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RESEARCH ARTICLE

COVID-19 Mortality Is Attenuated at High Tropical and Subtropical Altitude: An Observational Study of a Database Covering Five Latin American Countries

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ABSTRACT

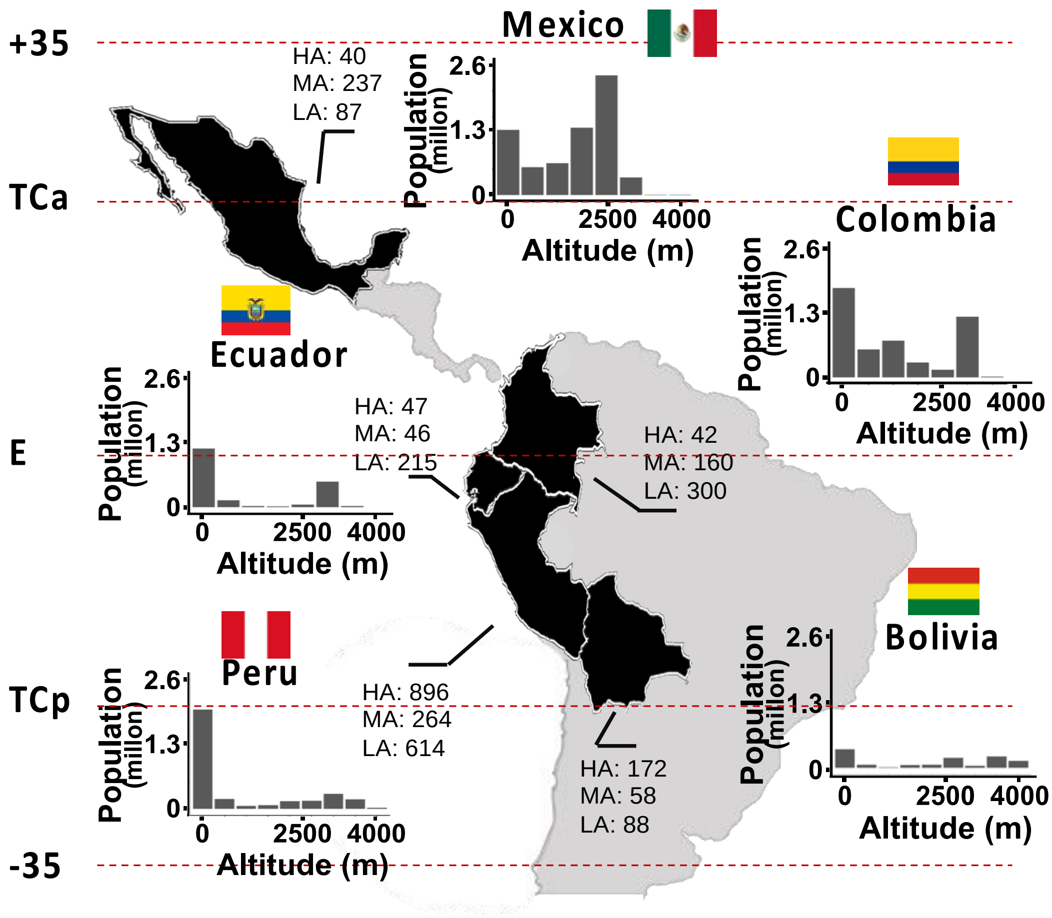
The COVID-19 pandemic, caused by the SARS-COV-2 virus, has had devastating consequences worldwide. Remarkably, the incidence, virus transmission capacity, and severity of COVID-19 have been reported to be significantly decreased in high-altitude human populations. The clinical significance of these findings is enormous, as they suggest that permanent inhabitants of high altitudes have developed adaptive protective changes against certain pathologies. However, these observations have been overshadowed by contradictory reports on the COVID-19 mortality rate at high altitude, ascribed to low population densities. These interpretations, however, fail to consider that the environmental conditions of high-altitude regions of the temperate and tropical geographical zones are radically different from each other. Contrary to common thought, the conditions of high-altitude areas of countries within the tropical zone are so benign that they have favored the growth and development of densely populated cities. In this work, we use data from a COVID-19 database covering five Latin American countries in the tropical and subtropical geographic zone that corresponded to the period between the start of the pandemic and the end of 2020, when no vaccine was yet available. Our results reveal that residing above 1,000 m in tropical countries was a protective factor against COVID-19 mortality. Interestingly, this protective effect was independent of population size. The findings presented here, and those from other similar studies, substantiate the need for more research to reveal the secrets of the physiology of permanent high-altitude residents. In conclusion, our findings clearly demonstrate that the high-altitude environment in tropical and subtropical geographic zones significantly contributes to the decreased mortality impact of the SARS-COV-2 virus in high-altitude-exposed populations.

