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COVID-19 in the Tibet, China, the roof of the world: a comparative analysis of high-altitude residents and newcomers

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Abstract

Background After a 920-day hiatus, COVID-19 resurged in the Tibet Autonomous Region of China in August 2022. This study compares the characteristics of COVID-19 between high-altitude residents and newcomers, as well as between newcomers and lowlanders.

Methods This multi-center cohort study conducted at the Third People's Hospital of Tibet Autonomous Region and Beijing University Shenzhen Hospital, included 520 high-altitude resident patients, 53 high-altitude newcomer patients, and 265 lowlander patients infected with the Omicron variant. Initially, we documented epidemiological, clinical, and treatment data across varying residency at admission. We compared the severity of COVID-19 and various laboratory indicators, including hemoglobin concentration and SpO2%, over a 14-day period from the date of the first positive nucleic acid test, as well as the differences in treatment methods and disease outcomes between highlanders and high-altitude newcomers. We also compared several characteristics of COVID-19 between high-altitude newcomers and lowlanders. Univariate analysis, multivariable logistic regression, and the generalized linear mixed model were utilized for the analysis.

Results No fatalities were observed. The study found no significant differences in COVID-19 severity or in the physiological measures of hemoglobin concentration and SpO_2% between high-altitude and lowland residents. Similarly, there were no statistically significant differences in the values or trends of hemoglobin and SpO_2% between high-altitude residents and newcomers throughout the 14-day observation period. However, compared to age- and sex-matched lowlander patients (1:5 ratio), high-altitude newcomers exhibited higher heart rates, respiratory rates, and average hemoglobin concentrations, along with lower platelet counts. There were no significant differences in hospital stays between the two groups.

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Conclusions High-altitude residents and newcomer patients exhibit clinical similarities. However, the clinical characteristics of high-altitude newcomers and lowlander patients differ due to the impact of the high-altitude environment. These results highlight potential considerations for public health strategies in high-altitude regions such as Tibet.

Keywords COVID-19, Tibet, High-altitude residents, Newcomers

Introduction

The global impact of the COVID-19 pandemic over the past three years has been profound, yet its effects on plateau regions remain a topic of debate [1–3]. Previous research has shown contrasting results, suggesting that living in plateau environments could either decrease or increase the infection rate, severity, or mortality of respiratory diseases [3–7]. Studies investigating the adaptive and coping mechanisms of both high-altitude natives and newcomers are limited, with most of the existing research dating back several decades. Nevertheless, a study suggests natives living in high-altitude areas may exhibit lower susceptibility to common respiratory risks compared to newcomers [8]. Researchers have attributed this to lifelong adjustment to hypoxic conditions, which can increase lung volume, pulmonary diffusion capacity for oxygen, arterial oxygen saturation levels, and strengthen the antioxidant system [9, 10].Therefore, the prevalence of related diseases varies between high-altitude natives and newcomers, such as pulmonary hypertension-related high-altitude heart disease and other chronic mountain diseases [11].

On August 7, 2022, the Tibet Autonomous Region, China, experienced its first large-scale COVID-19 epidemic after a 920-day period free from the disease. The dominant strain of the virus was identified as the Omicron subvariant of COVID-19, BA.2.76, confirmed by the Chinese CDC. Approximately 45.6% of Tibet's territory lies above an altitude of 5,000 m, corresponding to an average barometric pressure of < 500 mmHg and an ambient partial pressure of oxygen (pO2) of 80 mmHg [12]. This low environmental pO_2, known as hypobaric hypoxia, poses a notable physiological challenge, particularly for individuals infected with COVID-19, amplifying the severity of the condition.

Research indicates that cellular hypoxia leads to pathophysiological response to high-altitude environments. Typical responses to high altitude include hyperventilation, polycythemia, hypoxic pulmonary vasoconstriction, changes in oxygen affinity of hemoglobin, increases in oxidative enzymes, and increased concentration of capillaries in peripheral muscle [13]. Pulmonary diseases such as pulmonary hypertension and COPD are prevalent at high altitudes, significantly impair lung function [14, 15]. Therefore, Omicron-infected patients may face heightened risks of exacerbation. Moreover, the manifestation of severe COVID-19 infections might vary among distinct populations residing at higher altitudes. Variations in hypoxia tolerance between high-altitude residents and newcomers could potentially influence the severity of disease. Rashmi et.al [16] have found that genetic adaptations in individuals residing at high altitudes may enhance their ability to combat COVID-19 compared to newcomers. This assertion is supported by studies like Simbaña-Rivera et al. [17], which indicate better short-term survival rates among critically ill COVID-19 patients living at high altitudes. Furthermore, evidence from Stephens et al. [18] indicates a reduced infection and mortality rate within high-altitude populations.

In this cohort study, our objective was to delineate the clinical characteristics of COVID-19 among patients in the Tibet Autonomous Region, China, and to explore clinical variations between high-altitude residents and newcomers, as well as between high-altitude newcomers and the lowlanders.

