

ORIGINAL ARTICLE

Reference Intervals of Red Blood Cell Parameters in Healthy Adults of the Chinese Population in High-Altitude Areas

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SUMMARY

Background: Typically, red blood cell (RBC)-based parameters and platelet count vary with age and gender. Moreover, these variations may happen due to geographical origin and ethnicity. Nevertheless, the reference intervals (RIs) in healthy Tibetan adult populations are limited. This study aimed to determine the RIs for RBC parameters and platelet count (PLT) in Tibetans living at various high altitudes.

Methods: Initially, a total of 1,104 subjects were randomly recruited from Ali, Shigatse/Lhasa, and Nyingchi of Tibet. Further, RBC count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and PLT were measured using an automated hemacytometer (Sysmex XN-2100). Then, multiple linear regression and variance component analyses were employed to assess the effect of gender, age, and altitude on RBC parameters and PLT count. Finally, RIs were established using non-parametric methods and compared with those currently used in China.

Results: The notified blood parameters (RBC, HGB, HCT, MCV, MCH, and MCHC) were significantly higher in males than in females, while PLT count was higher in females than males. Notably, some parameters, including RBC, HGB, and MCHC values, increased with increasing altitude, while MCHC and PLT parameters increased with age. The RIs for RBC parameters and PLT were finally determined according to gender and altitude in healthy Tibetan adults.

Conclusions: In summary, the specific RIs for RBC parameters and PLT among Tibetans were significantly different, emphasizing the need to consider gender and geographical origin in the clinical use of IRs of hemogram parameters.

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KEYWORDS

platelet count, high altitudes, reference intervals

INTRODUCTION

Typically, red blood cell (RBC) parameters are one of the most commonly determined blood-related characteristics in clinical practice. Nevertheless, accurate and applicable reference intervals (RIs) of RBC parameters are essential for health assessment, disease diagnosis, and monitoring of treatment effectiveness. The International

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Organization for Standardization (ISO) and the Clinical and Laboratory Standards Institute (CLSI) have published ISO15189 and CLSI C28-A, encouraging every lab to establish its own reference intervals (RIs) [1]. Notably, the RIs for RBC parameters and platelet (PLT) count vary with age, gender, geographical origin, and ethnicity [2,3].

Habitants in the Tibetan plateau with an average altitude of more than 4,000 m have a different living environment, which is often characterized by its hypobaric hypoxia condition. The most significant phenomena in adapting to the hypoxia environment are the increase of bone marrow hematopoiesis and peripheral blood erythropoiesis [4,5]. The long-term adaptation may lead to altered RBC parameters in Tibetans, which are different from those in plain areas. Previous reports [6,7] established the RIs for blood cells from local people in the Kangma and Lhasa regions of Tibet. Nevertheless, representative RIs of RBC parameters among healthy Tibetans living at various high altitudes in Tibet remain unexplored.

Motivated by these aspects, this study aimed to establish the RI values for the RBC parameters and PLT count in healthy Tibetan adults living in the multi-altitude level of Tibet Autonomous Region in China.

MATERIALS AND METHODS

Study population

The collected samples taken from subjects from September 2016 through August 2018 from Ali, Shigatse/Lhasa, and Nyingchi of Tibet were analyzed. This study was approved by the Ethics Committee of the People's Hospital of Tibet Autonomous Region (approval no. ME-TBHP-2017-021). Notably, all the subjects provided a signed consent form.

