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Prevalence and Impact of Chronic Mountain Sickness on Quality of Life Among Urban Residents in Northwestern Sichuan, China: A Cross-Sectional Study

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Article

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Abstract

With rapid urbanization in high-altitude regions, the health impacts of chronic hypoxia on plateau urban residents remain understudied. This study aims to determine the prevalence of chronic mountain sickness (CMS) and its associated factors among urban residents of the Northwestern Sichuan Plateau and further assess the health-related quality of life (HRQoL) in this population. A cross-sectional survey study was conducted in urban residents of the Northwestern Sichuan Plateau aged ≥20 years residing at an altitude of 3500 to 4000 meters. Demographics, physiological parameters, hematological parameters, specified symptoms of CMS were recorded. CMS was diagnosed using the Qinghai CMS score criteria. Propensity score matching (1:3) was performed to adjust for age differences between the CMS group and the group without CMS. A segmented linear regression model was employed to identify the hemoglobin threshold associated with CMS. Multivariable conditional logistic regression was used to evaluate independent associated factors for CMS after age matching. 12-Item Short Form Health Survey (SF-12) was employed to assess the HRQoL in this population. Prevalence of CMS was 20.5% (95% CI: 16.2%-24.8%). Female and hemoglobin (Hb) levels ≥ 186g/L were independent associated factors for CMS after controlling for age with odds ratio (OR) as 3.02 (95% CI: 1.19–7.64) and OR 4.76 (95% CI: 1.41–16.06), respectively. The SF-12 assessment demonstrated significantly impaired physical and mental health status in CMS patients, with a more pronounced deterioration in physical health components. This study enhances understanding of CMS burden and associated factors in plateau urban populations, supporting sustainable development in these areas.

Introduction

Chronic mountain sickness (CMS) is a frequent and potentially fatal chronic condition caused by hypoxia in high-altitude population. It is characterized by excessive erythrocytosis, severe hypoxemia, and, in some cases, moderate to severe pulmonary hypertension. Patients of CMS are disabled with impaired memory, headache, breathlessness, fatigue, disturbed sleep, anorexia, and tinnitus that affect the quality of life. Currently, the most effective treatment for CMS is relocation of the patient to a lower elevation, but this is seldom feasible due to the socioeconomic.

The prevalence of CMS varies considerably across the world, influenced by multiple factors such as altitude of residence, ethnicity, duration of high-altitude residence, among others [1]. The prevalence of CMS ranges from 5–33% [2]. Based on the Qinghai Scoring System published in 2004, a study reported that prevalence of CMS among natives of Spiti Valley in the Greater Himalayas residing at an altitude of 3000–4200 meters was 28.7% [3]. With the progression of urbanization in high-altitude regions, a distinct gradient in socioeconomic status and lifestyle patterns exists between urban populations and pastoral populations. Previous research has indicated that urbanization and associated changes in lifestyle also could have role in development of CMS [4]. Moreover, studies have indicated that the mean Hb concentration of urban populations was higher than that of rural populations in the Andes and the Himalayas, with concomitant differences in oxygen saturation levels [5]. Thus, measuring the burden of CMS among urban population is important for high altitude researchers, clinicians and policy-makers.

However, the role of urbanization in modulating the prevalence of CMS remains poorly understood and reliable epidemiological data from urban populations are notably lacking globally.

The burden, associated factors, and health-related quality of life (HRQoL) of CMS have never been studied among urban populations of the Northwestern Sichuan Plateau in China. Hongyuan County, with an average altitudes of 3500 to 4000 meters, has emerged as a representative high-altitude city on the Northwestern Sichuan Plateau. The present epidemiological study was conducted in urban areas of Hongyuan County. CMS significantly impacts the physical and mental health of high-altitude populations. To effectively assess the health status of urban population at high altitude, particularly CMS patients, we evaluated their physiological function, psychological well-being, daily living activities, and social participation. We utilized the 12-Item Short Form Health Survey (SF-12). This instrument has been widely adopted in epidemiological studies due to its ability to capture both physical and mental health dimensions through 12 concise items, with validated Chinese versions available for local populations.

This study aimed to determine the prevalence of CMS and its associated factors among urban residents in the Northwestern Sichuan Plateau, while assessing their HRQoL. Our findings contribute to supplement the existing epidemiological data on CMS and provide valuable insights for early disease detection and sustainable development of urban populations in plateau regions.

Subjects and Methods

The study population was selected by a random cluster sampling method. The communities of Hongyuan County were listed and were selected using a random number table. From the selected communities, all individuals aged 20 years and above consenting to participate were screened, informed consent from each participant was obtained. After screening, 341 subjects were included in the analysis who met the following criteria: (1) no underlying cardiorespiratory diseases, (2) completed questionnaires, and (3) availability of all laboratory data necessary for CMS diagnosis. The diagnosis of CMS was made using Qinghai CMS scoring criteria. This study was conducted according to the Declaration of Helsinki and approved by the Ethics Review Committee of Mianyang Third People's Hospital.

