Clinical characteristics and risk factors of chronic obstructive pulmonary disease complicated with pulmonary hypertension at different altitudes

LiXia Wang  
Sichuan University

FaPing Wang  
Sichuan University

FengMing Luo (✉ fengmingluo@outlook.com)  
Sichuan University

Research Article

Keywords: Chronic obstructive pulmonary disease, Pulmonary arterial hypertension, High altitude, Risk factor

Posted Date: December 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2307961/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Pulmonary Medicine on April 18th, 2023. See the published version at https://doi.org/10.1186/s12890-023-02405-8.
Abstract

**Background:** Pulmonary hypertension (PH) is a common complication in patients with chronic obstructive pulmonary disease (COPD) and is closely related to poor prognosis. At present, researches about the risk factors of PH in COPD patients are limited, especially the human population at high altitude (HA).

**Objectives:** To investigate the differences of clinical characteristics and related risk factors of patients with COPD/COPD-PH from low altitude (LA, 600m) and HA (2200m).

**Methods:** We performed a cross-sectional survey of 228 COPD patients of Han nationality admitted to respiratory department of Qinghai People's Hospital (N=113) and West China Hospital of Sichuan University (N=115) From March 2019 to June 2021. PH was defined as a pulmonary arterial systolic pressure (PASP) >36 mmHg measured by transthoracic echocardiography (TTE).

**Results:** In this study, the proportion of PH in COPD patients at HA was higher than that at LA (60.2% vs 31.3%). COPD-PH patients at HA showed significantly different in baseline characteristics, laboratory tests and pulmonary function test. Multivariate logistic regression analysis indicated that the independent related factors of PH in COPD patients are different between HA and LA.

**Conclusions:** The proportion of COPD-PH at HA is higher than LA. At LA, increased BNP (B-type natriuretic peptide) and DB (direct bilirubin) were independent risk factors for PH in COPD patients. While at HA, higher BMI was independent protective factor and increased DB was independent risk factor for PH in COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a persistent respiratory symptoms and airflow limitation. It has been listed as one of the top three causes of death all over the world. (1) It is also the most common cause of deaths in patients with chronic respiratory disease, the fatality rate is 0.419‰. (2) Acute exacerbation of COPD is associated with higher morbidity, mortality and medical costs, which aggravate the burden of disease. (3) PH is a common complication in patients with COPD which mainly occurs in advanced airflow limitation due to hypoxic vasoconstriction, and the prevalence of PH in COPD patients depends on the population, the definitions applied, and the tools used to evaluate patients. (4, 5) In addition, PH is associated with increased exacerbation risk and mortality in patients with COPD. (6, 7) Plateau environment is characterized by hypobaric hypoxic, cold, dry and high ultraviolet light, which causes functional changes in human energy metabolism, neuroendocrine, hemodynamics and fluid balance by hypoxia and oxidative stress mainly, leading to various diseases. (8)

Information about the differences of risk factors for PH in COPD patients between HA and LA was limited, Lei S et al just compared the characteristics of PH patients between LA and HA, and suggested that PH patients at HA had lower BNP and less severe PH than those living at LA. (9) Aguirre-Franco C et al (10) investigated the risk factors of PH in COPD patients at HA, which showed that GOLD 4 and hypoxemia
were the independent risk factors of PH in COPD patients at HA, but patients from LA were not included. Lupi-Herrera E(11) et al suggested that alveolar hypoxia plays a role in producing PH in COPD at HA, and after compared to previous study, they found that effect of chronic alveolar hypoxia on PH was attenuated at HA, but they didn't analyze the characteristics of COPD-PH patients and risk factors of PH in COPD patients between LA and HA. So, it is reasonable to compare the characteristics and risk factors of PH in COPD patients between two regions.

Globally, around 500.3 million people living at HA (defined as ≥ 1500 m above sea-level),(12) and exposure to hypobaric hypoxia, colder temperatures and drier climates.(13) Some studies reveled that general populations from HA have greater pulmonary artery systolic pressure (PASP) than in LA which estimated by TTE.(14, 15) the HA setting combines social-economic factors and environmental conditions which may affect respiratory health. Thus, it is of great significance to recognize the characteristics and risk factors of PH in patients with COPD between HA and LA.

