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Regular Observation of De-Acclimatization and Randomized Controlled Research of Diagnostic Criteria of High Altitude De-Acclimatization Syndrome among Different Plateau Migrants Crowd after Their Return to the Plain

Qiquan Zhou[1,2*], Shengyue Yang[3], Zhencai Yuan[4], Yinhu Wang[5], Xuefeng Zhang[6], Wei Gao[7], Zifu Shi[8], Youli Yang[9], Yunhong Wu[10], Yong Fan[1,2], Fuling Wang[5], Guansong Wang[11*]

[1]Department of High Altitude Disease, College of High Altitude Military Medicine, Third Military Medical University, Chongqing, China
[2]Key Laboratory of High Altitude Medicine of Ministry of Education and Key Laboratory of High Altitude Medicine of PLA, Chongqing, China
[3]Department of Respiratory Medicine, Fourth Hospital of Chinese PLA, Xining, China
[4]Xianyang Hospital of China Railway First Group Co., Ltd., Xianyang, China
[5]Research Institute of High Altitude Diseases, 18th Hospital of Chinese PLA, Yecheng, China
[6]Research Center of High Altitude Medicine, People's Hospital of Golmud City, Golmud, China
[7]Department of Thoracic Surgery, Lanzhou General Hospital of Lanzhou Command, Lanzhou, China
[8]The 68303 Troop Hospital of Chinese PLA, Wuwei, China
[9]Department of Clinical Laboratory, Tenth Hospital of Chinese PLA, Wuwei, China
[10]Department of Endocrinology, Hospital of Chengdu Office of Tibet Autonomous Region, Chengdu, China
[11]Research Institute of Respiratory Diseases, Xinqiao Hospital, Third Military Medical University, Chongqing, China
Email: *zhouqq9918@163.com, ysyday@163.com, yuanzhencai@163.com, xj18yywyh@sina.com, gemzxf@163.com, gaoweizy@126.com, szfszf111@163.com, youliyang58@163.com, wu_yunhong@163.com, fangyongcq@163.com, wangfuling18@163.com, *wanggs2003@163.com

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Abstract

Objective: The objective of this study was to investigate the diagnostic methods of high altitude

*Corresponding authors.

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de-acclimatization syndrome and to formulate diagnostic criteria. Methods: This study was conducted using epidemiological surveys and a multi-center randomized controlled clinical trial. A total of 3011 subjects were studied, and the following indices were collected after their return to low altitude areas from the plateau: general health status, blood, urine and stool samples, myocardial enzyme levels, liver and kidney function, nerve function, sex hormone levels, microalbuminuria, electrocardiogram (ECG), echocardiography, pulmonary function, and hemorheological markers. These data were compared to those of randomized healthy subjects in the same age range who lived at the same altitude to determine the characteristics of high altitude de-acclimatization syndrome. Based on these characteristics, diagnostic criteria for high altitude de-acclimatization syndrome were formulated. Results: This study demonstrated that the incidence of high altitude de-acclimatization syndrome was 84.36%. Sixty percent of the cases were mild, 30% were medium, and 10% were severe. The incidence was higher among those who returned to a place of lower altitude, resided at a high altitude for a longer period of time, or engaged in heavy labor while at high altitude. Patients with high altitude de-acclimatization syndrome manifested hematological abnormalities and abnormal ventricular function, notably a right ventricular diastolic function, which recovered to baseline function after one to five years. Exposure to long-term hypoxia often caused obvious changes in cardiac morphology, *i.e.*, left and right ventricular hypertrophy, particularly within the right ventricle. In addition, patients with high altitude de-acclimatization syndrome often presented with low blood pressure, low pulse pressure, and microalbuminuria. A few patients presented with occult blood in their feces. The diagnosis of high altitude de-acclimatization syndrome can be made if a patient who recently returns to the plain from the plateau complains of dizziness, weakness, sleepiness, chest tightness, edema, memory loss, and other symptoms and signs that do not alleviate under short-term rehabilitation or symptomatic treatment, and if organic diseases of the heart, lung, kidney, and other organs have been excluded. Conclusion: The diagnosis of high altitude de-acclimatization syndrome should be made after a comprehensive analysis of the patient's clinical symptoms and signs.

Keywords

Plateau Migrants, Low Altitude, High Altitude De-Acclimatization Syndrome, Diagnostic Criteria, Multi-Center Study

1. Introduction

High altitude de-acclimatization syndrome was called "drunk oxygen syndrome" in the past, and occurs when people, who normally live in plains, return to the plain after living in the plateau for a period of time. When they live in the plateau, a series of functional and structural changes would take place to make them adjust to acclimate the plateau. When they return to the plain, the body would readjust itself to acclimate the plain, so known as the high altitude de-acclimatization syndrome [1] [2]. High altitude de-acclimatization is one's adaptation to a normal-oxygen environment after leaving an oxygen-deficient plateau [3] [4]. When returning to a normal oxygen environment after living in the oxygen-deficient plateau, an individual loses the plateau adaption, thus leading to de-acclimatization or de-acclimatization [5]. In the past, there were much available information regarding the syndrome, and the causes of de-acclimatization were rarely studied; therefore, no standard diagnostic criteria or even effective prophylactic measures have been developed. To some extent, this lack of knowledge affected the physical and mental health, work efficiency, or even daily life of patients with de-acclimatization syndrome [6]-[8]. Therefore, we conducted this multi-center randomized controlled clinical trial of individuals who returned from the plateau to the plain to formulate diagnostic criteria and guide treatment.

