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Generalized models and the impacts of population density on COVID-19 transmission

Modelos generalizados y los impactos de la densidad de población en la transmisión del COVID-19

Modelos generalizados e os impactos da densidade populacional na transmissão da COVID-19

Amaury de Souza[1], Marcel Carvalho Abreu[2], José Francisco de Oliveira-Júnior[3], Widinei Alves Fernandes[4], Flávio Aristone[5], Debora Martins de Souza[6], Silvania Donato da Silva[7], Elania Barros da Silva[8]

ABSTRACT

Objective: *to analyze epidemic curves based on mathematical models for the state of Mato Grosso do Sul and the impacts of population density on COVID-19 transmission.* ***Method****: the linear, polynomial and exponential regression model was used to make the numerical adjustment of the respective curves empirical.* ***Result****: it was found that the models used describe very well the empirical curves in which they were tested. In particular, the polynomial model is able to identify with reasonable reliability the appearance of the inflection point in the accumulated curves, which corresponds to the maximum point of the respective daily curves. The analysis indicates a weak positive correlation between infection, mortality, lethality and deaths from COVID-19 with population density, as revealed by the correlation and analysis of* R^2. ***Conclusion****: the models are very effective in describing the COVID-19 and epidemic curves in the estimation of important epidemiological parameters, such as peak case curves and daily deaths, allowing practical and efficient monitoring of the evolution of the epidemic.*

Descriptors*: COVID-19; Epidemiological Models; Health Policy.*

[1]Físico. Doutor em Tecnologias Ambientais. Universidade Federal de Mato Grosso do Sul (UFMS). Campo Grande, Mato Grosso do Sul, Brasil. E-mail: amaury.de@uol.com.br ORCID ID: http://orcid.org/0000-0001-8168-1482 **Autor para Correspondência** - Endereço: cidade Universitaria, s/n, Campo Grande/MS, CEP79070-900.

[2]Engenheiro florestal. Doutor em Agronomia. Universidade Federal Rural do Rio de Janeiro (UFRRJ). Rio de Janeiro, Brasil. E-mail: marcelc.abreu@gmail.com ORCID ID: http://orcid.org/0000-0002-6457-421X

[3]Metereologista. Doutor em Ciências Atmosféricas. Universidade Federal de Alagoas (UFAL). Maceió, Alagoas, Brasil. E-mail: junior_inpe@hotmail.com ORCID ID: http://orcid.org/0000-0002-6131-7605

[4]Físico. Doutor em Geofisica Espacial. Universidade Federal de Mato grosso do Sul (UFMS). Campo Grande, Mato Grosso do Sul, Brasil. E-mail: widinei.fernandes@ufms.br ORCID ID: http://orcid.org/0000-0001-9481-3413

[5]Físico. Doutor em Física. Universidade Federal de Mato Grosso do Sul (UFMS). Campo Grande, Mato Grosso do Sul, Brasil. E-mail: flavio.aristone@ufms.br ORCID ID: http://orcid.org/0000-0003-3172-7520

[6]Fisioterapeuta. Mestrado em Ciências da Saúde. Universidade Federal de Mato Grosso do Sul (UFMS). Campo Grande, Mato Grosso do Sul, Brasil. E-mail: deboramartins24@hotmail.com ORCID ID: http://orcid.org/0000-0003-2955-1036

[7]Acadêmica do Curso de Meteorologia. Universidade Federal de Alagoas (UFAL). Maceió, Alagoas, Brasil. E-mail: silvaniadonatodasilva@gmail.com ORCID ID: http://orcid.org/0000-0001-8519-5561

[8]Enfermeira. Mestranda em Engenharia de Biossistemas. Universidade Federal Fluminense (UFF). Niterói, Rio de Janeiro, Brasil. E-mail: barros.elania@gmail.com ORCID ID: https://orcid.org/0000-0003-3943-9769

RESUMEN
Objetivo: *analizar curvas epidémicas basadas en modelos matemáticos para el estado de Mato Grosso do Sul y los impactos de la densidad de población en la transmisión de COVID-19.* ***Método****: se utilizó el modelo de regresión lineal, polinomial y exponencial para hacer el ajuste numérico valor de las respectivas curvas empíricas.* ***Resultados****: se encontró que los modelos utilizados describen muy bien las curvas empíricas en las que fueron probados. En particular, el modelo polinomial es capaz de identificar con razonable fiabilidad la aparición del punto de inflexión en las curvas acumuladas, que corresponde al punto máximo de las respectivas curvas diarias. El análisis indica una correlación positiva débil entre la infección, la mortalidad, la letalidad y las muertes por COVID-19 con la densidad de población, según lo revelado por la correlación y el análisis de* R^2*.* ***Conclusión:*** *los modelos son muy efectivos para describir el COVID-19 y curvas epidémicas en la estimación de parámetros epidemiológicos importantes, como las curvas de casos máximos y las muertes diarias, lo que permite un seguimiento práctico y eficaz de la evolución de la epidemia.*
Descriptores: *COVID-19; Modelos Epidemiológicos; Políticas de Salud.*

RESUMO
Objetivo: analisar as curvas epidêmicas com base em modelos matemáticos para o estado de Mato Grosso do Sul e os impactos da densidade populacional na transmissão da COVID-19. **Método**: o modelo de regressão linear, polinomial e exponencial foi utilizado para fazer o ajuste numérico das respectivas curvas empíricas. **Resultados:** verificou-se que os modelos utilizados descrevem muito bem as curvas empíricas nas quais foram testados. Em particular, o modelo polinomial é capaz de identificar com razoável confiabilidade o aparecimento do ponto de inflexão nas curvas acumuladas, que corresponde ao ponto máximo das respectivas curvas diárias. A análise indica uma correlação positiva fraca entre infecção, mortalidade, letalidade e mortes por COVID-19 com a densidade populacional, conforme revelado pela correlação e análise de R^2. **Conclusão**: os modelos são muito eficazes na descrição das curvas epidêmicas de COVID-19 e na estimativa de parâmetros epidemiológicos importantes, como curvas de casos de pico e óbitos diários, permitindo um monitoramento prático e eficiente da evolução da epidemia.
Descritores: COVID-19; Modelos Epidemiológicos; Política de Saúde.

