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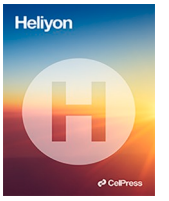

Research article

Altitude and prognosis after PCI: A propensity score-matched analysis

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ABSTRACT

Background: The impact of altitude on the prognosis of patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) deserves further discussion and research.
Methods: We conducted a post hoc analysis of a prospective observational study involving 5453 patients post-PCI, divided into medium-altitude and low-altitude groups. To control for confounding factors, propensity score matching was employed to pair patients with similar baseline characteristics between the two groups. The impact of altitude factors on patients' prognosis post-PCI was examined through endpoint events over a 2-year follow-up period.
Results: During the 2-year follow-up, patients at medium altitude exhibited a lower risk of MACE (including cardiovascular mortality, myocardial infarction, revascularization, and stroke) compared to those at low altitude (1196 versus 1196 patients [medium-altitude versus low-altitude, respectively]; hazard ratio [HR], 0.781 [95 % CI, 0.629–0.969]; P = 0.025) during 2-year follow-up. Even after excluding stroke, a significant difference in heart-related adverse events (HRAE) persisted between the two groups (HR, 0.794; 95 % CI, 0.636–0.991; P = 0.042). The incidences of individual MACE components were not significantly different between the two groups.
Conclusions: Patients post-PCI residing at medium altitude exhibited a lower risk of 2-year MACE compared to those at low altitude. Further research is necessary to provide more robust evidence.

1. Introduction

Cardiovascular disease (CVD) is associated with various factors, with environmental factors [1] receiving less attention compared to genetic factors [2,3]. In recent years, research has identified several environmental characteristics that significantly influence the risk and severity of CVD [4]. Recent global studies have demonstrated that higher altitude may exert a protective effect against CVD [5–10]. However, some studies suggest that exposure to high altitudes can have adverse effects on patients with CVD [11].

Coronary artery disease (CAD), a subset of CVD, is a leading cause of death [12]. Percutaneous coronary intervention (PCI) is a primary treatment for patients with CAD. In 2021, 1,164,117 patients underwent PCI in mainland China [13]. PCI can restore blood flow in severely narrowed coronary vessels but does not funda mentally cure CAD. The risk of major adverse cardiovascular events

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(MACE) within one year after PCI remains approximately 5–15 % [14,15]. Moreover, ascending to higher altitudes may increase the risk of ischemia, as atheromatous arteries cannot dilate in response to hypoxia [16]. Absolute contraindications for high-altitude exposure in patients with CAD include unstable angina, whether associated with decompensated heart failure, or uncontrolled atrial or ventricular arrhythmias [17]. Studies have shown inconsistent results regarding the association between altitude and outcomes in CAD patients. Several studies have demonstrated that higher altitudes are associated with lower CAD mortality rates [8,10,18]. However, other research indicates that prolonged high-altitude residence is link to an increase risk of stroke and death [8,19,20]. Patients with CAD are advised to avoid rapid ascents to altitudes exceeding 2000 to 2500 m [21]. However, studies also suggest that patients with stable CAD who are receiving optimal treatment and are in a good physical condition can tolerate travel to altitudes as high as 3500 m [22]. The prognosis of CAD patients post-PCI at various altitudes below 3500 m has not been evaluated. Therefore, we analyzed the prognosis of patients residing at altitudes below 3500 m post-PCI, dividing them into low and medium-altitude groups at a threshold of 1000 m. We hypothesized that the patients residing at medium-altitudes post-PCI would exhibit a better prognosis than those at lower altitudes.

2. Methods

2.1. Patients and groups

This was a post hoc analysis of a prospective cohort study [23] involving patients post-PCI, approved by the Ethics Review Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. 2016-786 on 2016-07-20). The study was conducted in accordance with the Declaration of Helsinki and relevant regulations by the Ethics Committee. Witten informed consent was obtained from all participants or their legal guardians. Patients undergoing PCI at Fuwai hospital, Chinese Academy of Medical Science, from September 2016 to August 2017 were included within one week, excluding individuals under 18 years old, those with cognitive or communication impairments, or participants in other clinical studies, resulting in a cohort study of 5453 unique patients followed for 2 years. We collected the baseline and prognosis information of the patients. The patients were classified into low and medium-altitude groups by 1000 m.