Methods

Study design and participants

This multi-center cohort study enrolled 520 high-altitude resident patients and 53 high-altitude newcomer patients confirmed Omicron-infected patients admitted to the Third People's Hospital of Tibet Autonomous Region, as well as 265 lowlander patients admitted to Beijing University Shenzhen Hospital. We collected the inpatient highlander and high-altitude newcomer cases data from electronic medical records (EMR) from Aug 7, 2022 to Sep 26, 2022. We collect the lowlander patient's data from December 26, 2022, to February 15, 2023. Lowlander patients were matched to high-altitude newcomer cases at a 1:5 ratio based on age and gender. Only aged 18 years and above and non-pregnant were included. Those with incomplete records were excluded from the study. Patients were followed up until discharge. The Third People's Hospital of Tibet Autonomous Region, designated as a COVID-19 treatment facility, is one of the tertiary hospitals in Lhasa, Tibet Autonomous Region, China, catering to the majority of severe cases in the region. Beijing University Shenzhen Hospital is also a tertiary hospital located in Shenzhen, Guangdong Province, China.

This study received ethics approval from the institutional ethics board of the Third People's Hospital of Tibet Autonomous Region (Approval No. 2022003). Informed consent was obtained from all the participants. We reported the study in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [19]. (Supplemental file). All procedures of the study were carried out in accordance with relevant guidelines and regulations.

Definition of high-altitude residents, newcomers and lowlanders

High-altitude residents are defined as individuals whose families have resided at high altitudes for two or more generations, while newcomers are those whose families have lived at high altitudes for fewer than two generations. Lowlanders are individuals who resided in plain areas.

Data collection

Epidemiological, clinical, and treatment information were obtained with data collection forms from EMR. A team of trained physicians and statisticians reviewed the data. Demographics, comorbidities, laboratory examinations, chest computed tomographic (CT) scans, treatment and medication were documented upon admission. Laboratory test results obtained during the hospital stay were also recorded. Additionally, information regarding patient outcomes such as date of death (if applicable), length of hospitalization, and duration from the initial positive SARS-CoV-2 nucleic acid tests (NAT) to two consecutive negative NAT results was documented.

The severity of COVID-19 was categorized according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia issued by the Chinese National Health Commission trial version 9 (https://www.gov.cn/zhengce/zhengceku/2022-03/15/5679257/files/49854a49c7004f4ea9e622f3f2c568d8.pdf). Four types of severity were defined: mild, moderate, severe, and critical. Demographic data, including high-altitude residential status, were self-reported by the patients. It is important to note that all COVID-19 vaccines referenced in this study were inactivated vaccines. Patients were classified based on severity and high-altitude residential status.

Laboratory examinations included serology, NAT, and routine blood examinations. Serology testing included COVID-19-specific IgG and IgM antibodies detection. Methods for NAT were described elsewhere [20]. Briefly, nasal or throat swab specimens were analyzed using the COVID-19 (ORF lab/N gene) nucleic acid detection kit (Hangzhou Dean Biological). Samples were considered positive if they exhibited a cycle threshold (Ct) < 35. Additionally, routine blood test, serum biochemical test, inflammation biomarker assessments, and coagulation examination were also conducted. Chest Computed Tomography (CT) scans were performed for all participants.

The CT diagnoses were conducted by experienced radiologists, characterized by the following features: COVID-19 infection cases typically displayed multifocal and diverse chest imaging manifestations, with a higher prevalence observed in the outer lung field and subpleural area. Lesions exhibited dynamic changes, presenting as nodular, patchy, or ground-glass opacities. After timely antiviral treatment, the lesions could have obvious absorption and fibrosis changes in a short timeframe. Pleural effusion and mediastinal and hilar enlarged lymph nodes were rare, while thickening of blood vessels within the lesions was more commonly observed.

Statistical analysis

The epidemiological, clinical, and treatment information of patients at admission were described. Univariate analyses were conducted for the comparison between the highlanders and the high-altitude newcomers, as well as the high-altitude newcomers and the lowlanders. Categorical variables are presented as frequencies and percentages, and the group comparisons were performed using Fisher's exact test. Continuous variables with a normal distribution are reported as mean and standard deviation, and the means were compared using t test. Non-normally distributed continuous variables are presented as median and interquartile range (IQR) values, with the comparisons made using the Wilcoxon rank sum test.

Then, we tested the hypothesis that high-altitude residential status (whether individuals were high-altitude residents or newcomers) is independently associated with COVID-19 severity. Severity groups were categorized based on patient conditions: the severe group included those identified as severe and critical, while the non-severe group comprised patients with mild and moderate symptoms. We conducted a multivariable logistic regression analysis, adjusting for potential confounders such as age, sex, ethnicity, vaccination status, and variables demonstrating statistical differences between COVID-19 severity groups in univariate analysis.

Next, we investigated whether high-altitude residential status was associated with resting SpO_2% using a multivariable linear regression model. Demographic variables and underlying comorbidities, which showed statistical differences in the univariate analysis, were included as covariates in the model. We visually assessed the normality assumption, and if it was not met, we conducted a data transformation accordingly.

Lastly, we compared hemoglobin concentration and SpO_2% between high-altitude residents and newcomers over 14 days from the first date NAT positive. The overall difference and the trends were compared utilizing a generalized linear mixed model. The repeated measurements of hemoglobin concentration and SpO_2% were treated as the outcome, with days since admission, high-altitude residential status, and their interaction terms included in the model. The overall trend of hemoglobin concentration and SpO_2%, the overall difference between the residential status groups and the trend difference between the residential status groups were examined, correspondingly.

