CASE-FATALITY RATE BY COVID-19: A HIERARCHICAL BAYESIAN ANALYSIS OF COUNTRIES IN DIFFERENT REGIONS OF THE WORLD

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▪ ABSTRACT: The main goal of this study is the statistical analysis of deaths/cases epidemiologically defined as Case-Fatality Rate (CFR) due to novel coronavirus (SARS-CoV-2) for 113 countries in different regions of the world in presence of some economic, health and social factors. The considered dataset refers to the accumulated daily counts of reported cases and deaths for a period ranging from the beginning of the COVID-19 pandemics in each country until July 25, 2020 the final follow-up day period. A binomial logistic regression model in presence of a random effect is assumed in the data analysis. The statistical analysis is considered under a hierarchical Bayesian approach using MCMC (Markov Chain Monte Carlo) methods do get the posterior summaries of interest. The results we found are interesting considering the epidemiological interpretation, which could be of great interest to epidemiologists, health authorities, and the general public in the face of a complex pandemic in all its aspects, like the one we are experiencing.

▪ KEYWORDS: Epidemiology; binomial regression models; latent variables; hierarchical Bayesian methods.

1 Introduction

Since the beginning of 2020, the world has been witnessing the major COVID-19 pandemic affecting health, the economy and practically all aspects of life in

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different countries around the world. The COVID-19 disease is a viral infection that is spreading quickly around the world since January 2020, after the first cases were diagnosed in the final of the year 2019 in the city of Wuhan, Hubei Province of China. COVID-19 is a respiratory disease that can affect people in different ways, where most people have a mild to moderate respiratory disease, with recovery without the need for specific treatments (World Health Organization, 2020). According to World Health Organization (WHO), the main symptoms of COVID-19 are fever, tiredness, dry cough, shortness of breath and sore throat, and some people may report diarrhea, nausea or runny nose. Some groups of people, such as the elderly and people with cardiovascular disease, diabetes, chronic respiratory diseases and cancer, are more likely to develop serious illnesses and death. The virus spreads mainly through droplets of saliva or nasal discharge when an infected person coughs or sneezes. There are several vaccines under development, some already in phase III and others in the initial testing phase. The literature shows a very large number of studies targeting COVID-19 in the first months of 2020 (see, for example, (KANDEL et al., 2020; PUNG et al., 2020; CHAN et al., 2020a, 2020b; HUANG et al., 2020; WU et al., 2020; LU et al., 2020; CHEN; LIU; GUO, 2020; CHEN, 2020; LI et al., 2020; LAI et al., 2020a; LAM et al., 2020; LUPIA et al., 2020; SHEREEN et al., 2020)).

According to the Situation Report 80 from the WHO, the number of global cases reached 16,687,774 people until July 28, 2020, among which 657,451 died due to COVID-19 and its clinical consequences.To track the morbidity and mortality rates caused by the SARS-CoV-2 virus, the, the WHO has updated the Laboratory Testing Strategy at March 21, 2020 (LAN et al., 2020) according to the different transmission scenarios: countries with no cases; countries with one or more cases (sporadic cases); countries experiencing a series of causes related to geographic location or common exposure (a group of cases); and countries experiencing massive outbreaks or sustained and pervasive local transmission (community transmission).

After seven months of the pandemics, it is observed in the literature that countries in different regions have different probabilities of deaths due to COVID-19 depending on different factors as the health structure (primary care units, specialized outpatient clinics and hospitals with and without intensive care units, ICU), as well as, number of diagnostic tests to detect coronavirus for the population, policy implemented in each country to isolate the population, that is, quarantine or total isolation and possibly other factors as ethical groups or climate differences that could affect the incidence and death rates. An important factor that affects the probability of death due to COVID-19 in each country (deaths/cases rates also denoted in epidemiology as the Case-Fatality Rate or CFR) is underdiagnoses and/or under-notification, especially in the poorest countries of the world where there is great lack of hospitals, medical equipment and diagnostic tests to detect COVID-19, leading to very low and misleading rates related to the epidemic.

Thus, given the above, this article aims to analyze the correlations/associations between probabilities of death by COVID-19 with some variables described below, so in this study, 113 countries from different regions of the world were considered to accomplish the goal of this study.

