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Altitude and COVID-19 in Colombia: An updated analysis accounting for potential confounders

Santiago A. Araque-Rodriguez [a], Iván Solarte [b,c], Néstor Rojas-Roa [d], Laura A. Rodriguez-Villamizar [e,*]

[a] Facultad de Ciencias de la Salud, Universidad Autónoma de Bucaramanga, Calle 157 14-55, 681001 Floridablanca, Colombia
[b] Facultad de Medicina, Pontificia Universidad Javeriana, Carrera 7 40-62, Bogotá, Colombia
[c] Unidad de Neumología, Hospital Universitario San Ignacio, Carrera 7 40-62, Bogotá, Colombia
[d] Facultad de Ingenierías, Universidad Nacional de Colombia, Edificio 401, Carrera 45 26-85, Bogotá, Colombia
[e] Departamento de Salud Pública, Escuela de Medicina, Universidad Industrial de Santander, Carrera 32 29-31 of 301, 68002, Bucaramanga, Colombia

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ABSTRACT

We assessed the relationship between the altitude of municipalities and the incidence, mortality, and fatality from COVID-19 and excess of mortality in Colombia between 2020 and 2022. We conducted an ecologic study including all 1122 municipalities in Colombia and used categories of altitude as main independent variable. We fit multivariable regression models for incidence, mortality, fatality rates, and excess of mortality controlling for several variables at municipality level. There was a higher incidence rate, similar mortality rate and lower case-fatality rate for COVID-19 during 2020–2022 in municipalities in the upper category of altitude (>=2500 masl) compared to the lower category (<1000 masl). The excess of mortality was lower but not statistically different in municipalities in the upper category of altitude, and significantly lower in the intermediate altitude category compared to the lowlands. Our findings provide evidence that municipalities with high altitude had similar mortality rate, and lower case-fatality rate and excess of mortality for COVID-19 compared to lowlands in Colombia.

1. Introduction

SARS-CoV-2 has progressively spread throughout the entire world since it first appeared in December 2019, prompting communities to use resources to lessen its effects (Waitzberg et al., 2022). It has since evolved into one of the greatest worldwide health issues of our time. In Colombia, the first confirmed case occurred in March 2020, and since then, the country experienced numerous challenges in limiting the spread of the virus (Prada et al., 2022). Put into context, social unrest, economic recessions, and health disparities are issues that Latin American nations encounter on a consistent basis (Lopez-Feldman et al., 2020). Most countries have > 10,000 COVID-19 infections per 100,000 people, which suggests the pandemic has had a significant impact in this region. Similar numbers of incidents have occurred in developed countries; the primary variation is the availability of resources for an effective crisis management strategy (Litewka and Heitman, 2020). The World Health Organization reported 6,364,636 cases and 142,713 fatalities attributed to COVID-19 in Colombia by the end of May 2023 ($author1$ et al., 2023). As more time has passed, research has improved our understanding of the pandemic and its care, beginning with our ability to spot comorbid people who were more vulnerable (Ahmad Malik et al., 2022). There is still a lot to be unraveled, but some elements have gained attention. One important environmental component is the connection between altitude and the COVD-19 disease's consequences.

Municipalities altitude has been proposed as a potential predictor of COVID-19 transmission and mortality because of its impact on physiological changes seeking to adapt to high altitudes (Moore, 2017). The pulmonary epithelium expresses a significant number of the angiotensin-converting enzyme 2 (ACE2) receptors, which are ubiquitous and used by the SARS-CoV-2 virus to infect its host and cause COVID-19 (Lu et al., 2020). Under normal oxygen conditions, there is an equilibrium between the expression of ACE2 receptors and ACE1 receptors. Chronic hypoxia, on the other hand, alters these enzymes' expression, with ACE2 being downregulated and ACE1 being upregulated (Zhang et al., 2009). People who live in places > 2500 m are

* Correspondence to: Carrera 32 29-31 of 301, 68002, Bucaramanga, Colombia.
E-mail address: laurovi@uis.edu.co (L.A. Rodriguez-Villamizar).

