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Establishing altitude-based coagulation reference ranges in Western Sichuan

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The diagnosis and treatment of diseases in plateau regions should incorporate altitude, sex, and age in addition to hematological indicators from plain regions. This study analyzed coagulation results among individuals living at different altitudes in the Western Sichuan Plateaus and belonging to different sex and age groups to examine patterns of change and determine normal ranges. By comparing the changes in coagulation indicators among healthy male and female residents of different age groups (< 40 years, 40–59 years, ≥ 60 years) from Guza (1,400 m), Kangding (2,500 m), Luhuo (3,400 m), and Litang (4,100 m), we analyzed the association between coagulation indicators and altitude, age, and sex. Under low temperature, hypoxia, and other plateau environment factors, coagulation indicators varied among different altitudes, with some indicators showing specific trends of change with increasing altitude. Different sexes and age groups also exhibited specific patterns of change in coagulation results. This study clarified the patterns of change in coagulation results at four different altitudes in the Western Sichuan Plateau and the effects of sex and age on coagulation function. Normal ranges of coagulation values were determined for different sexes and age groups at different altitudes, providing a scientific basis for healthcare in this region.

Keywords Plateau residents, Altitude, Sex, Age group, Coagulation, Reference range

The Western Sichuan Plateau, located in southwestern China, has an average altitude of more than 3,500 m and is renowned for its unique landscape. Under hypoxic, low-temperature, and other extreme conditions that characterize high-altitude regions, physiological functions can undergo a series of adaptive changes, with the most prominent being hematological changes[1]. These changes vary across altitudes, sexes, and age groups[2]. Therefore, the diagnosis and treatment of diseases in plateau regions cannot be based completely on the hematological indicators in plain regions but should incorporate altitude, sex, and age[3]. Recently, numerous scholars have explored the changes in coagulation indicators in the plateau environment[4]. However, their research focuses more on independently studying the impact of altitude on coagulation indicators, and there is relatively less research on the variation patterns of coagulation indicators under the combined influence of altitude, age, and sex. Coagulation indicators are crucial in clinical practice, particularly for preoperative preparations. Therefore, there is a need to conduct systematic and comprehensive research. This study aimed to collect blood samples from healthy individuals living at different altitudes on the Western Sichuan Plateau and test their coagulation-related indicators. Based on the analysis and comparison of these data, we aimed to elucidate the patterns of changes in coagulation findings among healthy individuals living at different altitudes. Based on these findings, coagulation reference ranges suitable for the Western Sichuan Plateau were established, which can serve as a scientific basis for local medical diagnosis and health management.

Materials and methods

Participants

The study was approved by the Ethics Committee of Yaan People's Hospital (approval number: 2023 011). Before blood collection, the purpose of blood collection and the rights of the subjects were fully explained to the participants, who provided written informed consent. All experimental methods were carried out in accordance with the relevant guidelines and regulations, including but not limited to the Helsinki Declaration

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Indicator		Male (n = 255)	Female (n = 266)	T	P
PT	(s)	14.13 ± 0.96	13.90 ± 0.82	2.927	0.004
APTT	(s)	36.40 ± 1.92	35.62 ± 2.49	4.020	< 0.001
TT	(s)	18.28 ± 1.43	17.87 ± 1.38	3.366	0.001
FIB	(g/L)	3.17 ± 0.61	3.04 ± 0.59	3.067	0.002

Table 1. Comparison of indicators between sexes among the residents of Guza. PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

Indicator		Male (n = 385)	Female (n = 595)	T	P
PT	(s)	14.84 ± 1.22	14.29 ± 0.97	7.370	< 0.001
APTT	(s)	38.16 ± 1.58	36.55 ± 2.48	12.424	< 0.001
TT	(s)	19.72 ± 1.33	18.55 ± 1.07	14.449	< 0.001
FIB	(g/L)	3.20 ± 0.06	3.13 ± 0.11	7.791	< 0.001

Table 2. Comparison of indicators between sexes among the residents of Kangding.

and its subsequent amendments, as well as any specific ethical and regulatory requirements applicable to this type of research.

