• Clinical Research •

High-altitude effect on corneal endothelial cells and prognosis in patients with cataract surgeries: a propensity score matched analysis

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Abstract

● **AIM:** To compare analysis of the impact of high altitude on corneal endothelial cells, and the prognosis in patients with cataract surgeries.

● **METHODS:** Totally 265 plateau patients with cataract surgeries performed between January 2019 and July 2022 (average altitude=3000 m), and 524 plain patients with cataract surgeries performed between January 2020 and July 2022 were included. The propensity score matching (PSM) method was applied to match the basic information of patients in both regions on a 1:1 basis. Corneal endothelial cell density (ECD), coefficient of variation (CV), hexagonal cell ratio (HEX), duration of surgery, and pre- and postoperative visual acuity (VA) were compared retrospectively, and correlation tests were done.

● **RESULTS:** Totally 223 pairs have been matched successfully. The HEX in the plateau group was higher than that in the plain group (61.95%±6.191% *vs* 44.91%±6.829%, *P*<0.001). For ECD and CV, no significant differences were observed between both groups (*P*>0.1). The pre- and postoperative VA of patients with cataract surgeries in the plateau group were lower (1.40±0.610 *vs* 0.71±0.514, *P*<0.001 & 0.68±0.479 *vs* 0.18±0.259, *P*<0.001), and the duration of surgery was longer than those in the plain group (27.06±14.900 min *vs* 16.03±8.033 min, *P*<0.001). No significant associations were found between the post-operative VA and the corneal endothelial parameters (*P*>0.05), while the post-operative VA was significantly related to the pre-operative VA and the duration of surgery (*P*<0.05).

● **CONCLUSION:** The relative hypoxic environment of the plateau does not promote the apoptosis of corneal endothelial cells, but may lead to the compensatory increase of their functions. In plateau patients, no significant associations are found between the poor VA and the corneal endothelial functions early after cataract surgeries.

● **KEYWORDS:** cataract surgery; corneal endothelial cells; hypoxia; plateau; propensity score matching

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INTRODUCTION

Worldwide, cataracts are the leading cause of blindness, especially in economically underdeveloped areas[1]. In the past ten years, the all-around development of the Chinese economy and the comprehensive medical assistance to the western region promoted the increase in cataract phacoemulsification surgeries in the Qinghai-Tibet plateau area. Based on our clinical experience, the intra- and postoperative corneal edemas were generally more severe in the plateau compared to the inland regions, resulting in increased surgical difficulty and early postoperative vision loss. The cornea's transparency depends on the arrangement of corneal stromal fibroblasts and its relatively dehydrated state[2]. The corneal endothelium acts as an internal barrier to the cornea, and its pumping role is essential to reducing corneal edema[3]. Studies have shown a significant correlation

between the quality of corneal endothelial cells and the incidence of intra- and postoperative corneal edema[4-5]. Given that the corneal endothelium cannot regenerate[6], and is sensitive to oxygen levels[7], it is important to understand the effects of long-term high-altitude hypoxia on the corneal endothelium. Recent studies have indicated that hypoxia and low atmospheric pressure can adversely affect corneal endothelial cells, potentially leading to increased cell loss and dysfunction[8-9]. However, there is limited research on the condition of corneal endothelium and cataract surgery prognosis in patients from high-altitude regions.

To address this gap, we applied the propensity score matching method (PSM) to compare the corneal endothelial cell density (ECD), coefficient of variation, and the hexagonal cell ratio in patients with cataracts in plateau and plain regions. We aimed to observe whether the high-altitude environment affects corneal endothelial functions and evaluate its influence on cataract surgery outcomes, specifically postoperative visual acuity (VA).

PARTICIPANTS AND METHODS

Ethical Approval This research was conducted following the ethical principles of the 2024 Declaration of Helsinki and was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine under the approval number IIT20220939A. All participants were orally informed and consented to publication of relevant data, and no stipend was provided.

