Clinical characteristics and laboratory features of COVID-19 in high altitude areas: A retrospective cohort study

Running title: Features of COVID-19 in high altitude areas

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Data Availability Statement: The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author Contributions: Hanxiao Chen: Writing- Original draft. Lang Qin: Supervision, Project administration. Sixian Wu: Formal analysis. Wenming Xu: Writing- Reviewing and Editing. Rui Gao: Validation. Xiaohong Zhang: Data curation, Conceptualization, Methodology.

Acknowledgments: This work was supported by the Science & Technology Department of Sichuan Province [2019JDKP0056 and 2020YFS0127] and Chengdu Science and Technology project [2020-YF05-00306-SN]. We would like to thank all patients included in this study. We thank Lan Ma and Zheng Wang from Sichuan Orient Software Technology Company Limited for statistical guidance.

Conflicts of Interest Disclosure: The authors have no conflicts of interest to declare.

Ethics Approval Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Medical Ethical Committee of Sichuan Provincial People's Hospital. The requirement of informed consent on the individual patient level was waived given the urgent need to collect clinical data and the retrospective nature of this study design.

Abstract

Background: Coronavirus disease 2019 (COVID-19) is highly contagious and has affected the whole world. We aim to investigate the clinical and laboratory characteristics of COVID-19 patients in high altitude areas of Sichuan, China.

Methods: In this retrospective cohort study, a total of 67 patients with laboratory-confirmed SARS-CoV-2 infection in Tibetan Qiang Autonomous Prefecture of Ngawa, Sichuan were included from February 1, 2020 to March 2, 2020. The clinical characteristics as well as their radiological and laboratory features were extracted.

Results: 4(6.0%) patients were categorized into severe cases, 39(58.2%) were non-severe cases, and 24(35.8%) were asymptomatic cases. 46(68.7%) patients were associated with cluster infection events in this study. The most common symptoms were cough, sputum production, dyspnea, fatigue or myalgia, and headache. 7(10.4%) patients showed leucopenia and 20 (29.9%) patients showed lymphopenia. Lymphocyte count and neutrophil-to-lymphocyte ratio (NPR) was different between three groups. 14 (20.9%) patients had thrombocytopenia, prothrombin time (PT) and fibrinogen levels differed between groups. We also found significant difference of sodium, chloride, and calcium levels between three groups. Antiviral therapy did not lead to obvious adverse event or shorter duration from initial positive to subsequent negative nuclei acid tests. Advanced age, hypertension, high neutrophil count, neutrophil-to-lymphocyte ratio, fibrinogen, and lactate dehydrogenase level were identified as independent risk factors for symptomatic cases of COVID-19.

Conclusions: The symptoms of patients in high altitude areas were mild and about one third were asymptomatic. We also identified several independent risk factors for symptomatic cases

of COVID-19.

Key words: SARS-CoV-2; COVID-19; high altitude areas; clinical characteristics; laboratory factors; risk factors

1. Introduction

In December 2019, a case of pneumonia of unknown cause was detected in Wuhan, Hubei province, China[1]. The pathogen was quickly revealed as a novel betacoronavirus named as 2019 novel coronavirus (2019-nCoV) and was subsequently renamed as Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). It is the seventh member of coronavirus family and belonged to the betacoronavirus 2B lineage, sharing a 96% identical genome with the BatCov RaTG13, a bat SARS-like coronavirus[2]. The outbreak of the disease was declared a public health emergency of international concern (PHEIC) by WHO on 30 January 2020[3]. Later, it was named as coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) on 11 February 2020[3]. COVID-19 is highly contagious and has rapidly affected the whole world, affecting more than 200 countries and territories.

Many studies have focused on the clinical characteristics of patients infected by SARS-CoV-2 in different countries and regions and we can easily found that the disease severity and manifestation were distinctive between different regions[4-8]. Previous reports showed that infection with COVID-19 at high altitude was reduced[9, 10]. But it remains unknown whether there are differences in the clinical characteristics of COVID-19 patient at different altitudes. Adapted to the hypoxic environment, patients at high altitudes might also behave distinctively from people at lower altitudes. However, there is very few information regarding the COVID-19 in high altitude areas. Therefore, in this retrospective cohort study, we aimed to provide an insight into the difference in clinical manifestation and treatment of COVID-19 between plain area and plateau area, and to explore the risk factors for symptomatic cases of COVID-19.

