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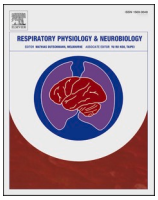

Oxygen therapy limiting peripheral oxygen saturation to 89-93% is associated with a better survival prognosis for critically ill COVID-19 patients at high altitudes

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ABSTRACT

Patients admitted to the Intensive Care Unit (ICU) with acute hypoxemic respiratory failure automatically receive oxygen therapy to improve inspiratory oxygen fraction (FiO_2). Supplemental oxygen is the most prescribed drug for critically ill patients regardless of altitude of residence. In high altitude dwellers (i.e. in La Paz [≈3,400 m] and El Alto [≈4,150 m] in Bolivia), a peripheral oxygen saturation ($SatpO_2$) of 89-95% and an arterial partial pressure of oxygen (PaO_2) of 50-67 mmHg (lower as altitude rises), are considered normal values for arterial blood. Consequently, it has been suggested that limiting oxygen therapy to maintain $SatpO_2$ around normoxia may help avoid episodes of hypoxemia, hyperoxemia, intermittent hypoxemia, and ultimately, mortality. In this study, we evaluated the impact of oxygen therapy on the mortality of critically ill COVID-19 patients who permanently live at high altitudes. A multicenter cross-sectional descriptive observational study was performed on 100 patients admitted to the ICU at the "Clinica Los Andes" (in La Paz city) and "Agramont" and "Del Norte" Hospitals (in El Alto city). Our results show that: 1) as expected, fatal cases were detected only in patients who required intubation and connection to invasive mechanical ventilation as a last resort to overcome their life-threatening desaturation; 2) among intubated patients, prolonged periods in normoxia are associated with survival, prolonged periods in hypoxemia are associated with death, and time spent in hyperoxemia shows no association with survival or mortality; 3) the oxygenation limits required to effectively support the intubated patients' survival in the ICU are between 89% and 93%; 4) among intubated patients with similar periods of normoxemic oxygenation, those with better SOFA scores survive; and 5) a lower frequency of observable reoxygenation events is not associated with survival. In conclusion, our findings indicate that high-altitude patients entering an ICU at altitudes of 3,400 – 4,150 m should undergo oxygen therapy to maintain oxygenation levels between 89 and 93 %.

Abbreviations: ICU, intensive care unit; FiO_2, inspired oxygen fraction; PaO_2, arterial partial pressure of oxygen; PB, barometric pressure; ARDS, acute respiratory distress syndrome; NIV, non-invasive ventilation; HFNC/NRM, high-flow nasal cannula or non-rebreather masks; ETI, intubated; $SatpO_2$, Peripheral oxygen saturation; APACHRE, Acute Physiological and Chronic Health Evaluation; SOFA, Sepsis Organ Failure Assessment; Nx, normoxemia; Hx, hypoxemia; Hpx, hyperoxemia.

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1. Introduction

The administration of supplemental oxygen to improve the inspired oxygen fraction (FiO_2) in patients admitted to the intensive care unit (ICU) with hypoxemic acute respiratory failure is a controversial issue for clinicians (Schjorring et al., 2021). In fact, at sea level, some clinical studies showed that 100% oxygen therapy was associated with increased mortality (Bellani et al., 2016; Schjorring et al., 2020). These findings suggest that limiting peripheral oxygen saturation may avoid fatal adverse events (Panwar et al., 2016). In line with these results, the treatment of patients with an arterial partial pressure of oxygen (PaO_2) between 70-100 mmHg has reportedly a lower fatality rate than patients treated with PaO_2 greater than or equal to 150 mmHg. All these reports have suggested that stabilizing sea level patients with acute respiratory distress at a PaO_2 between 55-80 mmHg is the best strategy that can be adopted in this type of emergency (Schjorring et al., 2021).

At high (between 2,500-3,600 m) and very high (between 3,600-5,500 m) altitudes (Taylor, 2011), the drop in barometric pressure (PB) leads to a reduction of about one third of the PaO_2. Although these conditions may seem life threatening, more than 150 million people successfully inhabit altitudes 2,500 m above sea level worldwide (Joseph et al., 2000; Zubieta-Calleja et al., 2011). To overcome this effect, short- and long-term physiological, cellular, and molecular adjustments prevent an imbalance in oxygen supply and demand (Arias-Reyes et al., 2021). These physiological modifications consist essentially of an increase in ventilation (regulated by the respiratory control system in the brainstem and carotid bodies), an increase in the number of red blood cells (Soliz et al., 2005; Zubieta-Calleja et al., 2007) (mediated by renal erythropoietin secretion), general vasodilation and angiogenesis (regulated by angiogenetic factors from the vascular endothelium) (Scheinfeldt and Tishkoff, 2010). Such relevant physiological differences between sea level and high-altitude dwellers raise the question of whether the clinical benchmarks used for sea level patients (especially in critical medicine) are incorrect, if not dangerous, in patients living at high altitudes. In fact, this is a recurrent concern for intensivist doctors in the cities of La Paz (3,400 m) and El Alto (4,150 m), in Bolivia. Since a PaO_2 of 50-67 mmHg and a saturation of peripheral oxygen ($SatpO_2$) of 89-95% (Viruez-Soto et al., 2020a) are considered normoxemic values in high altitude permanent dwellers, our medical practice guidelines lack a targeted oxygenation therapy to help ICU patients avoid episodes of hypoxemia, hyperoxemia, intermittent hypoxemia, which ultimately increases their chances of survival.

