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Original Article

Risk factors for cerebral venous sinus thrombosis in Xinjiang, China: a single-center case-control study with a focus on high-altitude exposure

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Abstract: Objective: Cerebral venous sinus thrombosis (CVST) is uncommon but clinically serious. Evidence regarding specific environmental factors, such as high-altitude exposure, remains limited. This study was done to identify patient-level and environmental factors associated with CVST and to summarize a single-center management model. Methods: We conducted a single-center retrospective case-control study. Participants included imaging-confirmed, consecutive adult patients with CVST (n = 33, study group) who were treated at a tertiary Hospital between March 2018 and January 2022, and controls (n = 882) without CVST during the same period. Pre-specified exposure factors included living or working at high altitudes (≥4000 meters for 6 consecutive months within the past 12 months), recent surgery (≤3 months), systemic diseases (e.g., autoimmune diseases or nephrotic syndrome), and exogenous hormone exposure (≤3 months). Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression analysis. Results: In the adjusted model, high altitude exposure, systemic disease, and recent surgery were all independently associated with a higher risk of CVST. Older age was negatively associated with CVST. By univariate analysis, exogenous hormone exposure showed a positive correlation, but this correlation was no longer significant after adjustment. Imaging studies most commonly showed involvement of the transverse sinus and superior sagittal sinus. Conclusions: In this single-center cohort, high altitude exposure, systemic disease, and recent surgery were independently associated with CVST, while the negative correlation with age may reflect residual confounding factors. These findings suggest a need for multicenter, altitude-stratified studies and careful consideration of environmental context factors when evaluating suspected CVST.

Keywords: Cerebral venous sinus thrombosis, risk factors, high-altitude living

Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon but clinically significant cerebrovascular disorder characterized by thrombosis of the dural venous sinuses and/or cortical veins, leading to impaired venous drainage, intracranial hypertension, venous infarction, and hemorrhage [1, 2]. Its clinical presentation is diverse, ranging from simple headache to focal neurological deficits, seizures, or encephalopathy, which often delays diagnosis and definitive imaging [3, 4]. Although advances in neuroimaging and anticoagulation therapy have improved prognosis, timely identification of high-risk patients remains a core challenge in clinical practice.

Classic risk factors are associated with prethrombotic states or inflammatory environments, including pregnancy and the puerperium, exposure to exogenous hormones, systemic autoimmune diseases, nephrotic syndrome, infections, malignancies, and hereditary/ac-

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quired thrombotic predispositions [5-8]. However, the relative impact of these factors varies by population and clinical context. Environmental factors, particularly persistent high-altitude exposure, are biologically plausible, but relevant research has been relatively insufficient. Hypobaric hypoxia, dehydration, hemoconcentration/polycythemia, endothelial dysfunction, and altitude-related changes in hemostasis collectively form the mechanistic framework of venous thrombosis. Limited existing reports suggest that living at high altitudes (above 2500 meters) can lead to polycythemia due to hypoxia, thereby increasing the risk of thrombosis. Polycythemia leads to a hypercoagulable state, which is associated with an increased risk of atherosclerotic thrombotic stroke [9-11]. However, data linking these pathways to individual patient CVST remain limited [12]. Furthermore, existing scientific literature suggests an increased risk of stroke at altitudes above 3500-4000 meters, particularly when unfit populations are suddenly exposed to this environment [13].

In this study, we evaluated patients visiting a tertiary hospital in Xinjiang, an area with a large population of residents and workers living or working at high altitudes. Our primary objective was to identify patient-level and environmental factors associated with CVST and to pre-select a focus on high-altitude exposure. High-altitude areas in Xinjiang are mainly concentrated in the Pamir Plateau, the Tian Shan Mountains, and the Karakoram Range, with an average elevation exceeding 3,000 meters. The highest peak, Qogir Peak, reaches 8,611 meters. While the original classification of 0 meters as a plain was considered, after further consideration, we propose using 800 meters (the elevation of Urumqi) as a more appropriate boundary for defining "plain" areas. Therefore, we recommend revising all 0-meter records in this study to 800 meters. Accordingly, we select 4,000 meters as the threshold for high altitude. We also describe the imaging patterns of sinus involvement and summarize our center's actual management practices. We hypothesize that, after adjusting for demographic and clinical covariates, sustained high-altitude exposure is independently associated with CVST, thus providing a reference for risk stratification and predictive probability in similar environments.

Materials and methods

Ethics and study design

Approval was obtained from the Institutional Ethics Committee of General Hospital of Xinjiang Military Command (Approval No. 2023-RR0205), and informed consent or waivers were documented in accordance with local regulations.

In this single-center, retrospective case-control study, participants included imaging-confirmed, consecutive adult patients with CVST (study group, n = 33) who were treated at the General Hospital of Xinjiang Military Command between March 2018 and January 2022, and controls (n = 882) without CVST during the same period.

Eligibility criteria and case ascertainment

Inclusion for study group: Patients with CVST confirmed by magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) or digital subtraction angiography (DSA).

Exclusion: Patients with missing key imaging or laboratory variables required for corrected analysis; patients whose diagnosis was inconsistent with CVST. Patients were not excluded based on in-hospital mortality; if residual data required exclusion of cases, the number was reported as a limitation of the study.

