Article

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Prevalence and Characteristics of Symptomatic Intracranial Atherosclerotic Plaques in People Residing at Middle and High Altitudes: A Preliminary Study

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Background: This study aims to determine how atherosclerotic plaque prevalence and characteristics vary between individuals residing year-round at middle and high altitudes who have intracranial atherosclerotic disease.
Methods: We conducted a retrospective analysis of patient data from our hospital, focusing on individuals with cerebrovascular symptoms who underwent high-resolution vessel wall imaging (HR-VWI). Patients who had lived at an altitude of <2500 meters for an extended period were classified in group A (n = 91), while those residing at an altitude of ≥2500 meters were placed in group B (n = 75). We examined the differences in plaque prevalence and characteristics between these two groups.
Results: The detection rate of basilar artery plaque was higher in group A compared to group B (16% vs. 7.6%, *p* = 0.036). Conversely, the detection rate of anterior cerebral artery plaque was significantly lower in group A than in group B (4% vs. 11.8%, *p* = 0.016). The eccentricity index (EI) was greater in group B than in group A (0.72 ± 0.11 vs. 0.68 ± 0.12, *p* = 0.012). The prevalence of intraplaque hemorrhage (IPH) was lower in group B than in group A (39.5% vs. 58.7%, *p* = 0.002).
Conclusions: IPH prevalence was lower in patients residing at high altitudes than in those residing at middle altitudes. However, patients living at high altitudes had a higher EI compared to those residing at middle altitudes. These findings underscore the presence of disparities in the prevalence and characteristics of intracranial atherosclerotic plaques between individuals residing at medium and high altitudes. It is essential to account for these distinctions when diagnosing plaques.

Keywords: high-resolution magnetic resonance imaging; high altitude; intracranial atherosclerotic plaque; moderate altitude; atherosclerosis

Introduction

Intracranial atherosclerotic disease (ICAD) is not only the most frequent cause of ischemic stroke (IS) but is also highly prevalent [1]. Recently, there has been an increasing focus on intracranial atherosclerotic plaques, leading to numerous domestic and international studies on the subject [2–5]. However, the majority of these studies have centered on lowland regions, with only a few conducted in middle- and high-altitude areas, representing a limitation of these investigations.

Epidemiological research has shown that individuals residing in high-altitude regions exhibit lower incidence rates of cardiovascular disease compared to those living at sea level [6,7]. For every 1000-meter increase in altitude, the risk of coronary artery disease and stroke decreases by 22% and 12%, respectively [6]. Studies, such as the one conducted by Cao *et al*. [8], have reported lower carotid plaque loads in individuals from high-altitude regions compared to those from lowlands. However, a nationwide assessment revealed that Tibet had the highest incidence of cerebrovascular disease in China [9]. Liu *et al*. [10] also demonstrated that in the Chinese plateau, IS occurs at an earlier stage and in a more severe form. Qinghai Province, located on the Tibetan Plateau, presents an average elevation of more than 3000 meters, resulting in a rare plateau environment with low-oxygen conditions. It is essential to accumulate evidence regarding the diagnosis and treatment of cerebrovascular diseases in this plateau to gain a comprehensive understanding of the prevalence and characteristics of intracranial atherosclerotic plaques in the intermediate- and high-altitude regions of Qinghai Province.

High-resolution vessel wall imaging (HR-VWI) has proven to be an effective imaging method for assessing the characteristics of vascular wall lesions, plaque morphology, and quantitative features [11,12]. We hypothesized that the characteristics of intracranial atherosclerotic plaques may differ between patients residing in middle-altitude regions in Qinghai Province and those residing in high-altitude regions. This study aims to investigate the differences in atherosclerotic plaque prevalence and characteristics between patients with symptomatic intracranial arteries residing in middle-altitude regions and those with symptomatic intracranial arteries residing at high-altitude regions by employing HR-VWI.

Materials and Methods

Study Population

Data were retrospectively collected from patients diagnosed with cerebrovascular symptoms who underwent HR-VWI examination at the Affiliated Hospital of Qinghai University between April 2020 and April 2022. The inclusion criteria encompassed: (1) the presence of intracranial atherosclerosis confirmed by HR-VWI or digital subtraction angiography (DSA) findings, (2) clinical symptoms of transient ischemic attack (TIA) or ischemic stroke attributed to plaques of atherosclerotic stenosis in the intracranial regions, (3) the presence of at least one atherosclerotic risk factor, including hypertension, diabetes mellitus, hyperlipidemia, or smoking, (4) HR-VWI examination had to be performed within 2 weeks of symptom onset, (5) patients were required to be year-round residents of Qinghai province. Exclusion criteria included: (1) stenoses exceeding 50% in the ipsilateral carotid artery and vertebral artery in the extracranial segment, (2) intracranial artery occlusion, (3) any nonatherosclerotic vascular diseases such as vasculitis, arterial dissection, thrombosis, and cardioembolism, (4) incomplete or missing clinical information or laboratory results, and (5) poor image quality. This retrospective study received approval from the Clinical Research Ethics Committee of the Affiliated Hospital, Qinghai University School of Medicine (No.SL-2022-079), and the need for informed patient consent was waived due to the retrospective study design.

According to Murdoch *et al*. [13], altitudes between 1500 m and 2500 m are considered moderate altitude, while altitudes above 2500 m are categorized as high altitude. High altitude is further classified into high altitude (2500–3500 m), very high altitude (3500–5800 m), and extreme altitude (>5800 m) [13]. In this study, the enrolled patients resided at altitudes ranging from 1800 to 4020 m for an extended period. An altitude of 2500 m served as the demarcation point, with patients residing at an altitude of <2500 m for an extended period included in group A, and those residing at an altitude of ≥2500 m included in group B.

