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Effect of High Altitude on the Survival of COVID-19 Patients in Intensive Care Unit: A Cohort Study

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Abstract

Purpose: The effect of high altitude ($\geq$ 1500 m) and its potential association with mortality by COVID-19 remains controversial. We assessed the effect of high altitude on the survival/discharge of COVID-19 patients requiring intensive care unit (ICU) admission for mechanical ventilation compared to individuals treated at sea level. **Methods:** A retrospective cohort multi-center study of consecutive adults patients with a positive RT-PCR test for COVID-19 who were mechanically ventilated between March and November 2020. Data were collected from two sea-level hospitals and four high-altitude hospitals in Ecuador. The primary outcome was ICU and hospital survival/discharge. Survival analysis was conducted using semi-parametric Cox proportional hazards models. **Results:** Of the study population (n = 670), 35.2% were female with a mean age of 58.3 $\pm$ 12.6 years. On admission, high-altitude patients were more likely to be younger (57.2 vs. 60.5 years old), presented with less comorbidities such as hypertension (25.9% vs. 54.9% with *p*-value <.001) and diabetes mellitus (20.5% vs. 37.2% with *p*-value <.001), less probability of having a capillary refill time > 3 sec (13.7% vs. 30.1%, *p*-value <.001), and less severity-of-illness condition (APACHE II score, 17.5 $\pm$ 8.1 vs. 20 $\pm$ 8.2, $p < .01$). After adjusting for key confounders high altitude is associated with significant higher probabilities of ICU survival/discharge (HR: 1.74 [95% CI: 1.46-2.08]) and hospital survival/discharge (HR: 1.35 [95% CI: 1.18-1.55]) than patients treated at sea level. **Conclusions:** Patients treated at high altitude at any time point during the study period were 74% more likely to experience ICU survival/discharge and 35% more likely to experience hospital survival/discharge than to the sea-level group. Possible reasons for these findings are genetic and physiological adaptations due to exposure to chronic hypoxia.

Keywords

COVID-19, SARS-CoV-2, high altitude, survival, ICU, sea level

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Introduction

The respiratory disease COVID-19 caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become one of the most important contemporary public health problems. So far, there have been more than 260 million confirmed cases and 5 million deaths worldwide,[1] many due to refractory hypoxemia. Several individual risk factors that increase the mortality of patients with COVID-19 have been identified, such as age, hypertension, diabetes, cardiovascular disease, chronic obstructive lung disease, obesity, and others.[2] Further, environmental factors such as high altitude spurred the interest of researchers as a potential modulator of infection and mortality rates since the very beginning of the COVID-19 pandemic.[3]

Reports in the literature have evaluated high-altitude infection rates and their associated relationship with mortality by COVID-19,[3-9] but none of them have studied the course of critically ill patients. Most of these studies reported lower infection and mortality rates in high-altitude regions than in sea-level regions in the same countries.[3-5,7,8] However, some studies reported no association with high altitude or even increased mortality in high-altitude regions.[6,7,9] Yet, the major limitation of these previous reports is that they have used population-level data, thus diminishing the possibility to control for potential confounders at the individual level, which ultimately jeopardized the robustness to give insight regarding infection and survival rates by COVID-19 in high altitudes. Further, these studies have not evaluated critically ill patients or those admitted to intensive care units (ICUs) and how geographical altitude could affect the treatment modality and survival rate.

Leveraging the geographical location of Ecuador, which has communities living from 0 to more than 4000 m above sea level,[10] allows us to assess the effect of high altitude on the survival of patients diagnosed with COVID-19 admitted to ICUs across the country. Based on the latest official census done in Ecuador in 2010, around 2,756,420 (15.4%) Ecuadorians live in areas above 2500 m sea level.[9] As in the rest of the world, Ecuador has also been deeply affected by COVID-19, as of 6 February 2022, more than 730,000 confirmed cases and 34,572 deaths,[1] placing Ecuador as one of the most affected countries in South America.

The present study hypothesized that after adjusting for key confounding variables, patients treated in ICUs in high-altitude regions are more likely to survive/discharge than their counterparts in sea-level regions. To answer this research question, we built a cohort study using individual-level data from six hospitals located across Ecuador.

