• Clinical Research •

Corneal endothelial characteristics and biometric parameters in microcornea

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Abstract

● **AIM:** To assess the corneal biometric parameters and endothelial cell characteristics in microcornea patients, and exploring their correlations.

● **METHODS:** This cross-sectional study included 28 patients of microcornea with uveal coloboma (MCUC), 13 patients of microcornea without coloboma (MCNC), and 30 age-matched healthy individuals (the control group). Corneal biometric parameters such as axial length (AL), anterior chamber depth (ACD), and white-to-white corneal diameter (WTW) were measured using the IOL Master. The corneal endothelial cell density (ECD), percentage of hexagonal cells (6A), average cell area (AVE), maximum cell area (MAX), minimum cell area (MIN), cell area standard deviation (SD), and coefficient of variation (CV) were collected by specular microscopy.

● **RESULTS:** This study included MCUC and MCNC patients with age- and sex-matched controls. All patients exhibited significantly reduced WTW (MCUC: 8.51±0.71 mm; MCNC: 9.08±0.42 mm) and worse logMAR BCVA (MCUC 0.62±0.43; MCNC 0.46±0.28) compared to controls (both $P<0.001$). The ECD was 3106.32±336.80 cells/mm² in the MCUC group and 2906.92±323.53 cells/mm² in the MCNC group, both significantly higher than the control group (2647.43±203.06 cells/mm², $P<0.05$). In contrast, the CV, AVE, SD, and ACD in the MCUC and MCNC groups were significantly lower compared to controls ($P<0.01$). In patients with microcornea, the WTW was negatively correlated with the ECD and 6A, but positively with the CV, MAX, AVE, and SD. The ACD was negatively linked to the ECD, but positively to the AVE.

● **CONCLUSION:** The corneal ECD and 6A are increased, while the CV is decreased in patients with microcornea, particularly in those accompanied by uveal coloboma. The ECD and morphology demonstrate close correlations with the WTW and ACD.

● **KEYWORDS:** microcornea; corneal endothelial cell; corneal biometric parameters; uveal coloboma; anterior chamber depth

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INTRODUCTION

Microcornea (MC) is a congenital developmental anomaly of the eye, characterized by a smaller cornea than the normal, typically less than 10 mm in horizontal diameter[1-3]. It may manifest as an isolated disorder or coexist with other ocular malformations due to genetic variability[4-5]. In certain cases, patients may exhibit iris or choroidal coloboma, along with microphthalmia, cataracts, retinal detachment or myopia, resulting in substantial visual impairment[6-7].

The cornea develops from surface ectoderm, neural crest cells, and additional tissues. The corneal endothelium, a single layer of hexagonal cells located in the innermost part layer of the cornea, is essential for maintaining corneal transparency and thickness[8-9]. Abnormal anterior segment development adversely affects the corneal endothelium[10-11]. Previous studies have indicated abnormal axial length (AL) development and

altered corneal thickness in MC[12-13]. Corneal endothelial cells (CECs) in patients with MC demonstrate changes in density and morphology[14]. However, the conclusions of these studies are inconsistent, and the systematic correlations between CECs and corneal biometric parameters, particularly in patients with MC and uveal coloboma, remain insufficiently investigated.

This study investigated corneal biometric parameters and endothelial cell characteristics (density and morphology) in MC patients. Additionally, it sought to analyze the correlation between CEC parameters and corneal biometric parameters, ultimately exploring the pathological characteristics of MC with or without uveal coloboma, and providing a novel strategy to guide clinical interventions and treatments.

PARTICIPANTS AND METHODS

Ethical Approval All procedures involving human participants were in accordance with the ethical standards of Shandong Eye Hospital and with the 2024 Helsinki Declaration and its later amendments. All patients were informed about the purpose and methods of this study and signed an informed consent form for participation. The study was approved by the Shandong Eye Hospital Ethics Committee (SDSYKYY202207-1). The registration number for this clinical trial is ChiCTR2400090005.