However, information about PH in COPD patients at different altitude was limited, some studies evaluated only the association between PH and COPD, or the prognostic factors of PH in COPD patients. (5, 16, 17) A study from Bogotá (2640 m) have evaluated the prevalence and risk factors of PH in COPD patients living at HA, but only the pulmonary function tests (PFT) and arterial blood gas(ABG) were enrolled.(10) No research analyzed the difference of characteristics and risk factors of PH in COPD patients between LA and HA.

The aim of the present study was to determine the clinical characteristics and risk factors of PH in COPD patients from Sichuan plain and Qinghai plateau.

2. Material And Methods

2.1 Subjects and selection criteria

The cohort was composed of 228 hospitalized patients who were Han nationality and admitted through the outpatient clinic with a diagnosis of COPD in Qinghai people’s Hospital and West China Hospital of Sichuan University from March 2019 to June 2021, and selection of all patients and the patients with COPD from the two reference centers were according to 1:1 pairing by gender and age. The subjects’ demographic characteristics, laboratory tests, pulmonary function test (PFT), and transthoracic echocardiography (TTE) were collected. The inclusion criteria were all patients were with chronic cough or sputum production and the forced expiratory volume in the first second / forced vital capacity ratio (FEV/FVC) post-bronchodilator < 0.7; the age of the patients was ≥ 18 years; all patients underwent echocardiography. We excluded patients with history of untreated hypertension or other diseases that might impact heart health; PH caused by other diseases (idiopathic PH; connective tissue disease, HIV infection, portal hypertension, congenital heart disease; PH due to left heart disease, silicosis and pulmonary artery obstructions); Pregnant and lactating women, patients with cancer. This study was approved by the ethics committee of Qinghai people's Hospital and West China Hospital of Sichuan
University (Ethics number: Review No. 716 of 2021), and was conducted according to the Declaration of Helsinki. Appropriate consent and assent were acquired from all participants.

2.2 Pulmonary function test (PFT). Spirometry was performed before and after bronchodilator, and arterial blood gasses (ABG) tests were performed according to the European Respiratory Society (ERS) standardization. Patients were grouped by airflow limitation severity (mild to moderate: GOLD 1 + 2, severe to very severe: GOLD 3 + 4) according to the Global Initiative for Chronic Obstructive Lung Disease.

2.3 Transthoracic echocardiography (TTE). The TTE were performed at baseline on admission by experienced cardiologist using Philips Sonos 5500® ultrasound machine. The diagnosis of PH was based on the tricuspid regurgitation peak velocity (TRV), the degree of dilation of right atrium to estimate right atrial pressure (RAP) was recorded by this machine and used in the estimation of PASP by Bernoulli equation: PASP = 4TRV² + RAP (when PASP is > 36 mmHg, PH is considered), and PH was graded into three groups: mild (36 mmHg < PASP ≤ 45 mmHg), moderate (45 mmHg < PASP ≤ 60 mmHg), severe (PASP > 60 mmHg).

2.4 Statistical analysis
Normally distributed data is represented by a mean ± standard deviation and number (percentage), skewness distribution data were represented by a median (P25, P75) and number (percentage). The independent samples t-test was used for comparison of measurement data fitting normal distribution, non-parametric test was used for comparison of measurement data fitting skewed distribution. Chi-squared test was used for comparison of categorical variables. Univariate and multivariate logistic regression analyses were used to find the effect of relevant variables on the development of PH in patients with COPD. The covariates of multivariate analysis were selected from the univariate analysis with statistically significant difference (P value < 0.05) and excluded collinearity. the cut-off value was determined by receiver operating characteristic (ROC) curve. SPSS software version 26 (IBM Corporation, Armonk, NY, United States) was used for all statistical analyses.

3. Results

3.1 The proportion of COPD-PH patients and baseline characteristics at different altitude
A total of 228 patients were enrolled in the analysis. There were 31.3% (36/115) of COPD-PH patients at LA and 60.2% (68/113) at HA with PASP > 36 mmHg measured by echocardiography, and the difference was statistically significant (P < 0.001) (Fig. 1).