In this study, missing data was not imputed. All *P* values were two tailed, and a *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using R software, version 4.1.3.

Results

The inclusion and exclusion processes are illustrated in Fig. 1. In summary, the study cohort comprised 520 high-altitude residents, 53 high-altitude newcomers, and 265 lowland COVID-19 inpatients. (Figure S1). The median age and interquartile range (IQR) were 55.00 [40.00, 70.00] for high-altitude residents (51.92% male), 39.00 [33.00, 54.00] for high-altitude newcomers (49.06% male), and 41.00 [33.00, 54.00] for lowlanders (36.6% male). No death occurred during the study.

Table 1, Table S1 and Table S2 presents the baseline characteristics of the high-altitude residents and the newcomer patients. Comparing the high-altitude residents and the newcomers, univariable analysis demonstrated that high-altitude residents were older (median [IQR]: 55.00 [40.00, 70.00] vs. 39.00 [33.00, 54.00], P < 0.001), had lower heart rate (88.00 [80.00, 98.00] vs. 90.00 [84.75, 105.50], *P* = 0.019), lower monocyte count (0.35 [0.26, 0.47] vs. 0.42 [0.31, 0.58], *P* = 0.013), higher total carbon dioxide (17.40 [15.70, 19.20] vs.17.10 [15.20, 18.20], *P* = 0.043), higher D-dimer (0.48 [0.23, 1.10] vs. 0.27 [0.11, 0.67], *P* = 0.012), and a higher prevalence of hypertension (143 (27.88) vs. 5 (9.62), *P* = 0.007). (Tables 1 and 2). Although Table 2 shows that high-altitude residents were less likely to require oxygen therapy compared to newcomers, age-stratified analysis revealed no significant differences in the proportions of high-altitude residents and newcomers requiring oxygen therapy across different age groups (Table S3). Similarly, we conducted an age-stratified comparison of the hospital stays and days from the first positive NAT to two consecutive negative tests between high-altitude residents and newcomers, and found no significant differences between the two groups within each age category (Table S4 and S5).

Table 3 illustrates that, after adjusting for age, sex, ethnicity, smoking status, COVID-19 vaccination history, and comorbidities such as cardiovascular disease and chronic lung disease, we did not find sufficient evidence of an independent association between high-altitude

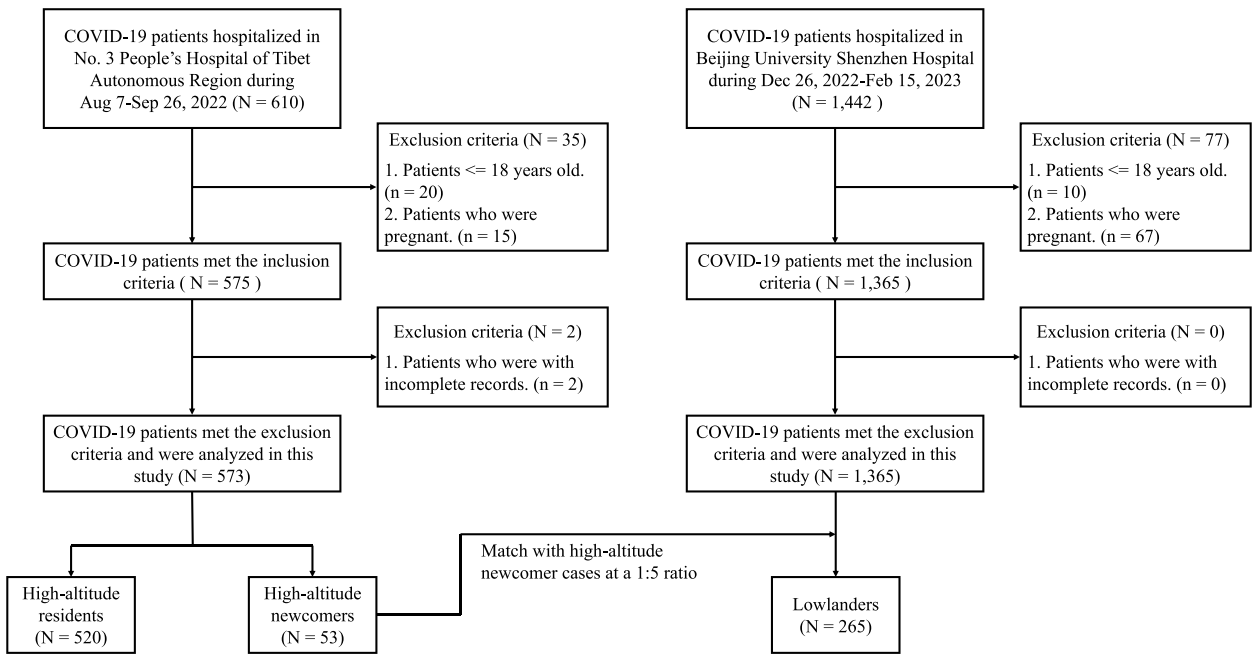

Fig. 1 Flow chart of inclusion and exclusion

Table 1 Comparison of baseline characteristics of COVID-19 between high-altitude residents and newcomers