Patient Information and Sample Size Calculation This cross-sectional study included 25 patients (41 eyes) with MC who were treated at Shandong Eye Hospital from May 2019 to July 2024, comprising 17 individuals (28 eyes) with concurrent uveal coloboma (the MCUC group) and 8 individuals (13 eyes) without uveal coloboma (the MCNC group). Twenty-four healthy individuals (30 eyes) of the same age were selected as the control group.

Based on previous studies[13-14], we assumed that the corneal endothelial cell density (ECD) of the control, MCNC, and MCUC groups was 2700, 2800, and 3400 cells/mm^2, and the corresponding cell area standard deviation (SD) was 300, 450, and 300 cells/mm^2, respectively. The study was powered at 90% to find a significant result, and a dropout rate of 15% was assumed. The one-way analysis of variance *F*-tests module in PASS (version 15; NCSS, LLC) was performed, using a list of means (μi's) for σm calculation, with α set at 0.05. The sample size was determined to be 13 cases in each group. Finally, the MCNC group included 13 cases, the MCUC group 28 cases, and the control group 30 cases.

Inclusion and Exclusion Criteria The corneal white-to-white diameter (WTW) was <10 mm in all patients with MC, who were assigned to the MCUC group if there was iris, choroidal or retinal coloboma and the MCNC group if there was no uveal coloboma. Healthy subjects were included if their WTW was >10 mm and they had no ocular dysplasia such as uveal coloboma. Patients with diabetes, glaucoma, keratitis, Fuchs corneal endothelial dystrophy, other ocular diseases, or a history of ocular trauma or surgery were excluded.

The following design elements were considered to mitigate potential bias. First, the examining technicians had access only to de-identified data and were unaware of the patients' clinical diagnoses. Grouping was conducted by three independent ophthalmologists based on objective criteria. The statistician used anonymized group codes during the data analysis phase and remained unaware of the study hypotheses prior to the assessment. Furthermore, the informed consent document only stated that structural differences in the cornea were explored and did not mention the association of uveal coloboma with the grouping hypothesis.

Eye Examination All patients and controls underwent comprehensive eye examinations. The international standard logarithmic vision meter was used for visual acuity (VA) and best-corrected visual acuity (BCVA) measurements. Slit-lamp microscopy (SL-D701, Topcon, Japan) was performed for the anterior segment examination. Intraocular pressure (IOP) was measured using a rebound tonometer (SW-500, Suoer, Tianjin, China). Ultrasound biomicroscopy (UBM; SW-3200 L, Suoer, Tianjin, China) was utilized to measure anterior segment parameters. Fundus photography was performed using Optos ultra-wide-field (UWF) scanning laser ophthalmoscopy (SLO, P200DTx, OPTOS, California, USA) and optical biometry (IOLMaster 700, Zeiss, Germany) for measuring the AL, corneal curvature, anterior chamber depth (ACD), and lens thickness (LT).

Corneal Biometric Parameter Measurement The AL, ACD, LT, keratometry spherical equivalent (SE), keratometry values at the flat axis (K1) and steep axis (K2), and corneal astigmatism based on keratometry measurements (ΔK) were measured using the IOL Master 700 (Zeiss, Germany). The WTW was noted as the horizontal corneal diameter, which was measured using the IOL Master 700 and adjusted by the Castroviejo calipers (E2404; Storz Ophthalmics, Tuttlingen, Germany). All measurements were conducted by experienced operators in a controlled examination environment to ensure all participants in a natural state of pupil dilation, including the use of standard lighting conditions (300-500 lx) and the discontinuation of medications that may affect the pupil size. Participants were seated, and their jaws were stabilized using a mandibular bracket. Forehead support was provided, allowing participants to fixate on a target within the instrument. Measurements were initiated following each blink, with three repetitions conducted to obtain an average value.