Clinical variables and standardized definitions

The following information upon admission (ideally before initiating anticoagulation therapy) was collected:

Demographic information: Age (years), sex.

Environmental exposure: High-altitude exposure is predefined as living or working at an altitude ≥4000 meters for 6 consecutive months within the past 12 months [14].

Systemic disease: Systemic lupus erythematosus, nephrotic syndrome, antiphospholipid syndrome, or active malignancy (present/absent).

Recent surgical history: Any surgery performed within 3 months prior to admission.

Exogenous hormones: Exposure to estrogen/progestin within 3 months prior to admission (present/absent).

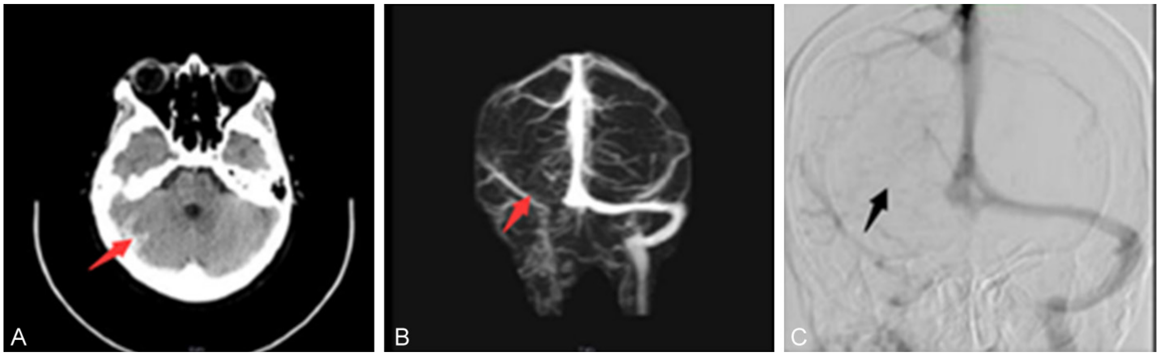

Figure 1. A 24-year-old female patient was admitted to the hospital with the main complaint of a persistent headache lasting for two days. She had a history of oral contraceptive use two months prior to admission. A. Plain head computed tomography (CT) scan showed increased density in the right transverse sinus, presenting the classic "delta sign" (δ sign; see red arrow). B. Cranial magnetic resonance venography (MRV) demonstrated non-visualization of the right transverse sinus and sigmoid sinus (see red arrow). C. Digital subtraction angiography (DSA) further confirmed the absence of visualization of the right transverse and sigmoid sinuses, accompanied by dilation of cortical veins in the right cerebral hemisphere (see black arrow).

Biochemistry/hematology: Collect the latest levels of relevant indices, including D-dimer (mg/L), fibrinogen (g/L), hemoglobin, platelet count, and white blood cell count (first values before anticoagulation therapy).

Obstetric status: If applicable, pregnant or postpartum. For the study group only: Main symptoms (headache, seizures, focal neurological deficits), affected venous sinuses (superior sagittal sinus, transverse sinus, sigmoid sinus, confluence of sinuses, straight sinus, internal jugular vein, great cerebral vein), and parenchymal lesions.

CVST-related complications included ischemic and hemorrhagic events (intracerebral and subarachnoid space: CT/MRI shows ischemic lesions as low-density foci, hemorrhagic lesions as high-density foci), pneumonia (chest X-ray diagnosed as pneumonia, chest CT showing infectious lesions in lung segments, lobes, and interstitial areas, consistent with clinical symptoms and signs), and recurrent seizures.

Imaging criteria

MRI/MRV: Dural venous sinuses/cortical veins are not visualized or have filling defects; or accompanied by parenchymal changes (venous infarction or hemorrhage).

DSA, if performed: Venous phase non-visualization, collateral circulation filling, or delayed flow. Representative archived images are used in **Figure 1**, labeled with the dense/empty triangle sign and affected venous sinuses.

Sample size calculation

This was a retrospective case-control study. The sample size was calculated based on the effect size of the primary exposure variable-high-altitude exposure (elevation ≥4000 meters) - and related statistical assumptions. Literature suggests that the prevalence of high-altitude exposure among CVST patients in high-altitude areas is estimated at 15%, compared to approximately 5% in low-altitude areas [10-12]. We set the significance level (α) at 0.05 (two-tailed test) and the statistical power (1-β) at 80%. The calculated total sample size was 187 participants.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median (interquartile range) according to their distribution, which was determined by the Shapiro-Wilk test.

Categorical variables were expressed as the number of cases with the corresponding percentage (n [%]).

For case-control comparisons, t-tests or Mann-Whitney U tests were used to analyze continuous variables, while categorical variables were analyzed using χ^2 tests or Fisher's exact tests,

Table 1. Data of study group (n = 33)