	Total	High-altitude residents	Newcomers	*P* value
No. (%)	573	520 (90.75)	53 (9.25)	-
Demographics				
Age, years	53.00 [38.00, 69.00]	55.00 [40.00, 70.00]	39.00 [33.00, 54.00]	< 0.001
Male, n (%)	296 (51.66)	270 (51.92)	26 (49.06)	0.8
Ethnic, n (%)				< 0.001
Han	65 (11.34)	21 (4.04)	44 (83.02)	
COVID-19 symptoms				0.075
Mild	202 (35.25)	184 (35.38)	18 (33.96)	
Moderate	296 (51.66)	263 (50.58)	33 (62.26)	
Severe	75 (13.09)	73 (14.04)	2 (3.77)	
Critical	0 (0)	0 (0)	0 (0)	
COVID-19 vaccination history, n (%)				0.327
Unvaccinated	145 (25.39)	136 (26.25)	9 (16.98)	
One dose	25 (4.38)	24 (4.63)	1 (1.89)	
Two doses	86 (15.06)	77 (14.86)	9 (16.98)	
Three doses	315 (55.17)	281 (54.25)	34 (64.15)	
Comorbidities				
Hypertension, n (%)	148 (26.19)	143 (27.88)	5 (9.62)	0.007
Cardiovascular disease, n (%)	80 (14.16)	76 (14.79)	4 (7.84)	0.252
Diabetes, n (%)	52 (9.20)	50 (9.73)	2 (3.92)	0.265
Chronic pulmonary disease, n (%)	80 (14.16)	76 (14.79)	4 (7.89)	0.252
Chronic liver disease, n (%)	37 (6.55)	36 (7.00)	1 (1.96)	0.275
Malignant tumor, n (%)	18 (3.19)	16 (3.11)	2 (3.92)	1
Immune deficiency, n (%)	8 (1.42)	7 (1.36)	1 (1.96)	1
Chronic kidney disease, n (%)	33 (5.84)	32 (6.23)	1 (1.96)	0.355
Hemodialysis, n (%)	22 (3.89)	22 (4.28)	0 (0.00)	0.259
Obesity, n (%)	12 (2.15)	12 (2.36)	0 (0.00)	0.547
Heavy smoking, n (%)	18 (3.19)	18 (3.50)	0 (0.00)	0.347
Chief complaints				
Fever, n (%)	116 (20.53)	104 (20.23)	12 (23.53)	0.708
Cough, n (%)	333 (58.94)	307 (59.84)	26 (50.00)	0.22
Fatigue, n (%)	146 (25.80)	130 (25.29)	16 (30.77)	0.488
Nasal congestion or runny nose, n (%)	17 (3.01)	16 (3.12)	1 (1.96)	0.974
Sore throat, n (%)	129 (22.87)	122 (23.78)	7 (13.73)	0.145
Dyspnea, n (%)	62 (10.97)	61 (11.87)	1 (1.96)	0.054
Hyposmia, n (%)	2 (0.35)	1 (0.19)	1 (1.96)	0.43
Physiological parameters				
Heart rate, bpm	88.00 [80.00, 98.00]	88.00 [80.00, 98.00]	90.00 [84.75, 105.50]	0.019
Respiratory rate, cpm	20.00 [20.00, 22.00]	20.00 [20.00, 22.00]	20.00 [20.00, 22.00]	0.791
MAP, mm Hg	95.67 [86.50, 104.67]	96.00 [86.67, 104.67]	91.67 [85.25, 102.67]	0.134
SpO_2, % at rest	88.00 [85.00, 91.00]	88.00 [84.00, 91.00]	89.00 [86.00, 90.75]	0.182
SpO_2, % after activity	88.00 [84.00, 90.00]	88.00 [84.00, 90.00]	88.00 [86.00, 89.50]	0.164
Laboratory findings				
Routine blood test				
Lymphocyte count, $\times 10^9$/L	1.19 [0.86, 1.60]	1.19 [0.86, 1.60]	1.10 [0.83, 1.46]	0.592
White blood cell count, $\times 10^9$/L	4.78 [3.81, 6.09]	4.78 [3.74, 6.02]	4.76 [4.31, 7.45]	0.092
Monocyte count, $\times 10^9$/L	0.36 [0.27, 0.48]	0.35 [0.26, 0.47]	0.42 [0.31, 0.58]	0.013
Eosinophils count, $\times 10^9$/L	0.04 [0.01, 0.10]	0.05 [0.01, 0.11]	0.03 [0.01, 0.08]	0.29
Platelet count, $\times 10^9$/L	176.00 [129.75, 222.25]	175.00 [126.50, 221.00]	188.00 [153.00, 232.00]	0.059

Table 1 (continued)