2. Methods

2.1 Data sources

We conducted a retrospective cohort study on the characteristics of laboratory-confirmed cases of COVID-19 in the Tibetan Qiang Autonomous Prefecture of Ngawa, Sichuan province from February 1, 2020 to March 2, 2020. All cases were diagnosed based on the WHO guidelines[11] and Chinese national guideline[12, 13]. Only the confirmed cases with SARS-CoV-2 infection, which were defined as positive results to high-throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assays for nasal and pharyngeal swab specimens, were enrolled in this study. This study was reviewed and approved by the Medical Ethical Committee of Sichuan Provincial People's Hospital. The requirement of informed consent on the individual patient level was waived given the urgent need to collect clinical data and the retrospective nature of this study design.

2.2 Data collection

We obtained the medical records of each patient, from which epidemiological information, history of smoking and comorbidities, clinical symptoms and signs, chest computed tomographic (CT) scan results, and laboratory findings on admission were extracted. Epidemiological information included travel history to Wuhan within 14 days, contact with the confirmed cases, and cluster infections. The durations from illness to first admission were also recorded. Laboratory tests consisted of complete blood count, coagulation test, serum biochemistry (including liver and renal function, serum proteins, creatine kinase (CK), lactate dehydrogenase (LDH), serum hypersensitive troponin I (cTnI). electrolytes, C-reactive protein (CRP), high-sensitivity C-reactive Protein (hs-CRP) and procalcitonin (PCT). The changes of radiological findings, laboratory findings, and results of RT-PCR assays of each patient as disease progressed during his/her hospitalization were also recorded in this study.

To achieve the laboratory confirmation of the SARS-Cov-2, pharyngeal swab specimens of each patient were collected and tested by RT-PCR assays. The tests of SARS-Cov-2 for all patients were performed by local Center for Disease Control and Prevention (CDC). Disease severity was defined based on the diagnosis and treatment of novel coronavirus pneumonia (trial version 6) by Chinese National Health Committee. Cases were described as severe cases when meeting any of the following criteria: 1) Respiratory distress (respiratory rate≥30 breaths/ min); 2) At rest, pulse oximeter oxygen saturation≤93%; 3) Arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤300mmHg. In high-altitude (over 1,000 meters above the sea level) areas, this value should be corrected by the following formula: PaO2/ FiO2×[Atmospheric pressure (mmHg)/760]. Additionally, cases with chest imaging that presented significant lesion progression >50% within 24-48 hours should be managed as severe cases. Specific treatments, clinical outcome, and days from nuclei acid tests positive to nuclei acid tests negative of each patient were recorded. Patients were discharged from hospital once the results of two RT-PCR tests taken one day apart were negative for pathogen.

2.3 Statistical analysis

Continuous variables were summarized as median and interquartile ranges (IQR) values, and categorical variables were expressed as frequencies and percentages. We divided the cohort into severe cases, non-severe cases and asymptomatic carriers, which were defined as asymptomatic patients with positive results of RT-PCR assays whose radiological images were normal. Mann-Whitney U test and Kruskal-Wallis H test were adopted to compare continuous variables between different groups, and chi-square and Fisher's exact test were used for categorical variables as appropriate. Logistic regression analysis was employed to analyze the independent risk factors for symptomatic cases of COVID-19. Odds ratios (OR) and the corresponding 95% confidence interval (CI) were calculated. For all analyses, a two-sided P value less than 0.05 was regarded as statistically significant. Logistic regression analysis was performed on JupyterLab, and other statistical analyses were generated using SPSS version 22.0 (IBM, Armonk, NY, USA).