We designed a standardized questionnaire including questions on the subjects' demographic characteristics, medical history, specified symptoms of CMS and SF-12, a professional research assistant was responsible for conducting face-to-face interviews with subjects and taking detailed records of their information. As per Qinghai CMS scoring system standard operating protocol to document the presence and severity of symptoms and signs related to CMS to maintain the uniformity in scoring CMS symptoms and signs. SF-12 standard scores (NBS) were calculated according to the original scoring manual. All anthropometric measurements followed WHO STEPS protocols. Height and weight were measured in triplicate, respectively, the average of three consecutive measurements was used for analysis. Blood pressure (BP) was measured twice at 5-minute intervals using a daily-calibrated electronic blood pressure monitor, and the average value was taken as the BP value. Heart rate (HR) was

measured in triplicate via 12-lead ECG after 15-minute rest, the median value was used to exclude arrhythmic outliers. Peripheral oxygen saturation (SpO_2) was measured after 5 minutes of seated rest using a handheld pulse oximeter (Nyco Pulse O2, Nyco Devices, Switzerland) with finger probe. Each subject were subjected to blood tests in a fasting state to estimate Hb level using an automated hematology analyzer (Sysmex XN-9000, Sysmex Corporation, Japan) at Hongyuan County People's Hospital.

Assuming a CMS prevalence of 10% based on the reported range of 5%-33% in previous studies [2], the minimum sample size required to estimate the prevalence with 95% confidence and a 5% margin of error was 138. Using a cluster correction factor of 2 [6], the approximate sample required was about 270. Statistical analyses were performed in R software (version 4.4.3). Continuous variables were described as mean ± standard deviation (SD) if normally distributed and compared using the *t*-test. Non-normally distributed continuous variables were expressed as median (interquartile range [IQR]) and analyzed using the Mann–Whitney *U* test. Categorical variables were presented as count and proportions (*n*, %) and compared using the Chi-square test. To minimize age-related confounding, we performed 1:3 nearest-neighbor propensity score matching (PSM), resulting in a final cohort of 223 subjects for univariable analysis. Multivariable conditional logistic regression analysis was used to calculate the odds ratio (OR) and its 95% confidence interval (CI) to identify the associated independent risk factors. Variance inflation factors (VIF) were used to test for the multicollinearity of variables in the model. Restricted cubic spline (RCS) analysis was used to assess potential nonlinear relationships of continuous variables. To model potential nonlinear associations, we applied segmented linear regression analysis, the optimal inflection points were determined through iterative optimization by minimizing the model's deviance. Based on these thresholds, Hb levels were then categorized into three groups (<166 g/L, 166–185 g/L, and ≥186 g/L) and incorporated into the multivariable logistic regression model. A two-sided P value of < 0.05 indicated statistical significance.

HRQoL was evaluated using the SF-12. The SF-12 generates two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Raw scores were first calculated according to the standard SF-12 scoring algorithm and then transformed into norm-based T-scores (mean = 50, SD = 10), with higher scores indicating better health-related quality of life. Comparisons between the CMS group and the non-CMS group were performed using t-tests. Effect sizes were reported using Cohen’s d, with thresholds defined as: small effect (Cohen’s d ≥ 0.2), medium effect (Cohen’s d ≥ 0.5), large effect (Cohen’s d ≥ 0.8). These criteria are consistent with Cohen’s conventions for behavioral and health sciences [7].

Results

A total of 377 urban residents aged 20 years and above were screened. 31 subjects were excluded due to presence of cardiorespiratory diseases, and an additional 5 were excluded because of incomplete questionnaires. The final 341 subjects were analyzed.

Prevalence of CMS, erythrocytosis, hypoxemia

The overall prevalence of CMS was 20.5% (95% CI: 16.2–24.8%). Severity stratification revealed mild cases accounted for 17.9% (95% CI: 14.0-22.4%), moderate cases for 2.3% (95% CI: 1.0-4.6%), and severe cases for 0.3% (95% CI: 0-1.6%). The prevalence of CMS was slightly higher in females (21.5%) compared to males (19.4%), although this difference did not reach statistical significance ($p = 0.718$). The prevalence of erythrocytosis (defined as Hb ≥ 210 g/L in males and ≥190 g/L in females) was 4.1% (95% CI: 2.3–6.8%) in the study population, males demonstrated a significantly higher prevalence than females (7.5%, 95% CI: 3.9–12.7% vs. 1.1%, 95% CI: 0.1–3.9%; $p = 0.007$). Hypoxemia ($SpO_2 < 85\%$) was observed in 8.2% (95% CI: 5.6–11.8) of the study population, with no significant difference between males and females (8.1%, 95% CI: 4.4–13.5% vs. 8.3%, 95% CI: 4.7–13.3%; $p = 1.000$).