Clinical Data and Laboratory Measurements

Data collection involved the retrieval of various clinical characteristics from the patients' medical records. These encompassed age, gender, usual place of residence, nationality, smoking and alcohol consumption status, as well as the medical history related to conditions such as hypertension, diabetes mellitus, coronary artery disease, stroke, statin use, and any family history of cardiovascular disease. Alongside these clinical details, laboratory test parameters were also obtained, which included triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum uric acid, serum creatinine, homocysteine (Hcy), and glycosylated hemoglobin (HbA1c) levels.

Definition of Traditional Atherosclerotic Risk Factors

In this study, the researchers assessed several risk factors to understand their association with a specific health outcome or condition. These risk factors include hypertension, defined as a mean systolic blood pressure >130 mmHg and/or a mean diastolic blood pressure >80 mmHg, or having a history of hypertension or using antihypertensive drugs [14]. Additionally, obesity, defined by a body mass index (BMI) of 28.0 kg/m^2 or higher, was considered (body mass index = weight [kg] / height [m]^2) [15]. Dyslipidemia, characterized by elevated total cholesterol, triglyceride levels, and LDL cholesterol, as well as the use of lipid-lowering drugs, was another factor (total cholesterol >5.18 mmol/L and/or triglyceride >1.7 mmol/L and/or low-density lipoprotein cholesterol >3.37 mmol/L and/or use of lipid-lowering drugs). Diabetes mellitus (HbA1c level >6.0% and/or history of diabetes mellitus and/or use of antidiabetic drugs) [16], hyperhomocysteinemia (homocysteine concentration ≥20 mmol/L), and current smoking status were also evaluated. These risk factors were investigated in relation to a particular health outcome, such as cardiovascular disease or stroke, to assess their potential impact.

HR-VWI Protocol

All patients underwent imaging using a 3.0 T superconducting magnetic resonance imaging machine (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. The scanning parameters were as follows: field of view = 230 mm × 230 mm, matrix = 320 × 320 × 320, spatial resolution = 0.53 mm × 0.53 mm × 0.53 mm. For T1-weighted 3D-SPACE imaging, the repetition time/echo time (TR/TE) was set to 700 ms/20 ms, slice thickness = 0.53 mm, with no slice gap, and a total number of slices equaling 224. In the case of T2-weighted 3D-SPACE imaging, the parameters were TR/TE = 130 ms/84 ms.

These rigorous imaging protocols were employed uniformly for all participants, ensuring high-quality data acquisition and consistency throughout the study.

HR-VWI Evaluation and Measurement

Two radiologists with significant expertise in plaque diagnosis examined patients' imaging data. They conducted their assessments without access to patients' clinical information or prior results. In this study, the primary focus was on analyzing specific vessel segments within the internal carotid artery (C3-C7 based on the Bouthillier segmentation method), middle cerebral artery (M1-M2), anterior cerebral artery (A1-A2), basilar artery, posterior cerebral artery (P1-P2), and vertebral artery (V4). Atherosclerotic plaques were identified by their characteristic eccentric vessel wall thickening, irrespective of whether these segments displayed luminal stenosis.

To facilitate the analysis, all magnetic resonance images were converted using RadiAnt DICOM Viewer (version 2021.2; Medixant, Poznan, Poland; http://www.radiantviewer.com). Using this software, all vessels were initially reconstructed in multiple directions perpendicular to the vessel centerline. Subsequently, they were manually outlined and measured to derive quantitative plaque indices. The reference site was selected as the nearest plaque-free segment, either proximal or distal to the site with the maximum lumen narrowing, and the thickest cross-section of the plaque was designated as the lesion site. Intracranial arterial stenosis was quantified by applying the WASID measurement method on the magnetic resonance angiography (MRA) maximum intensity projection image, denoted as (1 – Ds/Dn) × 100%. Here, Ds represents the diameter of the most stenotic intracranial artery, and Dn is the diameter of the normal intracranial artery. Stenosis degrees were categorized into three grades: (1) mild stenosis (<50%), (2) moderate stenosis (50%–69%), and (3) severe stenosis (70%–99%). Intracranial atherosclerotic plaques often exhibit asymmetric wall thickening, referred to as eccentric wall thickening. An eccentricity index (EI) of ≥0.5 indicated eccentric wall thickening, while an EI below 0.5 indicated concentric wall thickening [17]. Parameters for assessing intracranial arterial burden included lumen area (LA), wall area (WA), plaque volume, and normalized wall index (NWI) measurements. Maximum wall thickness (MWT), total vascular area (TVA), and LA were measured three times, and the average value was used. Accurate measurement of the remodeling ratio (RR) is crucial when analyzing intracranial arterial vessel wall lesions; RR >1.05 indicated positive remodeling, and RR <0.95 indicated negative remodeling [18]. Subsequently, WA, NWI, EI, and RR were calculated using the following formulas:

$$
\begin{aligned}
WA &= TVA - LA \\
NWI &= WA \,/\, (WA + LA) \times 100\% \\
EI &= (MWT - minimal\ thickness) \,/\, MWT \\
RR &= TVA_{maximum\ luminal\ stenosis} \,/\, TVA_{reference}
\end{aligned}
\tag{1}
$$

T1-weighted imaging (T1WI) hyperintensity is characterized by the presence of elevated signal intensity within the plaque on T1WI (with fat suppression), surpassing 150% of the signal intensity of the nearby muscles [19]. The occurrence of T1WI hyperintensity in intracranial arterial plaques frequently signifies the presence of intraplaque hemorrhage.

Reproducibility Assessment

In this study, 25 patients were selected using a random number method, and two evaluators independently conducted all measurements to assess interobserver reliability. The intraclass correlation coefficient (ICC) was computed to evaluate the agreement between observers in the measurement of MWT, TVA, and LA. The ICC values were categorized as follows: very good (r = 0.81–1.00), good (r = 0.61–0.80), moderate (r = 0.41–0.60), fair (r = 0.21–0.40), or poor (r < 0.20).

