Abdominal Aortic Aneurysm in Different Altitudes: Protocol for a Multi-Center Prospective Observational Study (ADAPT Study)

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Abstract

Abdominal aortic aneurysm (AAA) is a critical vascular condition with significant implications for morbidity and mortality. Current clinical practices and translational research in AAA predominantly derive from studies conducted at low to medium altitudes. However, the unique environmental and genetic factors prevalent in high-altitude regions may influence the risk factors, progression mechanisms, and overall prognosis of AAA, potentially leading to divergent clinical outcomes. To address this gap, we propose a multi-center prospective observational study across varying altitudes. This study will establish a distributed storage system tailored to "different altitudes," encompassing a comprehensive clinical database, an imaging library, and biological sample banks. Prospective data collection

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will include baseline characteristics, concomitant diseases, detailed imaging information, blood tests, surgical and anesthesia details, perioperative complications, and follow-up data. Blood and tissue specimens will be collected following informed consent and stored using a standardized protocol. This study aims to enhance both clinical and translational research in AAA, providing valuable insights into the altitude-specific dynamics of this condition and informing tailored therapeutic strategies.
Keywords: Abdominal aortic aneurysm; Endovascular aortic repair; Open surgery; Different altitudes; Biobank.

Background

Abdominal aortic aneurysm (AAA) refers to a dilation of the abdominal aorta with a lumen diameter greater than 30 mm or an increase of 50%. It is a leading cause of morbidity and mortality in vascular diseases, with rupture carrying a catastrophic mortality rate of up to 80%[1]. Current evidence-based guidelines for the diagnosis and management of AAA[2] are predominantly derived from studies conducted in low- to medium-altitude regions. However, the applicability of these guidelines to high-altitude areas remains uncertain due to the distinct environmental and genetic factors prevalent in these regions.

High-altitude regions are defined by distinctive environmental conditions, including chronic hypoxia, low atmospheric pressure, and heightened ultraviolet radiation, all of which may modulate the pathophysiology, risk profile, and clinical progression of AAA. For example, genetic adaptations observed in high-altitude populations, such as mutations in hypoxia-inducible genes[3,4], may influence vascular homeostasis and the progression of aneurysms. Furthermore, environmental factors like hypoxia and cold stress can aggravate vascular inflammation and remodeling processes[5], potentially leading to divergent AAA behavior compared with low-altitude settings. Despite these plausible variations, high-quality clinical studies focusing on AAA in high-altitude populations remain scarce. There is a particular shortage of comprehensive epidemiological data, along with insights into risk factors, underlying mechanisms, and long-term clinical outcomes.

To address this gap, this study aims to establish a multicenter prospective clinical database and biobank for AAA across different altitudes. By integrating clinical data, imaging, and biological samples, this study seeks to advance our understanding of AAA in high-altitude populations and improve patient outcomes. This initiative will provide a robust foundation for investigating altitude-specific variations in AAA, enabling the development of tailored diagnostic and therapeutic strategies for patients in these unique environments.

Methods

Study design

This study is a multicenter, prospective, observational investigation designed to establish a multidimensional cohort for AAA across varying altitudes. The cohort integrates a clinical database, an imaging library, and a biological sample repository, tailored to capture altitude-specific characteristics.

Ethical approval

The study adheres to the ethical principles outlined in the Declaration of Helsinki. The Medical Ethics Committee of Beijing Hospital has approved the establishment of the clinical and imaging databases, as well as the AAA biobank for different altitudes (Approval Letter No. 2023BJYYEC-390-01).

Participants

Starting from the study initiation date, eligible hospitalized cases of AAA will be consecutively enrolled across multiple participating centers, including Xizang Autonomous Region People's Hospital (high-altitude group), Beijing Hospital, Second Hospital of Shanxi Medical University, Taiyuan Central Hospital, Jiangsu Provincial People's Hospital (relativel low-altitude group). Each participating hospital will continuously

recruit new cases annually to ensure a robust and diverse cohort.

Inclusion criteria are listed as: a) Age ≥ 18 years; b) AAA diagnosis confirmed by computed tomography angiography (CTA) or ultrasound, defined as a maximum aortic diameter exceeding 30 mm; c) Availability of complete blood test data; d) Provision of informed consent for participation in the study.

