Annals of Medicine and Surgery 65 (2021) 102319

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Cross-sectional Study

Predictors of Covid-19 case fatality rate: An ecological study

Osama Y. Alshogran [a,*], Shoroq M. Altawalbeh [a], Sayer I. Al-Azzam [a], Reema Karasneh [b]

[a] Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
[b] Department of Basic Medical Sciences, Faculty of Medicine, Yarmouk University, Irbid, Jordan

ARTICLE INFO

Keywords:
Covid-19
Pandemic
Fatality
Predictors
Ecological study
Global

ABSTRACT

Background: The outbreak of novel coronavirus (Covid-19) has a significant burden on global health and could be associated with significant mortality. Limited information exists about determinants of its fatality worldwide. Thus, this ecological study examined the association of various predictors with Covid-19 fatality.

Methods: International data bases of Covid-19 statistics and health metrics available primarily at WHO were reviewed to collect information for 113 countries. The dependent variable was Covid-19 case fatality rate. Independent variables were demographic, social, clinical, economic, heath care and child health factors.

Results: Case fatality rate of Covid-19 varies across countries with an average of 4.2 ± 3.8%, and about half of countries had fatality rate >3.2% (median). Significant relationships were observed between Covid-19 fatality rate and socio-economic, clinical, and health variables at the unadjusted regression analysis. At the multivariate adjusted model, percentage of population with age>60 years was positively associated with Covid-19 fatality (B = 0.032, p = 0.005), while Polio-3 immunization at 1-year old was inversely related (B = −0.057, p = 0.017).

Conclusions: This ecological investigation highlights the higher risk of death among elderly with Covid-19 pandemic and suggests that Polio-3 immunization coverage among 1-year-olds may be associated with better survival. Future research is warranted to validate these findings.

1. Introduction

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or (Covid-19)) has first emerged in Wuhan, China in December 2019 [1]. As of April 2020, the disease has been rapidly spreading across international borders, affecting most countries in the world, with cases rising in an exponential fashion [2]. As of April 23, 2020, about 2.59 million confirmed cases and 182808 deaths were reported worldwide by the "Our World in Data" group. Covid-19 outbreak was considered as pandemic by NIH in March 2020. The disease is threatening and associated with adverse clinical outcomes and increased mortality, with people primarily dying from respiratory failure [3,4]. Multiple measures have been implemented by countries with the hope to minimize the disease spread, morbidity, and mortality [5]. Notably, Covid-19 has significant burden on people life as a as well as on global economics, and the battle continues.

Despite the wide spread, there are notable differences between countries in the way that Covid-19 behaves and it is associated mortality. The determinants of Covid-19 mortality are being explored in limited number of studies which were mainly conducted in a fragmented scope including single center or a group of patients at a country level [3,6,7]. For instance, a prospective cohort study of 179 patients with Covid-19 pneumonia in China showed 21 deaths which were significantly linked to age>65 years, concurrent cardiovascular disease (CVD), and increased $CD3^{+}CD8^{+}$ and troponin levels [8]. Other studies also confirmed that older adults and the presence of comorbid conditions were associated with disease mortality [7,9]. Patients with comorbid hypertension, diabetes, or CVD may require special attention [10]. Though, chronic liver disease was not associated with disease severity or mortality [11]. With the wide and global spread of the disease, a clear understanding of factors associated with varied-worldwide mortality of Covid-19 is of great importance. This ecological study investigated the association of multiple demographic, social, economic, heath care, child health and noncommunicable disease-factors with fatality of Covid-19 worldwide.

* Corresponding author. Jordan University of Science and Technology, Faculty of Pharmacy, Department of Clinical Pharmacy, P.O. Box 3030, Irbid, 22110, Jordan.