NO.	Sex	Age	Hb (10^9/L)	Plt (10^9/L)	DD (mg/L)	Alt (m)	Wbc (10^9/L)	FBG (g/L)
1	M	21	215	155	0.3	5300	6.16	1.77
2	M	21	179	211	1.85	4000	5.02	0.71
3	M	29	149	193	0.3	800	10.99	2.49
4	M	31	203	271	2.15	5000	10.29	4.87
5	M	20	180	247	0.9	5300	7.08	3.21
6	M	35	184	201	3.14	4600	6.7	4.63
7	F	46	87	339	0.21	800	5.89	3.5
8	M	25	148	375	0.21	800	7.06	3.48
9	F	24	116	198	7.49	800	8.61	3.08
10	M	43	120	221	2.2	800	5.09	3.5
11	F	28	103	522	3.56	800	9.84	5.39
12	M	35	153	276	6.2	800	11.73	4.92
13	M	21	143	250	5.78	4000	12.11	6.25
14	M	16	74	313	6.58	800	6.93	3.06
15	M	31	167	311	0.19	4500	9.51	7.56
16	M	20	196	372	1.18	5300	8.23	2.21
17	M	28	151	188	0.41	800	15.5	4.43
18	M	48	153	195	8.63	800	6.04	1.72
19	M	31	172	271	2.15	5000	10.29	4.87
20	M	21	215	155	30	5300	6.16	1.77
21	M	28	165	253	0.19	800	6	2.31
22	F	54	136	197	0.75	800	3.59	2.96
23	M	20	160	296	0.12	800	11.32	2.50
24	F	42	162	260	2.96	800	9.65	8.61
25	M	20	149	287	0.49	800	10.6	4.03
26	M	38	143	219	1.00	800	16.86	5.94
27	F	33	108	461	3.69	800	6.83	4.24
28	M	67	143	264	1.59	800	13.07	5.50
29	M	65	106	239	2.53	800	10.21	11.50
30	F	40	86	160	0.25	800	6.31	2.61
31	F	48	94	213	0.79	800	7.30	1.87
32	F	21	142	178	0.19	4000	4.61	18.1
33	F	33	119	168	1.71	800	5.37	7.72

Notes: Hb: hemoglobin; Plt: platelet; DD: D-dimer; WBC: white blood cell count; FBG: fibrinogen; Alt: altitude; M: male; F: female.

and a two-sided *p*-value <0.05 was considered significant.

The main software used for statistical analysis and visualization was SPSS version 25 and R 4.3.3, and several packages in R 4.3.3 were applied for modeling and plotting, including rms for logistic regression modeling, nomogram construction and calibration, pROC for ROC curve generation, area under the curve calculation and DeLong test, rmda for decision curve analysis, ggplot2 for data visualization, and boot for the bootstrap method.

Results

Cohort overview

In the CVST cases, 23/33 (69.7%) were male and 10/33 (30.3%) were female; the mean age was 32.82 ± 13.03 years (range 16-67 years). 11/33 (33.3%) had a history of sustained high-altitude exposure (≥4000 meters, exposure time > 6 months). Clinical data of the CVST patients are shown in **Table 1**, including sex, age, altitude, and blood test indicators.

Baseline characteristics and laboratory findings

Compared to the control group, the CVST cases were younger and had a higher proportion of males (both P < 0.05). Intergroup comparisons showed significant differences in altitude, sex, age, D-dimer, hemoglobin, platelet count, white blood cell count, and fibrinogen (**Table 2**, all P < 0.05). The mean hemoglobin level in the cerebral venous sinus thrombosis group was 146.09 ± 36.80 g/L (range 74-215 g/L), and the median D-dimer level before anticoagulation therapy was 0.41 mg/L (interquartile range 0.20-0.86 mg/L). More common pre-existing conditions included systemic diseases (e.g., systemic lupus erythematosus, nephrotic syndrome, antiphospholipid syndrome), recent surgery, and abnormal hormone exposure/status; hyperuricemia (> 420.0 μmol/L) and hyperhomocysteinemia (> 15.0 μmol/L) were also more common.

Clinical presentation and neuroimaging

Headache was the most common symptom (22/33, 66.7%), followed by seizures (8/33, 24.2%), and loss of consciousness occurred in 4/33 (12.1%) patients. Most patients had multiple sinus involvement. Transverse sinus

Table 2. Characteristics data of control-study group

Characteristic		Total n/N (%)	Control group n/N (%) (n = 364)	Study group (CVST group) n/N (%) (n = 33)	χ^2/t	P
Mean Age		54.29±19.19	56.16±18.43	32.82±13.03	7.124	< 0.0001
Mean Hb (g/L)		133.80±22.86	132.85±20.66	146.09±36.80	3.265	0.001
Mean Plt (10^9/L)		225.61±66.44	222.87±64.03	256.33±84.70	2.798	0.005
DD (mg/L)[1]		0.43 (0.20, 0.99)	1.59 (0.30, 3.35)	0.41 (0.20, 0.86)	4.687	< 0.0001
Mean Wbc (10^9/L)		6.92±2.89	6.77±2.83	8.51±3.15	3.350	0.001
Mean FBG (g/L)		3.06±1.40	2.92±0.97	4.57±3.32	5.388	< 0.0001
Sex	male	197/397 (49.6)	174/364 (47.8)	23/33 (69.7)	5.802	0.016
	female	200/397 (50.4)	190/364 (52.2)	10/33 (30.3)		
Alt	≥4000 m	26/397 (6.5)	15/364 (4.1)	11/33 (33.3)	42.191	< 0.0001
	≤800 m	371/397 (93.5)	349/364 (95.9)	22/33 (66.7)		

Notes: The D-dimer is not a normal distribution and is represented by the median and quartile. Hb: hemoglobin; Plt: platelet; DD: D-dimer, Wbc: White blood cell count; FBG: fibrinogen; Alt: altitude.

involvement occurred in 22/33 (66.7%), superior sagittal sinus in 20/33 (60.6%), sigmoid sinus in 16/33 (48.5%), confluence of sinuses, straight sinus, and internal jugular vein in 4/33 (12.1%) each; great cerebral vein involvement occurred in 1/33 (3.0%). Representative imaging findings (CT density/δ sign; MRV non-contrast; DSA venous phase) are shown in **Figure 1**; detailed clinical/imaging features are summarized in **Table 3**. Complications associated with CVST included ischemic and hemorrhagic events (intracerebral and subarachnoid hemorrhage), pneumonia, and recurrent seizures.

