



Effect of altitude on COVID-19 mortality rate and case incidence in Peru, the country with the highest cumulative mortality rate worldwide

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Abstract

Background Peru had the highest COVID-19 cumulative mortality rate worldwide. A greater disadvantage in the population infected with COVID-19 living under chronic hypoxia would be expected. However, previous studies reported a lower mortality at higher altitudes.

Aim The study assessed the relationship between altitude and COVID-19 mortality rate and case incidence in Peru at a district level from March 6, 2020, to February 28, 2022, and in its three waves.

Subject and methods This was an ecological, analytical study examining open data for 1874 Peruvian districts, ranging from 3 to 4675 m, with 3,372,962 COVID-19 cases and 212,017 deaths. Correlation statistics and a multivariate linear regression model were used to assess this relationship in this period and in three arbitrarily defined waves.

Results A negative coefficient of -0.00012 (95% CI -0.00015 to -0.00008) between altitude and mortality rate during the pandemic was obtained, corresponding to a 5.82% decrease in mortality for every 500 m. Similar findings for the three waves were observed, the first one with -0.000142 (95% CI -0.000178 to -0.000106); the second one, -0.000071 (95% CI -0.000101 to -0.000041); and the third one, -0.000017 (95% CI -0.000027 to -0.000006), equivalent to a decrease in mortality of 6.85%, 3.5%, and 0.85% for every 500 m. A coefficient of -0.0000905 (95% CI -0.000134 to -0.000047) between altitude and case incidence was observed, meaning a 4.42% decrease for every 500 m. In the first and third waves, a 5.06% and 3.92% decrease in incidence was found for every 500 m.

Conclusion Altitude had a protective effect against COVID-19 mortality and case incidence in Peru.

Keywords COVID-19 · Altitude · Hypoxia · SARS-CoV-2

Introduction

As of February 28, 2022, 3,548,559 confirmed cases and 212,299 deaths from COVID-19 had been reported in Peru, making it the country with the highest mortality rate

worldwide, with 646 deaths per 100,000 population (Our World in Data 2022). Lima, Peru's capital, was the city with the highest number of cases and deaths from COVID-19 (MINSA 2022a, b). At that time, the country had faced three waves: the first one from April 21, 2020, until November 20,

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2020; the second one from January 11, 2021, until August 31, 2021; and the third one from December 21, 2021, until February 28, 2022 (World Health Organization 2022). The distribution data for both the confirmed cases and deaths from COVID-19 are shown in Fig. 1.

It is well known that acute respiratory distress syndrome (ARDS) is a life-threatening condition and an important factor involved in mortality from COVID-19 (Boban 2021). People living at high altitudes are exposed to chronic hypobaric hypoxic conditions, leading to very low resting partial

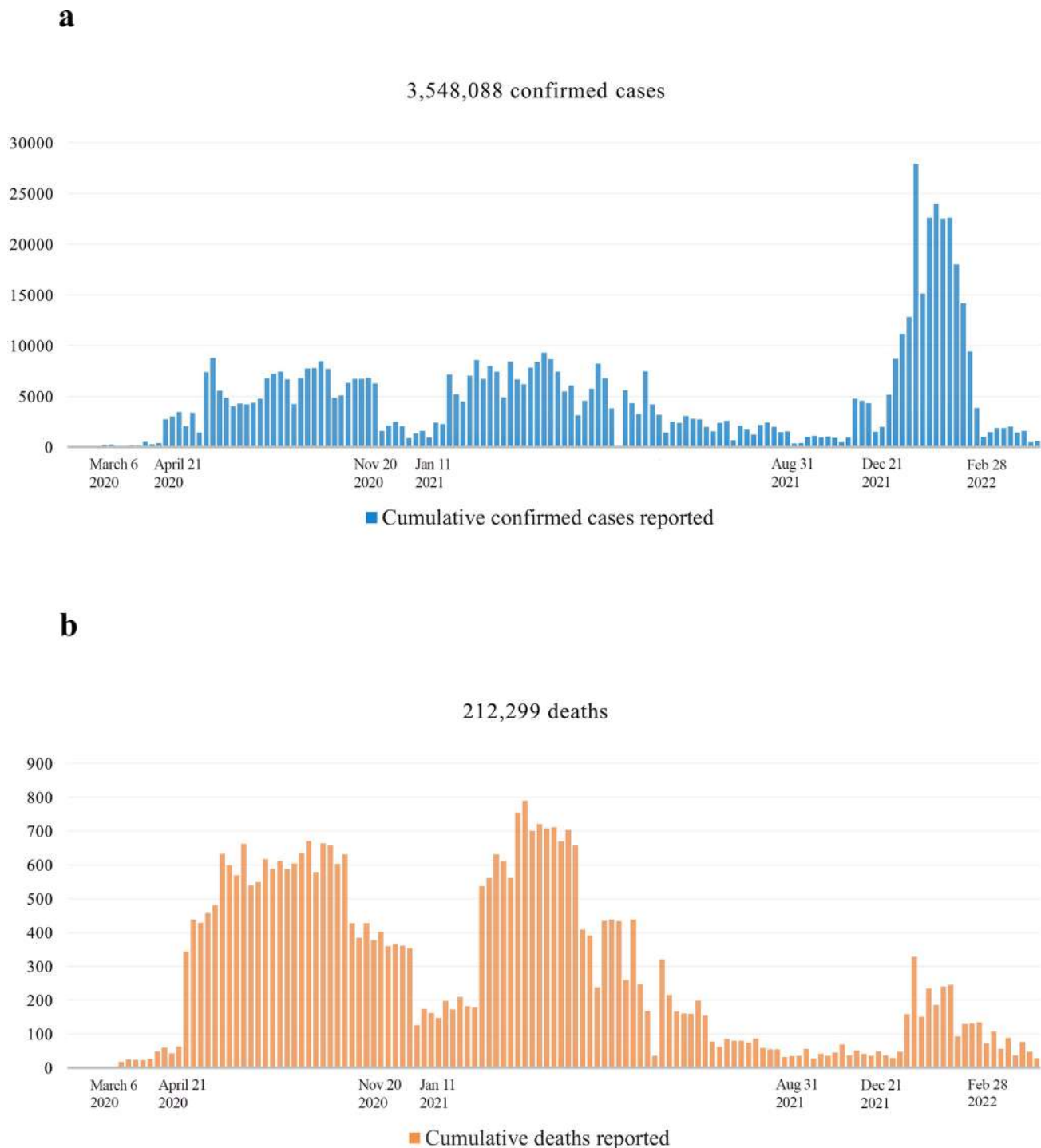


Fig. 1 (a) Distribution of COVID-19 confirmed cases throughout the pandemic (b) Distribution of COVID-19 deaths throughout the pandemic. Graphic was made with information available in WHO Corona virus Disease

pressure of oxygen (P_{aO_2}). The average P_{aO_2} in individuals living in Bogota, Colombia (2640 m), was reported as 68.6 mmHg (Miranda-De la Torre and Ramírez-Ramírez 2011); in Huancayo, Peru (3249 m), as 66.22 mmHg (Yumpo 2002); in Cusco, Peru (3350 m), 61.08 mmHg (Pereira-Victorio et al. 2014); in La Paz, Bolivia (3600 m), 55.9 mmHg (Vera 1991); and in Cerro de Pasco, Peru (4380 m), 54.18 mmHg (Tinoco Solórzano et al. 2017). Similar values were observed in different places around the world located above 2500 m (Rojas-Camayo et al. 2017; Peacock 1998). A P_{aO_2} value lower than 60 mmHg in individuals living at sea level is considered type 1 respiratory failure, indicating the need for supplementary oxygen (Mirabile et al. 2023). Therefore, people residing at high altitudes would be expected to have a greater disadvantage when infected with SARS-CoV-2, leading to higher mortality. However, at the beginning of the pandemic, a lower case fatality rate was observed at high altitudes, suggesting high altitude as a protective factor against COVID-19 disease. Arias-Reyes et al. were the first to describe this possible protective effect against SARS-CoV-2 infection. A low prevalence and less severe forms of COVID-19 were observed in high-altitude regions such as Tibet, Bolivia, and Ecuador (Arias-Reyes et al. 2020).

Fewer cases, a lower mortality rate, and lower severity of COVID-19 have also been reported within countries with high infection rates in cities located above 2500 m (Arias-Reyes et al. 2020). Aside from its cultural and ecological diversity, Peru encompasses natural regions divided into altitudinal floors, with the average altitude of its districts ranging from 3 to 4675 m. Even so, there are population centers within these districts that are located even higher, such as La Rinconada in the district of Ananea, Puno, located above 5000 m, with a population of 16,907 (Goyzueta and Trigos 2009).

High-altitude cities in Bolivia such as La Paz (2400 m), Oruro (3735 m), Potosí (4090 m), and Sucre (2810 m) were found to have a low infection rate and without the expected exponential growth described by the World Health Organization (WHO) (Arias-Reyes et al. 2020). Similar findings were observed in Ecuador, where the altitude seemed to be a protective factor against COVID-19 mortality, with a correlation factor of -0.45 ($p=0.03$) (Campos et al. 2021). Similarly, cities located below 200 m in Colombia had a fatality rate six times greater when compared with cities above 2000 m (Cano-Pérez et al. 2020). In Peru, the region of Pasco (4338 m) had a COVID-19 infection rate of 174 cases per 100,000 population, whereas in the region of Callao (7 m), the infection rate was 6.4 times higher (Accinelli and Leon-Abarca 2020).

As shown at the beginning of the pandemic, UV radiation and temperature might also play a role in COVID-19 case incidence (Ratnesar-Shumate et al. 2020; Gunthe et al. 2022). A negative correlation was observed between cases and temperature along with UV radiation, which could be partially attributed to the higher vitamin D concentrations in

populations living at high altitude (Mukherjee et al. 2022). Other environmental factors, such as the ambient temperature, absolute humidity, SO_2 , and CO values could also play a role in the relationship between altitude and COVID-19 infection (Song et al. 2022).