The coronavirus - 2019 (COVID-19) is a disease that, among others, causes acute respiratory distress syndrome (ARDS). ARDS is characterized by lesions in the pulmonary endothelium and the alveolar epithelium, which ultimately produce inflammation and diffuse alveolar damage (Soliz et al., 2020). Patients with ARDS experience viral and immune-mediated destruction of lung tissue in the alveolar-interstitial-endothelial epithelial complex (Soliz et al., 2020). Pneumolysis has also been described in COVID-19 (Zubieta-Calleja et al., 2020). Consequently, water and proteins transudate from the bloodstream to the interstitial and air space, and along with superimposed infections, can result in fibrosis of the lung tissue. In critical stages, this deterioration could lead to lung collapse and overstretch, resulting in a drastic reduction in ventilated lung volume. Such a decrease at the alveolar and complete pulmonary levels hinder oxygen diffusion from the pulmonary space to the arteries, thus producing severe hypoxemia (Xie et al., 2020; Zubieta-Calleja and Zubieta-DeUrioste, 2020). This, in extreme cases, may lead to multiple organ failure. For the first time, COVID-19-mediated ARDS in high-altitude residents led to recording oxygen desaturation levels rarely before observed in patients admitted to the ICU (unpublished observation). This new clinical urgency inarguably stresses the need to investigate adequate oxygen therapy limits in ICU patients. Thus, in this study we explore the association between the oxygen saturation periods, induced by oxygen therapy, and the survival/mortality of critically ill COVID-19 patients admitted to the ICU due to hypoxemic acute respiratory failure. Our results clearly suggest that stabilizing patients at a SaO_2 between 89-93% effectively increases their survival expectancy.

2. METHODS

2.1. Ethics declaration

The study was approved by the Bioethics Institutional Committees of the Los Andes Clinic, Agramont Hospital and Del Norte Hospital in La Paz, Bolivia, and carried out in accordance with the Helsinki declaration.

2.2. Study design

We conducted an observational, descriptive, and transversal multicentric study from January to July 2021 at Los Andes Clinic (3,400 masl in La Paz), and Agramont and Del Norte Hospitals (4,150 masl in El Alto) in Bolivia.

2.3. Patients

A total of 100 patients were studied, including 60 men and 40 women (Table 1). 26 patients were treated at the Los Andes Clinic (LAC), 35 patients at Agramont Hospital (AH), and 39 patients at Del Norte Hospital (DNH). 53% of the patients survived. Among survivors, 26% of were treated at LAC, 35% at AH, and 39% at DNH. 11% of the surviving patients received O_2 via non-invasive ventilation (NIV), 56% by high-flow nasal cannula or non-rebreather masks (HFNC/NRM), and 33% were intubated (ETI).

2.4. Inclusion / exclusion criteria

Patients were included if they were: 1) 18 years old or older, 2) high-altitude permanent residents (no history of migration from lower lands during the last year), 3) admitted to ICU due to diagnosis of acute hypoxemic respiratory insufficiency caused by COVID-19-related pneumonia, 4) supplemented with oxygen either by open systems (non-rebreather masks at least at 10 L/min or high-flow nasal cannula providing FiO_2 at least ≥ 0.5), or 5) via closed systems ($FiO_2 > = 0.5$) through non-invasive ventilation or endotracheal intubation (Schjørring et al., 2021). Patients with one or more of the following criteria were not considered: 1) non-COVID-19-related pneumonia diagnosis, 2) history of chronic obstructive pulmonary disease, 3) active hematologic cancer.

2.5. CT scanning protocol

CT scans were performed using a 16-slice multislice tomograph (SIEMENS, Somaton Emotion) using the following parameters: tube voltage = 130 KVp, Eff. mAs = 130 (regulated by Care Dose 4D automatic dose modulation), pitch = 1.5, table speed = 27 mm, matrix = 512 × 512, and slice thickness = 16 x 1.2 mm. The examinations were performed with the patient supine, with the arms above the head and at the end of inspiration (depending on the patient's ability to sustain apnea). After obtaining the raw data, series were generated applying filters for the mediastinal and pulmonary windows.

2.6. Data and statistical analysis

Upon ICU admission, patient sex, APACHE II (Acute Physiological and Chronic Health Evaluation) and SOFA (Sepsis Organ Failure Assessment) scores were registered. Peripheral oxygen saturation ($SatpO_2$) was monitored and recorded every hour (period) during the ICU stay until the patient was discharged or died. The final data set, including the patients' outcome (survival or deceased), was anonymized entirely for statistical analyses.

Table 1
Original set of patients. Individual data from all patients originally considered in the study. APACHE II_a and $SOFA_a$: Scores at the time of ICU admission. APACHE II_{48}: Score within 48 hours after admission to ICU. NIV: non-invasive ventilation, HFNC: high-flow nasal canula, NRM: non-rebreather mask, ETI: endotracheal intubation.