Treatment and short-term prognosis

The initial treatment regimen was low molecular weight heparin. Of the 33 patients, 8 (24.2%) experienced clinical deterioration, and 6 (18.2%) underwent endovascular interventional therapy. **Figure 2** shows a typical flowchart. Two patients (6.1%) required craniotomy to remove hematoma and monitor intracranial pressure. One week later, these patients were switched to warfarin. After discharge, vitamin K antagonists were used based on risk assessment and guidelines. At 3-month follow-up, 25 of the 33 patients (75.8%) had fully recovered, 4 (12.1%) had residual neurologic deficits requiring rehabilitation, and 4 (12.1%) were lost to follow-up.

Multivariate analysis of factors associated with CVST

In the multivariate logistic regression analysis (**Table 4**), age was negatively associated with CVST (β = -0.072; aOR = 0.93/year; 95% CI 0.90-0.96; P < 0.001). High altitude exposure (β = 1.128; aOR = 3.09; 95% CI 1.06-9.03; P = 0.039), systemic disease (β = 2.235; aOR = 9.35; 95% CI 3.24-26.96; P < 0.001), and recent surgery/procedure (β = 1.053; aOR = 2.87; 95% CI 1.16-7.07; P = 0.022) were all positively associated with CVST. Univariate analysis showed a positive trend for exogenous hormone exposure, but this did not reach independent significance after adjustment (β = 0.948; aOR = 2.58; 95% CI 0.71-9.33; P = 0.148). Sex, infection, malignancy, and puerperium did not show significant differences in the adjusted model (**Figure 3**). No collinearity was found in the model's diagnostics; variance inflation factor (VIF) all < 2 (**Figure 4**).

Discussion

In this single-center case-control study, after adjusting for demographic and clinical covariates, high-altitude exposure was independently associated with CVST. Similar results were found in a study of cerebral venous thrombosis in Tibet, which showed that 71.1% of the 38 patients with CVST included in the study were Tibetan. Their median altitude in Tibet was 3,800 meters (range: 3,657-4,054 meters) [15]. Systemic diseases and recent surgery were also positively associated with CVST, while older age was negatively associated, which we believe may be due to confounding factors in the case-control composition rather than a true protective effect [16, 17]. Imaging most frequently involved the transverse and superior

Table 3. Clinical features of patients with CVST

Involved sinuses	Number of involved sinuses	Time from symptoms onset	Symptoms on onset	Other symptoms and signs	Complications	Prior risk factors	course of the CVST
Superior sagittal	1	21 days	Blurred vision	Headache	-	High altitude	Full recovery
Superior sagittal; righ transverse and sigmoid; straight; torcular	5	10 days	Upper respiratory infection	Headache,vomiting	Fundus hemorrhage	High altitude; mastoiditis	Full recovery
righ transverse and sigmoid	2	15 days	Headache	Blurred vision	tristimania	Nephrotic syndrome	Full recovery
Superior sagittal; right transverse; left transverse; torcular	4	10 days	Headache	-	-	High altitude	Full recovery
Superior sagittal; left transverse and sigmoid	3	14 days	Upper respiratory infection	Headache, vomiting	-	High altitude	Full recovery
Straight; Galen vein	2	14 days	Headache	Weakness of limbs	Pneumonia	High altitude	Full recovery
Superior sagittal; left transverse and sigmoid	3	2 years	Headache	-	-	-	Full recovery
Superior sagittal; right transverse and sigmoid; left transverse and sigmoid; Straight	6	10 days	seizure	-	Haemorrhagic stroke, SAH; DVT	Thrombophilia; DAVF	-
right transverse	1	2 days	Headache	-	-	Oral contraception	Full recovery
right transverse	1	1 days	seizure	Somnolence	Pneumonia, Cushing ulcer; Haemorrhagic stroke	Under intraspinal anesthesia operation	Hemiplegic paralysis
Superior sagittal; left transverse	2	7 days	seizure	Coma	Ischaemic stroke	Postpartum period	Hemiplegic paralysis
Superior sagittal; left transverse and sigmoid	3	7 hours	Headache	seizure	Ischaemic stroke, Pneumonia	-	Hemiplegic paralysis
left transverse and sigmoid, left jugular vein	3	1 month	Fever; dyspnea	Coma	Haemorrhagic stroke, Pneumonia; pulmonary embolism, right ventricular thrombosis	High altitude	Full recovery
Superior sagittal	1	1 month	Headache	-	Occipital lobe contusion and laceration	Trauma	Full recovery
Superior sagittal; left transverse and sigmoid; Straight	4	6 days	Headache	vomiting	Ischaemic stroke	High altitude	Full recovery
Superior sagittal; left transverse and sigmoid; left jugular vein	4	14 days	Upper respiratory infection	Headache	-	High altitude	Full recovery
Superior sagittal	1	1 month	Headache	seizure	-	Dehydration	Full recovery
Left sigmoid; left jugular vein	2	2 days	Headache	-	-	-	Full recovery
Superior sagittal; right transverse; left transverse; torcular	4	10 days	Headache	-	-	High altitude	Full recovery
Superior sagittal	1	21 days	Blurred vision	-	-	High altitude	Full recovery
Left transverse; right transverse	2	6 month	Headache	-	-	Maligancy; hyperhomocysteinemia	Full recovery