Healthy individuals living in Guza Town of Kangding County, Lucheng Subdistrict of Kangding County, Luhuo County, and Litang County of Ganzi Prefecture, Sichuan Province, were screened in March and August 2024. The screening criteria were as follows: (1) absence of inflammatory diseases and use of oral antibiotics, anticancer drugs, and anticoagulants within the previous month; (2) body mass index (BMI) between 18.5 and 23.9 kg/m^2; (3) absence of abnormalities in cardiopulmonary function; and (4) absence of abnormalities in hepatic and kidney functions; (5) no history of immunological or hematological diseases; and (6) age > 18 years. After the screening, 521 individuals (255 male and 266 female participants) from Guza Town, 980 individuals (385 male and 595 female participants) from Lucheng Subdistrict, 821 individuals (361 male and 460 female participants) from Luhuo County, and 1,135 individuals (560 male and 575 female participants) from Litang County were included in the analysis.

Methods

Test methods

For coagulation function tests, 3 mL of venous blood was collected using a vacutainer containing 0.109 mmol/L sodium citrate as an anticoagulant, and the samples were centrifuged at 1500 × g for 15 min to separate the plasma. Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and thrombin time (TT) were measured within 2 h of blood sample collection using a Sysmex CS5100 (Tokyo, Japan) Fully Automated Blood Coagulation Analyzer from Sekisui Diagnostic Japan and its supporting reagents.

Test parameters

Test data were processed using Microsoft Excel 365, and the items included PT, TT, APTT, and FIB.

Statistical methods

Data were analyzed using SPSS 25.0(IBM Corporation, Armonk, NY, USA). Normally distributed quantitative data are shown as mean ± standard deviation (SD) and were compared between groups using one-way analysis of variance (ANOVA). Further pairwise comparisons of between-group differences were performed using the least significant difference (LSD) method. Differences were considered statistically significant at $P < 0.05$.

Results

Comparison of coagulation indicators between different sexes at the same altitude

After a meticulous analysis of the coagulation test results of the local population, we determined that the coagulation results across different altitudes, sexes, and age groups follow a normal distribution, and one-way ANOVA was employed for comparisons among various groups. Through group-by-group comparisons, we discovered that at the same altitude, male participants had significantly higher PT, APTT, TT, and FIB levels than female participants ($P < 0.05$) (see Tables 1, 2, 3 and 4).

Comparison of coagulation indicators among different altitudes within the same sex

Based on the analysis of coagulation indicators in male participants at different altitudes, we found the following sequences regarding PT, APTT, and TT: Litang > Luhuo and Kangding > Guza, with no difference between Luhuo and Kangding and significant differences for the remaining pairwise comparisons. For FIB, the sequence was Litang and Luhuo > Kangding and Guza, with no differences between Litang and Luhuo or between Kangding and Guza and significant differences for the remaining pairwise comparisons (Table 5).

Based on the analysis of coagulation indicators in female participants at different altitudes, we found the following sequence for PT and APTT: Litang > Luhuo and Kangding > Guza, with no difference between Luhuo

Indicator		Male ($n = 361$)	Female ($n = 488$)	t	*P*
PT	(s)	15.25 ± 0.94	14.58 ± 1.03	11.733	< 0.001
APTT	(s)	39.12 ± 1.86	36.97 ± 3.08	9.772	< 0.001
TT	(s)	20.62 ± 1.48	17.35 ± 1.40	12.604	< 0.001
FIB	(g/L)	3.47 ± 0.37	3.12 ± 0.53	2.697	0.007

Table 3. Comparison of indicators between sexes among the residents of Luhuo.

Indicator		Male ($n = 560$)	Female ($n = 575$)	t	*P*
PT	(s)	16.48 ± 1.37	16.06 ± 1.66	4.642	< 0.001
APTT	(s)	41.91 ± 3.1	39.48 ± 5.57	9.123	< 0.001
TT	(s)	21.69 ± 1.99	21.40 ± 2.11	2.311	0.021
FIB	(g/L)	3.52 ± 0.69	3.28 ± 0.71	3.277	0.001

Table 4. Comparison of indicators between sexes among the residents of Litang.

