DOI: 10.1002/pul2.12404

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI | WILEY

Characteristics and risk profiles of patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension living permanently at >2500 m of high altitude in Ecuador

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Funding information
None

Abstract

Over 80 Mio people worldwide live >2500 m, including at least as many patients with pulmonary vascular disease (PVD), defined as pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH), as elsewhere (estimated 0.1‰). Whether PVD patients living at high altitude have altered disease characteristics due to hypobaric hypoxia is unknown. In a cross-sectional study conducted at the Hospital Carlos Andrade Marin in Quito, Ecuador, located at 2840 m, we included 36 outpatients with PAH or CTEPH visiting the clinic from January 2022 to July 2023. We collected data on diagnostic right heart catheterization, treatment, and risk factors, including NYHA functional class (FC), 6-min walk distance (6MWD), and NT-brain natriuretic peptide (BNP) at baseline and at last follow-up. Thirty-six PVD patients (83% women, 32 PAH, 4 CTEPH, mean ± SD age 44 ± 13 years, living altitude 2831 ± 58 m) were included and had the following baseline values: PaO_2 8.2 ± 1.6 kPa, $PaCO_2$ 3.9 ± 0.5 kPa, SaO_2 91 ± 3%, mean pulmonary artery pressure 53 ± 16 mmHg, pulmonary vascular resistance 16 ± 4 WU, 50% FC II, 50% FC III, 6MWD 472 ± 118 m, BNP 490 ± 823 ng/L. Patients were treated for 1628 ± 1186 days with sildenafil (100%), bosentan (33%), calcium channel blockers (33%), diuretics (69%), and oxygen (nocturnal 53%, daytime 11%). Values at last visit were: FC (II 75%, III 25%), 6MWD of 496 ± 108 m, BNP of 576 ± 5774 ng/L. Compared to European PVD registries, ambulatory PVD patients living >2500 m revealed similar blood gases and relatively low and stable risk factor profiles despite severe hemodynamic compromise, suggesting that favorable outcomes are achievable for altitude residents with PVD. Future studies should focus on long-term outcomes in PVD patients dwelling >2500 m.

KEYWORDS
hypobaric hypoxia, pulmonary arterial hypertension, pulmonary vascular disease, risk stratification

INTRODUCTION

In the absence of relevant lung disease, the two major forms of precapillary pulmonary hypertension (PH) are pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH), summarized as pulmonary vascular diseases (PVDs). Precapillary PH is diagnosed by mean pulmonary artery pressure (PAP) >20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 WU.[1] The cardinal symptom of PVD is dyspnea on exertion, which may severely impair quality of life. Patients with PVD reveal exercise and sleep aggravated arterial hypoxemia, which worsens in a hypoxic environment at high altitude.[2–7] Over the last two decades, medical drug combination and in selected CTEPH patients surgical or interventional therapies have become increasingly available for patients with PVD, particularly in higher income countries with economies that offer these advanced therapies, and have resulted in improved exercise performance, quality of life and outcome.[8–11]

Over 80 Mio people worldwide live permanently at an altitude of over 2500 m in cities or rural mountain regions and are thus exposed to hypobaric hypoxia with lower inspiratory oxygen pressures.[12] This may lead to chronic altitude dwelling-associated diseases, such as chronic mountain sickness (CMS) or, more rarely, high-altitude pulmonary hypertension.[13,14] However, the vast majority of people who were born and live at moderate to high altitude between 2500 and 3500 m have no relevant altitude-related health problems and feel subjectively well, despite a higher prevalence of sleep-disordered breathing and comparatively increased PAP.[14–16] The prevalence of PVD defined as PAH or CTEPH is estimated to be around 100/Mio population at low altitude, and is presumably at least as high among the millions of people living >2500 m.[8,17] However, little is known about the impact of living at high altitude (> 2500 m) on symptoms, exercise capacity, and pulmonary hemodynamics in PVD patients.

The aim of the present study is therefore to investigate baseline characteristics and risk factor profiles of prevalent ambulatory patients with PVD who were born and live permanently at an altitude of >2500 in Ecuador.