Associated factors of CMS

Comparison of demographic, clinical characteristics between group with CMS and without CMS were described in Table 1. The mean age of population with CMS was significantly higher than population without CMS (47.03 ± 8.12 vs. 39.23 ± 9.30, $p < 0.001$) and as expected, the duration of high-altitude residence of population with CMS was significantly higher than the population without CMS (37.69 ± 16.82 vs. 29.70 ± 16.10, $p < 0.001$). The population mean of BMI (26.22 ± 4.62 vs. 24.61 ± 3.51, $p = 0.008$), SBP (132.03 ± 17.64 vs. 125.98 ± 17.41, $p = 0.01$), and HB (173.87 ± 27.61 vs. 163.18 ± 19.84, $p = 0.003$) were significantly higher among group with CMS than group without CMS, however, no intergroup disparity was observed in obesity rates (30% vs. 19.6%, $p = 0.084$). Compared to the non-CMS group, the CMS group demonstrated significantly lower SpO_2 (%) (88.79 ± 3.94 vs. 90.10 ± 3.49; $p = 0.007$).

Age, as a well-established risk factor for CMS, may confound the results through its associations with variables such as menstrual status and duration of high-altitude residence. Given significant baseline age disparities between group with CMS and group without CMS (standardized mean differences [SMD] = 0.961), we performed 1:3 nearest-neighbor PSM to minimize age-related confounding. The final matched cohort comprised 223 subjects (67 CMS cases and 156 non-CMS cases), demonstrating excellent age balance between groups (SMD = 0.032). Comparison of demographic, clinical characteristics between groups after age matching were described in Table 1. In the univariate analysis (Table 2), Hb level (OR = 1.01, $p = 0.034$) were significantly associated with the outcome. CMS was more prevalent among postmenopausal women (44.8% vs. 29.3%) and people with obesity (39.6% vs. 27.4%), though the differences were not statistically significant.

Variables with clinical significance demonstrated no evidence of multicollinearity (all VIFs < 3) were included in multivariable conditional logistic regression analysis. Nonlinearity analysis via RCS indicated a threshold effect of Hb levels on CMS risk. Segmented linear regression identified two inflection points at 166 g/L and 186 g/L in the Hb-CMS relationship (Fig. 1). Below 166 g/L, Hb showed no significant effect (β = 0.002, Z value = 0.137). Between 166–185 g/L, increase in Hb non-significantly reduced the log-odds of CMS (β = -0.039, Z value = -0.912). Above 186 g/L, each 1 g/L increase in Hb significantly

raised the odds of CMS by 12% (β = 0.117, Z value = 2.451). Based on these thresholds, Hb levels were then categorized into three groups (<166 g/L, 166–185 g/L, and ≥186 g/L) and incorporated into the multivariable conditional logistic regression model again. Key results of the multivariable conditional logistic regression were summarized in Table 3. Females had 3.02 times higher odds of CMS compared to males (OR = 3.02, 95% CI: 1.19–7.64, $p = 0.020$), Hb levels ≥ 186 g/L were associated with a 4.76-fold increased odds of CMS (OR = 4.76, 95% CI: 1.41–16.06, $p = 0.012$).

Prevalence and intensity of symptoms and signs of CMS

Among the total study population, the most prevalent symptoms and signs were cyanosis (52.8%), headache (49.0%), breathlessness (46.9%) and sleep disturbance (43.7%). The majority of cases reported mild intensity across symptoms, except for sleep disturbance, which was predominantly moderate (75.8% of affected cases). Among the CMS patients, the most common symptoms and signs remained breathlessness (88.6%), sleep disturbance (85.7%), headache (80%), and cyanosis (78.6%), however, moderate/severe breathlessness increased to 29.1% (vs. 14.4% overall), moderate/severe cyanosis increased to 50.9% (vs. 27.7% overall), and severe headache to 16% (vs. 6.6% overall). Among these most prevalent symptoms, females demonstrated significantly higher rates of both breathlessness (54.7% vs 38.1%, $p = 0.003$) and headache (60.8% vs 35.6%, $p < 0.001$) compared to males (Table 4).

HRQoL assessment

The SF-12 assessment revealed impairments in both physical and mental health among CMS patients with physical health being more severely affected (Table 5). PCS scores were markedly lower in the CMS group (33.50 ± 14.35 vs. 60.44 ± 13.69; $p < 0.001$, Cohen's d = -1.95, large effect). Similarly, MCS scores were significantly reduced in the CMS group (46.96 ± 12.96 vs. 53.71 ± 12.59; $p < 0.001$, Cohen's d = -0.53, medium effect). These effects exceeded the minimal important difference (MID) thresholds for both PCS (≥ 3 points) and MCS (≥ 5 points), indicating clinically meaningful deteriorations. The CMS group exhibited statistically significant impairments in all physical health domains compared to the group without CMS (all $p < 0.05$). Large effect sizes (Cohen's d > 0.8) were observed for General Health (GH) (Cohen's d = -0.83), Physical Functioning (PF) (Cohen's d = -1.40), and Role Physical (RP) (Cohen's d = -2.15), while Bodily Pain (BP) demonstrated a medium effect size (Cohen's d = -0.58). For mental health domains, significant between-group differences were only found in Mental Health (MH) ($p < 0.05$)and Role Emotional (RE). The MH showed a medium effect size(Cohen's d = -0.78), whereas the RE exhibited a small effect size (Cohen's d = -0.32). No significant differences were observed in other domains.

