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RESEARCH ARTICLE

Neutrophil/Lymphocyte Ratio (NLR) and Lymphocyte/CRP ratio (LCR) are Reliable Predictors of Adverse Outcomes in High-Altitude COVID-19 Patients

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ABSTRACT:
The neutrophil/lymphocyte ratio (NLR) and the lymphocyte/C-reactive protein ratio (LCR) are prognostic factors in inflammatory, cardiovascular, and oncological diseases. With the emergence of the COVID-19 pandemic, it has been recently shown that NLR and LCR are also useful for the prognosis of disease severity in patients infected with the SARS-CoV-2 virus at sea level. However, there are no studies demonstrating the reliability of NLR and LCR in high-altitude human populations (above 2,500 m). This is relevant because both the incidence and mortality from COVID-19 are decreased in high altitude. A possible explanation of this effect is a lower impact of this virus on the exaggerated inflammatory response induced by the viral infection. The aim of this study is to determine whether the NLR and LCR indices can be used as reliable predictive markers of COVID-19 severity in high-altitude permanent resident patients. Routine blood biochemistry and complete blood count were performed on 368 patients positive for the SARS-CoV-2 virus in Huaraz, Peru (3,050 m). Patients' follow up was carried out until home discharge or fatal outcome. The results show that: 1) NLR values are higher in deceased patients admitted to the intensive care unit due to COVID-19; 2) NLR and LCR are reliable predictors of death in patients with COVID-19; and 3) NLR and LCR are reliable predictors of intensive care unit requirement in COVID-19 patients. We conclude that NLR and LCR are reliable biomarkers and prognostic factors of COVID-19 severity and can be used in high-altitude permanent resident patients.

Keywords: SARS-COV-2, high altitude, disease severity, mortality, inflammation, prognosis

Introduction

Coronavirus disease 2019 (COVID-19), a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly throughout the world and remains a major threat to global public health (1). The clinical spectrum of patients with COVID-19 infection varies widely, from asymptomatic to subjects with mild, moderate, and severe symptoms (2). In patients with severe pneumonia, SARS-CoV-2 infection can lead to severe acute respiratory distress syndrome (ARDS), which rapidly progresses to multi-organ dysfunction syndrome (MODS) [1,2]. Similarly, many patients with mild symptoms can suddenly progress from mild to severe ARDS, septic shock, or multi-organ dysfunction [3]. These rapid changes in disease progression call for identifying markers for early diagnosis of potentially severe or critical cases. Such tools would allow for timely clinical decisions and appropriate and immediate treatment.

The neutrophil-to-lymphocyte ratio (NLR) is the ratio of the absolute number of neutrophils to the absolute number of lymphocytes. It is a new marker of subclinical inflammation with good predictive capacity for the progression and clinical outcome of various diseases, such as solid tumors [4], cardiovascular disease [5], chronic obstructive pulmonary disease [6], pancreatitis [7], renal disease [8,9], and diagnosis of colon cancer [10]. In addition, several studies have recently reported that the NLR can differentiate between mild/moderate and severe/critical groups and predict the likelihood of death in patients with COVID-19 infection. Indeed, several studies show that elevated NLR is associated with increased mortality in COVID-19 patients [11–16]. This evidence is highly relevant, as the NLR is an easily accessible parameter that can be obtained from a complete blood count (CBC), which is always on hand in first-contact care units. The lymphocyte to C-reactive protein ratio (LCR) is another interesting biomarker of disease progression [17]. LCR has been used as a suggestive indicator of inflammation in cancer [18], and has also been proven useful in predicting adverse outcomes in COVID-19 [19]. Compared to NLR, LCR predictability is less specific in mild and moderate cases, but it has adequate predictive ranges for mortality and worsening clinical status in hospitalized patients [20].