Table 1 shows the baseline characteristics of COPD-PH patients in two groups. As illustrated, the two groups of COPD-PH patients were mainly older men with similar BMI (P > 0.05). Compared with COPD-PH patients at HA, patients at LA had longer duration of cough (10.00 years vs 5.00 years, P = 0.007), and
lower PASP (45.00 mmHg vs 56.00 mmHg, P = 0.003). COPD-PH patients with mild stage of PH were mainly at LA (58.06%), moderate to severe were mainly at HA (75.3%) (P = 0.001). (Fig. 2)

3.2 laboratory examination and pulmonary function test of COPD-PH patients living at LA versus those living at HA

There were significant differences in HB levels, WBC counts, ALB, TB, IB, BNP, CRP levels, FEV1, VC, PaO2, PaCO2 levels and proportion of GOLD 1 + 2 between COPD-PH patients living at LA and HA (P < 0.05). The parameters in COPD-PH patients living at LA, such as WBC counts, ALB, BNP, CRP levels, FEV1, VC, PaO2, PaCO2 levels and proportion of GOLD 1 + 2 were higher than those patients living at HA; conversely, the HB levels and TB, IB levels were lower in COPD-PH patients living at LA than those patients living at HA. There were no significant differences in platelet (PLT) and lymphocyte (LY) counts, direct bilirubin (DB), alanine transaminase (ALT), glutamic oxalacetic transaminase (AST), total protein (TP), creatinine (Cr), and procalcitonin (PCT) levels, potential of hydrogen (pH), arterial partial pressure of carbon dioxide (PaCO2), and base excess (BE) levels, forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) levels in COPD-PH patients living in the two regions (Table. 2).

3.3 Risk factors of PH in COPD patients

In our study, the cut-off values of the skewed distribution variables that for logistic regression analysis were determined by ROC curve analysis (Fig. 3). BNP in both groups had the maximum AUC (area under the curve). At LA, 130.50 pg/mL was determined as cut-off for BNP (AUC = 0.76, Sens: 75.80%, Spec 71.40%) in ROC analyses. At HA, 42.00 pg/mL was determined as cut-off for BNP (AUC = 0.75, Sens: 82.50%, Spec 57.90%), AUC of FEV1/FVC was less than 0.5 which means the lower the cut-off value, the more PH was likely to complicate. Information about other variables of the two groups was listed in Table. 3.

We evaluated the independent risk factors associated with PH in patients with COPD by univariate and multivariate logistic regression analyses in two regions (Table. 4, Table. 5). As shown in Table 3, BNP (brain natriuretic peptide) ≥ 130.5 pg/mL (OR: 9.99, 95%CI: 3.52–28.31, p < 0.001) and TB (serum direct bilirubin) ≥ 8.90 umol (OR: 3.33, 95%CI: 1.09–10.19, p = 0.035) were independent risk factors for PH in COPD patients from LA after adjusting for PLT (platelet count). In Table 4, TB ≥ 17.35 umol (OR: 3.94, 95%CI: 1.24–12.51, p = 0.020) was the independent risk factor for PH in COPD patients and higher BMI (OR: 0.87, 95%CI: 0.76–0.99, p = 0.034) was the independent protective factor for PH in COPD patients from HA after adjusting for BNP, ALB (serum albumin), PaCO2 (arterial partial pressure of carbon dioxide), FEV1/FVC (forced expiratory volume in the first second/forced vital capacity). And increased BNP was the independent risk factor of PH in COPD patients at LA rather than HA, increased BMI was the independent protective factor of PH in COPD patients at HA rather than LA.

4. Discussion
Our study showed that patients with COPD living at HA had a higher proportion of PH compared to LA. COPD-PH patients at HA showed significantly higher TB, BNP, HB, PASP and proportion of moderate to severe PH, lower duration of cough, WBC, PaO$_2$, and poor lung function compared to patients at LA. Multivariate logistic regression analysis indicated that the independent related factors of PH in COPD patients are different between HA and LA (TB and BMI vs TB and BNP).

Previous studies showed that the rate of complicating PH in COPD patients and the PASP of COPD-PH patients at HA were higher than that at LA, which were similar to our results. (10, 14, 23–25) These findings suggested that PH could induced by HA,(26, 27) probably associated with chronic alveolar hypoxia which played a minor role in the development of PH in patients with COPD who resided at HA permanently. (11) Meanwhile, PH was more common in COPD patients with severe (GOLD 3) to very severe (GOLD 4) airflow restriction at HA, our result (HA: 73.53%, LA:47.22%) was similar to the previous studies, Aguirre-Franco C et al showed that the proportion of PH in COPD patients with severe to very severe airflow restriction at an average altitude of 2640m was 64.00%, (10) and Jatav V.S et al suggested that the proportion of PH in COPD patients with severe to very severe airflow restriction at an average altitude of 598m was 47.30%, (28) which suggested that a higher risk of complicating PH for COPD patients living at HA compared to COPD patients with similar airflow limitation living at LA. The main reasons for why the COPD patients with severe airflow limitation are more likely to have PH may be as follows: More severe airflow limitation could lead to more severe hypoxia in COPD patients, and then, resulting in severe hypoxic pulmonary vasoconstriction which is the main mechanism of PH; (29–31) Severe hypoxia leaded to endothelial cell injury along with impaired vascular regeneration and remodeling, and causing significant proliferation and resistance to apoptosis of pulmonary artery resident cells. (32–34)