INTRODUCTION

Since the first case of infection with the new coronavirus (Sars-Cov-2), which causes COVID-19, in Wuhan, China, in December 2019, the virus has already spread to virtually every country, leading to one of the biggest global health crisis in the last 100 years. In Brazil, Sars-Cov-2 infection was first confirmed in the city of São Paulo on February 26, 2020. Since then, the epidemic has spread throughout the country, which has forced several Brazilian states and municipalities to adopt measures of social isolation and other mitigation measures to contain the spread of the virus.

Mathematical models have received unprecedented attention and *have been widely used during the current pandemic as a strategic tool to predict the incidence, prevalence and mortality rate of COVID-19 worldwide. Popular statistical methods currently in use for studying and forecasting COVID-19 pandemic are based on the classical SIR model which consider Susceptible, Infectious and Recovered individuals[1], and its various modifications, in particular the incorporation of Exposed but non-contagious individuals producing the SEIR model[2]. Roda et al[3], for example, correlated the standard SIR and SEIR structures to the COVID-19 model in Wuhan, China. Fanelli[4] have incorporated the number dead individuals' data within a simple susceptible-infected-recovered-deaths (SIRD) model to studiy the temporal dynamics of the COVID-19 pandemic in mainland China, Italy and France. Anastassopoulou et al[5] also used the SIRD modelling approach to estimate the severe epidemiological restrictions, as well as the demonstration and prediction of the transmission of the COVID-19 pandemic in Hubei, China.*

Other commonly used, simple and direct statistical and time series models for forecasting the spread of outbreak include linear and logistic regression analyses. Ghosal et al[6] employed linear regression analysis to predict the short-term number of deaths in India due to SARS-CoV-2. Aviv-Sharon and Aharoni[7] utilized the generalized logistic model and generated short- and long-term projections of the outbreak spreading potential and the pandemic cessation dates in China, Iran, the Philippines and Taiwan. Ceylan[8] applied the integrated autoregressive moving average (ARIMA) model, a linear combination of past respective noise, to predict the prevalence of COVID-19 in Italy, Spain and France. Ayinde et al[9] subjected cumulative confirmed cases of COVID-19 in Nigeria to several statistical curve estimation models. Al-qaness et al[10] improved the Adaptive Neuro-Fuzzy Inference System (ANFIS) by implementing an improved flower pollination algorithm using the Salp Swarm algorithm to assess the number of confirmed COVID-19 crises in China. Wang and Su[11] established an algorithm based on patient information to assess the death rate of COVID-19 in real time, using openly accessible data sets. Li et al[12], for example, built a method to predict the continued trend with data-based analysis and estimate the size of the COVID-19 outbreak in China[13] predict the national and global spread of COVID-19 to determine the impact of the *metropolitan isolation of Wuhan and its neighbors.*

Appling different epidemiological and statistical models to estimate, with a certain reliability degree, the spread and peak of the current outbreak in areas of highly vulnerable populations is of great importance, as in the case of the state of Mato Grosso do Sul, Brazil. The state of Mato Grosso do Sul, located in the central-west region of Brazil, has an area of approximately 358159 km^2 (4.19% of the national territory) is distributed in 79 municipalities, where 73.41% of the inhabitants of these municipalities are classified as very vulnerable to COVID-19, especially within the municipalities with the largest population. Hence, this study aims to analyze epidemic curves based on mathematical models for the state of Mato Grosso do Sul and the impacts of population density on COVID-19 transmission.

METHOD

In this study, the incidences of COVID-19 from March 14, 2020 to January 1, 2021 for all 79 municipalities that make up the state of MS were analyzed. The official estimate of the population for the year 2020, of each municipality, as well as of that federative unit, was obtained from the system of the Informatics Department of the Unified Health System (DATASUS)/Health Information (TABNET)[14]. The officially daily counts of COVID-19 cases and deaths were obtained from the Health Department of the State of Mato Grosso do Sul through the electronic platform Integra SUS.

All data used were secondary, without personal identification and in the public domain, which, according to Resolution nº. 510/2016, of the National Health Council, dispenses with the need for prior approval by the Ethics Committee in Research with Human Beings[15].

To calculate the incidence coefficient of each municipality, the number of confirmed cases was divided by the resident population and multiplied by the population base of 100 thousand inhabitants. Descriptive statistics of the data, for each municipality, was performed onthe incidence coefficients.