2. Subjects and Methods

2.1. Methods

2.1.1. Subjects

The study subjects included 1320 officers and soldiers who returned from Yushu, Qinghai to their homes (Wu-

wei, Gansu; Zepu, Xinjinag; Tongliang, Chongqing; Xianyang, Shaanxi; Chengdu, Sichuang; Xining, Qinghai; Zhengzhou, Henan; Hangzhou, Zhejiang, etc.). The study subjects included 115 officers and soldiers who returned to the plain after working in Hargoolun Range for at least one year, 940 officers and soldiers who returned to the plain after working in the plateau for at least three years, 300 railway workers who returned to the plain after constructing the second stage of Qinghai-Xizang Railway for at least five years, 500 cadres who returned to the plain after working in Xizang for at least 10 years, and 110 cadres who came to the plain for short-time recuperation. The subjects were selected by the standard criteria. All subjects had recently returned to the plain from the plateau and did not have any heart, lung, brain, kidney, or other primary organ diseases. This study was approved by the medical ethical committee of the Third Military Medical University. All participants signed informed consent form.

2.1.2. Methods

This study was conducted as an epidemiological survey and prospective clinical trial. Specially assigned persons handed out self-designed health survey questionnaires on the second [9] [10], 16th, 30th, 90th, and 360th days after the subjects returned to the plain. The questionnaire mainly contained general information, the date on which the subject went to the plateau, the date of return to the plain, the altitude of the plateau, major symptoms and signs after returning to the plain (such as dizziness, fatigue, weakness, sleepiness, insomnia, dreaminess, cyanosis, chest tightness, palpitation, anorexia, constipation, diarrhea, abdominal distension, edema, memory loss, slow reaction, slow pulse, sexual dysfunction, weight loss, tooth loss, hair loss, precordial pain, numbness of hands and feet, hemorrhagic spots, and ecchymosis), and their severity and frequency. Some difficult medical terms were explained when the subjects were filling in the questionnaire. The questionnaires were filled in with facts and reclaimed as soon as they were completed. According to the inclusion and exclusion criteria for high altitude de-acclimatization syndrome, 3011 of the 3285 subjects were included in the study. The 3011 subjects were scored according to the grading and evaluation criteria for high altitude de-acclimatization syndrome. The prospective clinical trial consisted of physical examination at local clinics. The examination included 22 items such as routine blood tests, urine and stool tests, microalbuminuria, myocardial enzymes, liver and kidney function, nerve function, electrocardiogram (ECG), echocardiography, sex hormones, cytokines, oxygen free radicals, and neuron specific enolase.

2.1.3. Statistical Analysis

The data were analyzed using SPSS 17.0. The measurement data were recorded as $x \pm s$. The comparison between groups was first made using homogeneity of variance. Then, a one-way analysis of variance was used if the variance was homogenous; otherwise, Tamhane was used. Cluster and partial correlation analyses were used to compare the incidence. The differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. High Altitude De-Acclimatization Syndrome Symptoms and Their Frequency

Of the 3011 subjects, 2540 (84.36%) presented with de-acclimatization symptoms (**Table 1**). The most frequent symptoms were dizziness, fatigue, chest tightness, weakness, sleepiness, insomnia, anemia, vertigo, poor concentration, memory loss, cough, dreaminess, weight loss, slow reaction time, numbness of hands and feet, and increased appetite. The incidences of fatigue, weakness, and sleepiness were 69.4%, 65.6%, and 63.4%, respectively (**Table 2**). These three symptoms affected the subjects' daily life and ability to work. The incidence of high altitude de-acclimatization syndrome in some groups of subjects was 99% (**Table 1**).

3.2. Severity of High Altitude De-Acclimatization Symptoms

All subjects with high altitude de-acclimatization symptoms were classified. The severity of 11 other frequently occurring symptoms was analyzed (**Figure 1**). It was found that 60% of the symptoms were mild, 30% were moderate, and 10% were severe. Most subjects with high altitude de-acclimatization syndrome recovered without any treatment, while a few recovered after proper treatment. The disease affected the daily life and work of the subjects studied.

Table 1. Incidence of high altitude de-acclimatization in different populations.

Population	Number of subjects (n)	Altitude of the resided in (m)	Subjects with de-acclimatization (cases)	Incidence of de-acclimatization (%)
A motorized infantry brigade in Wuwei, Gansu	1014	1350	1004	99.00
An armed police unit in Chongqing	744	300	583	78.36
A fire corps in Chongqing	152	300	107	70.39
A cadres retreat in Chengdu	362	500	317	87.65
A cadres retreat in Zhengzhou	102	110	84	82.35
A border defense group in Zepu, Xinjiang	113	1215	95	84.07
An air force unit in Chongqing	123	300	75	60.97
A fire corps in Sichuan	210	500	139	66.19
A cadres retreat in Beijing	86	30	72	83.72
A cadres retreat in Kunming	105	1890	64	60.95

Table 2. Incidence of high altitude de-acclimatization in 1014 soldiers.

Symptoms	Number of subjects with symptoms (cases)	Incidence (%)	Symptoms	Number of subjects with symptoms (cases)	Incidence (%)
Dizziness	496	48.9	Unable to concentrate	487	48.0
Tiredness	704	69.4	Memory loss	416	41.0
Fatigue	665	65.6	Weight loss	393	38.8
Sleepiness	643	63.4	Unresponsive	301	29.7
Cyanosis	153	15.1	Numbness	211	20.8
Chest tightness	311	30.7	Increased appetite	206	20.3
Palpitation	299	29.5	Precordial pain	168	16.6
Anorexia	175	17.3	Slow pulse	109	10.8
Constipation	158	15.6	Lower extremity edema	94	9.3
Diarrhea	80	7.9	Sexual dysfunction	94	9.3
Abdominal pain	187	18.4	Hair loss	88	8.7
Abdominal distension	148	14.6	Nocturia	92	9.1
Cough	246	24.3	Unstable blood pressure	92	9.1
Sputum	250	24.7	Skin bleeding	81	8.0
Asthma	93	9.2	Skin ecchymosis	81	8.0
Sore throat	215	21.2	Weight gain	114	11.2
Light-headedness	392	38.7	Facial swelling	70	6.9