Population Inclusion This was a retrospective study including 265 and 524 patients located in plateau regions (plateau group), and plain regions (plain group), respectively. The plateau group consisted of patients subjected to cataract surgeries between January 2019 and July 2022 at the People's Hospital of Haixi Autonomous Prefecture of Qinghai Province (average altitude is 3000 m). The plain group included patients whose cataract surgeries were performed between January 2020 and July 2022 at the First Affiliated Hospital of Zhejiang University.

Inclusion criteria 1) Adults over 18 years old with successful one-eye cataract surgeries performed in either hospital; 2) No history of preoperative ophthalmic surgeries (including myopia laser surgery); 3) No history of eye trauma or vitreoretinal disease; 4) No previous anterior eye segment disease, like uveitis, keratitis, and Fuchs corneal endothelial dystrophy; 5) No active inflammation in the eye area; 6) No long-term history of ophthalmic medication, nor of wearing contact lenses; 7) Completion of the corneal endothelial examination, and the number of corneal endothelial cells counted by corneal specular microscope is greater than 50; 8) Completion of the fundus examination, and no obvious abnormality was detected in the optic nerve and macula.

Equipment inspection, processes and main observation indicators The corneal endothelial examination was performed within one week before the cataract surgery, with the corneal endothelial microscope Nidek (CEM-530), and the Tomey (EM-4000) in the People's Hospital of Haixi Autonomous Prefecture of Qinghai Province, and in the First Affiliated Hospital of Zhejiang University, respectively. To perform Phaco, we used the Centurion® Vision System (Alcon, USA). In both hospitals, the perfusion solution used was physiological sodium chloride (Sichuan Kelun Company), and the viscoelastic agent was sodium hyaluronate gel (Bausch and Lomb Company). All surgeries were performed by senior cataract specialists with a cumulative cataract surgery of more than 1000 cases.

The major observation and recording indicators included: corneal ECD, coefficient of variation (CV), hexagonal cell ratio (HEX), average cell size (ACS), duration of surgery (min), preoperative best-corrected VA (BCVA), and BCVA on the day after surgery (logMAR).

Statistical Analysis PSM was performed using SPSS 27.0 R statistical tools to ensure a balanced comparison between the plateau and plain groups. First, propensity scores for each patient were calculated using a logistic regression model, with the group (plateau or plain) as the dependent variable and age, gender, diabetes, and hypertension as independent variables. The nearest neighbor matching algorithm was used with a 1:1 match ratio, and a caliper value of 0.02 was set to ensure close matches, yielding 223 matched pairs between the plateau and plain groups. Post-matching, *t*-test and Chi-square test of independent samples were utilized to compare the corneal ECD, CV, HEX and the ACS between the two groups, with differences considered statistically significant at $P<0.05$. Focusing on the corneal endothelial parameters, we used the Spearman method to test whether a correlation exists between the extent of surgery and the BCVA on the day after surgery. To further eliminate the influence of surgery duration and cataract severity on visual outcomes, a secondary PSM was performed using surgery duration and preoperative VA as matching variables, maintaining a caliper value of 0.02 for 1:1 matching. This resulted in 69 matched pairs, which were subsequently analyzed using independent sample *t*-tests to evaluate differences in visual prognosis between the two groups.

RESULTS

The results of the PSM showed a total of 223 matches, with a significant difference in the proportion of age, sex and history of diabetes in both groups before PSM ($P<0.05$), but no differences were found after PSM (Table 1). The BCVA, before and after surgery, were significantly lower in the plateau group compared to the plain group (1.40±0.610

Table 1 Baseline information of the plateau and plain groups before and after PSM