In altitude-simulated conditions at 4500 m, lower expression of the angiotensin-converting enzyme 2 (ACE2) was described along with an increase in ACE1. People living at higher altitudes under chronic hypoxic conditions would have higher expression of ACE1, which counter-regulates ACE2, a key enzyme for COVID-19 entry into the cell, all through hypoxia-inducible factor 1 (HIF-1) (Hall 2015). This could explain why, at higher altitudes, lower dissemination and mortality from COVID-19 would be expected.

As the country with the highest cumulative mortality worldwide and a great number of cases, as well as the different range of altitudes in the country, Peru provides an ideal setting to assess whether residing at higher altitudes is a protective factor against COVID-19 case incidence and mortality. Compared to previous provincial and/or regional studies where altitude has been found to be a protective factor against infection and death from SARS-CoV-2, this is the first study to analyze this relationship at a district level. The district altitudes vary significantly within a province and even more within a region, which could be a confounding factor, altering the results. Our study aims to assess the association of altitude effects with COVID-19 mortality, taking into account other variables that have not been studied previously, including population density, age, latitude, poverty, gender, and access to drinking water, among others. This will allow us to gain a better understanding of the behavior of the virus in different environments, making the results relevant to the epidemiology of the disease and public health.

Methods

Study design

We conducted an ecological analytical study to assess the relationship between altitude and COVID-19 mortality at a district level in Peru. The average altitudes of all 1874 districts in Peru were included, as well as relevant variables for the transmission and mortality from COVID-19. The three COVID-19 waves that the country has overcome from March 6, 2020, until February 28, 2022, were also evaluated. The period of these waves was defined arbitrarily, with the first wave from April 21, 2020, to November 20, 2020; the second from January 11, 2021, to August 31, 2021; and the third from December 21, 2021, to February 28, 2022.

The obtained data were exported into Excel through Macro and analyzed with STATA 16.

Main outcomes

The three main COVID-19 altitude-related outcomes included in the study were mortality rate, fatality rate, and case incidence. The relationship of latitude and population density with the mortality rate, fatality rate, and case incidence of COVID-19 was also evaluated. The information used in this study was obtained from publicly available databases. COVID-19 deaths and cases per district divided by gender and age were obtained from “*Datos Abiertos*” published by the Health Ministry of Peru (Ministerio de Salud, MINSA). Mortality rate was defined as the estimated number of deaths in the population due to COVID-19, divided by the total number of this population, expressed per 1000 population, for a given period. The fatality rate was calculated by dividing the number of deaths from COVID-19 over a defined period by the number of COVID-19 cases during that time, multiplying the result by 100 to obtain a percentage. Finally, the case incidence was calculated as the total number of COVID-19 cases, divided by the total population in each period, multiplied by 100. Our final multiple linear regression model included the following variables at a district level: altitude, latitude, poverty rate, extreme poverty rate, population density, percentage of male population, percentage of population with access to drinking water, percentage of population living in non-collective housing, and percentage of population with certain sanitation facilities, all calculated per district.

Independent variables

Our main independent variable in this study is the average altitude per each Peruvian district. Since there are several other factors involved in increased risk of dying from COVID-19, variables including latitude, population density, age, sex, poverty rate, extreme poverty rate, percentage of the population with access to drinking water, percentage of the population living in non-collective housing, and percentage of the population with certain sanitation facilities are also included. Data regarding altitude, latitude, population density, and poverty and extreme poverty rate were obtained from “*Información Departamental, Provincial y Distrital de Población que Requiere Atención Adicional y Devengado Per Cápita 2017*” published by the National Center of Strategic Planning (*Centro Nacional de Planeamiento Estratégico*, CEPLAN). Population data divided by gender, age, access to drinking water, home type, and sanitation facilities were obtained from “*Resultados Definitivos del Censo Nacional 2017*” published by the National Institute of Statistics and Informatics (*Instituto Nacional de Estadística e Informática*, INEI).

Dependent variables

Our main dependent variable in this study was the mortality rate. The case fatality rate and case incidence were also included. At the beginning and throughout the pandemic, due to Peruvian reporting standards, a great number of deaths in the country were attributed to COVID-19 and reported as such, independently of a previous positive test. As a result, some districts had a calculated fatality rate greater than 100%, implying a greater number of deaths than confirmed cases.

For this reason, the mortality rate was taken as the most reliable metric to evaluate the effect of the altitude on COVID-19.

Statistical analysis

A descriptive statistic was first examined with the districts as the unit of analysis. Since data came from population censuses, weighted linear regression (weight = total population) was used to reduce the residual standard error and obtain accurate estimates. The three waves were included in the regression model. Values of $p < 0.01$ and $p < 0.05$ were considered highly significant and significant, respectively. Linear regression assumptions were evaluated, and the log transformation of the dependent variables was used, specifically $\ln(x+1)$, because of data containing values of 0. All of this was undertaken to meet the linear regression assumptions with a less skewed distribution (Wooldridge 2015). Heteroscedasticity-robust standard errors were used, justified by the large sample size so the estimated variance was fixed to the degrees of freedom. An inverse log transformation of the correlation coefficients was carried out for the interpretation of the results. A list of abbreviations can be found in Table 1.

Results

A total of 3,372,962 confirmed cases of COVID-19 were registered. Of these, 894,507 were from the first wave, 1,050,444 from the second wave, and 1,193,794 from the third wave. The district of Lima, Lima, Lima (161 m) had the highest numbers of confirmed cases throughout the pandemic and in the second and third waves, with 142,097, 37,819, and 62,973 cases, respectively. San Juan de Lurigancho (205 m), Lima, Lima, was the district with the highest number of cases during the first wave, with 35,329.

A total of 212,017 COVID-19 deaths were registered. Of these, 87,697 deaths occurred during the first wave, 102,596 during the second wave, and 7699 during the third. The district with the highest numbers of deaths throughout the pandemic and during the second wave was Lima, Lima, Lima, with 8532 and 4228 deaths, respectively. During the

Table 1 List of Abbreviations

Ln_T_CI	Total case incidence normal logarithm
Antiln_T_CI	Total case incidence inverse normal logarithm
%_T_CI	Total case incidence percentage change
Ln_T_MR	Total mortality rate normal logarithm
Antiln_T_MR	Total mortality rate inverse normal logarithm
%_T_MR	Total mortality rate percentage change
Ln_T_FR	Total fatality rate normal logarithm
Antiln_T_FR	Total fatality rate inverse normal logarithm
%_T_FR	Total fatality rate percentage change
Ln_W1/2/3	First, second or third wave (W1/2/3) normal logarithm
Antiln_W1/2/3	First, second or third wave (W1/2/3) inverse normal logarithm
%W1/2/3	First, second or third wave (W1/2/3) percentage change
% male	Percentage of the male population in a district
% pov	Population percentage in a district in poverty
% ext_pov	Population percentage in a district in extreme poverty
Pop_density	The population density of a district
% acc_H2O	Population percentage in a district with access to drinking water
% n-collective	Population percentage in a district that lives in non-collective households
% SF	Population percentage in a district with sanitation facilities
%<1/1–4/.../>80yo	Population percentage in a district that is part of an age group (younger than 1/1 to 4/.../older than 80 years old)
% SF_SSIH	Population percentage in a district with the subtype sewer system inside household of the sanitation facilities
% SF_SSOH	Population percentage in a district with the subtype sewer system outside household of the sanitation facilities
% SF_OF	Population percentage in a district with the subtype open field of the sanitation facilities
% SF_SP	Population percentage in a district with the subtype septic pit of the sanitation facilities
% SF_RG	Population percentage in a district with the subtype river and gutter of the sanitation facilities
% SF_C	Population percentage in a district with the subtype cesspool of the sanitation facilities
% SF_L	Population percentage in a district with the subtype latrine of the sanitation facilities

first and third waves, San Juan de Lurigancho had the highest numbers of deaths reported, with 3917 and 219, respectively. There were districts where no cases or deaths were reported, the majority above 2500 m.

The overall mortality rate in Peru was 7.22 deaths per 1000 population, with a fatality rate of 6.29%. The mortality rate was 2.98 deaths per 1000 population during the first wave, 3.49 deaths per 1000 during the second wave, and 0.26 deaths per 1000 in the third wave. The fatality rate was 9.8% in the first wave, 9.77% in the second wave, and 0.64% in the third wave. San Antonio, Huarochiri, Lima (3457 m) reported the highest mortality rate during the pandemic and in each of the waves. with 150, 46, 83, and 7 deaths per 1000 population, respectively. There were districts where no deaths from COVID-19 were reported, most of them located above 2500 m. Fourteen districts reported a 100% fatality rate and 74 districts 0%, all above 2500 m.

Altitude

La Brea district in Talara, Piura and the districts of Callao and La Punta, both in the Constitutional Province of Callao, Callao had the lowest altitude (3 m) and a mortality and fatality rate of 5 deaths per 1000 population and 6%, 13 deaths per 1000 population and 10%, 11 deaths per 1000 population and 8%, respectively. The district of Condoroma, Espinar, Cusco had the highest altitude (4675 m) with a mortality and fatality rate throughout the pandemic of 1.15 deaths per 1000 population and 9%, respectively. The district of Condoroma had no reported cases nor deaths during the first and third waves.

As part of the descriptive analysis, the districts were grouped every 500 m and the average of the number of cases, deaths and mortality rate were calculated for each group throughout the pandemic and in each of its waves.

The highest average number of cases, deaths as well as the highest mortality rate during the pandemic and in each of its waves were found in the districts below 500 m. The highest mortality rate was observed in the districts below 500 m with 8.82 deaths per 1000 population and the lowest above 4500 m with 2.04 deaths per 1000 population. The highest mortality rate throughout the pandemic was observed in the second wave and the lowest in the third one (Figs. 2, 3 and 4).

