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ORIGINAL ARTICLE

Epidemiological investigation of the factors affecting the COVID-19 case fatality rate

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Abstract

Background & Aims: The aim of the present study was to elucidate the possible factors responsible for the difference in the COVID-19 case fatality rate by country.

Methods: In reference to the reported studies, 14 factors possibly related to COVID-19 case fatality rate were identified. Of the 191 countries and regions listed on the global map of the COVID-19 dashboard by the Center for Systems Science and Engineering at Johns Hopkins University, 79 countries were selected taking into account the amount of data and its reliability. Correlations of the COVID-19 case fatality rate with 13 possible factors were investigated. Epidemiological data such as food consumption, and meteorological data were obtained from public online databases.

Results: Only fish and seafood consumption had a negative correlation with the case fatality rate by country. Seafood consumption decades ago correlated better than that in 2017. The correlation coefficient between sea food consumption and the COVID-19 case fatality rate decreased from -0.51 in 1970 to -0.29 in 2017.

Conclusion: Fish and seafood eating habit during childhood and young adulthood may be associated with decreased death by COVID-19 in their later years.

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Key words: COVID-19; Case fatality rate; Epidemiological factors; Seafood; Dietary habit.

Introduction

Aging, obesity, hypertension, diabetes mellitus, and chronic lung disease have been reported as major risk factors for critical illness in COVID-19. There are geographical differences in COVID-19 prevalence, mortality, and case fatality rates. However, COVID-19 prevalence and mortality are affected by the number of polymerase chain reaction (PCR) tests carried out in each country, as well as other social factors. Except for corticosteroids, there was no specific drug or widely available vaccine to prevent death from SARS-CoV-2 infection as of December 9, 2020. Under these conditions, the case fatality rate in each country was more likely to reflect basic physical conditions of the patients than the COVID-19 prevalence rate or death rate. Therefore, the differences in the case fatality rate among countries were investigated to identify factors affecting COVID-19 clinical outcomes.

Materials and Methods

Selection of countries

Of the 191 countries and regions listed on the global map of the COVID-19 dashboard of the Center for Systems Science and Engineering at Johns Hopkins University (https://coronavirus.jhu.edu/map.html), 43 least developed countries listed by the United Nations and the Diamond Princess, a cruise ship, were excluded. One

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country was excluded because of the high possibility of data manipulation[1]. Sixty-eight countries with less than 5000 cumulative cases of COVID-19 at the beginning of research design (June 1, 2020) were excluded. Though Taiwan and New Zealand had less than 5000 cumulative cases as of June 1, 2020, Taiwan and New Zealand were not excluded considering the accuracy of data and their remarkable success in controlling the first wave of the epidemic[2]. Seventy-nine countries and regions (Argentina, Algeria, Armenia, Australia, Austria, Bahrain, Belarus, Belgium, Bolivia, Bosnia and Hercegovina, Brazil, Bulgaria, Cameroon, Canada, Chile, China, Colombia, Cote d'Ivoire, Croatia, Cuba, Czech, Denmark, Dominican Republic, Egypt, Republic of El Salvador, Ecuador, Finland, France, Gabon, Germany, Ghana, Greece, Guatemala, Honduras, Hungary, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Japan, Kazakhstan, Kenya, Kuwait, Luxembourg, Malaysia, Mexico, Morocco, Netherland, New Zealand, Nigeria, Norway, Oman, Pakistan, Panama, Philippines, Poland, Portugal, Qatar, Romania, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Arab Emirates, the United States of America, Turkey, Ukraine, United Kingdom of Britain and Northern Ireland, Uzbekistan, Venezuela) were selected for analysis.

Selection of potential factors related to the death rate and case fatality rate of COVID-19

Among the possible factors responsible for COVID-19 deaths, 14 factors were selected based on the previously reported studies[3-14] and the quality of open data for these factors. Potential factors responsible for the death rate and case fatality rate of COVID-19 were categorized as follows: healthcare-related, economic, environmental, and food-related. The category of healthcare-related included deaths due to tuberculosis among HIV-negative people (/10^5 population), body mass index (BMI), aging rate (population aged ≥65 years/total population) and the prevalence rate of hypertension among the general population in each country, number of hospital beds, number of PCR tests conducted, and CT scanner density[3]. Deaths due to tuberculosis among HIV-negative people was selected based on the report by Brooks et al[4] suggesting the association of COVID-19 mortality and prior Bacillus Calmette-Guerin vaccination in countries with a high burden of tuberculosis. BMI[5], aging rate[7], and the prevalence of hypertension[8] have already been reported as risk factors for COVID-19 death. Mean annual temperature, relative humidity, and Gross Domestic Product (GDP) were used as environmental and economic factors. Meteorological factors were selected based on the report by Guo et al[9]. Consumptions of alcohol[10], meat, seafood, and vegetables were selected based on the several studies suggesting the effect of food on the pathophysiology of COVID-19[1-13].