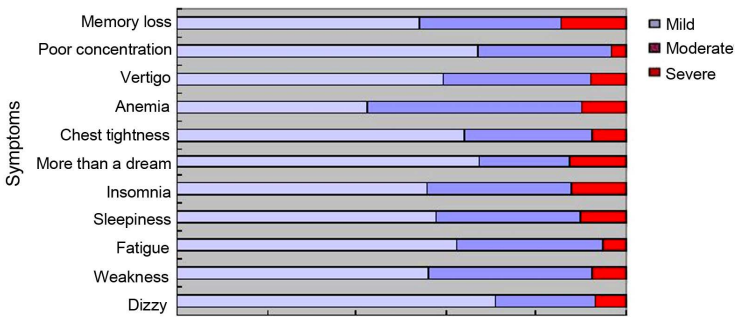

Figure 1. Severity of 11 additional frequently occurring high-altitude de-acclimatization symptoms.

3.3. Altitude of the Return Location and High Altitude De-Acclimatization Syndrome

High altitude de-acclimatization syndrome was related to the altitude of the plain to which the subjects returned. Subjects with a return location at lower altitudes exhibited higher incidence rates of high altitude de-acclimantization syndrome. For example, the incidences of high altitude de-acclimatization syndrome among the subjects who returned to Kunming (1891 m), Zhengzhou (111 m), and Beijing (31 m) were 60.95%, 82.35%, and 83.72%, respectively. The incidence in the subjects who returned to Beijing or Zhengzhou was significantly higher than that of Kunming (**Table 3**).

The incidences of high altitude de-acclimatization syndrome among the subjects who returned to Kunming, Zhengzhou, and Beijing after living in high altitude for 10 years were 47.50%, 66.67%, and 67.65%, respectively. The incidences of those who returned to Kunming, Zhengzhou, and Beijing after living in high altitude for more than 20 years were 69.63%, 93.33%, and 94.23%, respectively. The differences between the two groups were statistically significant (**Table 4**). The result demonstrated that the study subjects were more likely to suffer from de-acclimatization when returning to low altitude after living in high altitude for a longer period of time.

The incidences of high altitude de-acclimatization syndrome among the subjects who returned to Kunming, Zhengzhou, and Beijing from Xizang were 68.75%, 89.66%, and 92%, respectively. The incidences of those who returned to Kunming, Zhengzhou, and Beijing from Golmud, Qinghai were 48.78%, 72.22%, and 72.73%, respectively. The differences between the two groups were statistically significant (**Table 5**). The result indicated that the subjects were more likely to experience de-acclimatization syndrome if the returned from a higher plateau.

Table 3. Incidence of high altitude de-acclimatization in plateau migrants after their return to three low-altitude areas.

Areas (altitude)	Subjects	With symptoms	Without symptoms (cases)	Incidence (%)
Kunming (1891 m)	105	64	41	60.95
Zhengzhou (111 m)	102	84	18	82.35
Beijing (31 m)	86	72	14	83.72
Total	293	220	83	75.09

Table 4. Incidences of high altitude de-acclimatization in people who returned to three different low-altitude areas after living in the plateau for different periods of time.

Areas	Lived in high altitude for 10 years			Lived in high altitude for more than 20 years		
	Subjects	With symptoms (cases)	Incidence (%)	Subjects	With symptoms (cases)	Incidence (%)
Kunming	40	19	47.50	65	45	69.23
Zhengzhou	42	28	66.67	60	56	93.33
Beijing	34	23	67.65	52	49	94.23

Table 5. Incidences of high altitude de-acclimatization in subjects who returned to three different low-altitude areas after living in plateaus of different altitudes.

Areas	Lhasa areas (3650 m)			Golmud areas (2780 m)		
	Subjects	With symptoms (cases)	Incidence (%)	Subjects	With symptoms (cases)	Incidence (%)
Kunming	64	44	68.75	41	20	48.78
Zhengzhou	58	52	89.66	44	32	72.73
Beijing	50	46	92.00	36	26	72.22

3.4. Effects of Labor Intensity in the Plateau on Recovery from High Altitude De-Acclimatization Syndrome in the Plain

After returning to the plain, the subjects who performed heavy physical labor in the plateau were more likely to develop high altitude de-acclimatization syndrome than were those who did not. These subjects also required a longer recovery time (**Table 6**). In addition to the altitude-related symptoms, such as dizziness, fatigue, weakness, and sleepiness, the subjects experienced other symptoms related to labor intensity, *i.e.*, more intense labor led to more severe symptoms. The differences in the severity of the symptoms between those who did heavy labor and those who did light labor were statistically significant ($P < 0.05$). This result revealed that labor intensity on the plateau was correlated with high altitude de-acclimatization syndrome on the plain.

3.5. The Effects of Mountain Sickness on Ventricular Function and Pulmonary Arterial Pressure after Return to the Plain

The severity of mountain sickness among people who returned to the plateau from the plain was directly related to the severity of high altitude de-acclimatization syndrome after return to the plain. The subjects who had more severe mountain sickness in the plateau presented with more frequent and severe symptoms of high altitude de-acclimatization in the plain. In addition, these subjects recovered more slowly. Moreover, these subjects had higher pulmonary arterial pressure and lower cardiac function. The subjects who returned to the plateau from the plain rapidly and performed heavy labor for 50 days presented with obvious right ventricular hypertrophy and decreased left ventricular function that aggravated the deterioration of mountain sickness (**Table 7** and **Table 8**).

