Effect of Altitude on Covid-19 Mortality in Ecuador: an Ecological Study

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Abstract

Background

The SARS-CoV-2/COVID-19 pandemic has claimed nearly 900,000 lives worldwide and infected more than 27 million people. Researchers worldwide are studying ways to decrease SARS-CoV-2 transmission and COVID-19 related deaths. Several studies found altitude having a negative association with both COVID-19 incidence and deaths. Ecuadorian data was used to explore the relationship between altitude and COVID-19.

Methods

This is an ecological study examining province-level data. To explore a relationship between altitude and COVID-19, this study utilized publicly available COVID-19 data and population statistics. ANOVA, correlation statistics, and a multivariate linear model explored the relationship between different Ecuadorian altitudes against incidence, mortality, and case-fatality rates. Populations statistics attributed to COVID-19 were included in the linear model to control for confounding factors.

Results

Regional differences were observed for incidence, mortality, and case fatality rate suggesting an association between altitude and SARS-CoV-2 transmission and COVID-19 disease severity. In both the correlation analysis and linear model altitude showed a statistically significant negative correlation between altitude and COVID-19 mortality.

Conclusion

Altitude may have an effect on COVID-19 mortality rates. More research is needed to understand why altitude may have a protective effect against COVID-19 mortality and how this may be applicable in a clinical setting.

1.0 Background

SARS-CoV-2 was accidently discovered in China towards the end of 2019 when a cluster of unidentified viral pneumonia cases occurred in the Hubei providence. During the initial outbreak, the virus was discovered to cause an acute respiratory syndrome, named coronavirus disease 2019 (COVID-19), mostly affecting the elderly (i.e., over 60 years of age) and individuals with underlying health conditions (1, 2). However, the viral mode of transmission and globalization allowed this regional outbreak to spread throughout the world. By the spring of 2020 SARS-CoV-2 was present in every continent excluding Antarctica (3). At the time this article was written, SARS-CoV-2 has infected more than 27 million individuals worldwide and has caused nearly 900,000 deaths (4). From viral transmission mechanisms (5–8) to COVID-19 treatments (9), researchers are attempting to better understand the disease dynamics and reduce its burden on mankind. The global spread of COVID-19 cases drives research to attempt to understand how environmental factors may contribute to SARS-CoV-2 transmission and COVID-19 disease severity (5, 7, 10–14).

One ecological factor suggesting an effect on viral transmission and disease severity is altitude (14–17). There is growing body of evidence indicating altitude may have an effect on disease incidence (17, 18) as well as overall viral integrity (14–16, 19, 20). One study in particular illustrated a distinct decrease in COVID-19 affected populations above 3,000 meters above sea level (14). Furthermore, an Indian study found a similar conclusion (16). While the two aforementioned studies focused on disease incidence and altitude, there are also studies examining viral properties that may be affected by higher altitudes (15, 20). This associated decrease may be due to biological factors in susceptible humans, environmental factors affecting SARS-CoV-2 and its transmission dynamics, or perhaps a combination of both. Moreover, these studies propose a negative correlation between altitude and disease incidence.
There are few studies investigating the effect altitude may have specifically on COVID-19 mortality (21, 22). Of the two studies found, both offer different conclusions, indicating a need for additional research. One of the studies, conducted in Peru, found high altitude reduced SARS-CoV-2 infection rate, yet the case fatality rate (CFR) was not affected by altitude (21). However, a letter to the editor addressing the aforementioned study suggests their conclusion may be due to differences in regional testing rates (23). Another study examining the CFRs in United States and Mexican residents living at different altitudes concluded the CFR was only statistically lower in men younger than 65 years of age (22). It is evident additional research is required to further explore the relationship between altitude and COVID-19 mortality.

In order to further explore this relationship, the South American country of Ecuador was chosen as the study setting. It is known for its wide range of altitudes and has been significantly impacted by the COVID-19 pandemic. Ecuador contains numerous ecological regions ranging from the Galapagos Islands to the Amazon. In addition to its ecological diversity, Ecuador is home to populations in areas ranging from sea-level to 3000+ meters in altitude. During the early stages of the COVID-19 pandemic, Ecuador became one of the hardest hit South American countries, having one of the highest case fatality rates in the world (24). Its first case, confirmed in February 2020, appeared in its largest city, Guayaquil, and shortly thereafter cases started appearing in the rest of the Ecuadorian provinces (25–27). By the end of August 2020, nearly 100,000 cases and 10,000 deaths were confirmed (28). Ecuador’s high caseload and large altitudinal range provide the perfect setting to explore communities living at different altitudes during this pandemic. This study aims to explore how COVID-19 mortality statistics may be affected by altitude (Fig. 1).