right transverse and sigmoid	2	11 hours	Headache	vomiting	septicopyemia	Under intraspinal anesthesia operation	Full recovery
Superior sagittal; right transverse and sigmoid	3	14 days	Headache	-	-	Obesity	Full recovery
Superior sagittal; right transverse and sigmoid	3	14 days	Headache	-	Intracranial infection	Postpartum period	Full recovery
Superior sagittal	1	4 hours	seizure	-	SAH; Haemorrhagic stroke	-	Hemiplegic paralysis
Superior sagittal; right transverse and sigmoid; right jugular vein	4	2 hours	Blurred mind	-	Temporal lobe contusion and laceration; traumatic SAH; Pneumonia	Trauma	Full recovery
Left jugular veint	1	15 days	Headache	-	-	Hypothyroidism	Full recovery
Superior sagittal; left transverse and sigmoid; torcular	4	11 hours	Headache	seizure	Haemorrhagic stroke	-	Full recovery
left sigmoid	1	14 days	Visual filed defect	-	Emphysema	High altitude	Full recovery
Superior sagittal; left transverse	2	17 days	Headache	Numbness of limbs; seizure	SAH	General anesthesia	Full recovery

Notes: SAH: subarachnoid hemorrhage; DVT: deep venous thorombosis; DAVF: dural arteriovenous fistula.

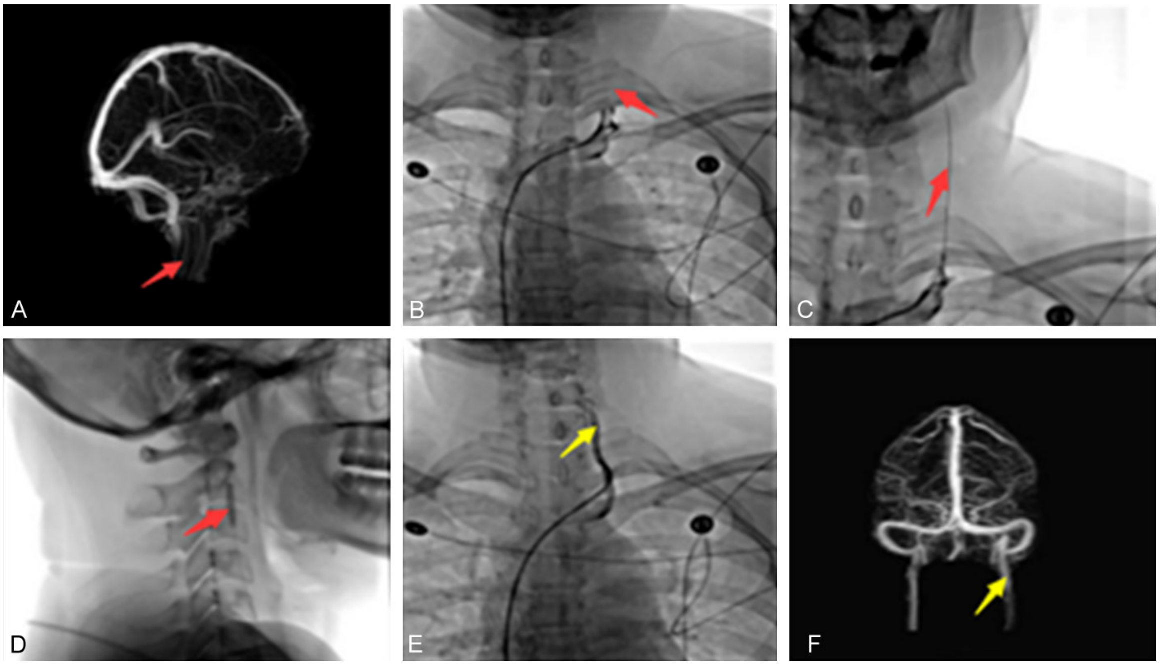

Figure 2. A 40-year-old female patient presented with the chief complaint of "severe headaches accompanied by fundus hemorrhage for two days". She had a medical history of hypothyroidism and was taking oral levothyroxine (100 μg each morning), with normal thyroid hormone levels at the time of admission. A lumbar puncture revealed an elevated intracranial pressure exceeding 400 mmH_2O. To address insomnia and reduce intracranial pressure, the patient underwent endovascular treatment. A. Cranial MRV indicated thrombosis in the left internal jugular vein (red arrow). B. Femoral venipuncture was conducted, followed by the insertion of an indwelling filter in the superior vena cava. Left internal jugular venography showed complete occlusion of the vascular lumen (red arrow). C. A coronary angiography guidewire was advanced to the distal end of the thrombus (red arrow). D. Balloon dilation and placement of an intermediate catheter were performed for subsequent contact intravenous thrombolysis (red arrow). E. Intraoperative review angiography showed partial blood flow signals in the left internal jugular vein (yellow arrow). F. After surgery, the patient was transferred to the neurosurgical care unit, where prourokinase was administered intraductally and low-molecular-weight heparin sodium was injected subcutaneously. Periodic reviews of intracranial venography were performed, and the catheter was gradually removed as thrombolysis progressed. On the 6th postoperative day, the catheter was successfully removed, and the patient was initiated on oral warfarin. A follow-up MRV two weeks later showed partial recovery of blood flow in the left internal jugular vein (yellow arrow).

sagittal sinuses, with some patients presenting with parenchymal venous infarction and hemorrhage. These findings collectively support the presence of an altitude-related risk signal in a clinically consistent CVST phenotype.