Parameters	Pre-PSM				Post-PSM			
	Plateau group (*n*=265)	Plain group (*n*=524)	t/χ^2	*P*	Plateau group (*n*=223)	Plain group (*n*=223)	t/χ^2	*P*
Age (y), mean±SD	66.68±9.017	72.24±9.966	-7.634	<0.001	67.46±7.955	67.57±8.521	-0.138	0.890
Sex (male), *n* (%)	119 (45)	197 (38)	3.917	0.048	96 (41)	90 (40)	0.332	0.564
Diabetes, *n* (%)	38 (14)	5 (1)	61.194	<0.001	3 (1)	3 (1)	0.000	1.000
HBP, *n* (%)	93 (35)	209 (40)	1.710	0.191	74 (32)	65 (28)	0.847	0.358
Operation eye (right), *n* (%)	138 (52)	277 (53)	0.044	0.834	113 (51)	124 (56)	1.089	0.297
Operation duration (min), mean±SD	27.47±16.094	16.57±9.186	9.770	<0.001	27.06±14.900	16.03±8.033	8.394	<0.001
BCVA pre-operation (logMAR)	1.43±0.601	0.74±0.534	16.279	<0.001	1.40±0.610	0.71±0.514	12.791	<0.001
BCVA post-operation (logMAR)	0.68±0.485	0.20±0.289	17.349	<0.001	0.68±0.479	0.18±0.259	13.712	<0.001

BCVA: Best corrected visual acuity; HBP: High blood pressure; SD: Standard deviation; PSM: Propensity score matching.

vs 0.71±0.514, *P*<0.001), and (0.68±0.479 *vs* 0.18±0.259, *P*<0.001), respectively. The cataract surgery duration was significantly longer in the plateau group than in the plain group (27.06±14.900min *vs* 16.03±8.033min, *P*<0.001; Table 1).

Regarding the corneal endothelium, the HEX ratio was significantly higher in the plateau than in the plain group (61.95%±6.191% *vs* 44.91%±6.829%, *P*<0.001). There were no significant differences between the corneal ECD (2634.38±398.607 cells/mm^2 *vs* 2636.31±271.268 cells/mm^2, *P*=0.952), the CV (39.84%±8.238% *vs* 39.83%±5.745%, *P*=0.984), and the endothelial ACS (391.29±86.603 μm^2 *vs* 383.91±52.097 μm^2, *P*=0.276; Figure 1).

We found no significant correlation between the corneal ECD, CV, and HEX ratio with cataract surgery duration, and the postoperative VA. The postoperative VA was significantly correlated with the duration of surgery (*P*<0.05), and the preoperative BCVA (*P*<0.01; Figure 2).

After PSM matching of pre-operation BCVA and operation duration in both group, 69 pairs has been matched. We found that the early postoperative VA of the plateau group was significantly lower than that in the plain group (0.85±0.566 *vs* 0.35±0.447, *P*<0.001), under balanced conditions of cataract severity, and surgery duration (Table 2).

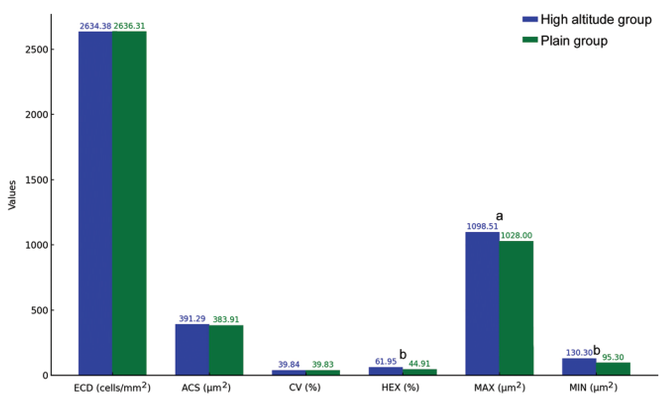

Figure 1 Comparison of corneal endothelium parameters in the plateau and plain groups after PSM [a]*P*<0.05, [b]*P*<0.01. ECD: Corneal endothelial cell density; ACS: Average cell size; CV: Coefficient of variation; HEX: Hexagonal cell ratio; MAX: Maximum cell size; MIN: Minimum cell size.