To recruit the subjects for the study, a standard questionnaire was designed for participants at Ali (altitude I: 4,298 - 4,352 m), Shigatse/Lhasa (altitude II: 3,670 - 3,835 m), and Nyingchi (altitude III: about 2,900 m) of Tibet. The recruited subjects ($n = 1,128$, 633 female and 495 male), with a median age of 40 years (ranging from 19 - 87 years), were deemed healthy to recruit for the study. The inclusion criteria were set as follows: 1) subjects should be Indigenous Tibetans; 2) subjects who were ≥ 19 years of age; 3) subjects who had lived in Tibet for > 1 year; and 4) subjects who self-reported that they were in good health and had no major organ or system disease. To this end, the exclusion criteria were set as follows: 1) subjects who provided incomplete basic information; 2) subjects who had a history of any malignancy, use of any medication, a smoking history, alcohol intake ≥ 75 g/day, smoking ≥ 20 cigarettes daily, recent episodes of illness in the past 4 weeks, history of hospitalization in the past 6 months, or blood donation in the previous 3 months; 3) subjects who were pregnant or within 1 year after childbirth; 4) subjects who possessed a carrier state of hepatitis B, hepatitis C, or

human immunodeficiency virus and sample collection after night shift or violent motion. It should be noted that the well-trained colleagues assisted the participants in completing the questionnaires.

Sample collection and laboratory assays

Prior to sample collection, all subjects were requested to fast for 10 - 12 hours and to avert night shifts or strenuous exercise 24 hours before tests. After relaxing for 10 to 15 minutes, venous blood samples of subjects were collected into tubes with K2-ethylenediaminetetraacetic acid (EDTA) as an anticoagulant by well-trained nurses. The collected samples were stored at room temperature and analyzed within 6 hours after blood sampling. The RBC parameters and platelet count (PLT) were measured by an automated hemacytometer (Sysmex XN-2100). The following hematology values were analyzed, including RBC count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and PLT. Moreover, alanine aminotransferase (ALT), albumin (Alb), glucose (Glu), and creatinine (Cr) were analyzed using an AU 5800 automatic biochemical analyzer (Beckman Coulter).

Quality control

Prior to analysis, all records of quality control were reviewed to ensure the reliability of the determined results. A Sysmex XN-2100 automated hemacytometer (Sysmex Corporation, Kobe, Japan) and its reagents and calibrators were used for measuring RBC parameters and PLT count. The parameter settings, calibration, and detection procedures were conducted in strict accordance with the standard operating procedures according to the manufacturer's instructions. Notably, our laboratory is accredited by the ISO-15189. Moreover, it participates in annual external quality assessment by the Clinical Laboratory Center of the National Health Commission (China).

Statistical analysis

Microsoft Excel 2016 (Redmond, WA, USA), SPSS 23.0 software (IBM, Armonk, New York, United States), R programming language (V 4.4.0), and the Medcalc Statistical software version 22.009 (Ostend, Belgium) were used for data analysis and presentation. Non-parametric methods were used to establish the RIs of RBC parameters and PLT count. These values were calculated using the 2.5th and 97th percentiles. Moreover, the 5th percentiles of the distribution included 95% of the reference sample group data and 90% CIs for both lower and upper reference limits according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [1]. The normality test of all data was analyzed using the Shapiro-Wilk test and frequency distribution histograms. The Dixon-Reed method was used to identify outliers [8,9]. The values of almost all parameters that do not follow the Gaussian distribution were

Table 1. A summary of participant characteristics according to gender [M (P25-P75)].

Variables	Male (n = 482)	Female (n = 622)	Total (n = 1,104)	Z	p-value
Age (years)	39 (30 - 49)	40 (30 - 51)	39.5 (30 - 50)	0.763	0.445
BMI (kg/m ²)	24.58 (22.07 - 27.36)	23.44 (21.09 - 26.29)	23.89 (21.46 - 26.81)	4.039	< 0.001
SBP (mmHg)	120 (110 - 130)	112 (104 - 128)	116 (106 - 130)	4.504	< 0.001
DBP (mmHg)	80 (70 - 90)	76 (70 - 86)	79 (70 - 88)	4.476	< 0.001
ALT (U/L)	34 (23 - 51)	20 (14 - 29)	25 (17 - 40)	12.72	< 0.001
Alb (g/L)	49 (47 - 51)	47 (45 - 49)	48 (46 - 50)	9.792	< 0.001
Glu (mmol/L)	4.7 (4.2 - 5.1)	4.5 (4.1 - 4.9)	4.59 (4.2 - 5)	4.054	< 0.001
Cr (μmol/L)	82 (75.5 - 89.0)	63 (58.0 - 68.0)	69 (61 - 81)	23.571	< 0.001

Alb - albumin, ALT - alanine transaminase, BMI - body mass index, Cr - creatinine, DBP - diastolic blood pressure, Glu - glucose, SBP - systolic blood pressure.