Biologic justification for the altitude signal is provided by several altitude-related processes that provide a mechanistic framework for venous thrombosis [5, 18, 19]: (i) hypobaric hypoxia and its downstream endothelial activation/dysfunction [20]; (ii) hemoconcentration/polycythemia and relative dehydration, increasing blood viscosity [21]; (iii) hypoxia-induced changes in the coagulation and fibrinolytic systems [22]; and (iv) sympathetic and inflammatory states that may amplify prothrombotic pathways. Our findings are consistent with these pathophysiological expectations, but do not demonstrate causality. The negative correlation with age may reflect residual confounding factors (e.g., a higher proportion of younger, high-altitude-exposed individuals in the study group compared to a higher proportion of older, multi-disease-prone individuals in the control group) [23]. Nevertheless, one study also found that high-altitude CVST is more common in younger patients and women [15]. In addition, a systematic review of high-altitude cerebral venous thrombosis [24] included 13 articles. The study population included 17 patients with a mean age of 32 years (range: 19-47 years). These findings also indicate that young people are susceptible to high-altitude CVST, but the underlying mechanisms still need to be studied.

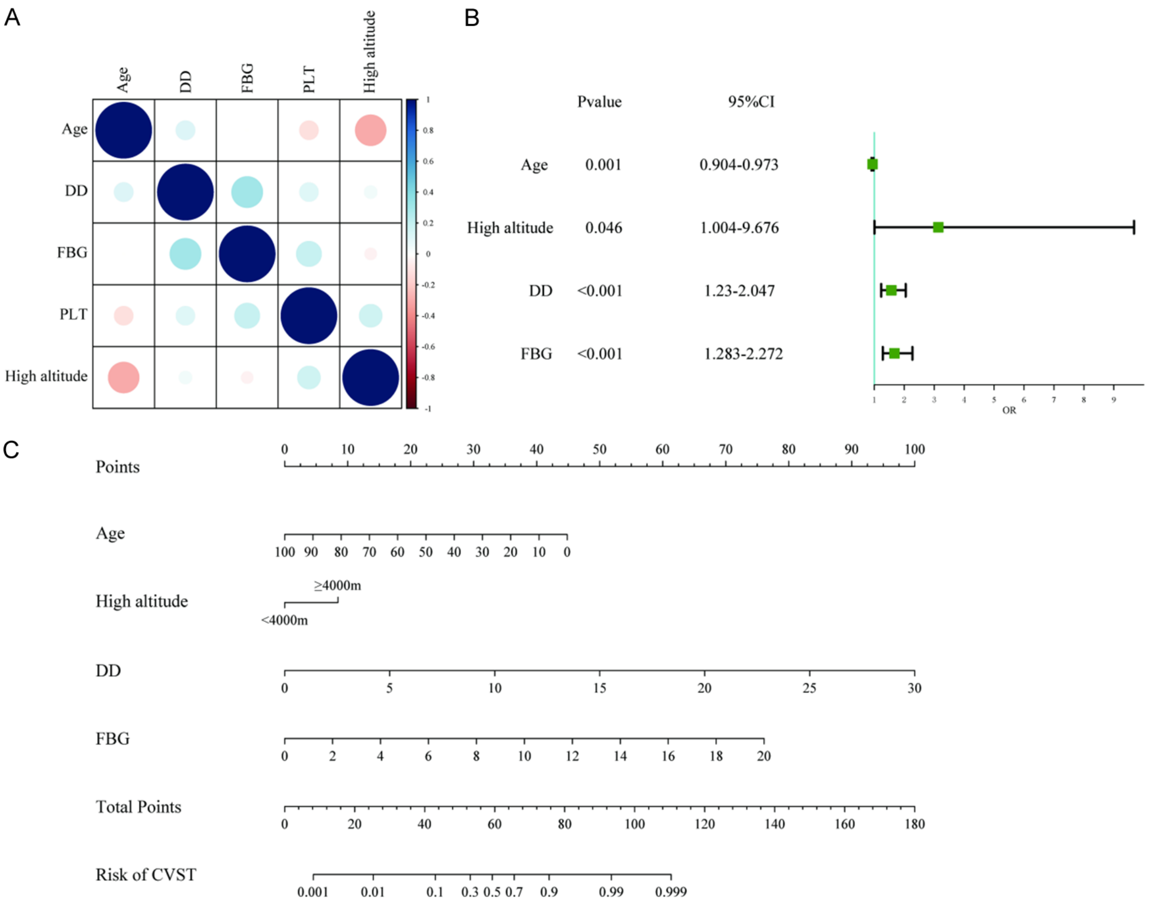

Figure 3. Model Building. A. Correlation matrix (bubble plot) among candidate predictors for CVST. Pairwise correlations were calculated between Age, D-dimer (DD), Fibrinogen (FBG), Platelet count (PLT), and High-altitude exposure using pre-anticoagulation values. The size of each circle scales with the absolute value of the correlation coefficient (|r|), and the color encodes the direction of the correlation (blue = positive correlation, red = negative correlation; the color bar ranges from -1 to +1). The diagonal represents self-correlation (r = 1). B. Multivariable forest plot of adjusted associations with CVST. Adjusted effect sizes (aOR, 95% CI) from the multivariable logistic regression are displayed for Age (per year), High-altitude exposure (≥4,000 m for ≥6 months in the prior year), D-dimer (DD; per unit increase), and Fibrinogen (FBG; per g/L). C. Nomogram for individualized prediction of CVST risk. The nomogram translates the multivariable logistic model into a point-based prediction tool. For each predictor-Age (years; inverse association), High-altitude exposure (≥4,000 m for ≥6 consecutive months within the prior year), D-dimer (DD; mg/L, pre-anticoagulation), and fibrinogen (FBG; g/L, pre-anticoagulation)-locate the patient's value on the corresponding axis and assign points based on the top "Points" scale.

Classically, CVST is often associated with prethrombotic states, such as autoimmune diseases, nephrotic syndrome, antiphospholipid antibodies, pregnancy/puerperium, malignancies, and drug exposure [25-27]. Our data are consistent with this framework, finding that systemic disease and recent surgery, like altitude, are independent contributing factors. Notably, exogenous hormone exposure showed a positive trend in the univariate analysis, but this was no longer significant after adjustment, suggesting either limited statistical power or confounding effects from stronger covariates in this cohort.

In our adjusted analysis, variables associated with education level, habitual physical activity, income, social support, and mental health status did not produce explainable or decision-related signals associated with CVST risk, and in this dataset, these variables were not biologically closely related to CVST. To avoid diluting the main information and preventing misinterpretation, these results were not highlighted or emphasized further.

In high-altitude areas, or among populations performing long-term high-altitude tasks/living, the assessment threshold for CVST should be