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constantly exposed to hypobaric hypoxia, which leads to physiological changes over time (Beall, 2013). However, there is conflicting evidence regarding the association between altitude and COVID-19 disease outcomes. Altitude is linked to a greater cumulative case count and a higher mortality rate in men under the age of 65 in the USA and Mexico, according to those who claim there is no substantial relationship or that it has negative consequences (Woolcott and Bergman, 2020). In Mexico, the risk of death increased by 8.9% for men and by 23.8% for women living at altitudes above 2000 masl compared to those living below 500 masl (Martínez-Briseño et al., 2022). Contrarily, in Ecuadorian cohorts of ICU patients, the high-altitude groups showed a better survival rate compared to the sea-level groups (Jibaja et al., 2022; Simbaña-Rivera et al., 2022). Additionally, in a broader perspective, the American continent showed lower transmission rates and a lower death-to-case ratio when comparing the highlands (>1000 masl) to the lowlands (Arias-Reyes et al., 2021).

The evidence from Colombia is likewise contradictory; the first preliminary analysis, which was based on data from 70 municipalities throughout the country, found an inverse relationship between altitude and the case fatality rate (CFR) (Cano-Pérez et al., 2020). A different study, however, concluded that there is no protective link between altitude and COVID-19 (Valverde-Bruffau et al., 2021) when all 1122 municipalities were included, and the prior relationship was not demonstrated. The factors intended to be examined in this study that could account for previously unaccounted-for confounders have not yet been used in any other Colombian investigation.

The purpose of this study is to examine the association between municipal altitude and the incidence, mortality, and fatality of COVID-19 in Colombia between 2020 and 2022. Along with correcting for potential confounders of the connection between altitude and COVID-19 outcomes, excess mortality analysis is included as an additional indicator to assess the pandemic's scope. This study can aid in a better understanding of the variables affecting the spread and mortality of COVID-19 in Colombia, which can aid in directing decision-making for both the present and upcoming epidemic management in the nation. The outcomes may also be helpful for other nations going through comparable circumstances, particularly for those having Colombia-like geographic and demographic characteristics.

2. Materials and methods

2.1. Study Population

The population of Colombia in 2020 was estimated to be 50,372,424 inhabitants distributed in 32 departments and 1122 municipalities (DANE, 2020). Estimations based on the national census 2018 shows that 77.1% of people live in urban areas and 9.1% of the total population is 65 years or older. This is an ecologic study including all municipalities of Colombia as units of observation and analysis.

2.2. Data sources

2.2.1. Altitude and sociodemographic data

Altitude measured in meters above sea level (masl) was retrieved from the Ministry of Housing (Republica de Colombia Ministerio de Vivienda, 2020). The 1122 municipalities are located in an altitude range between 1 and 3300 masl. For the purpose of this study, we grouped the municipalities into three altitude categories: the lower category, which ranges from sea level to 999 masl (529 municipalities, 47.15%); the intermediate category, which covers the range from 1000 to 2499 masl (465 municipalities, 41.44%); and the upper category, which includes minicipalities at 2500 masl or higher (128 municipalities, 11.41%).

The estimation of population 2020 based on the Colombian national census of 2018 (DANE, 2020) was used to obtain data at the municipality level on the total population, population by age groups, area of residence (urban/rural), and population density. As a measure of socioeconomic conditions, we used the Colombian Multidimensional Poverty Index (MPI) at the local level. The MPI is a composite index with values ranging from 0 to 100, with higher values indicating higher multidimensional poverty (DANE, 2022a). It is calculated based on five dimensions: education level, conditions for children and youth, employment, health coverage and access, public utilities access, and housing conditions.