Table 1
Comparison of descriptive statistics between group with CMS and without CMS before and after age matching.

Unmatched				Matched		
	Group with CMS (*n* = 70)	Group without CMS (*n* = 271)	*P*-value	Group with CMS (*n* = 67)	Group without CMS (*n* = 156)	*P*-value
Gender *	31 (19.4)	129 (80.6)	0.718	30 (26.8)	82 (73.2)	0.357
Male	39 (21.5)	142 (78.5)		37 (33.3)	74 (66.7)	
Female						
Age (years)**	47.03 ± 8.12	39.23 ± 9.30	< 0.001	46.49 ± 7.88	44.59 ± 7.68	0.094
Residents *	27 (20.5)	105 (79.5)	1	27 (31.8)	58 (68.2)	0.772
Migrant	43 (20.6)	166 (79.4)		40 (29.0)	98 (71.0)	
Native						
Menstrual status *	15 (48.4)	16 (51.6)	<0.001	13 (44.8)	16 (55.2)	0.194
Postmenopausal	24 (16)	126 (84)		24 (29.3)	58 (70.7)	
Premenopausal						
Years of high-altitude residence **	37.69 ± 16.82	29.70 ± 16.10	< 0.001	36.73 ± 16.56	35.39 ± 15.37	0.559
Obesity *	21 (28.4)	53 (71.6)	0.084	19 (39.6)	29 (60.4)	0.147
Height**	161.49 ± 6.77	163.10 ± 7.89	0.117	161.66 ± 6.81	163.03 ± 8.06	0.226
Weight **	68.41 ± 12.56	65.76 ± 12.27	0.110	68.20 ± 12.55	66.62 ± 11.46	0.357
BMI**	26.22 ± 4.62	24.61 ± 3.51	0.008	26.08 ± 4.59	24.96 ± 3.14	0.036
SBP**	132.03 ± 17.64	125.98 ± 17.41	0.010	131.81 ± 17.54	129.94 ± 17.84	0.472
DBP **	81.71 ± 14.43	78.96 ± 14.37	0.155	81.57 ± 14.36	81.62 ± 15.08	0.98
HR **	81.94 ± 12.52	81.48 ± 12.75	0.788	82.58 ± 12.23	81.34 ± 12.30	0.489
SpO_2 (%) **	88.79 ± 3.94	90.10 ± 3.49	0.007	89 ± 3.81	89.65 ± 3.47	0.231

Unmatched				Matched		
Hb (g/L) **	173.87 ± 27.61	163.18 ± 19.84	0.003	171.66 ± 30.31	164.10 ± 19.92	0.029

* n (%); ** mean ± sd.

Table 2
Univariate analysis of baseline characteristics after PSM between group with CMS and without CMS

	Group with CMS (*n* = 67)	Group without CMS (*n* = 156)	OR(95%CI)	*P*-value
Gender*	30(26.8)	82(73.2)	1.49 (0.81–2.73)	0.195
Male	37(33.3)	74(66.7)		
Female				
Residents *	27(31.8)	58(68.2)	0.82 (0.46–1.48)	0.514
Migrant	40(29.0)	98(71.0)		
Native				
Menstrual status*	13(44.8)	16(55.2)	1.96(0.81–4.72)	0.130
Postmenopausal	24(29.3)	58(70.7)		
Premenopausal				
Years of high-altitude residence**	36.73 ±16.56	35.39 ±15.37	1.00 (0.97–1.02)	0.732
Obesity*	19 (39.6)	29 (60.4)	1.51 (0.77–2.96)	0.235
Height**	161.66 ± 6.81	163.03 ± 8.06	0.97 (0.94–1.01)	0.175
Weight**	68.20 ± 12.55	66.62 ± 11.46	1.00 (0.98–1.03)	0.741
BMI**	26.08 ± 4.59	24.96 ± 3.14	1.06 (0.98–1.15)	0.148
SBP**	131.81± 17.54	129.94 ± 17.84	1.00 (0.98–1.02)	0.908
DBP**	81.57 ± 14.36	81.62 ± 15.08	1.00 (0.98–1.02)	0.682
HR**	82.58 ± 12.23	81.34 ± 12.30	1.01 (0.99–1.04)	0.317
SpO_2 (%)**	89.00 ± 3.81	89.65 ± 3.47	0.95 (0.88–1.03)	0.236
Hb**	171.66± 30.31	164.10 ± 19.92	1.01 (1.00-1.03)	0.034

* n (%); ** mean ± sd.