3. Results

3.1 Demographics and clinical characteristics

A total of 67 patients from Tibetan Qiang Autonomous Prefecture of Ngawa, Sichuan, China (2979 m) confirmed as COVID-19 were included in this study, with 4(6.0%) patients categorized into severe cases, 39(58.2%) non-severe cases, and 24(35.8%) asymptomatic cases on admission. All patients were Tibetan. The median age for all patients was 40.0 years (interquartile rage from 20.0 to 54.7). Compared with the fact that only 2(8.3%) asymptomatic patient were over 50, about half(48.7%) of the patient in non-severe group and the majority (75%) of severe patients were older than 50 years. Patients aged below 18 years account for 17.9% of overall case. About half (49.3%) of patients were female. Since no patients had a direct history of exposure to Wuhan or contacted with people from Wuhan, we assumed all patients in this study were community-infected cases. 46(68.7%) patients were associated with cluster infection events in this study. 25 (37.3%) patients had at least one underlying disorder, the most common of which were hypertension (29.9%). Only 2 (3.0%) diabetes patients were identified and 3(4.5%) were diagnosed with cardiovascular disease. 2 (3.0%) had chronic obstructive pulmonary disease (COPD), 3(4.5%) reported chronic gastritis, 2(3.0%) had a history of chronic cholecystitis or cholelithiasis, and 3(4.5%) had other pulmonary disease (i.e. bronchiectasis and tuberculosis). No self-reported malignant cancer, chronic liver disease or chronic renal disease was declared. Overall, 3(75.0%) severe patients, 18(46.2) non-severe patients, and 4(12.5) asymptomatic patients had underling comorbidities (Table 1).

The most common symptom was cough in 13(19.4) cases, followed by sputum production in 7(10.4) cases, chest tightness or dyspnea in 6(9.0) cases, fatigue or myalgia in 5(7.5) cases, headache in 5(7.5) cases. Interestingly, only 2(3.0%) patients developed fever on admission and during hospitalization. The median days from the illness onset to first admission for all patients were 3 days (interquartile rage from 1.0 to 7.0) (Table 1).

3.2 Radiologic and laboratory findings

Of 67 patients had chest CT scan on admission, abnormal results were detected among all of the severe cases and the majority (87.2%) of non- severe cases. Chest CT results of 24 asymptomatic patients, as described above, were normal. 26(38.8%) patients showed typical ground glass opacities, bilateral patchy shadowing was identified in 9(13.4%) cases, and 6(9.0%) patients showed local patchy shadowing. Interstitial abnormalities were merely spotted in 1(1.5%) patient (Table 2).

7(10.4%) patients showed leucopenia (low white blood cell (WBC) count), however we did not witness statistical difference of white blood cell counts between severe, non-severe and asymptomatic groups (P=0.269). 20 (29.9%) patients showed lymphopenia (low lymphocyte count), and the median lymphocyte count of asymptomatic patients was different from those of the severe and non-severe case (P<0.001). Although neutrophil count did not differ between three groups, neutrophil-to-lymphocyte ratio (NPR) of asymptomatic patients was also different from those of the severe and non-severe case (P=0.010). 14 (20.9%) patients had thrombocytopenia (low platelet count). Prothrombin time (PT) showed statistical difference between three subgroups (P=0.018), 4(6.0%) patients had prolonged PTs, and none of them had a PT longer than 18 seconds. Although fibrinogen levels differed between groups (P<0.001), no patient had a fibrinogen level lower than 1 g/L. Elevated Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels were identified in 26(38.8%) and 21(31.3%) patients, respectively. 15(22.4%) and 13(19.4%) patients had decreased sodium and magnesium levels, respectively. In addition, we also witness significant difference of sodium, chloride, and calcium levels between three groups (P=0.004, 0.027, and 0.003, respectively). Creatinine (Cr), CK, PCT and cTnI were normal in the majority of the cases. Elevated LDH levels were witnessed in 31 (46.3%) patients. CRP and hs-CRP levels were elevated in 11 (17.2%) and 23(35.4%) patients, and their differences between three groups were also statistically significant (P<0.001 and P=0.010, respectively) (Table 2).