Indicator		Guza ($n = 255$)	Kangding ($n = 385$)	Luhuo ($n = 361$)	Litang ($n = 560$)	F	*P*
PT	(s)	14.13 ± 0.96▪▽	14.84 ± 1.22▲▽	15.25 ± 0.94▲▽	16.48 ± 1.37▲□▪	284.130	< 0.001
APTT	(s)	36.4 ± 1.92□▪▽	38.16 ± 1.58▲▽	39.12 ± 1.86▲▽	41.91 ± 3.10▲□▪	393.243	< 0.001
TT	(s)	18.28 ± 1.43□▪▽	19.72 ± 1.33▲▪▽	20.62 ± 1.48▲□▽	21.69 ± 1.99▲□▪	294.570	< 0.001
FIB	(g/L)	3.17 ± 0.61▪▽	3.20 ± 0.06▪▽	3.47 ± 0.37▲□	3.52 ± 0.69▲□	32.160	< 0.001

Table 5. Comparison of indicators among male participants in different regions. "▲" indicates significant difference compared to Guza; "□" indicates significant difference compared to Kangding; "▪" indicates significant difference compared to Luhuo; "▽" indicates significant difference compared to Litang.

Indicator		Guza ($n = 266$)	Kangding ($n = 595$)	Luhuo $n = 488$	Litang ($n = 575$)	F	*P*
PT	(s)	13.90 ± 0.82□▪▽	14.29 ± 0.97▲▽	14.58 ± 1.03▲▽	16.06 ± 1.66▲□▪	292.575	< 0.001
APTT	(s)	35.62 ± 2.49□▪▽	36.55 ± 2.48▲▽	36.97 ± 3.08▲▽	39.48 ± 5.57▲□▪	88.905	< 0.001
TT	(s)	17.87 ± 1.38□▪▽	18.55 ± 1.07▲▪▽	19.35 ± 1.40▲□▽	21.40 ± 2.11▲□▪	453.364	< 0.001
FIB	(g/L)	3.04 ± 0.59□▪▽	3.13 ± 0.11▲▪▽	3.19 ± 0.53▲□▽	3.28 ± 0.71▲□▪	16.722	< 0.001

Table 6. Comparison of indicators among female participants in different regions. "▲" indicates significant difference compared to Guza; "□" indicates significant difference compared to Kangding; "▪" indicates significant difference compared to Luhuo; "▽" indicates significant difference compared to Litang.

and Kangding and significant differences for the remaining pairwise comparisons. For TT and FIB, the sequence was Litang > Luhuo > Kangding > Guza, with significant differences in all pairwise comparisons (Table 6).

Discussion

In the human hematological system, coagulation, fibrinolysis, and anticoagulation are interconnected and mutually regulated[4]. These processes involve a series of complex biochemical reactions[5], among which PT, TT, APTT, and FIB are key indicators. PT reflects the extrinsic pathway of coagulation and is mainly used to evaluate blood hypercoagulability and the efficacy of anticoagulant therapy[6]. TT is an indicator of the common coagulation pathway that reflects the extent of fibrinogen degradation and is used to evaluate blood hypercoagulability and the efficacy of anticoagulant therapy[7]. APTT reflects the intrinsic pathway of coagulation and is primarily used to evaluate the risk of blood hypercoagulability and thrombotic disorders[8]. FIB is a key protein in blood coagulation and a major target of the anticoagulation system[9]. It is a crucial factor that reflects blood hypercoagulability and thrombosis. Blood coagulation, fibrinolysis, and anticoagulation are the key processes in the maintenance of vascular integrity and blood fluidity[10]. Attaining a balance among these three processes is critical to human health; an imbalance may lead to the pathogenesis of various diseases, including thrombosis and bleeding disorders[11,12].

In high-altitude and hypoxic environments, the human body exhibits elevated red blood cell (RBC) and hemoglobin (HGB) levels[13]. The compensatory phenomenon known as high-altitude polycythemia (HAPC)[14], which is predominantly characterized by elevated RBC, is a physiological change that occurs when the human body adapts to high-altitude environments. Higher altitudes are associated with more pronounced HAPC[15]. An increase in RBC count can lead to higher blood viscosity and increased platelet adhesion and factor VIII-related antigens[2]. Hypoxia can also damage vascular endothelial cells[16]and activate the intrinsic and extrinsic pathways of coagulation, thereby promoting blood hypercoagulability[4,17].