Statistical Analysis

Statistical analyses were carried out using SPSS 27.0 software (IBM Corp., Armonk, NY, USA). Normally distributed measurement data were presented as mean ($\bar{x}$) ± standard deviation (s), and an independent-sample *t*-test was employed to compare data between groups. Non-normally distributed measurement data were expressed as median [M (P25, P75)], and the Mann-Whitney U test was utilized for group comparisons. Enumeration data were presented as frequency and percentage (%), with group comparisons made using the chi-square test. Logistic regression analysis (binary variable) was conducted to evaluate differences in plaque characteristics between individuals residing year-round at middle and high altitudes while adjusting for potential confounding factors. Results were expressed as regression slope (β) or odds ratio (OR) with corresponding 95% confidence intervals (CIs). Clinical risk factors were considered potential confounders if their *p*-value was <0.1 during the comparative analysis between those residing year-round at middle and high altitudes with intracranial atherosclerotic disease. The significance level (α) for all tests was set at 0.05, and a *p*-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 166 patients participated in this study, with 122 being male and 126 belonging to the Han Chinese ethnicity. The mean age of the participants was 59 ± 13 years. These patients had symptomatic intracranial atherosclerotic disease, with 91 individuals in group A and 75 in group B. For a visual representation of the patient selection process, please refer to Fig. 1.

Table 1 provides an overview of the patient characteristics in both groups. Notably, group A had a higher percentage of Han Chinese individuals compared to group B (90.1% vs. 58.7%, $p < 0.001$). Furthermore, group A exhibited significantly lower rates of hypertension (48.4% vs. 89.3%, $p < 0.001$) and coronary heart disease (7.7% vs. 38.7%, $p < 0.001$) in comparison to group B. Group B, on the other hand, had higher levels of homocysteine and serum uric acid ($p < 0.001$, $p = 0.013$). The proportions of

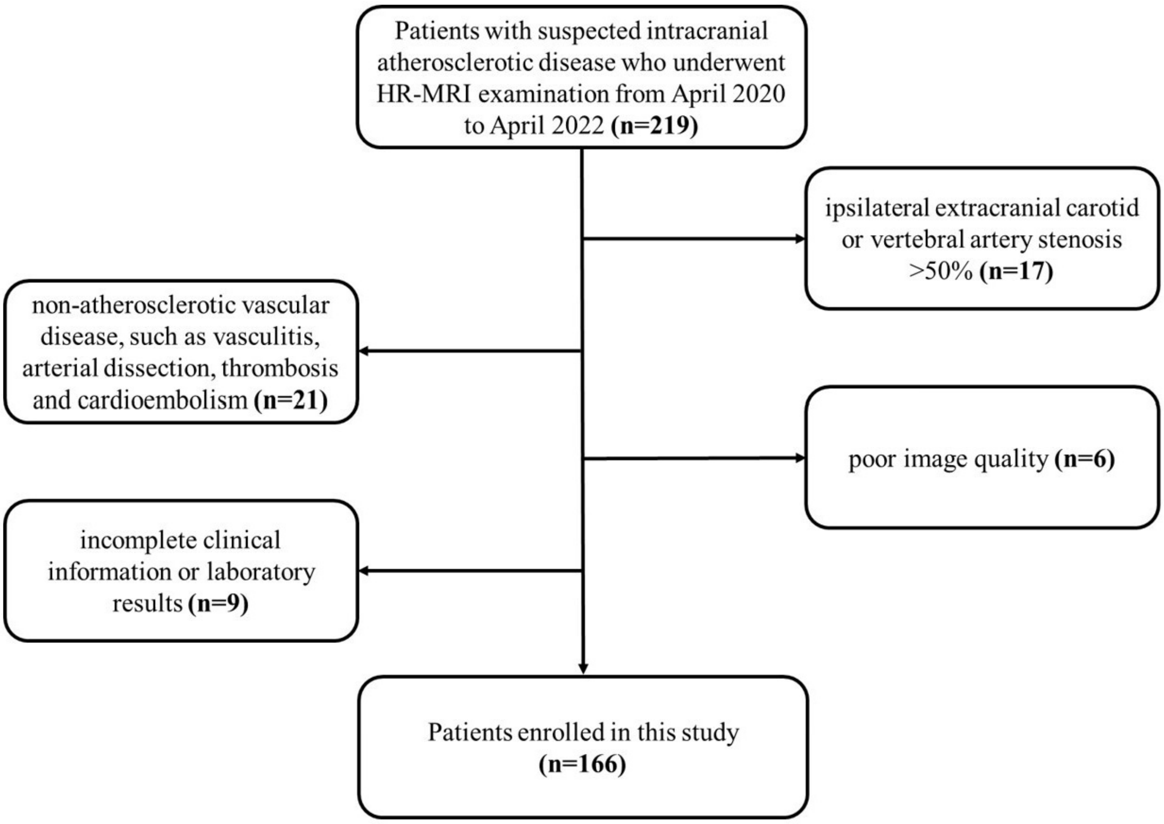

Fig. 1. Flow diagram showing the study population selection process.

patients with smoking status, alcohol consumption status, hyperlipidemia, and diabetes mellitus were similar between both groups.

Comparison of Intracranial Atherosclerotic Plaque Detection Rates

A total of 269 plaques were identified in the 166 patients, with 150 plaques found in group A and 119 in group B. Notably, the plaque detection rate in the anterior cerebral artery was significantly lower in group A compared to group B (4.0% vs. 11.8%, p = 0.016). In contrast, the plaque detection rate in the basilar artery was higher in group A than in group B (16.0% vs. 7.6%, p = 0.036). However, the plaque detection rates in the intracranial internal carotid artery, middle cerebral artery, posterior cerebral artery, and intracranial vertebral artery were similar in both groups, as shown in Table 2.