2.2. Determination of the elevation boundary

According to the classification of landforms in Chinese geography, areas above 1000 m are designated as plateaus [24]. On the other hand, previous studies have defined high altitudes as those above 2500–3500 m, where oxygen deprivation is typically observed [16,25–27]. The aim of this study is to determine whether significant differences exist in long-term prognosis among patients at different altitudes below 3500 m. Therefore, we classified patients living below 3,500 m into low and medium-altitude group by 1000 m.

2.3. Outcome measures

The primary endpoint was major adverse cardiovascular events (MACE), including cardiovascular mortality, myocardial infarction (MI), revascularization (a composite of PCI and CABG), and stroke. The secondary endpoints were the heart-related adverse events [HRAE (cardiovascular mortality, MI, revascularization)], and the components of MACE. All endpoint events of the patients were evaluated by an independent endpoint committee.

2.4. Statistical analysis

Baseline characteristics of the entire cohort were statistically analyzed and compared between the two groups (i.e., low-altitude group versus medium-altitude group) using T-tests or χ^2 tests. The characteristics described as continuous variables were depicted through their mean and standard deviation (SD), and the characteristics described by categorical variables are shown through frequencies and percentages. Following the description of the entire cohort's baseline characteristics, propensity score matching was conducted, calculating the propensity scores using multivariable logistic regression model. Propensity scores included covariates that may affect patient prognosis and clinical outcome, and that were unbalanced between groups before matching. We used a 1:1 nearest-neighbor algorithm with a caliper width of 0.20.

The new cohort with propensity score matching was further statistically analyzed. According to the data type of baseline variables, the T-test or $\chi 2$ test was used to determine the inter-group variable differences. Statistical description with the Kaplan Meier curve of inter-group was shown. The baseline variables that still had statistical differences after propensity matching were used as covariables to perform multivariate cox regression. The results were used to verify whether the association between the altitude and patients' outcomes is independent of other factors. The significance level of the statistical test was 5 % on two sides, and the statistical analysis software was intended to be SPSS 25.0.

3. Results

3.1. Study patients and baseline characteristics

The study cohort comprised 5453 patients who underwent PCI at Fuwai hospital from September 2016 to August 2017. Approximately three-quarters of the patients were male (76.8 %; N = 4189). Most of the patients were of middle to old age, with a mean age of 61.91 years (mean [SD] age, 61.91 [9.91] years). We categorized patients by province and indicated the number of patients from each on the map (Fig. 1). According to the altitude of the living area, the patients were divided into MA and LA. The incidence of MACE was 12.4 % (148/1196) in MA and 14.0 % (596/4257) in LA. This difference was not statistically significant, as indicated by $\chi 2$ test ($\chi 2 = 3.059$, P = 0.080) and univariate Cox regression (hazard ratio [HR], 0.847; 95 % CI, 0.706–1.016; P = 0.073) between the two groups. However, these results are inconclusive due to the significant disparity in patient numbers between the two groups and confounding factors arising from varying baseline characteristics.

To remove the disturbance caused by the reasons, we conducted propensity score matching on these two groups. We first described the characteristics of the patients in the whole cohort of MA and LA groups (Table 1). As shown in the table, significant statistical differences exist in the distribution of gender, overweight or obesity, course of CAD, first PCI, smoking, and hyperlipidemia. To eliminate these, we calculated the propensity scores with multivariable logistic regression models. Employing a 1:1 nearest-neighbor algorithm with a caliper width of 0.20, 1196 pairs of the patients were matched successfully.