	Total	High-altitude residents	Newcomers	*P* value
Potassium, mmol/L	3.92 [3.64, 4.32]	3.90 [3.62, 4.23]	3.97 [3.75, 4.32]	0.443
Sodium, mmol/L	141.60 [139.90, 143.10]	141.60 [139.90, 143.12]	141.60 [139.10, 142.10]	0.047
Calcium, mmol/L	2.21 [2.12, 2.34]	2.21 [2.12, 2.33]	2.32 [2.18, 2.39]	0.041
Chlorine, mmol/L	103.40 [99.70, 105.80]	103.45 [99.70, 105.80]	103.00 [99.70, 104.80]	0.532
Total carbon dioxide, mmol/L	17.40 [15.70, 19.10]	17.40 [15.70, 19.20]	17.10 [15.20, 18.20]	0.043
Average hemoglobin concentration	336.00 [329.75, 341.00]	336.00 [330.00, 341.00]	336.00 [328.00, 342.00]	0.58
ABO blood type, n (%)				0.736
A	65 (19.82)	54(19.39)	8 (23.53)	
B	118 (35.98)	104 (35.37)	14 (41.18)	
AB	21 (6.40)	19 (6.46)	2 (5.88)	
O	124 (37.80)	114 (38.78)	10 (29.41)	
CRP, mg/L	9.70 [2.20, 33.75]	9.60 [2.10, 34.10]	12.50 [2.90, 30.10]	0.495
First ORF1ab gene CT value	28.31 [24.94, 32.55]	28.20 [24.84, 32.41]	29.54 [25.94, 32.68]	0.4
First N gene CT value	26.61 [22.78, 31.02]	26.43 [22.75, 31.11]	27.75 [24.75, 29.57]	0.802
IgG positive, n (%)	243 (52.60)	226 (54.07)	17 (38.64)	0.073
IgG, g/L	20.95 [2.80, 179.07]	23.94 [2.80, 179.07]	5.46 [2.80, 72.61]	0.037
IgM positive, n (%)	11 (2.30)	10 (2.30)	1 (2.22)	1
IgM, g/L	0.77 [0.25, 0.77]	0.77 [0.27, 0.77]	0.36 [0.14, 0.77]	0.043
D-dimer, μg/ml	0.45 [0.23, 1.10]	0.48 [0.23, 1.10]	0.27 [0.11, 0.67]	0.012
Lung lesions in CT image n (%)	409 (78.96)	372 (78.65)	37 (82.22)	0.711

Categorical variables are presented as frequencies and percentages, and the group comparisons were performed using Fisher's exact test. Continuous variables with a normal distribution are reported as mean and standard deviation, and the means were compared using t test. Non-normally distributed continuous variables are presented as median and interquartile range (IQR) values, with the comparisons made using the Wilcoxon rank sum test

Abbreviations: *CRP* c-reactive protein, *DD* D-dimer, *MAP* Mean arterial pressure, SpO_2 Oxyhemoglobin saturation

Table 2 Comparison of the treatment approaches between high-altitude residents and newcomers

	Total	High-altitude residents	Newcomers	*P* Value
No. (%)	573	520	53	-
Age, years	53.00 [38.00, 69.00]	55.00 [40.00, 70.00]	39.00 [33.00, 54.00]	< 0.001
Oxygen therapy, n (%)				0.001
No oxygen therapy	81 (17.16)	64 (15.09)	17 (35.42)	
Nasal catheters or face masks	319 (67.58)	292 (68.87)	27 (56.25)	
High-flow nasal cannula	66 (13.98)	63 (14.86)	3 (6.25)	
NIV	4 (0.85)	4 (0.94)	0 (0.00)	
IMV	2 (0.42)	1 (0.24)	1 (2.08)	
Small molecule drugs (Paxlovid), n (%)	300 (53.96)	271 (53.56)	29 (58.00)	0.651
Monoclonal antibodies, n (%)	140 (25.36)	129 (25.70)	11 (22.00)	0.687
COVID-19 Immunoglobulin, n (%)	6 (1.09)	5 (1.00)	1 (2.00)	> 0.999
Omicron convalescent plasma, n (%)	2 (0.36)	2 (0.40)	0 (0.00)	> 0.999
Glucocorticoids, n (%)	2 (0.36)	2 (0.40)	0 (0.00)	> 0.999
Thymosin, n (%)	76 (13.74)	69 (13.72)	7 (14.00)	> 0.999
Low molecular weight heparin, n (%)	87 (15.70)	82 (16.27)	5 (10.00)	0.338
Prone position ventilation, n (%)	37 (55.22)	133 (27.65)	7 (14.00)	0.055
TCM therapy, n (%)	221 (41.70)	207 (43.12)	14 (28.00)	0.056

Categorical variables are presented as frequencies and percentages, and the group comparisons were performed using Fisher's exact test. Continuous variables with a normal distribution are reported as mean and standard deviation, and the means were compared using t test. Non-normally distributed continuous variables are presented as median and interquartile range (IQR) values, with the comparisons made using the Wilcoxon rank sum test

Abbreviations: *IMV* Invasive mechanical ventilation, *NIV* Non-invasive ventilation, *TCM* Therapy, traditional Chinese medicine therapy

Table 3 The results of the multivariable logistics regression model on the severity of COVID-19