Although several authors have shown that increased NLR [3,21–25] and decreased LCR [19,26–28] are useful for predicting disease progression in COVID-19, so far, there is no information about the predictive properties of NLR and LCR in COVID-19 in human populations living at high altitude (between 2,500-5,000 m). Our research group and others have reported that the incidence and mortality of COVID-19 are significantly lower in populations at high altitudes compared to populations at sea level [29–31]. At high altitude, the lower barometric pressure (about one-third compared to sea level) is the most important factor in this effect [32]. To cope with these conditions, high-altitude dwellers have developed physiological, cellular, and molecular adaptations that effectively prevent the imbalance between oxygen supply and demand [29]. These modifications include increased ventilation, increased oxygen-carrying cells in the blood, increased vasodilation, and augmented angiogenesis [33]. These physiological features are associated with lower incidence and mortality of COVID-19 disease at high altitude and suggest that the inflammatory response induced by the SARS-CoV-2 virus is less important (or better tolerated) in high-altitude residents. This observation raises the question of whether clinical biomarkers, such as the NLR and LCR, used to predict the progression and clinical outcome of COVID-19 in patients at sea level have the same predictive value at high altitude.

Accordingly, we investigated whether NLR and LCR can be used as predictors of severity in high-altitude permanent residents with a confirmed COVID-19 infection. To do so, we evaluated the serum NLR and LCR levels as a function of progressing COVID-19 severity. Our results show that NLR and LCR can be used reliably to predict the severity of COVID-19 disease in high-altitude patients.

Methods

ETHICS DECLARATION

The present study complies with the basic principles for research in human beings established by the Declaration of the World Assembly of the Helsinki Treaty, Nuremberg and Finland. The study was carried out per the General Health Law of the Republic of Peru on research for health.

STUDY DESIGN

We conducted an observational, descriptive, and cross-sectional study from August 2020 to March 2021 at San Pablo Clinic in Huaraz, Peru, located at 3,050 meters above sea level (masl).

PATIENTS AND CLINICAL PARAMETERS

A total of 368 patients were included, 249 men and 119 women. For each patient, sex and age were annotated, and the values of C-reactive protein (CRP), arterial partial pressure of oxygen (PaO_2), arterial partial pressure of CO_2 ($PaCO_2$), lactate in blood, total leukocytes, number of lymphocytes, number of neutrophils, and number of band neutrophils were recorded at admission to the hospital. The neutrophil/

lymphocyte (NLR) and the Lymphocyte/C-reactive protein (LCR) ratios were also calculated.

Inclusion/exclusion criteria

Patients were included in the study 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 the ICU due to diagnosis of acute hypoxemic respiratory insufficiency caused by COVID-19-related pneumonia. Patients were excluded if they were diagnosed with non-COVID-19 related pneumonia, uncontrolled endocrine metabolic disease, active hepatitis C virus infection, HIV infection, pregnancy, or taking vitamins and/or food complexes.

Patients' data were eliminated if informed consent was withdrawn, if medical history was incomplete, or if biological samples were improperly handled.

Statistical analysis

Statistical analyses, except for ROC curves analysis, 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). Test significances were set to $p<0.05$. Values are presented as medians and interquartile ranges (IQR).

Univariate analysis

Data were anonymized before processing. The difference between survivors and deceased patients within each clinical parameter was evaluated using multiple Student's *t*-tests for independent samples. The difference in NLR and LCR between survivors and deceased patients admitted or not to the ICU was tested via two-way ANOVA, where "survival" and "ICU requirement" were the factors. LSD Fisher's post-hoc analyses were applied to the results.

Multivariate analysis

We built two separate multivariate models, one including patients admitted or not to ICU, and a second one with only patients admitted to ICU.

First, we investigated the most important factors in predicting the probability of survival with a multiple logistic regression. For this, we used a subset of patients (30+ years old) admitted or not to ICU to determine the effect of age, sex, band neutrophils, total leukocytes, C-reactive protein, lactate, PaO_2, $PaCO_2$, NLR, LCR, and admission to ICU on survival probability. PRISM's built-in tests were used to check for multicollinearity and correlation between independent variables.