2.2.2. Health data

The Instituto Nacional de Salud (INS) website was used to acquire the total number of confirmed cases and fatalities for COVID-19 (Instituto Nacional de Salud, 2023). Anonymized personal data about each person, including their age, sex, date of diagnosis, final condition (death), date of death, and municipality of residence, is kept in the national database. The Cuenta de Alto Costo (CAC)-Fondo Colombiano de Enfermedades de Alto Costo (Fondo Colombiano de Enfermedades de Alto Costo, 2021) provided the raw prevalence of arterial hypertension and diabetes for the time period from June 1st, 2018, to June 20th, 2019, for all municipalities. The national registration of healthcare providers (https://prestadores.minsalud.gov.co/habilitacion/) was used to obtain data on hospital bed capacity prior to the pandemic as a metric of the number of intermediate and critical care beds per 100,000 people. The Ministry of Health and Social Protection's SegCOVID information system was used to get the excess mortality for 2020 and 2021, which was estimated based on annual deaths in comparison to the mean annual deaths from the previous five years (República de Colombia M de S y PS, 2022).

2.3. Statistical analysis

The rates per 100,000 inhabitants were used to compute the cumulative incidence and mortality rates for COVID-19 by municipality for the 2020–2022 period. The fatality rate was estimated using the denominator of confirmed cases and the numerator of confirmed fatalities. As an average measurement of the excess of mortality recorded for each year, the percentage of excess of mortality for the years 2020–2021 was determined. For summarizing the distribution of variables among the various altitude groups, we utilized the median and the percentiles 25 and 75 (p25, p75).

For the purpose of determining how different altitude categories affect incidence and mortality rates, we fitted a multivariable Poisson regression model. In order to determine incidence rate ratios (IRR) of incidence or mortality, we model the number of cases or deaths as the dependent variable and incorporate the entire population as the exposure term. We utilized the reported cases as the exposure term to calculate the fatality rate. We fitted a linear regression model for the excess mortality and derived coefficients of change with 95% confidence intervals (CI). To take into consideration any potential association in municipalities within the same department, we ran all models clustered by department. We used the categorical variable of altitude as the primary explanatory variable across all models, controlling for the impact of other relevant confounders. Age (>10% 65 years or older), the prevalence of hypertension and diabetes (>10% and 4%, respectively), population density (>=100 hab/Km2), and the number of hospital beds per population prior to the pandemic (>50 beds per 100,000 hab) were included as categorical variables with specific cut-off values oriented by their graphical inspection against outcome variables. The MPI and the proportion of the population living in cities were introduced as quintiles in the models. Stata® version 13 was used for all analyses.

3. Results

In Colombia, a total of 6,352,032 cases and 142,453 deaths from COVID-19 were reported to the national surveillance system during 2020–2022. There were 2,433,237 confirmed cases and 65,499 confirmed deaths for COVID-19 in the lower altitude category (<1000 masl), 1,619,609 cases and 37,601 confirmed deaths in the medium altitude category (1000–2499 masl), and 2,299,186 cases and 39,359 confirmed deaths f in the upper altitude category (>=2500 masl). In terms of demographic characteristics, certain differences were found among the groups of municipalities based on altitude categories., The median percentage of multidimensional poverty index was 46.1 (p25-p75: 34.3–60.3), 37.7 (p25-p75: 29.4–47.4), and 29.95 (p25-p75: 17.5–41.85) for the lower, intermediate, and upper altitude categories respectively, indicating higher levels of poverty in the lowest altitude category. In contrast, the population density was 33.09 habitants/Km2 (p25-p75: 14.33–79.21), 50.28 hab/Km2 (p25-p75: 26.34–96.97), and 67.56 hab/Km2 (p25-p75: 34.35–144.14) for the lower, intermediate and upper altitude categories, respectively, indicating higher density levels in the upper altitude category. Other sociodemographic characteristics of the municipalities by categories of altitude are shown in Table 1.