2 Material and methods

This is an ecological study that analyzes epidemiological indicators through a time series, with the following covariables in each of the countries included:

1. **General information:** population/km^2 and number of accumulated days (prevalence) under the COVID-19 epidemics.

2. **Economy:** GDP in millions of current US$ and GDP per capita in current US$.

3. **Social indicators:** urban population (% of total population); infant mortality rate - IMR (deaths by 1000 live births); physicians (number by 1000 inhabitants) a health indicator and current expenditure in health (% of GDP on health spending) another health indicator.

2.1 Dataset

The data set consists of the accumulated daily counting of new cases (incidence) and daily deaths due to COVID-19 for the period ranging since the beginning of the epidemics in each country until July 25, 2020 (final follow-up day for all countries) reported in the site European Union (EU) open data portal (⟨https://data.europa.eu/euodp/en/data/dataset/covid-19-coronavirus-data⟩). Some covariates associated to each country were obtained from United Nations site (⟨https://data.un.org/⟩), relative for the year 2019 and are considered in the data analysis assuming binomial regression models under a Bayesian approach. The response was given by the total numbers of deaths among the total numbers of diagnosed cases of COVID-19 (CFR) in each country to verify if there are significant effects of these covariates in the responses. It is observed that countries in different regions of the world have great heterogeneity of the COVID-19 Case-Fatality Rate (CFR) related to the accumulated data of the period. To discover important factors affecting this behavior, 113 countries were considered in this study selected from 11 regions of the world: 1) East Asia, 2) Central Asia, 3) Asia Middle East, 4) Europe, 5) North America, 6) Central America, 7) South America, 8) Oceania, 9) Caribbean, 10) North Africa and 11) Sub Saharan Africa.

2.2 Using binomial regression model for the number of COVID-19 deaths in each country

Different statistical modeling approaches could be considered in the analysis of daily and accumulated disease counting data. Under a probabilistic point of view, the epidemic curves related to disease counting data could be modeled as a stochastic process (in the form of a counting process) or using classical nonlinear models where standard inference methods are used to obtain point and interval estimates for the parameters of models (BATES; WATTS, 1980; RATKOWSKY, 1983; BATES; WATTS, 1988; SEBER; WILD, 2003).

In this study, it is considered the accumulated number of cases and deaths of 113 countries since the beginning of the pandemics in each country until July 25, 2020. Our approach is based on a binomial regression model for the response Y (CFR) - the total number of deaths among the accumulated number of diagnosed COVID-19 cases in each country, in presence of the following covariates: population/km^2 in logarithmic scale, GDP in millions of US$ in logarithmic scale, GDP per capita in US$ in logarithmic scale, urban population (% of total population), IMR in logarithmic scale, number of physicians/1000 inhabitants and % of GDP on health spending of each country in the study. In the regression model, are considered categorical variables related to 11 regions (use of dummy variables for categorical covariates regions where East Asia is considered as reference).

Let Y be defined as the number of deaths among the accumulated number n of diagnosed COVID-19 cases (CFR) in each country in the fixed assumed period of time with a binomial probability distribution given by,

$$P(Y=y)=\binom{n}{y}p^y(1-p)^{n-y} \tag{1}$$

where $y=0,1,2,\ldots,n$. The mean and variance of the binomial distribution are given respectively by $\mu=np$ and $\sigma^2=np(1-p)$. Observe that in this modeling approach, the probability of death p in the binomial distribution $\mathrm{b}(n,p)$ denotes the CFR (probability or risk of death in each country for the infected people with SARS-CoV-2). In addition, in presence of a vector of covariates $\mathbf{x}=(x_1,x_2,\ldots,x_k)^T$ with k covariates associated to each COVID-19 death response y, we assume a logistic regression model for the probability of death given by,

$$\mathrm{logit}(p)=\boldsymbol{\beta}^T x \tag{2}$$

where $\boldsymbol{\beta}=(\beta_1,\ldots,\beta_k)^T$ is the vector of regression parameters associated to the vector of covariates $\mathbf{x}=(x_1,x_2,\ldots,x_k)^T$.