Second, we repeated this analysis to determine the best predictor of ICU admission using a subset of patients (30+ years old) not admitted to ICU. The best predictors were selected according to the highest values of area under the curve (AUC). Values below 0.6 were considered poorly discriminative, while those above 0.75 were considered good. The optimal cut-off values for NLR and LCR as predictors of death and ICU admission were calculated from ROC curves analyses using the Youden index method in MedCalc Statistical Software version 20.114 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). For the analysis of fatal outcomes at 60+ days of follow-up after admission to the hospital, survival analysis was performed using the Kaplan-Meier method.

Results

1. NLR VALUES ARE HIGHER IN DECEASED HIGH-ALTITUDE COVID-19 PATIENTS ADMITTED TO INTENSIVE CARE UNITS.

Of 368 patients, 319 survived, representing 84.3% of the male population and 91.6% of the female population. Survivors had a median age of 46 years (interquartile range [IQR]: 36 to 59 years), with a median hospital stay of 9 days (IQR: 6-13 days), of which 34 patients were admitted to the ICU (10.7%) (Table 1).

Table 1. Description of the study population

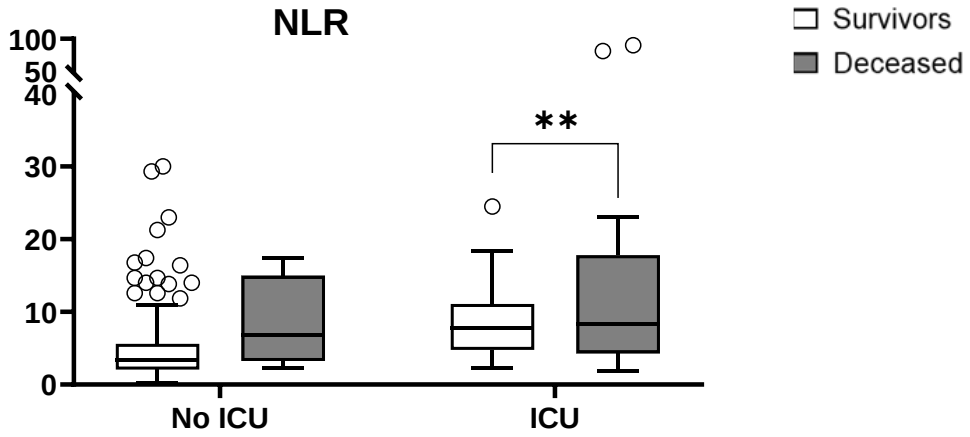
	Survivors (319)		**Deceased (49)**		***t***	***p*-value**
	n	%	n	%		
Sex: Female	109	34.2	10	20.4	-	-
Age (years), p50 (p25-p75)	46	(36-59)	63	(51.5-70)	5.86	<0.001
Days in hospital, p50 (p25-p75)	9	(6-13)	14	(5-25)	2.58	0.013
Admitted to ICU	34	10.7	45	91.8	-	-
Neutrophils, p50 (p25-p75)	71	(62-79)	81	(74-86.5)	6.54	<0.001
Lymphocytes, p50 (p25-p75)	20	(13-28)	10	(5-17.5)	-7.23	<0.001
Band neutrophils, p50 (p25-p75)	3	(2-5)	4	(3-7)	2.1	0.04

	Survivors (319)		Deceased (49)		*t*	*p*-value
Total leucocytes, p50 (p25-p75)	6.8	(5.28-9.43)	10	(6.5-14.4)	1.98	0.053
Protein C reactive, p50 (p25-p75)	33.01	(8.66-82.53)	126	(64.6-180.22)	4.9	<0.001
Lactate, p50 (p25-p75)	1.5	(1.1-1.9)	1.6	(1.2-2.2)	1.14	0.263
PaO_2, p50 (p25-p75)	59.2	(31-74.15)	47.8	(29.9-61.8)	-4.1	<0.001
$PaCO_2$, p50 (p25-p75)	33.7	(28.9-59.18)	50.55	(30.28-67.28)	2	0.51
NLR, p50 (p25-p75)	3.53	(2.17-6.15)	7.9	(4.32-17.6)	3.37	0.001
LCR, p50 (p25-p75)	0.63	(0.19-2.62)	0.09	(0.03-0.2)	-3.59	<0.001