Materials and Methods

Using a multicentric, retrospective cohort study, we assessed the effect of high altitude on the survival/discharge of COVID-19 patients treated in ICUs in Ecuador when adjusting for potential confounders.

Study Setting

The geographic setting of this study is Ecuador, an Andean country located in South America. Like other Latin American countries, Ecuador has an ethnically and racially diverse population living from 0 to $\geq$ 4000 m above sea level.[10,11] We collected data from six tertiary centers (two sea-level hospitals and four high-altitude hospitals) located in the cities of Babahoyo (3 m above sea level), Portoviejo (53 m above sea level), Ibarra (2225 m above sea level), Cuenca (2560 m above sea level), and Quito (2850 m above sea level).

Study Sample and Data Collection

The study sample consisted of a consecutive sample of all COVID-19 patients treated in ICUs of the participant hospitals from March to November 2020. We included patients who satisfied the following inclusion criteria: i) who were over 18 years old with confirmed COVID-19 by RT-PCR test; ii) admitted to an ICU; iii) who received non-invasive or invasive mechanical ventilation. Within the exclusion criteria were: i) patients admitted to ICU due to another cause besides COVID-19; ii) ventilated patients outside an ICU; iii) patients who had been less than 40 days in the city in which they were hospitalized to avoid misclassification bias due to physiological acclimatization time.[12] In order to collect the necessary study variables, research teams were made up of clinical chiefs and doctors from each invited ICU. They were in charge of collecting pertinent data regarding the hospital/ICU admissions and discharge. All data were collected by the REDCap platform from July 2020 to March 2021.[13] The present study received ethical approval to be conducted by a government *ad hoc* committee created to oversee national COVID-19 research activities (MSP-CGDES-2021-0065-O). Further, this *ad hoc* committee granted a waiver regarding the application of informed consent due to the context of the COVID-19 pandemic.

Measures

The study's primary hypothesis was that COVID-19´s patients treated in ICUs at high altitudes are more likely to survive/discharge from ICU and hospital than their counterparts in sea-level regions. High altitude was defined as terrestrial elevations over 1500 m (4921 ft).[14] It has been reported that PaO_2/F_IO_2 decreases at high altitude thus this value should be adjusted using a mathematical equation (PaO_2/F_IO_2*[barometric pressure/760]).[15,16] Hovewer, we did not follow this recommendation because in a multicenter study we found that in acclimatized patients (which is our case) undergoing invasive mechanical ventilation, the traditional equation for adjusting PaO_2/F_IO_2 according the elevation seems to be inaccurate.[17] In the bivariate analysis we considered the following covariates: APACHE II score, PaO_2/F_IO_2, invasive mechanical ventilation parameters (plateau pressure, driving pressure, and compliance), duration of mechanical ventilation, and ICU length of stay (LOS). For the Cox

regression model we used the following independent variables: age (a binary variable dichotomized by 62); presence of diabetes mellitus and hypertension; hemoglobin concentrations; creatine concentrations (≥ 2 vs. <2 mg/dl); APACHE II score, and capillary refill time.

Statistical Analysis

Descriptive statistics were used to estimate the incidence of survival/discharge among patients diagnosed with COVID-19 and treated in ICUs and to describe the demographic/clinical information retrieved from clinical records. Continuous variables were reported as mean $\pm$ SD or median (IQR), and categorical variables were reported as counts and percentages. Bivariate analysis was performed with parametric (t-test and X^2) and non-parametric (Wilcoxon and Fisher's exact test) tests to assess the relationship between altitude (sea level vs. high altitude) and baseline characteristics of the study population. We used semi-parametric Cox proportional hazards models to estimate the hazard ratios of being at the high altitude to experience ICU survival/discharge or hospital survival/discharge compared with being at sea level. Time to survival/discharge from ICU or hospital among COVID-19 patients treated at sea-level or high-altitude ICUs was portrayed by Kaplan-Meier plots and compared with a log-rank tests. Further, in the present study we did not impute missing data thus we conducted complete case analysis. Results with statistical significance were those with a p-value less than .05. Statistical analyses were done using RStudio software, version 1.4.1106.