METHODS

Thirty-six patients with PVD living permanently at an altitude of >2500 m in Ecuador who were ambulatory and were last treated for their PVD at the Hospital Carlos Andrade Marin in Quito between January 2022 and July 2023 were eligible for this cross-sectional study. All patients are regularly followed at the Hospital Carlos Andrade Marin in Quito and gave informed consent to be screened for a prospective trial approved by the ethical review board in Quito (Nr. PI-2023-0015) and have their data registered. Patients were included if they were diagnosed with precapillary PH by right heart catheterization according to current guidelines[8] with mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU and classified as PAH or CTEPH.

Patients were excluded if they had evidence of any other PH group including PH due to relevant heart- or lung disease (left ventricular ejection fraction [LVEF] <50%, forced expiratory volume in 1 s [FEV1] or forced vital capacity [FVC] <70% predicted), Eisenmenger syndrome due to uncorrected ventricular septal defects, erythrocytosis indicative for CMS (defined as hemoglobin >19 g/dL in women, >21 g/dL in men), other severe illness requiring chronic therapy, or severe disability.

At the time of PVD diagnosis, the following parameters were recorded: age, gender, height, weight, body mass index, classification of PH, hemodynamics by right heart catheterization (mPAP, cardiac output, PVR, PAWP, and right atrial pressure), arterial oxygen saturation by pulse oximetry (SpO_2), arterial blood gases (pH, SaO_2, PaO_2, and $PaCO_2$), pulmonary function tests (FEV1 and FVC), 6-min walk distance (6MWD), data of echocardiography including LVEF, systolic PAP, tricuspid annular plane systolic excursion, and NT-pro-brain natriuretic peptide (BNP). Follow-up (FU) time, maximal PH-targeted therapy during FU and last visit data on functional class, 6MWD, and systolic PAP by echocardiography were noted. The risk group, according to the comprehensive three-strata risk assessment proposed in the latest PH guidelines, was calculated for baseline data, and the simplified four-risk strata were calculated for data from baseline and last follow-up.[8]

Outcomes are presented as mean ± standard deviation (SD) or numbers (%) as appropriate and mean difference and 95% confidence interval (CI). Exploratory statistics were calculated by paired *t* test and chi-square test.

RESULTS

Patient population

Thirty-six PVD patients (mean ± SD)—age 44 ± 13 years, 30 (83%) females, 32 (89%) PAH, 4 (11%) CTEPH—fulfilling the inclusion criteria were identified. Patients had their baseline diagnostic right heart catheterization between November 2011 and July 2023 (see Table 1 for baseline characteristics). All patients were treated with a PDE-5 inhibitor, 12 (33%) combined with an endothelin receptor antagonist (ERA), and 13 (36%) combined with a calcium channel blocker (CCB). Additional therapies consisted of nocturnal oxygen therapy in 23 (64%), long-term oxygen therapy in 4 (11%), diuretics in 25 (69%), and oral anticoagulation in 22 (61%) over a mean follow-up of 1628 ± 1186 days (4.5 ± 3.2 years) (Table 2).

Baseline values

PVD patients had severely impaired hemodynamics at the diagnostic right heart catheterization with a mPAP of 53 ± 16 mmHg, a PVR of 16 ± 4 WU, a cardiac output of 3.2 ± 1.9 L/min, a PAWP of 11 ± 5 mmHg, and a RAP of 12 ± 4 mmHg. Arterial blood gases at room air at 2840 m showed a mean arterial SO_2 of 90 ± 6%, a PaO_2 of 62 ± 12 mmHg, and a $PaCO_2$ of 29 ± 4 mmHg. According to the three-strata risk assessment, most patients (26, 72%) were in the intermediate risk class, corresponding to a 1-year mortality risk of 5%–20%, whereas 1 patient (3%) was in the low-risk class, and 9 patients (25%) were in the high-risk class with an estimated 1-year mortality >20% (Table 3). Main characteristics were comparable between the 30 women and 6 men (age 45 ± 13 and 38 ± 16 years, mPAP 52 ± 16 and 55 ± 15 mmHg, PVR 16 ± 9 and 14 ± 7 WU, 6MWD 461 ± 122 and 527 ± 80 m, functional class II/III in % 46/54 and 66/34, respectively) and also between the 32 PAH and the 4 CTEPH patients (age 45 ± 14 and 39 ± 8 years, mPAP 53 ± 16 and 50 ± 11 mmHg, PVR 16 ± 9 and 14 ± 4 WU, 6MWD 472 ± 123 and 475 ± 68 m, functional class II/III 50/50 and 50/50%, females/males 87/13 and 50/50%, respectively).