The distinctive feature of our study is that our subjects are all the permanent residency of HA (2200m) and LA (600m). Similar to what has been described previously, we found people living at HA had lower PaO$_2$, SaO$_2$, FEV$_1$, VC and higher HB compared to LA, (14, 24, 35, 36) this probably related to chronic hypoxic environment of HA.

As for some infection indexes, our study showed that living at HA had lower WBC and CRP. Previous studies reported that general population and patients with thromboembolic disease had higher WBC than LA. (37–39) One hypothesis could be that hypoxia led to increased erythroid activity and relative decrease activity of the myeloid/monocytic lineage, another was that HA might change plasma volume. (37) However, a study on a small general population from HA ($\geq$ 4500 m) and LA (~ 850m) suggested that there was no significant difference from WBC between the two regions. (36) The difference may be due to that our subjects were patients and the previous study was based on general population, as well as the different altitude of subjects and different sample sizes. CRP was associated with bacterial infections and WBC levels closely, meanwhile, some researches showed prolonged hypoxia may cause inflammation to resolve, suggesting the adaptation of vascular endothelium to hypoxia. (40) However, a previous study showed that CRP of healthy subjects and patients with pulmonary oedema was increased after acute exposure to HA, most likely due to acute hypoxia stimulate inflammation by the way of
nuclear factor kappa B (NF-κB) gene transcription and the production of proinflammatory cytokines.\textsuperscript{(41–43)} The reasons for the difference might be that our subjects were permanent residents of their altitude, and the subjects of other studies with inverse result were acute exposure to HA, moreover, our study had larger sample sizes, different disease condition and different race.

We also found that the related factors of PH in COPD patients were different between LA and HA. Firstly, our results suggested that increased BNP was only the independent risk factor of PH in COPD patients at LA. BNP was a biomarker secreted by ventricular muscle that can evaluate cardiac function and prognosis in HF and other cardiovascular diseases, and hypoxia could stimulate its release.\textsuperscript{(44, 45)} So, the vascular adaptations to hypoxia may determine higher BNP in populations living at HA which was similar to our results (\textbf{Table 1.2}). However, a previous study on the relationship between PH and altitude arrived at inverse conclusions which reported that PH patients at LA had higher BNP levels than HA,\textsuperscript{(46)} the differences may be due to that the population was interstitial lung disease which was different from our subjects, meanwhile, all the subjects were Italians in the previous study. Increased BNP was associated with higher PASP and mortality in patients with PH, and plasma BNP could be regarded as a protocol to identify PH early.\textsuperscript{(47–49)} As for patients at HA, due to long-term exposure to hypobaric hypoxic environment, the body has some adaptive changes such as hypoxic pulmonary vasoconstriction and ventricular hypertrophy.\textsuperscript{(30, 50)} So, the increased BNP was not an independent risk factor of PH in patients with COPD at HA.

Secondly, our results suggested that increased BMI was only the independent protective factor of PH in COPD patients at HA. Overweight and obesity had positive association with cardiovascular and all-cause mortality.\textsuperscript{(51)} But many studies suggested that high BMI was associated with low mortality in COPD patients, we could explain this condition as “obesity paradox”,\textsuperscript{(52, 53)} and the definition of obesity paradox was that obesity in older patients or in patients with several chronic diseases may be protective and associated with decreased mortality.\textsuperscript{(54)} A previous study from Southeast Iran plateau suggested that low BMI was the independent risk factor for severe PH in patients with COPD, this means high BMI might be a protective factor in patients with severe PH in COPD, which was similar to our results of HA.\textsuperscript{(55)} However, our result about PH of LA was different from some previous studies which reported high BMI was a risk factor of PH and BMI was positively correlated with PASP,\textsuperscript{(56, 57)} and in our study, BMI was not a related factor of PH in patients with COPD at LA. The differences may be due to that subjects of the previous studies were general population or patients without specific background diseases, and there were more than 3000 and 8000 subjects enrolled in the previous studies respectively, meanwhile, the race between our study and the previous studies were different. In addition, the reason why BMI was not the same related factor for PH in COPD patients in both regions of our study could be that the baseline level of BMI of COPD patients with and without PH was different in HA group, but similar in LA group (LA: 22.64 ± 3.79Kg/ vs 22.77 ± 3.71Kg/ , P > 0.05; HA: 21.06 ± 3.91 vs 23.35 ± 3.56 Kg/ , P < 0.05).