Data collection

Deaths due to COVID-19 as of December 9, 2020 (per 100,000 population) and the case fatality rate by country were calculated using the data provided by the Corona Virus Resource Center, Johns Hopkins University of Medicine at https://coronavirus.jhu.edu/map.html. The number of PCR tests (per 1000 population) as of December 17, 2020 was calculated using data from Our World in Data, a database provided by the Global Change Data Lab, at https://ourworldindata.org/what-can-data-on-testing-tell-us-about-the-pandemic. Deaths due to tuberculosis among HIV-negative people in 2019 (per 100,000 population) and adult BMI in each country were obtained from data provided by the World Health Organization (WHO) (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/deaths-due-to-tuberculosis-among-hiv-negative-people-(per-100-000-population) and https://www.who.int/data/gho/data/indicators/indicator-details/GHO/mean-bmi- (kg-m-) - (age-standardized-estimate), respectively). The aging rate (population aged ≥65 years/total population) of each country in 2019 was obtained from data provided by GLOBAL NOTE Incorporated at https://www.globalnote.jp/post-3770.html. The prevalence of hypertension in each country was obtained from a private database based on WHO data in 2008 available at http://top10.sakura.ne.jp/WHO-BP-01-AGE25-PLUS.html#map. The number of hospital beds (per 10^3 population) in each country was obtained from a private database based on WHO data in 2009 available at http://top10.sakura.ne.jp/IBRD-SH-MED-BEDS-ZS.htm. CT scanner density by country 2019 (per million population) was obtained from the database provided by Statista Incorporated available at http://www.statista.com/statistics/266539/distribution-of-equipment-tomography/. The GDP of each country in 2019 was obtained from data provided by GLOBAL NOTE Incorporated at https://www.globalnote.jp/post-1409.html. Meteorological data were obtained from the databases provided by the United Nations Statistics Division, ClimaTemps.com, and the World Wide Travel Organisation available at http://data.un.org/Data.aspx?q=+humidity&d=CLINO&f=ElementCode%3a11, http://www.london.climatemps.com/humidity.php, and https://weather-and-climate.com/, respectively. Annual consumption of alcohol (L/population aged ≥15 years) of each country in 2018 was obtained from data provided by GLOBAL NOTE Incorporated at https://www.globalnote.jp/post-3958.html. Consumption of meat, seafood, and vegetables by country was obtained from Our World in Data at https://ourworldindata.org/. The data on consumption of food by country was provided as food supply per capita in every year from 1961 to 2017.

Statistical analysis: Data were analyzed using Statcel 3rd add-in forms on Excel. Pearson's correlation coefficient was used to determine the degree of relationship between linearly related variables. Spearman's rank correlation coefficient was used to determine the degree of association between two non-normally distributed variables. Non-normally distributed data such as the COVID-19 death rate and the case fatality rate by country are expressed as medians and interquartile range (IQR). A p value of less than 0.05 was considered significant.

Ethical approval

Ethical approval was not required for this retrospective study as it was based on freely available data in the public domain.

Results

COVID-19 death rate and case fatality rate had wide variations among countries. The median value of death rate and case fatality rate was 24.2 per 100,000 population and 1.67%, respectively (Figure 1).

The median death rates in the Asia Pacific region (median 1.80/100,000 population, IQR 0.50-5.25) and Africa (median 2.85/100,000 population, IQR 1.25-6.485) were significantly lower than those of countries in the Middle East (median 20.8/100,000 population, IQR 17.50-30.48), Latin America (median 77.10/100,000 population, IQR 22.90-81.45) and Europe and North America (median 57.70/100,000 population, IQR 33.60-85.30). The case fatality rate was not significantly different among these regions (Asia Pacific, median 1.39%, IQR 0.96-1.73%; Africa, median 1.69%, IQR 0.91-2.47%; Middle East, median 1.00%, IQR 0.45-1.66%; Latin America, median 2.71%, IQR 1.71-3.13%; Europe and North America, median 1.86%, IQR 1.46-2.73%). Of the 15 selected factors, deaths due to tuberculosis, BMI, aging rate, prevalence of hypertension, the number of beds per 1000 population, the number of PCR tests per 1000 population, mean annual temperature, alcohol