E-mail address: oyalshogran@just.edu.jo (O.Y. Alshogran).

https://doi.org/10.1016/j.amsu.2021.102319
Received 15 March 2021; Received in revised form 9 April 2021; Accepted 12 April 2021
Available online 27 April 2021
2049-0801/© 2021 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2. Methods

2.1. Study design, population, and outcome measure

In this cross sectional ecological study, data regarding number of Covid-19 confirmed cases, deaths and case fatality were obtained from the Coronavirus Resource Center of Johns Hopkins University as of April 13, 2020 (https://coronavirus.jhu.edu/data/mortality). The total number of countries with this information was 121, however, the following countries (Burma, Congo, Diamond Princess, Kosovo, Moldova, North Macedonia, Taiwan, Tanzania) were later excluded because of limited necessary information about predictor variables at the World Health Organization (WHO). Each country was considered as a unit of analysis. The outcome measure was the percentage of case fatality which was calculated as (number of deaths/numbers of confirmed cases)*100. The study was conducted according to the guidelines of strengthening the reporting of cohort studies in surgery (STROCSS) 2019 [12].

2.2. Study variables and information source

Data of this ecological study were primarily obtained from the international databases of health metrics available from the WHO (https://www.who.int/countries/en/). Predictor variables were divided into multiple categories including demographics and socioeconomics such as population number and density, WHO region, and world bank income group, health care system such as expenditures and worker density, child health such as breast feeding and vaccination, mortality including neonatal mortality and life expectancy, prevalence of non-communicable diseases such as hypertension, diabetes, and obesity. The Annual mean concentration of particulate matter of less than 2.5 μm of diameter was used as an indicator of air pollution. The latest available data was included in the analysis whenever a series of data is reported by WHO. The average country temperature from December to April was derived from www.weatherbase.com. Covid-19 diagnostic test numbers as of April 17, 2020 were obtained from https://www.worldometers.info/coronavirus/.

2.3. Statistical analyses

Descriptive analysis of variables was performed. Data were presented as mean ± standard deviation for continuous variables, and numbers (percent) for categorical variables. Due to the highly skewed distribution of case fatality rates, log transformation of case fatality rates was used to evaluate the association between case fatality and country related variables using univariable and multivariable regression analyses. Variables included in the multivariable regression model were selected using backward stepwise process with $P < 0.2$ to stay. Spearman correlation coefficients were estimated to examine the relationship between case fatality rates and selected variables. All reported P values were 2-sided with a 0.05 significance level. Statistical analyses were conducted using STATA version 23 or GraphPad Prism 8 as appropriate.

3. Results

3.1. Variables description

A total of 113 countries were included in the analysis. Of which 42.2% were with high income and 40.7% were form Europe. The mean fatality rate was 4.2 ± 3.8% and ranges between 0.2% in Qatar and 21.4% in Zimbabwe. It was noted that 50% of the studied countries had the case fatality rate >3.2% (median rate). Fig. 1 depicts case fatality rates A) for the highest 60 countries and b) by the WHO region. The lowest number of conducted corona tests per one million population was in Nigeria (31) and the highest was in Iceland (111955). The mean population density was 248.7 ± 822.6 person/Km^2. The percentage of population >60 years old was 10.9 ± 16.3% and ranges from zero in San Marino to 85.6% in Russia. The total expenditure in health was highest for United States (17.1% of gross domestic product) and lowest for Qatar (2.2%). There were 2.4 ± 1.7 physicians and 6.3 ± 4.4 nurses per 1000 population respectively, with the highest for Cuba (8.3) and Switzerland (18.2) respectively. The longest life expectancy was for Chile (97.5 years) and the shortest was in Cote d'Ivoire (54.6 years). The mortality from non-communicable disease was 505 per 100000 population and ranges from 242.5 in Japan to 944.9 in Cote d'lvoire. For the