Table 2 shows the measures of incidence, mortality, fatality, and excess of mortality by altitude categories. We found an increase in the median cumulative incidence rates as the altitude categories increased being 3569.58 per 100,000 habitants (percentile p252151.18-p755960.88) for the lower category (under 1000 asl) and 4767.68 per 100,000 habitants (p25-p75: 2770.87–7966.83) for the upper category (2500 masl or above). We found a similar pattern for the cumulative mortality rate with a median rate of 131.63 per 100,000 hab. in the lower altitude category (p25-p75: 72.41–202.55) and a median rate of 148.60 per 100,000 hab. (p25-p75: 104.44–205.88) in municipalities within the upper altitude category. In contrast, the fatality rate showed the opposite direction within the lowest altitude category having the highest median cumulative rate of 3448.28 deaths per 100,000 cases p25-p75: 2446.48–4724.41). Similarly, we found that the mean excess of mortality for 2020–2021 was higher in the lowest altitude category compared to the other categories (median of excess of mortality of 44% (p25-p75: 28.35–59.5)). For all altitude categories the excess of mortality in 2021 was higher compared to 2020 (see Table 2).

The results of the multivariable analysis adjusting for potential confounders at municipality level are presented in Table 3. The incidence rate risk for COVID-19 was 62% higher in the municipalities in the upper altitude category (>= 2500 masl) compared to municipalities in the altitude category lower than 1000 masl (IRR: 1.62; 95% CI 1.29–2.04) after controlling for the effect of the percentage of population older than 65 years, population density, urbanicity, multidimensional poverty index, prevalence of hypertension and diabetes and the hospital beds capacity before pandemic.

Controlling for the same covariables, the mortality risk difference between the upper and lower altitude categories was not statistically significant (IRR= 1.01; 95%CI 0.85–1.21) but the mortality rate in the intermediate altitude category was lower compared to the lower category (IRR 0.89; 95%CI 0.79–1.00). The mortality rate for COVID-19 was higher in municipalities with population density above 100 inhabitants per Km2, higher level of urban population, prevalence of diabetes above 4%, respectively, and those with more than 50 per 100,000 hospital beds before pandemic began. The case fatality rate risk in the upper altitude category was on average 38% lower compared to the lower altitude category (IRR 0.62; 95% CI 0.52–0.74) (Table 3).

The average excess of mortality during 2020–2021 was lower in the municipalities located above 2500 masl but not statistically different compared to the those located at < 1000 masl (coefficient −5.04; 95% CI −12.27 to 2.18) after controlling for sociodemographic and other health covariables at municipality level (Table 3). The average excess of mortality during 2020–2021 was higher for municipalities with higher population density and urban population. The municipalities in the most deprived quintile of poverty (MPI) showed higher excess of mortality compared to the least deprived quintile but this difference was not statistically significant. Conversely, the excess of mortality on average was lower in municipalities with 10% or more population older than 65 years. The sensitivity analysis eliminating Bogotá from the upper altitude category did not change the results (coefficient −5.05; 95% CI −12.36 to 2.26).

Table 1
Characteristics of municipalities across altitude categories, Colombia 2020–2022.

Variables	Altitud categories		
	Lower altitude < 1000 masl Median (P25-P75)	Intermediate altitude 1,000-2499 masl Median (P25-P75)	Upper altitude > =2500 masl Median (P25-P75)
Total population	18617 (9992–34403)	9634 (5303–19967)	8413 (5222–19357)
No. municipalities	529	465	128
Multidimensional Poverty Index	46.1 (34.3–60.3)	37.7 (29.4–47.4)	29.95 (17.5–41.9)
Population density (hab/Km2)	33.1 (14.3–79.2)	50.28 (26.3–96.9)	67.56 (34.4–144.1)
Percentage of population living in urban areas	49 (33–69)	34 (23–51)	34 (19–53.5)
Percentage of population over 65 years of age	8.1 (6.2–10.1)	12.25 (10.1–15.1)	11.02 (8.2–12.8)
Hospital beds per 100,000 inhabitants before pandemic	59.5 (31.4–101.5)	45.7 (0–89.9)	0 (0–57.5)
Diabetes prevalence (%)	1.2 (0.6–1.9)	1.3 (0.6–1.9)	1.08 (0.6–1.6)
Hypertension prevalence (%)	4.5 (2.6–7.0)	6.2 (3.8–8.7)	5.7 (3.9–7.8)
COVID-19 reported cases	560 (229–1658)	318 (162–778)	344.5 (162–1436)
COVID-19 reported deaths	22 (9–57)	12 (5–30)	13 (7–33)