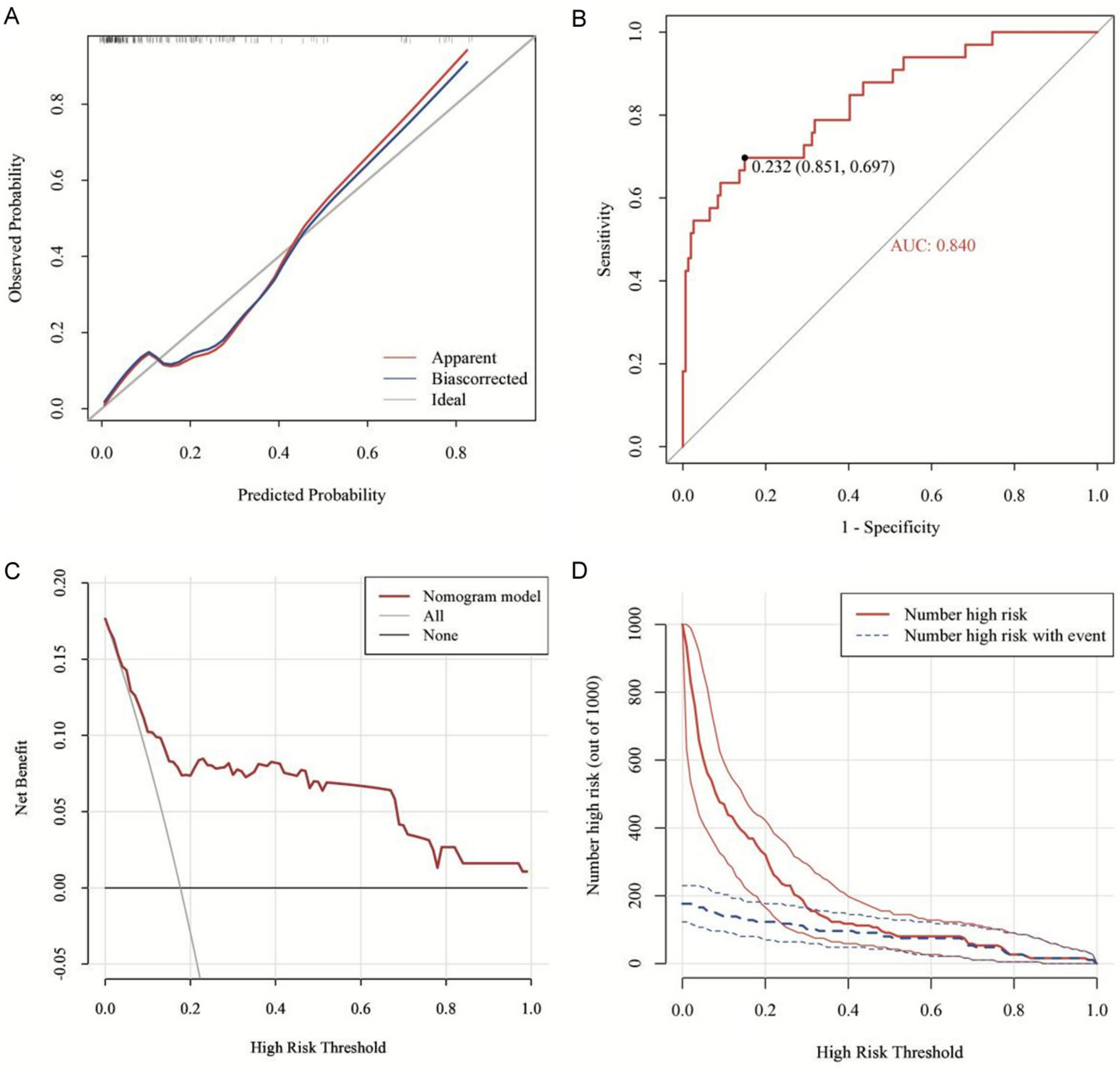

Figure 4. Model Validation and Evaluation. A. Calibration curve for the prediction model. The plot assesses the agreement between the predicted probabilities and the observed actual frequencies. The grey line (Ideal) indicates perfect calibration. The red line (Apparent) represents the performance of the model on the original data, where closer proximity to the diagonal indicates better calibration. The blue line (Bias-corrected) is the smoothed calibration curve after Loess fitting. B. Receiver operating characteristic (ROC) curve of the CVST risk model (nomogram). The curve plots sensitivity versus 1-specificity across all decision thresholds for the multivariable logistic model including Age, High-altitude exposure (≥4,000 m for ≥6 months), D-dimer (DD), and Fibrinogen (FBG). The gray diagonal denotes no-discrimination. The model achieved an area under the curve (AUC) of 0.840. The black dot marks the Youden-optimal threshold (pt = 0.232), yielding sensitivity 0.851 and specificity 0.697. C. The decision curve for the prediction model developed in this study (solid red line) is presented. The curve is compared against the strategies of 'intervene for all' ('All') and 'intervene for none' ('None'). The Y-axis represents the net benefit, and the X-axis is the threshold probability. Within the range of threshold probabilities where our model's curve is above both the 'All' and 'None' lines, using the model for clinical decision-making provides a net benefit (1-99%). D. This figure illustrates the clinical effect of the model's predicted risks across the cohort. The red curve ('Number of High Risk') shows the number of patients classified as high-risk by the model at various risk thresholds. The black curve ('Number of High Risk with Event') shows the observed number of patients with the event among those predicted to be high-risk. The closeness of the two curves reflects the calibration accuracy of the model.

lowered when patients present with persistent/severe headache, papilledema, focal neurological deficits, or seizures. Pre-test probability should take into account factors such as altitude exposure, recent surgery, and systemic diseases [28, 29]. Standard treatment (timely

Table 4. Multivariate logistic analysis of CVST-related risk factors

Variable	*β*	SE	Wald	*p*	95% *CI*	variance inflation factor (VIF)
Age	-0.072	0.016	20.381	0.000	0.901-0.960	1.405
Gender	0.385	0.488	0.623	0.430	0.565-3.821	1.442
Altitude	1.128	0.548	4.243	0.039	1.056-9.034	1.732
Hormone	0.948	0.656	2.091	0.148	0.714-9.329	1.209