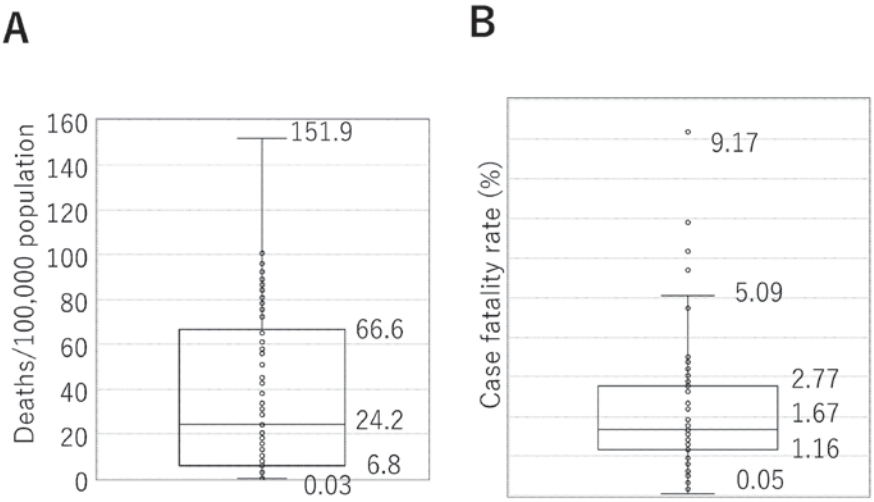

Figure 1 The COVID-19 death rate (per 100,000 population) and case fatality rate (%) by country
Panels (A) and (B) represent the COVID-19 death rate (per 100,000 population) and case fatality rate (%) of each country. The horizontal lines in the box denote the 25th, 50th, and 75th percentile values. The error bars denote the 5th and 95th percentile values.

Table 1. Correlations between death and case fatality rate and selected factors.

			Death rate		Case fatality rate	
Factors	**Mean (SD)**	**n**	**Correlation coefficient**	**p-value**	**Correlation coefficient**	**p-value**
Deaths due to tuberculosis among HIV-negative people (per 100,000 population)	7.0 (14.5)	78	**−0.35**	**0.002**	−0.009	0.93
BMI	26.2 (1.6)	78	**0.35**	**0.001**	0.19	0.1
Aging rate (Population aged 65≦/Total population)	36.9 (35.3)	79	**0.41**	**2.60E-04**	0.17	0.14
Prevalence rate of hypertension	40.2 (6.3)	77	**0.29**	**0.012**	−0.01	0.89
Number of beds (per 10^3 population)	3.6 (2.7)	78	**0.26**	**0.022**	−0.17	0.14
Number of PCR test (per 10^3 population)	333.2 (446.1)	64	**0.31**	**0.014**	−0.21	0.09
CT scanner density 2019 (per 10^6 population)	29.1 (22.5)	25	−0.16	0.42	−0.05	0.82
GDP (billion U.S. $)	874,414 (2,543,917)	77	0.17	0.13	0.2	0.07
Mean annual temperature (℃)	17.2 (7.1)	78	**−0.41**	**3.00E-04**	−2.1	0.07
Mean annual relative humidity (%)	71.1 (11.1)	77	−0.13	0.23	−0.19	0.1
Alcohol consumption (L/year, in population aged over 15y)	5.7 (3.8)	78	**0.42**	**2.50E-04**	0.11	0.33
Average meat consumption (kg/person/ year, 2017)	58.9 (28.5)	76	**0.44**	**1.10E-04**	0.04	0.74
Fish and seafood consumption (kg/person/ year, 2017)	18.5 (14.1)	75	−0.18	0.12	**−0.23**	**0.048**
Vegetable consumption (kg/person/ year, 2017)	109.9 (71.5)	76	0.04	0.71	−0.05	0.67

consumption, and meat consumption had mild to moderate correlations with the death rate. Except for seafood consumption, none of the selected factors correlated with the COVID-19 case fatality (Table 1). Considering the high COVID-19 case fatality rate in aged people and the possible long-term effect of dietary habits on one's health status, food consumption in 1961, 1970, 1980, 1990, 2000, 2010 and 2017 was examined using data from 65 countries. Data on food consumption was