Table 3
Multivariable conditional logistic regression analysis for independent predisposing factors of CMS

	β	S.E	OR	95% CI	Z-value	*P*-value
Gender(Female)	1.105	0.474	3.02	1.19–7.64	2.332	0.020
Residents(Native)	-0.100	0.321	0.90	0.48–1.70	-0.311	0.756
Hb≥186	1.561	0.620	4.76	1.41–16.06	2.517	0.012
BMI	0.037	0.082	1.04	0.88–1.22	0.456	0.648
SBP	0.003	0.010	1.00	0.98–1.02	0.280	0.780
SPO2	-0.026	0.045	0.97	0.89–1.06	-0.589	0.556
Obesity	-0.014	0.632	0.90	0.29–3.40	-0.023	0.982
Menstrual status (Postmenopausal)*	0.497	0.482	1.64	0.63–4.22	1.032	0.302

* Analyzed among females only.

Table 4
Gender comparison of symptoms and signs of CMS among the total study population

	Male (*n* = 160)	Female (*n* = 181)	χ2	*P*-value
Breathlessness *n* (%)	61(38.1)	99(54.7)	8.71	0.003
Sleep disturbance *n* (%)	63(39.4)	86(47.5)	1.97	0.161
Cyanosis *n* (%)	103(64.4)	77(42.5)	15.38	<0.001
Dilatation of veins *n* (%)	22(13.8)	9(5.0)	6.89	0.009
Paresthesia *n* (%)	42(26.3)	58(32.0)	1.11	0.292
Headache *n* (%)	57(35.6)	110(60.8)	20.50	<0.001
Tinnitus *n* (%)	52(32.5)	60(33.1)	0	0.991

Table 5
comparison of HRQoL between group with CMS and without CMS.

	Group with CMS (*n* = 70)	Group without CMS (*n* = 271)	*P*- value	Cohen's d
PCS*	33.50 ± 14.35	60.44 ± 13.69	< 0.001	-1.95
GH*	27.14 ± 17.42	45.30 ± 22.74	< 0.001	-0.83
PF*	50.00 ± 20.41	76.59 ± 18.63	< 0.001	-1.40
RP*	21.61 ± 19.26	61.30 ± 18.28	< 0.001	-2.15
BP*	47.14 ± 18.33	57.75 ± 18.26	< 0.001	-0.58
MCS*	46.96 ± 12.96	53.71 ± 12.59	< 0.001	-0.53
RE*	47.86 ± 22.32	53.74 ± 17.09	0.04	-0.32
VT*	44.64 ± 17.49	48.25 ± 18.49	0.13	0.20
MH*	39.64 ± 13.95	50.65 ± 14.42	< 0.001	-0.78
SF*	62.14 ± 17.42	65.22 ± 17.52	0.19	-0.18

* mean ± sd.

Discussion

In past decades, thousands of residents on the plateau have been investigated to determine prevalence of CMS, erythrocytosis, hypoxemia. The prevalence of CMS varies significantly across different regions worldwide from 5–33% [2]. Several studies examining physiologic adaptation to high-altitude in the East African Mountains have noted absence of CMS in this region of the world [8]. In Bolivia as a whole approximately two-thirds of the population live at altitudes greater than 3000 m and CMS is deemed a considerable public health problem, studies there have found CMS rates between 8% and 10% in the male active population [9]. More extensive research into the prevalence of CMS has been conducted in the Andes, several studies in Cerro de Pasco have found CMS prevalence rates of 14.8% and 18.2% [10], studies in the Peruvian central Andes located at 4100 m have found CMS prevalence rates as high as 32.6% [11]. Epidemiological investigations by Chinese researchers documented that prevalence of CMS among native Tibetans, Han Chinese immigrated to Qinghai plateau in Tibet were 1.21% and 5.57%, respectively [2]. The reasons for this large variability are not well-understood, though they may be associated with ethnic differences, residential altitude, lifestyle, and the diagnostic criteria for CMS used in different studies. Previous studies have also reported that urbanization and associated changes in lifestyle could have role in development of CMS [4]. Nevertheless, epidemiological studies on CMS remain relatively scarce for certain subpopulations, particularly among urban residents.