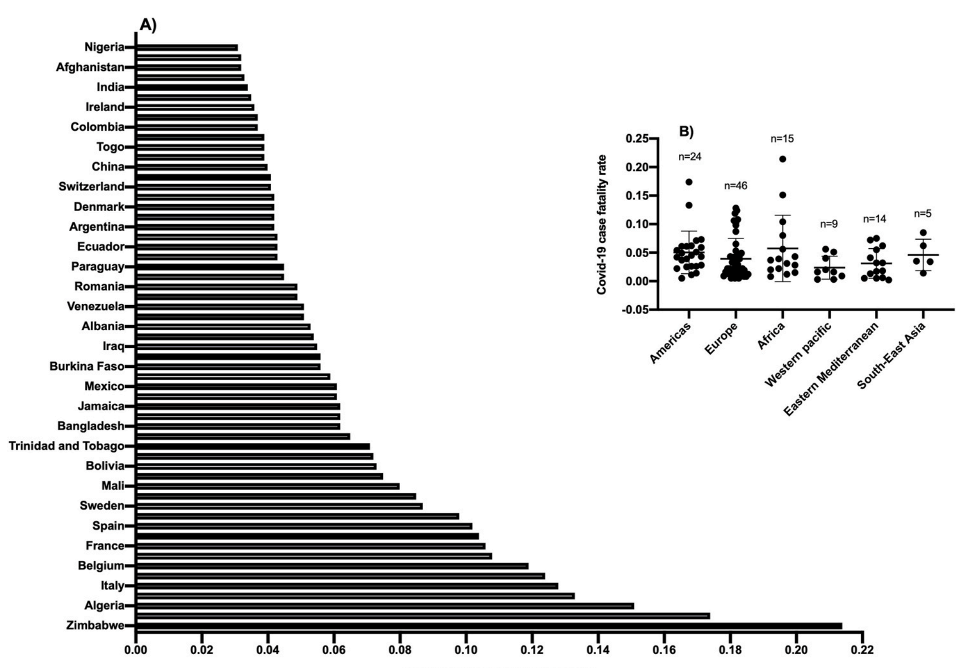

Fig. 1. A) Countries with the highest Covid-19 case fatality rates (top 60); B) Covid-19 case fatality rate of studied courtiers as categorized by WHO region where n = number of countries in that region.

vaccination, Polio immunization coverage among 1-year old kids, for instance, was the lowest in Ukraine (48%). The prevalence of raised blood pressure or fasting sugar was varied between (2.4%: Croatia and 33.4%: Niger) and (4%: Switzerland and 18.9%: Qatar) respectively. Other descriptive factors are listed in Table 1.

3.2. Factors associated with Covid-19 fatality

3.2.1. Unadjusted analysis

Being from western pacific and eastern Mediterranean regions, and having higher gross national income per capital, higher proportion of people using safety managed sanitation services, higher population density, higher hospitals density (per 100000 population), and higher Polio (Pol-3) immunization coverage among 1-year-olds were all significantly associated with lower case fatality rates ($P < 0.05$). However, having higher percent of population aged more than 60 years was associated with higher case fatality rates (marginally significant $P = 0.061$), Table 1.

3.2.2. Adjusted analysis

In the multivariate regression analysis model (Table 2), the results showed that after adjusting for other covariates, having higher percent of population aged more than 60 years was significantly associated with higher case fatality rates (coefficient of 0.032 on the log transformed case fatality rate, $P = 0.005$). On the other hand, having higher Polio (Pol-3) immunization coverage among 1-year-olds was significantly linked to lower case fatality rates (coefficient of −0.057 on the log transformed case fatality rate, $P = 0.017$).

3.2.3. Correlation analysis

Spearman correlation analysis showed that proportion of people >60 years old was positively correlated with fatality rate with a marginal significance ($r = 0.1778$, $P = 0.064$), while Polio-3 vaccination among 1-year-olds was negatively and significantly correlated with fatality rate ($r = -0.189$, $P = 0.044$), Fig. 2. For example, the case fatality rate was 0.029 in Ukraine which has the lowest Polio-3 vaccination coverage (48%), as compared to 0.002 in Russia which has a 96% Polio-3 immunization coverage among 1-year-olds. Fig. 3 depicts the world map with Covid-19 case fatality rates and Polio-3 immunization coverage among 1-year-olds in different countries.

4. Discussion

The present study examined factors associated with Covid-19 case fatality in an ecological study of 113 countries. The results indicate that increasing the percentage of elderly (>60 years) in a population is associated with higher Covid-19 fatality, while Polio-3 vaccination coverage among 1-year-olds is linked to decreased Covid-19 fatality. Overall, these novel findings suggest that the policies implemented to eradicate Covid-19 effect on survival should give priority to elderly diagnosed cases.