In the bivariate analysis, the altitude correlated negatively with the case incidence, mortality and fatality rate with highly significant values. For every increase of 500 m in altitude, the case incidence, mortality, and fatality rates decreased by 8.06%, 9.83%, and 2.07%, respectively (Table 2).

Similarly, for every altitude increase of 500 m, mortality decreased by 11.35%, 6.2%, and 0.85% in the first, second, and third waves, respectively, in the bivariate model (Table 3).

Regarding the case incidence and mortality rate in the final linear regression model, highly significant negative coefficients were obtained, with a decrease of 4.42% and 5.82%, respectively, for every increase of 500 m in altitude. The greatest decrease in case incidence, mortality, and fatality rates was seen during the first wave, where for every increase of 500 m in altitude, these variables decreased 5.06%, 6.85%, and 3.61%, respectively (Tables 4, 5, and 6).

During the second and third waves, a highly significant inverse relationship between altitude and mortality rate was observed (Table 5). Throughout the second wave, the mortality and fatality rates decreased by 3.5% and 2.79%, respectively, for every increase of 500 m in altitude, with no statistically significant results for the case incidence. Within the third wave, for every increase of 500 m in altitude, a highly significant percentage decrease of 3.92% and 0.83% in the case incidence and mortality rate was obtained, without statistically significant results for the fatality rate (Tables 4, 5, and 6). The altitude, mortality rate, and case incidence distribution by district is shown in Fig. 5a, b, and c, respectively. The relationship between altitude and mortality rate together with case incidence throughout the pandemic is shown in the scatter diagrams in Figs. 6 and 7.

Latitude

The district of Teniente Manuel Clavero, Putumayo, Loreto (199 m) is the closest to the equator, at -0.38° latitude, with mortality and fatality rates of 0.86 deaths per 1000 population and 1.74%, respectively. The district of La Yarada Los Palos, Tacna, Tacna (73 m) is the furthest from the equator, at -18.23° , with mortality and fatality rates of 5.58 deaths per 1000 population and 3.92%, respectively.

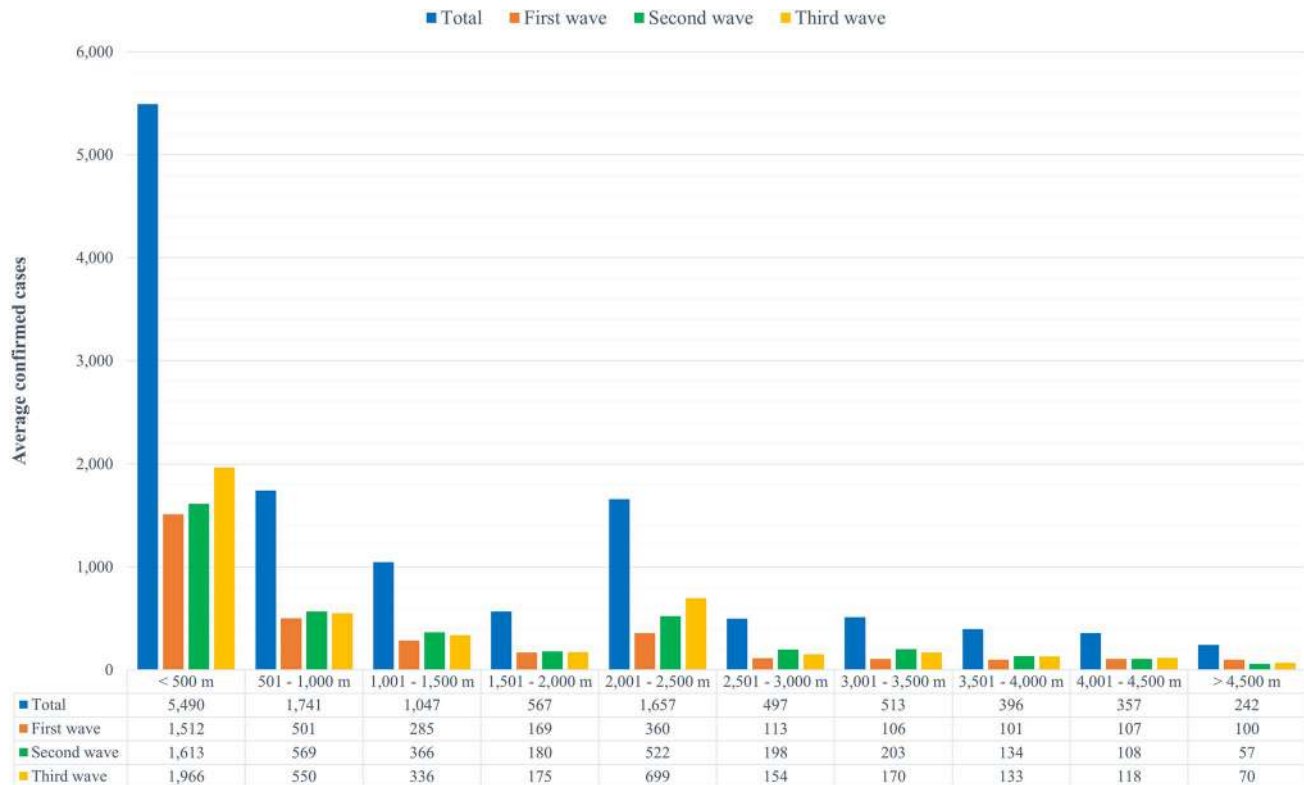


Fig. 2 Average number of COVID-19 confirmed cases in the districts grouped every 500 meters

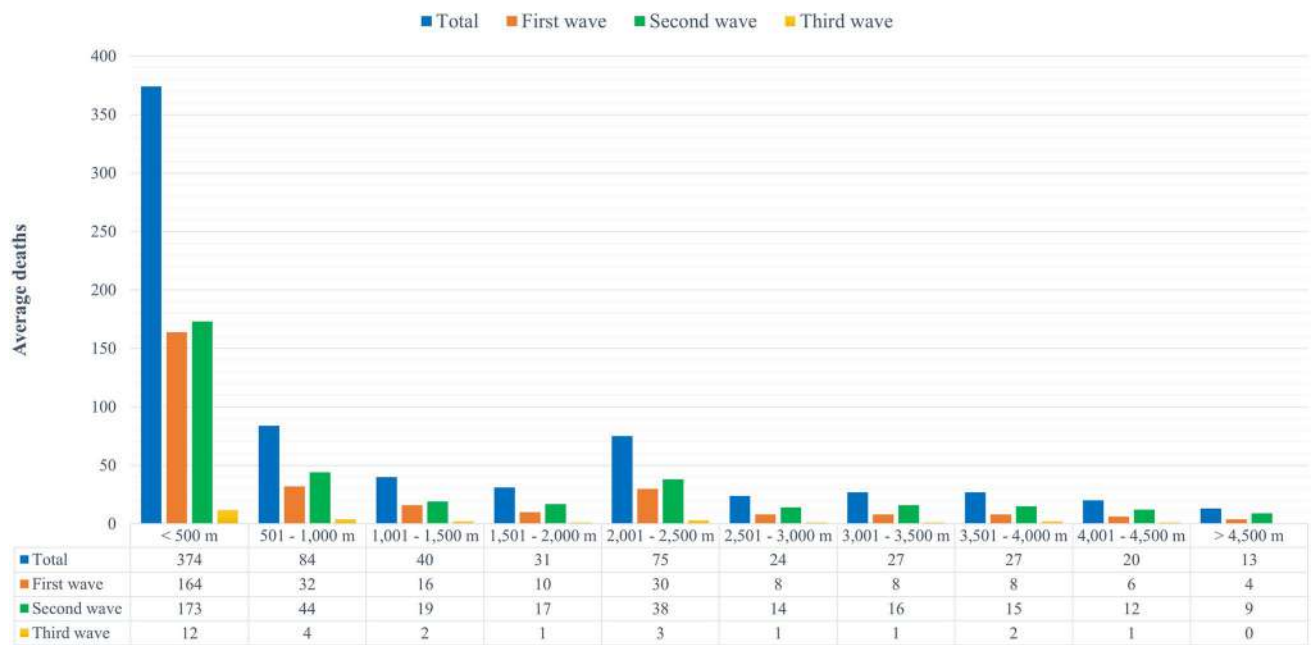


Fig. 3 Average number of COVID-19 deaths in the districts grouped every 500 meters