Furthermore, a hypoxic plateau environment can cause platelet activation, trigger the intrinsic coagulation system, and contribute to the consumption of coagulation factors[18]. Animal experiments[19,20]have also demonstrated that the expression levels of extrinsic and intrinsic coagulation factors are reduced in the hypoxic environment of plateaus. Therefore, we believe that a hypoxic plateau environment can give rise to coagulopathies[21,22], resulting in the gradual increase in APTT, TT, and PT with increasing altitude[22,23]. In addition, the compensatory increase in RBC and blood viscosity can lead to the relative suppression of fibrinolysis[12], which contributes to a hypercoagulable and hypofibrinolytic state[24], thereby resulting in higher FIB values than those in the population living in plain regions[25]. Regarding the impact of high altitudes and hypoxia on individuals of different sexes, hypoxic environments stimulate the production of erythropoietin (EPO)[26], which induces the formation of erythroid progenitors by hematopoietic stem cells, thereby promoting the increase in RBC levels[27]. As androgens can promote EPO secretion[28], the changes in relevant indicators were more pronounced among male participants than among female participants at the same altitude. These results indicate that the existing reference ranges of coagulation indicators for adults established in plain regions are not suitable for healthcare diagnosis and treatment of populations living in plateau areas.

Our findings revealed that the PT, TT, APTT, and FIB values of male participants were significantly higher than those of female participants at the same altitude. We believe that this phenomenon is related to the secretion of male androgens, which promote an increase in EPO. Analysis of the same indicators at different altitudes showed that the PT, TT, APTT, and FIB values increased gradually as altitude increased. After analyzing the ranges of the relevant indicators, we found that the upper limits of all reference ranges (except for PT, TT, APTT, and FIB values of individuals aged < 40 years in Guza; FIB values of those aged < 60 years in Guza and Kangding; and PT values of those aged < 40 years in Kangding) exceeded the existing range of normal values[29]. Based on these findings (Figs. 1, 2, 3, 4, 5, 6, 7 and 8), we can infer that PT, TT, APTT, and FIB values will increase with increasing altitude and age. Long-term exposure to the hypoxic environment of high-altitude areas can cause continuous damage to the inner wall of blood vessels[30], and the degree of this damage is significantly positively correlated with the length of time an individual lives in this hypoxic environment[31,32]. Once the inner wall of the blood vessels is damaged, the intrinsic and extrinsic coagulation pathways can be rapidly activated, thereby promoting a hypercoagulable state[33]. To maintain normal blood fluidity and ensure that all organs of the body can receive sufficient blood supply, the body automatically activates regulatory mechanisms that prolong the coagulation time[34]. Therefore, when observing participants of the same altitude, the cumulative time an individual lives in the hypoxic environment increases with age, resulting in a gradual prolongation of the coagulation time parameters. This confirms that the existing reference ranges of coagulation indicators for adults established in plain regions are not suitable for healthcare diagnosis and treatment of populations living in plateau regions.