The state of MS is located in the Midwest region of Brazil, according to the Brazilian Institute of Geography and Statistics (IBGE), has 79 municipalities and has a population of 2.62 million *inhabitants with a demographic density of 6.86 inhabitants / km² and a Municipal Human Development Index (IDHM) of 0.729.*

Except for the numbers of confirmed cases and deaths, number of suspected cases and deaths; the number of tests, total number of hospitalized patients (in intensive care unit (UTI) and infirmary), biological sex (male and female) and age group (<1, 1-9, 10-19, 20-29, 30-39, 40-49, 40-59, 60-69, 70-79 and 80 + years) variables were also analyzed.

The number of daily new and accumulated cases and deaths, as a function of time (in days), were analyzed by first and second degree linear regression functions (equations 2 and 3, respectively) and by a non-linear exponential type with 1 and 2 (equations 4 and 5 parameters, respectively). The statistical significance of the parameters of the regressions was tested by the Student's t test and the adjustments were evaluated by the coefficient of determination (R^2), Willmott's agreement index (d) and the root of the mean square of the error (RMSE).

$$Y = \beta_0 + \beta_1 \cdot \text{day} \qquad (1)$$

$$Y = \beta_0 + \beta_1 \cdot \text{day} + \beta_2 \cdot \text{day}^2 \qquad (2)$$

$$Y = e^{\beta_1 \cdot \text{day}} \qquad (3)$$

$$Y = \beta_0 \cdot e^{\beta_1 \cdot \text{day}} \qquad (4)$$

For both the daily counts of COVID-19 cases and deaths, a 7-day moving average for the period under analysis was calculated, and the modified Mann-Kendall (MK) test was applied to verify whether the fluctuations around the calculated average follow monotonic upward or downward trend over time. The MK test is a non-parametric trend verification test that consists of testing the null hypothesis of stationarity in the time series data. For a time series, the Mann-Kendal (S) statistic is defined by:

$$S = \sum_{k=1}^{n-1} \sum_{i=k+1}^{n} \text{sign}(x_i - x_k) \qquad (5)$$

S is computed by the number of positive differences minus the number of negative differences, where x_i is the i-th observation, x_k is the k-th *observation, immediately after the i-th observation, and n is the number of observations over time. The arrangement of sign(x_i - x_k) takes on the values 1,0, or -1 according to the sign of x_i - x_k, andis given by:*

$$\operatorname{sign}(x_i - x_k) = \begin{cases} +1 \text{ if } (x_i - x_k) > 0 \\ 0 \text{ if } (x_i - x_k) = 0 \\ -1 \text{ if } (x_i - x_k) < 0 \end{cases}$$

S>0 denotes that the observations later in time tend to be greater than observations made earlier, and vice versa. The variance of S is computed as:

$$\text{Var}(S) = \frac{n(n-1)(2n+5) - \sum_{i=1}^{m} t_i(t_i-1)(2t_{i+5})}{18} \quad (6)$$

Where m is the number of groups tied, ti is the number of loops of length equal to i. And finally, the MK test statistic (Z) is computed as follows:

$$Z = \frac{S-1}{\sqrt{VAR(S)}} \text{ if } S > 0 \quad (7)$$

Z>0 value indicates that the data tend to increase over time. On the contrary, Z<0 value indicates that the data tend to decrease with time.

The MK test requires that the sample data be serially independent (no self-correlation), sincecorrelated observations over time could affect the test's ability to correctly identify and assess a significant trend. To eliminate the effect of these potentially serially correlated observations in the MK test, which can increase the probability that the MK test will detect a significant trend (i.e. type I error), an autocorrelation analysis was performed. The autocorrelation analysis was done using a correlogram, consisting a graph of the sequential values of delay k = 0, 1, 2,. ., n. In case of verified autocorrelation, the MK test was applied with the modification[16]. In brief, this modification consists of a correction of variance to address the issue of serial correlation in trend analysis, while maintaining the significance of the test[17, 18].

Pettitt's statistics account for the number of exceedances in which the value of the first sample exceeds that of *the second sample. The null hypothesis of the test is that there is no breaking point in the data series.*

RESULTS

In the period from March 14, 2020 to January 31, 2021, in the state of Mato Grosso do Sul there were 133,721 confirmed cases and 2,329 deaths (and an average lethality rate of 1.7%). 47.4% and 52.6% of the confirmed cases were identified in males and females, respectively. A total of 130,510 tests were performed, (54.1%, 42.8% and 1.9%of them were RT-PCR, rapid or serology tests, respectively), and 29%,5.3% and 1.1% of the RT-PCR, rapid or serology tests, respectively, were positive (to a total of 11,224 cases and ~25% of all tests).

Of the 133,721 confirmed cases in MS; 14,382 people were subjected to household isolation, 116,280 patients have recovered and 2,329 died; from the 670 hospitalized cases 360, 239 and 121 werein clinical, public or private beds, respectively; out of the 310 cases admitted to the Intensive Care Unit (UTI), 220 and 90 were in public or private beds, respectively.

The high rates of allocation of patients in the UTI, corresponding to 45% of daily admissions, was what called the attention at COVID-19. However, this high number also reflects the concentration of testing of more severe individuals when compared to the official World Health Organization (WHO) data, which indicate that 15% of patients with COVID-19 require hospitalization with oxygen therapy and 5% need to be admitted to the UTI[19]. In this sense, the occupation of UTI beds is linked to admission due to critical health instability, with the need for life support intervention, with patients with a high probability of recovery being in high priority[20].