3.2. Primary outcome

Among the successfully matched patients, 333 experienced MACE within two years post-PCI. The incidence of MACE was 12.4 % (148/1196) in MA and 15.5 % (185/1196) in LA. χ^2 test showed that there was a statistically significant difference in the incidence of MACE between the two groups ($\chi^2 = 4.776$, P = 0.029). Univariate Cox regression showed that the patients in MA had a 21.9 % lower cumulative risk of MACE than those in the LA (HR, 0.781; 95 % CI, 0.629–0.969; P = 0.025) (Fig. 2). We analyzed and compared the

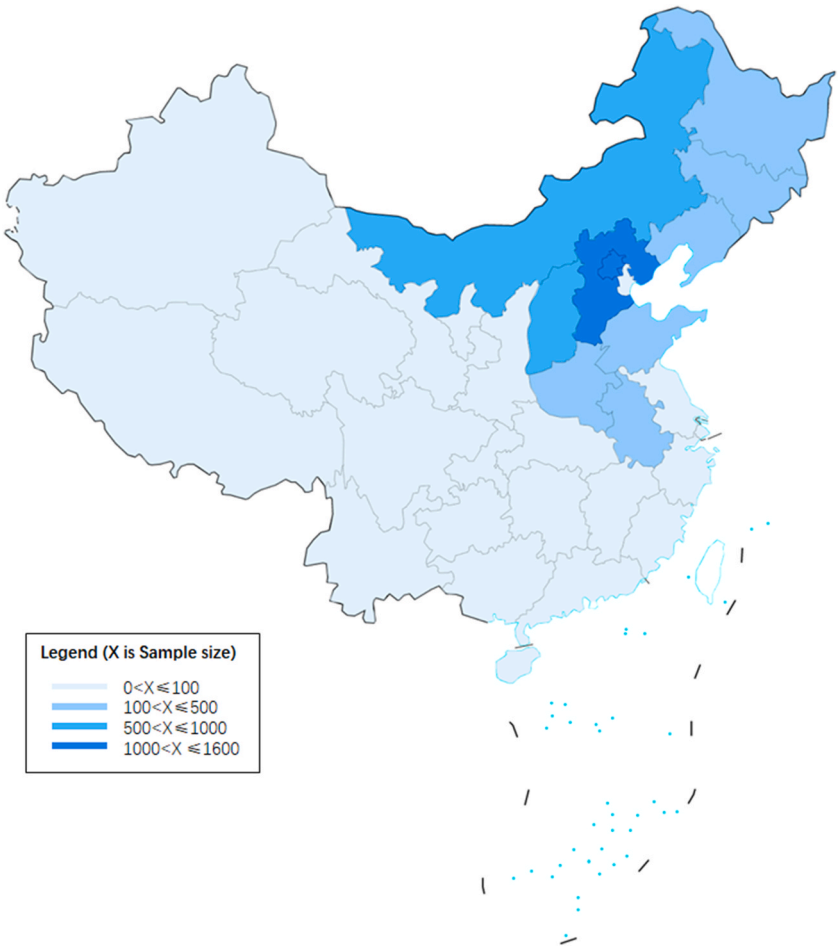

Fig. 1. Geographic distribution of the patients.

Table 1
The characteristics of the patients in the whole cohort and different altitude.