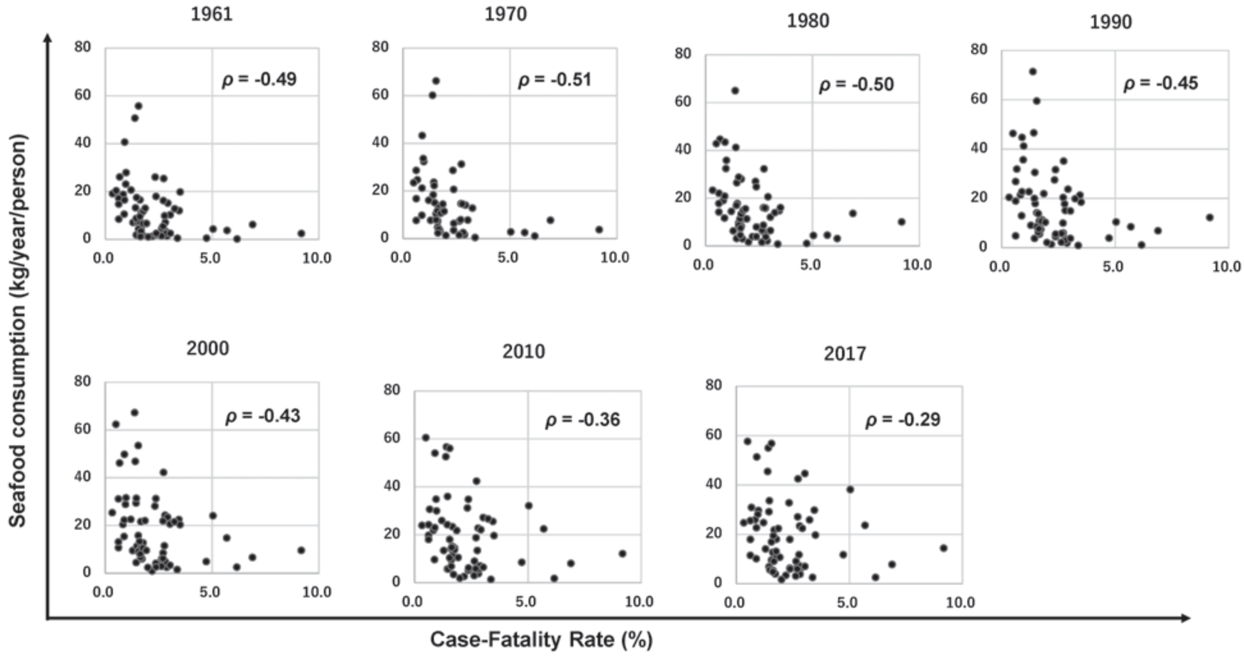

Figure 2 Scatter plots showing relationships between the COVID-19 case fatality rate and consumption of seafood in 1961, 1970, 1980, 1990, 2000, 2010 and 2017.
"ρ" shown on each plot indicates the correlation coefficient.

not fully available through 1961 to 2017 in 14 countries (i.e., Armenia, Bahrain, Belarus, Belgium, Bosnia and Hercegovina, Croatia, Kazakhstan, Luxembourg, Oman, Qatar, Serbia, Singapore, Ukraine and Uzbekistan) out of the 79 countries enrolled in this study.

Seafood consumption in 1961, 1970, 1980, and 1990 showed a moderate correlation with the case fatality rate (Figure2). The correlation coefficient showed a gradual decrease from -0.51 in 1970 to -0.29 in 2017 (Table 2).

Discussion

The COVID-19 death rate (deaths per 100,000 population) differs by geographic region in the world. The Asia-Pacific region and Africa have lower COVID-19 death rates than other regions. Reports from Europe and the United States of America have noted the difference in the death rate by race and ethnicity[15-17]; however, the death rate is affected by economic status and the medical and living environment for each ethnicity in a multiethnic country[15]. Conditions such as language barriers and higher uninsured rates make ethnic and racial minorities less likely to access healthcare services. In fact, as well as physical factors associated with patients, social and environmental factors were correlated with the death rate in the present study. The death rate is affected by the spread of COVID-19 and the availability of PCR tests in each country. Spread of SARS-CoV-2 may be mitigated by social measures such as mandatory mask-wearing, social distancing, air ventilation, and remote working. Availability of PCR tests may be mitigated by the economy and the medical service and health insurance system. Therefore, the death rate may not be appropriate for exploring the physical factors related to COVID-19 deaths.