2.0 Methods

2.1 Data Sources

All data used was publicly available and extracted from the Ecuadorian Ministry of Public Health [MOH] and the Ecuadorian National Institute for Statistics and Censuses [INEC]. Statistics on poverty, sex, population density, age groups, and race were taken from the INEC database (29). Additionally, due to the last census taking place in 2010, the INEC 2020 census estimates were used (29). Information included from INEC was based on two criteria: showing relevance to COVID-19 transmission based on current literature and being available on a provincial level. Information relating to COVID-19, such as the confirmed cases and deaths per province was extracted from the MOH monthly COVID-19 bulletin (28).

2.2 Methods

Due to the lack of current population values on the chosen covariates, the estimates for each covariate were taken using the 2020 INEC census estimates and the 2010 covariate proportions. The INEC estimates were combined with the MOH COVID-19 provincial values. Additionally, provinces were categorized into regions (e.g., Amazónica, Sierra [Mountainous], Costa, and Insular [the Galapagos Islands]). Ecuadorian regions are mostly divided on altitude/ecological level, with provinces categorized as “Costa” falling between 50 to 1000 meters, “Sierra” 800 to 3900 meters, “Amazónica” 500 to 1500 meters, and “Insular” 600 meters above sea-level. Due to the possible range of altitudes for each province, the altitude of each province’s capital was used, assuming a significant portion of each province’s population would be located in the capital as well as most of the province hospitals. Furthermore, an ANOVA conducted comparing altitude to region further confirmed this assumption with all regions being statically different and therefore allowing the use of regions as a valid proxy for altitude for the ANOVA. On provincial level, incidence, mortality, and case-fatality rates were calculated. Basic descriptive statistics on regions with provinces as unit of analysis were computed. The ANOVA procedure was used to compare regional incidence, mortality, and case-fatality rates. Due to Insular region having one province, to determine a better fit, an ANOVA was done with and without its inclusion and therefore, the subsequent analyses excluded this region. Univariate procedures to examine the incidence, mortality, and
CFRs distributions were conducted. Due to the covariate data being related specifically to the population and not to outcome, CFR was not deemed appropriate to create exploratory models, and therefore, the model outcome of interest was mortality rate. Correlation statistics were ran on all covariates against mortality rate. Based on the results of the regional ANOVA analysis and the correlation statistics, multivariate linear modeling was conducted. The model aimed to explore if altitude could explain the differences in the regional mortality rates. Due to the natural categorization of provinces, region and altitude were highly intercorrelated and therefore, region was not included in the final model, with altitude being the main area of interest. The final regression model controlled for population density, proportion of males, level of poverty, proportion about the age of 55, and race. Covariates listed were included due to its significance in the literature as potential confounders for COVID-19 mortality, regardless of level of statistical significance in either correlation or model. Statistical significance is defined as having a p-value less than or equal to 0.05. All data was analyzed using SAS/ACCESS® 9.4 software (30).

3.0 Results

3.1 Basic Descriptive Statistics and ANOVA

Twenty-three Ecuadorian provinces were analyzed (n = 11 Sierra, n = 6 Costa, n = 6 Amazónica). Regional differences were observed for mortality, case-fatality, and incidence rates (Table 1). The Amazónica mortality rate mean was 29.96 per 100,000, the Costa mean was 49.46 per 100,000, and the Sierra regional mean was 30.96 per 100,000. The ANOVA result for mortality rates between regions was statistically significant (p-value = 0.05, F-test = 3.44, df = 22). None of the individual regional comparisons were statistically significant (e.g., Sierra versus Costa, etc.). The CFR means for Amazónica, Costa, and Sierra were 2,971.84, 11,934.73, and 5,193.97 per 100,000, respectively. The regional CFR was significantly different (p-value = 0.01, F-test = 6.71, df = 22) and there were statistically significant region comparisons by Costa vs. Sierra and Costa vs. Amazónica (p-value < 0.05). The mean incidence rates for Amazónica, Costa, and Sierra were 1,074.86, 461.16, and 628.32 per 100,000, respectively. The regional incidence rates were significantly different (p-value < 0.0001, F-test = 18.64, df = 22), with Amazónica having a significantly higher incidence rate compared to both Costa and Sierra (p-value < 0.05).