	Age	Sex	Days in ICU	Device	APACHE II_a	APACHE II_{48}	$SOFA_a$	Freq. Hypoxemic periods	Freq. Hyperoxemic periods
Survivors (n = 53)									
Agramont Hospital	40	Female	15	HFNC / NRM	12	17	3	0.11	0.39
Agramont Hospital	44	Female	22	HFNC / NRM	13	9	5	0.52	0.16
Agramont Hospital	46	Female	8	HFNC / NRM	11	9	3	0.07	0.55
Agramont Hospital	42	Female	7	HFNC / NRM	14	5	12	0.01	0.30
Agramont Hospital	58	Male	26	ETI	17	14	8	0.33	0.18
Agramont Hospital	51	Male	17	ETI	15	12	9	0.12	0.36
Agramont Hospital	50	Male	28	ETI	14	16	8	0.18	0.19
Agramont Hospital	33	Male	24	ETI	13	12	10	0.44	0.11
Agramont Hospital	58	Male	33	ETI	16	15	6	0.25	0.32
Agramont Hospital	45	Male	28	ETI	18	18	7	0.41	0.09
Agramont Hospital	47	Male	13	ETI	17	14	6	0.13	0.20
Agramont Hospital	74	Male	8	HFNC / NRM	20	7	16	0.09	0.34
Agramont Hospital	86	Male	5	HFNC / NRM	18	9	15	0.01	0.44
Agramont Hospital	69	Male	21	HFNC / NRM	18	16	5	0.37	0.18
Agramont Hospital	45	Male	19	HFNC / NRM	17	15	6	0.59	0.05
Agramont Hospital	65	Male	13	HFNC / NRM	21	17	7	0.39	0.09
Del Norte Hospital	50	Female	20	ETI	12	12	11	0.14	0.26
Del Norte Hospital	39	Female	12	ETI	18	10	5	0.52	0.06
Del Norte Hospital	41	Female	8	ETI	18	17	6	0.06	0.69
Del Norte Hospital	38	Female	8	ETI	8	5	4	0.07	0.35
Del Norte Hospital	38	Female	3	HFNC / NRM	6	6	3	0.08	0.70
Del Norte Hospital	32	Female	4	HFNC / NRM	20	20	5	0.00	0.84
Del Norte Hospital	20	Female	7	HFNC / NRM	8	8	7	0.05	0.59
Del Norte Hospital	81	Female	12	HFNC / NRM	25	22	4	0.03	0.97
Del Norte Hospital	60	Female	5	HFNC / NRM	22	20	4	0.06	0.13
Del Norte Hospital	57	Female	24	HFNC / NRM	13	13	4	0.31	0.16
Del Norte Hospital	58	Female	21	NIV	10	9	4	0.17	0.25
Del Norte Hospital	33	Male	12	ETI	32	32	10	0.03	0.61
Del Norte Hospital	46	Male	22	ETI	21	18	10	0.45	0.18
Del Norte Hospital	39	Male	31	ETI	12	12	3	0.19	0.15
Del Norte Hospital	25	Male	12	ETI	14	13	4	0.21	0.32
Del Norte Hospital	40	Male	15	ETI	32	32	10	0.22	0.20
Del Norte Hospital	15	Male	13	HFNC / NRM	16	15	4	0.05	0.63
Del Norte Hospital	48	Male	12	NIV	10	10	5	0.13	0.24
Del Norte Hospital	39	Male	10	NIV	13	11	4	0.16	0.10
Del Norte Hospital	36	Male	7	NIV	14	14	4	0.20	0.30
Del Norte Hospital	50	Male	19	NIV	18	16	6	0.28	0.19
Los Andes Clinic	59	Female	34	ETI	18	18	10	0.01	0.06
Los Andes Clinic	78	Female	9	HFNC / NRM	8	8	6	0.00	0.31
Los Andes Clinic	90	Female	3	HFNC / NRM	12	10	8	0.00	0.02
Los Andes Clinic	80	Female	4	HFNC / NRM	12	12	8	0.00	0.00
Los Andes Clinic	72	Female	3	HFNC / NRM	12	12	7	0.00	0.18
Los Andes Clinic	63	Female	24	HFNC / NRM	14	14	10	0.14	0.07
Los Andes Clinic	39	Female	15	HFNC / NRM	14	14	10	0.20	0.10
Los Andes Clinic	62	Male	12	HFNC / NRM	12	8	5	0.01	0.04
Los Andes Clinic	54	Male	18	HFNC / NRM	12	10	8	0.13	0.08
Los Andes Clinic	44	Male	12	HFNC / NRM	12	10	7	0.03	0.04
Los Andes Clinic	34	Male	17	HFNC / NRM	12	11	8	0.00	0.03
Los Andes Clinic	59	Male	9	HFNC / NRM	12	12	6	0.00	0.13
Los Andes Clinic	65	Male	10	HFNC / NRM	12	12	5	0.02	0.01
Los Andes Clinic	34	Male	6	HFNC / NRM	12	12	8	0.29	0.05
Los Andes Clinic	37	Male	11	HFNC / NRM	12	12	7	0.16	0.04
Los Andes Clinic	60	Male	8	NIV	12	13	6	0.04	0.00
Deceased (n = 47)									
Agramont Hospital	39	Female	20	ETI	11	6	12	0.41	0.23
Agramont Hospital	49	Female	14	ETI	18	16	6	0.81	0.01
Agramont Hospital	73	Female	13	ETI	26	18	6	0.56	0.11
Agramont Hospital	67	Female	8	ETI	24	20	7	0.86	0.02
Agramont Hospital	52	Female	5	ETI	15	16	8	0.92	0.03
Agramont Hospital	56	Female	15	ETI	17	18	8	0.57	0.06
Agramont Hospital	50	Female	9	ETI	16	13	8	0.95	0.01
Agramont Hospital	68	Female	26	ETI	20	18	5	0.90	0.04
Agramont Hospital	47	Male	11	ETI	10	11	6	0.80	0.05
Agramont Hospital	88	Male	7	ETI	22	20	7	0.99	0.00
Agramont Hospital	46	Male	6	ETI	11	14	6	0.93	0.00
Agramont Hospital	47	Male	10	ETI	19	15	8	0.62	0.05
Agramont Hospital	69	Male	6	ETI	25	20	7	0.55	0.22
Agramont Hospital	52	Male	4	ETI	17	18	7	0.93	0.00
Agramont Hospital	41	Male	14	ETI	19	17	6	0.76	0.03
Agramont Hospital	42	Male	11	ETI	19	17	8	0.52	0.14
Agramont Hospital	48	Male	8	ETI	12	11	9	0.59	0.11

(*continued on next page*)

Table 1 (*continued*)