It is noteworthy that the practice of adequate health surveillance system accompanied by effective epidemiological investigation during epidemics is a mandatory in and must occur in an integrated manner and concurrently with prevention and control actions, with the dissemination of data with as soon as possible[21]. In this sense, according to the National Contingency Plan for Human Infection by the new Coronavirus of the Ministry of Health, it is up to the Health Surveillance services to establish risk communication strategies, with the collection and dissemination of information that help in combating and *controlling disease[22]. In view of this, the need is reinforced, in times of pandemic, to improve the notification systems and the transfer of information between different levels, as well as to invest in strategies for testing the population associated with monitored social distance policies, with a survey of local social isolation rate, as, as observed in the present study, municipal decrees of commercial closure, without adequate surveillance, may not be sufficient in the control of cases, deaths and hospitalizations.*

The age profile of confirmed cases by age group were: (<1 (0.6%), 1-9 (3.0%), 10-19 (6.6%), 20-29 (20.2%), 30-39 (24.3%), 40-49 (19.1%), 40-59 (13.5%), 60-69 (7.6%), 70-79 (3.4%) and> 80 (1.7%)).

The new cases and deaths presented a similar behavior over time, in which significant peaks were observed between July to October, and between November to December. The cumulative number of COVID-19 cases and deaths exhibited an increase from the beginning of July to October 20, and from November (Figure 1). A slight decrease in the number of cases and deaths was observed between the end of September to mid-November.

The moving average of the last 7 days, measured to verify the increase of COVID-19 cases and deaths in MS, Brazil showed a significant upward trend, both for new cases and deaths (Figure 2). It presented a constant increase until reaching the first peak, at the end of September, decreasing in October, with new growth in November, until reaching the second peak, greater in magnitude than the first, in December. A probable breaking point was observed on July 9, 2020, just before the break point of the 7-day moving average for new deaths on July 13, 2020. Likewise, a strong relationship (r> 0.90) between the 7-day moving average for the number of cases and number of deaths was observed (Table 1).

There is a reduction in the 7-day moving average for Mato Grosso do Sul, which showed a constant increase until reaching the first peak, at the end of September, decreasing in October, with new growth in November, until reaching the second peak, greater in magnitude than the first, in December. The trend tests for the moving average, used to monitor the number of cases, showed a significant upward trend, with a probable breaking point on July 9 and 13 for the number of new cases and the number of new deaths. There is a strong *relationship (r> 0.90) between the 7-day moving average for the number of cases and number of deaths.*

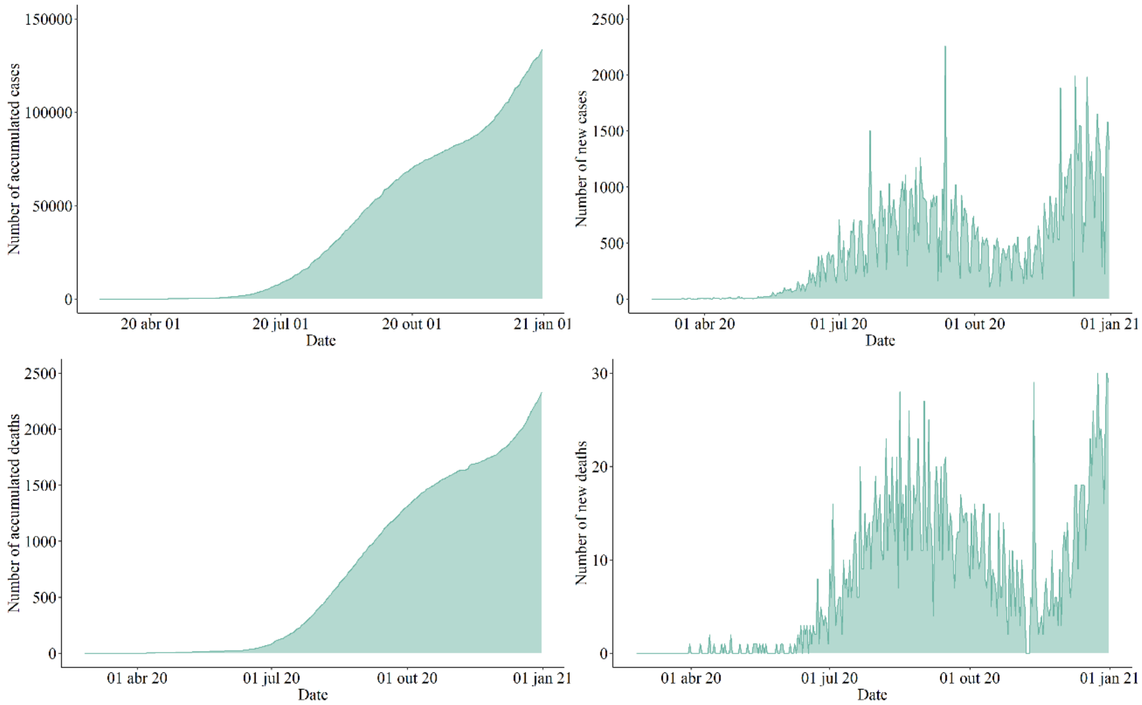

Figure 1 - Number of daily new and accumulated cases of COVID-19 in Mato Grosso do Sul in the period from March 14, 2020 to January 31, 2021.