Table 2. A summary of the population demographics of individuals enrolled in this study.

Index	Number	Gender		Age (years)			
		Male	Female	19 - 29	30 - 39	40 - 49	≥ 50
Altitude I	369	176	193	115	122	87	45
Altitude II	413	190	223	86	98	96	133
Altitude III	322	116	206	57	74	89	102
Total	1,104	482	622	258	294	272	280

Altitude I - Ali (altitude: 4,298 - 4,352 m), altitude II - Shigatse/Lhasa (altitude: 3,670 - 3,835 m), altitude III - Nyingchi (altitude: ~ 2,900 m).

subjected to the nonparametric Mann-Whitney U test to compare gender groups. The nonparametric Kruskal-Wallis analysis was used to compare altitude groups and age groups. The standardized regression coefficients of gender, altitude, and age were calculated by multiple linear regression. Moreover, the variance component model was used to calculate the variation of hemogram parameters in gender, altitude, and age, referred to as standard deviation or coefficient of variation. The residual standard deviation in the variance component model represented the individual variation of RBC parameters and PLT. The standard deviation ratio (SDR) was expressed as (SD_{sex}, SD_{altitude}, SD_{age})/SD_{residual} to determine whether the RI needed to be partitioned according to gender, altitude, or age. According to previous reports, an SDR of > 0.4 indicated the requirement to establish partitioned RIs [10,11]. A two-sided p < 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics of enrolled participants in the study

Initially, a total of 1,128 Tibetans who met the inclusion and exclusion criteria were enrolled in our study. Among them, 1,104 participants were finally examined to establish RIs for RBC parameters and PLT count after eliminating RBC, HGB, HCT, MCV, MCH, MCHC, and PLT outliers by the Dixon-Reed method and incomplete data. The notified characteristics are shown in Table 1. These findings showed statistically significant differences between genders for all the variables except for age (p = 0.445). Moreover, the body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), ALT, Alb, Glu, and Cr values were significantly higher in male subjects than in female subjects (p < 0.001).

Effect of gender, altitude, and age on RBC parameters and PLT count

The population demographics of recruited individuals enrolled in this study are shown in Table 2. Further, the

Table 3. The data show the effect of gender, altitude, and age on RBC parameters and PLT values.

Index	Gender			Altitude					Age						
	β	p	SDR	Al 1	p	Al 2	p	SDR	Ag1	p	Ag2	p	Ag3	p	SDR
RBC	-0.681	< 0.001	0.697	-0.375	< 0.001	-0.110	0.0014	0.313	0.079	0.049	0.084	0.041	0.137	0.001	0.097
HGB	-26.702	< 0.001	0.889	-15.075	< 0.001	-4.464	< 0.001	0.407	1.927	0.115	3.167	0.012	6.223	< 0.001	0.140
HCT	-6.760	< 0.001	0.811	-3.265	< 0.001	0.323	0.266	0.346	0.876	0.010	1.237	0.000	2.147	< 0.001	0.178
MCV	-1.240	< 0.001	0.131	0.266	0.417	1.254	< 0.001	0.138	0.314	0.379	0.943	0.010	1.744	< 0.001	0.142
MCH	-1.120	< 0.001	0.300	-0.587	< 0.001	-0.149	0.239	0.130	-0.098	0.509	0.152	0.316	0.418	0.006	0.090
MCHC	-7.960	< 0.001	0.390	-7.834	< 0.001	-6.636	< 0.001	0.324	-2.336	0.005	-2.048	0.017	-1.930	0.026	0.094
PLT	16.982	< 0.001	0.159	-4.987	0.263	2.220	0.594	0.062	-17.001	0.001	-13.861	0.005	-37.681	< 0.001	0.197