Keywords: SARS-CoV-2 first wave, ACE2, chronic hypobaric hypoxia, tolerance to hypoxia

Introduction

High altitude is defined as the altitudinal range between 2,500 and 5,000 meters above sea level (masl) [1]. However, when the scientific literature refers to this condition, it assumes that environmental characteristics in all high-altitude regions of the planet are similar. High-altitude areas in countries like the United States, Canada, and European ones are located within the northern temperate zone (between the Arctic Circle at 66° 33′ N and the Tropic of Cancer at 23° 27′ N) [2]. High-altitude regions in this geographical zone are generally arid, cold, and permanently covered in snow (less and less due to climate change). They also lack arable land and have conditions that make them ideal for short-term tourism and/or sports but not for developing large cities with large permanent populations [3]; except Lhasa in Tibet, which is within the temperate zone, but at its southernmost part (inside the subtropical geographic zone, see below). On the contrary, the southern half of Mexico and the tropical geographical zone, between the Tropic of Cancer and the Tropic of Capricorn (between latitudes of about 23° 27′ north and south of the Equator - Fig 1) [2]. Unlike the temperate zones, the high-altitude areas of the tropical zone have benign conditions for human life; an annual temperature variation of between -5°C and +27 °C, rare snow, and fertile soils (Fig. 1) [4]. In line with this, the capitals of many Latin American countries are large urban cities located at high altitude, including La Paz City in Bolivia (3,600 masl - 2,706,000 inhabitants); Quito in Ecuador (2,850 masl - 2,001,388 inhabitants); Bogota in Colombia (2,651 masl - 7,181,000 inhabitants); and Mexico City in Mexico (2,651 masl - 8,851,080 inhabitants) [5]. Furthermore, high-altitude areas in the tropical geographical area of the planet are the natural habitat of more than 38 181 350 people in Latin America [6].

Figure 1. Map showing (in black) the Latin American countries studied that are located within the tropical (between the Tropic of Cancer -TCa, and the Tropic of Capricorn -TCp) and subtropical (the northern half of Mexico; between the TCa and latitude +35 north) geographical zone: Tropical and subtropical high-altitude. For each country, the number of municipalities studied at low altitude (LA), moderate altitude (MA) and high altitude (HA) is detailed, as well as the distribution of the population according to altitude.



These geographical differences are critical to consider when examining the effect of high altitude on the incidence, virus transmission capacity, and severity of COVID-19. In fact, when our research group reported for the first time an attenuated effect of COVID-19 in high-altitude regions [7], many argued that the allegedly lower population density at high altitude explained this effect and not the lower oxygen availability (environmental hypoxia, which is the main characteristic of high altitude). However, subsequent reports have shown that COVID-19 infection rates are lower at higher altitudes [5,7-15]. As it concerns mortality, findings remain unclear[16-19] but again have been attributed to the low population density at high-altitude [20]. Thus, a comprehensive analysis of the relationship between COVID-19 mortality and altitude was conducted for the highlands of the United States. The study showed a consistent effect: COVID-19 mortality decreased at higher altitudes, even when controlling for comorbidities and sociodemographic factors [20]. Here, we conducted a new study using a database covering 5 Latin American countries; Bolivia, Colombia, Ecuador, and Peru (in the tropics) and Mexico (in the tropical and subtropical region - between the TCa and latitude +35 north). This database comprises complete records of COVID-19 cases and deaths during the first wave, before the advent of vaccines. Our results clearly show attenuated mortality from COVID-19 at high-altitude and that this effect is independent of the population size.

