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BRIEF ORIGINAL ARTICLE

Impact of altitude on Covid-19 mortality in Colombia: a cross-sectional study

Impacto de la altitud sobre la mortalidad por Covid-19 en Colombia: un estudio transversal

Cándida Díaz-Brochero[1], Laura C. Nocua-Baéz[1], Carlos F. Montoya-Cárdenas[1], Jorge A. Cortes[1]

[1]Department of Internal Medicine, Faculty of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia..

Abstract

Objective. To estimate the proportion of deaths in confirmed cases according to altitude categories (low, medium, and high), and to evaluate a possible association between altitude and COVID-19 mortality in Colombia during the first two waves of the pandemic. **Methods**. Cross-sectional, analytical study. Adults residing in Colombia during 2020, with microbiological confirmation of SARS-CoV-2 infection were included. We calculated CFR using a binomial confidence interval, dividing altitude in three categories. We also performed a logistic regression model to evaluate the association between altitude and COVID-19 mortality. **Results**. Data on confirmed cases of COVID-19 during the period from March 06, 2020, to December 15, 2020, reported in 1,112 municipalities in Colombia were analyzed. A total of 994,738 confirmed cases were reported, including 32,034 deaths (0,03%). The mean age of cases was 39,8 years and 504,476 (50,4%) were male. The altitude range varied between 0 m to 3,350 m. The CFR was 0,042 (CI 95% 0,042 - 0,043; p value <0.001); 0,027 (CI 95% 0,027 - 0,028; p value <0.001) and 0,026 (CI 95% 0,025 - 0.026; p value <0.001) for low, middle, and high altitude, respectively. We found that for each km increase in altitude, the probability of dying from COVID-19 decreases by 20% (OR 0.8; 95% CI 0.785 - 0.815; p value <0.001), controlled by biological sex, age and number of inhabitants per municipality. **Conclusions**. Our results demonstrate that the altitude is a potential protective factor against COVID-19 mortality according to data from a Colombian population during the first two waves of the epidemic.

Keywords: COVID-19, mortality, altitude, Latin America, Colombia (Source: MeSH BIREME).

Resumen

Objetivo. Estimar la proporción de muertes en los casos confirmados según las categorías de altitud (baja, media y alta) y evaluar una posible asociación entre el grado de altitud y la mortalidad por COVID-19 en Colombia, durante las dos primeras olas de la epidemia. **Métodos**. Estudio de corte transversal, analítico. La población de estudio fueron adultos residentes en Colombia durante 2020, con confirmación microbiológica de infección por SARS-CoV-2. Se calculó la tasa de letalidad utilizando un intervalo de confianza binomial, dividiendo la altitud en tres categorías. También se realizó un modelo de regresión logística para evaluar la asociación entre la altitud y la mortalidad por COVID-19. **Resultados**. Se analizaron los datos de casos confirmados de COVID-19 durante el periodo comprendido entre el 06 de marzo de 2020 y el 15 de diciembre de 2020, reportados en 1.112 municipios de Colombia. Se notificaron un total de 994.738 casos confirmados, incluidas 32.034 muertes (0,03%). La edad media de los casos fue de 39,8 años y 504.476 (50,4%) eran varones. El rango de altitud varió entre 0 m y 3.350 m. La tasa de letalidad estimada fue de 0,042 (IC 95% 0,042 - 0,043; valor de p <0,001); 0,027 (IC 95% 0,027 - 0,028; valor de p <0,001) y 0,026 (IC 95% 0,025 - 0,026; valor de p <0,001) para altitud baja, media y alta, respectivamente. Encontramos que, por cada km de aumento de altitud, la probabilidad de morir por COVID-19 disminuye un 20% (OR 0,8; IC 95% 0,785 - 0,815; valor de p <0,001), controlando por variables como sexo biológico, edad y número de habitantes por municipio. **Conclusiones**. Nuestros resultados demuestran que la altitud es un potencial factor protector frente a la mortalidad por COVID-19 de acuerdo con datos de población colombiana, durante las primeras dos olas de la pandemia.

Palabras clave: COVID-19, mortalidad, altitud, América Latina, Colombia (Fuente: DeCS BIREME).

