**Peer Review File**

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Reviewer A

Please reply to the following questions/comments:

1) In addition to chronic hypoxia, is there a potential influence of other environmental factors, such as prolonged cold, on development of pulmonary vascular disease in Qinghai-Tibet Plateau?

Response: Thank you for your comment. The plateau environment is characterized by hypoxia and reduced atmospheric pressure resulting from high altitude, a dry climate, intense ultraviolet radiation, and sparse vegetation. Hypobaric hypoxia is a well-established environmental factor that contributes to alterations in the cardiopulmonary vascular system. Although other environmental factors may worsen symptoms in patients with pulmonary diseases, such as pulmonary hypertension (PH), there is limited literature documenting additional etiological correlations.

Changes in the text: none

2) In the "Study design and subjects", the authors wrote: "Meanwhile, 52 non-PH inpatients during the same period were selected as the control group. Patients with chronic lung disease, chronic heart disease, hypertension, connective tissue disease, tumor, and chronic liver and kidney insufficiency were excluded." And yet, in the results, the authors wrote that compared to the control group the PH group had a higher rate of COPD, hypertension and so on. It is to expect that they had a higher rate of hypertension or chronic lung disease, since in the control group the subjects with such disorders were excluded from the study? Please explain this issue.

Response: Thank you for your valuable comment. We appreciate your attention to detail. The discrepancy you pointed out regarding the comparison between the PH group and the control group has been duly noted. It was indeed an oversight on our part, and we apologize for any confusion it may have caused. We have rectified this error by removing the incorrect comparison of exclusion criteria in the results section. Thank you for bringing this to our attention.

Changes in the text: Line 154-162

3) The authors wrote: "In the PH group, patients were divided into 3 subgroups according to disease history, including chronic pulmonary disease (n=26), left heart disease (n=37), and unknown reason (n=31)." In my opinion, only the PH group with "unknown reason" can be the group with chronic hypoxia-induced PH, isn´t it? The other 2 groups have PH due to chronic pulmonary disease or left heart disease, but the chronic hypoxia can play a role here as well. Please discuss this important issue in more details, despite the fact that the authors mentioned this aspect in the Discussion.

Response: Thank you for your comment.

According to the 2022 ESC/ERS Guidelines, PH is classified into five major groups: 1) Idiopathic pulmonary arterial hypertension; 2) PH secondary to left heart disease; 3)

PH secondary to lung diseases and/or hypoxia; 4) PH associated with pulmonary artery obstructions; and 5) PH with unclear and/or multifactorial mechanisms. High-altitude pulmonary hypertension belongs to group 3 (PH secondary to lung diseases and/or hypoxia). One of the primary limitations of our study was the inability to conduct comprehensive etiological investigations and right heart catheterization due to logistical constraints. Consequently, we were unable to classify the PH cases according to the guidelines. It should be pointed out that the "unknown reason" group in this study should be interpreted with caution. Strictly speaking, it cannot be solely attributed to high-altitude pulmonary hypertension as it may include cases with rheumatic diseases, idiopathic pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, or other types of PH that were not definitively ruled out.

The above information has been added to the discussion section.
Changes in the text: Line 364-371

Reviewer B

This retrospective observational study was aimed at establishing characteristics (by echocardiography) of patients (N = 94) suffering from pulmonary hypertension (PH), who are living on the Qinghai-Tibet Plateau (about 4000 m asl).

The authors deal with an interesting issue from a scientific and clinical perspective as well. Although they present a valuable data set several points need to be considered before a final recommendation can be made.

First, a clear hypothesis is lacking but could be stated based on the inclusion and discussion of appropriate literature findings in the intro section. The PH prevalence of the global population may amount to about 1%. Would you (a-priori) assume this figure is higher in your population living at high altitude? When yes, why?
Might high-altitude pulmonary hypertension (HAPH) play a role?
Response: Thank you for your comment.
The prevalence of PH globally is estimated to be approximately 1% [1]. Literature reports indicate varying rates of HAPH in certain regions. Studies from South America, for example, have demonstrated HAPH prevalence ranging from 5 to 18% [2,3]. Negi et al. found a HAPH prevalence of 3.23% among natives of Spiti Valley, India [4]. These studies indicate that the prevalence of HAPH exceeds that of PH in the global population. However, there is still a lack of precise epidemiological data on HAPH, especially in the Qinghai-Tibet Plateau region.

The above information has been added to the introduction section.
Changes in the text: Line 65-71

1 Cullivan S, Gaine S & Sitbon O. New trends in pulmonary hypertension. *Eur Respir Rev*. 2023; 32(167):

2 Hakim TS, Michel RP, Minami H & Chang HK. Site of pulmonary hypoxic vasoconstriction studied with arterial and venous occlusion. *J Appl Physiol Respir Environ Exerc Physiol*. 1983; 54(5):1298–1302.