	Age	Sex	Days in ICU	Device	APACHE II_a	APACHE II_{48}	$SOFA_a$	Freq. Hypoxemic periods	Freq. Hyperoxemic periods
Agramont Hospital	32	Male	4	ETI	23	20	8	0.93	0.05
Agramont Hospital	62	Male	11	ETI	24	7	9	0.77	0.00
Del Norte Hospital	30	Female	7	ETI	25	25	11	0.43	0.17
Del Norte Hospital	48	Female	13	ETI	24	26	12	0.58	0.03
Del Norte Hospital	50	Female	4	ETI	22	24	10	0.27	0.12
Del Norte Hospital	52	Female	6	ETI	11	10	4	0.46	0.30
Del Norte Hospital	58	Female	2	ETI	27	27	11	0.69	0.00
Del Norte Hospital	44	Female	8	ETI	20	18	10	0.45	0.07
Del Norte Hospital	68	Male	10	ETI	18	18	10	0.43	0.13
Del Norte Hospital	68	Male	6	ETI	22	22	12	0.28	0.08
Del Norte Hospital	49	Male	9	ETI	14	14	7	0.40	0.10
Del Norte Hospital	56	Male	5	ETI	15	10	7	0.20	0.18
Del Norte Hospital	72	Male	16	ETI	15	14	4	0.39	0.16
Del Norte Hospital	27	Male	7	ETI	24	26	10	0.45	0.15
Del Norte Hospital	51	Male	12	ETI	14	14	11	0.44	0.10
Del Norte Hospital	61	Male	11	ETI	26	28	12	0.67	0.05
Del Norte Hospital	47	Male	11	ETI	24	16	10	0.81	0.03
Del Norte Hospital	27	Male	8	ETI	24	24	11	0.63	0.07
Del Norte Hospital	73	Male	29	ETI	24	23	11	0.21	0.13
Del Norte Hospital	58	Male	14	ETI	24	24	11	0.16	0.14
Los Andes Clinic	55	Female	16	ETI	16	18	10	0.82	0.05
Los Andes Clinic	56	Female	7	ETI	18	18	12	0.94	0.01
Los Andes Clinic	53	Female	7	ETI	18	18	13	1.00	0.00
Los Andes Clinic	80	Female	7	ETI	14	14	12	0.18	0.65
Los Andes Clinic	73	Male	13	ETI	14	14	8	0.77	0.00
Los Andes Clinic	54	Male	12	ETI	15	16	8	0.90	0.00
Los Andes Clinic	63	Male	3	ETI	22	24	16	0.94	0.00
Los Andes Clinic	55	Male	28	ETI	16	18	10	0.76	0.03
Los Andes Clinic	63	Male	22	ETI	18	18	12	0.65	0.00
Los Andes Clinic	77	Male	37	ETI	18	18	14	0.25	0.30

Statistical analyses were performed using GraphPad Prism version 9.1 for Windows, GraphPad Software (San Diego, California USA, www.graphpad.com) or IBM SPSS Statistics for Windows (Version 26.0. Armonk, NY: IBM Corp).

Descriptive statistics and univariate tests were used to compare the groups of surviving and deceased patients.

The frequency of periods that patients spent in normoxemia, hypoxemia, or hyperoxemia was compared through two-way RM ANOVA tests. As such, "survival" (survivor or deceased) was considered the grouping variable and "state of oxygenation" (normoxemia, hypoxemia, and hyperoxemia) were the repeated measures. A multivariate analysis was performed using multiple logistic regression where "survival" (survivor or deceased) was the dependent variable and "hospital", "sex", "age", "device used to supply oxygen", "days in ICU", "APACHE II score", "SOFA score", "frequency of normoxemia events", "frequency of hypoxemia events", and "frequency of hyperoxemia events" were the initial independent variables. Built-in PRISM tests were used to check for multicollinearity and correlation between independent variables. The difference in frequency of reoxygenation events was evaluated by a Mann-Whitney's U test. Test significances were set to $p < 0.05$. Values are presented as mean ± S.D., unless otherwise stated.

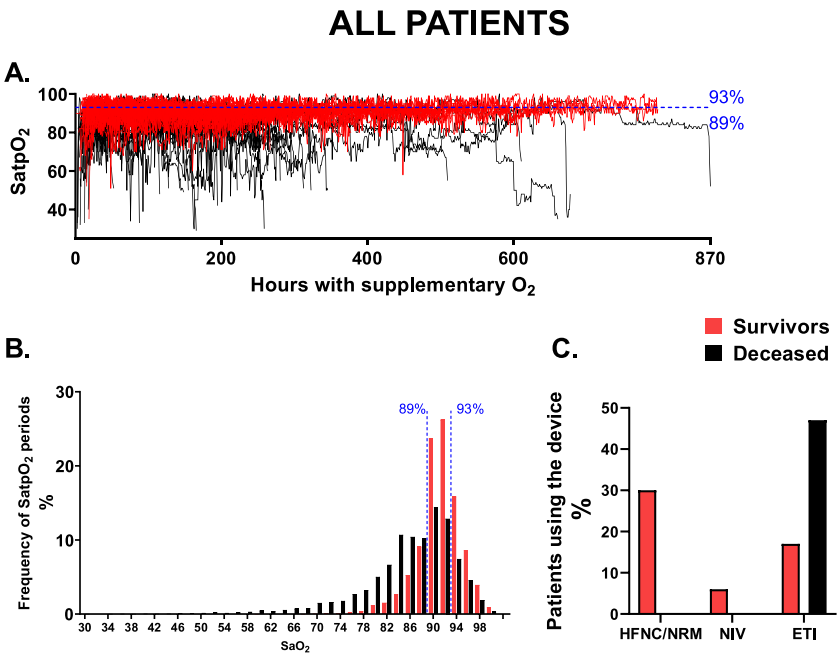

Fig. 1. Original set of patients. Surviving patients maintained more regular values of $SatpO_2$ during their stay in ICU, while low values of $SatpO_2$ were more frequently observed in deceased patients (A). 50% of the registered values of $SatpO_2$ in survivors (red bars) were between 89 and 93 (25th and 75th percentile, respectively – blue dotted lines). $SatpO_2$ values were more heterogeneous in the deceased patients and showed a slightly aggregated distribution to the left (lower $SatpO_2$ – black bars) (B). Only patients who received endotracheal intubation (ETI) died. NIV: non-invasive ventilation, HFC/NRM: high-flow cannula/non-rebreather mask (C).

3. RESULTS

3.1. A $SatpO_2$ between the limits of 89-93% emerges as a range of normoxia for ICU patients

All patients' peripheral oxygen saturation ($SatpO_2$) was monitored until discharge or death. Surviving patients showed fewer $SatpO_2$ fluctuations during their ICU stay. Not surprisingly, such values became more and more stable with time, ultimately leading to discharge (Fig. 1A). When analysing the distribution of frequencies of $SatpO_2$ values in all surviving patients, we observed that 50% of the data were between 89% (25th percentile) and 93% (75th percentile). Low $SatpO_2$ values were more common in deceased patients (25th percentile = 82, 75th percentile = 91). Based on these observations, we considered the $SatpO_2$ range between 89-93% as normoxemia (Nx), and values below and above these limits as hypoxemia (Hx) and hyperoxemia (Hpx), respectively (Fig. 1B and Table 2). It is noteworthy that all patients who died were part of the group receiving oxygenation by intubation (Fig. 1C). Therefore, all subsequent analyses compared intubated, survivors and deceased patients only.