Previous studies that described the severity and outcomes of Covid-19 outbreak have shown that mortality rate could vary from one country to another and also by age group [13,14]. For instance, in a retrospective study assessing survival among severe Covid-19 cases in China showed that elderly age (≥65 years) is a significant risk factor of death (adjusted hazard ratio = 1.72) [15]. In another analysis of 54 mortality cases of Covid-19 in the Republic of Korea [9], it was reported that the median age at death was 75.5 years. The same study showed that the fatality rate was 0.04% among <50 years old patients versus 0.77% among 50–70 years old. As of March 9, the highest fatality rate in Italy was among ≥80 years old group (13.2%). These observations match with our finding that the higher proportion of people with age >60 years in a country is linked to increased Covid-19 fatality. While previous investigations suggested that the high prevalence of chronic diseases such as hypertension and diabetes among elderly might increase Covid-19 fatality [7,10], the

Table 1
Study variables and their association with Covid-19 fatality (unadjusted model).

Indicators	Mean (SD)	Range	Regression coefficients[a]	P
Demographics and socioeconomics				
Total population (in thousands)	58527.2 (184930)	33–1411415	0.00001	0.388
Population density (person/km^2)	248.7 (822.6)	3 to 8353	−0.00026	0.014
Population>60 years (%)	10.9 (16.3)	0–85.6	0.01750	0.061
WHO region (n,%)				
Americas	24 (21.2)			
Europe	46 (40.7)		−0.39000	0.096
Africa	15 (13.3)		−0.03600	0.0905
Western pacific	9 (8)		−0.94400	0.01
Eastern Mediterranean	14 (12.4)		−0.72100	0.022
South-East Asia	5 (4.4)		−0.01800	0.969
Gross national income per capital ($)	21851 (19270)	790–123860	−0.00002	0
World bank income group (n,%)				
Low income	6 (5.5)			
Lower-middle income	20 (18.4)		−0.24000	0.591
Upper-middle income	37 (33.9)		−0.49500	0.242
High income	46 (42.2)		−0.68500	0.102
Mean BMI kg/m^2	26 (1.8)	20.6–29.6	−0.08170	0.106
Alcohol consumers (%)	45.5 (24.8)	0.7–91.8	−0.00290	0.432
Tobacco smokers (%)	23.4 (8.8)	4.7–43.4	−0.00440	0.672
Population using safety managed sanitation services (%)	70.6 (27.8)	10–100	−0.00880	0.027
Population using safe managed drinking-water services (%)	82.8 (23.3)	0.99–100	−0.00316	0.512
Health care				
Total expenditure on health as % of GDP	7.2 (2.5)	2.2–17.1	0.05000	0.165
Physicians density (per 1000 population)	2.4 (1.7)	0.036–8.3	−0.09699	0.061
Nursing and midwifery density (per 1000 population)	6.3 (4.4)	0.24–18.2	−0.03950	0.123
Hospitals density (per 100000 population)	1.6 (1.6)	0.05–8	−0.13611	0.04
Life expectancy and mortality				
Life expectancy at birth (years)	75.1 (7)	54.6–97.5	−0.02010	0.12
Probability of dying between 15 and 60 years (per 1000 population)	131.4 (73.3)	49–398	0.00189	0.127
Neonatal mortality rate (per 1000 live births)	8.8 (9)	0.9–42	0.01853	0.063
NCD mortality rate (per 100 000 population)	504.9 (159.4)	242.5–944.9	0.00024	0.667
Child health				
Infants exclusively breastfed for the first six months of life (%)	29.8 (17.1)	1 to 82	0.00414	0.478
Vaccination among 1-year-olds (n, %)				
DTP	91 (9.3)	50–99	−0.01718	0.077
BCG	91.9 (10.8)	26–99	−0.01578	0.102
Polio-3	90 (10.5)	48–99	−0.01696	0.048
Rotavirus	77.6 (20.5)	1 to 99	−0.00824	0.192
PCV	84.5 (17.4)	6 to 99	−0.01036	0.088
Noncommunicable diseases (%)				
Prevalence of raised blood pressure SBP≥140 or DBP≥90	22.6 (5.3)	2.4–33.4	0.02131	0.191
Prevalence of raised fasting blood glucose ≥7.0 mmol/L	8.8 (3.2)	4–18.9	−0.04435	0.12

(continued on next page)

Table 1 (*continued*)

Indicators	Mean (SD)	Range	Regression coefficients[a]	P
Prevalence of raised total cholesterol ≥5.0 mmol/L	44.3 (13.7)	15.2–69.8	−0.01209	0.067
Prevalence of obesity among adults, BMI ≥30	21.1 (8.7)	3.4–37.3	−0.01186	0.255
Others				
Average temperature (Celsius)	13.4 (10.9)	from −12.1-43	0.00781	0.345
Concentrations of fine particulate matter (ug/m^3)	23.9 (17.5)	5.7–90.3	−0.00781	0.129

GDP: gross domestic product; NCD: noncommunicable diseases; DTP: Diphtheria Tetanus toxoid and Pertussis; BCG: Baccille Calmette Guérin; PCV: Pneumococcal Conjugate vaccines.