Corneal Endothelial Cell Examination Measurements of CECs were performed using non-contact specular microscopy (Konan, Nishinomiya, Japan) by experienced technicians. Patients were positioned at the specular microscope with

forehead and chin rests properly adjusted. After focusing on the internal fixation target, central corneal endothelial images were captured. Over 75 consecutive endothelial cells were analyzed using the instrument's software (KSS-419II SP, v.15.23), which automatically generated metrics, including ECD, coefficient of variation (CV), hexagonal cell percentage (6A), average (AVE), maximum (MAX) and minimum (MIN) cell areas, and cell area SD.

Statistical Analysis The data are presented as means±SD for continuous variables and as proportions for categorical variables. The normality of continuous variables was assessed using the Shapiro-Wilk test, and the variance equivalence was assessed using the Levene's test. For categorical variables, Fisher's exact test was performed. Normally distributed continuous variables were analyzed with one-way ANOVA with variance-appropriate post hoc tests (Bonferroni for equal variances, Tamhane T2 for unequal). Non-normally distributed variables were analyzed using Kruskal-Wallis *H* test followed by Bonferroni-adjusted Mann-Whitney *U* pairwise comparisons. The correlations between corneal biometric and endothelial cell parameters were assessed using the Spearman correlation analysis. A *P*-value <0.05 was defined as statistically significant. The primary analysis was performed using the SPSS 26.0 software (IBM, Armonk, NY, USA), and the visualization of correlation tests was performed using the GraphPad Prism 9 software (GraphPad Software, Boston, MA, USA).

RESULTS

Demographic and Clinical Characteristics This study included 25 patients (41 eyes) diagnosed with MC, categorized into two groups: 17 patients (28 eyes) with uveal coloboma (MCUC) and 8 patients (13 eyes) without uveal coloboma (MCNC). There were 10 males with 17 eyes (41.46%) and 15 females with 24 eyes (58.54%) among patients with MC. The mean age was 43.50±11.04y in the MCUC group and 46.54±17.33y in the MCNC group. The control group included 10 males with 15 eyes (50%) and 14 females with 15 eyes (50.00%), with a mean age of 45.60±12.88y. Statistical analysis revealed no significant difference in age, gender, or IOP among the three groups (*P*>0.05). Both the MCUC and MCNC groups showed significantly worse logMAR BCVA (0.62±0.43 and 0.46±0.28, respectively) compared to controls (0.07±0.06; both *P*<0.001). No significant difference in age, gender, BCVA, or IOP was found between the MCUC and MCNC groups (*P*>0.05; Table 1).

Slit-lamp microscopy demonstrated reduced corneal diameters in all patients with MC, and also iris coloboma and cataracts in the MCUC group (Figure 1A). UBM disclosed a shallow anterior chamber in MC patients, with the MCUC patients presenting additional features such as inferior iris coloboma and anterior adhesions (Figure 1D, 1E). The UWF color fundus images of MCUC patients showed localized choroidal coloboma at the posterior pole (Figure 1G). Specular microscopy further revealed a dense and homogeneous arrangement of endothelial cells in patients with MC.

Table 1 Baseline characteristics of eyes included in the study

Characteristics	Normal	MCNC	MCUC	*P*
Number (eyes)	30	13	28	
Male/female	10/14	3/5	7/10	0.691
Age (y)	45.60±12.88	46.54±17.33	43.50±11.04	0.743
BCVA (logMAR)	0.07±0.06	0.46±0.28	0.62±0.43	<0.001
IOP (mm Hg)	15.50±2.80	16.08±4.11	17.07±3.28	0.146

Statistical tests: ANOVA for age; Kruskal-Wallis *H* test for BCVA and IOP. BCVA: Best corrected visual acuity; IOP: Intraocular pressure; MCNC: Microcornea without uveal coloboma; MCUC: Microcornea with uveal coloboma.