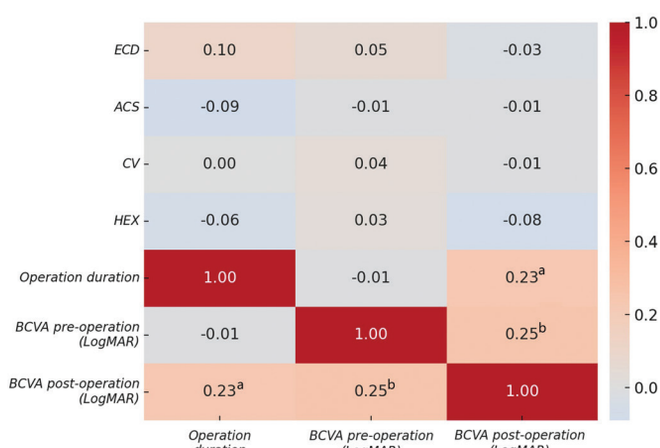

Figure 2 Heatmap of correlations between corneal endothelium parameters, operation duration, and BCVA [a]*P*<0.05, [b]*P*<0.01. ECD: Corneal endothelial cell density; ACS: Average cell size; CV: Coefficient of variation; HEX: Hexagonal cell ratio; BCVA: Best corrected visual acuity.

DISCUSSION

In this study, we compared the corneal endothelial parameters and the BCVA before and after cataract surgeries in plateau and plain regions and explored whether the long-term residence in the plateau hypobaric hypoxia environment had an impact on the corneal endothelium and the prognosis of cataract surgery. We found that, after the correction by PSM of the baseline age, and the chronic underlying diseases, like hypertension and diabetes, the plateau environment did not have an impact but rather increased the functional reserve of the corneal endothelium.

The corneal endothelium is sensitive to environmental oxygen concentrations, and exposure to prolonged chronic hypoxia may lead to apoptosis of the corneal endothelial cells[8]. Numerous studies have shown that the long-term use of contact lenses, chronic obstructive pulmonary disease, or obstructive sleep apnea syndrome may cause severe damage to the corneal endothelium of patients due to hypoxia, worsening the effect over time[10-13]. As the corneal endothelial cells do

Table 2 Post-operation BCVA after PSM matching of pre-operation BCVA, and operation duration mean±SD

Parameters	High altitude group (*n*=69)	Plain group (*n*=69)	*t*	*P*
BCVA pre-operation	1.26±0.583	1.33±0.591	-0.633	0.528
Operation duration	23.70±12.878	21.38±11.144	1.131	0.260
BCVA post-operation	0.85±0.566	0.35±0.447	5.706	<0.001

BCVA: Best corrected visual acuity; PSM: Propensity score matching.

not regenerate, the adjacent endothelial cells have expanded to fill the surrounding cell-deficient areas, resulting in varying sizes, and a decrease in the proportion of hexagonal cells[14-15]. Some studies suggested that if the endothelial cells lose the hexagonal mosaic pattern, this irregular arrangement becomes unstable and more sensitive to stimulation. Hence, the CV and HEX are significant clinical indicators for measuring the functional reserve of endothelial cells[16]. In this study, we found no significant differences in the corneal ECD, but a higher HEX in plateau patients compared with plain patients, suggesting that the relatively hypoxic environment in plateau regions could enhance corneal endothelial function. In line with these observations, an *in vitro* study by Bhadange *et al*[17] showed that in a hypoxic environment, corneal endothelial cells can be induced to enhance the protective effect of surgical operations and increase the stability of these cells. Cakmak *et al*[18] also found that obstructive sleep apnea syndrome measurement does not affect the corneal endothelial cells. The results of these studies suggested that the hypoxia-related damage to the corneal endothelium might develop under specific time and conditions which is accumulated to a certain degree. The patients involved in this study lived at an average altitude of 3000 m, with an oxygen content of approximately 14.4% in air, being 70% compared to that of the environment plain patients live in, with an average oxygen saturation of 90%[19]. Thus, exposure to relatively hypoxic environment for long periods would not damage the corneal endothelium and even increase the stability of endothelial cells.