[a] Univariable regression on log-transformed case fatality.

Table 2
Predictors of case fatality associated with Covid-19 outbreak (adjusted model).

Variable	Coefficients*	95% Conf. Interval		P#
Percentage of population >60 years	0.0320	0.0104	0.0536	0.005
Polio-3 immunization coverage among 1-year-olds	−0.0571	−0.1029	−0.0112	0.017
Prevalence of raised blood pressure (SBP≥140 or DBP≥90 mmHg)	0.0405	−0.0062	0.0871	0.086
Total expenditure on health as % of gross domestic product	0.1226	−0.0294	0.2746	0.109
Pneumococcal conjugate vaccines (PCV3) immunization coverage among 1-year-olds	0.0157	−0.0074	0.0389	0.173

Multivariable regression on log-transformed case fatality.
*Coefficients were estimated using multivariable linear regression.
Variables were selected by backward stepwise process with $p < 0.2$ to stay.
#Statistical significance was set at a 2-sided $P < 0.05$.

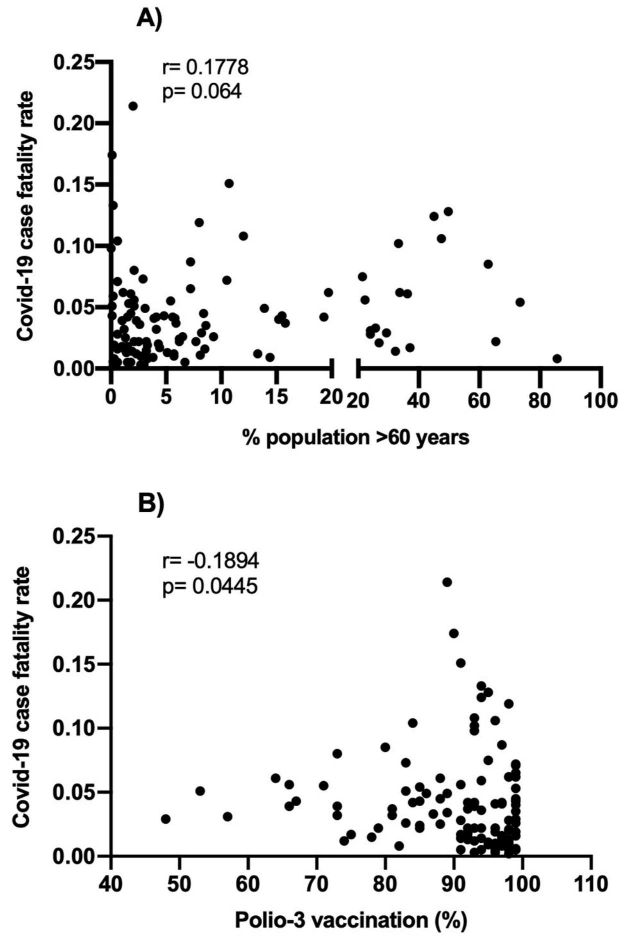

Fig. 2. The relationship between Covid-19 case fatality rate and A) percentage of population >60 years old; B) percentage of Polio-3 immunization coverage among 1-year-olds.

current study did not find that significant association at a country level. As the pathophysiology of Covid-19 includes evasion of immune system and sustained cytokine production [16], increased Covid-19 fatality among elderly could be attributed in part to impaired immunity [13,17]. Together, data imply that setting up priorities for elderly might be considered to control the epidemic mortality.