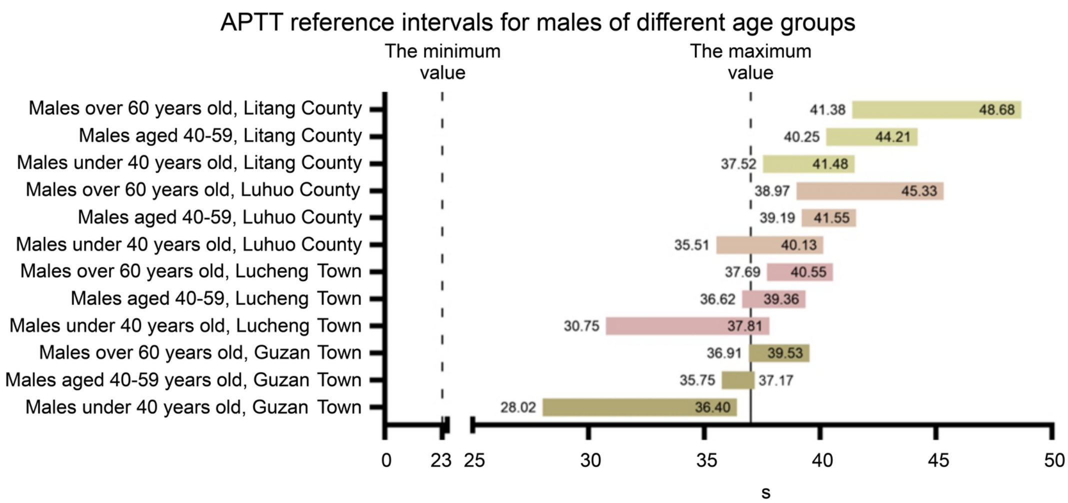

Fig. 1. APTT reference intervals for males of different age groups. APTT, activated partial thromboplastin time.

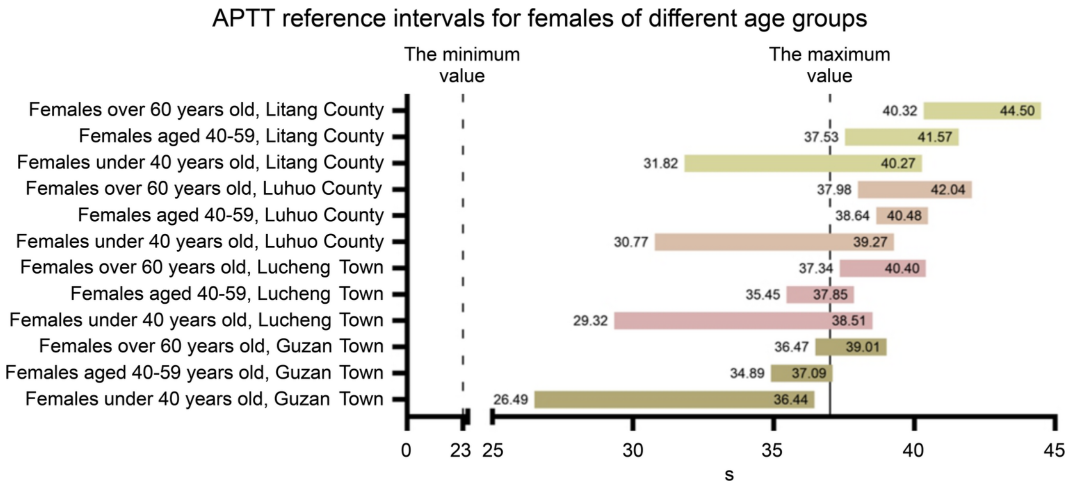

Fig. 2. APTT reference intervals for females of different age groups. APTT, activated partial thromboplastin time.

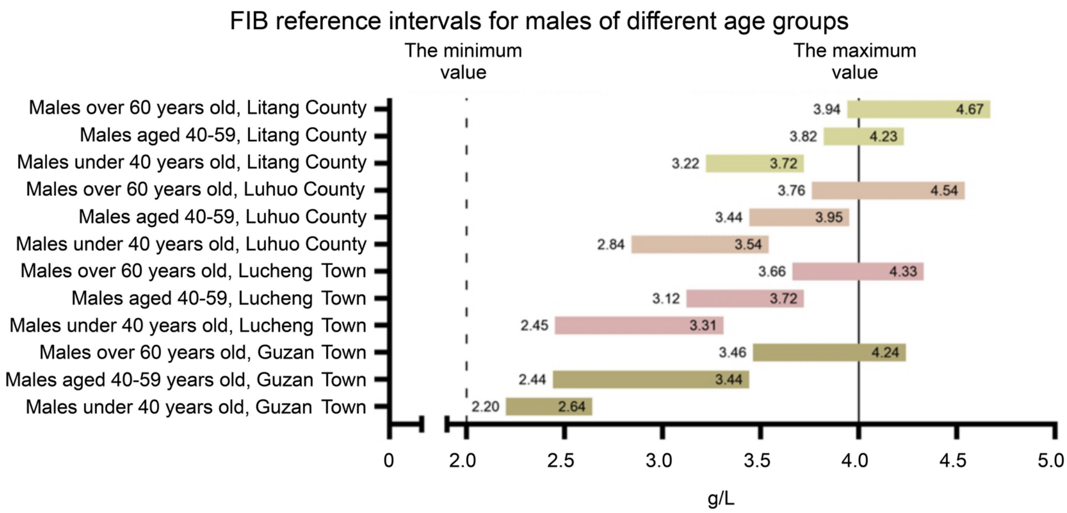

Fig. 3. FIB reference intervals for males of different age groups. FIB, fibrinogen.

