ORIGINAL ARTICLE

Clinical syndromes of acute and chronic COVID-19 infection among an indigenous high-altitude population during the first and second waves

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ABSTRACT

Objective: To classify into clinical syndromes the symptoms of acute and chronic COVID-19 infection among a high-altitude population during the first and second waves.
Materials and methods: A prospective and longitudinal study. An online questionnaire was administered to people infected with SARS-CoV-2 during the first and second waves from March 2020 to December 2021. The measures of central tendency were expressed as means and percentages with a 95 % confidence interval. The chi-square test associated the variables and considered a *p* value ≤ 0.05. IBM SPSS Statistics statistical software V22 was used.
Results: A total of 87 women and 63 men with an average age of 44.12 (± 14.56) years participated in the research, out of whom 48.70 % and 51.30 % were infected in the first and second waves, respectively. The 59 reported symptoms were grouped into 19 syndromes for the acute phase and 18 for the chronic phase. The most frequent syndromes in the acute phase were acute incomplete toxic infectious disorders (79.30 %), taste and smell disorders (60.70 %) and anxiety and depressive disorders (56.79 %). Chronic COVID was called post-COVID-19 syndrome and was subdivided into three phases: post-acute, chronic and long-haul. In the post-acute and chronic phases, muscle fatigue and weakness as well as pain and aches appeared, persisting until the long-haul phase, where lingering symptoms were considered sequelae. Post-COVID-19 syndrome occurred in 64.55 % of the participants.
Conclusions: This study has shown an increased frequency of symptoms affecting the central and peripheral nervous system in both the acute phase and post-COVID-19 syndrome. It is possible that hypobaric hypoxia, by prolonging inflammation and stimulating oxidative stress, may lead to a longer post-COVID-19 syndrome, with a greater impact on the nervous system.

Keywords: COVID-19; Hypoxia; Altitude (Source: MeSH NLM).

INTRODUCTION

In December 2019, an outbreak of viral pneumonia caused by a novel coronavirus called SARS-CoV-2, which causes the clinical entity COVID-19, was reported in Wuhan city, Hubei province, China [1,2].

SARS-CoV-2 replication begins as soon as the virus binds to the host cell through interactions between the spike protein (S protein) of the virus and the target protein of the cell. In this phase, the virus interacts with the angiotensin-converting enzyme 2 (ACE2) and a transmembrane serine protease 2 (TMPRSS2) on the outer surface of the cell membrane; inside the cell, the replication and transcription phases begin.

COVID-19 infection causes a multisystem inflammatory syndrome due to the action of the virus on the immune system, which severely compromises the function of all organs and systems. Symptoms in mild cases are fever, chills, headache, myalgia, pharyngitis, rhinorrhea, nausea, vomiting and diarrhea or lower respiratory tract symptoms such as cough. Typical symptoms are loss of taste and smell in early stages of the disease [1,2].

In severe cases, there are symptoms of respiratory failure, systemic complications such as pneumonia and acute kidney failure, determined by the presence of high levels of proinflammatory cytokines including interleukin 1 (IL-1), interleukin (IL-2), interleukin 6 (IL-6), granulocyte-colony stimulating factor (G-CSF), chemokine 10 (IP-10) and tumor necrosis factor alpha (TNF-α), a condition referred to as cytokine storm [2].

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The acute phase of COVID-19 is the two-week period following the onset of symptoms, which can extend for up to four weeks in moderate to severe cases [3].

Lingering symptoms have been reported and it has been observed that, 12 months after infection, only 22.9 % were asymptomatic [4]. The persistence of symptoms after the acute infection has led to coin the term post-COVID-19 syndrome, whose diagnosis includes signs and symptoms that develop during or after the acute infection, continue for more than four weeks and are not explained by an alternative diagnosis [5-7].

The most long-lasting symptoms are physical fatigue, difficulty breathing, myalgias, arthralgias, headache, cough, chest pain, loss of smell and taste, persistent diarrhea, cognitive impairment, memory loss, anxiety and sleep disorders; the persistence of such symptoms decreases the quality of life [8]. In Bolivia, there is no scientific evidence on the clinical characteristics of the acute phase or the post-COVID-19 syndrome.