Exclusion criteria are followed by: a) Pseudo-AAA; b) Isolated iliac artery aneurysm; c) Isolated abdominal aortic dissection; d) Patients diagnosed with or suffering from primary or secondary infected AAA, abdominal aortic stent infection, autoimmune diseases, Marfan syndrome, or other connective tissue disorders; e) Inability to undergo CTA examination due to contraindications (e.g. severe contrast allergy, renal impairment) or other limitations; f) Inability to complete the required follow-up protocol.

Endpoints

(1) Primary endpoints include all-cause mortality;

(2) Secondary endpoints include aneurysm-related mortality, re-intervention rate,aneurysm sac expansion.

Research procedure

(1) Informed consent: All participants will provide informed consent prior to enrollment.

(2) Data collection: The following clinical information will be collected:

a) Baseline characteristics: age, gender, body mass index (BMI), history of living in high-altitude areas, history of smoking, etc.

b) Concomitant diseases: hypertension, diabetes mellitus, hyperlipemia, stroke, etc.

c) Imaging data: detailed CTA or ultrasound findings.

d) Blood tests: comprehensive hematological and biochemical profiles.

e) Surgery and anesthesia details: procedural specifics and intraoperative events.

f) Perioperative complications: cardiovascular events, bleeding et al.

(3) Biospecimen collection: Blood and tissue samples will be collected and stored according to a standardized protocol:

a) Blood samples will be collected at admission, centrifuged and stored.

b) AAA tissues will be marked with spatial information and stored in paraffin, RNA later or directly in liquid nitrogen.

(4) Follow-up: Participants undergoing endovascular aortic repair (EVAR) or open surgical repair (OSR) will be followed up with ultrasound or CTA at 1, 3, 6, and 12 months postoperatively, and annually thereafter. Follow-up data will include:

a) Basic follow-up information: number and dates of follow-up visits.

b) Medication use during follow-up.

c) Complications: cardiovascular and cerebrovascular events, systemic complications and vascular reinterventions

d) Laboratory tests during follow-up.

e) CTA examination and retest of AAA-related indicators during follow-up.

(5) Study termination: The study will conclude when participants complete the follow-up protocol, die from any cause, or meet predefined exit criteria.

Biospecimen analysis plan

To investigate the mechanisms by which high-altitude environments may influence AAA progression, we plan to utilize stored plasma samples to investigate the altitude-associated biomarkers, such as Erythropoietin (EPO) and Homocysteine (Hcy), using state-of-art techniques. These levels will be determined if correlated with aneurysm diameter, growth rate, and clinical outcomes. Additionally, collected AAA tissue samples will be reserved for subsequent omic analysis to explore differential gene expression profiles linked to altitude adaptation and disease pathogenesis.

Statistical analysis

GraphPad Prism was used for statistical analysis. Continuous variable data were expressed as mean ± standard deviation, and categorical data were expressed as absolute number or percentage. Survival curves were used to represent the long-term survival of patients. Continuous variable analysis was performed using Student's *t* test, and categorical variable analysis was performed using chi-square test (χ^2) and Fisher's exact test. The P value < 0.05 was set as statistically significant. Univariate analysis was used to identify risk factors affecting perioperative complications of AAA, and binary logistic regression analysis was performed for factors with statistical significance in the univariate analysis to further screen out possible independent predictors. GraphPad Prism was also used for statistical analysis of the survival curves, and the comparison of survival rates between the two curves was performed using Landmark analysis, and P value < 0.05 was statistically significant.

Discussion

Studies have demonstrated that the average diameter of ruptured AAA in high-altitude regions is significantly larger, measuring 9.3 ± 1.2 cm[6], compared to the surgical intervention thresholds recommended by current guidelines, which are 5.5 cm for males and 5.0 cm for females[7]. This discrepancy suggests that AAA in high-altitude populations may exhibit distinct clinical behaviors. Supporting this observation, our team's prior analysis of AAA patients undergoing open surgery in high-altitude areas revealed that these patients were, on average, younger (mean age: 50.5 years) and presented with larger aneurysm diameters (mean diameter: 7.0 cm)[8]. These findings highlight potential differences in AAA progression and rupture risk in high-altitude populations compared to those in low-altitude regions.

In investigating the pathogenesis of abdominal aortic aneurysm (AAA), numerous research teams have established various biobanks, including the UK Biobank[9], the Munich Vascular Biobank[10], and the European Multicenter AAA Biobank, which specifically targets abdominal aortic aneurysm[11]. While these biobanks have significantly contributed to the foundational research on AAA, none of them specifically address the pathological characteristics of AAA in patients residing at different altitudes.