Table 6. Effects of different altitudes and labor intensity on the incidence of high altitude de-acclimatization after return to low altitude areas.

Symptoms	Strong physical labor group at 3700 m (243 persons)		Light physical labor group at 4200 m (300 persons)	
	With symptoms (cases)	Incidence (%)	With symptoms (cases)	Incidence (%)
Dizziness	150	61.7	193	64.3
Tiredness	194	79.8	250	83.3
Fatigue	184	75.7	234	78.0
Sleepiness	174	71.6	254	81.7[(1)]
Cyanosis	89	36.6	57	19.0[(1)]
Chest tightness	122	50.2	117	39.0[(1)]
Constipation	77	31.7	54	18.0[(1)]
Diarrhea	84	34.6	79	26.3[(1)]
Abdominal pain	95	39.1	66	22.0[(1)]
Abdominal distension	65	26.8	129	43.0[(1)]
Cough	101	41.6	85	28.3[(1)]
Sputum	105	43.2	95	31.7[(1)]
Light-headedness	130	53.5	128	42.7[(1)]
Lower extremity edema	58	23.9	29	9.7[(1)]
Unresponsive	112	46.1	105	35.0[(1)]
Slow pulse	54	22.2	29	9.7[(1)]
Numbness	84	34.6	72	24.0[(1)]
Facial swelling	140	57.6	26	8.7[(1)]
Unstable blood pressure	50	20.6	32	10.7[(1)]
Precordial pain	74	30.5	62	20.7[(1)]

[(1)]$P < 0.05$ compared with strong physical labor group at 3700 m.

Table 7. Relationship between the severity of mountain sickness and left ventricular function after return to low altitude from high altitude ($\overline{x} \pm s$).

Group	Cases	RVID/LVID (%)	Tei index	LVEF (%)	LVFS (%)
SAMS group	24	51.97 ± 3.22	0.59 ± 0.07	41.42 ± 3.97	23.24 ± 2.61
MAMS group	47	46.33 ± 3.37$^{(1)}$	0.49 ± 0.05$^{(1)}$	47.64 ± 5.05$^{(1)}$	26.72 ± 1.78$^{(1)}$
NAMS group	25	39.28 ± 3.26$^{(1)}$	0.38 ± 0.05$^{(2)}$	58.22 ± 4.34$^{(2)}$	32.15 ± 2.32$^{(2)}$
PC group	50	35.94 ± 2.86$^{(1)(2)}$	0.31 ± 0.03$^{(1)(2)(3)}$	64.73 ± 4.38$^{(1)(2)(3)}$	36.76 ± 2.37$^{(1)(2)(3)}$

$^{(1)}P < 0.01$ compared with SAMS group; $^{(2)}P < 0.01$ compared with MAMS group; $^{(3)}P < 0.01$ compared with NAMS group; SMS: Severe mountain sickness; MAMS: Mild mountain sickness; NAMS: No mountain sickness; PC: Plain control; RVID/LVID: Right ventricular internal diameter/Left ventricular internal dimension; Tei index. Myocardial performance index; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular tractional shortening.

Table 8. Relationship between the severity of mountain sickness and right ventricular function after return to low altitude from high altitude ($\overline{x} \pm s$).

Group	Cases	mPAP (mmHg)	RVID (mm)	RVOT (mm)	LVID (mm)
SAMS group	24	34.70 ± 2.94	24.64 ± 3.15	35.87 ± 4.26	47.62 ± 3.13
MAMS group	47	28.42 ± 1.32$^{(1)}$	21.57 ± 2.78	32.46 ± 4.12	46.75 ± 3.81
NAMS group	25	24.23 ± 1.56$^{(1)}$	18.91 ± 2.45$^{(1)}$	29.89 ± 3.77$^{(1)}$	47.68 ± 3.65
PC group	50	18.50 ± 1.30$^{(1)(2)(3)}$	16.76 ± 2.07$^{(1)(2)}$	27.33 ± 3.66$^{(1)(2)(3)}$	46.52 ± 3.49

$^{(1)}P < 0.01$ compared with SAMS group; $^{(2)}P < 0.01$ compared with MAMS group; $^{(3)}P < 0.01$ compared with NAMS group; SMS: Severe mountain sickness; MAMS: Mild mountain sickness; PC: Plain control; mPAP: Mean pulmonary arterial pressure; RVID: Right ventricular internal diameter; RVOT: Right ventricular outflow tract; LVID: Left ventricular internal dimension.

3.6. Recovery Time of Left and Right Ventricular Functions after Return to Low Altitude

The same group of people was observed at different times. After exposure to high altitude for 50 days, the mPAP, RVID, RVOT, Tei indices, and RVID/LVID increased significantly, whereas LVEF decreased significantly. Twelve hours after the return to low altitude, the mPAP, RVID, RVOT, Tei indices, and RVID/LVID decreased significantly, whereas LVEF increased significantly. Fifteen days after the return to low altitude, the mPAP, LVID, LVEF and Tei indices returned to normal in the plain controls, whereas RVID, RVOT, and RVID/LVID did not return to normal until 30 days after return to low altitude (**Table 9** and **Table 10**).

3.7. Changes in Cardiothoracic Ratios

Based on the altitude of their residence, 517 subjects who had lived in the plateau for more than three years were classified. X-ray examination showed that their cardiothoracic ratios were significantly higher than those of the plain controls ($P < 0.01$, **Table 11**). Forty months after they returned to the plain, their cardiothoracic ratios were still significantly higher than those of the plain controls ($P < 0.05$, **Table 12**). These results suggested that the cardiothoracic ratio would not return to normal after a short time on the plain.