Results

The information of 1007 patients admitted to ICU was collected from the participants tertiary care centers, but due to the inclusion and exclusion criteria, the sample size was reduced to 670 patients. Of the 670 patients enrolled, 33.7% (n = 226) resided at sea level and 66.3% (n = 444) above 1500 m. Table 1 summarizes the baseline demographic, laboratory, and clinical characteristics of the study sample. The study participants had a mean age of 58.3 $\pm$ 12.6 years, 35.2% of patients were female, and 98% of the population self identified as mestizo. The group living at high altitude was more likely to be younger (57.2 vs. 60.5 years old, respectively), have a higher median hemoglobin concentration on admission (14.2 vs. 12.8 g/dL), and have fewer comorbidities (20.5% vs. 37.2% with p-value <.001 for diabetes mellitus, and 25.9% vs. 54.9% with p-value <.001 for hypertension). Also, the high-altitude group had less anosmia when compared to the sea-level group (8.3% vs. 23%, p-value <.001). The high-altitude group was less likely to have a capillary refill time >3 sec (13.7% vs. 30.1%, p-value <.001). Regarding inflammatory biomarkers, d-dimer was lower on the high-altitude group, 7.1 versus 850 ng/ml ($p < .01$). Overall, the high-altitude group had a lower severity-of-illness condition (APACHE II score), 17.5 $\pm$ 8.1 versus 20 $\pm$ 8.2 ($p < .01$).

Regarding respiratory parameters and ventilatory management at the ICU admission (Table 2), individuals living at high altitude required less F_IO_2. Overall, the median (IQR) of PaO_2/F_IO_2 ratio in the study population was 92 (65-128), and 54.3% (n = 364) had a PaO_2/F_IO_2 ratio less than 100. No significant differences were found between PaO_2/F_IO_2 ratios and geographic altitude. Approximately 8% (n = 53) of the total population required the use of a high-flow nasal cannula (HFNC), while 15.1% (n = 101) required non-invasive mechanical ventilation (NIMV), and 77% (n = 516) required straight invasive mechanical ventilation. It is worth mentioning that all study participants received a protective mechanical ventilation strategy which is reflected with a median of tidal volume (ml/kg) of 7 (6-8) and a plateau pressure of 24.2 $\pm$ 4.8 (cmH_2O). Patients treated at high altitude were more likely to be ventilated with less plateau pressure (23.3 $\pm$ 4.7 vs. 26.2 $\pm$ 4.6 cmH_2O) and PEEP (9.5 $\pm$ 2.2 vs. 11.8 $\pm$ 3 cmH_2O) than those ventilated at sea level. In addition, individuals ventilated at sea level were more likely to require ventilation in the prone position than at high altitudes, 90.3% versus 66.2% ($p < .001$). Additionally, no ECMO was used in any of our patients.

Table 3 shows that the survival proportion of the ICU patients was higher in the high-altitude compared to the sea-level group, 47.5% vs. 26.5% (p-value <.001), respectively. Further, the survival proportion at hospital discharge was higher in the high-altitude compared to the sea-level group, 45.9% versus 24.3% (p-value <.001), respectively. The survival/discharge trends are depicted in the Kaplan-Meier curves (Log-rank $p < .001$), Figure 1. The Cox regression analysis, Table 4, showed that, adjusting for potentional confounders, individuals living at high altitudes had higher hazards of experiencing ICU survival/discharge (HR: 1.74 [95% CI: 1.46-2.08]) and hospital survival/discharge (HR: 1.35 [95% CI: 1.18-1.55]) than individuals treated at sea level.

Discussion

This is the first cohort multicentric study that assesses a large sample of mechanically ventilated patients admitted to the ICU due to COVID-19 in Ecuadorian hospitals. Upon admission to ICU, most of our sample study was categorized as being severely ill. Out of our 670 patients, 364 (54.3%) had a PaO_2/F_IO_2 lower than 100, with a median of 70 (53-85). Moreover, we find that after adjusting for the potential confounders, the ICU patients in the high-altitude group were 74% more likely to experience ICU survival/discharge than patients in the sea-level group, and were 34% more likely to experience hospital survival/discharge compared with patients at sea-level group at any time during the study.