A rough record of the beginning and end of the first two COVID-19 waves shows that the first wave started on March 9, 2020, and ended on August 8, 2020, and the second wave started on November 18, 2020, and ended on January 30, 2021 [9].

In the context of a high-altitude environment (2,000-4,150 meters above sea level [m a.s.l.]), it is important to generate scientific evidence to classify the acute and chronic clinical picture of this infection, based on the fact that hypobaric hypoxia may act as an additional risk factor. Moreover, it is known that high-altitude inhabitants of this region have not yet genetically adapted to high altitude and that severe complications of COVID-19 begin with respiratory compromise and gas exchange, although scientific evidence at some point considered that this environmental condition could behave as a protective factor, a fact that has not been proven over time [10,11].

The objective of this study was to classify the acute and chronic infection of COVID-19 into clinical syndromes in a high-altitude population from March 2020 to December 2021.

MATERIALS AND METHODS

Study design and population

A prospective and longitudinal study conducted in an indigenous high-altitude population (2,000–4,150 m a.s.l.) with SARS-CoV-2 infection—i.e., COVID-19—from March 2020 to December 2021 (first and second waves).

A convenience sampling was used; subjects were recruited through a survey created in Google Forms and sent by email, WhatsApp and/or telephone.

The survey considered the sociodemographic variables, significant history of diseases and symptoms of the acute phase; in addition, it included the option of mentioning symptoms not listed. The chronic phase was called post-COVID-19 syndrome and was subdivided into three phases: post-acute, chronic and long-haul (persistent COVID-19). During the post-COVID-19 syndrome follow-up, a survey which included lingering symptoms was sent every three weeks. A total of 223 subjects participated in the study and 150 were selected according to the inclusion and exclusion criteria.

Variables and measurements

Sociodemographic variables, such as place of origin and residence, age, gender, profession and occupation, were considered. Acute and chronic symptoms were surveyed; information on the latter was provided every three weeks until 36 weeks were completed.

People born or living in regions of the Bolivian plains were excluded, as well as those who did not complete the follow-up questionnaire, those with a history of underlying diseases, those under 17 years of age and those reinfected.

Statistical analysis

The measures of central tendency were expressed as means and percentages with the corresponding standard deviation and significance level. The variables were associated using the chi-square test with p value ≤ 0.05 and 95 % confidence interval. The results were processed using the IBM SPSS Statistics V22 statistical software.

Ethical considerations

The study meets the International Ethical Principles for Medical Research Involving Human Subjects and was approved by the Institutional Ethics Committee.

RESULTS

Data from 150 participants were analyzed. Out of these, 92.00 % were from the department of La Paz, 5.30 % from Oruro, 1.30 % from Cochabamba, 0.70 % from Potosí and 0.70 % from Chuquisaca; 95.30 % lived in the city of La Paz, 3.30 % in the city of El Alto and 1.30 % in the city of Cochabamba.

A total of 87 women and 63 men participated in the study. In the first wave, 48.70 % of the subjects were infected, 28.00 % of whom were females and 20.70 % were males. In the second wave, 51.30 % were infected, 30.00 % of whom were females and 21.30 % were males.

The mean age was 44.12 years (SD ± 14.56; CI: 41.77-46.47): 44.21 (SD ± 15.29) for females and 44 (SD ± 15.293) for males.

Regarding their marital status, 54.00 % were married, 31.30 % single, 8.00 % divorced, 5.30 % widowed and 1.40 % cohabiting.

As for their educational level, 38.00 % were professionals and 20.70 % university students; 17.30 % had a graduate degree; 5.30 % were high-level technicians and 4.70 % mid-level technicians; 11.30 % completed secondary school and 2.70 % only elementary school.

The 59 reported symptoms were divided into two groups: 19 syndromes for the acute phase and 18 for the chronic phase.