We also find that increased TB which was an independent risk factor of PH in COPD patients at HA and LA, and patients living at HA had significant higher TB than LA. Some studies about TB and PH similarly indicated that PASP levels were positively correlated with TB, and TB was an independent risk factor of
The reasons could be that HA was characterized by hypoxia and bilirubin was an endogenous antioxidant molecule which was related to oxidative stress.(60, 61) Moreover, transaminases in our study between the 2 groups (COPD-PAH at HA, COPD-PAH at LA) were not significantly different which revealed that serum bilirubin was more sensitive to hemodynamic changes than transaminases,(62) and the sensitivity of serum bilirubin and transaminases to altitude changes were needed to explore. Overall, hypoxic pulmonary vasoconstriction caused by hypoxia could lead to PH and PH aggravated hypoxia which entered a vicious cycle.

The highlight of the research was that subjects were from two reference centers and we reasonably excluded the subjects with other diseases associated with PH. But there were some limitations of this study ought to be expounded. Primarily, it was a cross-sectional retrospective study and we couldn't determine the causality from the results directly. Secondly, although we had two reference centers, it was like a single reference center for each altitude and the sample size was limited, so the results of our study could not be reliably extrapolated to the general population with COPD living at similar altitudes. Secondly, other diseases with coexisting pathologic conditions that could cause PH were excluded in our study, so we could not classify PH into different subgroups in this study. Thirdly, we could not obtain the rate of complicating PH in patients with COPD in different GOLD groups by the ABCD assessment tool, (19) since we didn't have the information on COPD exacerbations in the year prior, and a previous study had shown a higher rate of complicating PH in group C and group D.(63) Finally, TTE was used to estimate PASP instead of the right cardiac catheter, which allowed for complete hemodynamic assessment,(64) but was invasive, high cost and difficult to use on a large scale.(65, 66)

5. Conclusion

This study showed that the proportion of complicating PH and moderate to severe PH in patients with COPD living at HA was higher than LA. Higher TB was the common independent risk factor for PH in patients with COPD at LA and HA, higher BNP was the only independent risk factor for PH in patients with COPD at LA, and higher BMI just the independent the only protective factor for PH in patients with COPD at HA. Thus, more study centers and larger sample sizes were needed to explore the difference of related factors for PH in patients with COPD between different altitudes.

Declarations

Acknowledgements

We thank Lichun Zhong (Laboratory of Pulmonary Immunology and Inflammation) and Chunjie Li (Laboratory of Pulmonary Immunology and Inflammation) for the English editing.

Availability of data and materials

All data generated or analyzed during this study are included in the article and additional file.
Contributions

LXW drafted the manuscript. FPW helped and revised the manuscript. All authors were in charge of the data collection and read and approved the final manuscript.

Ethics declarations

The present study was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University. All aspects of the study complied with the Declaration of Helsinki. The need for informed consent was waived by the Medical Ethics Committee because the study was an observational, retrospective study. Patient information was collected from the hospital database, and no identifying information was disclosed. All data were anonymized before being analyzed.

Funding

This work was supported by “1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University ZYJC18021; Sichuan Province Science and Technology Support Program (No.2021YFQ0030).Post-Doctor Research Project, West China Hospital (2021HXBH074).

Consent for publication

Not applicable.

Competing interest

The authors declare no conflicts of financial interest.

References


Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures
Figure 1

The rate of complicating PH in COPD patients between LA and HA
Figure 2

The proportion of PH severity between LA and HA

---

**Figure 2**

The proportion of PH severity between LA and HA
Figure 3

The ROC curve of skewed distribution variables that for logistic regression analysis at LA. (A). The ROC curve of skewed distribution variables that for logistic regression analysis at HA. (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx
- Table5.xlsx