3.2. Surviving intubated patients show more stable patterns of oxygenation

The comparison of oxygenation pattern (Fig. 2A) and frequency distribution of $SatpO_2$ values (Fig. 2B) between surviving and deceased intubated patients (n = 64) was similar to that observed in all patients (Fig. 1). Furthermore, in this group of intubated patients the frequency distribution of $SatpO_2$ values between the limits of 89-93% also corresponds to 50% of the data, thus confirming that this is the appropriate range for normoxia. Moreover, though the frequencies of the Nx, Hx and Hpx periods were highly variable in patients, results show that survivors had a significantly higher frequency of Nx and Hpx periods than the deceased (Two-way RM ANOVA $F_{Survival\_x\_state\_of\_oxygenation\ (2,\ 124)} = 35.1$, $p < 0.01$; Fisher's LSD $p_{Nx}<0.001$; $p_{Hpx} = 0.047$), and lower frequency of Hx periods (Fisher's LSD $p < 0.001$ – Fig. 2C).

Table 2
Summary of descriptive and clinical parameters from the original set of patients. APACHE II_a and $SOFA_a$: Scores at the time of ICU admission. APACHE II_{48}: Score within 48 hours after admission to ICU. NIV: non-invasive ventilation, HFNC: high-flow nasal canula, NRM: non-rebreather mask, ETI: endotracheal intubation.

	Mean	S.D.	Minimum	Maximum
	Survivors (n = 53)			
Females (n)	22			
Age	44.24	9.57	25.00	59.00
Days in ICU	20.18	8.78	8.00	34.00
APACHE II_a	17.35	6.31	8.00	32.00
APACHE II_{48}	15.88	6.91	5.00	32.00
$SOFA_a$	7.47	2.55	3.00	11.00
NIV (n)	6			
HFNC / NRM (n)	30			
IET (n)	17			
Mean $SatpO_2$	91.01	1.65	88.42	94.78
Freq. Hypoxemic events	0.22	0.16	0.01	0.52
Freq. Hyperoxemic events	0.25	0.18	0.06	0.69
	Deceased (n = 47)			
Females (n)	18.0			
Age	55.23	13.63	27.00	88.00
Days in ICU	11.32	7.26	2.00	37.00
APACHE II_a	18.94	4.70	10.00	27.00
APACHE II_{48}	17.74	5.10	6.00	28.00
$SOFA_a$	9.15	2.66	4.00	16.00
NIV (n)	0			
HFNC / NRM (n)	0			
IET (n)	47			
Mean $SatpO_2$	83.75	5.02	70.66	91.83
Freq. Hypoxemic events	0.63	0.25	0.16	1.00
Freq. Hyperoxemic events	0.09	0.11	0.00	0.65

3.3. A higher frequency of hypoxic periods in intubated patients is strongly associated with a lower probability of survival

To conduct a more precise statistical analysis, we compared deceased intubated patients who maintained similar oxygenation states to surviving intubated patients. To do so, we selected ICU patients who spent less than 5% of the periods above a $SatO_2$ of 80% (Table 3; survivors n = 16; deceased n = 17). We reasoned that frequencies below 5% could be considered non-significant, as similarly done in statistical analyses. As shown in Fig. 3A, this new group of survivors and deceased patients showed similar oxygenation patterns. Furthermore, this analysis again revealed that 50% of the $SatpO_2$ in survivors was between the limits of 89 and 93% (pre-defined above), while deceased patients had lower $SatpO_2$ frequency, between 86% (25th percentile) and 92% (75th percentile) (Fig. 3B). Moreover, oxygenation events in the Nx and Hpx periods were not significantly different between survivors and deceased (Fisher's LSD $p_{Nx} = 0.068$; $p_{Hpx} = 0.104$ – Fig. 3C), but showed a significantly lower frequency of Hx periods among survivors (Two-way RM ANOVA $F_{Survival\_x\_state\_of\_oxygenation\ (2,\ 62)} = 5.87$, $p = 0.005$; Fisher's LSD $p = 0.003$). Then, we performed a multivariate analysis to determine the effect of the frequency of Hx and Hpx periods on the survival probability of these patients (the frequency of Nx episodes was excluded from the model to avoid multicollinearity with Hx - Spearman r=-0.54 $p = 0.001$- Fig. 3D). The effect of hospital admission, age, sex, the APACHE II and the SOFA scores were included in the analysis. However, the results did not show an effect of hospital admission, gender, APACHE II score, and the frequency of Hpx periods (Table 4). Thus, we re-adjusted our model including only the age, the SOFA score, and the frequency of the Hx periods as parameters affecting patient survival (Table 5). The results of this new analysis effectively showed that a higher frequency of Hx periods is strongly associated with a lower probability of survival ($\beta = -0.16$, $p = 0.021$). Furthermore, the analysis of odds ratios revealed that survival probability increases by 15% per a 1% reduction in the frequency of Hx periods. It is noteworthy that the sensitivity and specificity estimated with this model were excellent; 93.75% and 76.47%, respectively. In line with these results, CT scan images showed that lung damage is significantly more severe in deceased patients than in survivors (Fig. 4), suggesting that oxygen treatment is ineffective in providing them with more frequent periods of normoxia.

3.4. Reoxygenation events are not associated with a lower probability of survival

Since reoxygenation events are strongly associated with the production of reactive oxygen species (ROS) (Friedman et al., 2014), we carried out a final analysis where the frequency of reoxygenation events for each intubated patient was calculated. To do so, we defined a reoxygenation event as the passage of $SatpO_2$ from desaturation to above 89%. This analysis was performed in all intubated patients (Fig. 5A), in patients who spent less than 5% of their oxygenation periods below a $SatpO_2$ of 80% (previously defined in Table 3) (Fig. 5B), and in patients who spent more than 5% of their oxygenation periods below a $SatpO_2$ of 80% (Fig. 5C). These results revealed no significant association between the patients' observable reoxygenation events and their probability of survival.