Characteristics	Total	MA (n = 1196)	LA (n = 4257)	P value
Demographics				
Age, mean (SD), y	61.91 (9.91)	61.18 (9.50)	62.11 (10.01)	0.067
Male, No. (%)	4189 (76.80)	959 (80.20)	3032 (75.90)	0.002
Height, mean (SD), cm	168.32(7.21)	168.84(6.92)	168.17(7.29)	0.013
Weight, mean (SD), Kg	73.41 (11.10)	72.99(10.39)	73.52 (11.29)	0.007
BMI, mean (SD), Kg/m^2	25.84 (3.04)	25.55(2.90)	25.92 (3.08)	0.117
Information of CAD and PCI				
Family history of CAD, No. (%)	1141 (20.90)	243 (20.30)	898 (21.10)	0.559
Course of CAD, mean (SD), y	2.08 (3.89)	1.84 (3.52)	2.14 (3.99)	<0.001
ACS, No. (%)	3433 (62.90)	738 (61.70)	2695 (63.30)	0.311
First PCI, No. (%)	3488 (64.00)	795 (66.50)	2693 (63.30)	0.041
Single angiopathy, No. (%)	3954 (72.50)	878 (73.40)	3076 (72.30)	0.430
Cardiac risk factors				
Current smoker, No. (%)	3301 (60.50)	789 (66.00)	2512 (59.00)	<0.001
Hypertension, No. (%)	3662 (67.10)	778 (65.10)	2884 (67.70)	0.079
Hyperlipemia, No. (%)	4880 (89.50)	1033 (86.40)	3874 (90.40)	<0.001
Diabetes, No. (%)	1940 (35.60)	399 (33.40)	1541 (36.20)	0.070
Medication situation				
DAPT, No. (%)	5422 (99.40)	1187 (99.20)	4235 (99.50)	0.338
βblocker, No. (%)	4730 (86.70)	1031 (86.20)	3699 (86.90)	0.535
CCB, No. (%)	3141 (57.60)	745 (62.30)	2396 (56.30)	<0.001
ACEI/ARB, No. (%)	3271 (60.00)	721 (60.30)	2550 (59.90)	0.811
Statin, No. (%)	5363 (98.30)	1177 (98.40)	4186 (98.30)	0.849
Anticoagulants, No. (%)	60 (1.1 %)	15 (1.30)	45 (1.10)	0.564
Nitrate, No. (%)	5100 (93.5)	1102 (92.10)	3998 (93.90)	0.027
Diuretic, No. (%)	680 (12.50)	130 (10.90)	550 (12.90)	0.058
Antidiabetic, No. (%)	1470 (27.00)	296 (24.70)	1174 (27.60)	0.051

Abbreviations: BMI, Body Mass Index; CAD, Coronary Artery Disease; ACS, Acute Coronary Syndrome; PCI, Percutaneous Coronary Intervention; DAPT, Dual Anti-Platelet Therapy; CCB, Calcium Channel Blockers; ACEI, Angiotensin Converting Enzyme Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers.

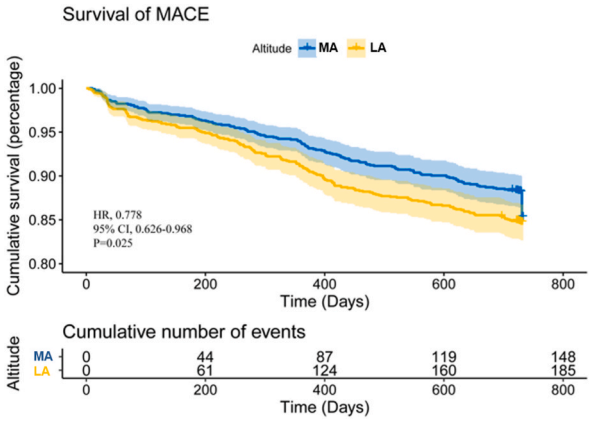

Fig. 2. Survival of MACE

baseline characteristics of the two groups following propensity score matching. T-test and χ^2 test showed that there were still statistical differences between the two groups in smoking, family history, and CAD course (Table 2). To further exclude the impact from these differences, we conducted a multivariate Cox regression analysis of MACE between the two groups, in corporating smoking, family history, and CAD course as covariates. The result showed that patients in MA had a 22.2 % lower cumulative risk of MACE than those in the LA (HR, 0.778; 95 % CI, 0.626–0.968; P = 0.025).

3.3. Secondary outcomes

After excluding stroke, the differences in HRAE between the two groups were analyzed. χ^2 test (χ^2 = 3.918, P = 0.048) and multivariate cox regression (HR, 0.794; 95 % CI, 0.636–0.991; P = 0.042) showed significant differences (Fig. 3).