Methods

STUDY DESIGN

An analytic, retrospective, multinational study was carried out. To do this, we obtained the official number of positive cases, recoveries, and deaths by COVID-19 for all municipalities in Bolivia, Colombia, Ecuador, Mexico, and Peru. Epidemiological data from official sources were matched with corresponding demographic (population) and geographical (average altitude over sea level) information per municipality. For each country, data per municipality were classified into three groups according to the average geographical elevation (altitude): 1) low-altitude municipalities (<1,000 m), 2) moderate-altitude municipalities (1,001 - 2,499 m), and 3) high-altitude municipalities (>2,500 m). The number of low-, moderate-, and high-altitude municipalities studied for each country are specified in Figure 1. The epidemiological data were obtained from official sources of each country (see below) from the beginning of the pandemic (first reported case) until the end of the first epidemic wave, before the arrival of the vaccines.

DATA SOURCES

Bolivia. Data were gathered from March 10th, 2020, to January 3rd, 2021, from the National Epidemiology Directorate of Bolivia (Dirección Nacional de Epidemiología) database. Demographic information for each municipality was extracted from the Bolivian National Institute of Statistics official website ("Instituto Nacional de Estadística - INE," 2021)[21]. The average altitude of each municipality was obtained from Google search for altitudes ("Google Maps Find Altitude," n.d.)[22].

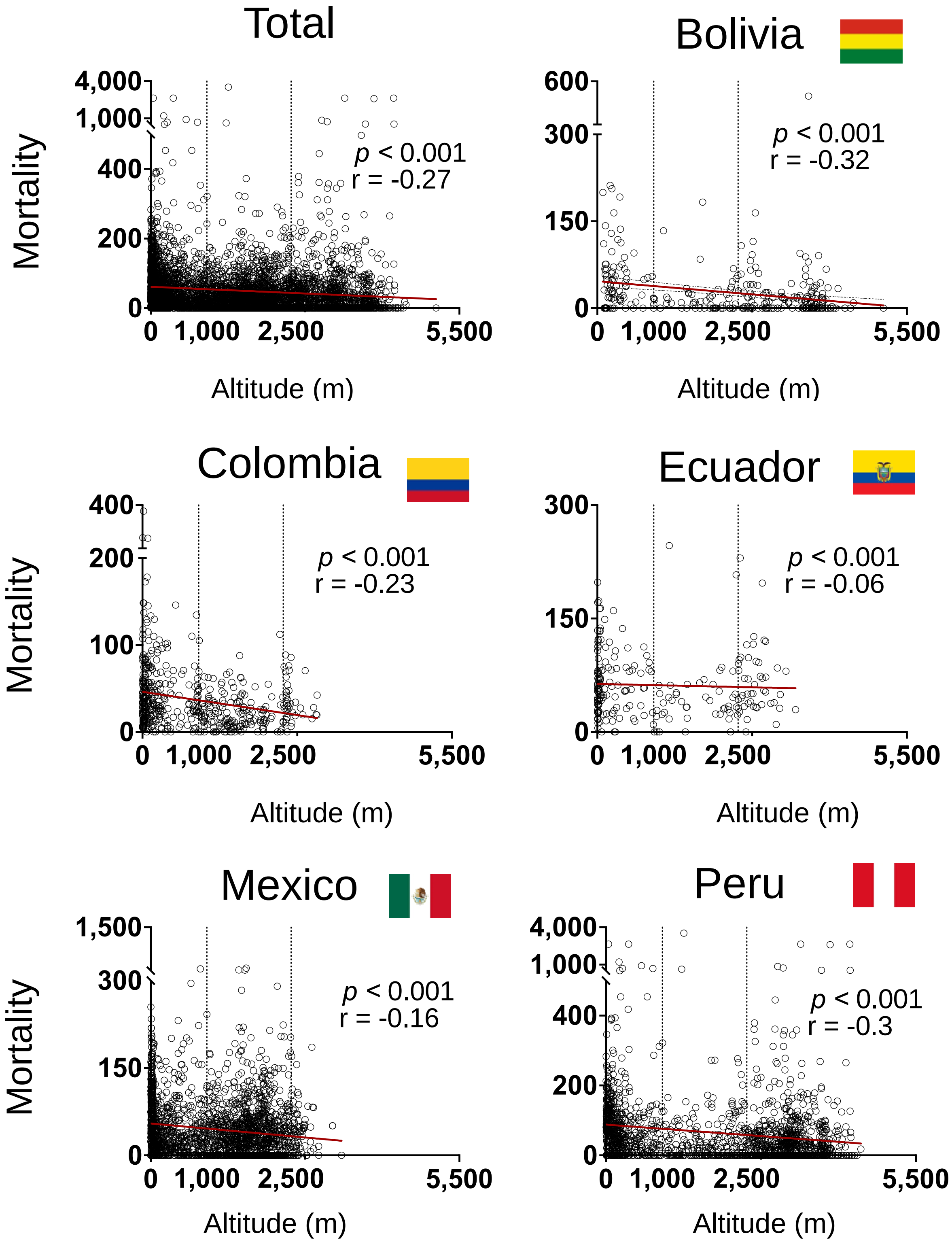
Colombia. Epidemiological data were gathered from February 1st, 2020, to January 24th, 2021, from the National Health Institute of Colombia (Instituto Nacional de Salud - INS) official database. The average altitude and total population size per municipality were retrieved from the Colombian Ministry of Housing.