Comparison of Corneal Biometric Parameters in MC Patients The ACD was significantly shallower in both the MCUC group (2.57±0.65 mm) and the MCNC group (2.55±0.51 mm) compared to controls (3.39±0.47 mm; both *P*<0.001). The LT was 4.50±0.50 mm in the MCUC group and 4.16±0.70 mm in the MCNC group, both significantly increased compared to the control group (both *P*=0.002). No significant difference in ACD or LT was observed between the MCUC and MCNC groups (*P*>0.05). Specifically, the MCNC group exhibited a reduced AL in comparison to the MCUC group and control subjects. The WTW in the MCUC group (8.51±0.71 mm) and the MCNC group (9.08±0.42 mm) was both significantly smaller than that of the control group (both *P*<0.001). Furthermore, the MCUC group showed significantly lower SE, K1, and K2 values in contrast to the MCNC group (*P*<0.05). The corneal curvature of the MCUC group was significantly flatter than that of the MCNC group (Table 2).

Characteristics of CECs in MC Patients There were notable alterations in the size and morphology of CECs in MC groups relative to controls. Statistically significant differences were observed in ECD, CV, 6A, MAX, AVE, and SD when compared to the control group (*P*<0.05). The ECD in the MCUC group (3106.32±336.80 cells/mm²) and the MCNC group (2906.92±323.53 cells/mm²) was markedly higher compared to controls (2647.43±203.06 cells/mm²; both *P*<0.001). The MCUC group demonstrated elevated ECD, indicative of a denser endothelial arrangement. The 6A percentage in patients with MC was 52.56%±10.83%, which suggested a greater regularity in the shapes of endothelial cells than that of controls. Moreover, the MCUC group exhibited lower AVE, MAX, CV, and SD for the cell area compared to the control group, indicating a smaller cell area and more uniform distribution of the cell size (*P*<0.01; Table 3).