Among the intracranial atherosclerotic plaques, the vertebral artery had the highest prevalence (91), followed by the middle cerebral artery (58), internal carotid artery (37), basilar artery (33), posterior cerebral artery (30), and anterior cerebral artery (20). Additionally, 73 out of the 166 patients had two or more intracranial atherosclerotic plaques, as illustrated in Fig. 2.

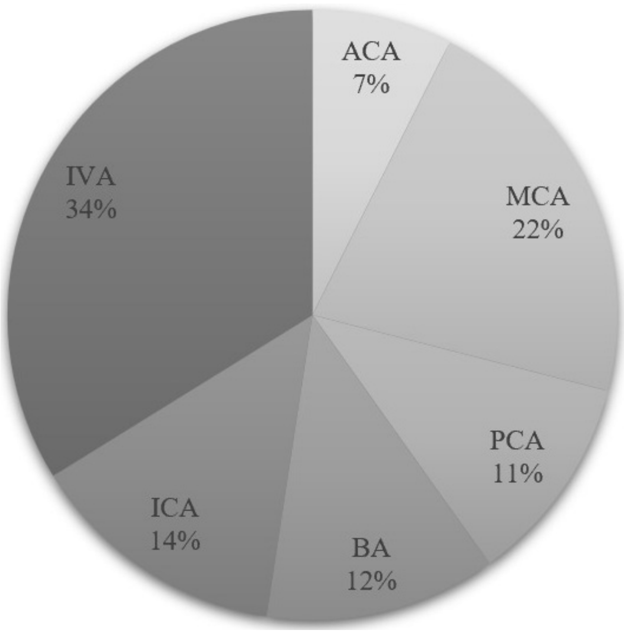

Fig. 2. Pie chart showing patient proportions based on the location of the intracranial atherosclerotic plaques in 166 patients.

Plaque Characteristics

Fig. 3 displays magnetic resonance images of the vessel wall of a plaque, along with the measurement of plaque

Table 1. Characteristics of the study patients in the two groups.

Characteristics	All patients (n = 166)	Group A (n = 91)	Group B (n = 75)	$\chi^2/t/Z$	*p*-value
Age (years)	59 ± 13	61 ± 13	57 ± 11	1.769	0.079
Males	122 (73.5)	65 (71.4)	57 (76.0)	0.441	0.507
Han Chinese	126 (75.9)	82 (90.1)	44 (58.7)	22.225	<0.001
Current smoker	85 (51.2)	48 (52.7)	37 (49.3)	0.192	0.661
History of alcohol consumption	71 (42.8)	38 (41.8)	33 (44.0)	0.084	0.771
History of HT	111 (66.9)	44 (48.4)	67 (89.3)	31.168	<0.001
History of DM	53 (31.9)	31 (34.1)	22 (29.3)	0.424	0.515
Dyslipidemia	112 (67.5)	58 (63.7)	54 (72.0)	1.279	0.258
History of CAD	36 (21.7)	7 (7.7)	29 (38.7)	23.226	<0.001
History of the previous stroke	28 (16.9)	13 (14.3)	15 (20.0)	0.957	0.328
HbA1c (%)	6.05 (5.5, 7.78)	6.1 (5.6, 8.0)	6.0 (5.2, 7.2)	1.621	0.105
Hcy (μmol/L)	14.3 (10.25, 21.65)	11.8 (8.6, 17)	19.7 (13.5, 25.9)	3.344	<0.001
TC (mmol/L)	4.07 ± 0.98	4.16 ± 1.00	3.96 ± 0.95	1.280	0.202
TG (mmol/L)	1.54 (1.18, 2.01)	1.58 (1.18, 2.03)	1.51 (1.17, 1.98)	0.070	0.944
LDL-C (mmol/L)	2.64 ± 0.89	2.74 ± 0.87	2.52 ± 0.90	1.613	0.109
HDL-C (mmol/L)	0.91 (0.79, 1.08)	0.91 (0.79, 1.11)	0.91 (0.8, 1.03)	0.683	0.495
UA (mmol/L)	351 (294, 411)	339 (271, 394)	343 (267, 408)	2.477	0.013
Scr (μmol/L)	75 (63, 95)	74 (60, 94)	76 (64, 103)	0.928	0.353
History of AF	5 (3.0)	4 (4.4)	1 (1.3)	1.320	0.251
Current statin use	21 (12.7)	8 (8.8)	13 (17.3)	2.715	0.099
Family history of stroke	8 (4.8)	5 (5.5)	3 (4.0)	0.200	0.655

HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HbA1c, glycosylated hemoglobin; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; Scr, serum creatinine; AF, atrial fibrillation. Data are expressed as Median (P25, P75), mean ± SD, or n (%). $p <$ 0.05 was considered statistically significant.

characteristics. To assess inter-observer agreement, two radiologists measured maximum wall thickness (MWT), TVA, and LA for 25 patients (43 plaques) selected using a random number method. Systematic errors were considered, and therefore, the calculation employed the absolute agreement type. Both radiologists provided original data (not calculated data), leading to the utilization of a single measure of standard results, ICC (A, 1). The final ICC values for MWT, TVA, and LA were 0.972 (95% confidence interval [CI]: 0.737–0.992), 0.971 (95% CI: 0.944–0.985), and 0.941 (95% CI: 0.850–0.973), respectively. An ICC value exceeding 0.9 suggests a high level of evaluation consistency, indicating that the measurements made by the two radiologists were highly reliable (see Table 3). Table 4 provides a comparison of plaque characteristics between the two groups. Group B had a lower WA (15.66 ± 7.76 vs. 18.05 ± 8.68 mm^2, $p = 0.020$) and NWI (68.89 ± 12.51 vs. 72.86 ± 8.90%, $p = 0.003$) compared to group A. However, group B exhibited a higher EI (0.72 ± 0.11 vs. 0.68 ± 0.12, $p = 0.012$). Furthermore, the prevalence of intraplaque hemorrhage (IPH) was significantly lower in group B than in group A (39.5% vs. 58.7%, $p = 0.002$). Fig. 4 provides an example of HR-VWI depicting IPH.