4. DISCUSSION

Results of this study show that fatal cases occur only in patients who were intubated as a last resort to improve their oxygen desaturation. Furthermore, the stabilization of intubated patients between 89% and 93 % of $SatpO_2$ showed a strong association with the probability of

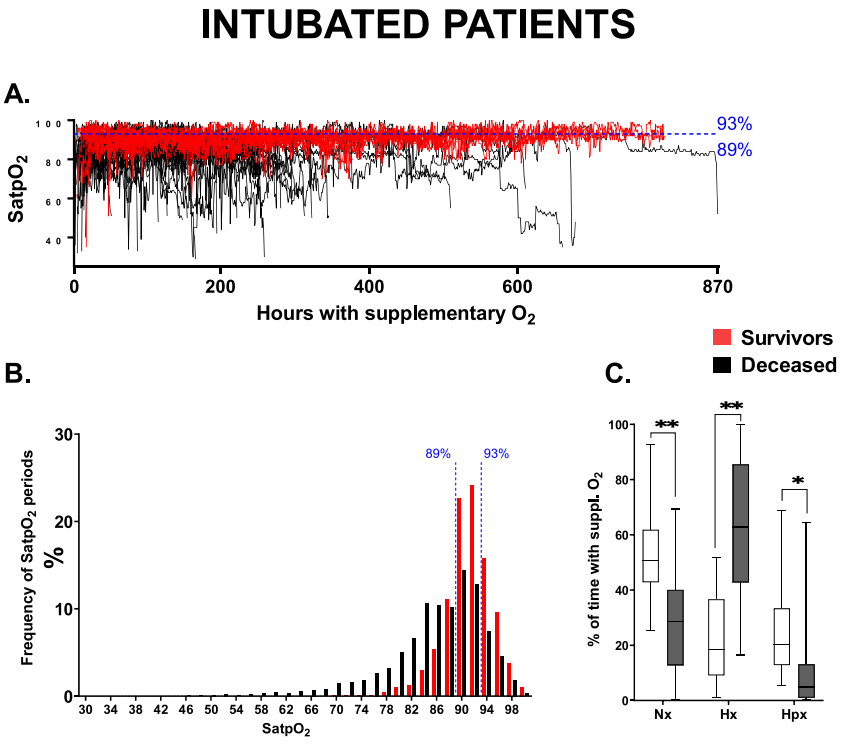

Fig. 2. Surviving intubated patients showed more stable $SatpO_2$ values during their stay in ICU than those who died (A, B). A higher frequency of normoxemic periods (Nx – 89-93% $SatpO_2$) and less hypoxemic (Hx – $SatpO_2$<89%) and hyperoxemic (Hpx – $SatpO_2$>93%) periods occurred in survivors (red bars) than in deceased (black bars - C). *, **: $p < 0.05$, $p < 0.01$.

Table 3
Final subset of patients. APACHE II_a and $SOFA_a$: Scores at the time of ICU admission APACHE II_{48}: Score within 48 hours after admission to ICU. NIV: non-invasive ventilation, HFNC: high-flow nasal canula, NRM: non-rebreather mask, ETI: endotracheal intubation.

	Mean	S.D.	Minimum	Maximum
	Survivors (n = 16)			
Females (n)	5			
Age	44.13	9.87	25	59
Days in ICU	20.06	9.05	8	34
APACHE II_a	17.13	6.45	8	32
APACHE II_{48}	15.75	7.11	5	32
$SOFA_a$	7.31	2.55	3	11
NIV (n)	0			
HFNC / NRM (n)	0			
IET (n)	16			
Mean $SatpO_2$	91.03	1.7	88.42	94.78
Freq. Hypoxemic events	0.21	0.15	0.01	0.52
Freq. Hyperoxemic events	0.26	0.18	0.06	0.69
	Deceased (n = 17)			
Females (n)	5			
Age	54.88	16.97	27	80
Days in ICU	12.82	8.88	4	37
APACHE II_a	18.41	4.81	11	25
APACHE II_{48}	18.06	5.97	6	26
$SOFA_a$	10.18	2.27	4	14
NIV (n)	0			
HFNC / NRM (n)	0			
IET (n)	17			
Mean $SatpO_2$	88.37	2.01	83.94	91.83
Freq. Hypoxemic events	0.41	0.22	0.16	0.9
Freq. Hyperoxemic events	0.16	0.14	0	0.65

survival. Indeed, among patients stabilized in similar oxygenation conditions (between 89 and 93 % of SaO_2), those with the best SOFA scores on ICU admission survived. On the other hand, our results suggest that both the hyperoxygenation and frequency of observable reoxygenation events are not strongly associated with a higher probability of mortality or survival. Hence, these results are highly relevant for critical care medicine practice in patients living permanently at high altitudes. Furthermore, our results provide, for the first time, reference interval values of oxygenation for optimal outcomes of patients admitted to ICU at altitudes of 3,400 - 4,150 m. Given that the cities of La Paz and El Alto are located between 3,400 and 4,150 m, respectively, and people travel between these altitudes frequently, these reference values apply to all these residents.

High and very high-altitude environments are characterized by barometric hypoxia. At the beginning of the COVID-19 pandemic, this condition predicted a devastating explosion of lethal cases in these regions. Surprisingly, it was found that high-altitude inhabitants, particularly in the countries of America and in the Tibet region (Arias-Reyes et al., 2020; Ortiz-Prado et al., 2020), present lower infection rates and/or less severe symptoms of COVID-19 compared to the inhabitants of the lowlands (Arias-Reyes et al., 2020; Lei et al., 2020; Ortiz-Prado et al., 2020). This epidemiological finding suggests that chronic exposure to hypobaric hypoxia in such extreme and harsh environments causes physiological adaptations that may provide some type of protection cushioning the infection and symptoms of SARS-CoV-2. In line with this hypothesis, our results show that the recovery rates of patients admitted to ICU between altitudes of 3,400 - 4,150 masl are similar to those reported at sea level during the first wave of the pandemic when COVID-19 vaccines were not yet available (Tobin, 2020). In fact, 53% of the patients admitted to the ICU with ventilatory support in high-altitude hospitals in Bolivia survived, of which 11% corresponded to the group of critically ill patients who required administration of oxygen by intubation. Also, we previously evaluated (and reported) arterial blood gases parameters in residents of the city of El Alto in Bolivia, located at 4,150 masl (Viruez-Soto et al., 2020a,b) to define appropriate therapies for the treatment of patients admitted to the ICU in high- and very high-altitude regions. These studies suggested that the baseline (normoxic) $SatpO_2$ in high-altitude permanent residents is between 89% and 95%. The results of this study confirmed 89% as the