Comparison with Other Studies

This finding is aligned with the work of other studies assessing the effect of high altitude and mortality attributed to COVID-19.[3-5,8] These previous studies using aggregate-level data found lower mortality by COVID-19 in high-altitude

Table 1. Baseline Characteristics of COVID-19 Patients Admitted to the Intensive Care Unit by Geographic Residence.

Variable	All n = 670	At Sea Level n = 226	High altitude n = 444	*p*-value	Missing values n (%)
Demographic characteristics					
Age (yr), mean ± SD	58.3 ± 12.6	60.5 ± 11.9	57.2 ± 12.7	<.001	—
Female sex, n(%)	236 (35.2)	81 (35.8)	155 (34.9)	.87	—
Race, n(%)				.75	—
White	1 (0.14)	0	1 (0.2)		
Mestizo	657 (98)	221 (97.8)	436 (98.2)		
Indigenous	8 (1.2)	4 (1.8)	4 (0.9)		
Black (Afro-Ecuadorians)	4 (0.6)	1 (0.4)	3 (0.7)		
Comorbities, n(%)					
Diabetes mellitus	175 (26.1)	84 (37.2)	91 (20.5)	<.001	—
Hypertension	239 (35.7)	124 (54.9)	115 (25.9)	<.001	—
Acute myocardial infarction	6 (0.9)	2 (0.9)	4 (0.9)	1	—
Body-mass index, median (IQR)	27.5 (24.6-30.5)	27.9 (25.5-30.1)	27.3 (24.3-30.5)	.22	96 (14.3)
Category of body-mass index				.15	—
<18.5	7 (1.2)	1 (0.7)	6 (1.4)		
18.5 to 24.9	150 (26.1)	28 (20.7)	122 (27.8)		
25 to 29.9	251 (43.7)	70 (51.8)	181 (41.2)		
>30	166 (28.9)	36 (26.7)	130 (29.6)		
Symptoms on admission, n(%)					
Fever	485 (72.4)	169 (74.8)	316 (71.2)	.37	—
Cough	533 (79.5)	166 (73.4)	367 (82.6)	<.01	—
Headache	214 (31.9)	75 (33.2)	139 (31.3)	.68	—
Rhinorrhea	31 (4.6)	16 (7.1)	15 (3.4)	.04	—
Myalgia	275 (41)	96 (42.5)	179 (40.3)	.65	—
Chest Pain	56 (8.3)	21 (9.3)	35 (7.9)	.63	—
Vomit	40 (5.9)	23 (10.2)	17 (3.8)	<.01	—
Diarrhea	109 (16.3)	29 (12.8)	80 (18)	.11	—
Anosmia	89 (13.3)	52 (23)	37 (8.3)	<.001	—
Dysgeusia	27 (4)	9 (3.9)	18 (4)	1	—
Other	49 (7.3)	2 (0.9)	47 (10.6)	<.001	—
Physiological parameters on admission					
Temperature, mean ± SD	36.7 ± 0.72	36.7 ± 0.70	36.7 ± 0.73	.93	—
Systolic blood pressure mm Hg, mean ± SD	123.6 ± 22.2	125.5 ± 24	122.6 ± 21.2	.13	—
Cardiac frequency, mean ± SD	92.8 ± 20.1	95.6 ± 21.3	91.4 ± 19.3	<.01	—
Respiratory rate, median (IQR)	28 (22-32)	28 (24-32)	28 (22-32)	.30	—
Oxygen saturation %, median (IQR)	89 (80-92)	90 (82-96)	88 (80-90.2)	<.001	1 (0.15)
Capillary refill time >3 s, n(%)	129 (19.2)	68 (30.1)	61 (13.7)	<.001	—
Laboratories on admission					
Complete Blood Count					
Leucocytes, $\times 10^3$ cells, median (IQR)	10 940 (6302-15 185)	11 645 (898-15 375)	10 380 (6443-15 000)	.87	—
Hemoglobin g/dl, median (IQR)	13.8 (12-15)	12.8 (11.4-14)	14.2 (12.8-15.6)	<.001	—
Glucose mg/dl, median (IQR)	143 (117-186)	153 (123-209)	140 (115-175.3)	<.001	29 (4.3)
Arterial blood gases					
Lactate mmol/l, median (IQR)	1.63 (1.1-2.5)	1.2 (0.97-1.84)	1.9 (1.2-2.7)	<.001	113 (16.9)
Liver function tests					
Total bilirubin mg/dl, median (IQR)	0.69 (0.50-1.00)	0.80 (0.60-1.10)	0.66 (0.47-1.00)	<.01	173 (25.8)
Alanine transaminase (ALT) U/l, median (IQR)	46 (30-75)	47 (31-76.2)	45 (28-73)	.19	70 (10.4)
Aspartate transaminsase (AST) U/l, median (IQR)	47.4 (33-72)	45 (33-70)	48 (33-72)	.56	68 (10.1)
Renal function tests					
Urea nitrogen mg/dl, median (IQR)	24 (15.9-40)	24 (15-36)	23 (16.4-42.9)	.34	185 (27.6)
Serum creatinine mg/dl, median (IQR)	0.87 (0.67-1.27)	0.94 (0.78-1.4)	0.81 (0.64-1.15)	<.001	—
Coagulation times					
Prothrombin Time (PT) seconds, median (IQR)	13.2 (12-14.6)	14 (12.9-15.3)	13 (12-14.4)	<.001	138 (20.6)