| Indicator          | Costa  | Amazónica | Sierra |
|--------------------|--------|-----------|--------|
| Mortality rate**   | 49.45  | 29.96     | 30.96  |
| Case Fatality rate*| 11,934.73 | 2,971.84 | 5,193.97 |
| Incidence rate*    | 461.16  | 1,074.86  | 628.32 |

* p-value < 0.05 ** p-value = 0.05 Measured by F-test (ANOVA)

3.2 Correlations

Correlation statistics between the covariates and the mortality rate were ran to explore any association between both independent and dependent variables that may be important to note in the final linear model. Altitude and Race (Other) were the only two statistically significant correlations to the mortality rate. Altitude showed a negative correlation of -0.45 (p-value = 0.03) and Race (Other) of 0.61 (p-value = 0.002). All other covariates showed small correlations against mortality rate.
3.3 Linear Model

The final linear model included population density, proportion of males, poverty level, proportion above 55 years of age, altitude, and Race (White) (Table 2). The model was nonsignificant with a p-value of 0.06 and explained 50% of the variance in mortality rate. Individually, altitude was statistically significant with a p-value of 0.01. Population density was the next closest to significance at p-value = 0.06. No other risk factors were statistically significant.

\[
\text{Mortality Rate} = 61.37 + 0.17 (\text{population density}) - 0.78 (\text{male}) + 0.29 (\text{poverty}) \\
-0.02 (\text{altitude}) + 1.76 (\text{above 55yrs}) - 520.52 (\text{white})
\]

Table 2

| Risk factor     | Univariate Estimates | Multivariate Estimates |
|-----------------|----------------------|-----------------------|
| Altitude        | -0.006*              | -0.015*               |
| Poverty         | 0.319                | 0.293                 |
| Male            | -0.047               | -0.775                |
| Population density | 0.031              | 0.170**               |
| Population > 55 years | -0.632           | 1.756                 |
| White           | 144.087              | -520.517***           |

*p-value < 0.05 **p-value = 0.06 ***p-value = 0.09 Measure by F-test (ANOVA)

4.0 Discussion

Results from the ANOVA regional analysis clearly indicated a difference between incidence, case-fatality, and mortality rates. Amazónica had the highest incidence yet the lowest case-fatality and mortality rates. Compared to the other regions, Amazónica had the highest poverty level and proportion of males which are believed to be positively associated with higher COVID-19 morbidity and mortality (31, 32) and lowest population density, which is associated with lower incidence (31), potentially contradicting our observations. The high incidence rate in the Amazónica region may be explained by case misclassification with reports showing concern for potential dengue cases being diagnosed as COVID-19 (33). Specifically in Ecuador, dengue misclassification and underreporting is a current concern during the COVID-19 pandemic (34). This could explain the significantly higher incidence rate in the Amazónica, yet lowest morality statistics. Furthermore, it is well known due to the lack of sufficient health care facilities in the Amazónica, most morbidity indicators are underreported. Conversely, the Costa region held the lowest incidence rate and highest case-fatality and mortality rate. Although the Costa region’s mortality rate was not statistically different than the Sierra region, the case-fatality rate was significantly higher. Since case-fatality rate is an indicator based on the number of deaths and the number of cases, not taking into account the population, it is important to acknowledge the differences in the number of case deaths varying from region to region. The high CFR in the Costa region may be due to a higher population density than both other regions. However, one of the strongest risk factors found in the literature for COVID-19 mortality, advanced age (2, 32), was significantly the highest in the Sierra region. This could indicate not only altitude differences but also resource-oriented healthcare factors which could explain the higher mortality statistics in the Costa region (35, 36).
In both the correlation analysis and the linear model, altitude was a protective factor against COVID-19 mortality. Based on standardized estimates, altitude was the factor with the highest effect on mortality rates followed by population density and identifying as White. The rest of the covariates in the model were not statistically significant nor had large effect on mortality rate. While, race (Other) was statistically significant in the correlation analysis, the proportion of the population identifying as “Other” was too small to be clinically relevant. White race fit the model best and therefore included in the model. Deemed COVID-19 risk factors, the covariates lack of significance may be due to lack of statistical power.