	Estimate	Std. Error	OR	z statistics	*P*-value
Gender					
Female	Ref	Ref	Ref	Ref	-
Male	0.04	0.20	1.04 [0.70, 1.55]	0.18	0.854
Age	0.04	0.01	1.04 [1.02, 1.06]	3.89	< 0.001
High-altitude residential status					
Newcomers	Ref	Ref	Ref	Ref	-
High altitude residents	0.73	1.21	2.07 [0.19, 22.13]	0.60	0.546
Ethnic					
Tibetan	Ref	Ref	Ref	Ref	-
Han	-0.93	1.26	0.39 [0.03, 4.76]	0.74	0.460
COVID-19 vaccination history					
None	Ref	Ref	Ref	Ref	-
One dose	-0.29	0.62	0.75 [0.22, 2.51]	-0.47	0.638
> = 2 doses	-0.80	0.30	0.45 [0.25, 0.81]	-2.66	0.008
Hypertension	-0.01	0.32	0.99 [0.53, 1.83]	-0.04	0.965
Cardiovascular disease	0.95	0.32	2.57 [1.37, 4.83]	2.94	0.003
Chronic lung disease	0.28	0.36	1.32 [0.65, 2.67]	0.76	0.446
Heavy smoking	0.61	0.60	1.83 [0.57, 5.94]	1.01	0.312

P-values were obtained through multivariable logistic regression analysis

Abbreviations: *COVID-19* Coronavirus disease of 2019, *OR* Odds ratio, *Std* Error, standard error

residents and the newcomers with COVID-19 severity in the multivariable analysis.

Table S6 illustrates that, after adjusting for age, sex, ethnicity, smoking status, COVID-19 vaccination history, and comorbidities such as hypertension, diabetes, cardiovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, malignant tumors, immune deficiency, and hemodialysis, we did not find sufficient evidence of an independent association between high-altitude residential status and resting SpO_2% among COVID-19 patients in the multivariable analysis.

Additionally, the hemoglobin concentration and SpO_2% differences between high altitude residents and newcomers over 14-day period from the NAT positive date were explored. However, no statistically significant differences were observed in either the values or the trends over time. (Fig. 2).

Finally, we compared high-altitude newcomers and lowlanders. The lowlander data were matched to the high-altitude newcomer data based on age and gender, resulting in no significant differences in these demographics between the two groups. Lowlanders had a higher prevalence of hypertension and diabetes upon admission. High-altitude newcomers exhibited higher heart rates, respiratory rates, and average hemoglobin concentrations, as well as lower platelet counts. Additionally, high-altitude newcomers had a higher incidence of fever. (Table 4) In terms of treatment, a higher proportion of high-altitude newcomers received small molecule drugs (Paxlovid), monoclonal antibodies, thymosin, low molecular weight heparin, and prone position ventilation. (Table 5) There were no significant differences in hospital stays between high-altitude newcomers and lowlanders. (Table 4).

Discussion

This study is a large-scale cohort study focusing on hospitalized COVID-19 patients in the Tibet Autonomous Region, China. During the time the data was collected, no death occurred among the study population, which may be attributed to nationwide vaccination, early identification of severe cases, timely referral, and effective treatment. In this study, we did not observe any statistically significant differences between high-altitude residents and newcomers in hemoglobin concentration, SpO2%, or COVID-19 severity, nor in their trends over 14 days from the NAT date.

The lack of significant differences between high-altitude residents and newcomers in our study may be explained by the following factors: First, the definition of "newcomer" includes individuals who have lived at high altitudes for up to two generations, which might have been long enough for them to develop some level of acclimatization. The duration of stay for newcomers at high altitudes might have been sufficient for them to acclimatize. Both groups may share similar physiological