Vaccination has been also studied with respect to Covid-19 outcomes as several vaccines were shown to have beneficial non-specific effects [18]. The current study revealed that Polio-3 vaccination coverage among 1-year-olds may be associated with lower Covid-19 fatality. Polio vaccine can positively induce a non-specific immunological effect mediated by heterologous lymphocytes effects and upregulation of innate immune memory cells (also known as "trained immunity") [19, 20], which may result in improving immune system response towards other non-mycobacterial pathogens [21]. This pivotal role of Polio vaccination in modulating immunity against other infectious species suggests a significant and a wider beneficial effect other than its original indication. In fact, this was evidenced in several randomized controlled trials. For instance, in a study that evaluated fifteen national immunization campaigns in Guinea-Bissau, seven randomized controlled trials were conducted between 2002 to 2014 and found that overall mortality rate was significantly lower after Polio vaccine campaigns than before, highlighting the beneficial non-specific effects of Polio immunization [18]. Furthermore, another clinical trial reported a reduction of bacterial diarrhea duration with the use of Polio vaccine and thus indicated a non-specific reduction in mortality [22]. Moreover, a nationwide cohort study in Denmark indicated that in comparison to non-live or inactivated vaccine, Polio immunization was associated with lower admissions rate for lower respiratory infections [23]. Together, these findings may suggest a novel implication of Polio vaccination in reducing Covid-19 associated mortality. We also observed that some countries with elevated fatality rate such as Italy (0.128) had high Polio-3 immunization coverage (95%), suggesting that other factors could explain the increased fatality in such countries. Thus, further studies are warranted to validate this observation.

Of note, epidemiological studies exploring the association of Bacillus Calmette-Guérin (BCG) vaccination with Covid-19 outcomes showed conflicting results. The study of Miller and colleague that compared BCG vaccination policy among countries with various Covid-19 morbidity and mortality showed that countries with long-standing BCG policies were less severely affected by Covid-19 outbreak, suggesting that variations in Covid-19 mortality could be attributed in part to country's BCG vaccination policy [24]. This contradicts the observations of Singh study who questions the benefit of BCG vaccination in reducing Covid-19 mortality [25]. The present study did not find an association between BCG immunization coverage among 1-year-olds and Covid-19 fatality.

Our study has limitations. The current analysis did not include all countries impacted by Covid-19 as fatality rate data were only available for the studied countries at the time of starting this research. Nevertheless, the sample is representative as it covers the six WHO regions. Also, information of predictor variables was not available for some countries. The nature of this ecological study may also produce an ecological bias [26]. Specifically, we did not have age and polio vaccine data for each of the individual Covid-19 cases. Likewise, we did not have important Covid-19 risk factors data for the individual Covid-19 cases,