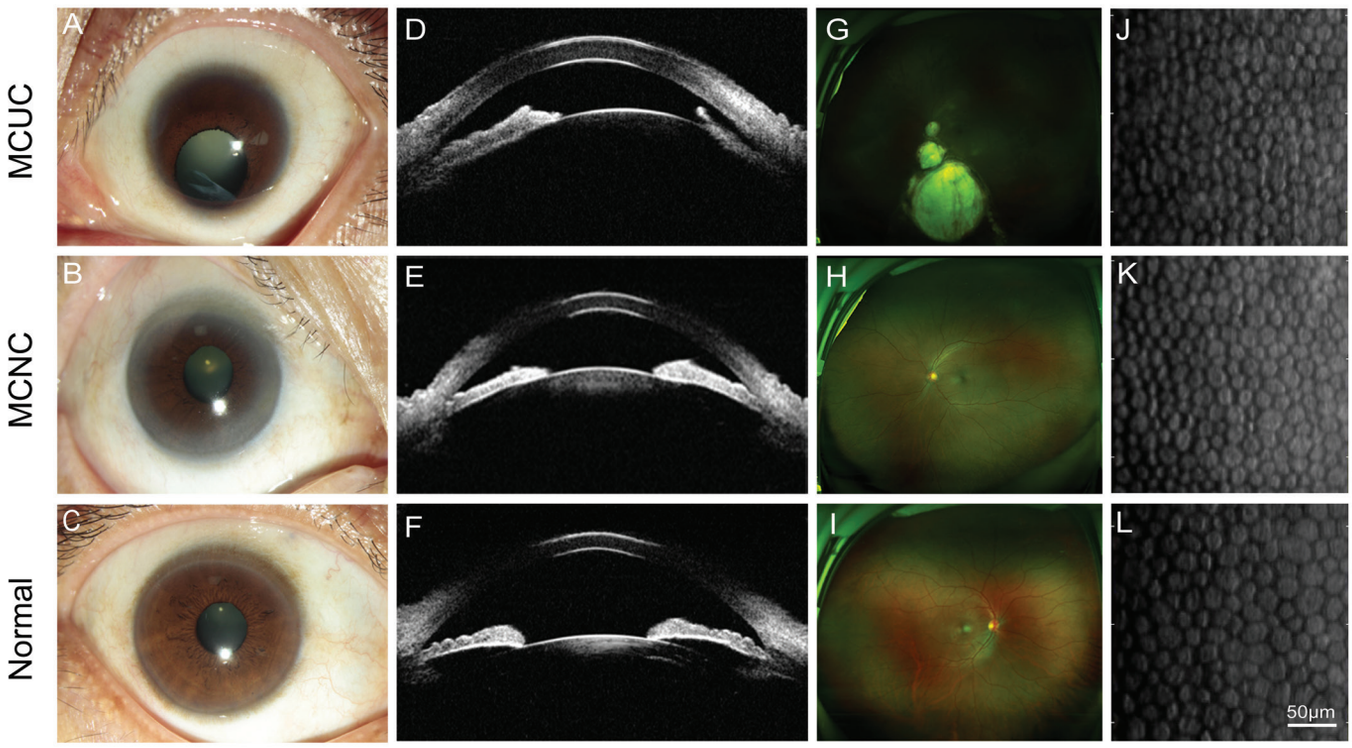

Figure 1 Comparison of the anterior chamber and corneal endothelial morphology between MC patients and the normal A-C: Corneal slit-lamp images of MC patients compared to normal subjects; D-F: Ultrasound biomicroscopy images illustrating a shallow anterior chamber in MC patients, accompanied by inferior iris coloboma and anterior adhesion in the MCUC group; G-I: Ultra-wide-field color fundus photographs revealing chorioretinal coloboma in the MCUC group; J-L: Specular microscopy showing dense and uniformly structured endothelial cells in the MC groups. MC: Microcornea; MCNC: Microcornea without uveal coloboma; MCUC: Microcornea with uveal coloboma.

Table 2 Ocular biometric parameters of patients

Characteristics	Normal	MCNC	MCUC	*P*
Number	30	13	28	
AL (mm)	23.95±1.53	22.66±1.48	24.45±2.39	0.047
ACD (mm)	3.39±0.47	2.55±0.51	2.57±0.65	<0.001
LT (mm)	3.94±0.61	4.16±0.70	4.50±0.50	0.002
WTW (mm)	11.89±0.37	9.08±0.42	8.51±0.71	<0.001
SE (D)	43.83±1.16	47.11±3.01	44.12±1.98	0.002
K1 (D)	43.32±1.17	46.39±3.27	43.30±2.03	0.005
K2 (D)	44.37±1.27	47.88±2.86	44.97±2.04	<0.001
ΔK (D)	-1.03±0.85	-1.50±1.33	-1.67±0.99	0.049

Statistical tests: ANOVA for ACD, LT, WTW; Kruskal-Wallis *H* test for AL, SE, K1, K2, ΔK. AL: Axial length; ACD: Anterior chamber depth; LT: Lens thickness; WTW: White-to-white distance; SE: Keratometry spherical equivalent; K1: Keratometry value at the flat axis; K2: Keratometry value at the steep axis; ΔK: Corneal astigmatism based on keratometry; MCNC: Microcornea without uveal coloboma; MCUC: Microcornea with uveal coloboma.

Correlations Between CECs and Biometric Parameters in MC Patients Both the ECD and 6A displayed significantly negative correlations with the WTW (ECD: r=-0.6929, P<0.0001; 6A: r=-0.3423, P=0.0035), while the CV, MAX, AVE, and SD were positively correlated with the WTW (CV: r=0.3413, P=0.0036; MAX: r=0.5650, P<0.0001; AVE: r=0.6851, P<0.0001; SD: r=0.5168, P<0.0001). Additionally, the ACD correlated negatively with the ECD (r=-0.2982, P=0.0116), while the AVE and SD demonstrated positive correlations with the ACD (AVE: r=0.2760, P=0.0198; SD: r=0.2342, P=0.0469). No significant correlations were found between the ECD and the morphology of CECs, as well as the AL, LT, and corneal curvature (all P>0.05). A smaller corneal diameter and a shallower ACD were associated with higher ECD, an increased 6A, and reduced cell variability (Figure 2).