In the logistic regression model, was considered the presence of some economic, social and health covariates (population/km^2, GDP, GDP per capita, urban population, IMR, number of physicians/1000 inhabitants and % of GDP on health spending. We used some dummy variables related to the unordered categorical variables regions of the world (Asia Middle East; Central America; Central Asia; Caribbean; East Asia; Europe; North Africa; North America; Oceania; South America and Sub Saharan Africa) where Asia East region is assumed as reference.

A fixed effects model assumes that for the selected countries there are the same quantitative effects of the covariates and that the differences observed are residual error. Since in our study, it is clear that the different countries respond differently from the others in the management of the COVID-19 pandemics, the spread in the data is caused not only by the residual error but also by between-country differences. In this way, it is required a random effects model (GIBBONS; HEDEKER, 1997;

LARSEN et al., 2000; CURTIS et al., 1993). Thus, we assume the following logistic regression model,

$$
\begin{aligned}
\text{logit}(p_i) &= \beta_0 + \beta_1\, Sub.Saharan.Africa_i + \beta_2\, Central.Asia_i \\
&+ \beta_3\, Asia.Middle.East_i + \beta_4\, Central.America_i + \beta_5\, Caribbean_i \\
&+ \beta_6\, Europe_i + \beta_7\, North.Africa_i + \beta_8\, North.America_i + \beta_9\, Oceania_i \\
&+ \beta_{10}\, South.America_i + \beta_{11}\, \log(pop.density/km_i^2) \\
&+ \beta_{12}\, urban.population_i + \beta_{13}\, \log(infant.mortality_i) \\
&+ \beta_{14}\, physicians.1000_i + \beta_{15}\, Health.GDP_i + \beta_{16}\, \log(GDP)_i \\
&+ \beta_{17}\, \log(GDP.capita)_i + \beta_{18} \log(accumulated.days.epid_i) + w_i \qquad (3)
\end{aligned}
$$

where $i = 1, 2, \ldots, 113$ (number of countries), W_i is a random effect (a non-observed variable) assumed to be independent with a normal distribution $N(0, \sigma_w^2)$. Moreover, assuming the regression model (3), we consider a hierarchical Bayesian approach combining the joint prior distribution for the parameters of the model $\boldsymbol{\beta} = (\beta_0, \ldots, \beta_{18})^T$ and $\zeta = 1/\sigma_w^2$ with the likelihood function based on the binomial density given by (2). The joint posterior distribution for all parameters is determined from the Bayes formula (BOX; TIAO, 1973) and the posterior summaries of interest are obtained using Markov Chain Monte Carlo (MCMC) methods (GELFAND; SMITH, 1990; CHIB; GREENBERG, 1995).

3 Results and discussion

Figure 1 shows the box-plots of the CFR for the countries in different regions of the world from where it is possible to see that countries in North America, Europe and Caribbean regions present larger CFR when compared to countries of other regions of the world, although these regions present very high variability as compared to the other regions. These results are in agreement with the findings of other studies, in which they suggest that this can be explained by a higher number of intergenerational interactions, co?residence, and commuting patterns typical of people culture speeding up accelerating the spread of the virus through greater social proximity of elderly people with infected in the community (GIANGRECO, 2020; DOWD et al., 2020; YUAN et al., 2020).

In addition, CFR show more variability among the 11 regions with larger values for the countries in North Africa region, certainly largely due to poor health service structures in the countries of that region, with little capacity to deal with good response to critically ill patients, due to the lack of ICU beds and trained medical personnel (OHIA; BAKAREY; AHMAD, 2020). On other hand, it is important to point out that for the Sub Saharan region, the epidemic is starting in the time of this study (data set until July 25, 2020), thus, it is expected that the infection/disease by COVID-19 in the countries of this region, can show its dynamics, which for some authors tends to be of lesser impact, for several reasons such as lower population mobility, for example, in addition, many Sub Saharan African countries established the entry block for foreigners early, delaying the arrival of the epidemic (CLIFFORD et al., 2020). However, for many other authors, the epidemic has the potential to have a major impact on these populations, considering poverty, the greater agglomeration, as well as the poor conditions of health services (LUMU, 2020; ONGOLE et al., 2020; OSSENI, 2020).