Table 2
Incidence and mortality indicators for COVID-19 according to altitude categories, Colombia 2020–2022.

Indicators	Altitud categories		
	Lower altitude < 1000 masl Median (P25-P75)	Intermediate altitude 1,000-2499 masl Median (P25-P75)	Upper altitude > =2500 masl Median (P25-P75)
Cumulative incidence rate x 100.000	3569.6 (2151.2–5960.9)	3650.1 (2357.0–5442.7)	4767.7 (2770.9–7966.8)
Cumulative mortality rate x100.000	131.6 (72.4–202.6)	134.9 (80.4–195.3)	148.6 (104.4–205.9)
Cumulative case fatality rate x 100.000	3448.3 (2446.5–4724.4)	3408.3 (2447.8–4651.2)	2920.9 (1911.8–4067.4)
Excess of mortality 2020 (%)	31.8 (14.8–52.1)	16.7 (2.6–30.3)	19.9 (2.4–38)
Excess of mortality 2021 (%)	54.0 (35.2–72.3)	39.6 (23.2–58.0)	47.9 (15.9–72.4)
Excess of mortality average 2020–2021 (%)	44.0 (28.4–59.5)	28.5 (17.6–40.6)	34.4 (17.8–49.6)

4. Discussion

Our findings provide evidence that people in Colombia residing in municipalities with high altitude (>=2500 masl) had a similar mortality rate for COVID-19 and lower CFR and excess of mortality when

Table 3
Multivariable models for the association between altitude categories and incidence and mortality indicators for COVID-19 in municipalities in Colombia, 2020–2022.

Variable	Incidence rate IRR* (95% CI)	Mortality rate IRR* (95% CI)	Case fatality rate IRR* (95% CI)	% Excess mortality (mean 2020–2021) Coefficient (95% CI)
Altitude category Lower (<1000 masl)	1	1	1	1
Intermediate (1000–2499 masl)	1.05 (0.91–1.22)	0.89 (0.79–1.00)	0.86 (0.72–1.02)	-5.87 (−10.59;−1.14)
Upper (>=2500 masl)	1.62 (1.29–2.04)	1.01 (0.85–1.21)	0.62 (0.52–0.74)	-5.04 (−12.27;2.18)
Age < 10% population over 65 years old	1	1	1	1
10% or more population over 65 years old	0.94 (0.82–1.07)	1.09 (0.93–1.29)	1.16 (1.01–1.34)	-14.34 (−19.41;−9.28)
Population density < 100 hab /Km2	1	1	1	1
> = 100 hab/ Km2	1.33 (1.16–1.51)	1.13 (1.03–1.23)	0.87 (0.74–1.01)	6.19 (1.91;10.48)
Diabetes prevalence < 4%	1	1	1	1
> = 4%	1.29 (1.04–1.59)	1.21 (1.05–1.38)	0.95 (0.76–1.18)	0.28 (−7.70; 8.27)
Hypertension prevalence < 10%	1	1	1	1
> =10%	1.11 (0.94–1.30)	0.90 (0.80–1.02)	0.80 (0.66-0.97)	-2.85 (−6.47; 0.77)
Hospital beds before pandemic < 5 beds per 1000 hab	1	1	1	1
> =50 beds per 100,000 hab	1.43 (1.31–1.56)	1.31 (1.21–1.42)	0.97 (0.90–1.04)	-1.78 (−5.04; 1.47)
Multidimensional poverty index -MPI quintiles Q1 (least deprived)	1	1	1	1
Q2	0.81 (0.70–0.93)	0.87 (0.78–0.98)	1.09 (0.89–1.33)	-2.86 (−7.54; 1.81)
Q3	0.67 (0.57–0.78)	0.73 (0.65–0.82)	1.09 (0.92–1.31)	-0.49 (−6.04; 5.07)
Q4	0.65 (0.50–0.84)	0.60 (0.50–0.72)	0.92 (0.76–1.11)	-0.90 (−7.13; 5.32)
Q5 (most deprived)	0.48 (0.41–0.57)	0.49 (0.39–0.62)	1.04 (0.88–1.25)	4.24 (−1.48; 9.95)
% Urban population quintiles Q1	1	1	1	1
Q2	1.26 (0.96–1.67)	1.17 (0.99–1.38)	0.92 (0.80–1.06)	0.84 (−3.38; 5.05)
Q3	1.39 (1.13–1.70)	1.31 (1.10–1.56)	0.93 (0.83–1.05)	2.40 (−1.01; 5.81)
Q4	1.80 (1.38–2.34)	1.52 (1.28–1.81)	0.86 (0.73–1.00)	4.79 (−1.17; 10.75
Q5	2.35 (1.78–3.10)	1.83 (1.51–2.23)	0.78 (0.64–0.94)	8.89 (2.86; 14.92)