3.3 Treatments and clinical outcomes

Overall, oxygen therapy, antiviral therapy and antibiotic therapy and supportive treatment were initiated in 45 (80.4%), 25(44.6%), 9 (16.1%) and 25(44.6%) patients, respectively (Table 3). Since most of the cases were non-severe and asymptomatic cases, mechanical ventilation and systemic corticosteroid were not given anyone. For antiviral therapy, the majority of the patients received ribavirin, some patients switch to abidol. During the antiviral therapy, we did not witness statistical variation of red blood cell (RBC) count, WBC count, haemoglobin (HB), platelet count, ALT, AST, albumin (all P>0.05). But elevated total bilirubin (TB) level was observed in both groups (P=0.017 and P=0.043). The occurrence rate of adverse effects after antiviral therapy was shown in Table S1.

At the end of this follow-up period (February 1, 2020 to March 2, 2020), 49(73.1%) patients were discharged from hospital, 15(22.4%) patients were still under hospitalization, and 3(4.5%) patients, who were severe cases, were transferred to another hospital (Table 3). The median days from initial positive to subsequent negative nuclei acid tests were 9.0 (IQR, 3.0-11.0) days, and it did not differ between antiviral therapy group and non- antiviral therapy group (P=0.951) (Table S2).

3.4 Risk factors for symptomatic cases

Several risk factors identified to be relevant to the symptomatic cases of COVID-19 were advanced age(OR, 1.076; 95%CI, 1.117-1.036), hypertension(OR, 1.013; 95%CI, 1.023-1.003), high neutrophil count(OR, 1.462; 95%CI, 2.100-1.018), neutrophil-to-lymphocyte ratio(OR, 1.574; 95%CI, 2.475-1.001), fibrinogen(OR, 1.927; 95%CI, 3.337-1.113), and lactate dehydrogenase level(OR, 1.005; 95%CI, 1.010-1.001). And high lymphocyte count was related with lower risk for symptomatic cases of COVID-19 (Table 4).

4. Discussion

In this observational study, we presented the clinical and laboratory characteristics of 67 Tibetan patients confirmed with SARS-Cov-2 infection in Tibetan Qiang Autonomous Prefecture of Ngawa, Sichuan province, China. There are several points needed to be highlighted: the majority of cases are cluster infection, which was reported as a major way of transmission outside of Hubei province, China[6, 14]; cough, sputum production, fatigue or myalgia, headache, and dyspnea were the most common symptoms, but fever was not as common as in other studies[8]; 24(35.8%) asymptomatic patient, who had no symptom, normal CT results but positive RT-PCR results, were mildly ill, which is consistent with the findings of previous studies[15]; fast changes in CT imaging were detected compared with those previously reported in Wuhan[16]; more patients had elevated hs-CRP levels than elevated CRP levels, suggesting that hs-CRP may yield a higher sensitivity; Interestingly, the disturbance of electrolyte in these patients was also significant. Although previous study has shown some patients had low sodium concentration[8]; the current study revealed that major electrolyte concentration of sodium, chloride, and calcium were changed in many cases, indicating the electrolyte disturbance is one of the important characteristics of COVID-19 patients in our cohort.

The patients' coagulation function showed some worth-noticing differences between the asymptomatic cases and other categories. One noticeable result was that fibrinogen concentration was decreased in asymptomatic cases, while the concentration was significantly increased in non-severe and severe cases in our cohort. It's hard to explain this result because fibrinogen is positive acute reaction protein. However, in our study, the declined fibrinogen levels of asymptomatic cases might be correlated with high attitude. And another characteristic of our patients was the decreased level of the platelet. Low platelet count was shown in severe infection, such as sepsis, which is related to patient's prognosis. This may result from the inhibition of platelet production. In our study, thrombocytopenia was more common in severe patients than in other groups, this may be associated with SARS-CoV-2 involved the lung where platelet is produced. Whether this is related to patient's prognosis requires more work to confirm. However, we did not observe the significant differences in coagulation function between non-severe patients and severe patients as seen in other studies[8, 14], possibly due to the limited sample size. Coagulation dysfunction in COVID-19 patients may be directly caused by the virus infection and indirectly stimulated by hypoxia[17], but the detailed underlying mechanism remains to be further investigated. Nevertheless, the coagulation dysfunction should be carefully monitored in COVID-19 patients.