We further investigated the incidence of MACE components. The incidence of cardiovascular mortality was 1.2 % (14/1196) in MA and 1.7 % (20/1196) in LA. The incidence of revascularization was 11.0 % (131/1196) in MA and 13.2 % (158/1196) in LA. The

Table 2
The characteristics of the patients in propensity score matching cohort.

Characteristics	MA (n = 1196)	LA (n = 1196)
Demographics		
Age, mean (SD), y	61.18 (9.50)	61.50 (9.92)
Male, No. (%)	959 (80.20)	936 (78.30)
Height, mean (SD), cm	168.84 (6.92)	168.89 (6.70)
Weight, mean (SD), Kg	72.99 (10.39)	74.34 (11.18)
BMI, mean (SD), Kg/m^2	25.55 (2.90)	25.98 (3.01)
Information of CAD and PCI		
Family history of CAD, No. (%)	243 (20.30)	141 (11.80)
Course of CAD, mean (SD), y	1.84 (3.52)	2.17 (4.33)
ACS, No. (%)	738 (61.70)	760 (63.50)
First PCI, No. (%)	795 (66.50)	750 (62.70)
Single angiopathy, No. (%)	878 (73.40)	844 (70.60)
Cardiac risk factors		
Current smoker, No. (%)	789 (66.00)	730 (61.00)
Hypertension, No. (%)	778 (65.10)	799 (66.80)
Hyperlipemia, No. (%)	1033 (86.40)	1043 (87.20)
Diabetes, No. (%)	399 (33.40)	414 (34.60)
Medication situation		
DAPT, No. (%)	1187 (99.20)	1188 (99.30)
βblocker, No. (%)	1031 (86.20)	1033 (86.40)
CCB, No. (%)	745 (62.30)	647 (54.10)
ACEI/ARB, No. (%)	721 (60.30)	717 (59.90)
Statin, No. (%)	1177 (98.40)	1172 (98.00)
Anticoagulants, No. (%)	15 (1.30)	9 (0.80)
Nitrate, No. (%)	1102 (92.10)	1099 (91.90)
Diuretic, No. (%)	130 (10.90)	123 (10.30)
Antidiabetic, No. (%)	296 (24.70)	303 (25.30)

Abbreviations: BMI, Body Mass Index; CAD, Coronary Artery Disease; ACS, Acute Coronary Syndrome; PCI, Percutaneous Coronary Intervention; DAPT, Dual Anti-Platelet Therapy; CCB, Calcium Channel Blockers; ACEI, Angiotensin Converting Enzyme Inhibitor; ACEI, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers.

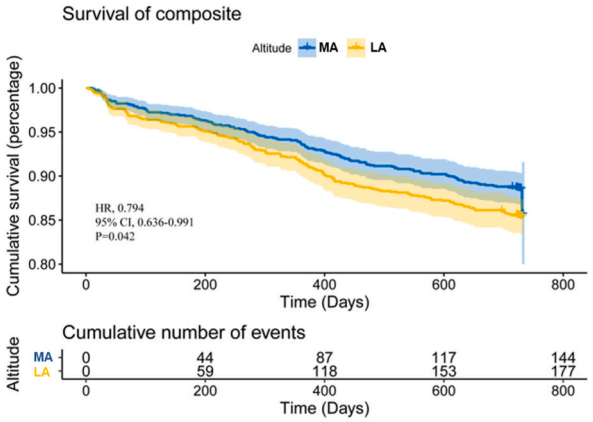

Fig. 3. Survival of the cardiovascular composite endpoint events.