1. Acute complete toxic infectious disorders syndrome: fever (temperature ≥ 38 °C), general malaise, asthenia, adynamia, hyporexia, odynophagia, dysphonia, aphonia, arthralgias, myalgias, night sweats, chills and headache.

2. Acute incomplete toxic infectious disorders syndrome: body temperature above normal or low-grade fever (temperature between 37.0 and 37.5 °C) and all the symptoms of the complete toxic infectious disorders syndrome with the exception of fever.

3. Chronic incomplete toxic infectious disorders syndrome: all the symptoms of the acute incomplete toxic infectious disorders syndrome, except for the low-grade fever, after the fourth week of infection.

4. Respiratory distress syndrome: respiratory distress or dyspnea.

5. Non-productive bronchial disorders syndrome: dry cough.

6. Productive bronchial disorders syndrome: coughing up mucus, purulent sputum or bloody mucus.

7. Gastrointestinal disorders syndrome: nausea, vomiting, diarrhea, biliary colic and constipation.

8. Muscle fatigue and weakness syndrome: muscle weakness, loss of muscle strength and loss of muscle mass.

9. Taste and smell disorders syndrome: anosmia, ageusia, dysgeusia, loss of taste, phantosmia and parosmia.

10. Anxiety and depressive disorders syndrome: mood disturbances, anxiety, depression and sleep disturbances (insomnia or excessive daytime sleepiness).

11. Neurosensory disorders syndrome: paresthesia in the face, palms and soles.

12. Eye pain syndrome: periorbital pain and burning sensation in the eyes and/or loss of visual acuity.

13. Skin and appendages disorders syndrome: hair loss, alopecia, changes in nail texture, skin lesions (spots, macules, etc.).

14. Autonomic disorders syndrome: palpitations and orthostatic/postural dizziness or lightheadedness.

15. Pain and aches syndrome: back pain, low back pain and thoracic back pain.

16. Chest pain syndrome: costal or intercostal pain.

17. Odontalgia syndrome: pain in dental pieces or gums.

18. Cognitive disorders syndrome: lack of concentration, loss of memory and memory lapses.

19. Ear disorders syndrome: earache, tinnitus, ringing and buzzing.

The chronic phase was called post-COVID-19 syndrome and was divided into three phases: a) post-acute, from week four to twelve; b) chronic, from week thirteen to twenty-three; and c) long-haul, from week twenty-four to thirty-six.

The following table shows that the most frequent syndromes in the acute phase were acute incomplete toxic infectious disorders syndrome, taste and smell disorders syndrome, and anxiety and depressive disorders syndrome (Table 1).

Table 1. Frequency of clinical syndromes: COVID-19 acute phase, first and second waves

COVID-19 acute phase - First and second waves						
Clinical syndromes	First wave *N* = 73		Second wave *N* = 77		Total first and second waves	
	n	%	*n*	%	*N*	%
Acute incomplete toxic infectious disorders	59	39.30	60	40.00	119	79.30
Acute taste and smell disorders	47	31.30	44	29.30	91	60.70
Acute anxiety and depressive disorders	43	28.70	42	28.00	85	56.70

COVID-19 acute phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Acute pain and aches	38	25.30	41	27.30	79	52.70
Acute muscle fatigue and weakness	36	24.00	45	30.00	81	54.00
Acute gastrointestinal disorders	24	16.00	25	16.70	49	32.70
Acute respiratory distress	24	16.00	25	16.70	49	32.70
Acute eye pain	19	12.70	23	15.30	42	28.00
Acute non-productive bronchial disorders	15	10.00	28	18.70	43	28.70
Acute cognitive disorders	19	12.70	14	9.30	33	22.00
Acute autonomic disorders	11	7.30	19	12.70	30	20.00
Acute peripheral disorders	14	9.40	15	10.10	29	19.50
Acute skin and appendages disorders	12	8.00	17	11.30	29	19.30
Acute productive bronchial disorders	8	5.30	13	8.70	21	14.00
Acute chest pain	4	2.70	9	6.00	13	8.70
Acute complete toxic infectious disorders	3	2.00	10	6.70	13	8.70
Acute odontalgia	8	5.30	4	2.70	12	8.00
Acute asymptomatic	7	4.70	3	2.00	10	6.70
Acute ear disorders	3	2.00	2	1.30	5	3.30