*IRR: Incidence Rate Ratio.

compared to residents in municipalities below 1000 masl. This is the most updated and comprehensive analysis of the effect of altitude on COVID-19 indicators in the country controlling for the ecological effect of other potential confounders. Furthermore, this is to our knowledge the first study to assess the effect of altitude on the excess of mortality during the COVID-19 pandemic accounting for potential confounders.

We found a highest COVID-19 incidence rate in the altitude category > 2.500 masl compared to the lower altitude category. This finding might be explained to some extent to the fact that incidence is calculated based on reported cases to the national surveillance system and municipalities within the highest altitude category might have a highest diagnostic capacity and lower underreporting as they have on average higher population counts and density. In a similar way, the differential diagnostic capacity and underreporting level might be explaining the higher CFR within the lowest altitude group. In this case, the possible underreporting might be affecting more the counts of confirmed cases in the denominator making the CFR artificially higher. Despite the great effort of the national surveillance system in Colombia to capture as most cases as possible, it was estimated that underreporting of cases was on average 83% with wide differences (89–96%) depending on the municipalities' capacities (Arias-Reyes et al., 2021; De la Hoz-Restrepo et al., 2020). In general, it is well known that challenges in diagnosis and reporting of COVID-19 confirmed cases might be more prone to underreporting compared to deaths, and that these diagnostic challenges lead to under ascertainment of incidence and mortality worldwide (Villeneuve and Goldberg, 2020; Arons et al., 2020; Li et al., 2020).

Divergent results have been found in earlier ecological research that examined the association between altitude and COVID-19 in Colombia. Up until August 1st 2020, (Cano-Pérez et al., 2020). carried out a preliminary analysis that covered 70 municipalities. While accounting for population density, they discovered that the CFR was inversely connected with altitude and that the counts of cases and deaths appeared to be positively correlated. They got to the conclusion that living at a high altitude can lessen the detrimental effects of COVID-19 after combining their findings. Later, Valverde-Bruffau et al. (2021). presented the findings of the analysis encompassing all 1122 municipalities of Colombia in a letter to the editor of the aforementioned paper and found no statistically significant correlations between altitude and CFR nor with counts of cases and deaths. Despite the fact that Valverde-Bruffau's analysis produced results that were not influenced by selection bias, the analyses were limited to CFR and counts of confirmed cases and deaths (up to November 2020), without any consideration of the incidence or mortality rates themselves or of other ecological sociodemographic variables that might confound the results. Our findings offer an updated analysis of the COVID-19 indicator in the post-pandemic period that takes into account all confirmed cases and fatalities between 2020 and 2022, analyzes incidence and mortality rates as well as CFR, and controls for a number of variables at the municipality level to lessen confounding. Additionally, three groups were the highest in our analysis's classification of altitude, which is deemed high-altitude from a physiological and clinical standpoint when above 2500 masl.