Ecuador. Epidemiological data were retrieved from February 1st, 2020, to February 23rd, 2021, from Ecuador's National Ministry of Public Health database (Ministerio de Salud Pública). Demographic data was obtained from the National Statistics and Census Institute of Ecuador. Average altitudes per municipality were obtained by searching on Google ("Google Maps Find Altitude," n.d.) [22].

Mexico. Data on confirmed COVID-19 positive cases and deaths from each municipality were obtained from the official database of CONACYT ("COVID-19 Tablero México - CONACYT - CentroGeo - GeoInt - DataLab," n.d.)[23] corresponding to the period between February 27th, 2020, and December 31st, 2020. Altitude data were obtained from ("Marco geoestadístico - Catálogo único de claves de áreas geoestadísticas estatales, municipales y localidades," n.d.)[24]. Population and delimitation areas were retrieved from ("COVID-19 Monitoreo de la Situación por Municipios," 2021) and https://www.gob.mx/conapo/documentos/delimitacion-de-las-zonas-metropolitanas-de-mexico-2015[25].

Peru. Data of confirmed COVID-19 patients and deaths from March 6th to December 17th, 2020, were obtained from the official Platform of open databases provided by the Peruvian State. Average altitudes per municipality were obtained by searching on Google ("Google Maps Find Altitude," n.d.) [22].

Figure 2. COVID-19 mortality decreases with altitude. COVID-19 mortality (deaths/100,000 people) is negatively correlated with geographical altitude in all five countries (total) and each of the countries (Bolivia, Colombia, Ecuador, Mexico, and Peru) studied. Each dot represents one municipality. The *p* and r values for Spearman correlations are presented for each country.



Data analysis

Information on the number of confirmed positive COVID-19 cases, recoveries, and deaths per municipality was organized in datasheets using MS EXCEL 2019 version 9.1.1. The mortality per municipality was calculated as the number of reported deaths per 100,000 inhabitants. The mathematical relation between altitude and

COVID-19 mortality in each studied country was evaluated by Spearman correlations using GraphPad Prism version 9.1.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). A generalized linear model (GLM) was performed in R (https://www.r-project.org) [26] to examine the effect of altitude and population size on COVID-19 mortality by pooling together the total populations of Bolivia, Colombia, Ecuador, Mexico, and Peru. Because of the nature of the data, we used a Poisson distribution for the model, and it was adjusted to consider the country effect according to:

$$\text{Mortality}_{ijk} = \beta_0 + \text{Total population}_i + \text{Altitude}_j + \text{Country}_k + \varepsilon_{ijk}$$

Additionally, the association between the altitude of residence (low, moderate, and high altitude) and COVID-19 mortality was evaluated for each country using Chi-square tests. Yates corrections were used when required. The protective effect of altitude residence against COVID-19 mortality was evaluated by calculating the odds ratios (OR). For all the analyses, the significance was set to $p<0.05$. Data are presented as means unless stated otherwise.