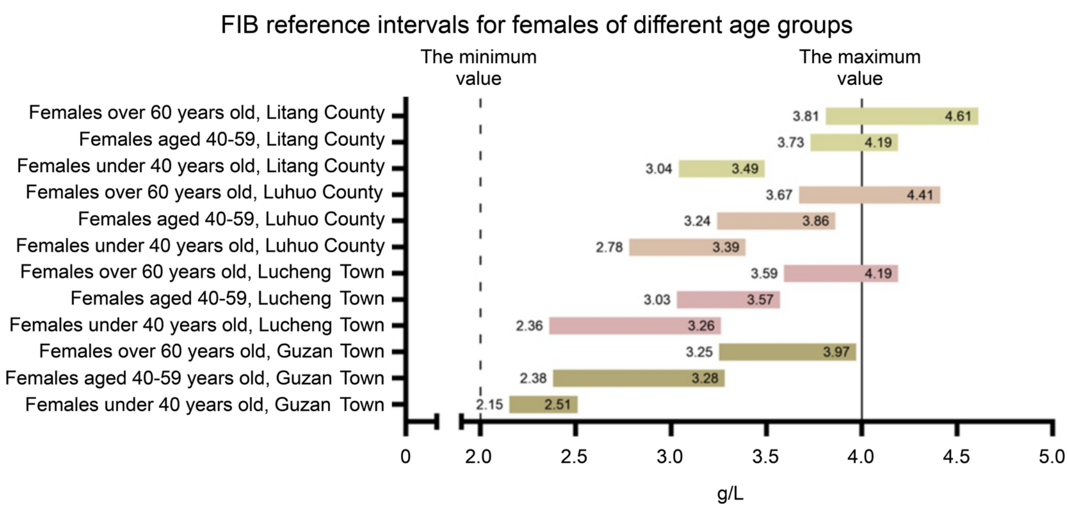

Fig. 4. FIB reference intervals for females of different age groups. FIB, fibrinogen.

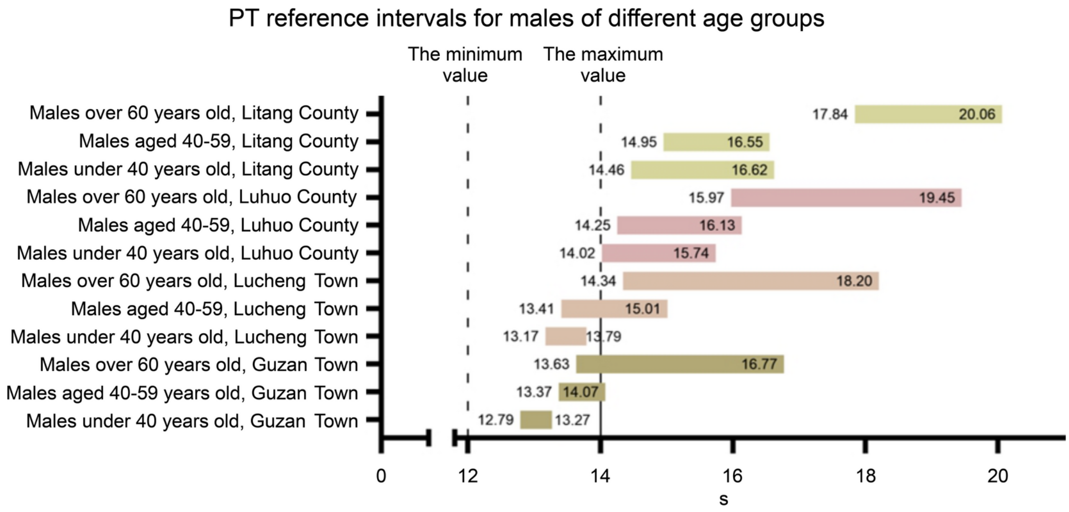

Fig. 5. PT reference intervals for males of different age groups. PT, prothrombin time.