Multivariate regression analysis indicated that the prevalence of hypertension, coronary heart disease, and high homocysteine levels remained significantly different between groups A and B ($p < 0.05$). Notably, the EI remained significantly increased (OR = 29.652; 95% CI: 2.771–317.289; $p = 0.005$). There was a significant difference in the prevalence of IPH between the two groups (OR = 1.955; 95% CI: 1.165–3.280; $p = 0.011$), while the prevalence of hyperuricemia was similar ($p = 0.137$) (refer to Table 5).

Discussion

In this pioneering study, we utilized HR-VWI to investigate disparities in plaque prevalence, plaque characteristics, and clinical factors among patients with intracranial atherosclerotic disease residing at different altitudes: middle and high. Our primary findings were as follows: (1) Patients living in high-altitude regions demonstrated a higher prevalence of hypertension and coronary heart disease, along with elevated homocysteine levels when compared to those residing at middle-altitude locations. (2) A notable variation in the distribution of plaques, with a higher prevalence of anterior cerebral artery plaques among patients in high-altitude areas and a greater number of basilar artery plaques among those in middle-altitude regions. (3) Plaques in patients from high-altitude regions exhibited a higher eccentricity index compared to those from middle-altitude regions. Furthermore, the prevalence of intraplaque

Table 2. Comparison of the intracranial atherosclerotic plaque detection rate between groups A and B.

	n	ICA	MCA	ACA	PCA	BA	IVA
Group A	150	19 (12.7)	35 (23.3)	6 (4.0)	16 (10.7)	24 (16.0)	50 (33.3)
Group B	119	18 (15.1)	23 (19.3)	14 (11.8)	14 (11.8)	9 (7.6)	41 (34.5)
Total	269	37	58	20	30	33	91
χ^2		0.338	0.630	5.813	0.081	4.389	0.037
p-value		0.561	0.428	0.016	0.776	0.036	0.847

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; IVA, intracranial vertebral artery.