B - standardized regression coefficient, female is the reference for gender groups. Al 1 and Al 2 are the dummy variable of altitude, Ali (altitude: 4,298 - 4,352 m) is the reference level, Al 1 stands for Shigatse/Lhasa relative to Ali, and Al 2 stands for Nyingchi relative to Ali. A1, A2, and A3 are the dummy variable of age, 19 - 29 years is the reference level, A1 stands for 30 - 39 years relative to 19 - 29 years, A2 stands for 40 - 49 years relative to 19 - 29 years, A3 stands for age 50 or older relative to 19 - 29 years. Effect of gender, altitude, and age on RBC parameters and PLT.

Table 4. The data show RI values of RBC parameters and PLT count.

Parameter	Group	Median	Lower limits of RI	90% CI	Upper limits of RI	90% CI	WS/T 405-2012
RBC ($\times 10^{12}/L$)	Male	5.5	4.42	4.32 - 4.50	6.83	6.68 - 7.03	4.3 - 5.8
	Female	5.4	4.37	4.28 - 4.44	6.78	6.65 - 7.03	3.8 - 5.1
HGB (g/L)	Male	168.0	127.07	125.00 - 132.00	215.77	208.00 - 224.00	130 - 175
	Altitude I	168.0	127.00	122.00 - 137.00	216.00	207.00 - 251.00	
	Altitude II	173.0	128.78	125.00 - 138.00	224.00	210.00 - 234.00	
	Altitude III	165.0	125.36	120.34 - 130.43	205.86	200.06 - 221.70	
	Female	165.5	125.57	123.00 - 129.00	211.85	207.00 - 218.00	115 - 150
	Altitude I	153.0	121.00	115 - 125	194.45	185.00 - 211.00	
	Altitude II	171.0	128.60	125.00 - 138.00	216.80	211.00 - 236.00	
Altitude III	168.0	127.53	123.00 - 134.00	209.48	202.00 - 228.00		
HCT (%)	Male	49.0	39.00	38.60 - 40.00	61.77	60.00 - 64.70	40 - 50
	Female	48.1	38.80	37.60 - 39.20	60.74	59.80 - 63.40	35 - 45
MCV (fL)	Total	89.3	79.60	77.60 - 80.20	97.30	96.80 - 98.10	82 - 100
MCH (pg)	Total	30.6	25.70	25.30 - 25.90	33.70	33.50 - 34.00	27 - 34
MCHC (g/L)	Total	341.0	318.00	316.00 - 319.00	364.00	361.00 - 371.00	316 - 354
PLT ($\times 10^9/L$)	Total	219.0	117.62	111.00 - 125.00	355.00	345.00 - 367.00	125 - 350

source variations of each RBC parameter and PLT were analyzed (Table 3). As shown in Figures 1 and 2, gender has apparently shown a substantial effect on RBC, HGB, HCT, MCV, MCH, MCHC, and PLT count, indicating that male subjects presented higher RBC, HGB, HCT, MCV, MCH, and MCHC levels than female subjects. Nonetheless, PLT levels were lower in male subjects than in female subjects.