Our results on cataract surgeries and postoperative VA indicated that the early postoperative VA of plateau patients was significantly lower compared to plain patients. Also, according to most cataract surgery specialists, the intraoperative and postoperative corneal edemas seemed to be more severe in plateau patients than in plain patients. The correlation test results showed that there was no correlation between the postoperative VA and the corneal endothelial parameters, but the postoperative VA was significantly related to the duration of surgery and preoperative VA. The duration of surgery and preoperative VA can significantly indicate a higher severity of cataract, often necessitating greater phacoemulsification energy during the surgical procedure. Based on our data, significant differences were observed in the average age at the time of cataract surgery, the duration of surgery, and preoperative VA between the plateau group and the plain group. These differences may be attributed to the significantly worse cataract status observed in plateau patients compared to those in the plain region. This may be associated with the strong ultraviolet radiation in the plateau regions, and the habits of participating in outdoor activities of highland populations[20]. Severe cataracts, long surgical duration, and more phacoemulsification energy used are probably the main causes of postoperative corneal edema[21]. To exclude the potential causes of postoperative corneal edema like severe cataracts, long surgical duration, and more phacoemulsification energy, the duration of surgery and preoperative VA were used as matching variables for another PSM. We found that the early postoperative VA of the plateau group was still significantly lower than that in the plain group, under balanced conditions of cataract severity, and surgery duration, thus indicating that there are other causes for corneal edema after cataract surgery in the plateau regions.

Early postoperative VA is typically influenced by corneal edema. No evidence of postoperative corneal edema due to the difference in the surgical process, and proficiency was observed, based on the absence of differences in the phacoemulsification instruments and the intraoperative perfusion fluid between the plateau and the plain groups, and that the surgeries were performed by senior cataract experts in the plain region. Numerous studies have demonstrated that hypoxic environments can readily induce corneal edema[22]. Research indicates that corneal thickness tends to be greater in high-altitude areas compared to low-altitude regions[23]. Hypoxia is believed to disrupt the local microenvironment, leading to the accumulation of lactic acid and a decrease in pH, which impairs the metabolic activity of corneal epithelial and endothelial cells and subsequently affects ATP production[24-25]. Furthermore, hypoxia can intensify oxidative stress and inflammatory responses, increasing the generation of reactive oxygen species. This results in lipid peroxidation of cell membranes, and damage to proteins and DNA, further compromising the barrier and pump functions of the cells, ultimately causing corneal edema[26]. Thus, despite no differences in corneal endothelial cell parameters between the plateau and the plain groups, the hypoxic conditions in high-altitude regions may contribute to and exacerbate postoperative corneal edema through local metabolic disturbances. However, further studies are needed to determine whether the local

oxygen supply, reaching the concentration of oxygen in plain areas, could alleviate corneal edema during and after cataract surgery.

This study is one of the first researches on corneal endothelial cells and cataract surgeries in plateau regions compared with plain regions. But some limitations must be addressed: 1) This was a retrospective study with missing data on the recovery of vision at one week and one month after surgery, with the difficulty of comparing the duration of postoperative corneal edema and the final prognosis. Besides, there is no standardized record of the CNP (cortical, nuclear, posterior subcapsular) cataract grading, and the degree of postoperative corneal edema, which can only be reflected by BCVA. 2) The corneal endothelial microscopes used in both regions were different, thus the equipment may cause a certain degree of systemic bias. 3) No measurement of tear fluid, anterior chamber oxygen concentration, pH value and other data was done to reflect the local corneal metabolism and environment. There is speculation on the relative cause of corneal edema after cataract surgery in the plateau group. Thus, further studies are needed to confirm this hypothesis.

In conclusion, the results showed that the relatively hypoxic environment at an average altitude of 3000 m does not promote the apoptosis of corneal endothelial cells, but it may compensate for the increased stability of the corneal endothelium by augmenting the proportion of endothelial hexagonal cells, thus enhancing their function. The poor VA due to relative corneal edema in the early postoperative period after cataract surgery in plateau patients was not associated with corneal endothelial function but may be associated with the relatively severe cataracts, long surgery duration, and the local metabolic abnormalities of the cornea that resulted from environmental hypoxia.

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