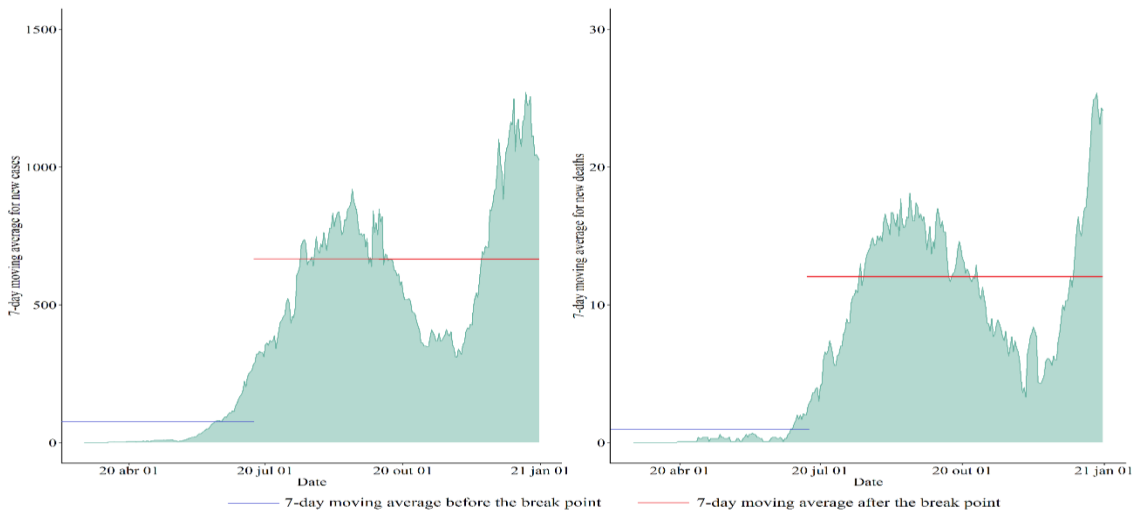

Figure 2 - Moving average of the last 7 days for the number of new and new deaths due to COVID in Mato Grosso do Sul in the period from March 14, 2020 to January 31, 2021.

Table 1 - Non-parametric tests for verifying trends in the moving average of cases and deaths by COVID in Mato Grosso do Sul in the period from March 14, 2020 to January 31, 2021.

Test	*Statistics*	*7-day moving average for new cases*	*7-day moving average for new deaths*
Mann-Kendall	*z*	*18.12*	*14.96*
	Variance	*3167576.00*	*3161013.00*
	p-value	*0.00*	*0.00*
Modified Mann-Kendall	*Z*	*8.80*	*5.67*
	Variance	*13426100.00*	*22021790.00*
	p-value	*0.00*	*0.00*
Pettitt	*Probable change point at time K*	*09/07/2020*	*13/07/2020*

The linear and non-linear regressions of the cumulative number of cases and deaths as a function of time were both significant. For the cumulative number of cases, the best fit was achieved using the second-degree linear regression, while for the cumulative number of deaths, the exponential regression with 2 parameters was the best model (Table 2). The curvilinear shape of the total cases and accumulated deaths (Figure 3). The parameters β1 and β2 of the second-degree linear regression represent the linear and quadratic effects, respectively, which shows that the accumulation of cases and deaths had a higher rate of increase in the periods between July and October, with a slight decrease before a more expressive new rate, starting in November.

From the second week of May 2020, there was a significant increase in the number of cases of COVID-19, mainly until 07/22 where it reached a value of 1503 cases. Later, a decrease to 968 cases on 07/29 was observed, rising again until 08/22 with 1177 cases, decreasing on 11/11 to 138 cases, rising again until 12/31 with 1220 cases. For deaths, there was also variation, but to a lesser degree. The highest growth rates occurred mainly in the first half of the analyzed period (08/16) with 28 deaths, then there was a fall from 11/13 to 11/30, with greater stabilization in this period, growing again on 12/2 and reaching the highest value of deaths during 12/24-30 with 30 deaths.

On average, the incubation period is estimated at five to six days and can vary from zero to 14 days[23]. Clinical criteria and case definition can be performed in a clinical and laboratory manner. The laboratory diagnosis for the identification of the SARS-CoV-2 virus is carried out using real-time RT-PCR techniques (considered the gold standard for the identification of the new coronavirus) or rapid serological test validated by reference institutions[23].

The scatter plot of the total (cumulative) of cases of infection, mortality, lethality and deaths of people in relation to population density for the declared municipalities is shown in Fig. 4. It was found that the rate of infection and mortality is higher in metropolitan cities with high population density. On the other hand, it is noted that the spread of COVID-19 and related deaths are low in districts with low population density. The situation is not very clear in districts with moderate density; data points spread across the graphics area with a slight tendency to increase infection and death with density.

Table 2 - Adjustment parameters and statistics for linear and non-linear regressions in Mato Grosso do Sul in the period from March 14, 2020 to January 31, 2021.

Variable	Regression	B_0	B_1	B_2	r^2	d	RMSE
Accumulated number of cases	RL1	-28535.68	435.61	-	0.90	0.85	12796.18
	RL2	-1969.00	-73.65	1.63	0.99	0.94	5028.47
	RE1	-	0.00	-	0.57	0.67	35833.57
	RE2	5018.00	0.01	-	0.95	0.87	9701.79
Accumulated number of deaths	RL1	-528.54	7.90	-	0.89	0.84	246.69
	RL2	-48.04	-1.31	0.03	0.97	0.92	124.74
	RE1	-	0.03	-	0.68	0.74	523.98
	RE2	0.01	92.98	-	0.93	0.84	211.81

RL1 = first degree linear regression; RL2 = second degree linear regression; RE1 = exponential regression with 1 parameter; RE2 = exponential regression with 2 parameters.