We found a significant effect of the NLR on survival in patients admitted to the ICU but not in those not admitted to the ICU (Two-way ANOVA $F_{survival}$ (1, 364) = 5.30, p=0.022; $F_{ICU\ requirement}$ (1, 364) = 4.71, p=0.031). NLR values were highly heterogeneous in patients who did not require ICU admission; consequently, no significant differences were found between survivors and deceased patients (Fisher's LSD test p_{No_ICU} = 0.281). However, among patients admitted to the ICU, those who eventually died had significantly higher NLR values than survivors (p_{ICU} = 0.004). Thus, these results suggest that NLR values may indicate the probability of mortality in ICU-admitted patients. (Fig 1A). On the other hand, LCR was not significantly different in patients admitted or not to the ICU (Fig 1B).

FIGURE 1

A)



B)

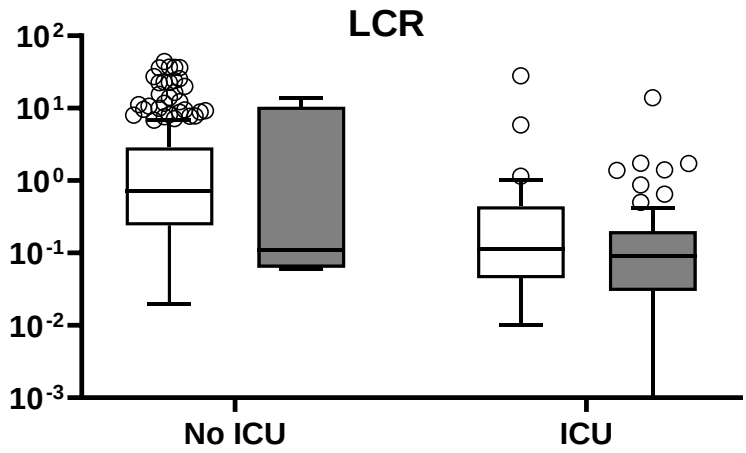


Figure 1. A. NLR values are higher in deceased COVID-19 patients in high-altitude admitted to ICU. **B.** LCR values are highly heterogeneous in survivors and deceased patients. The vertical axis indicates $\log_{10}$ values. $n_{Survivors\_No\_ICU}$ = 285; $n_{Deceased\_No\_ICU}$ = 4; $n_{Survivors\_ICU}$ = 34; $n_{Deceased\_ICU}$ = 45.**: $p<0.01$

2. NLR AND LCR ARE PREDICTORS OF DEATH IN HIGH-ALTITUDE COVID-19 PATIENTS

2mine predictors of mortality in high-altitude COVID-19 patients (Table 2). Our results show that older age, male sex, high band neutrophil count, low PaO_2, high NLR, low LCR, and admission to the ICU are significant predictors of mortality. However, only NLR, LCR, and admission to ICU have good discriminative capacity based on the AUC values (>0.75). ICU admission is the most important predictor of mortality (Table 2).