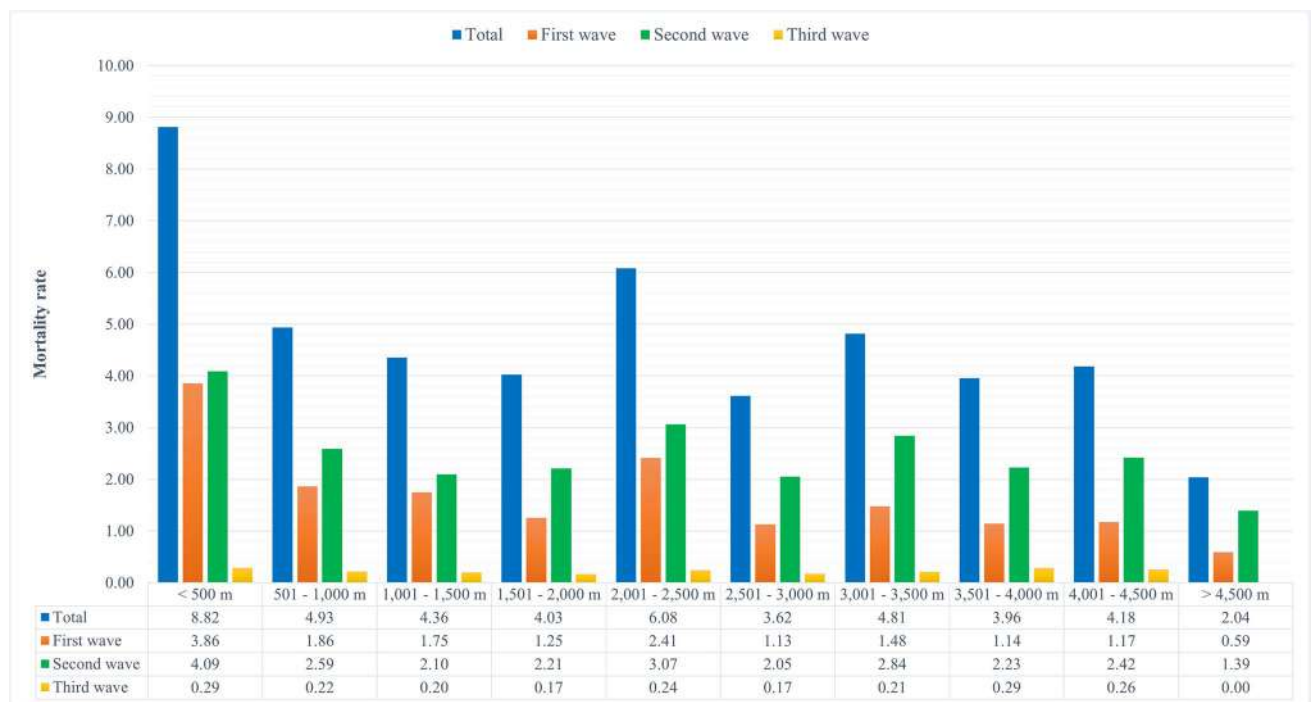


Fig. 4 COVID-19 mortality rate in the districts grouped every 500 meters

Table 2 Bivariate analysis

Variables	Ln_T_CI	Antiln_T_CI	%_T_CI	Ln_T_MR	Antiln_T_MR	%_T_MR	Ln_T_FR	Antiln_T_FR	%_T_FR
Altitude	-0.000168***	-1.00016801***	-0.01680141***	-0.000207***	-1.00020702***	-0.02070214***	-0.0000419***	-1.0000419***	-0.00419009***
% male	-0.114***	-1.12075212***	-12.0752125***	-0.0972***	-1.10208077***	-10.2080768***	0.00632	1.006340013	0.634001334
% pov	-0.025***	-1.02531512***	-2.53151205***	-0.0212***	-1.02142632***	-2.14263165***	0.00263***	1.00263346***	0.26334615***
% ext_pov	-0.0402***	-1.04101896***	-4.10189572***	-0.037***	-1.03769302***	-3.76930208***	0.00153	1.001531171	0.153117105
Pop_density	0.0000515***	1.0000515***	0.00515013***	0.0000511***	1.0000511***	0.00511013***	0.000000432	1.000000432	0.0000432
Latitude	-0.0479***	-1.04906574***	-4.90657435***	-0.0285***	-1.02891001***	-2.89100108***	0.0169***	1.01704361***	1.70436129***
% acc_H2O	0.0167***	1.01684022***	1.68402245***	0.014***	1.01409846***	1.40984589***	-0.00198**	-1.001981961**	-0.198196149**
% n-collective	-0.00772	-1.00774988	-0.7749876	0.00362	1.00362656	0.36265601	0.0130***	1.01308487***	1.30848674***
% SF	-0.0318	-1.03231102	-3.23110225	-0.0138	-1.01389566	-1.38956595	0.0214	1.021630622	2.163062217
% < 1yo	-0.902***	-2.46452724***	-146.452724***	-0.775***	-2.17059213***	-117.059213***	0.0596	1.061411897	6.141189686
% 1-4yo	-0.249***	-1.28274203***	-28.2742033***	-0.213***	-1.23738465***	-23.7384651***	0.0172	1.017348772	1.734877173
% 5-9yo	-0.205***	-1.22752506***	-22.7525065***	-0.176***	-1.19243806***	-19.2438059***	0.0141	1.014199874	1.419987386
% 10-14yo	-0.238***	-1.26870919***	-26.8709193***	-0.21***	-1.23367806***	-23.367806***	0.0115	1.011566379	1.156637921
% 15-19yo	-0.25***	-1.28402542***	-28.4025417***	-0.24***	-1.27124915***	-27.124915***	-0.0135	-1.013591536	-1.359153645
% 20-24yo	0.166***	1.1805731***	18.0573102***	0.151***	1.16299666***	16.2996658***	-0.0136	-1.013692901	-1.369290067
% 25-29yo	0.21***	1.23367806***	23.367806***	0.165***	1.17939312***	17.9393119***	-0.0404***	-1.04122718***	-4.12271818***
% 30-34yo	0.205***	1.22752506***	22.7525065***	0.142***	1.15257665***	15.2576649***	-0.0553***	-1.05685762***	-5.68576244***
% 35-39yo	0.383***	1.46667803***	46.667803***	0.286***	1.33109246***	33.1092455***	-0.0798***	-1.08307043***	-8.30704319***
% 40-44yo	0.516***	1.67531298***	67.5312977***	0.411***	1.50832536***	50.8325357***	-0.0708**	-1.073366531**	-7.336653109***
% 45-49yo	0.527***	1.69384315***	69.3843149***	0.451***	1.56988128***	56.9881282***	-0.0408	-1.041643756	-4.164375596
% 50-54yo	0.383***	1.46667803***	46.667803***	0.362***	1.43619894***	43.6198942***	0.00918	1.009222265	0.922226543
% 55-59yo	0.316***	1.37163026***	37.1630256***	0.32***	1.37712776***	37.7127764***	0.0361	1.036759517	3.675951726
% 60-64yo	0.273***	1.31390024***	31.3900245***	0.277***	1.31916637***	31.9166371***	0.0354	1.03603404	3.603403954
% 65-69yo	0.229***	1.25734204***	25.7342039***	0.227***	1.25482987***	25.4829868***	0.0297	1.030145444	3.014544396
% 70-74yo	0.141***	1.15142465***	15.1424648***	0.15***	1.16183424***	16.1834243***	0.0369	1.037589257	3.758925672
% 75-79yo	0.0925**	1.09691314**	9.69131416**	0.0959***	1.10064899***	10.0648994***	0.0257	1.026033092	2.603309237
% > 80yo	0.171***	1.18649075***	18.6490749***	0.147***	1.15835396***	15.8353963***	0.000627	1.000627197	0.062719661
% SF_SSIH	0.0177***	1.01785757***	1.78575733***	0.0166***	1.01673855***	1.67385456***	-0.000108	-1.000108006	-0.010800583
% SF_SSOH	0.0392***	1.03997846***	3.99784585***	0.0246***	1.02490508***	2.49050765***	-0.0142***	-1.0143013***	-1.43012989***
% SF_OF	-0.034***	-1.03458461***	-3.45846067***	-0.0314***	-1.03189818***	-3.18981806***	0.000248	1.000248031	0.024803075
% SF_SP	-0.0404***	-1.04122718***	-4.12271818***	-0.0398***	-1.04060263***	-4.06026329***	-0.003	-1.003004505	-0.30045045
% SF_RG	-0.0707***	-1.0732592***	-7.32591998***	-0.054***	-1.0554846***	-5.54846022***	0.00138	1.001380953	0.138095264
% SF_C	-0.0246***	-1.02490508***	-2.49050765***	-0.0228***	-1.02306191***	-2.30619067***	0.000837	1.00083735	0.083735038
% SF_L	-0.0418***	-1.04268592***	-26859207***	-0.0372***	-1.03790058***	-3.79005802***	0.00402*	1.004028091*	0.402809104*

* $p < 0.1$ ** $p < 0.05$ *** $p < 0.01$

Table 3 Bivariate mortality rate analysis by waves with altitude

Variables	Ln_W1	Antln_W1	%W1	Ln_W2	Antln_W2	%W2	Ln_W3	Antln_W3	%W3
Altitude	-0.000241***	-1.00024103***	-0.0241029***	-0.000128***	-1.00012801***	-0.01280082***	-0.0000171***	-1.0000171***	-0.00171001***

* $p < 0.1$ ** $p < 0.05$ *** $p < 0.01$ **Table 4** Multivariate analysis of case incidence

Variables	Ln_T	Antln_T	%T	Ln_W1	Antln_W1	%W1	Ln_W2	Antln_W2	%W2	Ln_W3	Antln_W3	%W3
Altitude	-0.000091***	-1.000091***	-0.00905***	-0.000104***	-1.000104***	-0.010401***	-0.0000179	-1.0000179	-0.000179	-0.0001790016	-0.00008***	-0.008***
Latitude	-0.0114	-1.011465228	-1.146522763	-0.00611	-1.006128704	-0.612870412	-0.0039	-1.003907615	-0.39076149	-0.0224***	-1.022653***	-2.265276***
% pov	-0.0163***	-1.016434***	-1.643357***	-0.0121***	-1.012174***	-1.21735***	-0.0127***	-1.012781***	-1.278098***	-0.0169***	-1.017044***	-1.704361***
% ext_pov	0.00236	1.002362787	0.236278699	0.00309	1.003094779	0.309477897	0.00494	1.004952222	0.495222192	0.00881***	1.0088489***	0.8848922***
Pop_density	0.0000235	1.0000235	0.000235	0.00000782*	1.00000782*	0.000782003*	0.0000264	1.0000264	0.000264	0.0000148	1.00000148	0.000148
% acc_H2O	0.00376***	1.0037671***	0.3767078***	0.00113	1.001130639	0.113063869	0.00451***	1.0045202***	0.4520185***	0.00353***	1.0035362***	0.3536238***
% male	-0.0705***	-1.073045***	-7.304457***	-0.0202*	-1.0204054*	-2.04054007*	-0.0503***	-1.051587***	-5.158653***	-0.0939***	-1.09845***	-9.84499***
% n-collective	-0.033***	-1.033551***	-3.355054***	-0.0191***	-1.019284***	-1.928357***	-0.0246***	-1.024905***	-2.490508***	-0.0338***	-1.034378***	-3.43777***
% SF	-0.0581***	-1.059821***	-5.982097***	-0.0323*	-1.03282731*	-3.2827307*	-0.0501***	-1.051376***	-5.137623***	-0.0673***	-1.069616***	-6.961631***
% SF_SSOH	0.00862**	1.00865726**	0.86572592**	0.00129	1.001290832	0.129083241	0.0108***	1.0108585***	1.0858531***	0.00695*	1.006974207*	0.69742073*
% SF_OF	-0.00151	-1.001511141	-0.151114062	-0.00286*	-1.00286409*	-0.28640937*	-0.0019	-1.001901806	-0.190180614	0.000869	1.000869378	0.086937769
% SF_SP	-0.0102***	-1.010252***	-1.02522***	-0.012***	-1.012072***	-1.207229***	-0.00251	-1.002513153	-0.251315269	-0.00842***	-1.008456***	-0.845555***
% SF_RG	-0.0157	-1.015823893	-1.582389252	-0.00311	-1.003114841	-0.311484107	-0.00416	-1.004168665	-0.416866481	-0.0238*	-1.02408548*	-2.40854803*
% SF_L	-0.00189	-1.001891787	-0.189178718	0.00141	1.001410995	0.141099452	-0.000809	-1.000809327	-0.080932733	-0.00534*	-1.00535428*	-0.53542832*