(continued)

Table 1. (continued)

Variable	All n = 670	At Sea Level n = 226	High altitude n = 444	*p*-value	Missing values n (%)
Partial Thromboplastin Time (PTT) seconds, median (IQR)	33 (28.3-40)	31.9 (27.6-36.2)	33.2 (28.5-40.4)	.02	139 (20.7)
International Normalized Ratio (INR), median (IQR)	1.2 (1.1-1.3)	1.2 (1-1.4)	1.2 (1.1-1.3)	.35	142 (21.2)
D-dimer ng/ml, median (IQR)	13.8 (2.16-1000)	850 (10-4375)	7.1 (1.4-550)	<.001	328 (48.9)
Ferritin ng/ml, median (IQR)	1259 (709-1884)	1302 (781-2000)	1250 (675-1721)	.08	194 (28.9)
Severity of disease					
APACHE II score, mean (SD)	18.4 ± 8.2	20 ± 8.2	17.5 ± 8.1	<.001	7 (1)
SOFA score, median (IQR)	7.8 (4-11)	7 (4-10)	7 (4-11)	.81	1 (0.15)

SD, Standard deviation; IQR, Interquartile range.

Table 2. Respiratory Parameters and Ventilatory Management at Intensive Care Unit Admission by Geographic Altitude.

Variable	All n = 670	At Sea Level n = 226	High altitude n = 444	*p*-value	Missing values n (%)
F_IO_2, median (IQR)	80 (56-100)	100 (90-100)	65 (50-100)	<.001	—
PaO_2/ F_IO_2 Ratio, median (IQR)	92 (65-128)	91 (64-139)	92.5 (66-125)	.37	21 (3.1)
PaO_2/ F_IO_2 Ratio < 300, median (IQR)[c]	213 (206-249)	228 (212-257.5)	212 (203-243)	.24	—
PaO_2/ F_IO_2 Ratio < 200, median (IQR)[b]	128 (114-150)	133 (111-159)	127 (114-149)	.26	—
PaO_2/ F_IO_2 Ratio < 100, median (IQR)[a]	70 (53-85)	66.5 (52-83.7)	73 (54-85)	.12	—
Use of high-flow nasal cannula, n (%)	53 (7.9)	39 (17.2)	14 (3.1)	<.001	—
Use of noninvasive mechanical ventilation, n (%)	101 (15.1)	5 (2.2)	96 (21.6)	<.001	—
Invasive mechanical ventilation					
Tidal volume (ml/kg ideal body weight), median (IQR)	7 (6-8)	6 (5-7)	7 (6-9)	<.001	184 (27.4)
Plateau pressure (cmH_2O), mean ± SD	24.2 ± 4.8	26.2 ± 4.6	23.3 ± 4.7	<.001	154 (22.9)
Driving pressure (cmH_2O), mean ± SD	14.1 ± 3.9	14.2 ± 3.7	14 ± 4.1	.67	208 (31)
PEEP (cmH_2O), mean ± SD	10.2 ± 2.7	11.8 ± 3	9.5 ± 2.2	<.001	54 (8.1)
Compliance (ml/cmH_2O), median (IQR)	28.5 (22-35)	27 (20-32)	30 (22-39)	.01	185 (27.6)
Prone position, n(%)	498 (74.3)	204 (90.3)	294 (66.2)	<.001	—