3.8. Changes in the Hematological Indices among Plateau Migrants after Return to the Plain

3.8.1. Changes in the Hematological Indices among People Who Returned to the Plain after Short-Term Exposure to the Plateau

The hematological indices among people who returned to the plain after short-term exposure to the plateau were observed. It was found that 30 days after return to the plain, the white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were all significantly higher than those of the plain controls ($P < 0.05$), but the platelet (Plt) count was much lower than that of the plain controls ($P < 0.05$, **Table 13**). Over time, these test parameters tended to return to normal.

Table 9. Metergasis of the right ventricles of plateau migrants after they returned to low altitude at different times ($\bar{x} \pm s$).

Time points	Cases	mPAP (mmHg)	RVID (mm)	RVOT (mm)	RVID/LVID (%)
50 d exposure to high altitude	96	29.08 ± 4.22	21.63 ± 2.79	32.73 ± 4.05	45.86 ± 3.53
12 h after return to low altitude	96	23.05 ± 3.18$^{(1)}$	19.75 ± 2.48$^{(1)}$	30.96 ± 3.52	42.16 ± 3.34
15 d after return to low altitude	96	18.96 ± 1.75$^{(2)}$	18.01 ± 2.23$^{(1)}$	29.29 ± 3.22	38.22 ± 2.96
30 d after return to low altitude	96	18.63 ± 1.22$^{(1)(2)(3)}$	16.82 ± 1.87$^{(1)(2)}$	27.47 ± 3.34$^{(1)(2)}$	35.43 ± 2.77$^{(1)(2)}$
Plain control	50	18.50 ± 1.30$^{(1)(2)}$	16.76 ± 2.07$^{(1)(2)}$	27.33 ± 3.66$^{(1)}$	35.94 ± 2.86$^{(1)(2)}$

$^{(1)}P < 0.01$ compared with 50 d exposure to high altitude; $^{(2)}P < 0.01$ compared with 12 h after return to low altitude; $^{(3)}P < 0.01$ compared with 15 d after return to low altitude; mPAP: Mean pulmonary arterial pressure; RVID: Right ventricular internal diameter; RVOT: Right ventricular outflow tract; LVID: Left ventricular internal dimension.

Table 10. Metergasis of left ventricles of plateau migrants after return to low altitude at different times ($\bar{x} \pm s$).

Time points	Cases	LVID (mm)	LVEF (%)	Tei index
50 d exposure to high altitude	96	47.21 ± 3.58	48.71 ± 6.81	0.49 ± 0.05
12 h after return to low altitude	96	46.82 ± 3.37	55.87 ± 6.07$^{(1)(2)}$	0.39 ± 0.05$^{(1)}$
15 d after return to low altitude	96	47.12 ± 3.46	63.50 ± 4.45$^{(1)(2)}$	0.31 ± 0.04$^{(1)(2)}$
30 d after return to low altitude	96	46.78 ± 3.24	63.96 ± 4.11$^{(1)(2)}$	0.30 ± 0.03$^{(1)(2)}$
Plain control	50	46.52 ± 3.49	64.73 ± 4.38$^{(1)}$	0.31 ± 0.03$^{(1)(2)}$

$^{(1)}P < 0.01$ compared with 50 d exposure to high altitude; $^{(2)}P < 0.01$ compared with 12 h after return to low altitude; LVID: Left ventricular internal dimension; LVEF: Left ventricular ejection fraction; Tei index. Myocardial performance index.

Table 11. Cardiothoracic ratio of subjects residing at different altitudes ($\bar{x} \pm s$).

Altitude (m)	People of investigation (cases)	Cardiothoracic ratio (%)
Plain control	220	0.494 ± 0.018
3000 - 3750	200	0.498 ± 0.023$^{(1)}$
3751 - 4500	120	0.499 ± 0.024$^{(1)}$
>4500	197	0.504 ± 0.023$^{(1)}$

$^{(1)}P < 0.05$ compared with plain control.

Table 12. Cardiothoracic ratio of subjects residing in plateau after return to the plain at different times ($\bar{x} \pm s$).

Time (months)	People of investigation (cases)	Cardiothoracic ratio (%)
Plain control	220	0.494 ± 0.018
0 - 20	82	0.496 ± 0.022
21 - 40	358	0.498 ± 0.023$^{(1)}$
>40	77	0.499 ± 0.024$^{(1)}$

$^{(1)}P < 0.05$ compared to the plain controls.

Table 13. Select hematological indices of rescue personnel after return to low altitude ($\bar{x} \pm s$).

Group	Cases	WBC ($\times 10^9$/L)	RBC ($\times 10^{12}$/L)	Hb (g/L)	Hct (%)	Plt ($\times 10^9$/L)
Plain control group	133	6.12 ± 1.58	4.72 ± 0.69	139.26 ± 20.11	0.43 ± 0.06	128.20 ± 32.29
15 d after return to low altitude	613	6.57 ± 1.63$^{(1)}$	5.41 ± 0.58$^{(1)}$	162.23 ± 15.83$^{(1)}$	0.50 ± 0.05$^{(1)}$	113.21 ± 36.54$^{(1)}$
30 d after return to low altitude	464	6.74 ± 1.48$^{(1)(2)}$	5.07 ± 0.54$^{(1)(2)}$	151.28 ± 4.78$^{(1)(2)}$	0.47 ± 0.05$^{(1)(2)}$	125.24 ± 34.29$^{(2)}$

$^{(1)}$ $P < 0.05$ compared with plain control group; $^{(2)}$ $P < 0.05$ compared with 15 d after return to low altitude.

3.8.2. Changes in Hematological Indices among People Who Returned to Low Altitude after Living in the Plateau for Five Years

The hematological indices among people who returned to the plain after working in the construction sites of Qingzang for more than five years were determined. It was found that their Hb, Hct, and MCH were all higher compared with those of the plain controls, the Plt count was lower than that of the plain controls ($P < 0.01$), and the RBC count was similar to that of the plain controls (**Table 14**).