DISCUSSION

MC is a rare congenital anomaly often associated with developmental abnormalities in various ocular structures, resulting in significantly impaired vision[3,15-16]. Previous studies have primarily examined parameters like AL and WTW in MC patients, while the density and morphology of CECs remain underexplored[3]. This study innovatively investigated the pattern of changes in CECs and corneal biometric parameters in patients with MC, providing significant clinical insights into the pathological mechanisms and guiding clinical interventions and surgical treatments[17].

In our series, we found that the WTW and ACD were significantly lower in MC patients compared to controls, while the LT was significantly greater. The UBM examination revealed a more crowded anterior segment structure in MC

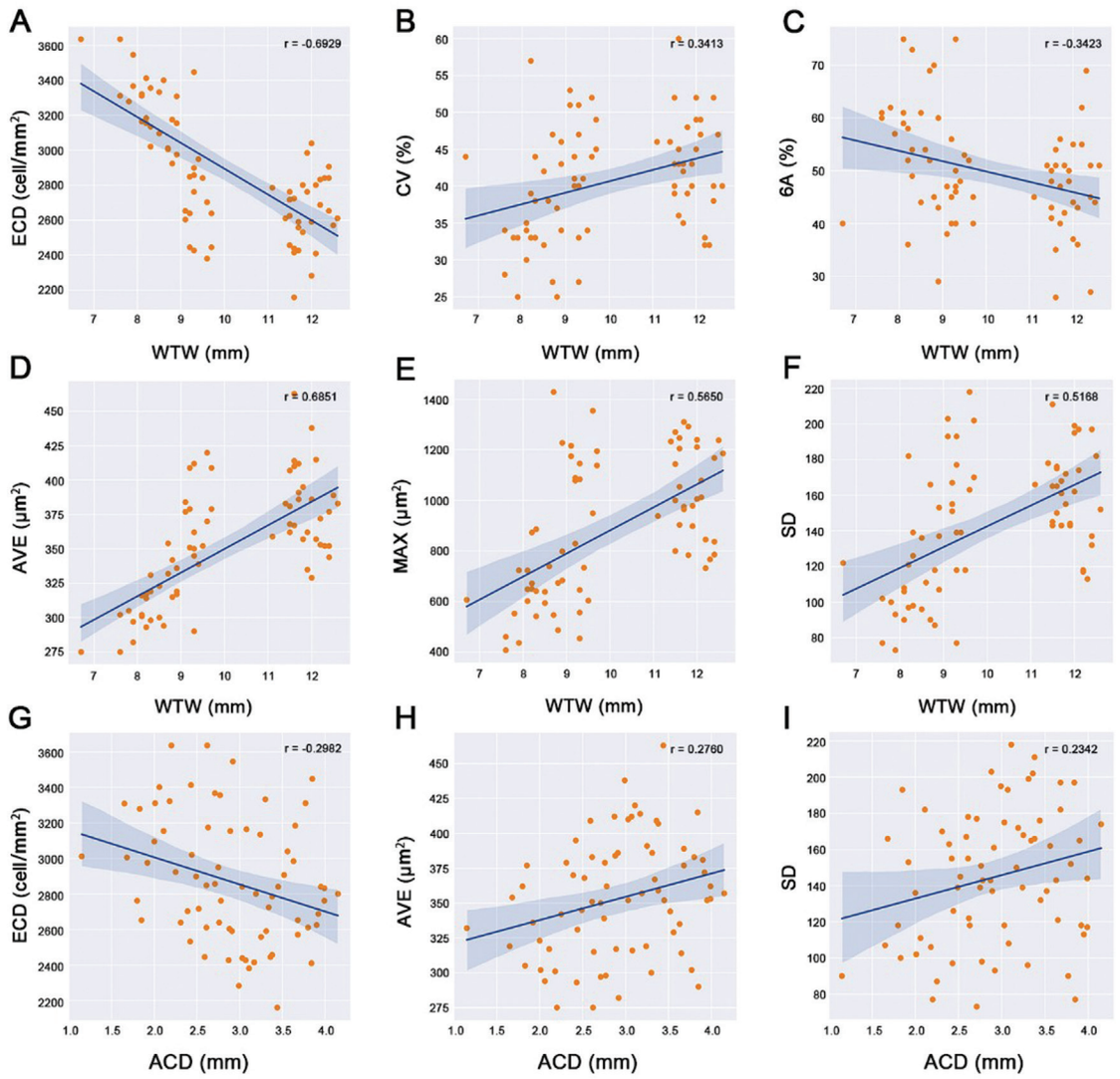

Figure 2 Analysis of the correlations between corneal biometric and endothelial parameters in MC patients A-F: The correlations of the ECD, CV, 6A, AVE, MAX, and SD of CECs with the WTW; G-I: The correlations of the ECD, AVE, and SD of CECs with the ACD. ECD: Endothelial cell density; 6A: Percentage of hexagonal cells; CV: Cell area coefficient of variation; AVE: Average cell area; MAX: Maximum cell area; SD: Cell area standard deviation; WTW: White-to-white distance; ACD: Anterior chamber depth; MC: Microcornea.

Table 3 Corneal endothelial parameters of all participants

Characteristics	Normal	MCNC	MCUC	*P*
Number	30	13	28	
ECD (cells/mm^2)	2647.43±203.06	2906.92±323.53	3106.32±336.80	<0.001
6A (%)	46.57±9.16	49.08±10.23	54.18±10.90	0.019
CV (%)	43.20±6.53	42.15±5.47	37.68±8.86	0.036
MAX (μm^2)	1036.77±181.73	961.46±280.11	714.29±242.89	<0.001
MIN (μm^2)	109.40±27.56	98.85±18.30	122.71±40.70	0.143
AVE (μm^2)	379.97±30.26	351.00±37.88	325.86±37.90	<0.001
SD	161.17±25.26	148.54±31.06	124.54±40.50	0.001

Statistical tests: ANOVA for ECD, 6A, AVE; Kruskal-Wallis *H* test for CV, MAX, MIN, SD. ECD: Endothelial cell density; 6A: Percentage of hexagonal cells; CV: Cell area coefficient of variation; AVE: Average cell area; MAX: Maximum cell area; MIN: Minimum cell area; SD: Cell area standard deviation; MCNC: Microcornea without uveal coloboma; MCUC: Microcornea with uveal coloboma.