3 Audi SH, Dawson CA, Rickaby DA & Linehan JH. Localization of the sites of pulmonary vasomotion by use of arterial and venous occlusion. *J Appl Physiol*. 1991; 70(5):2126–2136.

4 Negi PC, Marwaha R, Asotra S, Kandoria A, Ganju N, Sharma R, Kumar R V. & Bhardwaj R. Prevalence of high altitude pulmonary hypertension among the natives of spiti valley - A high altitude region in Himachal Pradesh, India. *High Alt Med Biol*. 2014; 15(4):504–510.

In the intro section, you refer to PH definition with a mean PAP ≥ 25 mmHg and in the method section PH is defined as a pulmonary artery systolic pressure (PASP) ≥35 mmHg. Please, use clear criteria for the PH definition and then stay consistent.
Response: Thank you for your comment. The discrepancy in the definition of PH arises from different diagnostic criteria utilized in the literature. In the introduction, we cited the widely accepted definition of PH, which is based on a mean PAP greater than 25 mmHg as diagnosed via right heart catheterization, particularly applicable in lowland areas.
However, in this study, we employed echocardiography to determine pulmonary artery systolic pressure as a proxy for PH diagnosis. It's important to note that echocardiographic criteria for diagnosing PH lack uniformity. Therefore, following the precedent set by Nakatsuji et al. [5], we defined PH as a PASP ≥ 35 mmHg. We appreciate your attention to this matter.
Changes in the text: none

5 Nakatsuji A, Miyauchi Y, Iwasaki YK, Tsuboi I, Hayashi H, Uetake S, Takahashi K, Yodogawa K, Hayashi M & Shimizu W. Detection and evaluation of pulmonary hypertension by a synthesized right-sided chest electrocardiogram. *J Nippon Med Sch*. 2015; 82(3):136–145.

The “selection process” of study participants should be described in more detail. Had all these patients (N = 1689) echocardiography and determinations of PAP?
Response: Thank you for your comment. Not all these patients (N = 1689) received echocardiography and determinations of PAP. The statement about “study participants” has been revised as follows:

> From March 2019 to October 2020, the medical records of 1,689 inpatients in the Internal Medicine Department of Chaya County People's Hospital in Changdu,

Tibet, China, were reviewed. Patients who had undergone echocardiography and determine pulmonary artery pressure were screened. Among them, 116 cases were diagnosed with pulmonary hypertension (PH) based on echocardiographic measurement of pulmonary artery systolic pressure (PASP) ≥35 mmHg. After excluding cases with unclear medical history or missing data, 94 PH patients (44 males and 50 females, mean age = 66.51 ± 12.35 years) were included.

Changes in the text: Line 99-106

Do you have data on lifestyle characteristics like smoking, alcohol consumption, and physical activity, etc.? Such information would likely provide valuable information on potential risk factors for PH.

Response: Thank you for your comment. This study was retrospective, and unfortunately, we did not have data on lifestyle factors such as smoking, alcohol consumption, and physical activity. However, we appreciate your suggestion, and we will consider incorporating these factors into future prospective studies. We have strengthened this limitation and future work in the discussion section as follows:

This retrospective study lacked data on lifestyle characteristics such as smoking, alcohol consumption, and physical activity. Such information could offer valuable insights into potential risk factors for PH. Incorporating these factors into future prospective studies will be considered.

Changes in the text: Line 374-377

Major: How did you select and match the controls (non-PH patients) to create an appropriate control group? I do not understand the usefulness of this control group, e.g., none of them suffered from “systemic hypertension” which is very unusual for people of this age. Thus, it seems this is a very selected control group likely not suitable for comparison.

Response: Thank you for your comment. The hospital setting encompasses a range of internal medicine conditions. The selection of the control group was based on the principle of excluding underlying diseases (chronic lung disease, chronic heart disease, hypertension, connective tissue disease, tumor, and chronic liver and kidney insufficiency) due to the unavailability of pulmonary artery pressure measurements. While it's true that not all internal medicine inpatients had hypertension, the criteria focused on excluding patients with specific conditions rather than matching specific characteristics of the PH group.

Changes in the text: none

Why not simply present the characteristics of PH patients?

Whether doing so or not differences in characteristics of PH patients living at low altitude and the potential influence of high altitude (hypoxia) on PH development should be better pointed out.

Response: Thank you for your comment. Our study focuses on analyzing the clinical characteristics of PH patients in high-altitude Tibetans. Compared to individuals from low-altitude regions, Tibetan PH patients face unique environmental challenges,

particularly chronic hypoxia, which is a recognized risk factor for PH development. Additionally, the Tibetan population has undergone physiological adaptations to high-altitude conditions over generations, potentially leading to differences in the clinical presentation and etiology of PH when compared to low-altitude populations. The above information has been added to the discussion section.
Changes in the text: Line 334-340

What are main differences of your PH patients compared to those of low-altitude populations? What is the clinical relevance (and consequences) of your findings?
Response: Thank you for your comment. Our study focuses on analyzing the clinical characteristics of PH patients in high-altitude Tibetans. Compared to individuals from low-altitude regions, Tibetan PH patients face unique environmental challenges, particularly chronic hypoxia, which is a recognized risk factor for PH development. Additionally, the Tibetan population has undergone physiological adaptations to high-altitude conditions over generations, potentially leading to differences in the clinical presentation and etiology of PH when compared to low-altitude populations.