F_IO_2, Fraction of inspired oxygen; PaO_2, Partial pressure of oxygen; IQR, Interquartile range; PEEP, Positive end-expiratory pressure.
[a]This category includes 364 individuals (At Sea level, n = 110; High altitude, n = 254).
[b]This category includes 240 individuals (At Sea level, n = 72; High altitude, n = 168).
[c]This category includes 34 individuals (At Sea level, n = 15; High altitude, n = 19).

Table 3. Clinical Outcome.

Variable	All n = 670	At Sea Level n = 226	High altitude n = 444	*p*-value	Missing values n(%)
Duration of mechanical ventilation, days, median (IQR)	10 (6-16)	10 (6-17)	9 (6-15)	.11	28 (4.2)
ICU length of stay, days, median (IQR)	11 (6-17)	11 (6-19)	10 (6-17)	.24	—
Hospital length of stay, days, median (IQR)	17 (10-25)	17 (9-26)	16.5 (11-24)	.47	—
Survival to ICU, n (%)	271 (40.4)	60 (26.5)	211 (47.5)	<.001	—
Overall survival to hospitalization, n (%)	259 (38.6)	55 (24.3)	204 (45.9)	<.001	—

IQR, Interquartile range; ICU, Intensive care unit.

regions of Tibet, Bolivia, USA, and Peru. In addition, an epidemiological analysis of 23 American countries found that the incidence, the transmission capacity and the severity of COVID-19 significantly decrease starting at 1000 m above sea level.[18] On ther other hand, previous studies conducted in Peru, USA, and Mexico, have shown that the mortality rate by COVID-19 is not dependent on altitude, or on the contrary, that the mortality rate can be higher in high-altitude regions.[6,7,9] A potential reason for the difference in results could be that these studies used population-level data and were not able to adjust for key confounders at the individual level.

The mortality rate in patients diagnosed with COVID-19 undergoing mechanical ventilation has been widely discussed in various studies, ranging from 28% to 35% in New York