Table 2. NLR and LCR are predictors of death in high-altitude COVID-19 patients

	Odds ratio	95% CI	*p*-value	AUC	95% CI
Age	1.1	1.0 to 1.1	<0.0001	0.73	0.66 to 0.80
Female sex	0.49	0.23 to 0.99	0.06	0.57	0.49 to 0.65
Band neutrophils	1.1	1.0 to 1.1	0.03	0.61	0.53 to 0.70
Total leukocytes	1	1.0 to 1.1	0.02	0.66	0.57 to 0.75
C-reactive protein	1	1.0 to 1.0	0.0001	0.75	0.67 to 0.83
Lactate	1	0.99 to 1.1	0.15	0.58	0.47 to 0.68
PaO_2	0.98	0.97 to 0.99	0.004	0.63	0.56 to 0.70
$PaCO_2$	1	1.0 to 1.0	0.05	0.59	0.50 to 0.68
NLR	1.2	1.1 to 1.2	<0.0001	**0.76**	0.69 to 0.83
LCR	0.82	0.65 to 0.95	0.04	**0.78**	0.65 to 0.95
Admission to ICU	94	36 to 327	<0.0001	**0.91**	0.86 to 0.95

CI: confidence intervals; ICU: intensive care unit

Table 3. NLR and LCR are predictors of ICU requirement in high-altitude COVID-19 patients

	Odds ratio	95% CI	*p*-value	AUC	95% CI
Age	1	1.0 to 1.1	<0.0001	0.68	0.62 to 0.75
Female sex	0.42	0.22 to 0.75	0.01	0.58	0.52 to 0.65
Band neutrophils	1.1	1.0 to 1.1	0.06	0.6	0.53 to 0.67
Total leukocytes	1.1	1.1 to 1.2	<0.0001	0.67	0.60 to 0.74
C-reactive protein	1	1.0 to 1.0	<0.0001	0.76	0.70 to 0.83
Lactate	1	0.97 to 1.1	0.31	0.61	0.53 to 0.69
PaO_2	0.99	0.98 to 1.0	0.02	0.58	0.51 to 0.64
$PaCO_2$	1	0.99 to 1.0	0.27	0.55	0.48 to 0.62
NLR	1.2	1.1 to 1.3	<0.0001	**0.79**	**0.74 to 0.84**
LCR	0.82	0.69 to 0.93	0.009	**0.8**	**0.74 to 0.86**

CI: confidence intervals

3. NLR AND LCR ARE GOOD PREDICTORS OF INTENSIVE CARE UNIT REQUIREMENT IN HIGH-ALTITUDE COVID-19 PATIENTS

Since patients admitted to ICU are clearly at higher risk of death, we investigated which clinicalparameters can be used as predictors of requiring ICU admission. We found that male sex, high total leukocytes, low PaO_2, high NLR, and low LCR can significantly predict ICU requirement. Moreover, NLR and LCR are the only parameters with good discriminative power (Table 3).

Table 4. ROC curve analysis for NLR and LCR in high-altitude COVID-19 patients

NLR as predictor of:	**AUC**	**95% CI**	**Cut-off value**	**Sensitivity**	**Specificity**
ICU requirement	0.79	0.74 to 0.83	>4.47	77.22	68.17
Death	0.76	0.71 to 0.8	>5.06	71.43	68.03
LCR as predictor of:					
ICU requirement	0.8	0.75 to 0.84	≤0.2	72.0	78.17
Death	0.78	0.73 to 0.82	≤0.2	76.6	73.93

ICU: intensive care unit

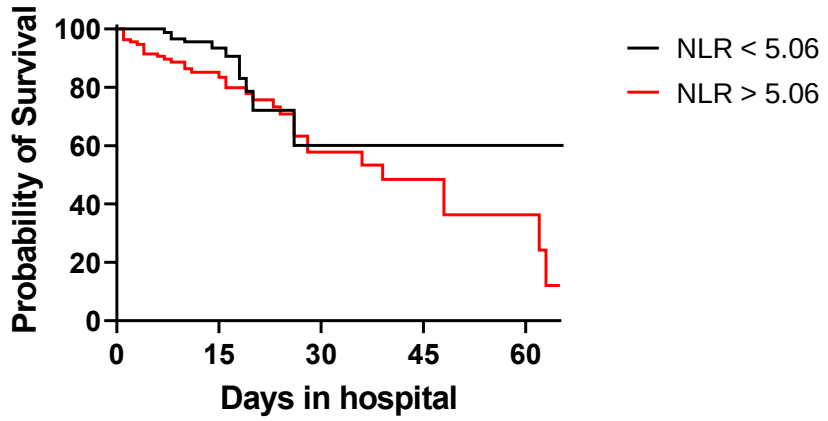
4. ROC CURVE ANALYSIS FOR NLR IN HIGH-ALTITUDE COVID-19 PATIENTS