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Correspondence author: Cándida Díaz Brochero; **e-mail**: cdiazbr@unal.edu.co

Orcid: Díaz-Brochero C.: https://orcid.org/0000-0002-2176-7388
Nocua-Báez L.C.: https://orcid.org/0000-0003-2869-2339
Montoya-Cárdenas C.F.: https://orcid.org/0000-0003-1315-7421
Cortes J.A.: https://orcid.org/0000-0002-0882-9652

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Introduction

The COVID-19 pandemic is one of the most important events of our time. The pandemic has had unprecedented global consequences, not only in terms of global health but also economically, socially, and politically. This has prompted research into possible environmental factors related to disease prognosis and mortality risk[1].

Altitude has been one of the most debated environmental factors when analyzing the course of the pandemic, leading to different hypotheses about its possible role in the pathogenesis of infection and prognosis of COVID-19 disease[2]. However, the results of studies analyzing the relationship between altitude and COVID-19 outcomes have been contradictory, varying according to geographic location and the specific characteristics of the population analyzed[3]. For example, in Mexico, mortality has been reported between 9.6% and 14.2% in women living at ≥2500m compared to those living at <500m, and for men, mortality varied between 8.9% and 23.8% at ≥2500m compared to <500m[4].In contrast, Bolivia found COVID-19 mortality of 56.1% at <1500m, 24.2% between 1500-2500m and 19.7% at >2500m; and in Peru, it has been documented a mortality of 53.6% at <1500m, 28.7% at 1500-2500m and 17.7% at >2500m[5].

Colombia is considered one of most varied geographic soils in the world, with tropical rainforests, arid regions and paramos[6]. Its geographical distribution has been associated with the seasonality of rainfall in the country[7], which has been related to the development of outbreaks of respiratory infections, such as COVID-19 and other infections[8]. This distribution could explain part of the behavior of the disease in the country, however, each region has many ecosystems, making it difficult to make predictions with certainty[9]. These geographical variations play a very important role in the diversity of the evolution of the pandemic in the regions, which is why some studies have evaluated the role of altitude in the behavior of COVID-19[10]. Therefore, the objective of this study was to estimate the case fatality rate (CFR) according to altitude categories and to evaluate the association between altitude and COVID-19 mortality in adults in Colombia, controlling for potential confounding variables such as relevant sociodemographic factors and population density.

Methods

Study design

Cross-sectional, population-based, analytical study.

Study population

Adults, reported as confirmed cases of COVID-19, during the period from March 2020 to December 2020, in any of the 1,112 local administrative entities belonging to the 32 departments of Colombia.

Sampling and sampling: no sample size calculation was performed for this study, because all reported cases of adults with COVID-19 in Colombia during the period in question were included, according to the data provided by the Colombian Ministry of Health (population census).

Variables

The dependent variable analyzed was defined as the mortality due to COVID-19 (qualitative, nominal, dichotomous -Yes/No-). The independent variables analyzed were: 1) Altitude (continuous, interval variable); 2) Age in years (continuous); 3) Biological sex (qualitative, nominal, dichotomous -Yes/No-) and inhabitants per municipality (continuous, ratio variable).

Procedures

Altitude and population density values for each municipality were obtained from the official web pages of the Geographical Institute Agustín Codazzi 11 and the National Administrative Department of Statistics 12. Data on confirmed cases and deaths associated with COVID-19 were compiled from de-identified data on confirmed cases of COVID-19 in Colombia, provided by the Ministry of Health and Social Protection 13. The information obtained from each of the aforementioned sources is available online as free data for consultation and research.

Statistical analysis

Data processing and analysis: Initially, a descriptive analysis was made of the variables included in the analysis (number of confirmed cases, final status -alive or dead-, sex, age, date of diagnosis of COVID-19, altitude, and number of inhabitants of each municipality). Descriptive statistics (absolute values and measures of central tendency) were used for quantitative variables and frequency tables for qualitative variables.

The statistical analysis was performed using R software through the R Studio interface, version 4.2.1 14. We calculated the CFR (proportion of reported cases that die from COVID-19) using a binomial confidence interval, dividing the altitude in three categories (low -less than 1,000 m-; middle -between 1,000 m and 2,000 m-; and high -greater than 2,000 m-), using the R package "binom" 15. We reported the point estimators of CFR from each category with its respective 95% confidence interval and p values. Subsequently, to evaluate whether there is an association between altitude and mortality due to COVID-19, a logistic regression was performed, considering the outcome variable as the mortality due to COVID-19 and the exposure variable as the altitude, controlling for age, sex and number of inhabitants of each municipality. The results were presented in terms of odds ratio (OR) with their respective 95% confidence intervals and p values.