On the other hand, the case fatality rate by country had no correlations with healthcare-related, economic, and environmental factors in the present study. Since there was no drug outstandingly better than steroids or a widely available vaccine for SARS-CoV-2 during the

Table 2. Correlations between case fatality rate in each country and food consumption for the years 1961, 1970, 1980, 1990, 2000, 2010 and 2017.

Fish and seafood consumption (kg/year)			Case fatality rate	
Year	**n**	**Mean (SD)**	**Correlation coefficient**	**p-value**
2017	65	19.3 (14.4)	−0.29	0.02
2010	65	19.2 (14.6)	−0.36	0.004
2000	65	18.1 (15.2)	−0.43	5.95E-04
1990	65	16.8 (14.7)	−0.45	3.17E-04
1980	65	15.5 (12.9)	−0.50	6.16E-05
1970	65	13.6 (13.0)	−0.51	3.37E-05
1961	65	11.5 (11.3)	−0.49	7.88E-05

Meat consumption (kg/year)			Case fatality rate	
Year	**n**	**Mean (SD)**	**Correlation coefficient**	**p-value**
2017	65	59.8 (29.4)	0.06	0.63
2010	65	59.8 (29.2)	−0.001	0.99
2000	65	55.5 (32.0)	0.01	0.94
1990	65	50.5 (32.4)	−0.04	0.73
1980	65	47.8 (33.0)	−0.05	0.67
1970	65	38.7 (29.3)	−0.05	0.66
1961	65	34.0 (27.1)	−0.06	0.64

Vegetable consumption (kg/year)			Case fatality rate	
Year	**n**	**Mean (SD)**	**Correlation coefficient**	**p-value**
2017	65	(61.4)	0.03	0.78
2010	65	100.0 (59.4)	−0.07	0.96
2000	65	103.0 (66.4)	−0.002	0.99
1990	65	89.7 (59.5)	0.07	0.60
1980	65	80.9 (53.1)	−0.02	0.89
1970	65	71.8 (47.5)	0.01	0.95
1961	65	62.5 (39.4)	0.13	0.30

period of this study, the case fatality rate would reflect the physical factors more directly than the death rate.

Though the aging rate of the population in each country had no correlation with the case fatality rate among countries in the present study, the age of COVID-19 patients is one of the factors that appears responsible for deaths in each country. It has been suggested that cytokine storm plays an important role in critically ill COVID-19 patients[18] with several severe manifestations, such as acute respiratory distress syndrome, acute kidney injury, thromboembolic diseases, and vasculitis[18]. The physiological mechanisms making aged people far more vulnerable to COVID-19 death than other age groups are still unknown.

In the present study, meat consumption was positively correlated with the COVID-19 death rate but not with the case-fatality rate. The clinical relevance of the correlation between meat consumption and the death rate is hard to interpret, because, the death rate is influenced by many social factors such as the density of human contacts and accessibility to medical services. On the other hand, there was a negative correlation between seafood consumption and the COVID-19 case fatality rate. Furthermore, the absolute value of the correlation coefficient increased gradually as the data of seafood consumption went back from -0.29 in 2017 to -0.51 in 1970. This observation may be associated with a long-term effect of regular seafood consumption on the physical conditions in later years.

Omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid are contained in fish oil. It has been reported that omega-3 fatty acids inhibit cytokine storm[19] and decrease ACE2 mRNA, the receptor for SARS-CoV-2[20], in the blood[21]. A decreased ACE2 level with aging is suspected as one of the pathophysiological mechanisms for the high COVID-19 case fatality rate in elderly people[22]. Furthermore, fish oil has an anti-aging effect on cardiovascular functions[23-25]. Together with the present results and these reports, fish and regular seafood consumption during childhood and young adulthood may be associated with decreased death by COVID-19 in their later years.

Conclusion

Regular consumption of fish and seafood during childhood and young adulthood may be associated with decreased death by COVID-19 in later years.

Study limitation: The data analyzed in this study were provided by a wide variety of countries with different social systems. Therefore, the accuracy and quality of the provided data may vary from one country to another to some extent. Though eating seafood regularly in childhood and in young adulthood may be associated with decreased death by COVID-19 in elderly people, the mechanism is yet to be clarified.

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Conflict of interest: None of the authors has any conflicts of interest to declare.

Authorship: Tsuchiya J analyzed the data and wrote the manuscript. Tasaka S and Itoga M supervised and helped Tsuchiya J write the manuscript. Saito N gave suggestions to Tsuchiya J on the statistical analysis and interpretation. Kayaba H designed the study and checked the final version of this manuscript.

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