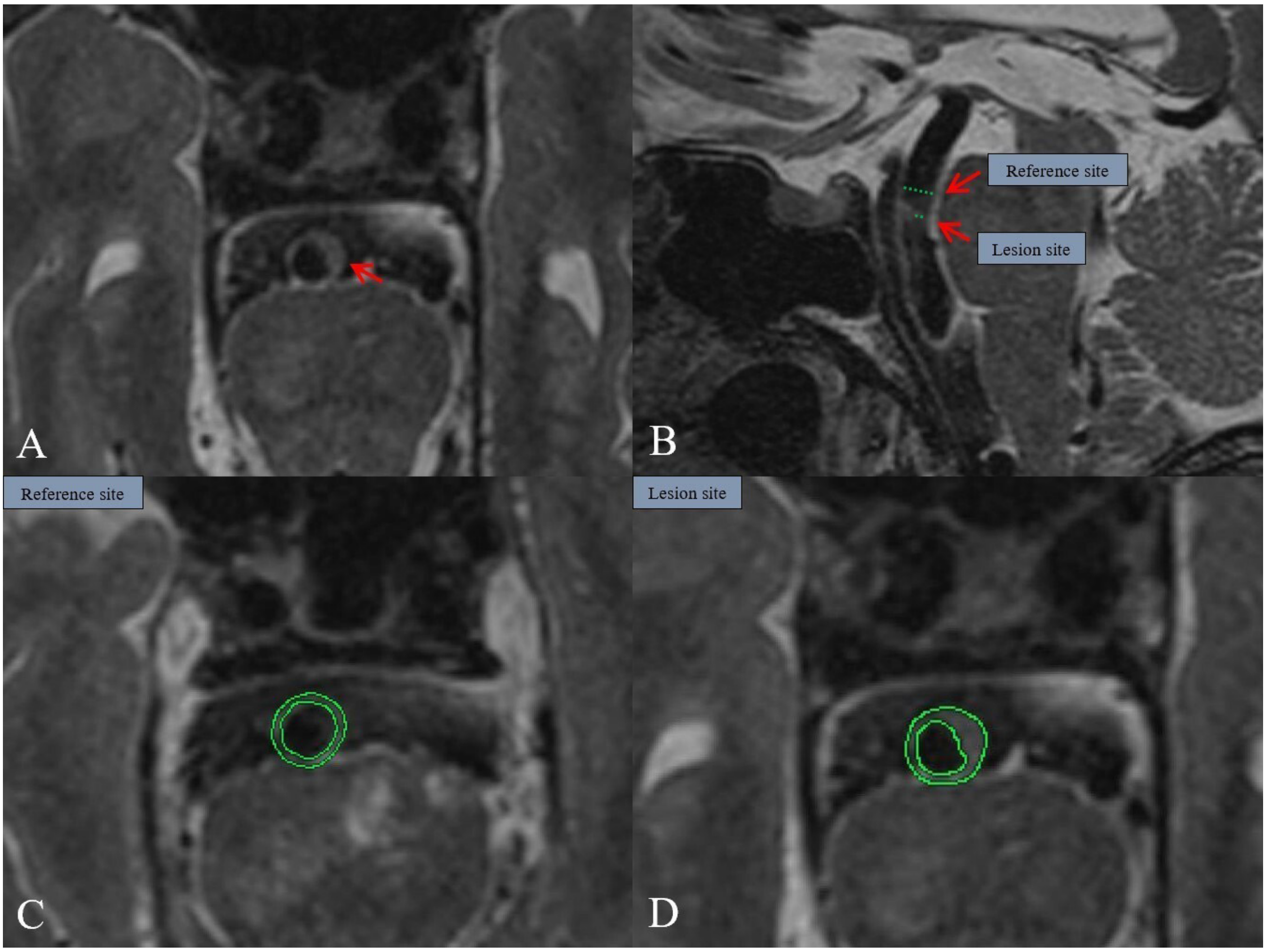

Fig. 3. Magnetic resonance images of the vessel wall of a basilar artery plaque. Multiplanar reconstruction of the basilar artery was conducted using dedicated software. The morphology of the intracranial plaque at the site of maximum luminal stenosis (MLN) was thoroughly analyzed, and quantitative indices were measured (A). (B) (Red arrow) The reference site was selected as the nearest plaque-free segment that was either proximal or distal to the MLN site (C). (D) The thickest cross-section of the plaque was determined as the lesion site. For each of the measurements, including maximum vessel wall thickness, total vascular area, and lumen area, the process was repeated three times, and the average value was recorded for accuracy and consistency.

hemorrhage was lower among patients in high-altitude regions than their middle-altitude counterparts. Our findings present a new perspective on diagnosing and managing cerebrovascular disease in high-altitude settings, potentially addressing existing research gaps in the field of intracranial atherosclerotic disease within these regions.

Homocysteine has the potential to impair endothelial cell function, thereby facilitating increased platelet adhesion, leading to vascular sclerosis and thrombosis [20, 21]. A prospective nested case-control study has reported that hyperhomocysteinemia and hypertension act as independent risk factors for stroke, with their combined ef-

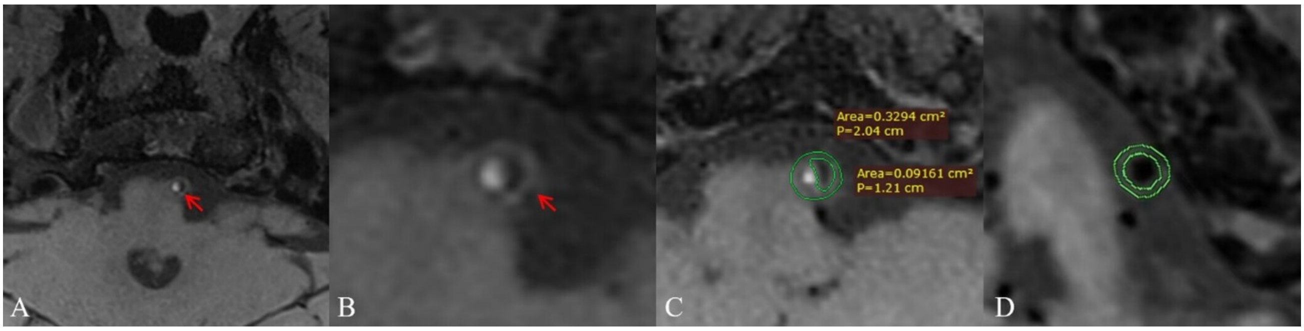

Fig. 4. Images of a patient who resides year-round at an altitude of less than 2500 m. (A,B) (Red arrow) Hemorrhagic plaque located in the left vertebral artery. (C) The quantitative measurements of the plaque at the site of maximum luminal stenosis are provided. The maximum wall thickness was determined to be 2.1 mm, the total vascular area measured 33 mm^2, and the lumen area was found to be 9 mm^2. (D) The measurements at the reference site are presented. The MWT at this reference site was notably thinner, measuring 0.68 mm, while the TVA was 27.6 mm^2, and the LA was 15.1 mm^2.

Table 3. Interobserver agreement in the measurement of MWT, TVA, and LA.

	ICC	95% CI
MWT	0.972	0.737∼0.992
TVA	0.971	0.944∼0.985
LA	0.941	0.850∼0.919

CI, confidence interval; ICC, intraclass correlation coefficient; MWT, maximum wall thickness; TVA, total vascular area; LA, lumen area.

fect resulting in an 11.7-fold elevated risk of cardiovascular disease [22]. Serum uric acid, the end product of purine nucleotide metabolism, is considered a risk factor for atherosclerosis [23]. A community-based study examining serum uric acid levels and multiregional atherosclerosis has demonstrated a significantly higher cumulative incidence of stenosis in patients with hyperuricemia compared to those without hyperuricemia. Furthermore, the study suggests that the impact of uric acid on intracranial atherosclerotic stenosis (ICAS) is more pronounced in men than in women, and prolonged exposure to hyperuricemia may accelerate ICAS progression [24]. Our study revealed that patients from high-altitude regions had a higher prevalence of hypertension and coronary heart disease, along with elevated homocysteine levels compared to patients from middle-altitude regions. Several factors may contribute to these results: (1) Diet and Lifestyle Factors: Dietary choices and lifestyle factors may play a role, particularly if diets in high-altitude regions are rich in fat or salt, or if physical activity levels differ from those in middle-altitude regions. For instance, the higher prevalence of hypertension among Tibetan patients in high-altitude regions, as reported by Chen *et al.* [25], may be attributed to the high-sodium, low-potassium diet commonly found in plateau regions. Diets deficient in folic acid and vitamins can result in elevated homocysteine levels in high-altitude residents. A randomized field trial conducted by Kotwal *et al.* [26] demonstrated that intervention with folic acid and vitamins could reduce homocysteine levels in Indian soldiers residing in high-altitude regions. (2) Ethnic Diversity: High-altitude regions are predominantly Tibetan areas, and patients from these regions are primarily ethnic minorities (only 58.7% are Han Chinese). These areas typically have low local population density, limited medical resources, and lower disease awareness. Previous studies have confirmed that the prevalence of hypertension is much higher in the Tibetan plateau compared to other regions of China [27–31]. In a 2012 study of herders living in a 4300 m Tibetan area, only 19.9% of patients with hypertension were aware of their hypertensive condition, and only 2.6% of these patients were taking antihypertensive medication. In these areas, the rates of disease awareness, treatment, and control are often very low. (3) Lower Oxygen Levels: High-altitude areas experience reduced air pressure, leading to decreased oxygen availability. This prompts the body to produce more red blood cells to compensate for the lower oxygen levels, increasing blood viscosity and blood pressure, potentially resulting in hypertension and coronary heart disease. The body's adaptation to the low-oxygen environment may lead to high hemoglobin levels and increased blood viscosity [25,32]. Acute and chronic physiological adaptations occur at high altitudes, including an increase in hemoglobin concentration, known as high-altitude polycythemia [33,34]. Tymko *et al.* [35] showed that acute and chronic physiological adaptation occurred when the body was exposed to high altitude (>2500 m), including an increase in hemoglobin concentration. Studies have shown that high hemoglobin levels are associated with increased blood viscosity [36,37]. A cross-sectional study of 1487 patients reported that individuals with high whole-blood viscosity had a higher prevalence of silent cerebral infarction [38]. Although these findings support the results of our study, further research is needed to validate our hypotheses.

