

Letter to the Editor

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Common laboratory tests as indicators of COVID-19 severity on admission at high altitude: a single-center retrospective study in Quito (ECUADOR)

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To the Editor,

The current outbreak of SARS-Cov-2, a virus responsible for the coronavirus disease (namely COVID-19) in Wuhan (CHINA), has infected 107.1 million and caused over 2.34 million deaths worldwide (<https://www.worldometers.info/coronavirus/>). The main symptoms after infection are fever, dry cough, and fatigue, although disease severity can increase thereafter showing strong inter-individual differences. At worst, severe cases (4.7–6.1%) quickly progress to an acute respiratory distress syndrome (ARDS), septic shock, difficult-to-correct metabolic acidosis, coagulation dysfunction, and multiple organ failure. The fatality rate indeed reaches a 61.5% of the critically ill patients. In the fight against the coronavirus pandemic, prediction of disease severity is an urgent clinical need. COVID-19 prognosis

largely relies on the clinical symptoms and computed tomography exams. In the hope to help risk-stratification and guide the timing of admission, some studies have also reported laboratory fluctuations in routine blood tests, which could become the mainstay for the forecasting of COVID-19 patients and the lessening of mortality [1]. Nevertheless, the characterization of the hematological and biochemical findings predicting COVID-19 severity are preliminary due to the low sample sizes, different proportions of severe patients, and geographic selection bias, and should therefore be taken with caution. Hematological biomarkers of COVID-19 severity requires validation by using larger samples of patients from different geographic localizations and ethnic groups across the globe.

We retrospectively analyzed the laboratory tests of 4,009 confirmed COVID-19 patients at the time of admission in the IESS Hospital Quito Sur in Quito (Ecuador) from March 13 to June 17, 2020. The hospital is the main COVID-19 medical center in the Quito metropolitan area, and it was ideally chosen given its privileged location at 2,850 m height over sea level. Considering the poor tolerance of the Andeans to high altitude illnesses [2], we described the hematological findings associated with COVID-19 severity in a population permanently exposed to the hypoxic environment induced by high altitude (>2,500 m). Written informed consent was waived due to the retrospective nature of the study. We followed the STROBE guidelines to conduct this study. In addition, we also had no access to identifying patient information.

The epidemiological analysis focused on 24 relevant laboratory variables including a hemogram, arterial blood gases, and some combined laboratory tests as biomarkers of systemic inflammation (Table 1). Hematological analysis were performed using a Sysmex XN-550™ Hematology Analyzer (Sysmex America Inc., USA). Arterial blood gasometry was conducted on a RAPIDPoint® 500 blood gas system (Siemens Healthcare GmbH; Germany). Normal

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Table 1: Hemogram and arterial blood gases on admission of COVID-19 patients.

Variable, units	Non-severe		Severe		p-Value	RBC	Reference values
	n	Mean (\pm SD)	n	Mean (\pm SD)			
Hematocrit, %	3,215	43.4 (5.4)	459	43.9 (5.6)	0.046	0.058	38.4–47.3
RBC, $\cdot 10^{12}/L$	3,192	5.1 (0.6)	454	5.2 (0.6)	0.002	0.092	4.5–5.7
MCV, fL	3,240	86.0 (6.6)	466	85.2 (6.6)	0.012	0.092	78–100
RDW-SD, fL	2,891	42.8 (2.9)	408	43.4 (3.0)	<0.001	–0.085	40–55
Hemoglobin, g/dL	3,225	14.9 (2.0)	463	15.4 (2.0)	<0.001	0.148	13.0–16.1
MCH, pg	3,125	29.7 (1.8)	457	29.7 (1.8)	0.521	0.124	26–34
MCHC, g/dL	3,269	34.4 (1.9)	471	34.8 (2.0)	<0.001	–0.014	32–36
Platelets, $\cdot 10^9/L$	3,192	258.9 (73.6)	459	234.7 (74.7)	<0.001	–0.384	150–400
MPV, fL	3,248	8.1 (0.9)	472	8.0 (0.9)	0.573	0.235	7.5–10.0
WBC, $\cdot 10^9/L$	3,152	7.7 (2.9)	441	7.9 (3.1)	0.216	–0.011	4.5–11.0
Neutrophils, $\cdot 10^9/L$	3,143	5.0 (2.7)	430	5.8 (2.8)	<0.001	0.025	2.5–8.0
Lymphocytes, $\cdot 10^9/L$	3,298	1.9 (1.2)	473	1.4 (0.8)	<0.001	–0.038	1–4
Neutrophils, %	3,282	64.5 (15.0)	476	74.3 (12.8)	<0.001	0.286	40–70
Basophils, %	3,200	0.6 (0.3)	464	0.5 (0.3)	<0.001	0.378	0–1
Eosinophils, %	2,636	1.3 (1.2)	300	0.7 (0.9)	<0.001	–0.043	0–5
Monocytes, %	3,212	7.0 (2.4)	466	6.8 (2.9)	0.129	–0.164	0–7
Lymphocytes, %	3,273	25.9 (12.7)	476	17.5 (10.4)	<0.001	–0.337	22–44
NLR	3,298	3.6 (4.5)	473	5.8 (8.6)	<0.001	–0.39	0.83–3.92
PLR	3,298	171.4 (147.7)	473	240.7 (258.0)	<0.001	–0.206	61–239
LeuCR	1,755	4.4 (11.0)	352	0.96 (3.5)	<0.001	–0.386	–
LyCR	1,714	1.6 (4.7)	346	0.5 (2.4)	<0.001	–0.436	–
O ₂ Sat, %	765	94.7 (2.1)	379	88.2 (3.3)	<0.001	–0.95	90–100
PaO ₂ , mmHg	726	72.1 (9.5)	489	49.4 (8.8)	<0.001	–1.000	75–100
PaCO ₂ , mmHg	751	30.5 (4.9)	462	32.9 (5.2)	<0.001	0.244	38–42