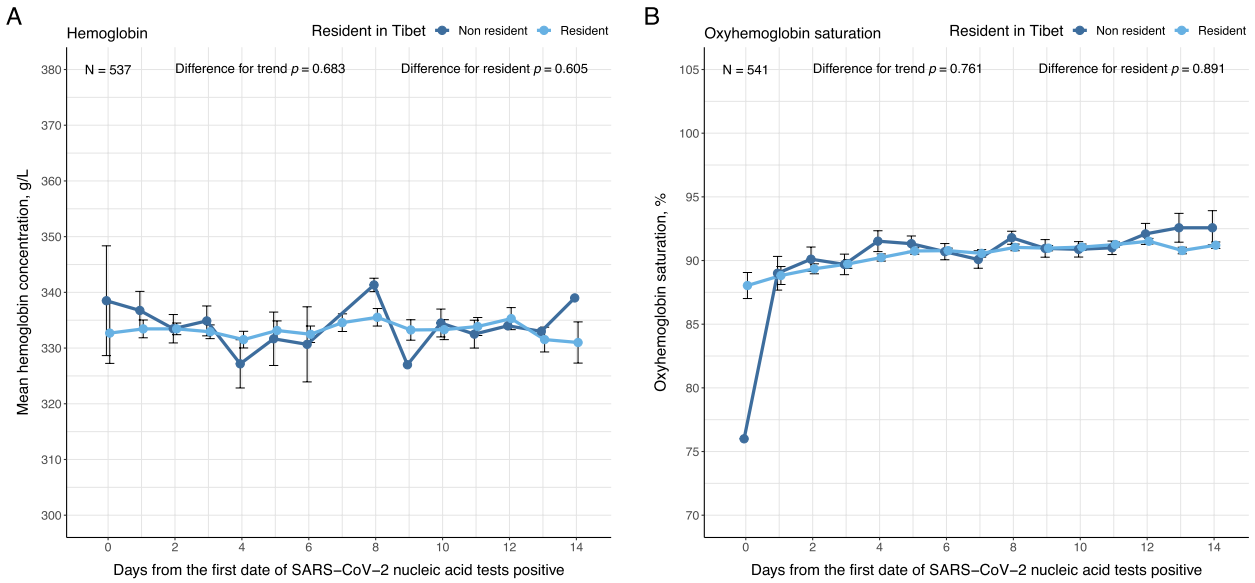

Fig. 2 Dynamic profile of hemoglobin concentration and SpO_2% in COVID-19 patients. The bars represented in the figures indicated the standard error of the mean. **A** Difference on hemoglobin concentration trend between 493 high-altitude residents and 44 newcomers; **B** Difference on SpO_2% trend between 497 high-altitude residents and 44 newcomers, over 14 days from the first date SARS-CoV-2 nucleic acid tests positive

Table 4 Comparison the baseline characteristics of COVID-19 and the hospital stays between high-altitude newcomers and lowlanders

	High-altitude newcomers	Lowlanders	*p* value
No	53	265	-
Male, n (%)	26 (49.06)	97 (36.60)	0.122
Age, years	39.00 [33.00, 54.00]	41.00 [33.00, 54.00]	0.808
Height, cm	165.94 (8.22)	169.80 (8.30)	0.181
Weight, kg	61.75 (12.56)	67.87 (14.71)	0.136
Hypertension, n (%)	5 (9.60)	64 (24.20)	0.032
Diabetes, n (%)	2 (3.90)	67 (25.30)	0.001
Hemodialysis, n (%)	0 (0.00)	4 (1.50)	0.842
Fever, n (%)	12 (23.50)	25 (9.40)	0.009
White blood cell count, $\times 10^9$/L	4.76 [4.31, 7.45]	6.28 [4.68, 8.36]	0.037
Heart rate, bpm	90.00 [84.75, 105.50]	90.00 [78.00, 102.00]	0.268
Respiratory rate, cpm	20.00 [20.00, 22.00]	20.00 [19.00, 20.00]	< 0.001
SpO2, % at rest	89.00 [86.00, 90.75]	97.00 [94.25, 99.50]	< 0.001
Systolic pressure, mm Hg	113.00 [106.00, 124.75]	118.00 [109.00, 131.00]	0.073
Diastolic pressure, mm Hg	81.50 [73.00, 93.75]	78.00 [70.00, 85.00]	0.183
CRP, mg/L	12.50 [2.90, 30.10]	8.90 [0.50, 32.89]	0.071
Average hemoglobin concentration	336.00 [328.00, 342.00]	330.00 [321.00, 338.00]	0.002
Platelet count, $\times 10^9$/L	188.00 [153.00, 232.00]	228.50 [167.00, 295.25]	0.003
Hospital stays, days	6.00 [4.00, 9.00]	5.00 [3.00, 8.00]	0.319

Categorical variables are presented as frequencies and percentages, and the group comparisons were performed using Fisher's exact test. Continuous variables with a normal distribution are reported as mean and standard deviation, and the means were compared using t test. Non-normally distributed continuous variables are presented as median and interquartile range (IQR) values, with the comparisons made using the Wilcoxon rank sum test

Abbreviations: *CRP* c-reactive protein, *No* Number, SpO_2 Oxyhemoglobin saturation

Table 5 Comparison of the treatment approaches between high-altitude newcomers and the lowlanders

	Total	High-altitude newcomers	Lowlanders	*p* value
No. (%)	318	53	265	
Small molecule drugs (Paxlovid), n (%)	29 (9.20)	29 (58.00)	0 (0.00)	< 0.001
Monoclonal antibodies, n (%)	21 (6.70)	11 (22.00)	10 (3.80)	< 0.001
Thymosin, n (%)	7 (2.20)	7 (14.00)	0 (0.00)	< 0.001
Low molecular weight heparin, n (%)	11 (3.50)	5 (10.00)	6 (2.30)	0.021
Prone position ventilation, n (%)	17 (5.40)	7 (14.00)	10 (3.80)	0.009

All the continuous variables followed a normal distribution. They are reported as mean and standard deviation, and the means were compared using t test

adaptations to hypoxia, reducing potential variances in COVID-19 severity. These adaptations include increased red blood cell production and alterations in blood oxygen affinity, which could normalize hemoglobin and SpO_2% levels across the two groups [21]. Future research should further investigate this issue by considering different definitions of "newcomer" based on varying lengths of time spent at high altitudes. In addition, although the high-altitude residents are predominantly Tibetan and the newcomers are mostly Han Chinese, the two groups are genetically close to each other. This similarity in genetic predispositions related to COVID-19 responses among both populations could thereby dilute any potential effects of altitude on the disease's severity. Whether the hypoxic adaptation genes, such as EPAS1 genes etc [22]., affects the COVID-19 severity, remains to be studied. Notably, despite similar disease severity, high-altitude residents exhibited significantly higher D-dimer levels, suggesting complex interactions between coagulation alterations and COVID-19 response, necessitating further investigation.