* $p < 0.1$ ** $p < 0.05$ *** $p < 0.01$

Table 5 Multivariate analysis of mortality rate

Variables	Ln_T	Antln_T	% T	Ln_W1	Antln_W1	% W1	Ln_W2	Antln_W2	% W2	Ln_W3	Antln_W3	% W3
Altitude	-0.00012***	-1.00012***	-0.012001***	-0.000142***	-1.000142***	-0.014201***	-0.000071***	-1.000071***	-0.00713***	-0.000017***	-1.000017***	-0.00168***
Latitude	-0.00759	-1.007618877	-0.761887706	0.00458	1.004590504	0.459050423	-0.0153***	-1.015418***	-1.541764***	-0.00632***	-1.00634***	-0.634001***
% pov	-0.0054***	-1.0054146**	-0.5414606**	-0.00531***	-1.005324***	-0.532412***	-0.00746***	-1.007488***	-0.74879***	-0.000651	-1.000651212	-0.065121195
% ext_pov	-0.0105***	-1.010555***	-1.055532***	-0.00812***	-1.008153***	-0.815306***	-0.00234	-1.00234274	-0.234273994	-0.000361	-1.000361065	-0.036106517
Pop_density	0.0000108***	1.0000108***	0.00108***	0.0000159***	1.0000159***	0.00159***	0.00000705**	1.00000705**	0.000705**	0.000000949	1.000000949	0.0000949
% acc_H2O	0.0028***	1.0028039***	0.2803924***	0.00208***	1.0020822***	0.2082165***	0.00239***	1.0023929***	0.2392858***	0.000314	1.000314049	0.03140493
% male	-0.0643***	-1.066412***	-6.641227***	-0.0389***	-1.039667***	-3.966651***	-0.0569***	-1.058549***	-5.854995***	-0.0152***	-1.015316***	-1.531611***
% n-collective	-0.0276***	-1.027984***	-2.798441***	-0.0214***	-1.021631***	-2.163062***	-0.021***	-1.021222***	-2.122205***	-0.00465***	-1.004661***	-0.466083***
% SF	-0.0249*	-1.02521259*	-2.52125941*	-0.0143	-1.014402734	-1.440273412	-0.0263*	-1.02664889*	-2.6648897*	-0.00293	-1.002934297	-0.293429665
% SF_SSOH	-0.000761	-1.00076129	-0.076128963	-0.00574*	-1.0057565*	-0.57565054*	0.00351	1.003516167	0.351616726	-0.000252	-1.000252032	-0.025203175
% SF_OF	-0.00473***	-1.004741***	-0.47412***	-0.00514***	-1.005153***	-0.515323***	-0.00306**	-1.0030647**	-0.3064687**	0.001*	1.0010005*	0.100050017*
% SF_SP	-0.0131***	-1.013186***	-1.318618***	-0.0157***	-1.015824***	-1.582389***	-0.00784***	-1.007871***	-0.787081***	-0.00125	-1.001250782	-0.125078158
% SF_RG	-0.00145	-1.001451052	-0.145105176	0.00604	1.006058278	0.605827758	-0.0048	-1.004811538	-0.481153845	-0.00519**	-1.0052035**	-0.5203491**
% SF_L	-0.00104	-1.001040541	-0.104054099	0.000327	1.000327053	0.032705347	-0.00241	-1.002412906	-0.241290638	-0.00113**	-1.0011306**	-0.1130638**

* $p < 0.1$ ** $p < 0.05$ *** $p < 0.01$ **Table 6** Multivariate analysis of fatality rate

Variables	Ln_T	Antln_T	% T	Ln_W1	Antln_W1	% W1	Ln_W2	Antln_W2	% W2	Ln_W3	Antln_W3	% W3
Altitude	-0.0000323	-1.000032301	-0.003230052	-0.000074***	-1.000074***	-0.00737***	-0.0000567**	-1.0000567**	-0.0056702**	0.00000519	1.00000519	0.000519001
Latitude	0.00285	1.002854065	0.285406511	0.0173***	1.0174505***	1.7450512***	-0.0126	-1.012679714	-1.267971445	-0.00657	-1.00659163	-0.659162979
% pov	0.00921***	1.0092525***	0.9252543***	0.00706***	1.007085***	0.7084981***	0.00478*	1.004791442*	0.479144242*	0.00684***	1.0068634***	0.6863446***
% ext_pov	-0.0116***	-1.011668***	-1.166754***	-0.0193***	-1.019487***	-1.948745***	-0.00599	-1.006007976	-0.600797592	-0.0015	-1.001501126	-0.150112556
Pop_density	0.0000535	1.00000535	0.000535001	0.00000729***	1.00000729***	0.000729**	0.00000177	1.00000177	0.000177	-0.000003	-1.000003	-0.0003
% acc_H2O	-0.000995	-1.000995495	-0.099549518	0.00089	1.000890396	0.089039617	-0.00369***	-1.0036968**	-0.3696816**	-0.00229*	-1.00229262*	-0.22926241*
% male	0.00104	1.001040541	0.104054099	-0.0344***	-1.034999***	-3.499852***	-0.0155	-1.015620748	-1.562074806	0.00366	1.003666706	0.366670598
% n-collective	0.00527	1.005283911	0.528391088	-0.00813	-1.008163138	-0.816313819	0.00541	1.00542466	0.542466048	0.00741*	1.007437522*	0.743752199*
% SF	0.0326	1.033137202	3.31372017	0.0284	1.028807125	2.880712498	0.0361	1.036759517	3.675951726	0.0556	1.057174729	5.717472926
% SF_SSOH	-0.00945***	-1.009495***	-0.949479***	-0.0149***	-1.015012***	-1.501156***	-0.0102***	-1.010252***	-1.02522***	-0.00789***	-1.007921***	-0.792121***
% SF_OF	-0.00443**	-1.0044398**	-0.4439827**	-0.00442*	-1.00442978*	-0.44297826*	-0.0046*	-1.0046106*	-0.46105962*	-0.00187	-1.00187175	-0.187174954
% SF_SP	-0.00599**	-1.006008**	-0.6007976*	-0.0106***	-1.010656***	-1.065638***	-0.00915***	-1.009192***	-0.919199***	-0.0000943	-1.000094304	-0.009430445
% SF_RG	0.0000625	1.000062502	0.006250195	-0.00214	-1.002142291	-0.214229143	-0.0146	-1.014707101	-1.470710059	0.00384	1.003847382	0.384738225
% SF_L	0.00298	1.002984445	0.298444461	0.00215	1.002152313	0.215231291	-0.000922	-1.000922425	-0.092242517	-0.00279	-1.002793896	-0.279389567