During the first year of the pandemic, numerous studies in Latin American nations with significant altitude variation sought to evaluate the association between altitude and COVID-19. Some of these investigations, like the ones for Colombia above, were carried out in Peru, a nation with a broad range of altitudes, and they too produced inconsistent results (Segovia-Juarez et al., 2020; Castagnetto et al., 2020; Nicolaou et al., 2022). Our results are consistent with those of Nicolaou et al. (2022), who found no evidence of a lower risk of COVID-19 death for those who live in higher altitudes after adjusting for a number of sociodemographic characteristics in municipalities from Peru. Similar to this, Martínez-Briseño et al. (2022). found that, after controlling for a number of sociodemographic health-related variables at the municipality level, men living above 2000 masl and women living above 2500 masl have higher mortality risks in Mexico than inhabitants living below 500 masl. In contrast, a comparative study using data from Tibet, Bolivia, and Ecuador found that people who live at higher altitudes there are less likely than people who live in low-lying areas to experience significant unfavorable effects from acute SARS-CoV-2 infection Arias-Reyes et al., 2020. In addition, until May 2020, Arias-Reyes et al. (2021). examined the COVID-19 data for cases and fatalities from 23 nations on the American continent. They discovered that the COVID-19 transmission rate and CFR were lower in the highlands (defined as >1000 masl) using Pearson correlation analysis, ANOVA, and population density control. These results are likely impacted by confounding and the impact of underreporting, which was estimated but not taken into account in the analyses, while giving an interesting, pooled study for various American countries.

In this study, we incorporated excess mortality as a key indicator of the impact of the COVID-19 pandemic. Excess mortality is defined as the difference between the number of deaths from a particular cause during an emergency and the expected deaths under "normal conditions," with the difference representing excess mortality. This difference is viewed as a measurement of the direct or indirect impact of the emergency on mortality attributable to the emergency (DANE, 2022b). The World Health Organization (WHO) developed strategies for rapid mortality surveillance, particularly estimating the true magnitude of the burden and impact of the pandemic based on excess mortality estimation (WHO, 2020), in response to the difficulties surveillance systems and vital statistics faced during the pandemic. The average excess mortality rate between 2020 and 2021 as stated by the Ministry of Health was considered in our research. According to DANE's examination of Colombia's excess mortality trends through April 2022, particular mortality rates rose among the population over 80 years old, mainly in men starting at the age of 40 and women starting at the age of 50. In June 2021, the population aged 40–49 years experienced the highest excess mortality rate (293%), followed by the population aged 50–59 years (247%). Contrary to the number of deaths and specific mortality rates, which have shown that those over 60 are most affected, this report shows that the mortality impact of COVID-19 in Colombia was greater in the population aged 30–69 years, particularly in men aged 40–49 years. This condition is reflected in our findings from the multivariable analysis of excess mortality, as shown by the ecological analysis, which found that municipalities with an older adult population that made up more than 10% of the total population had an excess mortality that was on average lower in the years 2020–2021. Furthermore, when compared to the intermediate altitude group, our data point to higher excess mortality in the lower lands (1000 masl), although this difference is not statistically significant when compared to the highlands (>2500 masl). Our results are in line with two earlier descriptive reports from Peru and Ecuador that discovered a link between excess pandemic mortality and altitude but did not control for relevant confounders (Quevedo-Ramirez et al., 2020; Ortiz-Prado et al., 2021).