Results

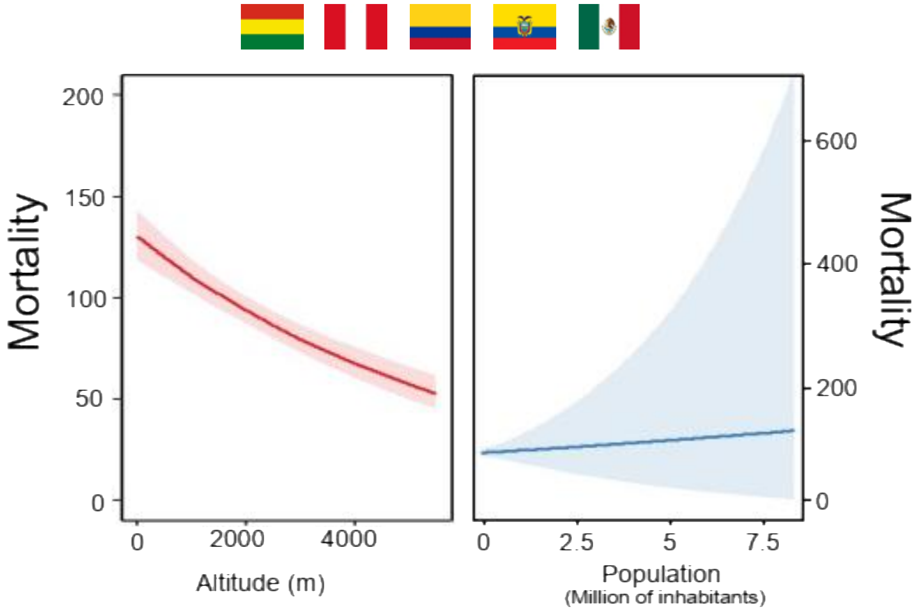
COVID-19 MORTALITY DECREASES WITH ALTITUDE.

We investigated the impact of altitude on mortality from COVID-19 in the five countries together (total) and separately. Our results show that despite the large variability in mortality among these countries, COVID-19 mortality decreases significantly with increasing altitude (Spearman correlations $r_{\text{Total}} = -0.27$, $p< 0.0001$; $r_{\text{Bolivia}}= -0.32$, $p< 0.0001$; $r_{\text{Colombia}}= -0.23$, $p< 0.0001$; $r_{\text{Ecuador}}= -0.06$, $p< 0.0001$; $r_{\text{Mexico}}= -0.16$, $p< 0.0001$; $r_{\text{Peru}}= -0.3$, $p< 0.0001$ - Fig. 2).

ALTITUDE, BUT NOT POPULATION SIZE, EXPLAINS THE LOW COVID-19 MORTALITY.

We tested whether the correlation between altitude residence and COVID-19 mortality was biased by the size of the population (that decreases significantly above 4,000 m). Our generalized linear model shows that altitude, not population size, significantly affects COVID-19 mortality (Fig. 3).

Figure 3. A Generalized Linear Model (GLM) was applied to examine the association between COVID-19 mortality with altitude and population size (pooled total population). Mortality values are expressed per 100 000 inhabitants.



Coefficients

	Estimate	Std. Error	*p* value
Intercept	3.610	9.04×10^{-2}	<0.001 ***
Altitude	-1.642×10^{-4}	-1.928×10^{-5}	<0.001 ***
Population	3.397×10^{-8}	9.489×10^{-8}	0.72

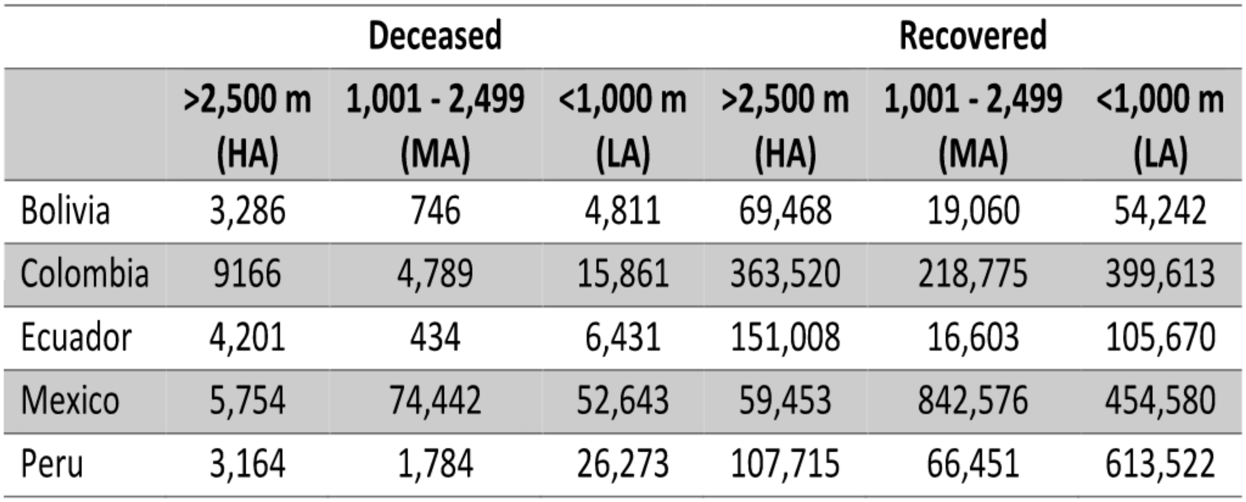
RESIDENCE IN HIGH ALTITUDES REPRESENTS A PROTECTION FACTOR AGAINST COVID-19 MORTALITY.