Table 4. Plaque features in groups A and B.

Plaque features	Group A (n = 150)	Group B (n = 119)	χ^2/t	*p*-value
MWT (mm)	2.18 ± 0.63	2.30 ± 0.57	1.576	0.116
TVA (mm^2)	25.25 ± 13.47	23.18 ± 11.95	1.310	0.191
LA (mm^2)	7.20 ± 5.79	7.53 ± 5.43	0.674	0.634
WA (mm^2)	18.05 ± 8.68	15.66 ± 7.86	2.339	0.020
NWI (%)	72.86 ± 8.90	68.89 ± 12.51	3.041	0.003
DS			0.553	0.758
Mild	108 (72.0)	89 (74.8)		
Moderate	36 (24.0)	27 (22.7)		
Severe	6 (4)	3 (2.5)		
RR	1.59 ± 0.55	1.53 ± 0.56	0.848	0.397
EI	0.68 ± 0.12	0.72 ± 0.11	2.520	0.012
Eccentric distribution	138 (92.0)	114 (95.8)	1.617	0.204
Positive remodeling	136 (90.7)	102 (85.7)	2.910	0.233
IPH	88 (58.7)	47 (39.5)	9.755	0.002

WA, wall area; NWI, normalized wall index; DS, degree of stenosis; RR, remodeling ratio; EI, eccentricity index; IPH, intraplaque hemorrhage.

Table 5. Results of multivariable regression analysis showing factors associated with who reside year-round at high altitudes individuals with intracranial atherosclerotic disease.

	OR	95% CI	*p*-value
TVA	1.020	0.891∼1.168	0.773
WA	0.940	0.767∼1.152	0.552
NWI	0.399	0.002∼96.663	0.743
EI	29.654	2.771∼317.289	0.005
IPH	1.955	1.165∼3.280	0.011
History of CAD	6.778	2.337∼19.656	<0.001
History of HT	9.690	3.742∼25.094	<0.001
HbA1c (%)	1.041	0.879∼1.233	0.643
HHcy	5.027	1.968∼12.840	<0.001
HUA	1.964	0.842∼4.582	0.118

OR, odds ratio; HHcy, hyperhomocysteinemia; HUA, hyperuricemia.

It's important to note that these explanations offer insights into the observed health differences, but the disparities may be due to a combination of these factors or other variables not discussed here.

In 2013, the Chinese IntraCranial Atherosclerosis Study Group reported differences in the distribution of intracranial and extracranial atherosclerosis between patients with IS in the south of China and those in the north of China [39]. The results indicated that the proportion of patients with ICAS was higher in the north, and patients in the north were more likely to have multiple intracranial atherosclerotic and occlusive lesions than those in the south. The authors suggested that this difference might be related to socioeconomic status, lifestyle, dietary habits, and environmental factors. Another study on the distribution of intracranial arterial stenosis in Zhuang and Han patients with IS in Guangxi revealed a higher proportion of posterior circulation stenosis and a lower proportion of anterior circulation stenosis in Zhuang patients compared to Han patients [40]. The highest frequency of occlusion in the intracranial segment of the vertebral artery was reported in a multicenter registry study conducted in 2019 [41]. A 2005 study reported that the pattern of intracranial atherosclerosis differed between races [42]. These reports collectively confirm differences in the prevalence of atherosclerotic disease based on geographical location, race, age, and gender. These differences arise from a combination of factors, including environmental conditions, lifestyle, intracranial arterial anatomy, and genetics, all potentially influencing the progression of intracranial atherosclerosis. In our study, we analyzed data from patients residing at different altitudes in Qinghai Province and found that the detection rate of atherosclerotic plaques in the intracranial segment of the vertebral artery was the highest (34%). Additionally, the detection rate of plaques in the anterior cerebral artery was higher in patients from high-altitude regions than in those from middle-altitude regions, while the detection rate of plaques in the basilar artery was higher in patients from middle-altitude regions than in those from high-altitude regions. The regional preference for plaque deposition likely results from a complex interplay of physiological, environmental, and lifestyle factors. Further studies are necessary to establish an altitude gradient for investigating the incidence and distribution patterns of atherosclerotic plaques across extracranial and intracranial arteries and between anterior and posterior circulation arteries. Furthermore, in this study, we observed a significantly higher proportion of Han patients in group A compared to group B. In essence, the majority of patients in plateau areas are ethnic minorities. This predominance is due to the plateau areas of Qinghai Province primarily being Tibetan regions, resulting in a predominantly Tibetan population. Various studies have suggested that differences in plaque characteristics may exist across ethnic or racial groups, potentially influencing the risk and nature of cardiovascular and cerebrovascular diseases. These disparities could encompass variations in the composition, location, and rate of progression of atherosclerotic plaques among different ethnic or racial groups. Importantly, these distinctions may be influenced by a multitude of factors, including genetics, lifestyle, diet, socioeconomic status, access to healthcare, and the prevalence and management of cardiovascular risk factors. Therefore, race or ethnicity should be considered as one of many facets in the comprehensive management of atherosclerotic disease.