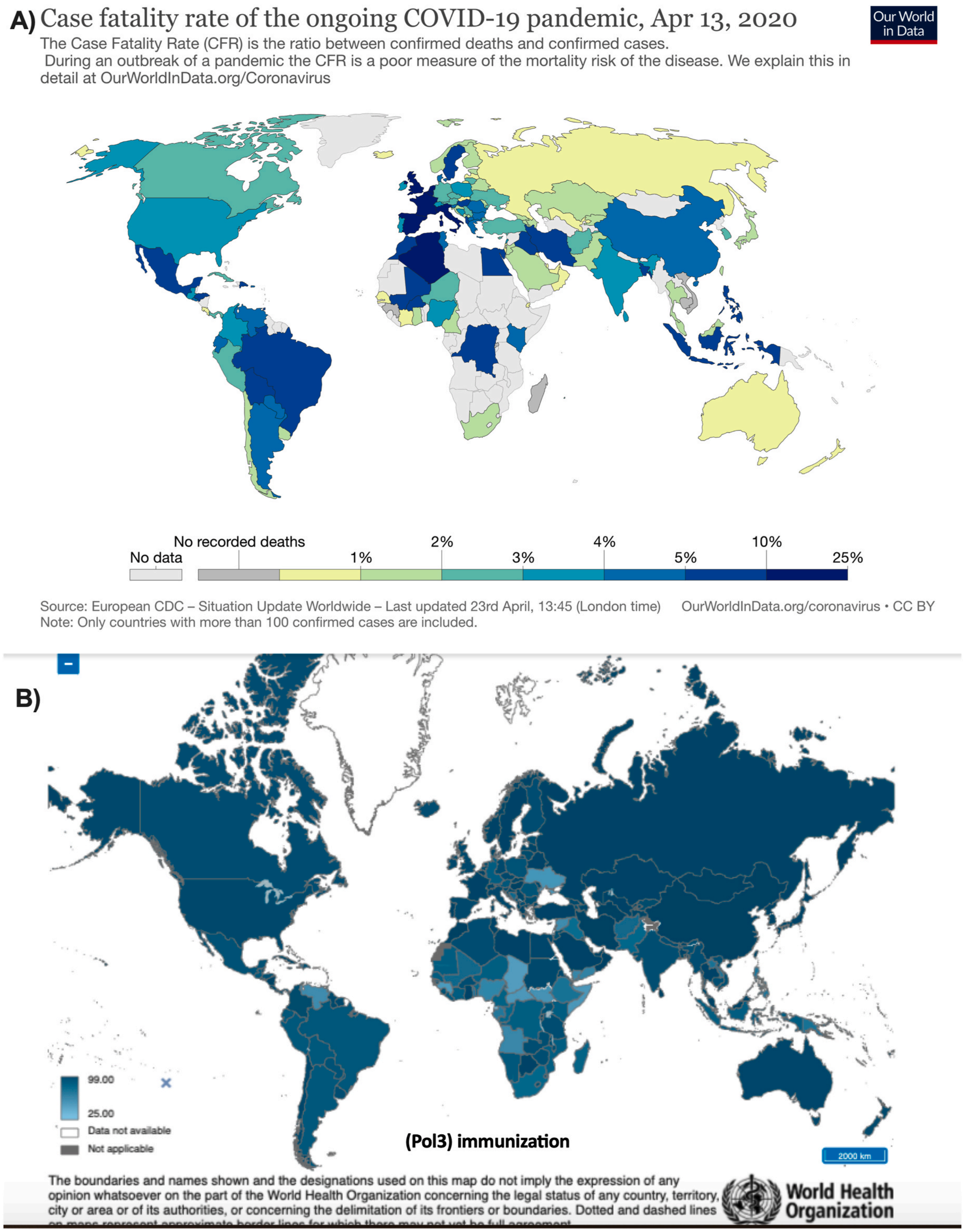

Fig. 3. The world representation of A) covid-19 case fatality rate (adapted from: https://ourworldindata.org/coronavirus) and B) the percentage of Polio-3 immunization coverage among 1-year-olds (adapted from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/polio-(pol3)-immunization-coverage-among-1-year-olds-(-)).

such as having serious underlying medical conditions. However, it is reassuring that our findings remained significant even after adjusting for potential confounders.

5. Conclusion

Covid-19 outbreak represents a significant fatal global health threat. This ecological analysis supports the previous findings that elderly may have higher risk of death from Covid-19 and suggests that Polio-3 immunization at one year old may be associated with lower fatality rate. Further global studies are needed to better understand Covid-19 related fatality.

Ethics approval and consent to participate

Not applicable.

Funding

None.

Author contribution

OYA: Conceptualization, Investigation, Methodology, Supervision, Data Interpretation, Writing - review & editing.

SMA: Conceptualization, Methodology, Data Analysis and Interpretation, Writing - review & editing.

SIA: Conceptualization, Methodology, Data Interpretation, Writing - review & editing.

RK: Conceptualization, Methodology, Data Interpretation, Writing - review & editing.

All authors approved the final version of the manuscript.

Registration of research studies

Name of the registry.

Unique Identifying number or registration ID.

Hyperlink to your specific registration (must be publicly accessible and will be checked).

Guarantor

Osama Y. Alshogran.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no competing interests related to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102319.

References

[1] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.

[2] J.T. Wu, K. Leung, G.M. Leung, Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study, Lancet 395 (2020) 689–697 (10225).

[3] G. Grasselli, A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, et al., Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy, JAMA : J. Am. Med. Assoc. 323 (16) (2020) 1574–1581.

[4] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intensive Care Med. 46 (6) (2020) 1294–1297.

[5] I.N. Abdullahi, A.U. Emeribe, J.O. Mustapha, S.A. Fasogbon, I.B. Ofor, I. S. Opeyemi, et al., Exploring the genetics, ecology of SARS-COV-2 and climatic factors as possible control strategies against COVID-19, Infezioni Med. Le 28 (2) (2020) 166–173.

[6] G. Lippi, C. Mattiuzzi, F. Sanchis-Gomar, B.M. Henry, Clinical and demographic characteristics of patients dying from COVID-19 in Italy versus China, J. Med. Virol. 92 (10) (2020) 1759–1760.