incidence of stroke was 0.5 % (6/1196) in MA and 0.9 % (11/1196) in LA. The number of patients who experienced MI was insufficient for statistical analysis (3 patients in MA and 2 patients in LA). χ^2 test showed that there were no statistically significant differences in cardiovascular mortality, revascularization, and stroke between the two groups ($\chi_1^2 = 1.074$, $P_1 = 0.300$; $\chi_2^2 = 1.869$, $P_2 = 0.090$; $\chi_3^2 = 1.481$, $P_3 = 0.224$). Combined with the Kaplan-Meier curve (Fig. 4), patients in MA exhibited a lower risk of cardiovascular mortality and revascularization compared to those in LA. However, multivariate cox regression, adjusting for smoking, family history, and CAD course, revealed no statistically significant differences in cardiovascular mortality (HR, 0.767; 95%CI, 0.386–1.521; P = 0.447), revascularization (HR, 0.803; 95%CI, 0.636–1.015; P = 0.067), or stroke (HR, 0.574; 95%CI, 0.211–1.559; P = 0.276).

4. Discussion

For the first time, this post hoc analysis demonstrated that the incidence of MACE (including cardiovascular mortality, MI,

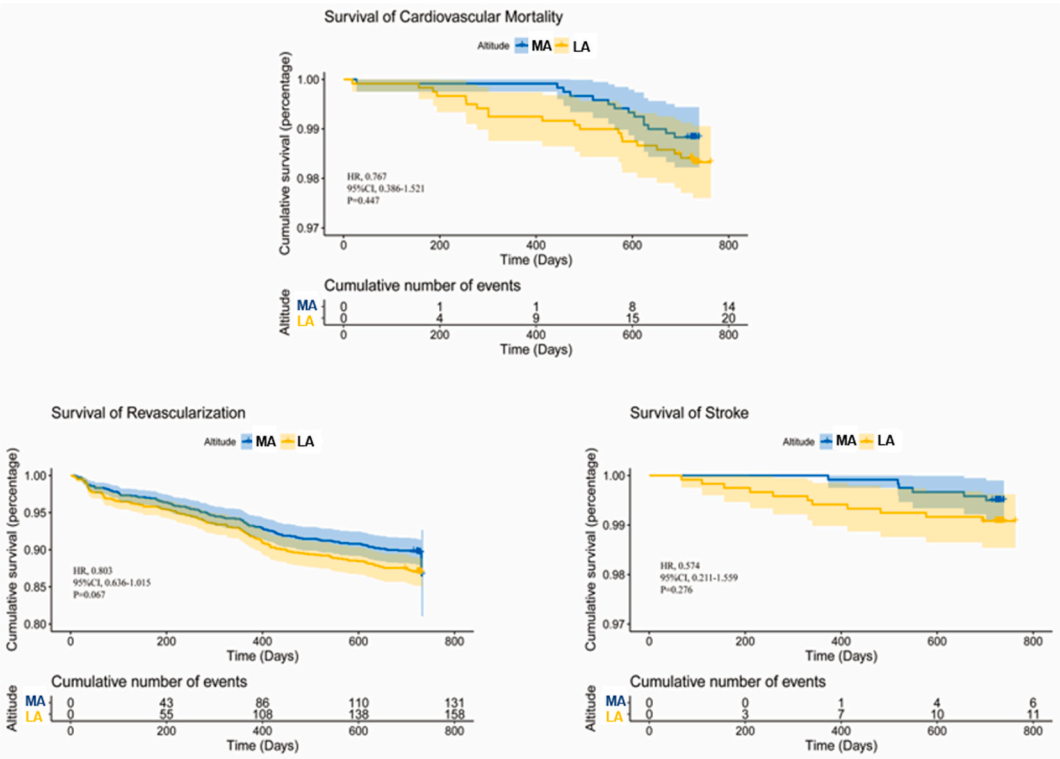

Fig. 4. Survival of the components of MACE

revascularization, and stroke) among patients residing at medium altitude was significantly lower than among those at low altitude within two years post-PCI. This significant difference persisted in the HRAE, even after excluding stroke. This finding is consistent with the previous studies [28–30] that demonstrate the cardiovascular protective effects of altitude.