In the acute incomplete toxic infectious disorders syndrome, general malaise occurred in 60.70 %, headache in 58.00 %, myalgias in 50.00 %, arthralgias in 40.00 %, hyporexia in 40.00 %, night sweats in 38.00 %, odynophagia in 37.30 %, chills in 37.30 % and body temperature above normal in 29.30 % of the study subjects.

Acute taste and smell disorders syndrome was reported by 60.70 % of the participants, out of whom 48.70 % had anosmia, 45.30 % ageusia, 28.70 % nasal congestion, 22.70 % loss of taste and 13.30 % rhinorrhea.

Anxiety and depressive disorders syndrome were reported by 56.70 % of the participants: anxiety by 45.30 %, depression by 32.00 %, insomnia by 30.00 % and excessive daytime sleepiness by 25.30 %.

The syndromes of the post-COVID-19 syndrome are described by phases hereinbelow.

In the post-acute phase, post-acute incomplete toxic infectious syndrome was reported by 66.00 % of the participants, out of whom 33.30 % had general malaise, 27.30 % headache, 26.00 % myalgias, 21.30 % arthralgias, 17.30 % odynophagia, 16.70 % night sweats, 14.00 % hyporexia and 5.3 % chills. Taste and smell disorders syndrome was reported by 35.30 % of the subjects, out of whom 48.70 % reported anosmia, 45.30 % dysgeusia, 28.70 % nasal obstruction, 22.70 % loss of taste and 13.30 % rhinorrhea. Anxiety and depressive disorders syndrome was reported by 30.00 % of the participants, out of whom 21.30 % had anxiety, 19.30 % depression, 16.00 % insomnia and 15.30 % excessive daytime sleepiness (Table 2).

Table 2. Frequency of clinical syndromes: COVID-19 post-acute phase, first and second waves

COVID-19 post-acute phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Post-acute incomplete toxic infectious disorders	52	34.70	47	31.30	99	66.00
Post-acute taste and smell disorders	26	17.30	27	18.00	53	35.30
Post-acute anxiety and depressive disorders	24	16.00	21	14.00	45	30.00
Post-acute muscle fatigue and weakness	25	16.70	19	12.70	44	29.30
Post-acute pain and aches	29	19.30	13	8.70	42	28.00
Post-acute respiratory distress	18	12.00	13	8.70	31	20.70

COVID-19 post-acute phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Post-acute skin and appendages disorders	15	10.00	13	8.70	28	18.70
Post-acute gastrointestinal disorders	15	10.00	11	7.30	26	17.30
Post-acute cognitive disorders	15	10.00	10	6.70	25	16.70
Post-acute non-productive bronchial disorders	10	6.70	12	8.00	22	14.70
Post-acute odontalgia	11	7.30	7	4.70	18	12.00
Post-acute eye pain	8	5.30	9	6.00	17	11.30
Post-acute autonomic disorders	11	7.30	5	3.30	16	10.70
Post-acute peripheral disorders	14	9.30	2	1.30	16	10.70
Post-acute asymptomatic	9	6.00	5	3.30	14	9.30
Post-acute complete toxic infectious disorders	3	2.00	5	3.30	8	5.30
Post-acute productive bronchial disorders	4	2.70	3	2.00	7	4.70
Post-acute chest pain	4	2.70	2	1.30	6	4.00
Post-acute ear disorders	3	2.00	1	0.70	4	2.70

In the chronic phase, 36.70 % of the participants were asymptomatic; chronic incomplete toxic infectious disorders syndrome was reported by 28.70 % of the study subjects, out of whom 18.00 % had headache, 10.70 % arthralgias, 9.30 % myalgias, 6.70 % night sweats, 5.30 % odynophagia and 2.70 % hyporexia (Table 3).