Last visit and change during follow-up

Results of 6MWD test, echocardiography, and BNP at baseline and the last visit of on average 4.5 ± 2.3 years of

TABLE 1 Baseline characteristics.

Baseline characteristics	Number (%) or mean ± SD
Number of patients	36
Sex (f/m), *n* (%)	30/6 (83/7)
Mean living altitude, m	2831 ± 58
Age, years	44 ± 13
Height, cm	155 ± 9
Weight, kg	63 ± 20
Body mass index, kg/m^2	26 ± 9
WHO functional class, *n* (%)	
II	18 (50)
III	18 (50)
Pulmonary vascular disease classification	
Pulmonary arterial hypertension, *n* (%)	32 (89)
Idiopathic/hereditary	24 (70)
Associated with connective tissue disease	2 (6)
Associated with congenital heart disease	6 (20)
Chronic thromboembolic pulmonary hypertension, *n* (%)	4 (11)
Baseline hemodynamics by right heart catheterization	
Mean pulmonary artery pressure, mmHg	53 ± 16
Right atrial pressure, mmHg	12 ± 4
Cardiac output, L/min	3.2 ± 1.9
Cardiac index, L/min/m^2	2.0 ± 1.4
Pulmonary artery wedge pressure, mmHg	11 ± 3.3
Pulmonary vascular resistance, WU	16 ± 4
Arterial blood gases on ambient air at 2840 m	
SaO_2, %	91 ± 3
PaO_2, kPa (mmHg)	8.2 ± 1.6 (62 ± 12)
$PaCO_2$, kPa (mmHg)	3.9 ± 0.5 (29 ± 4)
pH	7.43 ± 0.03
HCO_3−, mmol/L	19.4 ± 2.8
Hemoglobin, g/dL	16.0 ± 2.3

(Continues)

TABLE 1 (Continued)

Baseline characteristics	Number (%) or mean ± SD
Spirometry	
FEV_1, % predicted	92 ± 13
FVC, % predicted	96 ± 14
Comprehensive risk assessment average score of the three-strata model	1.8 ± 0.4
Low/intermediate/high	1/26/9 (3/72/25)

Note: Data are given as number (%) or mean ± SD.

Abbreviations: DLCO, diffusion lung capacity for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HCO_3-, arterial bicarbonate; $PaCO_2$, arterial partial pressure of CO_2; PaO_2, arterial partial pressure of oxygen; PH, pulmonary hypertension; SaO_2, arterial oxygen saturation; TLC, total lung capacity.

TABLE 2 Characteristics at last visit.

Follow-up (FU) time and medication at last visit	Number (%) or mean ± SD
Time elapsed since diagnostic right heart catheterization, days (years)	1628 ± 1186 (4.5 ± 2.3)
Phosphodiesterase inhibitors (sildenafil)	36 (100)
Endothelin receptor agonists (bosentan or macitentan)	12 (33)
Calcium channel blockers	13 (36)
Diuretics	25 (69)
Oral anticoagulation therapy	22 (61)
Supplemental oxygen therapy	23 (64)
Nocturnal	19 (53)
Nocturnal and daytime	4 (11)

Note: Data are given as number (%) or mean ± SD.

follow-up are shown in Table 3. While functional class improved (FC II vs. III chi-square $p < 0.001$), most other risk assessment parameters were similar at the last visit of FU compared to baseline (Table 3). However, the four-strata risk group distribution improved with 47% and 89% being in the low-risk or low-to-intermediate low-risk group at follow-up compared to 33% and 75% (low-risk vs. non-low-risk chi-square $p = 0.04$), respectively (Table 3). The changes in the four-strata risk assessment from diagnosis to last visit are shown in Figure 1. Systolic PAP slightly improved and the resting heart rate decreased, whereas none of the other parameters significantly deteriorated.