Finally, we determined the cut-off values for NLR and LCR as predictors of ICU requirement and death. ROC curves showed that NLR values higher than 4.47 indicate a high risk of requiring ICU admission, while values greater than 5.06 predict a high risk of death. On the other hand, for LCR ≤ 0.2 was determined as

the cut-off value for both the odds of requiring ICU and death (Table 4). Consistently, patients with NLR greater than 5.06 had a lower probability of survival after 20 days of hospitalization. A similar trend was observed in patients with LCR equal to or lower than 0.2 (Figure 2).

FIGURE 2

A)



B)

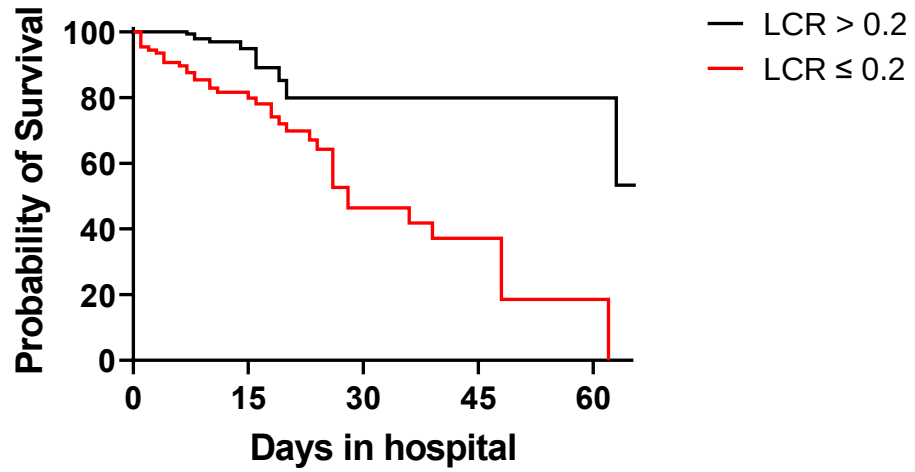


Figure 2. High-altitude COVID-19 patients with NLR > 5.06 AND LCR ≤ 0.2 have lower probabilities of survival.

Discussion

In this work, we investigated the potential predictive capacity of NLR and LCR for the severity of SARS-CoV-2 infection in patients permanently residing at high altitude (3,050 masl, Huaraz, Peru). The main findings are that: (i) patients with NLR values lower than 4.47 do not require ICU admission, (ii) patients with NLR values between 4.47 and 5.06 will require ICU but are at low risk of death, (iii) patients with NLR greater than 5.06 are at high risk of death, and (iv) patients with LCR less than or equal to 0.2 are at high risk of death.

COVID-19 presents a wide range of symptoms, with most cases being mild and self-limited [34]. However, the disease can have fatal consequences when it progresses to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) and multiple organ failure [35]. Inflammation plays an important role in the development and progression of COVID-19 as the hemostatic system acts in concert with inflammation. Following the inflammatory response, various mediators activate the hemostatic system through endothelial dysfunction, platelet activation, and coagulation, promoting thrombosis, also known as thromboinflammation [36–38]. The inflammasome acquires special relevance in this process since stimulation promotes innate and adaptive immune responses [36–38]. This results in a generalized inflammatory response with the release of proinflammatory cytokines and interleukins [39,40]. It is known that people infected with COVID-19

have a dysregulated immune system that can cause an abnormal immune response [41]. For patients who become critically ill, timely identification and intervention are necessary to reduce hospital stays and mortality. Circulating inflammatory biomarkers can be used to assess disease severity and potentially predict disease progression. One of these biomarkers is the NLR, which can be easily obtained from a simple blood test by dividing the number of neutrophils by the number of lymphocytes. Traditionally, the NLR has been used as a predictor of morbidity and mortality in critically ill patients, including cancer [42], heart disease [43], and sepsis [44]. More recently, the NLR was also shown to predict the prognosis of patients with COVID-19[45,46]