This epidemiological study of CMS among urban residents of the Northwestern Sichuan Plateau in China revealed 20.5% (95% CI: 16.2–24.8%) of the population were affected with CMS, with the clinical

spectrum dominated by mild presentations. Females have a higher prevalence of CMS compared to males. The prevalence of CMS observed in the present study was higher than that reported in previous studies from the Indian Himalayas at comparable elevations [12]. The relatively high prevalence of CMS observed in our study may be explained by several factors. Our study primarily focused on urban populations at high altitude. Previous research has reported that urbanization and associated changes in lifestyle could have role in development of CMS, and our findings support this hypothesis. Existing evidence suggests that physical inactivity may contribute to the development and progression of CMS [3]. We speculate that the predominantly sedentary lifestyle characteristic of urban high-altitude residents may represent a potential contributing factor to their increased susceptibility to CMS. Recent studies have demonstrated that regular physical exercise provides numerous physiological benefits, not only in healthy individuals at high altitude, but also in patients with CMS. Exercise training, especially moderate-intensity aerobic exercise, might be used as a non-pharmacological therapy for CMS [13]. The participants in our study live at elevations ranging from 3,500 to 4,000 meters, which is higher than the altitudes reported in many prior studies, altitude of residence is a significant risk factor for the development of chronic mountain sickness. Much of the historical research on CMS has focused on male populations, while our study included both male and female participants, notably, our findings revealed a higher prevalence of CMS among females compared to males in the studied population, this could be one of the contributing factors. In this study, we applied the latest diagnostic criteria for CMSthe Qinghai CMS score criteria. Differences in diagnostic criteria may partially account for this discrepancy. It should be noted that some researchers have raised concerns that current CMS diagnostic criteria may be overly sensitive but lack specificity, furthermore, some researchers argue that most CMS symptoms are also commonly shared with cardiac, pulmonary, and other diseases, which lead the scoring system less reflect maladaptation to high altitudes after long-term hypoxic exposure, but instead may reflect lung or cardiac malfunction [14].

The diagnostic setting of Hb threshold for erythrocytosis remains a contentious issue in clinical practice. Erythrocytosis is essentially an adaptive response to long-term hypoxic exposure, making it difficult to be distinguished from a maladaptive response. Currently, the Qinghai CMS score criteria is used to diagnose CMS, with Hb levels of more than 210 g/L in male and more than 190 g/L in female as the cut-off values for diagnosing excessive erythrocytosis (EE) [2]. The cut-off points were originally established based on the Gaussian distribution. However, several studies suggest that EE defined by these cutoffs shows no significant association with the symptoms and signs of CMS, despite it has been presumed this elevated Hb levels as responsible of the signs and symptoms of CMS. Given this discrepancy between Hb concentration and symptoms, different Hb thresholds have been proposed by medical researchers from different groups and countries [15, 16]. For instance, Jiang et al. have applied k-means clustering methods, recommending Hb ≥ 200 g/L as a more clinically relevant threshold for EE in CMS diagnosis [17]. In the first population (Hb < 200 g/L), which represents the physiologic response of erythrocytosis, the SaO2 remains stable as Hb increases; in the second population (Hb ≥ 200 g/L), which represents the pathologic response part of erythrocytosis, the SaO_2 decreases as the Hb increases.

Reeves and Leon-Velarde in their study showed that optimal Hb level at high altitude, which allows greater oxygen extraction, was 175 g/L [18] .

In our study, we employed segmented linear regression to identify two inflection points in the HB-CMS relationship, which were 166 g/L and 186 g/L, respectively. When hemoglobin levels were < 166 g/L, the prevalence of CMS showed no significant change as Hb increases. Between 166–185 g/L, the prevalence of CMS slightly decreased as the Hb increases. However, when hemoglobin levels exceeded 186 g/L, the prevalence of CMS significantly increased with further rises in hemoglobin. So, we recommended the hemoglobin threshold for this population to be 186 g/L. The association we observed between Hb levels and CMS is consistent with the known relationship between Hb levels and blood oxygen-transport capacity. When the Hb concentration is below the “optimal” value, physiologic erythrocytosis response helps

to elevate ability of blood to transport oxygen. When the Hb exceeds this “optimal” value, the erythrocytosis response aggravates the oxygen supplication-demanding imbalance and triggers CMS pathologic processes[19]. Of course, further studies are needed to explore the relationship between this threshold and the symptoms and signs of CMS in subsequent research.

Increasing age are well established risk factors for CMS [20–22].Given significant baseline age disparities between group with CMS and group without CMS, which may confound outcomes through associations with variable, such as menstrual status and duration of high-altitude residence. 1:3 nearest-neighbor PSM was performed to minimize age-related confounding. After age matching, univariate analysis revealed that Hb levels were significantly associated with CMS. Although CMS was more prevalent among postmenopausal women, the differences were not statistically significant. Multivariable conditional logistic regression analysis revealed that females and Hb level emerged as independent associated factors for CMS. Menopausal status was analyzed only in the female subgroup due to its inapplicability to males. No significant association was observed between menopausal status and the prevalence of CMS.