A correlation analysis demonstrated that when the body mass index (BMI), blood pressure, and age were restricted, Hb, Hct, MCH, and platelet large cell ratio (P-LCR) positively correlated with the altitude and duration of high altitude residence and negatively correlated with the duration of their return to low altitude. The Plt count was negatively correlated with the altitude and duration of high altitude residence and positively correlated with the duration of their return to low altitude (**Table 15**).

3.8.3. Changes in the Hematological Indices among People Who Returned to Low Altitude after Living in the Plateau for a Long Time

The RBC, Hb, and Hct counts of the subjects who returned to the plain after living in the plateau for a long time were similar to those of the plain controls ($P > 0.05$). To rule out the effects of the duration of their return to the plain on the hematological indices, the duration was divided into the following time periods: less than one year, 1 - 5 years, 5 - 10 years, 10 - 20 years, 20 - 30 years, and more than 30 years. The hematological indices at different periods were compared with those of the plain controls. The study showed that the Hb and Hct counts of those who returned to the plain for less than one year were higher than those of the plain controls ($P < 0.05$); over time, the differences disappeared. The results also demonstrated that the RBC and Hb counts of subjects who returned to the plain for more than 30 years were clearly lower than the plain controls. Because the RBC and Hb counts can be influenced by other factors, such as gender and age, the results were adjusted for gender and age. After this adjustment, the Hb level of subjects who returned to the plain for less than one year was still higher than the level of the plain controls, and the Hb level of other groups was similar to that of the plain controls (**Table 16**).

The Plt counts of subjects who returned to the plain after living in the plateau for a long time was similar to that of the plain controls; however, the Plt count of those who returned to the plain for less than one year, 1 - 5 years, 5 - 10 years, and 10 - 20 years was significantly lower than that of the plain controls. Moreover, after the adjustments for gender and age, the differences were still significant (**Table 16**). After the adjustment for gender and age, the Plt count of those who returned to the plain for more than 20 years was similar to that of the plain controls. The Plt count was positively related to the duration of the return to the plain ($r = 0.137$, $P < 0.05$).

3.8.4. Effects of Mountain Sickness on Hematological Indices of Plateau Migrants after They Return to Low Altitude

The RBC count of those plateau migrants with mountain sickness was significantly higher those without mountain sickness. After the adjustment for gender and age, the differences in RBC count were also significant ($P < 0.05$), while the differences in Hb and Hct were not significant (**Table 17**).

Table 14. Select hematological indices of plateau construction workers 45 months after they returned to low altitude areas ($\bar{x} \pm s$).

Group	Cases	RBC ($\times 10^{12}$/L)	Hb (g/L)	Hct (%)	MCH (pg)	Plt ($\times 10^{9}$/L)
Plain control group	225	4.998 ± 2.296	145.58 ± 15.23	0.436 ± 0.059	30.11 ± 3.95	208.85 ± 59.49
Observation group	560	4.984 ± 1.618	156.02 ± 15.56(1)	0.442 ± 0.053(1)	31.68 ± 3.51(1)	179.47 ± 55.96(1)

(1)$P < 0.05$ compared with plain control group; MCH: Mean corpuscular hemoglobin.

Table 15. Partial correlation analysis of some hematological indices and plateau factors.

Factors	RBC		Hb		Hct		MCH		Plt		P-LCR	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Altitude of construction	0.130	0.029	0.147	0.013	0.265	0.000	0.040	0.497	−0.172	0.000	0.145	0.000
Time of altitude residence	0.065	0.275	0.184	0.002	0.210	0.000	0.129	0.030	−0.193	0.000	0.139	0.001
Time of return to low altitude	−0.099	0.096	−0.187	0.002	−0.259	0.000	−0.106	0.075	0.194	0.000	−0.193	0.000

MCH: Mean corpuscular hemoglobin; P-LCR: Platelet large cell ratio; Control condition. Body mass index, blood pressure, age.

Table 16. Select hematological indices of subjects who returned to low altitude after living in the plateau for a long time ($\overline{x} \pm s$).

Time of return to plain (year)	Cases (male)	Age (year)	RBC ($\times 10^{12}$/L)	Hb (g/L)	Hct (%)	Plt ($\times 10^{9}$/L)
Plain control	114 (73)	58.6 ± 14.4	4.75 ± 0.52	141.3 ± 13.2	42.04 ± 5.28	158.31 ± 47.69
<1	15 (10)	45.7 ± 6.3	4.82 ± 0.62	149.1 ± 19.4$^{(1)}$	43.13 ± 5.09	129.53 ± 36.41$^{(1)}$
1 - 5	69 (29)	53.9 ± 9.9	4.75 ± 0.49	142.7 ± 14.6	42.22 ± 3.68	136.84 ± 59.43$^{(1)}$
5 - 10	84 (46)	60.4 ± 7.5	4.72 ± 0.53	141.4 ± 15.6	42.31 ± 3.97	137.04 ± 52.87$^{(2)}$
10 - 20	92 (51)	63.2 ± 10.7	4.66 ± 0.59	138.2 ± 14.3	41.52 ± 3.89	139.22 ± 57.80$^{(2)}$
20 - 30	53 (27)	65.6 ± 10.4	4.66 ± 0.47	139.7 ± 13.1	42.08 ± 3.52	149.83 ± 45.70
≥30	49 (16)	69.6 ± 10.3	4.5 ± 0.32	135.7 ± 10.8	40.08 ± 3.03	180.73 ± 55.01

Table 17. The effect of mountain sickness on the hematological indices of plateau migrants upon returned to low altitude ($\overline{x} \pm s$).