Reference ranges: <https://labtestsonline.org/articles/laboratory-test-reference-ranges>. Alpha-value set at 0.05. Rank-Biserial Correlation (r_{bc}) coefficient: <0.10=trivial; 0.10–0.20=small; 0.21–0.40=medium; ≥ 0.50 =large. RBC, red blood cell count; MCV, medium corpuscular volume; RDW-SD, red cell distribution width based on standard deviation; MCH, medium hemoglobin concentration; MCHC, medium corpuscular hemoglobin concentration; MPV, medium platelet volumen; WBC, white blood cell count, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LeuCR, leukocyte-to-C-reactive protein ratio; LyCR, lymphocyte-to-C-reactive protein ratio; O₂ Sat, hemoglobin oxygen saturation; PaO₂, partial arterial O₂ pressure; PaCO₂, partial arterial CO₂ pressure.

distribution of the data was determined by the Kolmogorov–Smirnov test. Confirmed COVID-19 patients were categorized as severe (489 cases: PaO₂ < 60 mmHg; O₂ Sat < 90%) and non-severe (3,520 cases: 726 patients with PaO₂ \geq 60 mmHg; O₂ Sat \geq 90% in addition to 2,794 patients with a pneumonia score index below three) upon admission. The Mann-Whitney U test was conducted for statistical comparisons of non-parametric continuous variables between both Severe and Non-Severe groups, whereas the effect size was estimated by the Rank-Biserial Correlation coefficient (r_{bc}). The demographic analyses of the dataset using the Chi-square test analysis revealed that the prevalence of severe COVID-19 pneumonia in males was greater than in females ($\chi^2(1)=28,382$, $p<0.001$) and increased with age ($W=1.176 \cdot 10^6$, $p<0.001$), which was in agreement with prior studies [3]. As a disease reference, we also presented the laboratory tests of a group of 83 community acquired pneumonia (CAP) patients, which were

performed on admission in the same hospital between November and December of 2018. It was split into Survivors and Non-Survivors groups based on patient mortality (Table 2). These laboratory results were only considered like a reference of the hematological findings found in regular pneumonia at high altitude.

Empowered by one of the largest sample size so far reported, this retrospective epidemiological study describes some peculiar characteristics of COVID-19 patients recruited at high altitude. Firstly, changes in the erythrogram parameters (Table 1) were unexpectedly trivial, at least at high altitude, and therefore not consistently associated with COVID-19 pneumonia severity (Table 1). A reduction of either hemoglobin or red blood cells (RBCs) were not observed in severe COVID-19 as reported by others [1, 3]. Anemia is a determinant risk factor for not only COVID-19 severity [4, 5], but also for CAP in patients permanently living at high altitude

Table 2: Hemogram and arterial blood gases on admission of CAP patients.