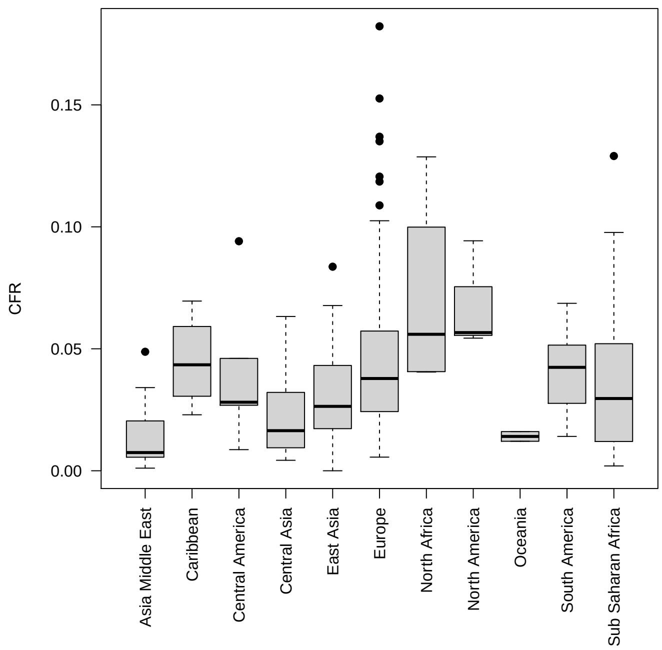

Figure 1 - Box-plots for the CFR in different regions of the world (the numbers are based on the cumulative number of cases and deaths).

Figure 2 shows the scatter plots of the observed CFR of each country versus each covariate from where it is difficult to say about correlations among the CFR and each covariate, but we see that some covariates as GPD, GPD per capita, infant mortality and urban population, apparently affect CFR. To discover if these covariates and the different regions have statistical effects on the response CFR for each country, we propose the use of a binomial regression model considering the accumulated number of deaths among the accumulated number of diagnosed cases in presence of a latent variable under a Bayesian approach.

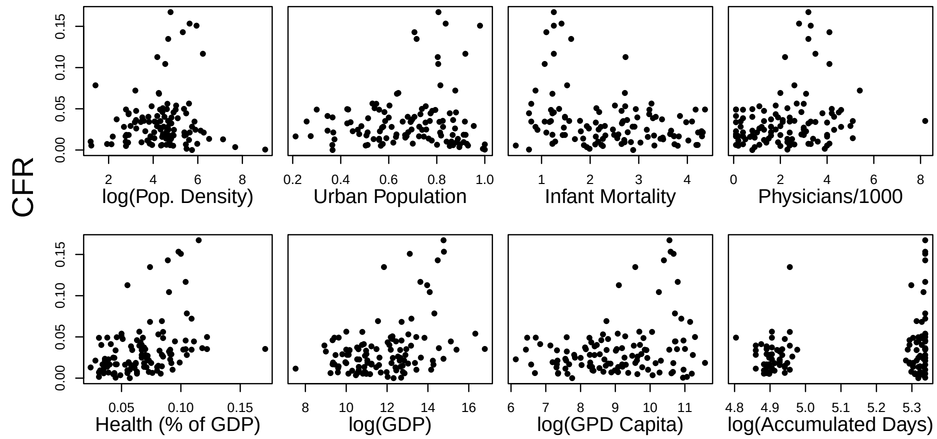

Figure 2 - Scatter plots for the observed CFR of each country versus each covariate, until July 25, 2020.

In this way, using data from daily reported cases (incidence) and deaths caused by COVID-19 in 113 countries until July 25, 2020, we have fitted the binomial logistic regression model (3) assuming normal N(0,1) prior distributions for the parameters β_j, where $j = 0, 1, 2, \ldots, k$ and a gamma G(10,10) prior distribution for the parameter ζ where G(a,b) denotes a gamma distribution with mean a/b and variance a/b^2. That is, we are assuming approximately non-informative priors for the parameters of the model.

We further assume prior independence. The statistical analysis was carried out in the Openbugs software (SPIEGELHALTER et al., 2003). The R2OpenBUGS and the coda packages were used obtain and monitor the Bayesian estimates and the convergence of the MCMC algorithm by usual time series plots for the simulated samples and Gelman and Rubin's methods (BROOKS; GELMAN, 1998).