At this phase, the pain and aches syndrome persisted in 18.00 % of the participants. Taste and smell disorders syndrome was still reported by 16.70 % of the participants, out of whom 6.70 % had loss of taste, 4.0 % dysgeusia, 4.0 % phantosmia (perception of non-existent odors), 2.0 % parosmia (perception of odors different from the real ones) and 0.7 % anosmia.

Table 3. Frequency of clinical syndromes: COVID-19 chronic phase, first and second waves

COVID-19 chronic phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Chronic asymptomatic	18	12.00	37	24.70	55	36.70
Chronic incomplete toxic infectious disorders	27	18.00	16	10.70	43	28.70
Chronic pain and aches	16	10.70	11	7.30	27	18.00
Chronic taste and smell disorders	15	10.00	10	6.70	25	16.70
Chronic muscle fatigue and weakness	16	10.70	7	4.70	23	15.30
Chronic anxiety and depressive disorders	16	10.70	6	4.00	22	14.70
Chronic gastrointestinal disorders	4	2.70	1	0.70	22	14.70
Chronic cognitive disorders	12	8.00	8	5.30	20	13.30
Chronic skin and appendages disorders	10	6.70	9	6.00	19	12.70
Chronic eye pain	6	4.00	10	6.70	16	10.70
Chronic respiratory distress	8	5.30	7	4.70	15	10.00
Chronic autonomic disorders	13	8.70	2	1.30	15	10.00
Chronic odontalgia	7	4.70	5	3.30	12	8.00
Chronic peripheral disorders	7	4.70	4	2.70	11	7.30
Chronic non-productive bronchial disorders	3	2.00	5	3.30	8	5.30
Chronic ear disorders	3	2.00	2	1.30	5	3.30
Chronic productive bronchial disorders	1	0.70	3	2.00	4	2.70

COVID-19 chronic phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Chronic chest pain	0	0.00	1	0.70	1	0.70
Chronic complete toxic infectious disorders	0	0.00	0	0.00	0	0.00

There is an association between muscle fatigue and weakness syndrome and wave number. Chi square: 0.029. There is an association between muscle fatigue and weakness syndrome and gender. Chi-square: 0.032.

In the long-haul phase, 60.00 % of the participants were asymptomatic; chronic incomplete toxic infectious disorders syndrome was reported by 21.30 %, out of whom 10.70 % still had headache, 8.70 % arthralgias, 5.30 % myalgias, 4.00 % hyporexia, 2.70 % odynophagia and 0.7 % general malaise. Muscle fatigue and weakness was reported as a lingering symptom by 12.07 % of the participants, out of whom 11.30 % had back pain (Table 4).

Table 4. Frequency of clinical syndromes: COVID-19 long-haul phase, first and second waves

COVID-19 long-haul phase - First and second waves						
Clinical syndromes	First wave N = 73		Second wave N = 77		Total first and second waves	
	n	%	n	%	N	%
Long-haul asymptomatic	35	23.3	55	36.70	90	60.00
Long-haul incomplete toxic infectious disorders	23	15.30	9	6.00	32	21.30
Long-haul muscle fatigue and weakness	12	8.00	7	4.70	19	12.70
Long-haul pain and aches	12	8.00	3	2.00	15	10.00
Long-haul anxiety and depressive disorders	9	6.00	5	3.30	14	9.30
Long-haul skin and appendages disorders	7	4.70	5	3.30	12	8.00
Long-haul cognitive disorders	9	6.00	2	1.30	11	7.30
Long-haul taste and smell disorders	2	1.30	8	5.30	10	6.70
Long-haul respiratory distress	8	5.30	2	1.30	10	6.70
Long-haul eye pain	4	2.70	5	3.30	9	6.00
Long-haul peripheral disorders	6	4.00	2	1.30	8	5.30
Long-haul odontalgia	5	3.00	2	1.30	7	4.70
Long-haul autonomic disorders	4	2.70	2	1.30	6	4.00
Long-haul non-productive bronchial disorders	3	2.00	0	0.00	3	2.00
Long-haul chest pain	3	2.00	0	0.00	3	2.00
Long-haul productive bronchial disorders	1	0.70	0	0.00	1	0.70
Long-haul ear disorders	1	0.70	0	0.00	1	0.70
Long-haul complete toxic infectious disorders	0	0.00	0	0.00	0	0.00
Long-haul gastrointestinal disorders	0	0.00	0	0.00	0	0.00

Table 5 summarizes the frequency of the post-COVID-19 syndrome phases.

