2020 [cited 2020 May 12]. Available from: <https://data.un.org/Search.aspx?q=gdp>
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet (London, England). 1986 Feb;1(8476):307–10.
14. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet (London, England). 2016 Dec;388(10062):e19–23.
15. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 Mar;

Acknowledgments: We express gratitude to Dr. Petter Brodin, Dr. Ioannis Siavelis, and Dr. Emilie Friberg for reading the draft and providing fruitful feedback.

Patient and public involvement: The study is conducted with publicly available data, and does not include individual patient or public involvement.

Ethical standards: The study was performed according to the ethical standards expressed in the Declaration of Helsinki. This study does not require ethical approval.

Contribution: HB designed the study, derived the hypotheses, collected, analysed and interpreted the data, and wrote and edited the manuscript. JL and MP assisted in design and interpretation of the study, supervised the work, reviewed and edited the manuscript.

Transparency: The corresponding author (HB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination: not applicable.

Competing interests: The authors declare no conflict of interest.

Funding: The authors have not received funding for this work.