Common risk factors for abdominal aortic aneurysm (AAA) include smoking, hypertension, atherosclerotic disease, hyperlipidemia, advanced age (over 60 years), and male sex[12]. Plateau regions exhibit distinct environmental characteristics, such as hypoxia, low atmospheric pressure, extreme cold, and intense solar radiation. These factors represent unavoidable environmental exposures for plateau residents. To adapt to such conditions, the Xizang population has evolved two key genes associated with plateau adaptation: *EPAS1* (endothelial PAS domain protein 1) and *EGLN1* (egl-9 family hypoxia inducible factor 1). These genes are implicated in hypoxia-induced physiological responses[13] and the reduction of tissue factor pathway inhibitor (TFPI)[14], which may elevate von Willebrand factor (vWF) levels[15] and potentially influence AAA progression[16]. However, their specific mechanisms in AAA development within plateau regions require further investigation. Additionally, genome-wide association studies (GWAS) in large populations have identified multiple AAA-related genetic loci, such as *SORT1*[17]. Whether these genetic associations hold true for AAA populations in plateau areas remains to be elucidated. In addition to the above factors, hyperhomocysteinemia (HHcy) is a risk factor for AAA[18,19], which is affected by genetic factors and regional environmental factors. Human and animal experiments have shown that Hcy levels increase significantly after high altitude and hypoxia exposure[20]. Therefore, elevated Hcy may be one of the risk factors for plateau AAA, but further clarification is needed.

In addition, chronic mountain sickness, a region-specific clinical syndrome, is significantly associated with elevated rates of hypertensive heart disease and chronic obstructive pulmonary disease, both of which are robust risk factors for AAA. As a form of chronic high-altitude disease, high-altitude chronic erythrocytosis is frequently accompanied by increased EPO levels. EPO has been shown to promote AAA formation in a dose-dependent manner in both wild-type and ApoE$^{-/-}$ mice, an established atherosclerosis model[21]. EPO-induced AAA in mice exhibits pathological features similar to human AAA, including increased microvascular density,

angiogenesis, inflammation, and reduced collagen and smooth muscle cell content[21]. This may be attributed to EPO's role in endothelial cell proliferation, migration, and microtubule formation via the JAK2/STAT5 signaling pathway[22]. Furthermore, previous studies have demonstrated a positive correlation between EPO levels and AAA size in patients. Therefore, monitoring EPO dynamics in individuals residing in chronic hypoxia and high-altitude regions, along with AAA screening for those with elevated EPO levels, may be beneficial for prevention. However, large-scale clinical studies are currently lacking to substantiate this approach.

Hypoxia is a significant risk factor for cardiovascular diseases, including AAA. Anemia, a common cause of hypoxia, increases in prevalence with age, making it a modifiable risk factor in later life[23]. Indicators reflecting red blood cell size, number, and oxygen-carrying capacity have been extensively studied in AAA research. Previous studies indicate that one-third of AAA patients undergoing EVAR suffer from anemia, with hemoglobin levels independently negatively correlated with AAA maximum diameter[24] and significantly associated with 30-day post-EVAR mortality and in-hospital complications[25]. Another red blood cell-related index, red cell distribution width, can predict mortality following ruptured AAA surgery[26] or implant syndrome post-EVAR[27]. AAA patients exhibit higher EPO levels compared to healthy individuals. Similarly, other hematological indices, such as the neutrophil-to-lymphocyte ratio[27] and platelet activation[28], are closely linked to AAA size and complications. However, the relationship between these hematological indices and AAA in high-altitude regions remains understudied.

However, key unresolved questions include whether hematological indices correlate with AAA diameter at high altitudes, whether current clinical guidelines are applicable for AAA management in high-altitude areas, whether altitude influences AAA progression, and whether the pathogenesis of AAA differs between high- and low-altitude regions. These issues require further investigation.

Conclusion

In summary, whether and how the unique environmental and genetic factors in plateau areas affect the progression of AAA remains unclear. Establishing a comprehensive research platform with a large, high-quality AAA cohort that integrates biological samples and imaging data is essential for further validation.

Author contributions

NZ, YZ, and SC contributed to conception and design of the study. NZ organized the database. SC performed the statistical analysis. NZ wrote the first draft of the manuscript. YZ, WZ, YW, LG, RL, DS, WC, ZC, SY, JZ, YL, ZW, PC, and YD wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Data availability statement

Currently, no data have been collected. But in the future, all data can be obtained from the ADAPT study team after reasonable application.

Patient consent statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of interest

The authors declare no conflicts of interest.

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