Table 1 shows the posterior means (use of squared error loss function) for the regression parameters associated to each covariate, the posterior standard deviations (Std. Dev.) and 90% credible intervals for all parameters from where it is observed that the following covariates show significant effects (90% credible intervals do not contain the zero value for the respective regression parameters), associated to the logistic regression model:

1. log(IMR) (parameter β_{13}).

2. log(GDP) (parameter β_{16}).

3. log(GDP per capita) (parameter β_{17}).

Regions (Caribbean, Europe and North America) when compared to the reference region East Asia (parameters β_5, β_6 and β_8). It is observed that two of the significant covariates are linked to the economic situation of each country log(GDP) and log(GDP per capita) and one covariate is linked to socioeconomic status and is an important health indicator of these countries (infant mortality [IMR]). On the other hand, the CFR for the regions Caribbean, Europe and North America are statistically different of the reference region East Asia. The correlation between GDP, GDP per capita and cases of COVID-19 is suggested by some authors (RITCHIE et al., 2020), as a trace that these economic indicators interfere in the occurrence of infection/disease by SARS-CoV-2, and in some countries there is a positive correlation, while in others, it is negative. (CHODCIK; WEIL, 2020) assessed the association of these indicators with number of COVID-19 cases, deaths per million, and CFR in Israel and 39 countries in Europe. They found that countries located to the three lower GDP quintiles, the COVID-19 incidence and mortality per million rates were significantly lower compared to countries in the fourth/fifth quintiles. There was no significant differences in CFR between GDP quintiles.

Table 1 - Posterior summaries the binomial regression parameters associated to each covariate for COVID-19 deaths

Parameters	Mean	Std. Dev.	90% Cred. Int.	
			Lower Limit	Upper Limit
β_0	-1.1640	0.6514	-2.2461	-0.2028
β_1(Sub-Sahara)	0.1094	0.3543	-0.4581	0.6765
β_2(Central Asia)	0.1006	0.4128	-0.5842	0.7944
β_3(Asia Middle East)	-0.2734	0.3572	-0.8676	0.3318
β_4(Central America)	0.5386	0.4161	-0.1388	1.2312
β_5(Caribbean)	1.0190	0.5431	0.0996	1.8671
β_6(Europe)	1.1821	0.3917	0.5706	1.7380
β_7(North Africa)	0.4465	0.4549	-0.2919	1.1720
β_8(North America)	1.1591	0.4681	0.3476	1.9301
β_9(Oceania)	0.0605	0.5697	- 0.8579	1.0180
β_{10}(South America)	0.5005	0.3545	-0.0958	1.0751
β_{11}(log(pop/km2))	-0.0685	0.0823	-0.2075	0.0613
β_{12}(urban population)	0.3682	0.4761	-0.4609	1.1380
β_{13}(log(infant mortality))	-0.3546	0.1673	-0.6220	-0.0704
β_{14}(physicians by 1000)	-0.0777	0.0834	-0.2123	0.0602
β_{15}(GDP spent in health)	0.5090	0.9644	-1.0731	2.1541
β_{16}(log(GDP))	0.2434	0.1114	0.0105	0.3702
β_{17}(log(GDP per capita))	-0.5279	0.0683	-0.6319	-0.4113
β_{18}(log(accum days epid))	-0.0320	0.4120	-0.5978	0.6844
ζ	1.3860	0.2035	1.0491	1.7381

From the Monte Carlo estimates based on the simulated Gibbs samples for the posterior means (Table 1) for the regression parameters, it is possible to see the effects of the covariates on the regression parameters on the probability of death due to COVID-19: $\beta_{16}(\log(GDP))$ is positive while $\beta_{13}(\log(IMR))$ and $\beta_{17}(\log(GDPpercapita))$ are negative. That is, the probability of death due to COVID-19 increases when the values of the covariate GDP in logarithmic scale increases. This result is in agreement with the scatter plots of Figure 2. In other direction, since the parameter β_{13} is estimated by a negative value, it is possible to interpret that when there is increasing of IMR, there is a decreasing in the probability of death due to COVID-19, this finding of ours is not parallel to any other study, considering the scarcity or lack of publications that assess this association, and what is certain is that the COVID-19 pandemic has a negative impact on the infant mortality rate, probably the increasing in the near future (UNICEF, 2020). The same behavior is verified for the covariate log(GDP per capita).