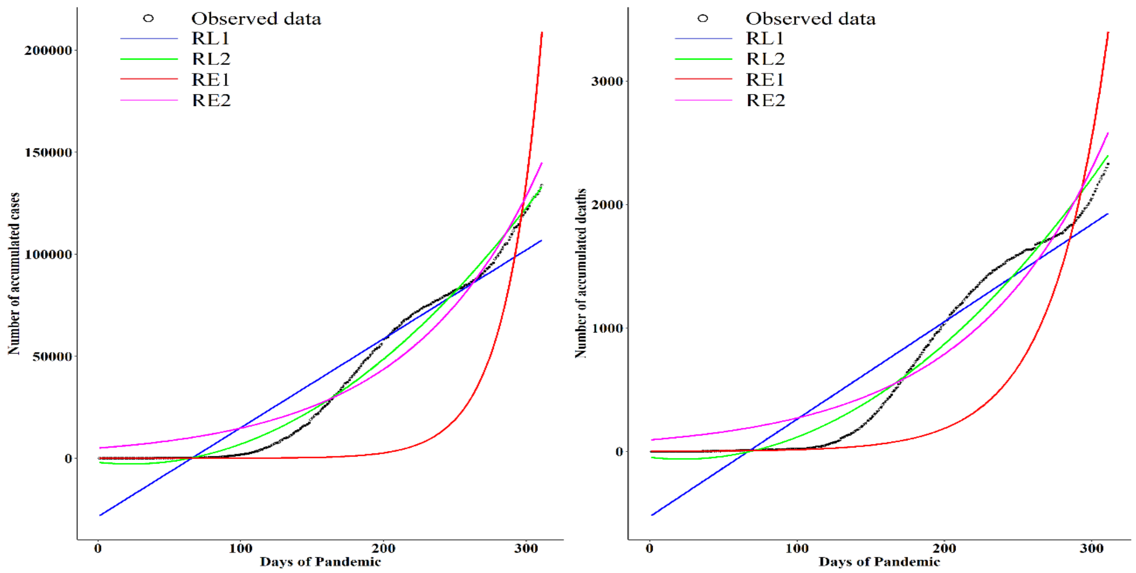

Figure 3 - Linear and non-linear regressions for temporal characterization of the number of accumulated cases and number of accumulated deaths in Mato Grosso do Sul in the period from March 14, 2020 to January 31, 2021.

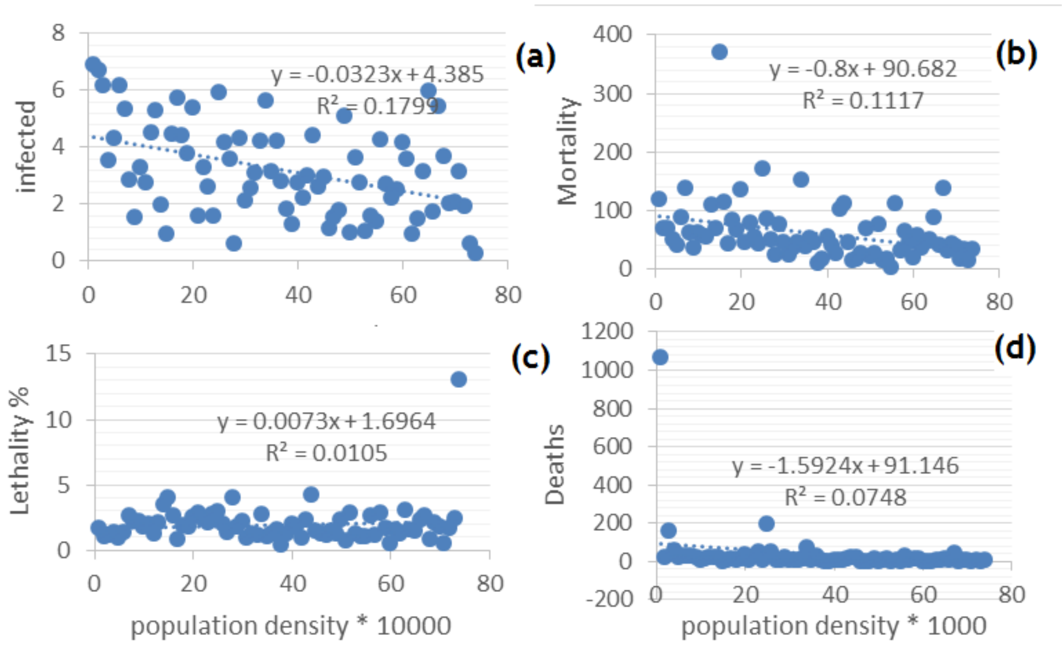

Figure 4 - Variation in the rate of a) infected, b) mortality, c) lethality and d) deaths due to COVID-19 with population density in the municipalities of Mato Grosso do Sul.

DISCUSSION

The state of Mato Grosso do Sul adopted measures of social isolation at the beginning of the pandemic, at the end of March, which reflected in an isolation rate above 50% by the end of April. In May, the isolation rate was less than 50%, which reflected an increase in the number of COVID-19 cases and deaths due to COVID-19. The rate of increase in the number of cases decreased slightly at the end of October, although the isolation rate remained around 37%[24]. It is evident that only at the beginning of the pandemic in Mato Grosso do Sul, the contingency of the virus was effective. Reports in which the increase in cases of COVID-19 in Brazil occurred since April are extensive[25].