[7] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062 (10229).

[8] R.H. Du, L.R. Liang, C.Q. Yang, W. Wang, T.Z. Cao, M. Li, et al., Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study, Eur. Respir. J. 55 (5) (2020) 2000524.

[9] Prevention, KSoIDaKCfDCa. Analysis on 54 mortality cases of coronavirus disease 2019 in the Republic of Korea from january 19 to March 10, 2020, J. Kor. Med. Sci. 35 (12) (2020) e132.

[10] A.K. Singh, R. Gupta, A. Misra, Comorbidities in COVID-19: outcomes in hypertensive cohort and controversies with renin angiotensin system blockers, Diabetes Metabol. Syndrome 14 (4) (2020) 283–287.

[11] G. Lippi, M.H.S. de Oliveira, B.M. Henry, Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis, Eur. J. Gastroenterol. Hepatol. 33 (1) (2020) 114–115.

[12] R. Agha, A. Abdall-Razak, E. Crossley, N. Dowlut, C. Iosifidis, G. Mathew, et al., STROCSS 2019 Guideline: Strengthening the Reporting of Cohort Studies in Surgery, vol. 72, 2019, pp. 156–165.

[13] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, et al., Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China, JAMA Internal Med. 180 (7) (2020) 934–943.

[14] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. 8 (5) (2020) 475–481.

[15] X. Li, S. Xu, M. Yu, K. Wang, Y. Tao, Y. Zhou, et al., Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, J. Allergy Clin. Immunol. 146 (1) (2020) 110–118.

[16] E.J. Giamarellos-Bourboulis, M.G. Netea, N. Rovina, K. Akinosoglou, A. Antoniadou, N. Antonakos, et al., Complex immune dysregulation in COVID-19 patients with severe respiratory failure, Cell Host Microbe 27 (6) (2020) 992–1000.

[17] A. Saghazadeh, N. Rezaei, Immune-epidemiological parameters of the novel coronavirus - a perspective, Expet Rev. Clin. Immunol. (2020) 1–6.

[18] A. Andersen, A.B. Fisker, A. Rodrigues, C. Martins, H. Ravn, N. Lund, et al., National immunization campaigns with oral polio vaccine reduce all-cause mortality: a natural experiment within seven randomized trials, Front. Publ. Health 6 (2018) 13.

[19] B.A. Blok, R.J. Arts, R. van Crevel, C.S. Benn, M.G. Netea, Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines, J. Leukoc. Biol. 98 (3) (2015) 347–356.

[20] K.J. Jensen, C.S. Benn, R. van Crevel, Unravelling the nature of non-specific effects of vaccines-A challenge for innate immunologists, Semin. Immunol. 28 (4) (2016) 377–383.

[21] L.C.J. de Bree, V. Koeken, L.A.B. Joosten, P. Aaby, C.S. Benn, R. van Crevel, et al., Non-specific effects of vaccines: current evidence and potential implications, Semin. Immunol. 39 (2018) 35–43.

[22] A. Upfill-Brown, M. Taniuchi, J.A. Platts-Mills, B. Kirkpatrick, S.L. Burgess, M. S. Oberste, et al., Nonspecific effects of oral polio vaccine on diarrheal burden and etiology among Bangladeshi infants, Clin. Infect. Dis. : Off. Publ. Infect. Dis. Soc. Am. 65 (3) (2017) 414–419.

[23] S. Sorup, L.G. Stensballe, T.G. Krause, P. Aaby, C.S. Benn, H. Ravn, Oral polio vaccination and hospital admissions with non-polio infections in Denmark: nationwide retrospective cohort study, Open Forum Infect. Dis. 3 (1) (2016) ofv204.

[24] Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between Universal BCG Vaccination Policy and Reduced Morbidity and Mortality for COVID19: an Epidemiological Study, doi:10.1101/2020.03.24.20042937.2020.

[25] S. Singh, BCG vaccines may not reduce COVID-19 mortality rates. https://doi.org/10.1101/2020.04.11.20062232, 2020.

[26] S. Greenland, H. Morgenstern, Ecological bias, confounding, and effect modification, Int. J. Epidemiol. 18 (1) (1989) 269–274.