To determine whether residence at high altitude protects against COVID-19 mortality, we performed separate chi-square tests for each country, comparing the total number of deceased and recovered people in the municipalities located below 1,000 m (low altitude), between 1,001 m and 2,499 m (moderate altitude), and above 2,500 m (high altitude – Table 1). We found significant and strong associations between residence at high and moderate altitudes and lower numbers of deaths in the five countries. In agreement with these findings, the calculated odds ratios revealed that living above 1,000 m is a protective factor against COVID-19 death in the five Latin American countries studied (Table 2).

Discussion

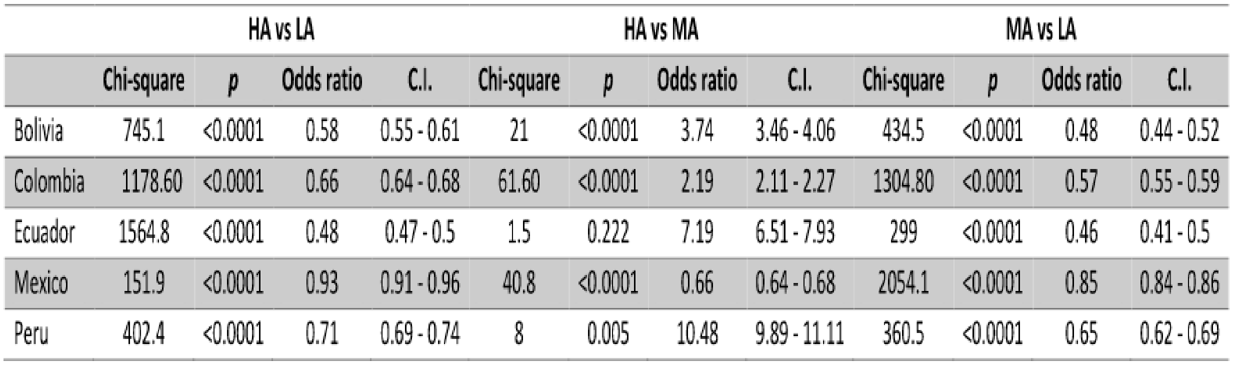
In this paper, we investigated whether living at high altitudes within the tropical and subtropical geographic zone was a protective factor against COVID-19 mortality at the onset of the pandemic when no vaccines were available using data from five Latin American countries. We found that COVID-19 mortality was reduced in the moderate- and high-altitude regions of Bolivia, Colombia, Ecuador, Mexico and Peru compared to the lowlands (< 1,000 m). Thus, residence above 1,000 m altitude in tropical countries was a protective factor against COVID-19 mortality, and the protective effect was independent of population size.

Table 1. Association between the altitude of residence (low, moderate, and high altitude) and COVID-19 mortality.



	Deceased			Recovered		
	>2,500 m (HA)	1,001 - 2,499 (MA)	<1,000 m (LA)	>2,500 m (HA)	1,001 - 2,499 (MA)	<1,000 m (LA)
Bolivia	3,286	746	4,811	69,468	19,060	54,242
Colombia	9166	4,789	15,861	363,520	218,775	399,613
Ecuador	4,201	434	6,431	151,008	16,603	105,670
Mexico	5,754	74,442	52,643	59,453	842,576	454,580
Peru	3,164	1,784	26,273	107,715	66,451	613,522

Table 2. Effect of altitude residence against mortality by COVID-19 evaluated by odds ratios (OR).