In the case of COVID-19, there is a need for a critical assessment of epidemiological data related to human mobility to understand the dynamics of virus transmission at the local, regional and global scales. The continuous integration of these data flows helps to guide the deployment of resources to mitigate the transmission of COVID-19[26]. However, the social isolation index and the analysis of the number of daily new cases and new deaths are strong evidence of the lack of commitment to mitigate the effects of the pandemic. Restrictions of social isolation is a recognized preventive measure for controlling the circulation of COVID-19 *and several studies have shown that the spread of the virus can be significantly reduced by this measure[27].*

The positive spatial coefficient correlations found between the COVID-19 incidence coefficient and the measured social development, although weak, are unprecedented in Brazil, which can also be limiting from the perspective of comparing a few initial works on the topic addressed. In general, epidemiological research on communicable diseases finds in the average IDH an indirect indicator for health, since its greatest constitutive values are related to longevity,income and education [28, 29].

The identified upward trends in the moving average of COVID-19 cases and deaths by COVID-19 are worrying and tend to reach worrying peaks, probably due to the holiday season, coupled with holidays and school breaks, in which the population tends to travel and expand social relationships. The values of new cases and deaths represented by the 7-day moving average showes values not previously observed, which raises concerns about the consequences on the health system of MS, at the beginning of the year 2021, since the consequences of these peaks occur days after the diagnosis of the case. As Brazil does not have a coordinated national public health policy, the expected situation is catastrophic[30-32].

Considering the spatial distribution of COVID-19 in MS, given its high magnitude of morbidity and mortality, and the absence of effective immunization available and the pandemic spread potential, it is clear that it has not yet reached its maximum growth peak. Georeferencing proves to be a useful tool for epidemiological surveillance of communicable diseases and association with social determinants, in micro or spatial macro-analysis[33].

From a socioeconomic perspective, it is important to note that the elderly population represents one of the groups most subject to COVID-19 infection and symptomatology, with a higher risk of this cause of death for men. The pandemic caused by COVID-19 put the metropolises on alert, especially the large ones, which have high densities and facilitate the spread of the disease, as can be seen in the high incidence coefficient in Campo Grande and surrounding municipalities and in the municipalities that receive tourists as Bonito and Corumba, with a tendency to diffuse less concentrated in the other *municipalities of the state, although the measures taken by the state management contribute to limit the speed of occurrences, since the MS had an explosion of cases in COVID-19 in July. The first cases of contamination occurred in the city of Campo Grande with the best in MS and all those infected had made a trip abroad.*

The virus is already circulating on the outskirts of the city, with areas of high population density and worse sanitary conditions, which increases the concern with the speed of contagion. The metropolitan region of Campo Grande generates income and services, a tourist hub, has a high population density and urban mobility. This set of factors may corroborate the present study, suggesting that a greater average human development index-IDHM may also facilitate the conditions of intense viral circulation, transmissibility and the increase in the clinical picture of COVID-19. The low levels of IDHM reveal not only the population's vulnerability, but also difficulties in health services regarding the diagnosis and treatment of the disease in the municipalities of Mato Grosso do Sul, similarly to the expected fragility of health services in Brazil[34] and in Latin American countries in tackling the pandemic [35].

Given the great mobility of the population and the intense social and economic relations that the municipalities of the interior have with their respective capitals, the dissemination of COVID-19 should strongly affect the infrastructure in the interior. Unlike other illnesses at other times, this time there may not be enough time to transfer to the capitals or the capacity to attend to all the demands of critically ill patients, which may reflect on different coefficients of lethality associated with social inequalities.

In the same way, there is concern with the maintenance of jobs, since the weakening of employment ties was already underway because of the context of the current economic crisis in Brazil, but it is being exacerbated by the pandemic. In this sense, the number of people invisible to social policies, especially the homeless population, tends to increase, and ways of protecting the whole society against the new coronavirus need to be rethought.

Despite the evolution of the Brazilian public health system, it is noteworthy that neglected diseases or those associated with health care in low-income populations can emerge secondary to COVID-19 and have an even *more bleak impact on their cure prognosis.*

The study is valid in demonstrating the need for the articulation of epidemiological surveillance services in private health services with SUS, the first most sought after by population groups with greater purchasing power. The findings contribute to the knowledge about the COVID-19 epidemic process in the state of MS, as well as pave the way for constant analyzes that indicate the disease's behavior.

The demographic density indicator has often been used to justify or explain COVID-19's low potential for contamination, thinking that if we have a low number of inhabitants per square kilometer, people would be further away from each other and, as a result, would decrease the chance of contamination. When we consider the distribution of the population of the state of Mato Grosso do Sul, we find that more than half of the state's population is concentrated in a single municipality. In this case, the capital, Campo Grande.