* $p < 0.1$ ** $p < 0.05$ *** $p < 0.01$

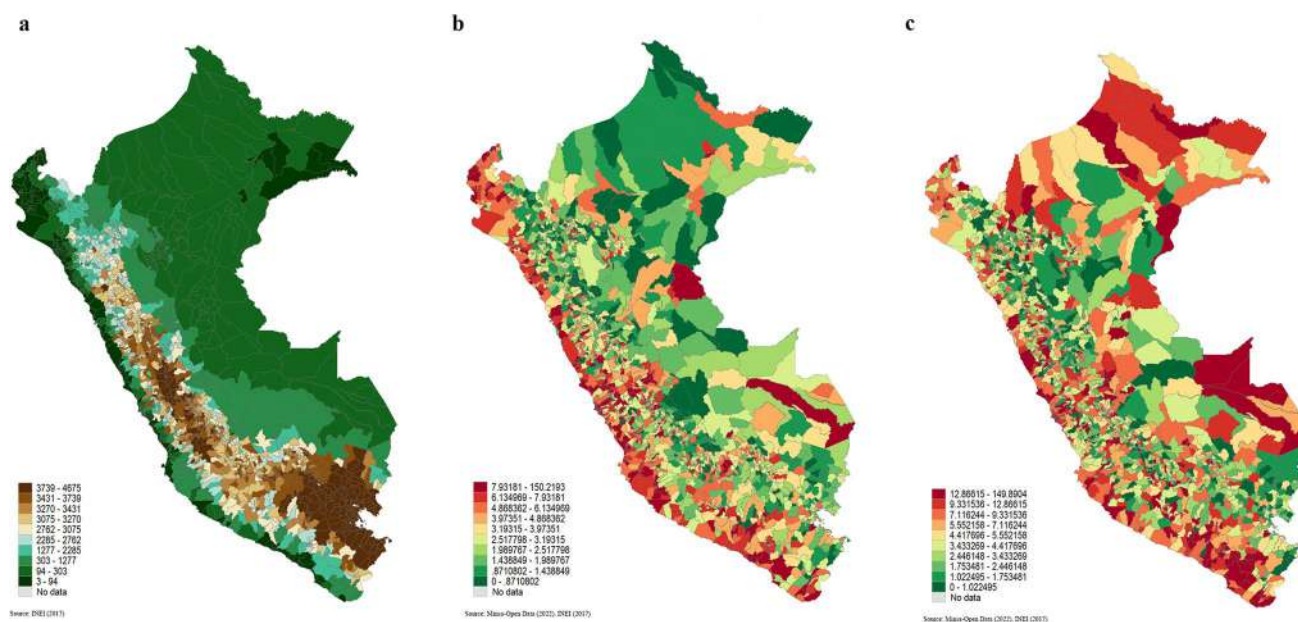
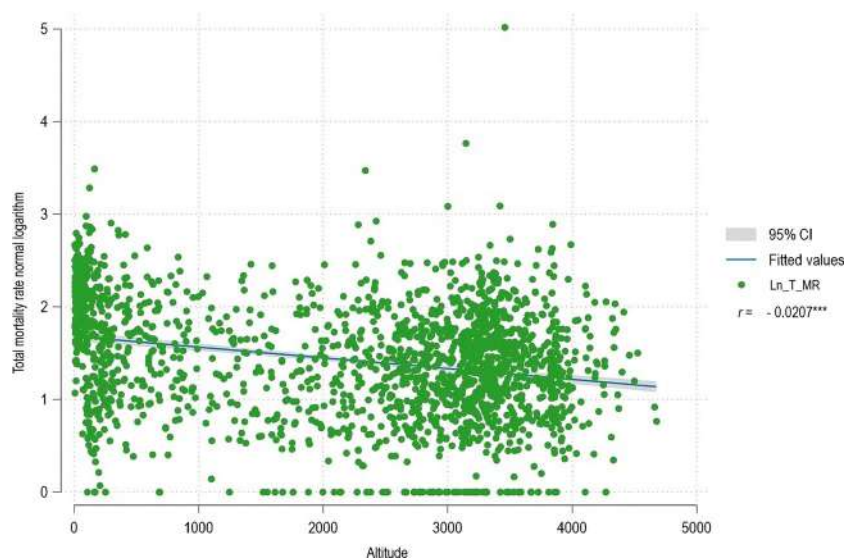


Fig. 5 Altitude, COVID-19 mortality rate and case incidence by districts. (a) Altitude distribution by districts in Peru. (b) COVID-19 mortality rate distribution by districts in Peru. (c) COVID-19 case incidence distribution by districts in Peru

Fig. 6 Linear distribution of total mortality rate and altitude



The bivariate analysis showed highly statistically significant values, where for each degree closer to the equator, the case incidence and mortality rate throughout the pandemic decreased by 4.9% and 2.89%, respectively. Highly statistically significant values were also obtained in the final linear model, where the proximity to the equator was related to a decrease of 1.54% and 0.63% in the mortality rate during the second and third waves, respectively (Table 5). During the third wave, the case incidence decreased by 2.26% for each degree of proximity to the equator (Table 4). The

relationship between latitude and mortality rate together with case incidence throughout the pandemic is shown in the scatter diagrams in Figs. 8 and 9.

Population density

The district of Surquillo, Lima, Lima (122 m) had the highest population density, with 30,341 people (ppl)/km² and mortality and fatality rates of 11.43 deaths per 1000 population and 5.22%, respectively. The lowest population

Fig. 7 Linear distribution of total case incidence and altitude

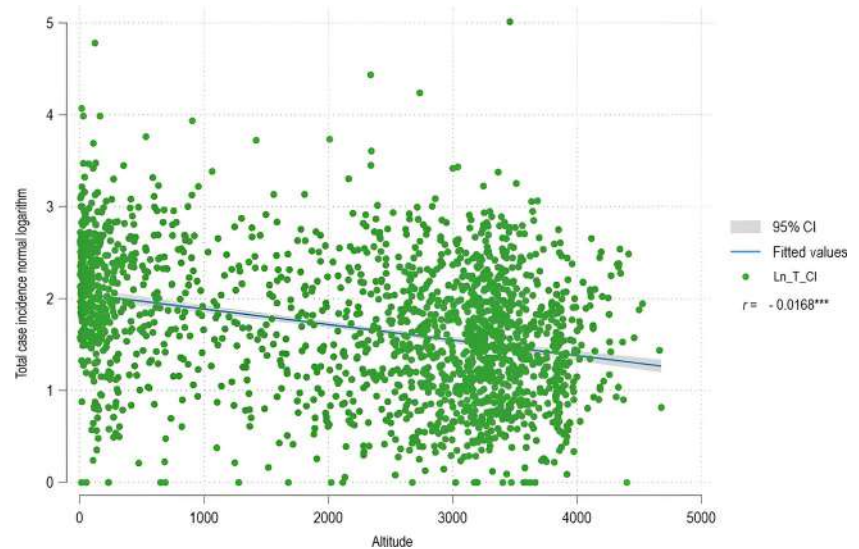
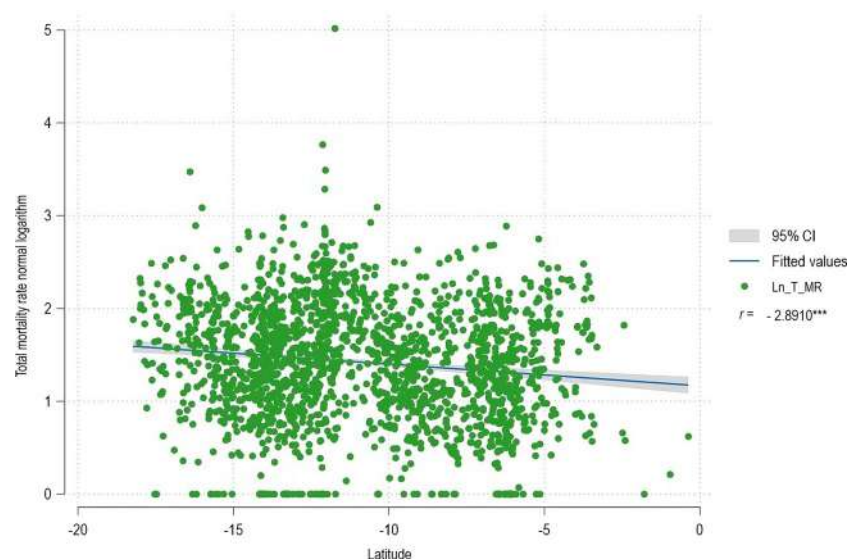


Fig. 8 Linear distribution of total mortality rate and latitude



density was reported in the district of Yaguas, Putumayo, Loreto (107 m), with 0.072 ppl/km² and mortality and fatality rates of 0.78 deaths per 1000 population and 0.68%.

In the bivariate analysis, for every 1000 ppl/km² increase, an increase of 5.02% and 4.98% was found in the case incidence and mortality rate throughout the pandemic (Table 2). In the final linear regression model, the mortality rate increased by 1.07%, 1.57%, and 0.7% for every 1000 ppl/km² throughout the pandemic and in the first and second waves, respectively (Table 5). The fatality rate increased by 0.72% for every 1000 ppl/km² during the first wave (Tables 4 and 6). The relationship between population density and mortality

rate together with case incidence throughout the pandemic is shown in the scatter diagrams in Figs. 10 and 11.

Other variables

There were other variables (age, sex, poverty and extreme poverty rate, percentage population with access to drinking water, etc.) included in the bivariate analysis (Table 2), and some were also included in the final linear regression model (Tables 4, 5, and 6). This information was used to increase the significance of our main variables (altitude, latitude, and population density) and adjust our final model as close to reality as

Fig. 9 Linear distribution of total case incidence and latitude

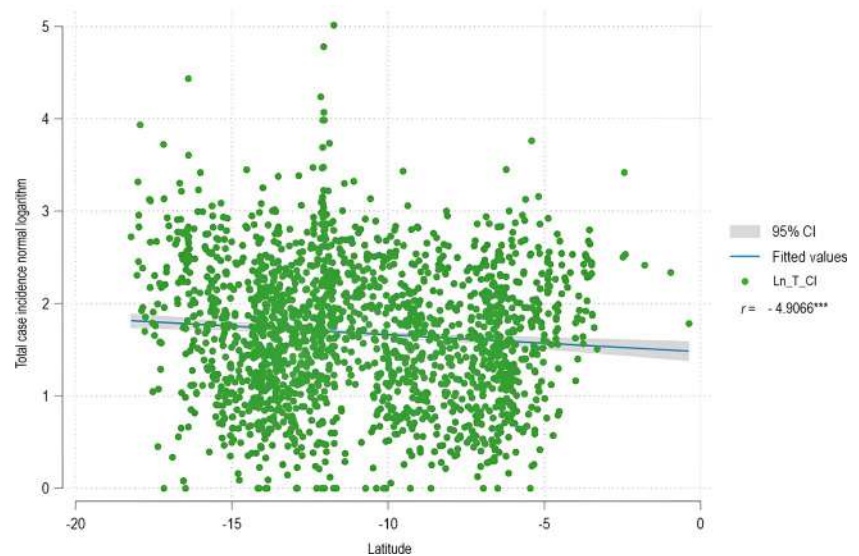
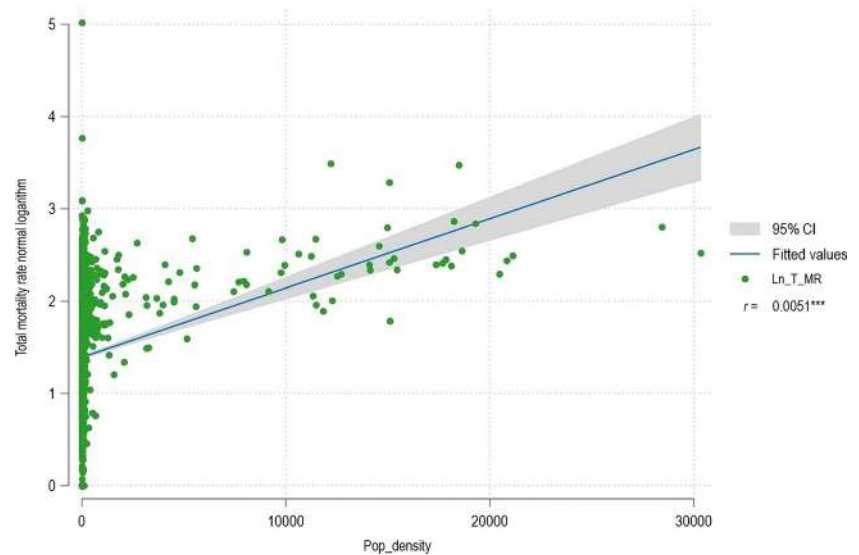


Fig. 10 Linear distribution of total mortality rate and population density



possible. This study did not find a significant correlation trend between case incidence, mortality, and fatality rate, and the other variables described above.