DISCUSSION

This cross-sectional study describes for the first time a cohort of ambulatory, prevalent patients with PVD classified as PAH (Group 1) or CTEPH (Group 4) according to the latest guidelines who permanently live >2500 m (mean living altitude 2831 ± 58 m) in Ecuador and were regularly followed in the national PVD reference center of the Hospital Carlos Andrade Marin. The cohort included mainly patients with typical PAH reflected by the high percentage of women (83%) and the comparable young mean age (44 ± 13 years), in accordance with cohorts included in randomized-controlled trials investigating drug efficacy in PAH or a PAH-registry in high-income countries.[18,19] Despite severely compromised hemodynamics at baseline, these patients were in an intermediate- to low-risk class with 75% being in FC II and having a mean 6MWD of 496 ± 108 m.[18,19] Of interest, the average PaO_2 in this group of PVD patients permanently living >2500 m was 8.2 ± 1.6 kPa and thus within the limits expected for healthy newcomers at a similar altitude and comparable to PVD patients living at low altitude, according to the Swiss registry.[18,20]

It is estimated that 1% of the global population suffers from PH, with the vast majority being classified as having PH associated with left heart or chronic lung disease.[17] The prevalence of PVD classified as PAH or CTEPH is much lower and can roughly be estimated to be again up to 1% of the PH population, which would correspond to 0.01% or 100/Mio. Based on registry data from PVD lowlanders.[21] With the assumption of an at least equal prevalence of PVD at high altitude, this would mean that in Ecuador in the Quito area with an estimated population of 4 Mio, this would result in roughly 400 patients with PVD classified as PAH or CTEPH, who are born and live permanently at around 2800 m of high altitude. However, local prevalence might differ depending on socioeconomic factors, the availability of health care systems that allow diagnosis and treatment of PVD and different prevalence of PVD-associated conditions such as connective tissue disease, congenital heart disease, infections (HIV, Schistosomiasis).[15] The definition of PH at high altitude has not yet been clarified. An expert consensus from 2005 suggests to use an mean PAP threshold of >30 mmHg at HA, which is higher than 25 mmHg as suggested since the first world PH symposium 1968 and the 20 mmHg recommended in the latest guidelines.[13] In a meta-analysis of apparently healthy men living between 3600 and 5050 m, the systolic PAP assessed as tricuspid regurgitation pressure gradient without adding right atrial pressure was 25.3 mmHg (CI 24.0–26.7) and thus only slightly higher compared to

TABLE 3 Main risk factor profiles at baseline and last visit.

	At diagnosis	At last visit	Mean difference (CI)	*p* Value
WHO functional class, *n* (%)				
II	18 (50)	27 (75)		
III	18 (50)	9 (25)		<0.001*
Mean WHO functional class, *n* (%)	2.50 ± 0.51	2.25 ± 0.44	−0.26 (−0.51 to 0.00)	0.051
BNP, ng/dL	490 ± 823	576 ± 774	257 (−34 to 479)	0.102
6-min walk test				
6-min walk distance, m	472 ± 118	496 ± 108	35 (−6 to 77)	0.011
SpO_2 at rest, %	93 ± 3	94 ± 3	1.22 (−0.33 to 2.77)	0.134
SpO_2 at end walk, %	85 ± 7	85 ± 7	0.85 (−1.48 to 3.48)	0.480
Heart rate rest, bpm	75 ± 11	70 ± 10	−5.1 (−9.5 to −0.7)	0.033
Heart rate end walk, bpm	120 ± 18	125 ± 20	4.7 (−4.3 to 13.8)	0.311
Echocardiography				
Systolic pulmonary artery pressure, mmHg	83 ± 25	78 ± 21	−6 (−12 to 0)	0.053
Tricuspid annular plane systolic excursion, mm	19 ± 04	18 ± 05	−0.8 (−2.0 to 0.4)	0.185
Left ventricular ejection fraction, %	67 ± 07	65 ± 05	−2 (−5 to 1)	0.186
Risk classes according to guidelines				
Average four-risk strata including FC, 6MWD, and NT-proBNP	1.7 ± 0.7	1.5 ± 0.5	−0.3 (−0.52 to 0.01)	0.468
Low/intermediate-low/intermediate-high/high	12/15/9/0	17/15/4/0		0.04**

Note: Data are given as number (%) or mean ± SD.

Abbreviations: FC, functional class; NT-proBNP, N-terminal pro-B-type natriuretic peptide' SpO_2, pulse oximetric oxygen saturation; 6MWD, 6-min walk distance.

*FC II versus FC III.