Notably, in coordination with other studies[4, 18], decreased lymphocyte counts in COVID-19 patients in the current study, especially in severe cases, demonstrated that SARS-CoV-2 might influence the immune system. Besides, we also witnessed the increased level of NLR in severe and non-severe patients compared with asymptomatic patients. This finding nodded in agreement with the research of Qin et al. that severe cases tend to have higher NLR[19]. Moreover, Liu et al. identified that NLR was an independent risk factor for severe illness in COVID-19 patients and may benefit the early detection of severe cases[20]. We did not observe obvious adverse event of the drugs among patients received antiviral therapy, including ribavirin and abidol. The median days from initial positive to subsequent negative nuclei acid tests were 9.0 (IQR, 3.0-11.0) days and it may be associated with the recovery of lymphocyte and immune system. But the duration did not differ between antiviral treatment group and non-antiviral treatment group. The question whether the clinical application of antiviral drugs could improve the prognosis of patients remains uncertain and needed to be explored further[6]. Advanced age, hypertension, lymphopenia, leucocytosis, elevated lactate dehydrogenase have been reported to be associated with increasing odds of in-hospital death[21]. Also, advanced age, hypertension and elevated lactate dehydrogenase level were significantly associated with the severity of COVID-19[22, 23]. Our results were similar with the results of previous studies. In this study, advanced age, hypertension, high neutrophil count, neutrophil-to-lymphocyte ratio, fibrinogen, and lactate dehydrogenase level were identified as independent risk factors for symptomatic cases of COVID-19. On the other hand, high lymphocyte count was identified as protective factors. This finding suggested that elevated neutrophil-to-lymphocyte ratio and fibrinogen may also be indicators of symptomatic cases of COVID-19.

In our study, we summarize the differences of characteristics of COVID-19 patients between high altitude areas and low altitude areas as follows: (1)patient with SARS-CoV-2 infection has lower oxygen saturation in plateau areas, and hypoxia may be more obvious; (2)COVID-19 patients has a higher probability of progressing to pulmonary edema and brain edema in plateau areas. At present, current clinical studies have revealed that severe and critical COVID-19 may cause poor gas exchange in the lungs, leading to hypoxia[24]. Therefore, oxygen therapy plays an important role in the treatment of the disease. Furthermore, there are several points that need to be addressed in the oxygen therapy of COVID-19 in high altitude areas. First of all, pay attention to oxygen concentration and method of oxygen delivery. Low flow oxygen therapy is recommended, that is, the oxygen flow rate should be maintained at 2-4 L per minute, so as to ensure the efficacy of oxygen therapy and avoid side effects at the same time. Maintaining a continuous pattern of oxygen delivery, instead of an intermittent pattern, is important. In view of the characteristics of the disease, the oxygen therapy should be scheduled in the afternoon or in the evening. Secondly, physicians need to be alert to the occurrence of cerebral edema, especially for children, and pay attention to the amount and speed of intravenous fluid therapy in order to prevent cerebral edema. Last but not least, in high-altitude (over 1,000 meters above the sea level) areas, as described above, PaO_2/ FiO_2 value should be corrected. The implementation of these measures in oxygen therapy would be effectively in the treatment of COVID-19 in plateau areas. The interaction between hypoxia and virus is complicated, and the underlying mechanism may be different for different virus. Some studies have reported that hypoxia may inhibit or stimulate propagation of viruses and HIF-1α is essential in modulating the process[25]. Herein, more studies regarding hypoxia are needed to unearth the mechanism and provide a potential treatment target for COVID-19.

Our study has several limitations and the findings should be interpreted with caution. Firstly, only a small sample of 67 patients was included in the current study and the number of severe cases was also limited, so the lack of statistical significance may not rule out difference between the subgroups. Secondly, the patients were all from one hospital in Sichuan province, where medical supplies and equipment may differ from other regions. Meanwhile, we were not able to compare the clinical characteristics of patients in high altitude areas and patients in low altitude areas. Thirdly, since the data of D-dimer results and the specific subsets of lymphocytes were not available, further studies are required to investigate the role of coagulation and immune response in COVID-19 patients.

In conclusion, this study presented a detailed description of clinical and laboratory characteristics of COVID-19 patients in high altitude areas which can help clinicians better manage patients.

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