Systemic disease	2.235	0.540	17.105	0.000	3.241-26.956	1.321
Surgical status/Operation	1.053	0.460	5.232	0.022	1.163-7.066	1.343
Infection	0.521	0.458	1.295	0.255	0.686-4.129	1.046
malignancy	-0.909	1.101	0.682	0.409	0.047-3.484	1.089
Puerperium	-1.086	1.097	0.979	0.322	0.039-2.900	1.126

anticoagulation, management of intracranial hypertension, and selective endovascular intervention) remains applicable; our data do not change the treatment regimen consistent with guidelines, but support increased vigilance in populations exposed to high altitudes [30].

This study has limitations. The retrospective nature, single-center design, and small sample size limit the generalizability and precision of the results. Selection of a control group from a heterogeneous hospital population may introduce selection bias; residual confounding factors (including occupational and environmental co-exposure at high altitudes) cannot be excluded. Exposure was defined dichotomously (altitude ≥4000 meters and exposure time ≥6 months), which may underestimate the dose-response relationship between altitude and exposure duration and outcomes. Differences in laboratory sample collection times among patients complicate the interpretation of biomarkers such as D-dimer.

Future research should focus on prospective, multicenter cohort studies, incorporating detailed altitude metrics (continuous altitude, cumulative exposure time, and recent exposure), standardized hydration/hematology analyses, and propensity score or instrumental variable strategies to enhance causal inference. Parallel mechanism studies (endothelial function, viscoelasticity testing, and hypoxia-driven coagulation/fibrinolysis assays) may help elucidate intermediate biological processes [31]. Finally, high-altitude-specific risk assessment tools combining clinical, environmental, and laboratory signals may improve early identification and triage [32].

In summary, within the context of this study, high altitude exposure, systemic disease, and recent surgery were independently associated with CVST, while the negative association between age and the disease may have been influenced by confounding factors. Highlighting altitude as a background risk factor helps optimize pre-screening probabilities and encourages susceptible populations to receive timely imaging examinations and treatment. It also provides impetus for conducting targeted prospective studies to validate and expand these findings.

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Disclosure of conflict of interest

None.

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