patients, likely due to inadequate expansion of the corneal limbal band during the in utero development, alongside relatively normal corneal and lens volumes[18]. Lin *et al*[7] and Wang *et al*[19] reported that most MCNC patients exhibited normal or shorter AL, whereas other studies demonstrated an obvious increase in AL among some MCUC patients[20-21].

This discrepancy may be related to whether the included MC patients had uveal coloboma and individual differences among them. However, our study yielded innovatively findings, showing shorter AL in MCNC patients compared to controls and a significant increase in AL in MCUC patients. These variations may be attributed to the development of form-deprivation myopia and amblyopia during the critical postnatal period for vision development in MCUC patients[4]. Additionally, there was a flatter corneal curvature in patients with MCUC compared to patients with MCNC.

This study revealed that patients with MC had greatly higher ECD than normal controls, but there was no significant difference between the MCUC and MCNC groups. In contrast, the differences in CV, 6A, MAX, AVE, and SD between the MCUC group and controls were all statistically significant. CECs originate from the migration of neural crest cells. Failure of corneal limbal ring expansion during the development can result in a smaller cornea, which reduces the area available for CEC spread. This smaller corneal diameter may lead to the aggregation and increased density of CECs, reduced cellular pleomorphism, and a more regular arrangement[22]. Another hypothesis posits that the elevated ECD in MC patients may be attributed to a lower rate of injury to CECs[23-25]. Due to the smaller corneal area, these patients may be better protected from UV and other external radiations by the eyelids. Moreover, most MC patients experience poorer vision and live in restrictive settings, which severely limits their access to outdoor activities[26].