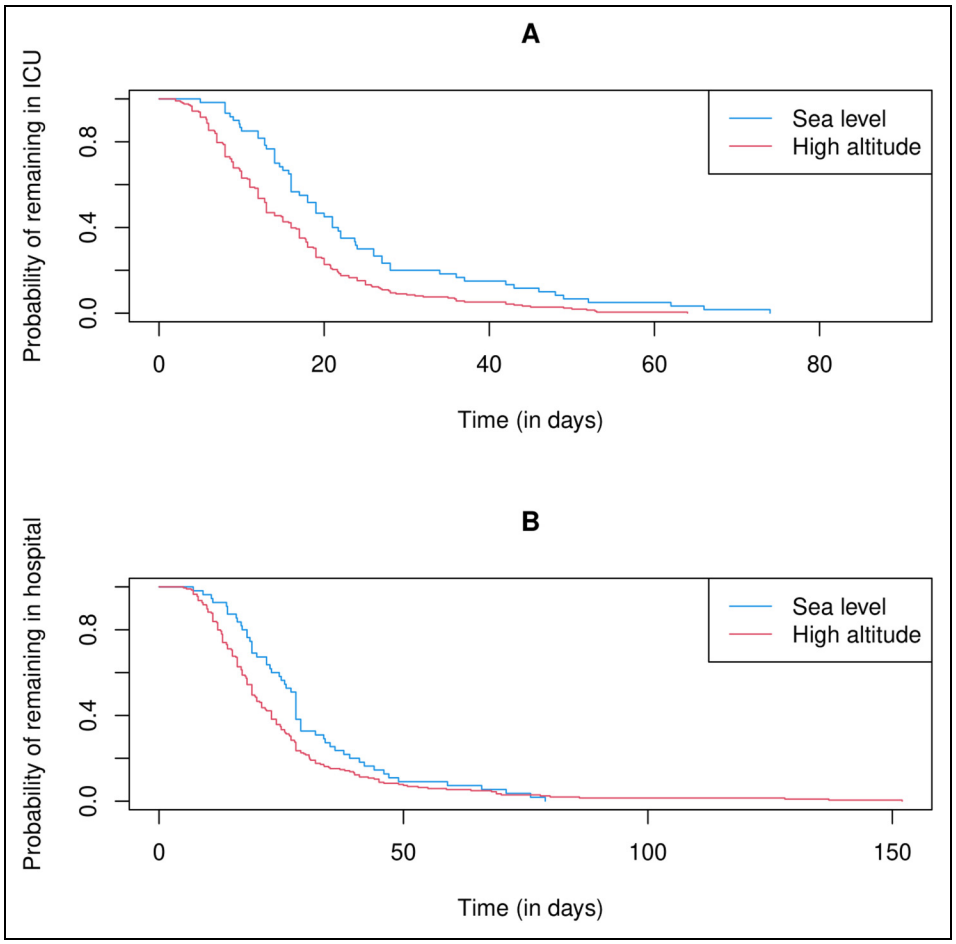

Figure 1. Kaplan-Meier analysis of the primary outcome in the study population. Panel A shows the probability of being discharged from Intensive Care Unit. Panel B shows the probability of being discharged from Hospital. In overall, for a given time, the probability of being discharged alive at sea level is smaller than the probability at high altitude.

and Europe,[19-21] and even higher rates such as 57% in Argentina, 76% in Mexico, and 80% in Brazil.[22-24] Our cohort found overall ICU mortality of 59.6% with a statistical difference by geographic altitude (73.5% at sea level vs. 52.5% at high altitude, $p < .001$).

This higher survival at high altitude could be explained by several factors, including i) genetic and physiological adaptations which allow individuals living at high altitude in the Andes region to have an efficient adaptation to chronic hypoxia.[25,26] Some examples of these adaptations include somewhat larger lung volumes, higher arterial oxygen content, and increase cardiac O_2 utilization.[26,27] Contemporary single nucleotide polymorphism and whole-genome sequencing studies have disclosed the multiple gene regions involved in this process (eg, *EGLN1*).[25,27,28]; ii) reduction in the ACE2 receptor expression in epithelial cells due to the chronic hypoxia which could reduce the binding of the S protein of COVID-19 to host cells.[3,8,28,29] However, this claim remains speculative and needs to be confirmed[30]; iii) living with chronic hypoxia may also boost antioxidant systems, mitochondrial function and immune capacities.[31] In addition, chronic hypoxia induces a constant state of inflammation among healthy people living at high altitude. Valle-Mendoza and colleagues, found that COVID-19 patients and healthy individuals living at high altitude had higher concentrations of inflammatory cytokines (IL-6 and TNF- α) than patients/individuals living at sea level.[28] This constant exposure to inflammatory factors has been proposed to induce an adaptation and immune tolerance[32] which ultimately might cause patients with COVID-19 to develop less severe disease.[28]

Noninvasive respiratory support strategies used in this study such as HFNC and NIMV were lower compared to other studies treated COVID-19 patients,[33-36] 7.9% and 15.1%, respectively. A possible explanation for this finding is that the present study reports COVID-19 cases treated during the first wave of the pandemic in Ecuador. Hence, during this time the use of HFNC and NIMV were not common among local critical care physicians compared to others waves of the pandemic.

Strengths and Limitations

Our investigation has several strengths. First, to our knowledge, this is the first cohort study that analyzes the effect of altitude on

Table 4. Association of Geographic Residence (High Altitude vs sea Level) with Intensive Care Unit and Hospital Discharge.