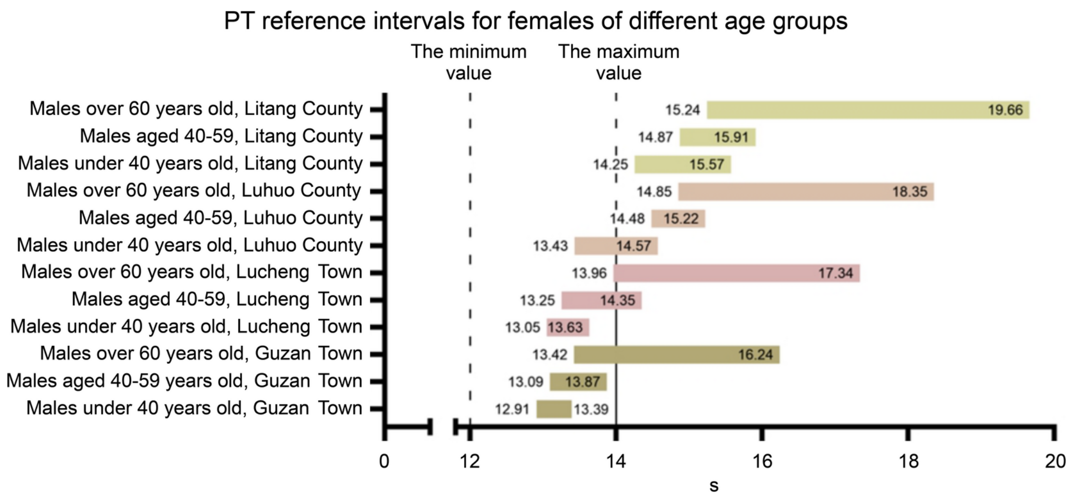

Fig. 6. PT reference intervals for females of different age groups. PT, prothrombin time.

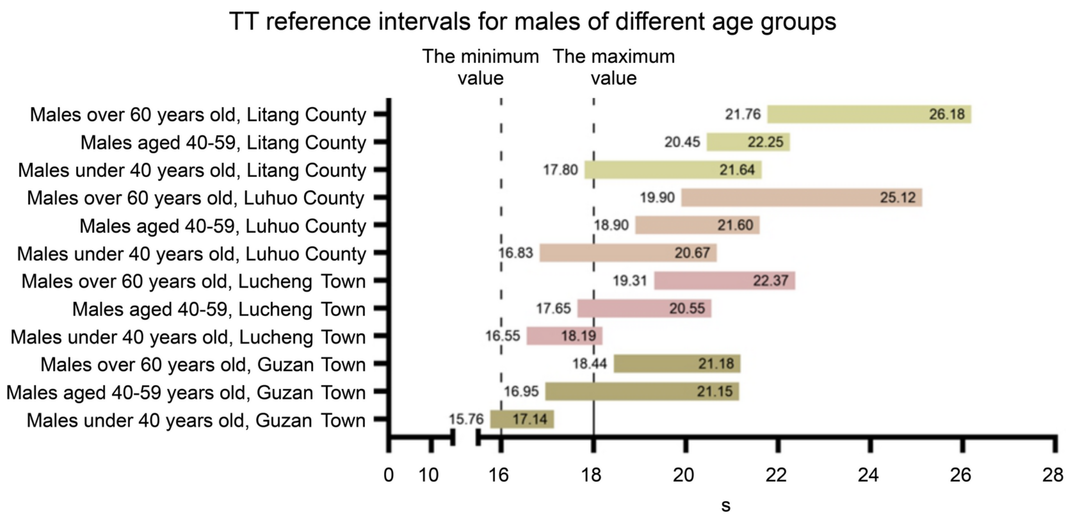

Fig. 7. TT reference intervals for males of different age groups. TT, thrombin time.