Table 5. Frequency of post-COVID-19 syndrome vs. first and second waves, according to sexual identity

COVID-19 phases	Wave number													
	First wave						Second wave						Total first and second waves	
	♀		♂		Total		♀		♂		Total			
	n	%	*n*	%	*N*	%	*n*	%	*n*	%	*N*	%	*N*	%
Post-acute	38	43.70	26	41.30	64	87.60	43	49.40	28	44.40	71	92.20	135	90.00
Chronic	36	41.40	17	27.00	53	72.60	30	34.50	11	17.50	41	53.20	94	66.66
Long-haul	25	28.70	14	22.20	39	53.42	15	17.20	6	9.50	21	27.27	60	40.00

DISCUSSION

Given the scarce scientific evidence on the behavior of SARS-CoV-2 infection in a population chronically exposed to hypobaric hypoxia, there is an urgent need to describe the symptoms in order to classify the specific clinical features of the acute and chronic phase of the disease. For this reason, the present study classified the symptoms of the acute and chronic phase of COVID-19 into different clinical syndromes.

In Bolivia, the first wave started between March 9 and 10, 2020, and ended around August 4, 2020; the second wave started on November 11, 2020, and ended in January 2021. In both waves, SARS-CoV-2 vaccine was not available in the country [12].

This study included people who were infected in the first and second waves (confirmed by real-time reverse-transcription quantitative polymerase chain reaction [RT-qPCR] and/or a rapid test) and had a mild to moderate disease. They were treated at home with or without the help of medical personnel, in person or virtually, and no hospitalization was required.

All participants were indigenous and residents of high altitude (2,500–4,150 m a.s.l.), most of whom lived in the city of La Paz, at 3,600 m a.s.l.

The results of this study show that, in the acute phase, acute incomplete toxic infectious disorders, taste and smell disorders, and anxiety and depressive disorders syndromes were the most frequent ones.

The symptoms of the incomplete toxic infectious disorders syndrome appear in any viral infection and depend on the systemic inflammatory activity; however, in the context of COVID-19, these symptoms are more severe and occur due to an atypical innate immune response, given that there is a sustained release of proinflammatory interleukins [13,14].

Regarding the taste and smell disorders syndrome, different studies have determined that it is linked to the SARS-CoV-2 infection, such that hyposmia, anosmia and dysgeusia are considered pathognomonic symptoms of this infection. In the present study, anosmia was the main symptom. It occurs because inflammation decreases the sensory function of the olfactory receptor neurons and because of the preferred cytotoxic action of the virus on nerve cells and perivascular cells. The lingual epithelium is rich in ACE2 receptors and sialic acid receptors; upon binding to them, the virus increases the taste detection threshold, resulting in dysgeusia and/or ageusia.

The prevalence of this syndrome is variable; however, prevalences of up to 50 % have been reported and it is known that the figure is underestimated due to the fact that it is not diagnosed early. The frequency found in this study exceeds 50 % [5,15,16].

Another frequent syndrome in the acute phase was the anxiety and depressive disorders syndrome. The symptoms respond to the activation of toll-like receptors which, after several molecular reactions, decrease the generation of serotonin and dopamine. In addition to these molecular actions, during the first and second waves, the Bolivian government—as in the rest of the world—was forced to take restrictive measures such as a strict quarantine, with the resulting consequences on mental health [5,17,18].