Moreover, it was observed that RBC, HGB, and MCHC values showed an increase with altitude. The HCT and

MCHC levels were lower in Nyingchi (altitude III) than in Shigatse/Lhasa (altitude II) and Ali (altitude I). Contrarily, the MCV level was higher in Shigatse/Lhasa than in Nyingchi and Ali. Nevertheless, the distribution of PLT count during altitudes showed no significant difference ($p = 0.114$). Moreover, Tibetans aged over 50 years presented higher HCT levels than those aged between 19 and 29 years ($p < 0.05$). In addition, MCV levels were decreased with an increase in the age of the subject ($p < 0.001$). Contrarily, the MCHC and PLT

Reference Intervals of Red Blood Cell Parameters

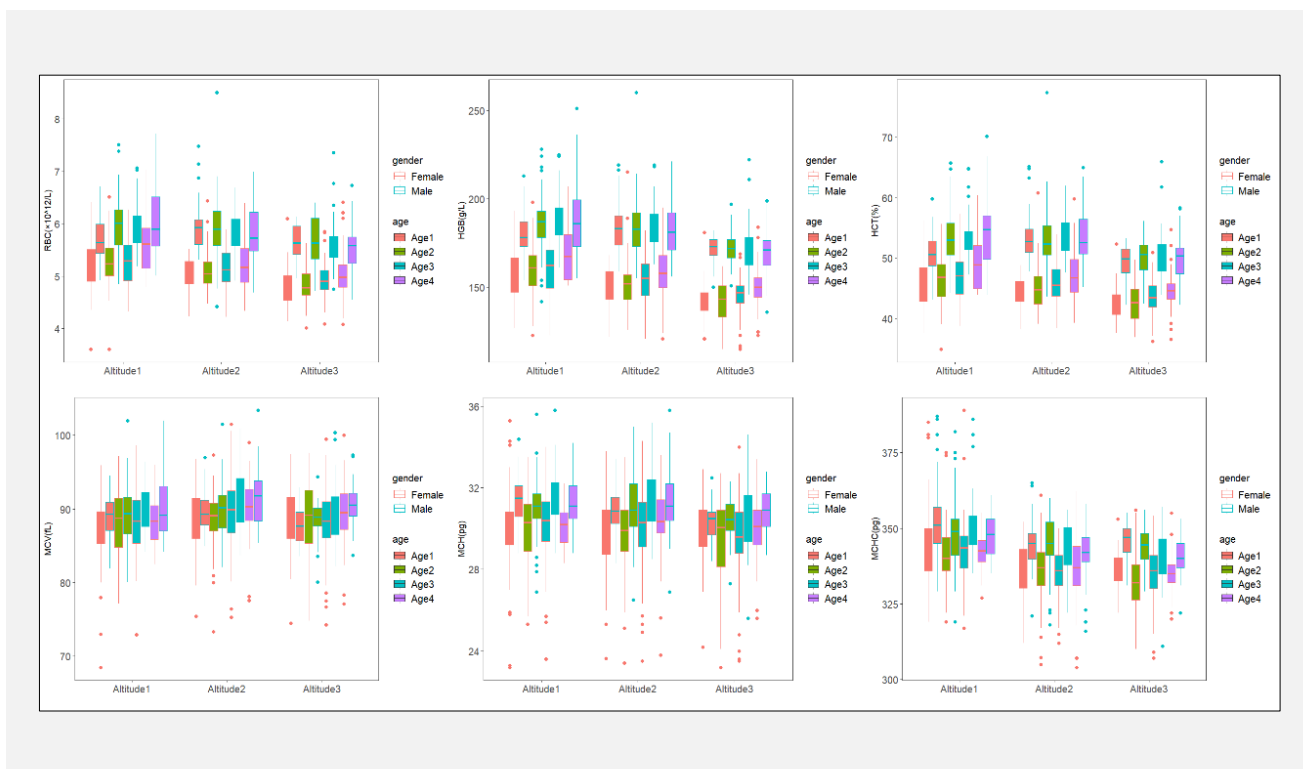


Figure 1. The graphs show the distribution of RBC parameters in the Tibetan population by gender, altitude, and age.