A study utilizing a dataset comprising all deaths (n = 467834) over ten years in Austria indicated that the reduction in mortality at higher altitudes primarily stems from cardiovascular diseases and cancer [9]. Several studies [12,31,32] have noticed a possible correlation between CAD mortality and altitude. However, it is hypothesized that the protective effect of higher altitude may be attributed to factors such as ultraviolet light [33], temperature [34], climate [8], and diet [35,36]. However, stable differences in altitude may play a more significant role. The data from the National Elevation Dataset, National Center for Health Statistics, and US Census showed that living at a higher altitude may have a protective effect on IHD after adjusting for socio-demographic factors, migration, solar radiation, and smoking [10]. Recently, a Swiss study [29] of 4.2 million 40-84-year-old people, a longitudinal, association study based on the census records, found that there is still a negative correlation between elevation and ischemic heart disease (IHD) after adjusting sunlight, rainfall, temperature, and road distance. It suggests that the protective effect of higher altitude on CAD may mainly arise from the stable differences rather than the other factors. The reasons for the low mortality of CAD on higher altitude also have been widely discussed concerning the patient's health condition. The results of several studies have shown that people living at higher altitudes have lower total cholesterol and/or low-density lipoprotein (LDL) levels [37], higher high-density lipoprotein (HDL) levels [6], and lower blood leptin levels [27]. Another study from the Austrian Health Interview Survey (2019) confirmed differences in altitude-dependent regular physical activity levels and the prevalence of cardiovascular risk factors [38]. Therefore, higher altitude may have a protective effect on healthy people or patients by reducing these risk factors for the occurrence and development of CAD.

Conversely, recent studies [2–4] have suggested that multiple genes may be involved in the adaptive mutation of the patients on a plateau. The plateau residents have lived there for generations and may have developed a protective mechanism according to this. For example, compared with sea-level residents, high-altitude residents have higher vagal tone, a decreased tendency to vasoconstriction, and an increased ability of red blood cells to carry and release oxygen at the tissue level [39], and lower pulmonary pressure response [18]. However, a related Swiss study emphasizes that the cardiovascular protective effects of plateau are unlikely to be entirely explained by genetic differences between populations, due to the large scale of migration between different altitudes [29]. In our study, the patients were widely distributed, and population mobility is also widespread in China, hence a particular gene is less likely to account for the difference in prognosis. In addition, a study has shown that even a brief sojourn at high altitudes may lead to beneficial changes in insulin resistance [7]. The protective effect of the plateau on the cardiovascular is more likely to influence a wide range of people rather than the specific population with the genetic mutation.

In our study, significant differences in cardiovascular composite endpoint events were observed between the two groups after

excluding stroke, which were not present in stroke cases. This is consistent with previous studies [8,29] showing that high altitude has stronger protective effect on CAD than stroke. This may be caused by specific physiological adaptive change of heart in plateau environment [29]. Notably, the components of MACE in our study were not statistically different between the two groups, including cardiovascular mortality, MI, and revascularization. This might be attributed to the limited sample size and follow-up duration of this study. Because most of the previous studies that showed differences in cardiovascular mortality between different altitudes were based on large-scale epidemiological investigations.

5. Limitation

This analysis has the following limitations: To begin with, as a post hoc analysis of a prospective observational study, the comparison of the patients' prognosis between different altitudes was not a predefined objective. Therefore, the results of this analysis can only suggest that differences in patients' prognosis post-PCI may be associated with altitude, without establishing causality. Additionally, this study was conducted at a single center, and both the sample size and follow-up duration were limited, potentially leading to insignificant differences in individual event outcomes. However, the single-center design also ensures the consistency in the level of PCI performed.

6. Conclusions

Patients residing at medium altitude post-PCI exhibited a lower risk of 2-year MACE compared to those at low altitude. This significant difference persisted in the cardiovascular composite endpoint events after excluding stroke.

Conflict of interest disclosures

Authors have no conflict of interest to declare.

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Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data availability statement

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Si-Yu Yan: Writing – original draft, Investigation. **Li-Hong Ma:** Writing – review & editing, Project administration, Data curation, Conceptualization. **Wei-Xian Yang:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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