The LCR, another circulating biomarker, has also been investigated as a predictor of COVID-19 severity. Historically, LCR has been used as a prognostic marker for various types of cancer, including colon and gastric carcinomas [47,48]. The rationale behind this is that the LCR serves as a good surrogate for the complex host-tumor immunological interactions that result in a systemic inflammatory process, which is believed to contribute to the pathogenesis and progression of these carcinomas [49]. Since COVID-19 also precipitates a systemic inflammatory response, LCR has also been reported as a good prognostic marker for this disease [19].Many mechanisms have been postulated regarding the response of neutrophils and lymphocytes to coronavirus infection. Neutrophils activate the immune system and release reactive oxygen species that can induce damage to cellular DNA and release virus from cells, which is then targeted by antibodies. In addition, neutrophils trigger the production of various cytokines and effector molecules. On the other hand, although the viral infection itself triggers a predominantly lymphocytic response, systemic inflammation, especially elevated interleukin 6, paradoxically lowers the lymphocyte count and resulting cellular immunity. Both factors result in an elevated NLR and LCR [45,50,51]. Therefore, elevated NLR and reduced LCR levels predict inflammation severity.

High and very high-altitude environments are characterized by barometric hypoxia. At the onset of the COVID-19 pandemic, this condition predicted a devastating number of fatalities in these regions. Surprisingly, high-altitude inhabitants, particularly in countries in the Americas and the Tibetan region [29,52] , were found to have lower infection rates and/or fewer severe COVID-19 symptoms compared to lowland inhabitants [29,52]. This epidemiological finding suggests that chronic exposure to hypobaric hypoxia in such high-altitude environments elicits physiological adaptations that may provide some protection against SARS-CoV-2 infection and symptoms. Indeed, these results suggest that the exaggerated immune response (cytokine storm) in low-land is diminished in high-altitude patients.

The results clearly show that NLR values are higher in deceased high-altitude COVID-19 patients who were admitted to the ICU. Indeed, there is a significant effect of NLR on survival in patients admitted to the ICU, suggesting that NLR values may indicate the probability of mortality in patients admitted to the ICU. Indeed, in the ICU-admitted group, patients who eventually died showed significantly higher NLR values than survivors ($p_{ICU} = 0.004$). On the contrary, this effect is absent in patients not admitted to the ICU, in whom NLR values showed great heterogeneity. Furthermore, we found that older age, male sex, high neutrophil band, low PaO_2, high NLR, low LCR and ICU admission are significant predictors of mortality. Of these, ICU admission is clearly the most important risk factor. Furthermore, we investigated whether older age, male sex, high total leukocytes, low PaO_2, high NLR and low LCR can significantly predict the need for ICU admission. Of all these parameters, NLR and LCR have the best discriminative power. Finally, ROC analysis showed that patients with NLR higher than 5.06 and LCR lower than 0.2 had lower odds of survival after 20 days of hospitalization. However, there are some limitations to our study. Our data was collected from a single hospital, and the results need to be validated in other high-altitude medical centers. Moreover, multicenter studies with larger cohorts are required to validate the reproducibility of the optimal cut-off point and the prognostic value for NLR and LCR found in this work.

In conclusion, although our results suggest that both NLR and LCR have good predictive power of mortality, only NLR is sensitive enough to identify patients requiring ICU admission at low risk of death. The cut-off values calculated for LCR are not useful in distinguishing the probabilities of ICU need and death. Since NLR and LCR are simple and readily available indicators, our results are of high clinical value in high-altitude hospitals.

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