	Time to ICU discharge[a]		Time to hospital discharge[b]	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Geographic residence				
Sea level	1.0§		1.0§	
High altitude (≥ 1500 m)	1.74 (1.46-2.08)	<.001	1.35 (1.18-1.55)	<.001
Age				
<62 years old	1.0§		1.0§	
≥ 62 years old	0.90 (0.71-1.14)	.40	0.96 (0.76-1.21)	.74
Diabetes				
No	1.0§		1.0§	
Yes	0.97 (0.61-1.55)	.90	1.23 (0.98-1.53)	.07
Hypertension				
No	1.0§		1.0§	
Yes	0.86 (0.77-0.97)	.01	0.73 (0.68-0.78)	<.001
Capillary refill time				
<3 seconds	1.0§		1.0§	
>3 seconds	0.96 (0.85-1.07)	.47	0.84 (0.53-1.34)	.47
Hemoglobin, g/dl				
Low	1.0§		1.0§	
Normal[c]	1.19 (0.95-1.49)	.13	1.16 (1.03-1.32)	.02
Creatinine				
<2 mg/dl	1.0§		1.0§	
≥ 2 mg/dl	0.77 (0.61-0.96)	.02	0.72 (0.62-0.84)	<.001

ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.
§Reference group.
[a]Correspond to the time origin as admission to hospital and end point as ICU discharge.
[b]Correspond to the time origin as admission to hospital and end point as hospital discharge.
[c]Defined as ≥ 12 g/dl at sea level and ≥ 15 g/dl at high altitude.

the survival of patients with COVID-19, which allows clarity of the temporal sequence of the outcome. Second, we built a Cox proportional hazards models for time to two events of interests (ICU discharge and hospital discharge) where we adjusted to a key set of confounders. Third, our findings are based on a heterogeneous population characteristic of a Latin American country. Fourth, due to the geographical location of Ecuador, the findings would not be affected by seasonality interaction. Limitations of the current work must also be considered. Due to the significant challenges (economic, medical equipment/supply, and human resources) imposed by the COVID-19 pandemic on private and public health hospitals, we had important missing values in key biomarkers, such as d-dimer and ferritin. Also, the study did not assess differences in coagulation parameters or inflammatory cytokines. In addition, admission criteria were affected by the pressure of each surge and available ICU resources, and no standardized guidelines for ICU triage were followed. Further, inherent to the retrospective design, the absence of data on potential confounding factors cannot be discarded such as air pollution, socioeconomic status and chronic lung-related diseases. Survival analysis was performed to adjust for confounding factors, but the possibility of considerable residual confounding remains. Lastly, follow-up was limited to the hospitalization period, and no information is available on the impact on quality-of-life post-discharge or residual sequela, such as post-COVID-19 acute syndrome.

Clinical Implications

There is a large population living in high-altitude areas, for example, 140 million people live in high-altitude areas above 2500 m above sea level; from those, 80 million are from Asia, and 35 million are from South America.[37] Unfortunately, despite this scenario there is no consensus regarding how mechanical ventilation should be modified in this situation. There is abundant information regarding mechanical ventilation,[38-40] but the majority does not consider the effect of geographical altitude. This study is one of the first to take into consideration this important parameter, giving primary results from which further investigations can develop. These differences can translate into different oxygenation and ventilation strategies. Further investigations are needed to elucidate the biological and environmental pathways involved in the higher survival that could improve clinical management of COVID-19 patients treated at high-altitude areas.

Conclusions

In summary, this multicenter cohort study found that ICU patients in the high-altitude group were 74% more likely to experience ICU survival/discharge than patients in the sea-level group, and were 34% more likely to experience hospital survival/discharge compared with patients at sea-level group. This diference could be

due to genetic and physiological adaptations of individuals living at high altitude that might allow them a more efficient handling of chronic hypoxia, prevent against tissue damage and immune tolerance to constant inflammation.

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Declaration of Conflicting Interests

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Data Availability

Data are available on reasonable request to the corresponding author.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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