Related to the dummy variables associated to regions, it is observed that the parameters β_5, β_6 and β_8 have positive estimates, indicating higher probabilities of deaths due to COVID-10 for the regions Caribbean, Europe and North America when compared to the reference region East Asia, these results may suggest the interference of variables such as older population, greater social mobility, as well as, great social inequalities, as observed by Rollston e Galea (2020). The other covariates did not show significant effects on the probability of death due to COVID-19 for the diagnosed people.

Using the proposed binomial logistic regression model in presence of random effects, it is observed an excellent fit of the model when comparing the Bayesian estimated means $n_i p_i, i = 1, 2, \ldots, 113$ for the binomial distribution when compared to the observed data (number of deaths due to COVID-19 in each country) as seen in Figure 3. The estimated values of CRF not close to the diagonal refer to the estimated values of the two countries with the lowest numbers of deaths by COVID-19 until July 25, 2020, Trinidad-Tobago (8 deaths) and Vietnam (0 deaths).

The diagnostic plots for the regression model, as residuals and PACF, are presented in Figure 4. Observing the residual plot, it is possible to notice that the assumption of normality of residuals is not violated, this fact is supported by symmetric distribution of residuals and by the Shapiro-Wilk test for normality (p-value = 0.2656, i.e. not reject normality). There is no evidence of autocorrelation in the PACF plot.

In summary, from the obtained results of this study some economic indicators as GDP and GDP per capita, health indicators (infant mortality rate) and some differences in regions are the most important factors which could impact in better or worse results for the COVID-19 pandemic deaths in different countries of the world. However, all of these results must be considered with great caution, since the pandemic of COVID-19 has been shown to be extremely dynamic, with patterns of distribution, contagion, transmissibility among continents, and even often within the same country, where marked differences have been observed (NEPOMUCENO et al., 2020; RACIBORSKI et al., 2020). It is important to note that, while writing this manuscript, we observed the interiorization and ruralization of COVID-19 in some countries (JOOB; WIWANITKIT, 2020; SRIWIJITALAI; WIWANITKIT,

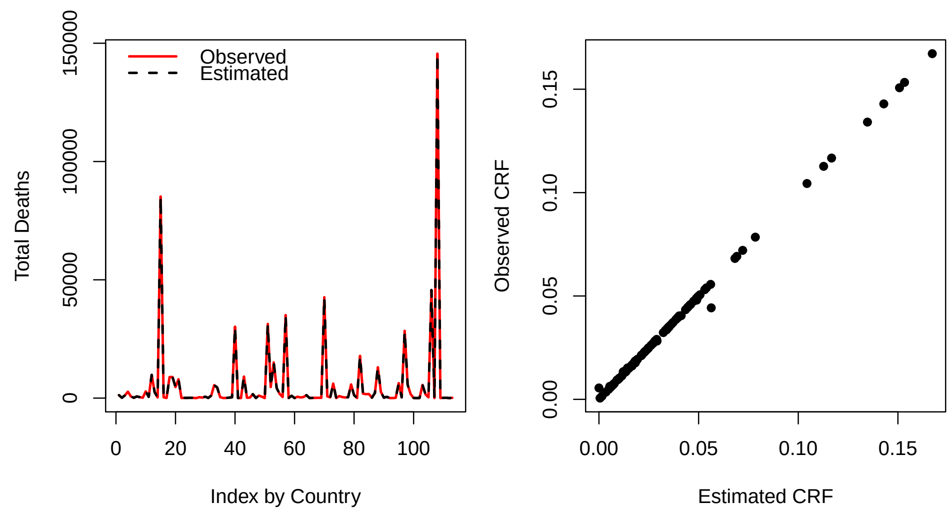

Figure 3 - Number of observed and estimated deaths and observed and estimated CRF for the considered model.