In the post-acute phase of the post-COVID-19 syndrome, post-acute incomplete toxic infectious syndrome was also the most frequent one and headache the most frequently reported symptom. In this phase, it is called post-infectious headache; its presence and persistence evidence the neuroinvasive action of the virus and the increase of IL-6, which are responsible for meningitis and activation of the trigeminovascular system. It occurs irrespective of the gender, in middle-aged people, in people with a history of migraine and generally together with taste and smell disorders [19-21].

In the chronic phase, although a high percentage of subjects were asymptomatic, chronic incomplete toxic infectious syndrome prevailed, and headache was the most frequent symptom. In this phase, such symptom predicts a more prolonged post-COVID-19 syndrome [19-21].

Muscle pain was also a frequently reported symptom in the chronic phase. It has been determined that, together with anxiety and depressive disorders and cognitive disorders syndromes, chronic muscle fatigue and weakness syndrome is a debilitating entity whose pathophysiology (as in COVID-19) produces impaired immune system, chronic inflammation, increase of cytokines and neuroinvasive effect of the virus [22,23].

In the long-haul phase, the toxic infectious syndrome persisted and headache was the most frequent lingering symptom. This condition is called persistent headache, which can be bilateral or holocranial and moderate to severe; moreover, as in the previous phases, it occurs from the sustained action of inflammatory cytokines in the central nervous system [21].

A syndrome that deserves special attention is the cognitive disorders syndrome which, although infrequent in this study, its presence in post-COVID-19 syndrome has been widely discussed and has been described as a major effect due to its negative consequences on quality of life. The alterations remain over time and especially affect concentration and memory, which is known as "brain fog." [24-26]

The results of this study reveal a high frequency of symptoms that depend on the viral infection in the nervous tissue, which is invaded by the transneuronal and retrograde hematogenous pathways. Therefore, it has been proved that SARS-CoV-2 is neurotropic with the resulting neurological involvement in all stages [19,27].

The sequelae of the infection and how to treat them are of concern. Currently, it is stated that the post-COVID-19 syndrome occurs due to a compensatory anti-inflammatory response syndrome (CARS) that lasts for an unknown time—not knowing how it will end—and leads to post-infectious immunosuppression. This happens with the aim of counteracting the systemic inflammatory response syndrome, so that the patient enters a state of prolonged immunosuppression and catabolism, responsible for the lingering symptoms [28,29].

In the context of the hypobaric hypoxia environment, hypoxia has an major impact on inflammation, inducing an increase in proinflammatory cytokines. In turn, hypobaric hypoxia generates reactive oxygen species (ROS), resulting in increased oxidative stress which, together with inflammation, produces oxi-inflammation. This mechanism leads to increased organ and tissue damage with a tendency for lingering symptoms to last longer, especially in nervous tissue [30].

The most remarkable limitation of this study was that, when administering the online questionnaire, the symptoms were not verified, so participants' answers could have been biased by an inadequate perception.

In conclusion, this study has shown that the most frequent clinical syndromes in the acute phase and in the post-COVID-19 syndrome are a consequence of the atypical inflammatory process and neurotropism of the SARS-CoV-2 virus, and that the post-COVID-19 syndrome is more frequent in high-altitude populations than in the populations living in the plains. It is possible that hypobaric hypoxia, by prolonging inflammation and stimulating oxidative stress, causes a more prolonged post-COVID-19 syndrome and has a greater impact on the central and peripheral nervous systems, which deserves further research.

Author contributions: IGMP substantially participated in the conception and design of the study, logistics, analysis and interpretation of the data, writing of the drafts and the final document, as well as writing and approval of the final version of the article. EBE cooperated in the conception and design of the study, logistics, and approval of the content of the final version of the study.

Funding sources: The study was funded by Instituto Boliviano de Biología de Altura of the School of Medicine, Nursing, Nutrition and Medical Technology at Universidad Mayor de San Andrés.

Conflicts of interest: The authors declare no conflicts of interest.

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Reception date: May 31, 2023
Evaluation date: June 19, 2023
Approval date: July 24, 2023

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