Ethical aspects

This study complies with the requirements for research in humans and was conducted within the ethical principles for medical research in humans according to the Declaration of Helsinki of the World Medical Association and the Council for International Organizations of Medical Sciences (CIOMS). The sources of information were secondary, obtained from the data of the primary national institutions. In accordance with the Habeas Data Law, the confidentiality of the participants was respected by de-identifying the information obtained.

Results

Data on confirmed cases of COVID-19 during the period from March 06, 2020, to December 15, 2020, reported in 1,112 municipalities in Colombia were analyzed. A total of 994,738 confirmed cases were reported, including 32,034 deaths (0,03%). Cases ranged from 1 to 109 years, with a mean of 39,8 years. 495,523 (49,5%) were female and 504,476 (50,4%) were male. The altitude range varied between 0 m to 3,350 m. Table 1 presents information related to the altitude level and number of inhabitants of the main municipalities of Colombia. A map of the number of deaths due to COVID-19 by department during the mentioned period is presented in figure 1.

Table 1: Main municipalities in Colombia, number of inhabitants and altitude

Municipalities of Colombia	Department of Colombia	Population (total)[†]	Altitude (m)
Bogotá	Capital District	7 968 095	2600
Medellín	Antioquia	2 653 729	1475
Cali	Valle del Cauca	2 297 230	991
Barranquilla	Atlántico	1 327 209	32
Cartagena	Bolivar	1 065 570	1
Soacha	Cundinamarca	831 259	2555
Cúcuta	Norte de Santander	795 608	325
Bucaramanga	Santander	623 378	960
Valledupar	Cesar	559 462	169
Villavicencio	Meta	558 299	467
Santa Marta	Magdalena	557 388	2
Ibagué	Tolima	545 210	1286
Monteria	Córdoba	516 217	17
Pereira	Risaralda	490 464	1415
Manizales	Caldas	458 442	2126
Pasto	Nariño	393 476	2559
Neiva	Huila	373 129	442
Popayán	Cauca	333 382	1738
Armenia	Quindío	316 926	1500
Tunja	Boyacá	182 828	2778

Fuente: elaboration propria. m = metros sobre el nivel del mar. † Data from projections of municipal population for the period 2023, based on the national census of population and housing for 2018.

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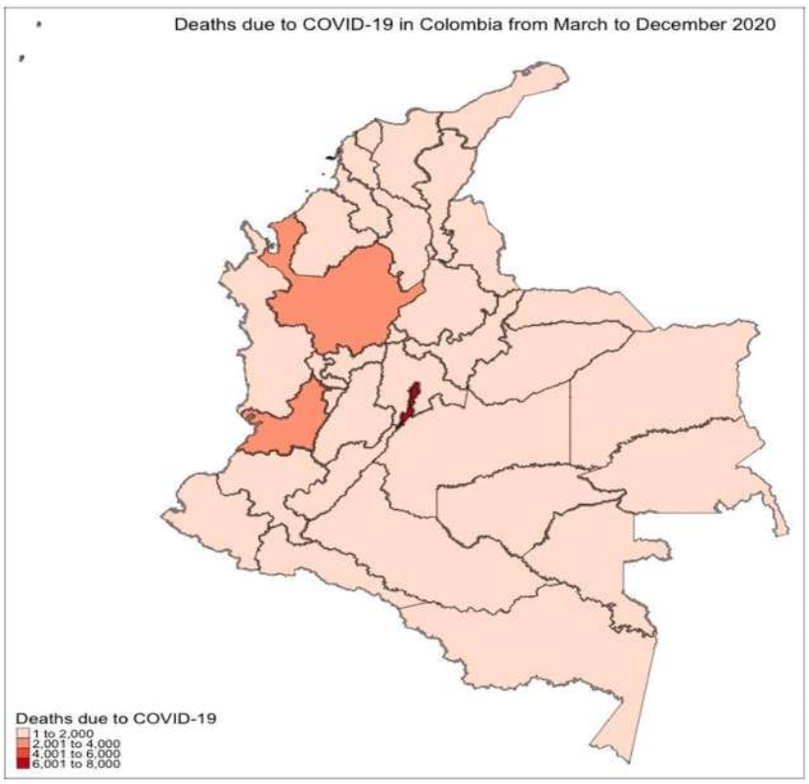