In contrast to most previous studies identifying males as a primary risk factor for CMS [2, 23], our study demonstrate females as an independent associated factor. This finding is consistent with a epidemiological study conducted in natives of Spiti in greater Himalayas, which similarly reported higher CMS prevalence among females [3]. Notably, this study attributed this sex disparity to women's prolonged exposure to indoor air pollution and consequent pulmonary dysfunction - a potential contributory mechanism that may partially explain elevated CMS susceptibility in females. In our study, the higher CMS symptom score was recorded in women than in men, but the lower prevalence of excessive erythrocytosis and comparable hypoxemia rates were observed. This may point out the lack of specificity of contemporary symptoms based diagnostic criteria in females for diagnosis of CMS or may be that the threshold for symptoms related to hypoxemia and erythrocytosis in females is lower than in males. Moreover, in contrast to prior researches, our study employed age-based matching to mitigate age-related confounding effects between genders. The observed inconsistency in the association

between female sex and CMS risk—initially non-significant in univariate analysis but significant in multivariable analysis—may result from confounding protective factors in the female population, including younger age (43 vs. 46 years), shorter high-altitude exposure (34 vs. 37 years), and lower Hb levels (152 vs. 181 g/L). These factors likely attenuated the true physiological susceptibility of females in unadjusted models, which became apparent only after multivariate adjustment.

Building upon our segmented regression results identifying 186 g/L as the critical hemoglobin threshold, subsequent multivariable analysis demonstrated that Hb levels ≥ 186 g/L was an independent associated factor. Many studies of adaptation to high-altitude hypoxia have focused on the blood because of its role in oxygen transport. Below the optimal hemoglobin threshold, numerous of individuals effectively increase oxygen delivery capacity through elevated hemoglobin concentrations, thereby reducing CMS risk. However, beyond this optimal level, excessive erythrocytosis impairs oxygen transport through increased blood viscosity, triggering a vicious cycle of tissue hypoxia and further erythrocytosis. Previous studies have suggested that the Tibetans lived at altitudes of 3,800–4,065 meters without significant erythrocytosis [24]. Relatively low Hb concentrations among Tibetan high-altitude natives have also been widely reported in numerous studies [5]. In our study population, the prevalence of EE was 4.1%, which is higher than previously reported rates among Tibetan pastoralists. Our findings suggest potential differences in hemoglobin concentrations between urban residents and pastoral populations in high-altitude regions. These findings also suggest that CMS screening and intervention should be prioritized for urban residents in the northwestern Sichuan plateau when hemoglobin levels exceed 186 g/L. Further studies with more diverse populations are required to establish population-specific hemoglobin thresholds.

Previous studies identified menopause as a risk factor for CMS [25]. This phenomenon may be attributed to postmenopausal elevation of the testosterone-to-estradiol ratio and cessation of periodic blood loss, both contributing to increased hemoglobin levels. Contrary to previous reports, our analysis revealed no significant association between menopausal status and CMS among female participants. A previous study also failed to observe an increase in Hb levels after menopause [26]. The exact cause underlying this phenomenon require further investigation. One possible explanation for this difference is that they did not account for the confounding effect of age, as postmenopausal women are generally older than premenopausal women and advancing age is a well-established risk factor for CMS.

The growing recognition of the value of real-world data on HRQoL in informing disease management and policy development is increasingly evident. Patients of CMS are disabled with impaired memory, headache, breathlessness, fatigue, disturbed sleep, anorexia, and tinnitus that affect the quality of life. These limitations may force patients to discontinue prolonged residence at high altitudes or full-time work. Even clinicians may underestimate this impact. Study has demonstrated a significant correlation between the HRQoL of high-altitude urban residents and the occurrence of CMS [11]. Therefore, research on the effects of CMS on patients' quality of life is crucial for understanding the characteristics of this disease and the associated disease burden it imposes.

The SF-12 is a widely used and validated HRQoL assessment instrument in populations at sea level and at high altitude, serving as an abbreviated version of the SF-36 (Short Form-36). This 12-item questionnaire evaluates an individual's overall physical and mental health status. The results of our study indicate that populations without CMS exhibit significantly better health scores compared to those with CMS. CMS adversely affects both the physical and mental health of patients, with a more pronounced impact on physical health. In terms of physical health, compared to non-CMS high-altitude populations, CMS patients showed poorer performance across multiple dimensions of physical health, with the most pronounced impairment observed in the RP dimension. This suggests that physical health limitations predominantly manifest as restrictions in occupational functioning, which is particularly critical for high-altitude urban populations who constitute the primary workforce in plateau development. Regarding mental health, CMS patients demonstrated the most significant deterioration in the MH domain compared to non-CMS populations, suggesting that emotional disturbances (e.g., depression and anxiety) likely constitute the primary psychological burden. This phenomenon may be attributed to chronic hypoxic-induced hippocampal atrophy and prefrontal cortex dysfunction, which elevate susceptibility to mood disorders, compounded by persistent sleep disturbances exacerbating emotional dysregulation [27–29]. Furthermore, limited healthcare resources and inadequate psychological support in high-altitude regions often result in prolonged untreated mental health conditions. Given the substantial MH domain impairment, routine depression/anxiety screening and targeted psychological interventions should be integrated into CMS patient management.