Group	Cases (male)	Age (years)	RBC ($\times 10^{12}$/L)	Hb (g/L)	Hct (%)
Plain control	114 (73)	58.60 ± 14.40	4.75 ± 0.52	141.30 ± 13.20	42.04 ± 5.28
Observation group A	83 (41)	62.54 ± 11.54	4.82 ± 0.64$^{(1)}$	141.42 ± 17.93	42.43 ± 4.66
Observation group B	279 (138)	60.99 ± 11.09	4.64 ± 0.46$^{(2)}$	139.60 ± 13.35	41.69 ± 3.47

Observation group A. With mountain sickness history; Observation group B. Without mountain sickness history; $^{(1)}P < 0.05$ compared to the plain control group; $^{(2)}P < 0.05$ compared to observation group A.

4. Discussion

Savourey [11] [12] and Grover [13] compared physiological indices of climbers before they ascended the mountain, while they were climbing the mountain, and after they returned to the plain. These studies found that the erythropoietin (EPO), adenosine triphosphate (ATP) concentration, partial pressures of oxygen, red blood cell count and volume, and other indices changed dramatically after the study subjects arrived at the mountain top. The indices restored to normal one to two months after the climbers returned to the plain. Risso and others [14] assumed that when mountain climbers returned to the plain from the plateau, abnormal environmental stimulants disappeared and brought no harm to the human body. However, most scholars reported that when high altitude natives (43 - 50 years old) traveled to sea level, their stroke index (SI) increased, their heart rate decreased, and the cardiac index (CI) remained unchanged [15] [16]. Du and others [17] investigated 590 cases of high altitude de-acclimatization syndrome in Golmud and found that 38% of the subjects presented with chest tightness, dizziness, sleepiness, weakness, anorexia, abdominal distension, and other clinical manifestations when they returned to the plain. The symptoms were related to age, the duration of high altitude residence, and labor intensity in the plateau. Older age and a longer duration of residence at high altitude both correlated with the development of high altitude de-acclimatization syndrome. Physical laborers were more likely to develop the disease than were mental workers. Cui and others [18] investigated 626 cases of high altitude de-acclimatization syndrome and found that the early symptoms were nervous and digestive, followed by respiratory and circulatory. After approximately one year, most subjects could overcome de-acclimatization and adapt to the new living environment.

In our study, the incidence of high altitude de-acclimatization syndrome was very high (84.36%), and several body systems were affected, such as the hematological, digestive, circulatory, respiratory and nervous systems, which were consistent with studies by Cui and others [19]. However, we found that it took approximately one year for the hematological indices to return to normal, and in some cases, this process took more than four years [20]. The ventricular function and structure recovered slowly among plateau migrants after they returned to the plain. In subjects who lived on the plateau for a short time, the ventricular function and structure recovered one month after they returned to the plain, and the left ventricle recovered faster than the right ventricle. In subjects who lived in the plateau for more than five years, the ventricular function and structure recovered two to three years after the returned to the plain. In a few cases, the recovery time was more than four years. In subjects who lived on the plateau for more than ten years, the ventricular function and structure recovered five to ten years af-

ter the return to the plain [20]. The results suggested the plateau migrants experienced high altitude de-acclimatization for a long time after they returned to the plain. These migrants may develop high altitude de-acclimatization syndrome if they do not overcome de-acclimatization, thus affecting their daily life and work and forcing a few to return to high altitude areas. Therefore, it is of great practical and clinical significance to improve the prophylaxis, diagnosis, and early treatment of high altitude de-acclimatization syndrome.

Because the diagnosis of high altitude de-acclimatization syndrome has not been standardized, it is vital to formulate diagnostic criteria. Our study demonstrated that high altitude de-acclimatization syndrome is different from other high altitude diseases. The latter often has typical symptoms and signs while the former does not have specific symptoms; instead, it has a series of non-specific symptoms such as dizziness, fatigue, weakness, sleepiness, diarrhea, cough, palpitation, chest tightness, vertigo, hair loss, increased appetite, and weight gain [21]. Physical examination shows no specific signs but may demonstrate some abnormal changes. First, the RBC, Hb, and Hct are higher than those of plain natives, and the Plt count is lower than that of plain natives [19]. Second, the plateau migrants experience cardiac abnormities, such as abnormal ventricular diastole, increased pulmonary arterial pressure, ventricular hypertrophy, and decreased left ventricular contraction. Right ventricular hypertrophy and increased RVOT and RVID/LVID are major changes experienced by this population [22]-[24]. Third, an examination of the urinary system may reveal proteinuria and increased microalbuminuria. Fourth, a chest X-ray examination could show an increased cardiothoracic ratio. Fifth, these patients may have low blood and pulse pressure [20]. Other tests, such as liver and kidney function, ECG, serum enzyme, and humoral immune function, cannot detect specific changes. Therefore, the diagnosis of high altitude de-acclimatization syndrome should be based on clinical symptoms, signs, and other examination results such as heart, lung, and hematological examinations.

In summary, although high altitude de-acclimatization syndrome does not have typical symptoms and signs, it manifests some specific changes in clinical symptoms, signs, and laboratory examinations. The changes are of high value in the diagnosis of high altitude de-acclimatization syndrome. Based on our epidemiological survey and multi-center randomized controlled clinical trial of more than 3000 subjects who returned to the plain from the plateau and the relevant literature, we have formulated diagnostic criteria for high altitude de-acclimatization syndrome.

4.1. Necessary and Assistant Conditions of the Diagnosis

The necessary conditions for the diagnosis [25]-[27] are recent return to the plain and more than three of the following symptoms, *i.e.*, dizziness, fatigue, weakness, sleepiness, insomnia, palpitation, chest tightness, decreased appetite, general malaise, and memory loss, or presentation with dizziness, weakness, sleepiness, or general malaise. In addition, heart, lung, brain, kidney, and other organ diseases must be excluded, and the patient must not experience obvious alleviation of the above symptoms after short-term rest or symptomatic treatment.