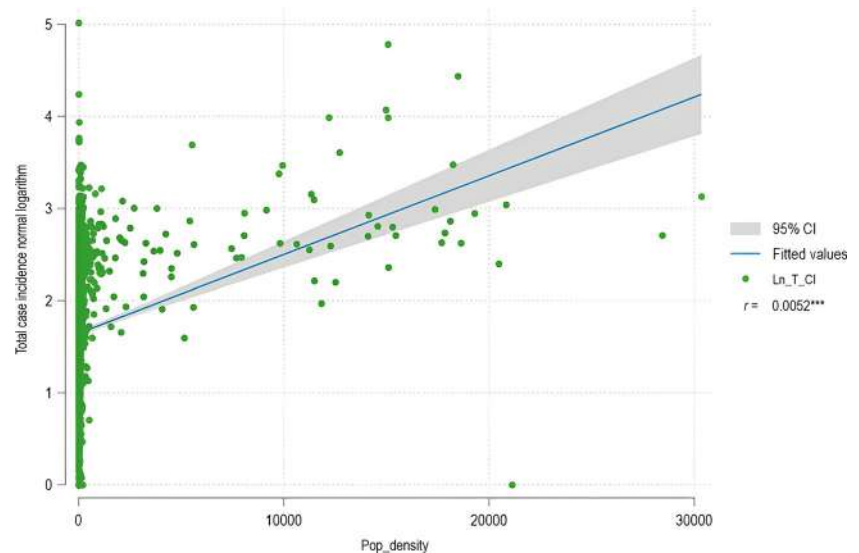
The linear regression formula for the mortality rate can be expressed as follows:

$$\begin{aligned} \log(\text{total mortality rate} + 1) &= 10.37 - 0.012001(\text{altitude}) - 0.761887706(\text{latitude}) - 0.5414606(\%pov) \\ &\quad - 1.055532(\%ext_pov) + 0.00108(\text{Pop_density}) + 0.2803924(\%acc_H2O) \\ &\quad - 6.641227(\%male) - 2.798441(\%n - collective) - 2.52125941(\%SF) \\ &\quad - 0.076128963(\%SF_SSOH) - 0.47412(\%SF_OF) - 1.318618(\%SF_SP) \\ &\quad - 0.145105176(\%SF_RG) - 0.10454099(\%SF_L) \end{aligned}$$

Discussion

During the COVID-19 pandemic in Peru, between March 6, 2020, and February 28, 2022, a negative correlation was found between altitude and mortality rate at a district

Fig. 11 Linear distribution of total case incidence and population density



level, where in our bivariate analysis, for every increase of 500 m in altitude, the mortality rate from COVID-19 decreased by 9.83%.

In our final regression model, the mortality rate dropped by 5.82% for every increase of 500 m in altitude. A similar correlation was found with the case incidence, where a decrease of 4.42% for every 500 m was observed.

Until now, the relationship between altitude and COVID-19 mortality rate has not been fully established. Most studies carried out in Peru and in other Andean regions have shown that altitude exerts a protective effect against COVID-19 (Campos et al. 2021; Cano-Pérez et al. 2020; Accinelli and Leon-Abarca 2020; Seclén et al. 2020); however, Nicolaou et al. concluded that living at high altitudes in Peru may not confer a lower risk of death from COVID-19 (Nicolaou et al. 2022). Although their study showed a lower cumulative daily mortality rate (CDMR) in provinces located above 500 m when compared with those located below 500 m, the trend was not consistently linear with altitude (Nicolaou et al. 2022). In addition, that study was carried out at a provincial level, including 196 provinces, thus possibly overlooking that the altitude between districts varies greatly within each province. In contrast, our study included the 1874 districts in Peru and a greater range of altitudes. A clear example of this is the province of Huarochiri, where, although its altitude according to its capital Matucana is 2380 m, its districts vary from 953 m to 3825 m, all of which increases the power of our analysis even more.

Thomson et al. found a significant association between living at high altitudes and a lower risk of infection and death from COVID-19, also providing evidence that a late surge in cases and deaths in high-altitude regions could be explained by internal migration following a specific land route used in the study, negating the overall protection against COVID-19 conferred by high altitude (Thomson

et al. 2021). In a Peruvian study conducted from March 6 to June 13, 2020, an inverse relationship between infection and high altitude was found, but according to this study, the case fatality rate was not dependent on altitude (Segovia-Juarez et al. 2020). It is worth mentioning that it was not until May 31, 2021, that the actual extent of the mortality from COVID-19 in the country was reported and the total number of deaths was updated (BBC News Mundo 2021), with the revised total deaths resulting in around a 2.5-fold increase from the previous numbers, all of which could have potentially affected the results in this study, and a protective effect of altitude against the case fatality rate could have been found using these new values. The protective qualities of high altitude would not be limited to South America, since a study conducted in Saudi Arabia also showed a less severe form of COVID-19 disease and a lower mortality rate in individuals at high altitude when compared to those living at sea level (Abdelsalam et al. 2021).

In our study, an association between living at high altitudes and a lower COVID-19 case incidence, mortality, and fatality rate was found in all three waves. At high altitudes, chronic hypobaric hypoxia is common, and it has been reported that hypoxia might regulate the replication of certain viruses (Kalter and Tepperman 1952; Berry et al. 1955; Zhuang et al. 2020). This was seen in mice that were acclimatized to 9100 m and exhibited a smaller viral load and a slightly better survival rate when inoculated with influenza virus and kept at high altitudes when compared with mice inoculated with the virus and kept at sea level (Kalter and Tepperman 1952; Berry et al. 1955). In 2020, it was demonstrated that a deficiency of HIF-1 α , a transcription factor activated by reduced oxygen concentrations, in alveolar type II epithelial cells decelerates glycolysis and enhances AMPK α -ULK1-mediated autophagy (AMP-activated protein kinase and Unc-51-like autophagy-activating kinase),

facilitating influenza virus replication in the mice inoculated at sea levels (Zhao et al. 2020). In human pulmonary artery smooth muscle cells (hPASMC) exposed to chronic hypoxic conditions (O₂ 2% for 12 days), it was found that ACE1 was upregulated by HIF-1, whereas ACE2 expression was markedly decreased (Zhang et al. 2009). Similarly, increased levels of ACE1 and decreased expression of ACE2 was found in heart cells of rats exposed to 4500 m for 28 days (Dang et al. 2020).

Therefore, the spike (S) protein from SARS-CoV-2 would have a lower number of ACE2 receptors to join to in the population residing at high altitudes due to overexpression of hypoxia-induced HIF-1 (Arias-Reyes et al. 2020; Zhang et al. 2009). Hypoxia, via an HIF-1 α -dependent pathway, would not only reduce ACE2 but also decrease transmembrane protease serine 2 (TMPRSS2) expression, inhibiting SARS-CoV-2 entry and replication in lung epithelial cells (Wing et al. 2021). Both TMPRSS2 and neuropilin-1 (NRP1) contribute to SARS-CoV-2 entry into the host cells. At least two mechanisms are involved in the effect of hypoxia on the decreased binding of protein S to the epithelial cells. Hypoxia decreases the expression of ACE2 receptors and NRP1 and reduces the total amount of an attachment factor called cellular heparan sulfate (HS) and syndecan-1 (HS-containing proteoglycan), resulting in reduced receptor-binding domain (RBD) binding to the surface of epithelial cells (Prieto-Fernández et al. 2021). Furthermore, under hypobaric hypoxic conditions, the reno-protective effects of the erythropoietin hormone (EPO) would be increased (Suresh et al. 2020; Basu et al. 2007), allowing better tissue oxygenation while preventing renal microvascular injury and inflammatory response seen in COVID-19 (Stoyanoff et al. 2018). Lower EPO concentrations were found in critical, ventilated, and deceased patients with SARS-CoV-2 compared to those with mild disease (Yağcı et al. 2021). In El Alto, Bolivia (4150 m), and COVID-19 infected patients admitted to the intensive care unit (ICU) who survived had 2.5 times the levels of EPO levels as patients who died (Viruez-Soto et al. 2021). The antiapoptotic, anti-inflammatory, and cytoprotective effects of EPO might be a safe therapeutic choice for COVID-19 patients at the early stages (Begemann et al. 2021; Sahebnaşagh et al. 2020), as EPO would act on brainstem centers and the phrenic nerve to improve respiration, counteract the inflammatory response caused by the cytokine storm, and play a neuroprotective role in the central and peripheral nervous systems (Ehrenreich et al. 2020). The EPO anti-inflammatory effects come into play by impeding inflammasome activation, which manifests as a response of elevated angiotensin II and aldosterone after SARS-CoV-2-induced downregulation of ACE2 expression together with reduced nitric oxide (NO) bioavailability (Papadopoulos et al. 2022). All of these factors provide a possible explanation of why COVID-19 is less severe at higher altitudes.