Regarding the clinical relevance of our findings, our study highlights the significance of PH in high-altitude regions, shedding light on the prevalence of chronic pulmonary and left heart diseases as common causes. This underscores the importance of implementing tailored interventions to address these specific conditions effectively. Moreover, our findings reveal systemic impacts of PH, as evidenced by abnormal liver and metabolic indexes. Understanding these associations can guide comprehensive patient management, emphasizing the necessity for tailored approaches in high-altitude settings. Furthermore, our research contributes to the understanding of PH characteristics in regions with limited medical resources and sparse population distribution. Given that over 1.4 million people globally live at high altitudes, with approximately 800,000 in Asia alone, providing insights into PH disease characteristics in these areas holds significant research value, particularly for medical practices in specialized regions.

The above information has been added to the discussion section.
Changes in the text: Line 334-350

The results start with “Patient’s clinical and clinical characteristics”; what do you mean?
It does not make sense to describe all your data presented in tables in the result section.
If you refer to “hypertension”, it would be better to use “systemic hypertension” to avoid confusion with pulmonary hypertension.
Response: Thank you for your comment. The first subheading of the results section has been corrected to “Patient’s demographic and clinical characteristics.”
Additionally, we have made changes throughout the results, tables, and discussion sections, replacing the term “hypertension” with “systemic hypertension” to prevent confusion with pulmonary hypertension.
Changes in the text: Line 153, 158, 263, Table 1

The authors (very) recently reported on ECG parameters derived from the study sample and may refer to this publication (PMID: 38177015) and potentially also other ones??

Response: Thank you for your thoughtful review. We appreciate the opportunity to address your concerns regarding the relationship between our two studies. We would like to clarify that the two studies under discussion utilize the same cohort of patients and control subjects but focus on different aspects of their medical data. Specifically, this study investigated echocardiographic parameters, while our previous study (PMID: 38177015) examined electrocardiogram (ECG) parameters associated with pulmonary hypertension (PH) diagnosis in high-altitude Tibetan populations. The decision to split the data into two separate publications was made to allow for a comprehensive exploration of each aspect of our research findings, given the complexity and richness of the dataset. By analyzing echocardiographic and ECG parameters separately, we aim to provide a detailed understanding of the clinical characteristics of Tibetan PH patients from multiple perspectives.

We have strengthened out this fact in the methods section as follows:

> It should be pointed out that the current study utilized the same cohort of patients and control subjects but focus on different aspects of their medical data with our previous study [6]. Specifically, this study investigated echocardiographic parameters, while our previous study [6] examined electrocardiogram (ECG) parameters associated with pulmonary hypertension (PH) diagnosis in high-altitude Tibetan populations.

Changes in the text: Line 112-116

In addition, we acknowledge the previous study (PMID: 38177015) cited in your comment and have discuss any overlap or complementarity between its findings and our current study in the discussion section as follows:

> Our findings regarding the clinical characteristics of Tibetan pulmonary PH patients in Chaya County, Changdu, Tibet, contribute to the growing body of literature on this topic. It is noteworthy that the current study complements our own recent investigation [6], where we focused on analyzing ECG parameters associated with PH diagnosis in high-altitude Tibetan populations. While the current study primarily examines echocardiographic parameters, the findings from both studies collectively provide a comprehensive understanding of the multifaceted nature of PH in this population. Specifically, the abnormalities observed in liver function and metabolic indexes among Tibetan PH patients in the current study align with the ECG parameters identified as independent factors associated with PH diagnosis in our previous investigation [6]. These converging findings underscore the complex interplay between cardiac and systemic manifestations of PH in high-altitude settings and highlight the importance of multimodal approaches in its diagnosis and management.

Changes in the text: Line 351-362

6 Dong R, Liang Y, Ni M, Wang D, Zhang J & Dun Z. Electrocardiogram Parameters

Associated With the Diagnosis of Pulmonary Hypertension in High-Altitude Tibetan Populations: A Retrospective Single-Centre Study. *Heart Lung Circ*. 2024; 33(2):240–250.

This discussion will enhance the contextualization of our research within the existing literature and provide readers with a clearer understanding of the contributions of our work. We hope this explanation clarifies the rationale behind splitting the data into two publications and assures you of our commitment to providing thorough and impactful research in the field of pulmonary hypertension. Thank you once again for your valuable feedback, which helps strengthen the quality and relevance of our work.