Figura 1. Deaths due to COVID-19 in Colombia by department, from March to December 2020

We also reported the CFR for each municipality during the period analyzed, divided according to their corresponding altitude category. For low altitude, the mean CFR was 0,042 (CI 95% 0,042 - 0,043); for middle altitude, the mean CFR was 0,027 (CI 95% 0,027 - 0,028); and for high altitude, the mean CFR was 0,026 (CI 95% 0,025 - 0.026) (see figure 2).

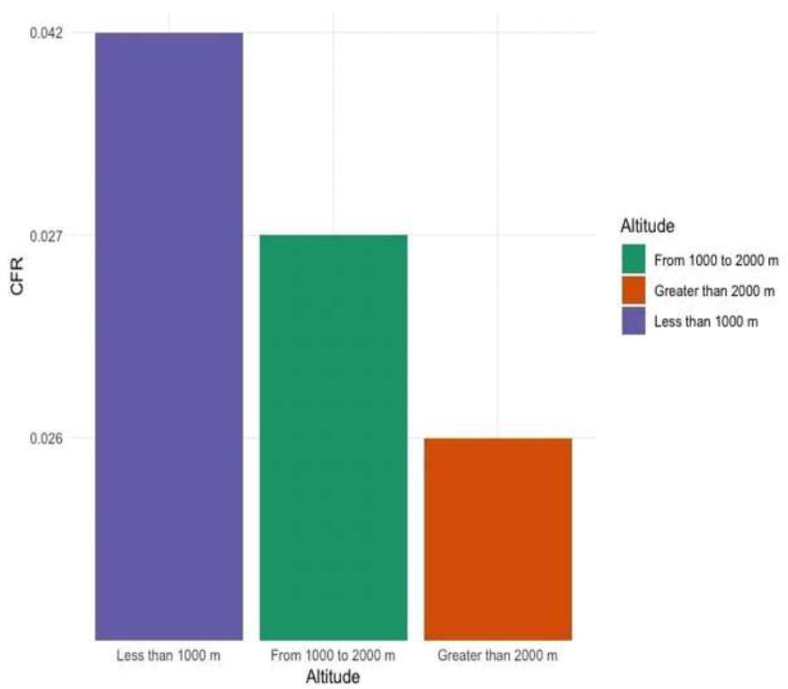

Figure 2: Case fatality rate (CFR) according to the altitude level (low, middle and high)

Regarding the results of the regression model applied, we were able to demonstrate that for every one kilometer increase in altitude, the probability of dying from COVID-19 in a person with confirmed infection decreases by 20%, controlling for sex, age and number of inhabitants of the local administrative entity, with statistically significant results (OR 0.8; 95% CI 0.785 - 0.815; p <0.001) (see Table 2). We also found that the male sex and older age were potential risk factors for COVID-19 mortality (OR 2.2; 95% CI 1.97 - 2.07; p <0.001) and (OR 1.1;

95% CI 1.10 - 1.10; p <0.001), respectively.

Table 2: Findings of the logistic regression model

Variables	Odds Ratio (OR)	95% CI	p value
Altitude (km)	0.8	0.78 - 0.81	<0.001
Sex (Male)	2.02	1.97 - 2.07	<0.001
Age (years)	1.1	1.10 - 1.10	<0.001
Number of inhabitants	1	1.0000 - 1.0000	<0.001

Fuente: elaboration propria.

Discussion

Our results demonstrate that altitude is a potential protective factor against COVID-19 mortality. We could evidence that the CFR was significantly lower in confirmed COVID-19 cases living in middle and high altitude compared to those living in low altitude levels. Likewise, for every one-kilometer increase in altitude, the probability of dying from COVID-19 in a person with confirmed infection decreases by 20%, controlling for sex, age and number of inhabitants of the local administrative entity.