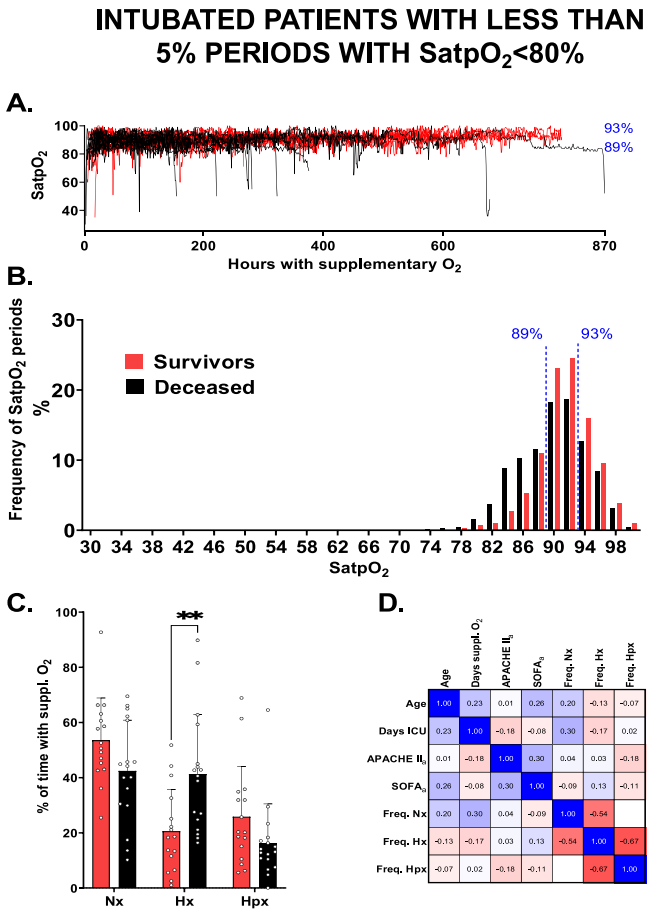

Fig. 3. Only intubated patients who spent less than 5% of their time in ICU with $SatpO_2$<80% were included in this analysis. The values of $SatpO_2$ observed in survivors were consistently stable within an 89-93% range. The deceased patients showed lower values of $SatpO_2$ more frequently (A, B). Survivors had significantly less hypoxemic (Hx – $SatpO_2$<89%) periods than the deceased (C). The frequency of normoxemic (Nx) periods was excluded from the multivariate model to avoid multicollinearity with the frequency of hypoxemic events (Spearman r=-0.54 $p = 0.001$). Values of Spearman r are shown. (D). **: $p < 0.01$.

Table 4
Initial multivariate analysis. Hospital [HA] and [HDN]: Agramont and Del Norte Hospitals compared to Los Andes Clinic. APACHE II_a and $SOFA_a$: Scores at the time of ICU admission.

Variable	|Z|	*p* value
Hospital [HA]	0.003	0.998
Hospital [HDN]	0.03	0.978
Age	2.06	**0.039**
Sex [Female]	0.34	0.734
APACHE II_a	1.15	0.250
$SOFA_a$	2.16	**0.030**
Freq. Hypoxemia (%)	2.3	**0.021**
Freq. Hyperoxemia (%)	0.13	0.896

lower limit of $SatpO_2$ but adjusted the upper limit to 93%. Indeed, our data report that 50% of the $SatpO_2$ values were between 89% and 93%, corresponding to the 25th –75th percentiles, respectively, in surviving patients. Furthermore, our study shows that there is a strong association between the stabilization of intubated (critically ill) patients within these saturation ranges and the probability of survival. In contrast, deceased patients were found to have spent significantly longer periods in oxygen saturation conditions below 89% (hypoxic). These results are highly valuable for high-altitude medical practice, especially critical

Table 5
Final multivariate analysis. $SOFA_a$: SOFA score at the time of ICU admission.

	Estimate	|Z|	*p* value	Odds ratio	95% CI
Age	−0.17	2.06	0.039	0.85	0.69 to 0.96
$SOFA_a$	−0.89	2.16	0.030	0.41	0.14 to 0.77
Freq. Hypoxemia (%)	−0.16	2.3	0.021	0.85	0.71 to 0.95
Sensitivity	93.75				
Specificity	76.47				

medicine, since they can be used as a guiding reference to help monitor the progress of patients admitted to the ICU.

However, treatments to alleviate the disease in critically ill patients, both at sea level and at high altitudes, remain highly challenging. In COVID-19, the direct viral attack on the alveolar-capillary membranes produces a gradually increasing hypoxia. This effect generates insufficient hyperventilation since the lung surface cannot ventilate sufficiently to reduce it. In these cases, the administration of oxygen by mechanical ventilation is the last resort to overcome life-threatening desaturation in the patient (Ehrenreich et al., 2020; Yuan et al., 2020). However, this practice is ineffective when severe cases rapidly evolve to dyspnea, gasping, tachycardia and acute pulmonary failure. This condition is generally associated with a dramatic reduction in the ventilatory surface due to the destruction of the alveoli and adjacent capillary tissue (pneumolysis), and is also associated with inflammation, local bleeding, transudates and exudates, edema and hypoxia-induced pulmonary hypertension, leading to greater failure due to capillary stress (Zubieta-Calleja and Zubieta-DeUrioste, 2021; Zubieta-Calleja et al., 2020). Comparing lung damage between patients of this study clearly shows that the lung surface is dramatically more affected in deceased patients than survivors (Fig. 5). Specifically, these results suggest that the lower degree of lung damage in intubated surviving patients allowed greater stabilization in the Nx and Hpx periods than the deceased. Furthermore, although intubated patients with high levels of desaturation are those who die, the comparison between surviving and deceased intubated patients who maintained similar oxygenation periods (less than 5% of the time in the ICU with a $SatpO_2$ greater than 80%), showed that intubated patients with significantly longer periods of Hx are those who died. Thus, these data suggest that aggravated lung damage in critically ill patients is difficult to stabilize despite intubation oxygen therapy. Indeed, a higher frequency of hypoxic periods also suggests a deterioration associated with multi-organ dysfunction.