In the current study, the ECD was disclosed to be negatively correlated with both the WTW and ACD, while the CV, MAX, AVE, and SD were positively correlated with the WTW in all patients. A smaller corneal diameter and shallower ACD were associated with higher ECD, a greater 6A, and lower CV. This may be related to reduced space for the development of the anterior segment of the eye, possibly due to inadequate expansion of the corneal limbal ring[27]. Müller *et al*[28] and Elbaz *et al*[29] reported a significant negative correlation between the ECD and corneal diameter in a specific group of developing children. Karmiris *et al*[30] demonstrated a negative correlation between the 6A and WTW in healthy individuals, suggesting a potential correlation between the morphology of CECs and corneal diameter. Furthermore, Karatepe Haşhaş *et al*[31] noted that patients with iris defects exhibited developmental abnormalities, including shallow ACD and increased ECD, suggesting a correlation between the ACD and ECD. In our study, we further verified that the ACD was negatively correlated with the ECD and positively correlated with the AVE and SD, which was important for the evaluation of patients' ocular conditions and development.

In terms of clinical implications, it is recommended that the clinical diagnosis and treatment process enhances the detection of ECD and ACD for MC patients. Preoperative evaluations should emphasize corneal endothelial changes. Despite the higher ECD observed in MC patients, the reduced morphological homogeneity may indicate a lower tolerance to stress[32]. Therefore, corneal endothelial protection during surgery can be optimized through the modification of perfusion parameters and implementation of the soft-shell technique[33]. In MC patients with shallow anterior chambers, cataract surgery necessitates careful selection of anterior chamber intraocular lenses and early identification of the risk of intraoperative posterior capsule rupture[34]. This study offers novel insights for the individualized treatment of MC patients.

There are some limitations in this study. Due to the cross-sectional nature of this study, correlational analysis between central corneal thickness (CCT) and endothelial parameters could not be completed for some patients lacking CCT measurements. We will incorporate this parameter in the subsequent research for a more comprehensive analysis. Due to the combination of nystagmus in MC patients, this study only collected the parameters of CECs at the central position of the cornea, and failed to analyze the CECs of different regions, which will be further supplemented in our follow-up study. Ultra-wide angle endothelial microscopy combined with eye movement compensation algorithms should be used to detect the characteristics of the peripheral corneal endothelium in MC patients. As a cross-sectional study, this study lacked long-term follow-up of patients; therefore, future analyses of long-term changes in corneal biometric parameters and endothelial cell characteristics in MC patients could be conducted. Due to the small sample size, future investigations should incorporate longer follow-up periods, larger sample sizes, and a multi-center design to minimize errors and bias.

In summary, patients with MC, particularly those presenting with concurrent uveal coloboma, exhibit reduced corneal diameter, increased ECD and hexagonality, as well as decreased MAX, CV, and SD. There exist strong correlations between corneal endothelial and biometric parameters in this population. These findings should be taken into account in both adjust therapeutic strategies and optimize surgical interventions in the management of MC patients, which is important for guiding the clinical interventions and surgical treatments of MC disease.

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Shi JN, Zhong XW investigated the literature and collected the data. Zhang XZ, Pei L, Lu X, Ding RY, Wang X, Zou DL analyzed the data and drafted the manuscript. Wang T, Zhao C reviewed the manuscript.

Data Availability: The corresponding author has full access to all the data in the study and takes responsibility for the data's integrity, the data analysis's accuracy, and the decision to submit for publication. Data reported in this work are available upon request from the corresponding author.

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