Variable, units	Survivors		Non-survivors		p-Value	Reference values
	n	Mean (\pm SD)	n	Mean (\pm SD)		
Hematocrit, %	65	42.0 (8.8)	18	36.7 (7.9)	0.026	38.4–47.3
RBC, $\cdot 10^{12}/L$	56	4.6 (1.1)	16	4 (0.9)	0.020	4.5–5.7
MCV, fL	54	90.7 (5.9)	17	91 (4.5)	0.843	78–100
RDW-SD, fL	47	46.7 (6.1)	14	49.7 (11.1)	0.150	40–55
Hemoglobin, g/dL	63	14.0 (2.9)	17	12.2 (2.6)	0.021	13.0–16.1
MCH, pg	54	30.3 (2.5)	15	30.4 (1.5)	0.856	26–34
MCHC, g/dL	54	33.3 (1.2)	15	33.2 (1.1)	0.305	32–36
Platelets, $\cdot 10^9/L$	63	222 (105)	18	248 (118)	0.315	150–400
MPV, fL	52	9.7 (1.1)	15	9.5 (1.5)	0.535	7.5–10.0
WBC, $\cdot 10^9/L$	65	9.2 (3.9)	18	9.2 (5.1)	0.749	4.5–11.0
Neutrophils, $\cdot 10^9/L$	54	7.7 (4.0)	16	8.1 (4.8)	0.983	2.5–8.0
Lymphocytes, $\cdot 10^9/L$	53	1.2 (0.7)	15	1.1 (0.7)	0.314	1.0–4.0
Neutrophils, %	60	76.2 (12.3)	18	81.9 (10.3)	0.087	40–70
Basophils, %	53	0.3 (0.3)	16	0.4 (0.4)	0.474	0–1
Eosinophils, %	56	1.1 (1.6)	16	0.9 (1.2)	0.973	0–5
Monocytes, %	55	6.5 (2.2)	16	5.5 (3.5)	0.039	0–7
Lymphocytes, %	58	15.5 (10.6)	17	11.9 (6.6)	0.366	22–44
NLR	53	9.1 (7.8)	15	11.1 (8.7)	0.482	0.83–3.92
PLR	54	216.2 (145.6)	15	337.4 (202)	0.021	61–239
O ₂ Sat, %	39	86.7 (9.8)	8	84.8 (22.8)	0.697	90–100
PaO ₂ , mmHg	39	63.3 (20.0)	8	75.4 (33.4)	0.153	75–100
PaCO ₂ , mmHg	39	33.4 (7.5)	8	33.6 (10.9)	0.989	38–42

Reference ranges: <https://labtestsonline.org/articles/laboratory-test-reference-ranges>. Alpha-value set at 0.05. RBC, red blood cell count; MCV, medium corpuscular volume; RDW-SD, red cell distribution width based on standard deviation; MCH, medium hemoglobin concentration; MCHC, medium corpuscular hemoglobin concentration; MPV, medium platelet volumen; WBC, white blood cell count, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; O₂ Sat, hemoglobin oxygen saturation; PaO₂, partial arterial O₂ pressure; PaCO₂, partial arterial CO₂ pressure.

(Table 2). It was then surprising that the average hemoglobin levels in the Severe group was slightly higher compared to the Non-Severe group (Table 1), perhaps because of alteration of the hemoglobin mass [2]. The increase of the red width distribution (RDW) with COVID-19 severity [5] was trivial in our analysis. Some hypothesis should be put forward. Perhaps the high altitude-induced alteration of RDW [6] could specifically dampen RBCs and hemoglobin changes associated with COVID-19 severity, since it did not prevent anemia leading to fatal CAP outcomes (Table 2). A comparative study between the hematological findings in COVID-19 patients living at sea level with those residing at high altitude may shed some light on this hypothesis.

A second striking finding is that we found no significant differences in the counts of WBCs across Non-Severe and Severe groups as a metanalysis stated [1]. The reason is unknown, but an excessive neutrophil percentage in severe cases was likely to provoke a compensatory reduction in lymphocytes (Table 1) during the severe progression of COVID-19 [7]. In support of this hypothesis the neutrophil-

to-lymphocyte ratio (NLR), a biomarker of systemic inflammatory response (Table 1) actually predicted admission to the intensive care unit in the patients of the Severe group [8]. Of note, COVID-19 severity was not associated with a significant reduction of the percentage of monocytes as it was the case of CAP (Table 2). Another inflammation biomarker, the platelet-to-lymphocyte ratio (PLR) predicted illness severity either in COVID-19 or in CAP patients living at high altitude. Finally, the leukocyte-to-C-protein ratio (LeuCR), a novel composed laboratory test parameter based on prior evidence [7], showed the largest reduction with COVID-19 severity, so that its potential as a biomarker of systemic inflammation in COVID-19 awaits future research.

In summary, even if there is no doubt that specific hematologic fluctuations contribute to the worst clinical outcomes of COVID-19 [1], largely those denoting a hyperinflammation state [9, 10], the influence of the erythrogram changes were unexpectedly trivial in patients suffering from severe COVID-19 at high altitude. This posits the intriguing hypothesis that hematological fluctuations associated with the exposure to high altitude-induced

hypoxia could have an impact in the progression of coronavirus disease to ARDS.

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