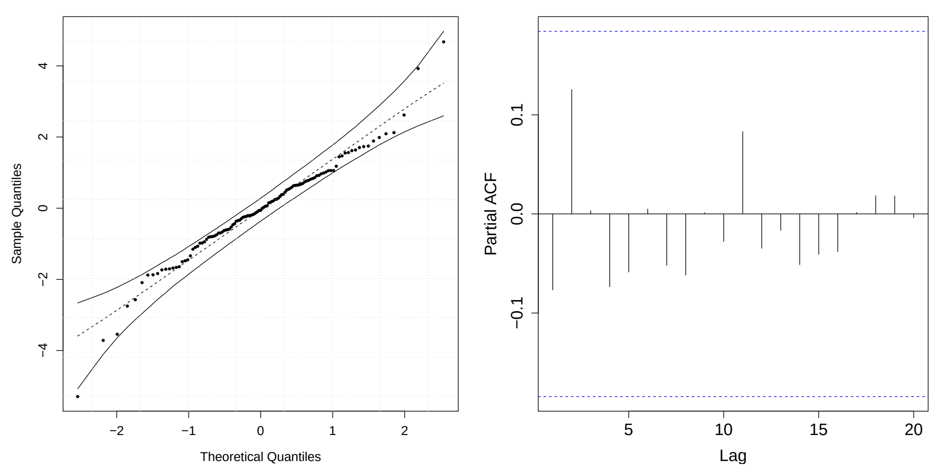

Figure 4 - Residuals and PACF plot for the considered model.

2020), which suggests that we know very little about the properties of SARS-CoV-2 and its interaction/adaptation with the environment and the human beings (CHAN et al., 2020b). In addition, the implementation of policies to fight infection/disease by SARS-CoV-2 vary widely among all countries, intra and intercontinentally, such as population testing, more or less restrictive measures of social distance, financial assistance to unemployed and business financing, etc (CHU et al., 2020; LAI et al., 2020b). All of this has a direct impact on the economic, social and health indicators evaluated by us in this study.

Obviously, due to the ecological design, this study has limitations, such as the fact that we use a database, which we cannot guarantee that all your information is completely reliable or updated systematically. In addition, we analyze data from an ongoing pandemic that has been changing continuously around the world, so its dynamism may present a result today and a completely different one tomorrow.

4 Concluding remarks

The main goal of this paper was to evaluate the association among socioeconomic and epidemiological indicators in the context of the COVID-19 epidemic, using use a binomial logistic regression model to understanding the different probabilities of deaths due to COVID-19 around the world based on the daily reported cases and deaths by COVID-19 until July 25, 2020, for 113 countries, and the results we found are interesting considering the epidemiological interpretation, in the face of a complex pandemic in all its aspects, like the one we are experiencing.

The proposed methodology can also be extended by using other factors, such as the daily rate of social isolation. When available, the inclusion of additional covariates may provide more accurate model fits, whose underlying results may offer suggestions on how fast the virus will spread in the short-term period. Nevertheless, the present methodology can also be used to provide a comprehensive understanding of the lethality of COVID-19, which may alert authorities to keep restrictive strategies to control the advance of the pandemic, especially in more impoverished regions and with precarious health systems.

PERES, M. V. O.; OLIVEIRA, R. P.; ACHCAR, J. A.; NUNES, A. A. Taxa de mortalidade de casos por COVID-19: Uma análise bayesiana hierárquica de países em diferentes regiões do mundo. *Braz. J. Biom.,* Lavras, v.40, n.2, p.198-212, 2022.

- *RESUMO: O objetivo principal deste estudo é a análise estatística de óbitos/casos, definido epidemiologicamente como a taxa de fatalidade de caso (CFR) devido a novo coronavírus (SARS-CoV-2) para 113 países em diferentes regiões do mundo na presença de alguns fatores econômicos, fatores de saúde e sociais. O conjunto de dados considerado refere-se às contagens diárias acumuladas de casos notificados e óbitos por um período que vai do início da pandemia do COVID-19 em cada país até 25 de julho de 2020, o período final do dia de acompanhamento. Um modelo de regressão logística binomial na presença de um efeito aleatório é assumido na análise de dados. A análise estatística é considerada sob uma abordagem Bayesiana hierárquica usando métodos MCMC (Markov Chain Monte Carlo) para obter as estatísticas posteriores de interesse. Os resultados encontrados são interessantes considerando a interpretação epidemiológica, que pode ser de grande relevância para epidemiologistas, autoridades de saúde e público em geral diante de uma pandemia complexa em todos os seus aspectos, como a que estamos vivenciando.*

- *PALAVRAS-CHAVE: Epidemiologia, modelos de regressão binomial, variáveis latentes, métodos Bayesianos hierárquicos.*

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