	HA vs LA				HA vs MA				MA vs LA			
	Chi-square	p	Odds ratio	C.I.	Chi-square	p	Odds ratio	C.I.	Chi-square	p	Odds ratio	C.I.
Bolivia	745.1	<0.0001	0.58	0.55 - 0.61	21	<0.0001	3.74	3.46 - 4.06	434.5	<0.0001	0.48	0.44 - 0.52
Colombia	1178.60	<0.0001	0.66	0.64 - 0.68	61.60	<0.0001	2.19	2.11 - 2.27	1304.80	<0.0001	0.57	0.55 - 0.59
Ecuador	1564.8	<0.0001	0.48	0.47 - 0.5	1.5	0.222	7.19	6.51 - 7.93	299	<0.0001	0.46	0.41 - 0.5
Mexico	151.9	<0.0001	0.93	0.91 - 0.96	40.8	<0.0001	0.66	0.64 - 0.68	2054.1	<0.0001	0.85	0.84 - 0.86
Peru	402.4	<0.0001	0.71	0.69 - 0.74	8	0.005	10.48	9.89 - 11.11	360.5	<0.0001	0.65	0.62 - 0.69

It is not uncommon to find in the scientific literature a negative conception of the effect of physiological hypoxia at high altitude, regardless of whether it refers to acute, long-term or permanent exposure. In fact, in many medical schools it is still taught that environmental and organismic hypoxia are equivalent and can only be considered detrimental to life and humans [27]. This flawed concept is a legacy of the colonialist mentality of the 20th century [28-30], and must be radically changed in the minds of new physicians and researchers; high-altitude physiology is a heritage of biological richness that hides key secrets for understanding life and discovering new cures. Our work is a wonderful example of the latter, where high-altitude hypoxia has been a key factor in protecting high-altitude populations from a pandemic that has been devastating worldwide. These results align with our previous observations showing that the incidence, severity and transmission capacity of the COVID-19 virus decreases significantly above 1,000 meters of altitude [5]. However, this effect seems to depend on the type of virus. For instance, previous studies have shown that hypobaric hypoxia reduces the incidence of influenza by 35% [31] while the SARS-CoV-2 infection rate decreases by 350% [14]. Thus, this finding suggests that in addition to environmental causes (radiation, temperature, decrease in air density), adaptive physiological factors must also be involved in this phenomenon. Among these factors, angiotensin-converting enzyme 2 (ACE2) [7] and an elevated level of erythropoietin (EPO) [11,12,32] may play an important role. Indeed, ACE2 and EPO are target molecules of Hypoxia Inducible Factor (HIF), master regulator of the response to hypoxia. Furthermore, studies in human lung epithelial cells have shown that hypoxia and pharmaceutical HIF stabilization reduce ACE2 expression and inhibit SARS-CoV-2 entry and replication via a HIF-1α dependent pathway [33], similar to what happens on human pulmonary artery smooth muscle cells (hPASMC) where ACE2 expression decreases dramatically under hypoxic conditions [34]. Analogous studies have also shown decreased expression of ACE2 in cardiac cells from rats exposed to hypoxia for four weeks [39]. Moreover, decreased ACE2 bioavailability in women reportedly explains the lower incidence and mortality of COVID-19 in women than in men [35,36]. Furthermore, it is known that EPO (beyond its canonical role in increasing red blood cells) is produced endogenously by many nonhematopoietic tissues, where it acts as a protective and reparative factor against injury [37]. All these factors may help explain the attenuated effect of SARS-CoV-2 at high altitudes.

Despite all this evidence, certain preliminary studies carried out during the pandemic reported a negative effect of high-altitude hypoxia on the mortality rate [17]. Divergences between those results and ours lie in methodological differences (statistical analyses, data interpretation) and, most importantly, not accounting for the fact that the high-altitude environment of the tropical zone has completely different characteristics from those of the temperate zone. Furthermore, these studies may have also overestimated the risk of mortality due to suboptimal disease diagnosis at the beginning of the pandemic. Indeed, at the beginning of the pandemic, diagnostic tests were performed only in patients presenting symptoms, without considering those who were asymptomatic. Since a higher proportion of asymptomatic cases of COVID-19 have been reported in high-altitude populations[44], the mortality data may have been overestimated.

In conclusion, the highland environment of the tropical and subtropical geographic zone has favored the growth of large human populations. These populations have developed physiological, cellular, subcellular, and molecular characteristics that seem to be responsible, at least in part, for the attenuated effect of the SARS-COV-2 virus mortality. Finally, the results of this work, together with others [5,7-15], strongly suggest that the physiology of highland dwellers is not a simple extension of the physiology described at sea level.

DECLARATION OF INTEREST

None

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