A 2020 study of patients with carotid atherosclerosis residing in high-altitude regions, compared to those in the plains, found that symptomatic patients at high altitudes had significantly greater wall area and lower normalized wall index than their sea-level counterparts [8]. Our present study revealed that patients from high-altitude regions had a lower NWI compared to those from middle-altitude regions, which aligns with previous research findings. However, it contrasts with the results related to WA. This discrepancy may stem from morphological and embryological differences between the extracranial and intracranial segments of the carotid artery, resulting in distinct hemodynamic conditions [43]. The deeper anatomical location and finer internal lumen diameter of intracranial vessels can render the spatial resolution and signal-to-noise ratio of images susceptible to various interferences. Additionally, differences in the altitude gradient between patients in previous studies and our present study might account for the inconsistency in results. After adjusting for confounding factors, the results in our study did not achieve statistical significance. Future longitudinal studies involving large sample sizes are necessary to elucidate the impact of altitude on plaque characteristics.

Our study also revealed a high eccentricity index in patients from high-altitude regions. We used a cutoff index value of 0.5, and in both groups, 92.0% and 95.8% of patients had eccentric intracranial artery plaques, respectively. However, this proportion might be too high to effectively compare clinical characteristics between eccentric and concentric plaque distributions. One study reported that eccentric wall thickening was present in 90.1% of patients with intracranial atherosclerotic lesions. However, Yang *et al*. [44] reported that concentric plaques accounted for 63.9% of cases of intracranial atherosclerotic disease, indicating that the EI alone might not be sufficient to distinguish ICAD from other intracranial arterial lesions. These studies demonstrate that the shape of plaques may vary at different stages of ICAD development. Hemodynamic changes induced by eccentric plaques could be a significant factor contributing to cerebrovascular events. A study by Steinman *et al*. [45] found that platelet and monocyte-sized particles deposited more significantly in the vessel wall near eccentric stenoses than near concentric stenoses. Consequently, eccentric stenoses might lead to a higher propensity for thrombosis, increasing the risk of cerebrovascular events. Some pathophysiological studies have suggested that eccentric morphology may serve as a mechanism to protect the normal lumen, ensuring blood supply to the distal vascular region and enhancing cerebral blood flow [46]. In a high-altitude environment, reduced partial pressure of oxygen can affect adequate oxygenation of brain tissue. Its localized impact on ICAD is reflected in the elevated EI, possibly associated with the preservation of hypoxia-related reductions in cerebral blood flow. Although our current retrospective analysis found an association between stenosis geometry and altitude gradient, prospective trials are needed to assess the relationship between eccentric stenosis and ICAD in patients residing at high altitudes.

Intracranial plaque hemorrhage is believed to result from the rupture of thin-walled microvessels lined by a discontinuous layer of endothelial cells without the support of muscle cells [47]. A study examining the correlation between blood pressure parameters and IPH determined that pulse pressure was the most significant factor associated with IPH [48]. However, this study did not record patient-specific blood pressure parameters, and these aspects will require further validation in prospective studies. The relationship between traditional cardiovascular risk factors and IPH is intricate, with numerous factors contributing to its occurrence. While the increase in IPH at middle altitudes, despite fewer cardiovascular risk factors, may seem puzzling, altitude-related physiological adaptations could provide an explanation. People living at high altitudes might develop adaptations that offer protection against IPH, possibly linked to the regulation of blood pressure, blood coagulation, and vascular remodeling. To understand these disparities, a detailed investigation is warranted. This understanding could guide targeted interventions and preventive strategies. Few studies have explored the correlation between altitude gradient and IPH, highlighting the need for future prospective trials to investigate this relationship.

To the best of our knowledge, this study is the first to employ high-resolution vessel wall imaging to investigate differences in intracranial atherosclerotic plaques between individuals residing at middle altitudes and those at high altitudes. However, our study has certain limitations. Firstly, it had a retrospective, non-randomized, single-center design, which may limit the generalizability of the results to patients with different conditions in other plateau regions. Large-sample multicenter studies are essential to comprehensively assess the impact of altitude on intracranial atherosclerotic plaque characteristics and provide more robust evidence. Secondly, the analysis was based solely on non-enhanced images of space-T1WI of the vessel wall, precluding the confirmation of plaque enhancement and enhancement grade. Lastly, the measurement of quantitative plaque indices is subject to potential subjective errors. Nonetheless, our study demonstrated good inter-reader consistency in this regard.

Conclusions

Compared to patients from middle-altitude regions, those residing in high-altitude areas exhibited lower plaque wall eccentricity index in their intracranial atherosclerotic plaques, along with a reduced prevalence of intraplaque hemorrhage. Our study contributes to bridging the research gap in the field of intracranial atherosclerotic disease among individuals living in high-altitude regions. Further prospective longitudinal studies are warranted to explore the impact of altitude on plaque characteristics and establish effective prevention strategies.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

XC contributed to writing the manuscript and interpretation of the data. JW and GXY contributed to data analysis and manuscript revision. YZX, HBW and ML contributed to manuscript revision and project management. All authors approved the submitted version. All authors agreed to be 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.

Ethics Approval and Consent to Participate

During the check-up, all participants were informed of the potential use of their check-up data for future research and that subject information would be anonymized at collection prior to research analysis. All methods were performed in accordance with the approved guidelines and in line with the Declaration of Helsinki. The study was approved by the Clinical Research Ethics Committee of the Affiliated Hospital, Qinghai University School of Medicine (No.SL-2022-079). Written consent was not required because of the retrospective observational design of the study.

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Conflict of Interest

The authors declare no conflict of interest.

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