**low versus non-low-risk group.

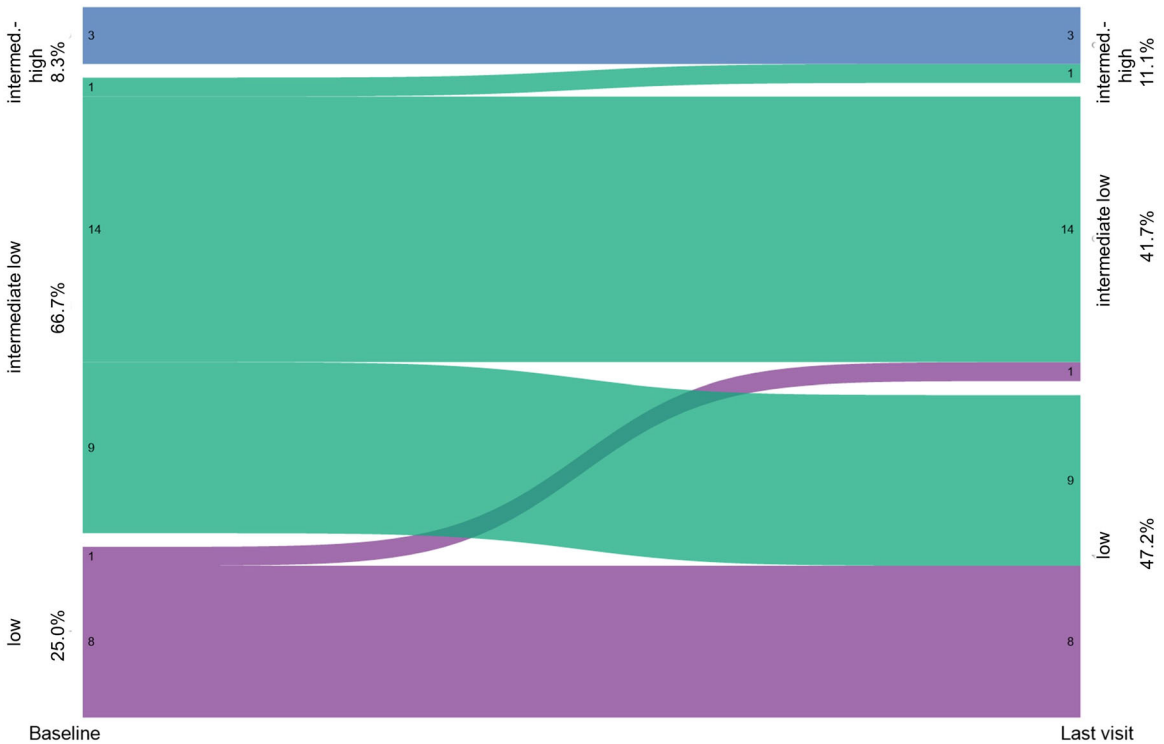

FIGURE 1 Alluvial plot demonstrating the change in the four-strata risk assessment from the time of diagnosis to the last follow-up.

healthy low-altitude controls (average 18.6 mmHg) and Kyrgyz men and women who permanently live around 3000 m revealed a systolic PAP of 30 ± 10 mmHg with a PVR as estimated by echocardiography of 2.8 WU.[15,16] Regarding the much higher PVR and PAP, it is clear that the present collective suffers from PVD and can be clearly distinguished from healthy highlanders, as highlighted above.

However, compared with low-altitude PVD collectives, as described in the French, Compera, Swiss, or REVEAL registry, the presently described PVD patients have more severely compromised hemodynamics with a baseline mPAP of 53 ± 16 mmHg and a PVR of 16 ± 4 WU.[18,22–24] For comparison, the latest analysis of the Swiss PVD registry has shown a baseline mPAP of 41 ± 11 mmHg and a PVR of 7 ± 4 WU.[18] This might be due to (1) initial diagnosis in a more advanced course of the disease, (2) predominantly "typical" PAH patients in this cohort (supported by the fact that the present collective encompasses 83% women), (3) exclusion of patients with comorbidities, which tend to have less impaired hemodynamic profiles compared to typical PAH, and (4) measurement discrepancies, or last but not least a potentially aggravated hemodynamic profile in a hypoxic environment at high altitude.[23,25] Of interest, the described PVD collective had a PaO_2 in the range of what would be expected from healthy newcomers at a comparable altitude and similar or only slightly below a level as expected from recent low-altitude PVD collectives. The $PaCO_2$ was with 3.9 ± 0.5 slightly below the lower boundary of a 90% confidence interval as found in healthy newcomers to altitude, indicating the known relative hyperventilation in PVD.[18,20,26]