To our knowledge, this represents the first study to investigate both the burden of CMS and its HRQoL impacts among urban residents in high-altitude regions. this study also represents the first application combining matching with multivariable logistic regression in cross-sectional research on CMS. The integrated use of matching and multivariable logistic regression addresses the limitations of conventional approaches: it compensates for traditional regression's neglect of intergroup comparability while overcoming matching's inability to perform model-based adjustments. This dual-control strategy for confounding factors creates synergistic effects where 'the whole is greater than the sum of its parts' (1 + 1 > 2). The combined methodology can be extended to other high-altitude-related disorders (e.g., high-altitude pulmonary hypertension) or similar cross-sectional studies, providing a replicable methodological framework for future research in high-altitude medicine.

conclusion

Prevalence of CMS amongst urban residents of the Northwestern Sichuan Plateau in China residing at an altitude of 3500 to 4000 meters was 20.5%. After age matching, female, and hemoglobin levels ≥ 186 g/L were identified as significant associated factors for CMS. Populations with CMS exhibit poorer health status compared to those without CMS, with more pronounced impairments in physical health. Observations made in the present study have important implications for health policy makers and public health providers for creating awareness among urban residents of the Northwestern Sichuan Plateau about CMS burden, associated factors and appropriate preventive measures in order to reduce morbidity and improve quality of life.

Declarations

Additional information

Competing interests

The authors declare no competing interests.

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Author Contribution

C.H. conceived the study, analyzed data, drafted the manuscript and gave final approval. P.B. and Z.J. contributed to conception and design of study, analysis of data, and gave final approval. L.Y., H.M., D.P., and F.S. contributed to acquisition of data and gave final approval. L.W. contributed to conception and design of study, analysis and interpretation of results, critically revised the manuscript and gave final approval. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Data Availability

The data presented in this study are available upon request by contacting Dr. Wenjun Li mylwj0197@163.com

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Figures

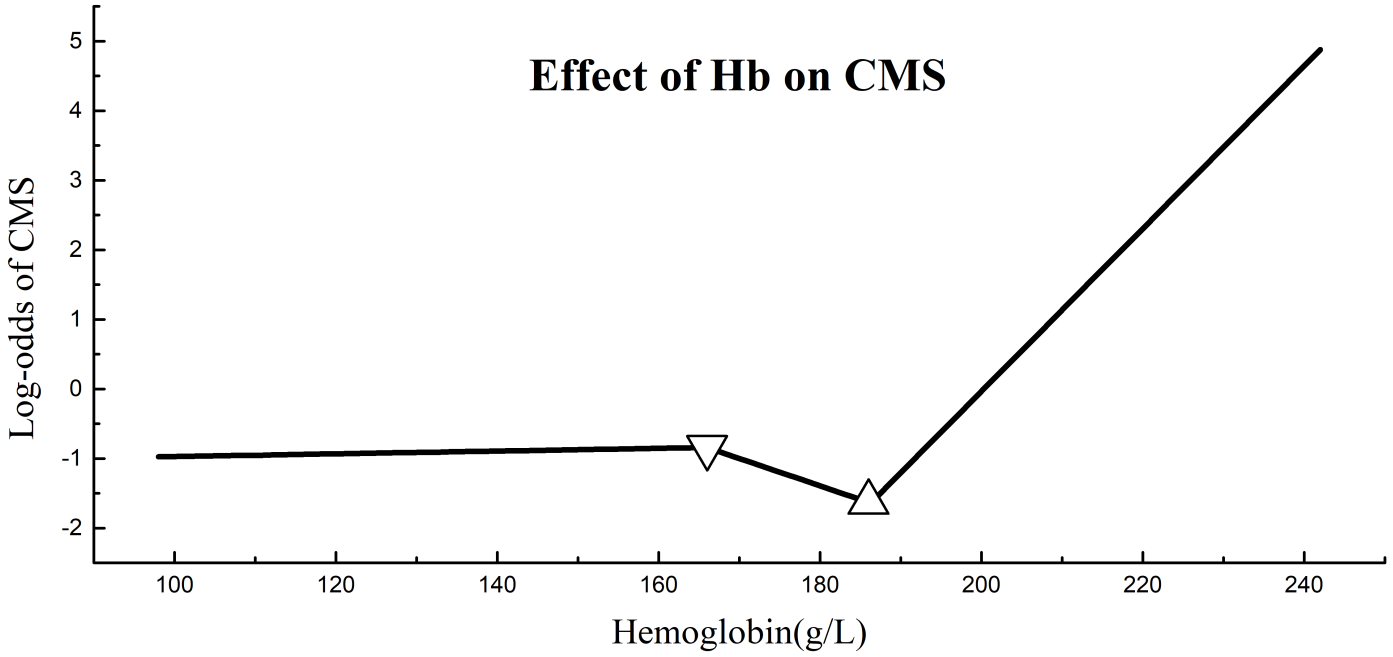


Figure 1

Segmented linear regression of hemoglobin (Hb) levels on CMS.