Our data are in line with findings of other studies, reporting that environmental factors associated with higher altitude may reduce the risk of developing COVID-19. In Brazil, a direct association was reported between a lower relative incidence and a lower relative mortality rate with higher altitude in cities with a population greater than 200 thousand inhabitants 16. Other studies in the U.S, Peru and Ecuador have shown that mortality attributed to COVID-19 may decrease with increasing altitude[17,18,19,20]. However, not all evidence points to a possible protective effect of altitude on COVID-19 mortality. In Mexico, U.S, Peru and Colombia, some studies have reported that there could be an inverse association between altitude and death due to COVID-19 [4,21,22]. We believe the observed contradictory findings may be partially explained due to environmental and geographical factors that are independent of altitude and may vary across different world regions.

The impact of altitude on COVID-19 has been studied in patients with critical illness requiring intensive care unit (ICU) stay; a paper conducted in Ecuador on 670 ICU patients living in geographic locations with an altitude ≥ 1500 m, showed after adjusting for key confounders such as age, diabetes mellitus, arterial hypertension and severity of illness, that high altitude was significantly associated with higher odds of survival/ICU discharge (HR: 1.74 [95 % CI: 1.46-2.08]) and hospital survival/discharge (HR: 1.35 [95 % CI: 1.18-1.55]) compared with patients treated at sea level; the authors of this research propose that the reasons for these investigations may be related to genetic and physiological adaptations resulting from chronic exposure to hypoxia, with which we agree[23]. This association between higher altitude and increased survival in ICU patients with COVID-19 has been confirmed in other studies, with differences even in survival time of a median of 39 days in the higher altitude group vs. 21 days. at low altitude, with a greater effect in individuals who do not have comorbidities[24].

Some upper and lower respiratory tract infections are more frequent and severe at higher altitudes, as is the case of respiratory syncytial virus infection. In this scenario, it has been found an increase of 25% to 53% in the need for hospitalization in patients related to an increase in altitude of 1,000 m[25]. Apparently, this finding is due to the physiological changes that occur in the respiratory system depending on the altitude, such as the alteration of the nasal mucociliary transport, nasal congestion, and alteration of the epithelium, that favor colonization by microorganisms and the development of the disease[26]. The previous anatomical and physio pathological changes related to higher altitude could potentially lead to hypoxemia, associated with functional alteration of phagocytic cells, natural killer lymphocytes and T-lymphocytes and reduce production of IL-6, tumor necrosis factor α and IL-10[27].

In the case of COVID-19, several mechanisms have been proposed to explain the lower frequency and potentially better outcomes in patients at higher altitude locations, such as lower angiotensin-converting enzyme 2 activity, changes in normal vitamin D production, availability of thin air, temperature fluctuations during the day and night, and exposure to ultraviolet rays. Physiological acclimatization/adaptation that counteracts the hypoxic environment at higher altitude may protect the individual from the severe impact of infection, due to the decreased half-life of the virus(18, 28, 29).

Our study has some methodological limitations. First, we did not analyze separately the results according to the timeline of COVID-19 waves in the country, during which mortality rates may differ, related to the differences in access to healthcare. Second, we did not control for other potential confusion variables such as comorbidities, severity of COVID-19 and economic incomes of each municipality.

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In conclusion, our results demonstrate that altitude is a potential protective factor against COVID-19 mortality in adults in Colombia. The CFR rate was significantly lower in adults with this disease living at medium and high altitude compared to those living at low altitude levels.

Specification of the authors' contribution

1. Conceived the idea of the manuscript: Cándida Diaz-Brochero and Jorge Alberto Cortes
2. Methodology: Cándida Diaz-Brochero and Jorge Alberto Cortes
3. Data Collection: Cándida Diaz-Brochero, Laura C. Nocua-Báez, Carlos F. Montoya-Cárdenas, Jorge Alberto Cortes.
4. Conducted the analyses of the study: Candida Diaz-Brochero
5. Wrote the first draft of the article: Cándida Diaz-Brochero, Laura C. Nocua-Báez, Carlos F. Montoya-Cárdenas, Jorge Alberto Cortes.
6. Critical editing of the article: Cándida Diaz-Brochero, Laura C. Nocua-Báez, Carlos F. Montoya-Cárdenas, Jorge Alberto Cortes.
7. I accept the final content of the article: Cándida Diaz-Brochero, Laura C. Nocua-Báez, Carlos F. Montoya-Cárdenas, Jorge Alberto Cortes.
8. Approved for publication: Cándida Diaz-Brochero, Laura C. Nocua-Báez, Carlos F. Montoya-Cárdenas, Jorge Alberto Cortes.

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