Microbes, Infection and Chemotherapy

IDEAS AND OPINIONS

https://doi.org/10.54034/mic.e1172

Geographic Altitude and COVID-19: Parameters for a better recognition of severe disease

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Submitted: june 26, 2021
Reviewed : july 28, 2021
Approved : august 18, 2021

How to cite: Pecho-Silva S, Navarro-Solsol AC, Panduro-Correa V, Bonilla-Aldana K, Rodriguez-Morales AJ. Geographic Altitude and COVID-19: Parameters for a better recognition of severe disease. Microbes Infect Chemother. 2021; 1: e1172.

Infection with SARS-CoV-2 and COVID-19 disease has already claimed the lives of 3,122,538 people globally. Although official figures indicate that until April 25, 2021 there are 147,783,379 people in the world who have had or have the infection (1), the real seroprevalence for SARS-CoV-2 is really unknown. The first study indicated that 643 million people in the world would have been infected by SARS-CoV-2 when at that time 56.5 million cases were reported worldwide (2). This is almost 10 times the official figure, therefore, in May 2021, we would expect that more than 1.4 billion people will have been infected by this virus, this is equivalent to 23% of the world population. About 2% of the entire world population lives above 2,500 meters above sea level (masl) (3).

Some authors postulate that living at a higher geographic altitude, especially above 2,500 meters above sea level, provides some protection against SARS-CoV-2 infection due, among other factors, to higher production of angiotensin-converting enzyme and lower number of receptors for this enzyme, greater tolerance to Hypoxemia, a higher level of hemoglobin, greater presence of ultraviolet radiation that would inactivate the virus, lower temperature and lower humidity, adaptive processes to inflammation caused by lower barometric pressure, greater relative physical activity, greater exposure to ultraviolet rays and greater synthesis of vitamin D, among others; however, all these aspects are no more than unconfirmed hypotheses(4,5).

On the other hand, another argument in favor of the supposed protection of geographical altitude and lower barometric pressure revolves around the fact that a lower prevalence of COVID-19 has been reported at a higher level of geographical altitude. However, this fact has two objections: 1) in developing countries, cities that are at a higher level of geographical altitude tend to be of less socioeconomic development with less access to health systems, therefore, they were evaluated and diagnosed less frequently. giving a false sense of a lower prevalence; and 2) in many cities located at a higher geographical altitude, especially in developing countries, the main economic activities are cattle ranching, grazing, or agriculture, so the houses are very far from each other and the population density is much lower than predominantly urban cities. This factor of social distancing typical of these cities also causes less transmission from person to person(6–8).

Thus far, it cannot be said that living above 2,500 meters above sea level entails a lower risk of acquiring the SARS-CoV-2 infection, of developing the COVID-19 disease or of presenting a severe disease (9–13), therefore, it is expected that at least 23% of the inhabitants of the high-altitude cities will present the infection by SARS-CoV-2.

Some authors have tried to calculate what PaO2 and SatO2 are from small samples or from healthy participants and / or athletes who are far from the common population. Therefore, it is not possible to extrapolate the results to be able a priori to determine the normal value of PaO2 or SatO2 for each altitudinal floor and thus be able to define the degree of severity of the COVID-19 disease (14,15). On the other hand, the clinical classification of severity of the disease by COVID-19 is based fundamentally on clinical criteria: respiratory rate, oxygen saturation measured at sea level, in some cases, the measurement of PaO_2 / FiO_2 is used and in other cases the extension of bronchopneumonic lesions in the lung parenchyma is used (Table 1). However, to date it has not been possible to determine a crucial point: What would be the oxygen saturation value that defines the severity of the COVID-19 disease best suited to determine hypoxemia or respiratory failure at different geographical altitudes? (16–21).

This pandemic has surprised us when we find ourselves without knowing what the normal average saturation is at different altitudinal floors, and it is a priority to start the respective scientific studies to obtain them. Likewise, we need a practical attitude at this time to detect hypoxemia at each altitude level and the corresponding acute respiratory failure.

A proposal of our work group is the measurement of oxygen saturation by pulse oximetry in healthy relatives, the health team, and the population of different ages and sexes in the community to empirically determine a normal saturation range (22,23). As a second step and taking into account that for the CDC the severe degree of disease in patients with chronic lung disease (chronic hypoxemia) is defined by a 3% decrease from the baseline value (19), it is that we propose that this is the way to determine the degree of hypoxemia / acute respiratory failure in city dwellers that are above 2,500 meters above sea level, that is, it is defined as severe in-hospital management disease that requires the use of oxygen therapy for patients with COVID-19 who present a decrease of 3% in $SatO_2$ with respect to the lower limit of normality of the average normal range determined for the geographical altitude in which the patient is located.

The other components such as respiratory rate, extent of lung lesions, and PaO_2 / FiO_2 could not be taken as references because both respiratory rate and PaO_2 / FiO_2 are directly influenced by barometric pressure and therefore by higher geographical altitude and there are no references for adaptation (13). While the extension of the pulmonary lesion itself as the only parameter does not determine a real clinical severity, taking into account that in the evolution of COVID-19 lesions in “ground glass”, “crazy paving” and consolidation can occur and that the clinical severity may be determined more by the type of injury than by the extent: consolidation rather than "ground glass" (16–21).

We believe it is convenient to promote the development of an altitude medicine that is responsible for determining the standardized normal values of $SatO_2$, PaO_2, and PaO_2 / FiO_2, among others, for each geographical altitude. This determination will not be easy since these parameters will have to be adapted to each condition of the inhabitant of high altitudes, such as sociodemographic and adaptive factors (residence time, acclimatization, coexistence of other altitude-related diseases: acute mountain sickness or bad of chronic mountain, etc.) but for

Author	Severe COVID-19 at Sea Level up to 2500 masl	Severe COVID-19 for residents residing at ≥ 2500 masl
OMS(16) NICE(17)	Severe pneumonia: SatO2 <90% or respiratory rate (RR)> 30 or Signs of ARDS. NICE further indicates that to identify severe COVID-19 patients in the community, a threshold of <94% should be used.	Not established
NIH(18)	At least some of them: SatO2 <94%. RR> 30. PaO2 / FiO2 ≤ 300 mmHg. Pulmonary infiltrates> 50%	Not established
CDC(19)	At least some of them: SatO2 <94% (for patients with chronic hypoxemia, a decrease from baseline of> 3%). RR> 30. PaO2 / FiO2 ≤ 300 mmHg. Pulmonary infiltrates> 50%	Not established
IDSA(20)	SatO2 ≤ 94 including patients receiving supplemental oxygen	Not established
Australian guide (21)	Any: RR ≥30, SatO2 ≤ 92 at rest or PaO2 / FiO2 ≤ 300	Not established
Pecho-Silva et al.	One or more of: RR ≥ 30 or PaO2 / FiO2 ≤ 300 mmHg. o, SatO2 / FiO2 <310-460 o, Respiratory Work ≥ 2 o, ARDS Type L or Pulmonary infiltrates> 50%, predominant consolidation type, or SatO2 <94%. In patients with chronic hypoxemia, a decrease from the baseline of> 3%.	Proposal: For patients residing above 2500 masl, Severe COVID-19 is defined as a decrease of ≥ 3% from the lower limit of normality estimated as normal in SatO2 for the geographical altitude in which the patient resides

the moment we need to standardize the definitions and be able to intervene early with oxygen therapy to reduce mortality from this disease.

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Conflict of interest: None

Funding: None

Authors' contributions: All authors wrote the draft, reviewed the manuscript, and approved the final version.