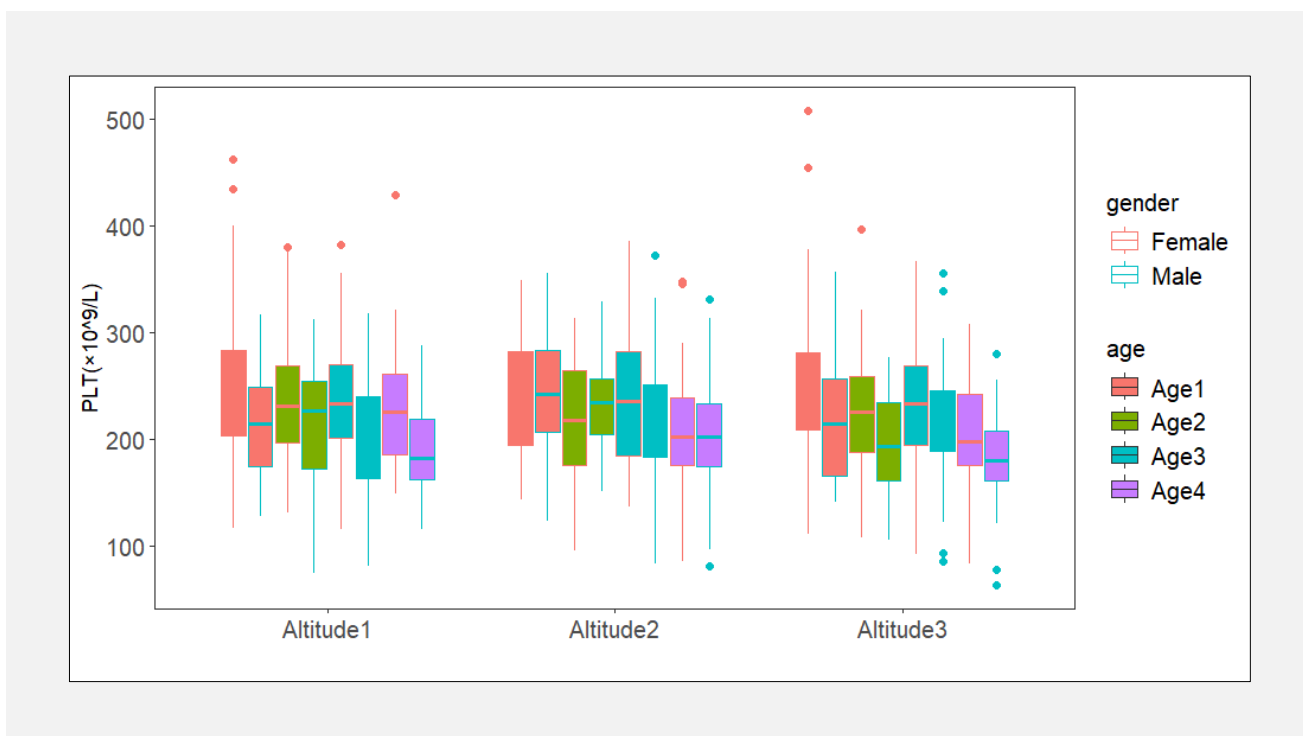


Figure 2. The graph shows the distribution of PLT count in the Tibetan population by gender, altitude, and age.

counts showed an increase with age ($p < 0.001$), while RBC, HGB, and MCH levels presented less influence with age. The results of multiple linear regression and the variance component analysis are presented in Table 3. Together, these findings indicate that gender-specific RIs for RBC, HGB, and HCT should be considered with $SDR > 0.4$. Moreover, the RIs for HGB should be partitioned by altitude with $SDR > 0.4$.

RIs of RBC parameters and PLT for the population at high altitude

Finally, the non-parametric methods were used to establish the RI values of RBC parameters and PLT count. The specific results are shown in Table 4. The resultant RI values of HGB were divided by gender and altitude, while RIs for RBC and HCT were divided by gender. Compared with the RIs provided by the Ministry of Health, PRC (WS/T 405-2012), the upper limits of the obtained RIs for RBC, HGB, and HCT were higher in this study.