Other major corollaries of this study are those referring to hyperoxygenation strategies and the putative negative effects induced by frequent reoxygenation events. Regarding the first point, although our results show that surviving intubated patients spend a significant longer time in hyperoxic conditions than deceased patients (Fig. 2C), hyperoxic conditions are not statistically associated with survival. This result is relevant because our data indicate no differences between a conservative versus a liberal oxygen therapy strategy in critically ill COVID-19 patients. However, since oxygen is an expensive resource in the ICU of our hospitals, these results support a sensible use of this resource. Our results also show no associated differences in reoxygenation events between survivors and deceased (Fig. 5). Although this is an interesting result, it is not conclusive. In fact, as mentioned previously, the $SatpO_2$ data in this work were registered once every hour (period). This implies that between one measurement of $SatpO_2$ and the next (after one hour), patients may have experienced several other events of deoxygenation/reoxygenation. Therefore, although the trend shown here is interesting, more studies should be carried out to evaluate oxidative stress markers in these patients.

In conclusion, our findings suggest that high-altitude residents who are admitted to ICU for COVID-19 disease at altitudes between 3,400 - 4,150 m and can maintain oxygenation levels between 89 and 93 % with different types of oxygen therapy will survive. Moreover, the results of

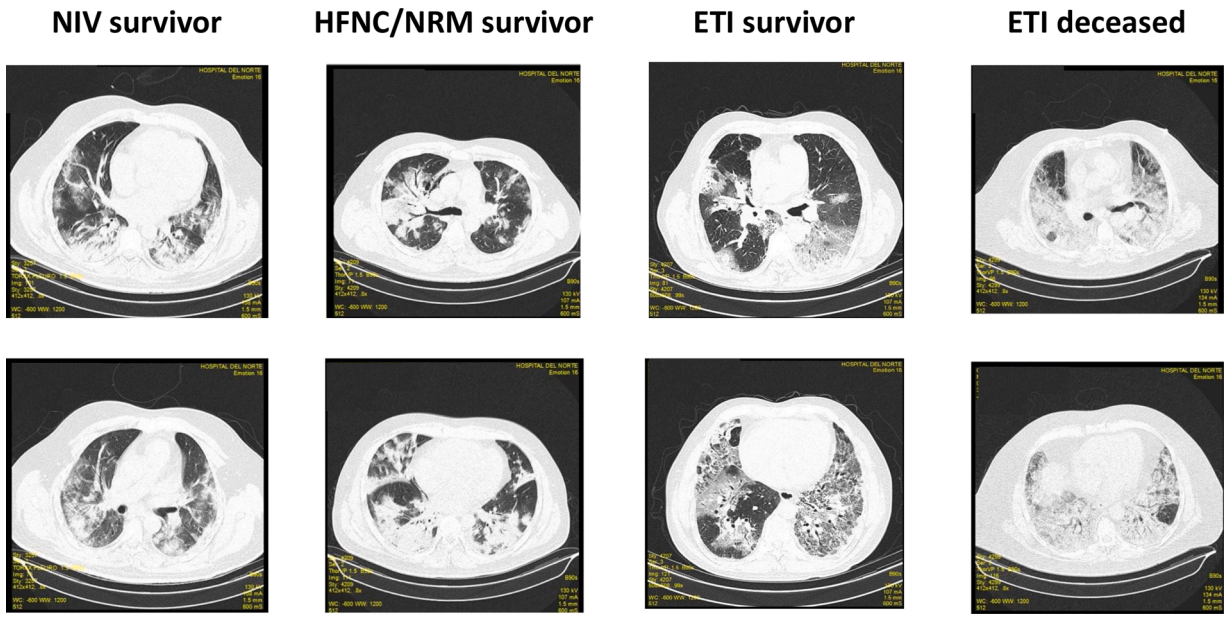

Fig. 4. Representative CT scans images comparing lung damage of UCI patients who received non-invasive ventilation (NIV), high-flow cannula/non-rebreather mask (HFC/NRM), and endotracheal intubation (ETI).

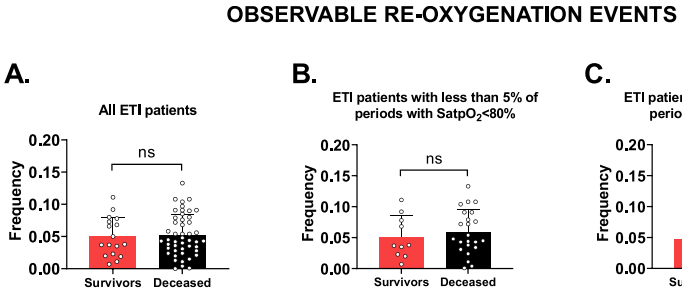

Fig. 5. Observable repeated reoxygenation events do not affect survival. No significant differences were observed in the frequency of reoxygenation events between survivors and deceased patients who received O_2 supplementation via endotracheal intubation (ETI - A). This observation also was consistent among stable ETI patients (spent less than 5% of their time in ICU with $SatpO_2$<80% - B) and patients with more frequent periods of harsh hypoxemia (spent more than 5% of their time in ICU with $SatpO_2$<80% - C).

this study highlight the importance of redefining the physiological parameters used in clinics for high-altitude populations. In fact, the mathematical (mainly linear) relationship between various physiological parameters measured at sea level (such as PaO_2 and SaO_2) appears to differ under high altitude conditions. Indeed, the alteration of variables such as the temperature, acid-base status, hydration, and the relative humidity of the environment greatly impacts the reformulation of all arterial gas parameters (Paulev and Zubieta-Calleja, 2005; Viruez-Soto et al., 2020a,b).

Data Availability

Data will be made available on request.

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