Our findings about the moderate category of altitude's larger protective effect on the excess of death are noteworthy. The inhabitants of municipalities in the intermediate group have better oxygen availability than people living in highlands, but they also have better adaptability to hypoxic settings than those living in lowlands, which is a possible physiological reason for this observation. For this reason, it's likely that a combination of both conditions could lead to a better adaptability and less negative consequences in cases of acute respiratory distress brought on by infections. Living at moderate altitudes has been also associated with protection from ischemic heart diseases, probably related to a combination of factors, including increased solar radiation, milder temperatures, physiological adaptation to low environmental oxygen, and lifestyles of residents at such altitudes (Burtscher et al., 2021). Alternative reasons for our findings could be connected to unmeasured confounding factors like vaccination coverage and usage of medical services during the acute pandemic phase.

Our study has a number of significant advantages that merit attention. First, we used extensive national data from reliable national sources, which included excess mortality as one of the effect indicators for COVID-19. This large dataset made it possible to analyze the topic in detail. The impact of numerous socioeconomic, demographic, and health-related variables that have a big impact on COVID-19 mortality and incidence was also carefully taken into account. We attempted to improve the accuracy and dependability of our findings by accounting for these factors. Last but not least, our study used altitude categories that were developed based on prior research, concentrating on the point at which physiological changes in the human body start to show themselves (over 2500 m above sea level). This strategy made sure that altitudes were classified in a methodical and knowledgeable manner, strengthening the validity of our analysis.

We were unable to account for the lack of publicly available and trustworthy information about COVID-19 vaccination coverage and access to healthcare services during the pandemic, which was a significant limitation of our study. Similarly, underreporting, a factor that was not taken into consideration, may have affected our findings regarding incidence, mortality, and CFR. As a result, we highlighted the significance of our findings regarding excess mortality because this indicator is unaffected by underreporting and offers a more precise assessment of COVID-19's effects. It is also important to keep in mind that the results of our study are particular to the 2020–2022 period, when SARS-CoV-2 with strong respiratory affinity predominated in circulation. It is important to note that more recent virus strains could differ in their severity or influence various systems, which should be taken into account in future study.

As an ecological variable that may be quantified at the municipality level, altitude was used in our investigation using an ecological study design. Studies on disease mapping and associations can benefit from this approach (Wakefield, 2008). It is important to remember that this study is still ecological, and that summarizing COVID-19 impact indicators at the municipal level may introduce ecological bias, which could result in imprecise conclusions about the studied effect when extrapolated to individuals, even when considering how environmental factors affect COVID-19 (Villeneuve and Goldberg, 2020). As a result, we underline that our findings should only be used at the municipal level and do not suggest extrapolating these results to the level of the individual.

5. Conclusion

This study extends earlier studies by performing a thorough investigation of the relationship between altitude and COVID-19 variables in Colombian municipalities. Our study adds to the body of research on the association between altitude and COVID-19, finding little indication of meaningful protection in terms of mortality rates but pointing to protection in terms of excess mortality in Colombian municipalities during the pandemic. Despite our efforts to minimize selection bias and confounding, given the ecological design of the study and the lack of an evaluation of the potential impact of vaccination coverage on this association, it is crucial to interpret these results with caution. Our findings may contribute to a better understanding of the possible effects of altitude on COVID-19 or other epidemics that attack the respiratory system, as well as the necessity of health care planning for the prevention and early identification of potentially serious consequences, especially in lowlands.

Ethical approval

No ethical approval was needed for this study as no individual data were identifiable and only aggregated data were retrieved, analyzed and presented.

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CRediT authorship contribution statement

SAAR: Data curation, Formal analysis, Investigation, Writing – original draft. **IS**: Conceptualization, Investigation, Writing – review & editing. **NRR**: Investigation, Writing – review & editing. **LARV**: Conceptualization, Methodology, Formal analysis, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors do not have any declaration of interest to declare.

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