With regard to the severely compromised hemodynamic profile, the present PVD collective revealed a favorable risk factor profile as assessed by FC, 6MWD, and BNP at the time of the diagnoses and unchanged or even better (FC) at the last follow-up. At follow-up on drug mono- or combination therapy and supportive treatments such as nocturnal oxygen and diuretics, almost 90% of the patients were in the low- or intermediate- to low-risk group according to the four-strata risk assessment, and this is even better than in low-altitude residents with PAH as described in the latest COMPERA analysis.[27] We are aware that this may be due to a positive selection of ambulatory prevalent patients (survivors), as we did not have the chance to identify severely ill, non-ambulatory patients in FC IV yet or patients who died. Future analyses of a broader altitude PVD cohort are planned. But despite this limitation, we feel that it is of high interest for physicians involved in the treatment of PVD and PVD patients living at all altitudes that favorable outcomes can be achieved for PVD patients who are born and permanently live >2500 m. The result of sustained 6MWD and low-risk group profiles despite severely impaired hemodynamics in patients with PVD living at altitude was also evident in another cohort study, which, however, only examined patients living at moderate altitude around 1200 m and these authors suggested the existence of a high-altitude phenotype in PAH.[28] In the present study, it is noteworthy that these favorable outcomes could be achieved in a country with a relatively weaker economy where health authorities may not be able to finance expensive combination therapies. All patients included were treated with sildenafil; one third received a PH-targeted combination therapy with Bosentan and another third had a CCB in addition to sildenafil. The proportion of patients treated with combination therapy is lower due to socioeconomic reasons compared to other registries.[18,27] To date, it is unfortunately not possible to perform vasodilator testing during right heart catheterization in Quito, due to the lack of equipment, drugs and time constraints in the catheter laboratory.[8,29] Thus, treating physicians must monitor the clinical response to the relatively inexpensive CCB and continue or change treatment accordingly. Therefore, we cannot exclude that part of the present PVD-collective at high altitude are CCB responders. However, we assume that this is not the majority, because echocardiographically determined systolic PAP and other hemodynamic parameters were similar at baseline and follow-up. In addition, 53% received nocturnal oxygen therapy, 11% even all-day oxygen therapy, which is comparably high for patients in favorable low- or intermediate- to low-risk classes, intended to reduce a potential additive hypoxia-induced vasoconstrictive challenge to the pulmonary vasculature in these PVD patients.[30]

Limitations to be considered as mentioned above are a selection bias of relatively fit, ambulatory PVD patients, some of whom potentially being vasodilator responders, the impossibility of systematically including all PH patients, ambulatory or stationary, with and without the possibility of right heart catheterization (as some patients with very severe disease may not even make it to be catheterized). We could not report on potential patients who had died in recent years, as this would have been out of the possibilities for the present report due to time and funding constraints, but we hope to do so in the near future. Ventilation perfusion scans or dual-energy thoracic CTs were not available and thus, the diagnosis of CTEPH relied upon pulmonalis-angiography performed during the diagnostic right heart catheterization. Therefore, we cannot exclude that some distal CTEPH patients are misclassified as PAH. Despite these limitations, we are convinced that the publication of this

cohort of PVD patients born and permanently living at an altitude of around 2800 m advances knowledge in the field.

We can conclude that ambulatory patients with PVD living permanently at >2500 m of altitude have a favorable risk factor profile and long-term outcome despite severely compromised hemodynamics while being treated with vasodilator therapies and that they resemble patients with so-called typical PAH. Future studies will focus on more comprehensive data on PVD patients living at high altitude including patients in FC IV, long-term, and mortality data.

AUTHOR CONTRIBUTIONS

Contribution to the concept or design of the work: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafted the article: SU, revised article critically for important intellectual content: all authors. Approved the version to be published: all authors.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee of the Hospital de Especialidades Carlos Andrade Marìn (PI-2023-0015).

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How to cite this article: Hoyos R, Lichtblau M, Cajamarca E, Mayer L, Schwarz EI, Ulrich S. Characteristics and risk profiles of patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension living permanently at >2500 m of high altitude in Ecuador. Pulm Circ. 2024;14:e12404. https://doi.org/10.1002/pul2.12404