Several hypotheses have been proposed as possible explanations for the protective nature of altitude. One hypothesis focuses on the effects of chronic hypoxia in high altitude environments (37). Specifically, examining the effects of chronic hypoxia on Angiotensin-converting enzyme 2 (ACE2), the enzyme SARS-CoV-2 binds to enter host cells. Under conditions of chronic hypoxia, Angiotensin-converting enzyme 1 (ACE1) is upregulated by Hypoxia inducible factor 1 (HIF-1) in human pulmonary artery smooth muscle cells shifting the balance of the oxygen sensitive renin–angiotensin system (RAS) away from the vasodilator ACE2 and towards the vasoconstrictor ACE1. This process markedly decreases ACE2 expression in the pulmonary artery smooth muscle cells (17, 18). Due to SARS-CoV-2 utilization of the ACE2 receptor for cellular entry, it is hypothesized populations living in constant hypoxia may be less susceptible to SARS-CoV-2 infection. Additionally, HIF-1, activated in chronic hypoxia, may ameliorate a COVID-19 infection (38). In addition to biological mechanisms that may be affected by living in higher altitudes, environmental factors are also theorized reasons for the observed negative correlation between altitude and COVID-19 mortality. A possible explanation of decreased SARS-CoV-2 infection rates in populations at high elevation is a higher level of O₃ (ozone). Considered a disinfecting agent, ozone disrupts the reproductive cycle via peroxidation, affecting virus-to-cell contact and damaging the viral capsid (15, 39). Further suggesting the potential impact ozone may have on SARS-CoV-2 transmission, one study, conducted from January to March 2020, showed a statistically significant negative correlation between ambient average ozone levels and number of confirmed cases (40). Lastly, another common element found in high altitudes an increase of ultraviolet (UV) radiation. UV radiation was found to effectively eliminate SARS-CoV (41), suggesting a similar effect for SARS-CoV-2. However, studies on this hypothesis are limited and a recent study found no association between UV radiation and COVID-19 cases (42). In addition to the sterilization effect of UV radiation, UV radiation’s effect on Vitamin D production is also an area of interest. Vitamin D is theorized to help maintain a healthy immune system and its deficiency is associated with increased risk of respiratory infectious diseases (43–46). This is further supported by recent studies examining finding a protective effect of Vitamin D₃ against COVID-19 (47, 48).

Lastly, there may be behavioral factors affecting the relationship between COVID-19 mortality and altitude. Numerous other socioeconomic and lifestyle factors could explain the differences seen in regard to the infectivity and mortality in high altitude populations. A recent publication cautioned the researchers against associating altitude to decreased COVID-19 pathogenicity based solely on altitude arguing factors such as population density, access to commodities, clinical care, and ability to “social distance” may all be contributing to the observed reduced pathogenicity (49). Health benefits of communities living in high altitude is not new knowledge, with high altitude associated with higher levels of physical activity, lower rates of obesity, cardiovascular disease, and cancer (50–52).

Limitations in the study mainly include lack of access to smaller unit-sized data and individual data. This study is an ecological study, focusing on province-level data, and should be noted that there may be individual cities that may be influential or leveraging the results. Regardless, of the limitations, altitude was significantly protective against COVID-19 mortality rate in both the correlation analysis and final model.

5.0 Conclusion
Altitude was a protective factor against COVID-19 mortality. More research is needed in understanding why populations living in different altitudes may have different disease outcomes. Furthermore, in the Ecuador population there seemed to be a protective factor in COVID-19 mortality and identifying as White. Although not statically significant, this finding may be of clinical relevance and help identify areas of improvement in Ecuadorian healthcare.

**Declarations**

**Ethics approval and consent to participation**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets analyzed during the current study are publicly available from the Ecuadorian Ministerio de Salud Publica national COVID-19 bulletins, [https://www.salud.gob.ec/wp-content/uploads/2020/08/INFOGRAFIA-NACIONALCOVID19-COE-NACIONAL-08h00-25082020.pdf](https://www.salud.gob.ec/wp-content/uploads/2020/08/INFOGRAFIA-NACIONALCOVID19-COE-NACIONAL-08h00-25082020.pdf) and the Ecuadorian Instituto National de Estatisticas y Censos [https://www.ecuadorencifras.gob.ec/estadisticas/](https://www.ecuadorencifras.gob.ec/estadisticas/).

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

AC performed data analysis and was the major contributor in writing the manuscript. BS performed a literature review of the subject and was a major contributor of the manuscript. JP cleaned, analyzed, and created the models for the study in addition to being a major contributor in writing the manuscript. SH cleaned, pulled data, and was a major contributor in writing the manuscript. RI and ET were major contributors in the planning and interpretation of the data, as well as contributing to the manuscript.

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Not applicable

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