In relation to COVID-19, the capital of Campo Grande concentrates almost 45% of the confirmed cases in the state. The demographic density of Campo Grande is of the order of 97 inhabitants per km^2*. Getting very close to the demographic density of many European countries. As we can see, analyzing the spatial profile where people actually live is more relevant than considering the total area of the administrative political profile as a whole, as it changes our reading of data a lot if we compare the density of the State of Mato Grosso do Sul (6.8 inhab / km*^{2}*) with that of its capital.*

After all, if the capital is the place with the highest occurrence of cases, what is the point of considering the total area of the state and its density? The density of Mato Grosso do Sul is very low due to the fact that a large part of its territory is not inhabited and its total area is very large (Territorial Area. 357,145.534 km^2*). Thus, when we distribute the population in this gigantic area, we have a density indicator that can mask the most important information: how close people are to each other and, for example, assess the potential for contagion of the new coronavirus. But we can specify a little more this relationship of proximity to people. Campo Grande is a municipality with a large territorial extension and almost* *the entire population lives in its urban area.*

The urbanized area of Campo Grande corresponds to approximately 154.5 km^2. Thus, the demographic density that would best represent the proximity between people to the potential contagion in the municipality of Campo Grande would be the urban demographic density and not the total demographic density of the municipality, since few people live outside the urbanized area. Therefore, the use of demographic density as a relevant indicator for considering the potential for contagion must take into account the territorial profile of what we intend to analyze. That is, how close people live to each other. In Brazil and in the world, people live concentrated in urban areas. In this sense, it would be better to use urban demographic density as a spatial cutout to contagion.

Anyway, it is not contradictory that the state of MS has a very low density and at the same time has a high number of cases. We are not here stating that it is the demographic density of the urban population of Campo Grande or Mato Grosso do Sul that explains the large number of infections by COVID-19, but it is evident that it is wrong to assume that the contamination will be low due to the use improper use of the density indicator. In other words, the demographic density may be one of the elements that contribute to the spread of the disease, but it needs to be thought out according to the appropriate territorial outline in order not to cause distortions and misuse of information.

Dispersion graphs of the total (cumulative) cases of infection, mortality, lethality and death of people in relation to population density for the 79 municipalities of Mato Grosso do Sul are shown in Fig. 4. Although there are large fluctuations, particularly in the average population density, in general, there is a tendency for cases of infection and death to increase with population density. We estimated the correlation coefficients considering R^2 and and a Pearson correlation coefficient between infection, mortality, lethality and death rates as dependent variables and population density as the independent variable that are found as 0.18 and 0.35 (for infection); 0.11 and 0.12 (mortality); 0.01 and 0.07 (lethality); 0.07; 0.81 for deaths respectively, indicating a weak positive correlation.

In the present analysis, we considered the population density *obtained by dividing the total population of a municipality by its total area, which implicitly assumes a uniform spatial distribution of populations within a municipality. COVID-19's spread and death cases are also considered uniform. These assumptions lead to some uncertainty in estimating the correlation between the spread of COVID-19 and population density. For example, population density in the municipality of Ribas do Rio Pardo, is among the lowest in the state, although cases of infection and mortality are relatively high in the municipality. The R^2 value of the relationship between the infection / mortality rate and population density is weak, which implies that only part of the infection / mortality rate due to COVID-19 can be explained in terms of population density.*

This can be understood by the fact that the spread of COVID-19 and related mortality in a municipality can depend on several other factors, including geographical characteristics, economic conditions, professional occupation, prevailing health conditions, violence, genetic factors, health infrastructure, policies adopted by regulatory authorities, the average age of city residents, number of tests, etc[36-40]*. It is already known that COVID-19 has a greater impact on the elderly population (and the population with comorbidities). The share of the elderly population is not the same in all districts, nor is the total number of exams. However, there is no prevailing, direct and unambiguous method of interweaving different likely dependent factors.*

Bhadra et al[41]*, investigated the influence of population density on the spread of COVID-19 and related mortality in the context of India. After a detailed correlation and regression analysis of infection and mortality rates due to COVID-19 at the district level, he found a moderate association between the spread of COVID-19 and population density. Kodera et al*[42] *analyzed the pandemic coronavirus disease (COVID-19) morbidity and mortality rates in different prefectures in Japan. The correlations between morbidity and mortality rates and population density were statistically significant (p-value <0.05). Diao et al*[43] *found a significant correlation ($p <0.05$) of propagation and decay durations with population density in the four countries analyzed (China, England, Germany and Japan). Specifically, the duration of propagation showed a high correlation with* *population density and absolute humidity ($p < 0.05$), while the duration of decay showed the highest correlation with population density, absolute humidity and maximum temperature ($p < 0.05$).*

It is worth noting that the present analysis is subject to the limitations inherent in modeling complex systems in a scenario of 'incomplete information', as is the case with the COVID-19 epidemic.

CONCLUSION

There is a significant influence of the degree of commercial openness in the indicators of the disease, the low availability of tests, significant underreporting and lack of adequate and organized information about the control of the pandemic. The influence of the degree of commercial openness on the increase in the frequency of positive tests, cases and deaths, with important maintenance of cases in wards and ICU. In this work, we apply the model RL1 = first degree linear regression; RL_2 = second degree linear regression; RE_1 = exponential regression with 1 parameter; RE_2 = exponential regression with 2 parameters. The models proved to be quite effective for adjusting the respective empirical curves. From the parameters obtained from the adjustments, it was possible to estimate important epidemiological parameters. However, it cannot be said yet when the inflection for the death curve occurred (or will occur), since it is still better described (until the present date) by a purely exponential growth. As more data has been added, better convergence of functions is expected.

The analysis indicates a weak positive correlation between infection, mortality, lethality and deaths by COVID-19 with population density, as revealed by the correlation and analysis of R^2. There is a big difference in people's living conditions, which may be responsible for the different behavior of cases of infection / mortality due to COVID-19 with the population density in the municipalities. The density is reflected in the pressure of people against each other on the street, public vehicles, trains, lines, etc. COVID-19 cases were found in greater numbers in large cities. Therefore, containing a highly infectious disease like COVID-19 is a serious challenge for a country like Brazil of continental dimensions.

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