This paradoxical situation of fewer confirmed COVID-19 cases and a lower mortality rate at high altitudes can be explained not only by the important role of hypoxia in virus entry and replication, but also by the possible effects of hypoxia on the immune system of high-altitude inhabitants, stimulating innate and adaptive immune responses. An enhanced immunological response to an innate immune challenge via lipopolysaccharide (LPS) in the form of higher antibody titers and tumor necrosis factor alpha (TNF- α) expression was reported in mice over the course of 36 days of hypoxic exposure (Baze et al. 2011). Differentiated immune activation was also seen in healthy individuals exposed to an altitude of 3200 m and a yearlong isolation and confinement in Antarctica (Feuerecker et al. 2018). Moreover, women exposed to altitude of 5050 m for 21 days had increased white blood cells, as well as reduced CD3⁺ and CD4⁺ T cells, increased natural killer cells, and decreased interferon gamma (IFN- γ) expression (Facco et al. 2005). This better infection response at higher altitudes could also explain why individuals from Tañi del Valle, Argentina (2014 m) showed increased and long-lasting antibodies against RBD compared with individuals from San Miguel de Tucumán, Argentina (431 m) (Tomas-Grau et al. 2021). In Ecuador, ICU patients admitted at high altitude had a substantial survival improvement, especially in patients with no comorbidities, compared with patients admitted at sea level (Simbaña-Rivera et al. 2022), which once again would prove the protective effect of altitude against COVID-19 infection and death.

This is the first study to include latitude as part of the analysis, where it was found that each degree of proximity to the equator was associated with a decrease in mortality of 1.54% and 0.63% in the second and third waves, respectively, while the case incidence was decreased 2.26% during the third wave. According to our study, 22% of the Peruvian population reside at altitudes above 2500 m. The country's proximity to the equator associated with warmer climates allows human and animal survival at high altitudes under such hypobaric hypoxic conditions (Accinelli and Leon-Abarca 2020). Because of the curved surface of the earth, the proximity to the equator results in higher temperatures, rainfall, and UV radiation, which was associated in our study with lower COVID-19 case incidence and mortality rates.

In Spain, it was found that provinces with an average temperature lower than 10 °C had almost twice the cumulative incidence when compared with provinces with an average temperature higher than 16 °C. Similarly, provinces with higher rainfall amounts (mm) had the lowest cumulative incidence, which was also seen in Italy (Valero et al. 2022; Agapito et al. 2020).

UV radiation is higher at high altitudes and air density is lower. The disinfectant effects of UVA and UVB rays, because of the ability to modify molecular DNA and RNA bonds, together with the effects of low air density, result in

a reduced half-life of organisms, time they remain in the environment, and viral inoculum size. UV radiation also favors the production of vitamin D, which appears to have an immunoregulatory role against viral infections, and its deficiency has been linked to the progression of severe COVID-19 presentation (Whittemore 2020; Grant et al. 2020; MacLaughlin and Holick 1985).

The case incidence and mortality from COVID-19 increased 5.02% and 4.98% for each 1000 ppl/km² in our bivariate analysis, and when adjusted for the rest of the variables, an increase in mortality of only 1.57% per 1000 ppl/km² was found in the first wave, and the overall increase in the mortality rate was 1.07%. The probability of infection increases as the viral exposure increases, which is associated with the people whom one is in contact with, and the latter would be represented by the population density (Martins-Filho 2021).

In Ecuador, a protective effect of altitude was found, with population density being the only variable with a positive correlation (Campos et al. 2021). In Colombia, a country with Andean regions like Peru, data for 70 municipalities with average altitudes ranging from 1 to 3180 m were used, revealing a negative correlation between altitude and COVID-19 fatality rate, but it was better explained by the population density (Cano-Pérez et al. 2020). In India, high population density was associated with a higher number of COVID-19 cases and deaths (Bhadra et al. 2021).

It is also worth mentioning that a great difference was observed between the number of confirmed cases and mortality rates in the first two waves when compared with the third, with the third wave having 1.33 and 1.14 times as many cases as the first and second waves, but 11.46 and 13.42 times lower mortality, respectively. In Peru, Omicron was the predominant variant during this wave, with the lowest number of deaths, hospitalizations, and ICU admissions when compared with the other variants, and Omicron accounted for around a quarter of the number of deaths from the Gamma and Lambda variants (Fano-Sizgorich et al. 2022). Omicron contains the highest number of mutations, which gives it greater replication and reinfection potential than the Delta variant, and when compared with the original strain, its infectivity rate is up to 10 times as great (Tian et al. 2022). Despite Omicron's high affinity for ACE2 receptors, this variant does not affect lung cells in the same way as upper respiratory tract cells, which were found to have a higher viral load than cells infected with the Wuhan variant in hamsters (McMahan et al. 2022).

Before Omicron, its predecessor variants had to carry out proteolytic degradation of transmembrane serine protease type II (TMPRSS2), followed by protein S activation, to enter cells (Al-kuraishy et al. 2021). However, Omicron's new entry pathway permits the virus to enter the cell directly through cell fusion independently of the proteolytic degradation of TMPRSS2, which would confer this variant a

greater predilection towards cells that do not express this protease, found predominantly in the upper respiratory airway, altering the pathogenesis and severity of the disease (Peacock et al. 2021). Likewise, the great antigenic distance of protein S between Omicron and Wuhan would explain the low efficacy of the current vaccines as well as the high reinfection rates. The mutations found in Omicron also alter the different epitopes in RBD, conferring this variant with increased immune evasion capacity, showing a greater resistance against the neutralizing antibodies from convalescent plasma and against the current available vaccines (Peacock et al. 2021).

This is the first Peruvian ecological analytical study to assess the relationship between altitude and COVID-19 mortality at a district level during the pandemic and for each of its waves considering multiple variables to control for confounding factors. This allowed us to evaluate the association between the most relevant independent variables seen during the pandemic regarding the case incidence, mortality, and fatality rates, working with an extensive population. Using the districts instead of the provinces or departments for the analysis allowed us to obtain more precise results to assess the relationship between COVID-19 and altitude. The duration considered for the study constitutes an advantage, since it also allowed us to evaluate this relationship from the first confirmed case reported in Peru up to February 28, 2022, including each of the three waves the country has faced, whose behavior was seen to change over time in respect to our dependent variables.

This study has several limitations due to its ecological nature, which makes it impossible to extrapolate the associations found to an individual level and increases sensitivity to certain biases, such as confounding, migration, and effect modification. Moreover, the databases used in the current study only considered confirmed cases as those with a positive diagnostic test, which could have resulted in fewer confirmed cases registered in the database because of the possibility of false negatives or positive cases where access to these tests was not possible. It is also worth mentioning that there could have been more COVID-19 deaths registered on the database since the operational definition for it did not require a positive test. There was no publicly available information for overcrowding in housing at a district level, which is a crucial variable when evaluating infectious diseases. Our results also suggest a nonlinear relationship; therefore, a nonlinear regression analysis should be carried out for additional associations.

Would these findings suggest a protective effect of altitude against other infectious diseases? Tuberculosis (TB) is an infectious disease that is still prevalent around the world and remains a major health threat. A lower TB notification rate has been reported at higher altitudes (Gelaw et al. 2019), suggesting a negative correlation between these two

(Mansoor et al. 1999; Vargas et al. 2004). This was also observed as early as 1814, where sanatoriums were established in Davos, Switzerland (1560 m), aiming to help in the recovery of TB-infected patients (Rogers 1969).

In conclusion, a negative correlation was found for both COVID-19 mortality and case incidence with respect to residence altitude at a district level in Peru along the pandemic and in each of its three waves. The population density, especially in the first wave, demonstrated a positive correlation with the mortality rate. In all the Peruvian districts, the second wave was the deadliest and the third the most infectious.

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Author contributions All authors contributed to the study conception and design.

Material preparation and data collection and analysis were performed by Betsabe M. Cucho-Vásquez, Fernando R. Chu-Rivera, Valeria A. Castillo-Urbe, and Zoë L. Contreras-León.

Writing, review, and editing were performed by Valeria A. Castillo-Urbe, Roberto A. Accinelli, Zoë L. Contreras-León, Betsabe M. Cucho-Vásquez, and Leonardo Huayanay-Falconi.

The study was conducted under the supervision of Roberto A. Accinelli and Leonardo Huayanay-Falconi.

All authors commented on previous versions of the manuscript.

All authors read and approved the final manuscript.

Data availability All data used for this study are directly downloadable from the publicly available databases “Datos Abiertos” published by the Health Ministry of Peru (Ministerio de Salud), “Información Departamental, Provincial y Distrital de Población que Requiere Atención Adicional y Devengado Per Cápita 2017” published by the National Center of Strategic Planning (Centro Nacional de Planeamiento Estratégico), and “Resultados Definitivos del Censo Nacional 2017” published by National Institute of Statistics and Informatics (Instituto Nacional de Estadística e Informática). The compiled dataset used for this study is available as an Excel spreadsheet at the GitHub repository: <https://bit.ly/3K5VFp2>

Code availability The obtained data were analyzed with STATA 16. All the statistical code used for this analysis is provided at the GitHub repository: <https://bit.ly/3K5VFp2>

Declarations

Ethical statement As we have used freely available databases, it was not necessary to obtain informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Universidad Peruana Cayetano Heredia (No. SIDISI: 202671, Date: August 3, 2020)

Ethics approval The Ethics Committee from the Universidad Peruana Cayetano Heredia approved this study registered under SIDISI 202671.

Consent to participate Not applicable

Consent for publication Not applicable

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose.

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