Our study also found that lowlanders had a higher prevalence of hypertension and diabetes upon admission, which may be due to the fact that all lowlanders were intensive care unit patients. High-altitude newcomers exhibited higher heart rates, respiratory rates, and average hemoglobin concentrations, as well as lower platelet counts, likely due to the hypoxic environment of high altitudes. The higher incidence of fever among high-altitude newcomers may be attributed to the different manifestations of the disease in various regions or the use of antipyretics. High-altitude newcomers received a higher proportion of treatments with small molecule drugs (Paxlovid), monoclonal antibodies, thymosin, low molecular weight heparin, and prone position ventilation compared to lowlanders, possibly due to the hypoxic environment requiring more aggressive treatment to achieve similar outcomes.

The current study has several limitations, which may also account for the negative findings observed. First, the sample size of the high-altitude newcomers was relatively small compared to high-altitude residents. Nonetheless, we computed the sample size and statistical power using the "pwr" function in R 4.0.3. With a significance level of 0.05 for a two-sided test, and sample sizes of 520 highlanders and 53 newcomers, the power is 0.93 when the effect size is moderate (0.5), as recommended by Cohen [23]. Additionally, for a power of 0.8, with 520 highlanders, only 34 newcomers are needed. Our study includes 53 newcomers, which meets the minimum sample size requirement. Second, given the observational nature of the study, it is unlikely to completely avoid residual confounding, potentially introducing bias when estimating associations. Third, demographic, clinical, treatment, and laboratory data were extracted from electronic medical records, resulting in missing data. To maintain the integrity of the samples, missing data were not imputed. Fourth, some measured parameters, such as heart rate, CO2, and Monocyte count, are subject to measurement error, as each sample was measured only once at each time point, which may lead to bias. Fifth, certain metrics such as arterial blood gas, lactate, chest ultrasound, and mechanical ventilation parameters were not collected during the study. In the current study, SpO_2% was used to replace blood gas metrics even though previous study indicated SpO_2% should be interpreted with caution in high-altitude settings, as hypocapnia significantly shifts the oxygen-hemoglobin dissociation curve and improves blood oxygen saturation [19]. This study also showed that SpO_2%, as one determinant of need for intensive care resources, is notably lower in severe patients. Also, finger pulse oximetry was shown to be a valuable tool at high altitude [15]. Thus, SpO_2% was used to make up for the lack of blood gas metrics. Lastly, when comparing high-altitude newcomers with lowlanders, the data for lowlanders in lowland hospitals were collected three months after the high-altitude data collection, and the data from the high-altitude and lowland areas were collected from two different provinces. This introduces uncertainty regarding potential strain variations or distinct latitudes and climates, making it difficult to rule out factors other than altitude that could introduce different COVID-19 characteristics. Additionally, we have tried our best, but we were unable to obtain all the clinical indicators in the

lowlander data that were available in the high-altitude data. Therefore, we only compared the indicators that we could obtain.

Despite the aforementioned limitations, this study has several strengths. Firstly, to the best of our knowledge, this is the first large-scale high-altitude COVID-19 cohort study that compares differences between high-altitude residents and newcomers, as well as between high-altitude newcomers and lowlanders, a research question that has been rarely explored in prior studies. Secondly, it is noteworthy that during the COVID-19 pandemic, the ability of doctors to manage a large influx of patients and provide timely and effective treatment while simultaneously collecting such comprehensive data is commendable. Thirdly, the study uses rigorous statistical methods. The comparison between high-altitude residents and newcomers involves not only univariable analysis but also multivariable linear regression that accounts for confounding factors. In analyzing differences in the temporal trends of hemoglobin concentration and SpO2% between high-altitude residents and newcomers, the study employs generalized linear mixed models. The rigorous statistical approach enhances the credibility of the results.

This study contributes to a deeper understanding of COVID-19 in high-altitude regions and lays a foundation for future research on the adaptation to hypoxia among individuals residing at different altitudes.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Y. Shan and W. Wang had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. T. Pingcuo, X. Yan, X. Jin were responsible for study concept and design. Y. Shan, D. Liu, W. Wang, W. Chen, X. Wang, J. Zeng were responsible for acquisition of data. Y. Shan, W. Wang were responsible for analysis and interpretation of data. Y. Shan, W. Chen were responsible for drafting of the manuscript. Y. Shan, W. Wang were responsible for statistical analysis. Y. Shan, Q. Zhou and X. Jin were responsible for funding. T. Pingcuo, X. Yan, X. Jin, Y. Shan, Q. Zhai, Q. Luo, Y. Zhang, Z. Zhou, B. La, L. Thuen, Q. Li, G. Tian, X. Chen, Q. Ci, X. Zhu were responsible for administrative, technical, or material support. T. Pingcuo, X. Yan, X. Jin, Y. Shan and Q. Zhou were responsible for study supervision. J. Yan and Q. Zhai were responsible for critical revision of the manuscript for important intellectual content.

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Availability of data and materials
The data underlying this article will be shared at reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
This study obtained ethics approval from the institutional ethics board of the Third People's Hospital of Tibet Autonomous Region (No. 2022003). Informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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