DISCUSSION

Typically, the obtained RI values of blood parameters relevant to the local population may serve as a reliable reference for the assessment of health status and diagnosis of diseases. To adapt to the hypoxic environment, the indigenous Tibetans living in the hypoxic (low-oxygen) environment for an extended time demonstrate an increased number of RBCs, platelet aggregation, and HGB levels [12,13]. In the current study, RI values for RBC parameters and the platelet count were established for healthy indigenous Tibetan adults living in a hypoxic environment. To the best of our knowledge, the multi-altitude study, for the first time, collected health information and blood samples from Tibetan participants.

In our study, it was observed that there was a statistically significant difference between all RBC parameters of male and female adults, which was consistent with reported studies in Japan [3] and Saudi Arabia [10]. Male subjects showed higher values for most RBC parameters (RBC, HGB, HCT, MCH, and MCHC) than female subjects, which is consistent with the reported studies [14-16]. These findings might be explained by the inhibitory effect of estrogen on erythropoiesis and menstrual blood loss in adult female subjects. Moreover, these parameters of RBCs increased with the rise in altitude. To adapt to the low oxygen atmosphere at a higher altitude, hypoxia-inducible factor-1 alpha (HIF-1 α) and erythropoietin could increase RBC parameters. Together, these differences indicate the importance of the establishment of gender-specific and region-specific RIs for the high-altitude region of China.

Moreover, age is one of the important factors that significantly influence the RBC parameters. In this study, it was observed that the HCT value was lower in healthy individuals of 19 - 29 years than those of ≥ 50 years.

Moreover, MCHC value was higher in healthy individuals at 19 - 29 years of age than ≥ 50 years. However, age-specific changes in the RBC, HGB, and MCH values were absent in adult Tibetans in our study. It should be noted that these results were consistent with a previous study from Hawaii [17]. However, the findings of this study were inconsistent with some previous studies reported in China [18,19]. Notably, these differences among studies might be due to the differences in ethnicity and geographic location, population reference, methodology, or equipment, among others.

In our study cohort of 1,104 individuals, it was observed that MCV levels showed an age-related increase over the entire age range and were higher in male subjects than in female subjects. These results were consistent with the previously reported studies [20-22]. Notably, the possible biological explanations for this trend included the decrease in the lifespan of RBC with age, the increasing frequency of age-related clonal hematopoiesis, and disorders in elderly subjects, among others. At the same time, the MCV value in the medium-altitude area (Shigatse/Lhasa) was higher compared with the low-altitude area (Nyingchi) and high-altitude area (Ali). These findings might suggest that the degree of hypoxia could exhibit less effect on MCV.

Using a cutoff of 0.4 as a threshold, SDRs for between-age differences were below the threshold in all the examined RBC parameters. Moreover, SDR for between-gender differences exceeded the level in reference parameters only for RBC, HGB, and HCT. In addition, SDR for between-altitude differences exceeded the HCT level. From our study, it was evident that female subjects showed a significantly higher PLT count compared to male subjects in Tibet. Contrarily, the PLT count showed a decreasing trend with an increase in age. These findings were in agreement with the previously reported relevant studies [7,23,24]. Moreover, the upper and lower limits of PLT count in our study were consistent with the currently used RIs in China [7]. However, no significant difference among the selected three areas for PLT count was observed.

CONCLUSION

In summary, our research has demonstrated a multi-altitude cross-sectional study for the first time to set the RI values of RBC parameters and PLT count in a healthy Tibetan adult population at the plateau. The important differences in the hematological parameters based on gender, altitude, and age were observed. Significant differences were found when comparing the currently used RIs in China. These findings could support the need to establish gender- and/or altitude-specific hematological reference intervals for people living in high-altitude areas.

Ethical Approval Statement:

This study has been approved by the Ethics Committee of the People's Hospital of Tibet Autonomous Region (approval No. ME-TBHP-2017-021). All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Every patient provided an informed consent form.

Availability of Data and Materials:

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Declaration of Interest:

The authors declare that they have no conflicts of interest.

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