The following conditions can assist in the diagnosis of de-acclimatization syndrome [28]-[30]: higher RBC, Hb, and Hct than the maximum of the controls at the same altitude; Plt lower than the minimum of the controls at the same altitude; Serum myocardial enzyme creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) activity lower than or equal to the mean of the controls at the same altitude; microalbuminuria; abnormal cardiac function; slightly higher pulmonary arterial pressure than the mean of the controls at the same altitude; weakened left and right ventricles (Tei indices increase and LVEF, RVEF, LVFS and RVFS decrease); right ventricular hypertrophy; increased RVOT and RVID/LVID; short-term memory loss; and higher total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) levels than the mean of the controls at the same altitude; Serum testosterone and estradiol levels are lower, especially the estradiol level significantly lower than control group; bone mineral density testing. The ulna, radias and femoral or tibial fibular mineral density decreased significantly.

One can be diagnosed with high altitude de-acclimatization syndrome if one meets all of the necessary conditions and one of the assistant conditions.

4.2. Evaluation Criteria of High Altitude De-Acclimatization Syndrome

To accurately evaluate the severity of high altitude de-acclimatization syndrome, it is necessary to grade its symptoms and signs, which can assist in the objective evaluation of the symptoms. Thus, based on the studies by Cui and others [31], as well as our study, we have established the following grading and evaluation criteria (**Table 18** and **Table 19**).

Table 18. Grading and scoring criteria for the symptoms of high altitude de-acclimatization.

Symptom classification	Evaluation standard	Score
±	Mild symptoms, daily work not affected	z
+	Mild symptoms, daily work affected, greatly improved after medication	1
++	Severe symptoms, daily life affected, some alleviation after medication	2
+++	Severe symptoms, daily life affected, no significant relief after medication	3

Table 19. Grading diagnosis of high altitude de-acclimatization.

Classification	Diagnostic criteria
Almost no reaction (±)	Suspicious symptoms (±) or total scores 0 - 5
Mild reaction (+)	Slight symptoms (+) or total scores 6 - 15
Moderate reaction (++)	More serious symptoms (++) or total scores 16 - 25
Severe reaction (+++)	Very serious symptoms (+++) or total scores ≥ 26

4.3. Precautions in Scored Diagnosis of High Altitude De-Acclimatization Syndrome

One can be diagnosed with high altitude de-acclimatization syndrome after the following diseases are ruled out: primary organ diseases such as heart, kidney, brain or lung diseases; malignant tumors such as leukemia and regenerative anemia; high altitude heart disease and erythema; and flu, upper respiratory tract infection, infectious diarrhea, and primary heart disease that are diagnosed after one returns to the plain.

In addition, subjects who live in different altitudes or perform different jobs in the plateau have different high altitude de-acclimatization syndrome frequencies after they return to the plain because the incidence of symptoms is positively correlated to the altitude of the plateau, the length of high altitude residence, and the labor intensity while on the plateau. Therefore, the physician should inquire about these details to ensure an accurate diagnosis. High altitude de-acclimatization syndrome indicates a poor adaptation to the environment among plateau migrants who return to low altitude or the plain. It is a non-specific syndrome with complex manifestations. It is not difficult to diagnose; however, one must consult diagnostic criteria and consider all of the clinical symptoms and signs to make an accurate diagnosis.

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Authors' Contributions

Zhou Q. Q., Yang S.Y., Yuan Z.C., Zhang X.F., and Wang G.S. designed the trial and analyzed the data. Zhou Q.Q. drafted the manuscript and obtained the funding. Zhang X.F., Shi Z.F., Yang Y.L., Wu Y.H., and Wang G.S. collected data. Wang Y.H., Zhang X.F., Shi Z.F., Yang Y.L., Wu Y.H., and Wang G.S. contributed to administrative, technical, and material support with project design guidance from a Zhou Q. Q. project. All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Competing Interests

All the authors certify that there is no actual or potential conflict of interest. In this study, Zhou Q.Q. is responsible for project design and data collection, paper writing, Yang S.Y., Yuan Z.C., Zhang X.F., Shi Z.F., Yang

Y.L., Wu Y.H., Wang F.L., Wang G.S. and Zhou Q.Q., etc. are responsible for data acquisition and experimental observation respectively. Each division of labor is clear, everyone's responsibility is clear, and there is no conflict of interest among all the authors.

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Abbreviation

ECG: Electrocardiogram;
SMS: Severe mountain sickness;
MAMS: Mild mountain sickness;
NAMS: No mountain sickness;
PC: Plain control;
RVID/LVID: Right ventricular internal diameter/left ventricular internal dimension;
Tei index: Myocardial performance index;
LVEF: Left ventricular ejection fraction;
LVFS: left ventricular tractional shortening;
mPAP: Mean pulmonary arterial pressure;
RVID: Right ventricular internal diameter;
RVOT: Right ventricular outflow tract;
LVID: Left ventricular internal dimension;
WBC: White blood cell;
RBC: Red blood cell;
Hb: Hemoglobin;
Hct: Hematocrit;
MCV: Mean corpuscular volume;
MCH: Mean corpuscular hemoglobin;
Platelet: Plt;
BMI: Body mass index;
SI: Stroke index;
CI: Cardiac index;
P-LCR: Platelet large cell ratio;
EPO: Erythropoietin;
ATP: Adenosine triphosphate;
CK-MB: Creatine kinase-MB;
LDH: Lactate dehydrogenase;
ALT: Alanine transaminase;
AST: Aspartate transaminase.

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