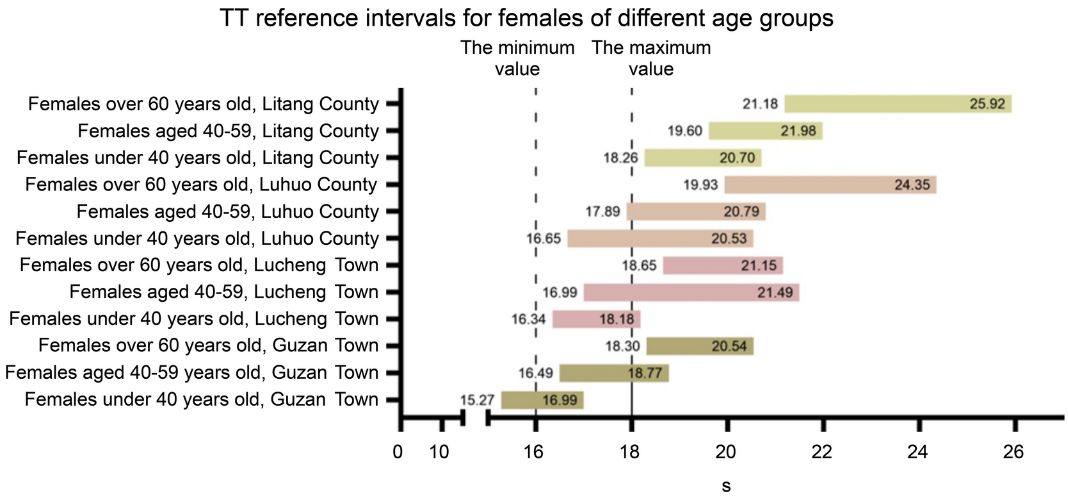

Fig. 8. TT reference intervals for females of different age groups. TT, thrombin time.

This study has certain limitations. First, the effects of different races were not fully considered. Due to genetic differences and varying lifestyles, different races may have different blood indicators. For example, previous research has shown that a particular race that lives at the highest altitude and has the longest history of adaptation has developed a comprehensive oxygen supply and utilization system effective at the level of the entire body, organs, cells, and molecules. This situation has enabled them to demonstrate the most remarkable adaptability to the plateau environment[35]. The western Sichuan plateau is also inhabited by multiple ethnic groups such as the Han, Qiang, and Yi. However, this study did not differentiate between the local population by ethnicity; therefore, the results may differ from the actual situation. Second, the study did not consider factors such as season and temperature, which are known to significantly influence both cardiovascular health and associated blood indicators[36]. Therefore, to achieve accurate results, the influence of season and temperature cannot be ignored. Third, there is a lack of continuity in the choice of altitudes. In the future, we plan to compare and classify individuals based on their ethnicity and the blood collection season, fully incorporating ethnic and seasonal factors. Additionally, we will refine the altitude points to achieve high precision and personalization.

In summary, we believe that in high-altitude environments, sex, age, and altitude can alter coagulation indexes, in addition to other factors[37,38]. China has a vast territory, a complex variety of climate types, and a rich ethnic composition. Especially in high-altitude areas, the diversity of the ecological environment and lifestyle further exacerbates the complexity of physiological indexes. A single coagulation index simply cannot meet the actual needs in such complex and variable situations. Therefore, there is an urgent need for more accurate and targeted coagulation indexes to assist in the diagnosis of local patients' diseases, the formulation of treatment plans, and the planning of public health strategies, in order to improve the quality and efficiency of medical services in plateau areas and safeguard the health and well-being of residents. For example, when diagnosing altitude-specific diseases closely related to coagulation function, such as high-altitude pulmonary edema and high-altitude cerebral edema, accurate coagulation indexes can help doctors judge the condition more timely and accurately and improve patient survival. When formulating public health strategies in plateau areas, these indexes can also provide a scientific basis for preventing the occurrence of thrombotic diseases and optimizing the allocation of medical resources.

Data availability

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

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Author contributions
Qing Yuan and YanWu Liu wrote the manuscript. All authors were involved in data collection. JiaYu Liu, MingXia Tang, and Jian Yang performed the analyses and interpreted data. ShuZhi Zhou, Ling Zhang, JunWu Du, KongJie Yang, and XiaoXue Li gathered relevant information and prepared the tables in the paper. Zhenglin Huang critically revised the manuscript for important intellectual content. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
This study was approved by the Ethics Committee of Yaan People's Hospital [2023 011]. Written informed consent was obtained from all participants.

Additional information
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