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Correlative Characteristics of Multidimensional Clinical Parameters and Predictive Value of Epithelial Thickness Variation in Chinese Patients with Keratoconus

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Research Article

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Abstract

Background

Keratoconus (KC) is a bilateral, progressive, and non-inflammatory corneal ectatic disorder. This study aimed to characterize disease-specific features of KC in a Chinese population and analyze correlations among multidimensional clinical parameters using a large-scale clinical dataset, to support precision clinical screening and personalized treatment strategies.

Methods

Clinical records of 1,219 patients with KC treated between January 2019 and December 2023 were retrospectively analyzed. Collected variables included demographic characteristics, axial length (AL), intraocular pressure, and corneal parameters, including morphology and epithelial thickness. Statistical analyses were performed using SPSS version 26.0. Pearson's correlation analysis was used to assess linear relationships between continuous variables, while one-way analysis of variance followed by Tukey's honest significant difference post-hoc test were used to compare differences among the KC severity groups.

Results

The mean patient age was 22.32 ± 6.65 years, with adolescents and young adults accounting for more than 80% of the cohort. Unilateral surgery was performed in 90.0% of the cases, with a median interval of 17 days between bilateral procedures. The thinnest corneal point was predominantly located inferotemporally (right eye mean vector: 0.34 ± 0.22; left eye mean vector: 0.73 ± 0.26). The AL was significantly shorter in the maximum keratometry (Kmax) ≥ 58 D group than in the Kmax < 48 D group ($P < 0.001$). The AL was significantly longer in the thinnest corneal thickness (TCT) > 490 μm group than in the groups with TCT < 490 μm ($P < 0.01$). Non-contact tonometry exhibited a strong negative correlation with Kmax ($r = -0.7$) and a strong positive correlation with the TCT ($r = 0.61$). Among epithelial parameters, the difference between the minimum and maximum corneal epithelial thickness demonstrated the strongest correlation with Kmax ($r = -0.83$).

Conclusions

KC in the Chinese population is characterized by a marked clustering in adolescence and a tendency toward initial unilateral presentation. Shorter AL may be associated with an increased risk of severe disease. Corneal epithelial thickness variation, particularly the minimum–maximum difference, serves as a highly sensitive indicator of KC severity, offering valuable insights for the development of precision screening and early intervention strategies.

BACKGROUND

Keratoconus (KC) is a bilateral, non-inflammatory, and progressive corneal ectatic disorder characterized by corneal thinning and cone-like protrusions, with a reported prevalence of approximately 1 in 2,000 in the general population [1]. Its pathogenesis involves a complex interplay of genetic, environmental, and corneal biomechanical factors. However, disease-specific clinical characteristics, patterns of interrelationships among clinical parameters, and sensitive predictive indicators for the Chinese population with KC remain insufficiently characterized [2]. Existing research has predominantly focused on isolated associations between individual parameters and disease status, lacking a systematic and integrated analysis of multidimensional parameters, such as axial length (AL), intraocular pressure (IOP), and corneal epithelial thickness variations [3].

Building on our extensive experience in KC research, including pioneering work on epithelium-off-accelerated corneal cross-linking in China, our study moves beyond traditional single-parameter analyses. This study aimed to characterize disease-specific patterns in a Chinese population by integrating demographic features, corneal morphology, AL, and IOP from a large clinical cohort, particularly focusing on the clinical value of corneal epithelial thickness variation. The primary objective was to identify highly sensitive indicators of disease severity, thereby providing a theoretical and clinical basis for early screening, personalized treatment, and prognostic assessment.

METHODS

Study Population

This retrospective study included 1,219 patients diagnosed with KC at our hospital between January 2019 and December 2023. Patients aged 5–60 years who met the established diagnostic criteria for KC were included. The exclusion criteria were the presence of other organic ocular or systemic diseases, autoimmune disorders, or psychiatric conditions. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Eye & ENT Hospital of Fudan University.Informed consent to participate was obtained from the parents or legal guardians of any participant under the age of 18.

Clinical Examinations

All patients underwent comprehensive ophthalmic examinations, including slit-lamp microscopy, refraction, IOP measurement using noncontact tonometry (NCT, mmHg), and AL measurement (mm). A Pentacam system (Oculus Optikgeräte GmbH, Wetzlar, Germany) was used to measure the maximum anterior keratometry (Kmax, D), central corneal thickness (CCT, μm), thinnest corneal thickness (TCT, μm), and apical corneal thickness (ACT, μm). The location of the thinnest point was recorded as its displacement from the corneal apex (mm). Corneal epithelial thickness was measured within a 5-mm central zone using optical coherence tomography. The minimum and maximum epithelial thickness

values within this zone were extracted to calculate the minimum-maximum (min-max) epithelial thickness difference (μm).

Statistical Analysis

Data were analyzed using the SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the basic characteristics of the data. Pearson's correlation analysis was performed to assess linear relationships between continuous variables. One-way analysis of variance was used to compare differences among groups, followed by Tukey's honest significant difference post-hoc test for multiple comparisons. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic and Surgical Characteristics

The mean age of the patients was 22.32 ± 6.65 years (median: 22 years), with 68.3% of patients aged 17–26 years (interquartile range). The overall age range was 8–56 years, with a peak incidence in adolescence and young adulthood. Unilateral surgery was performed in 1,098 patients (90.0%), while bilateral surgery was performed in 121 patients (9.9%). For bilateral procedures, the mean interval between surgeries was 55.74 ± 105.87 days, with a median of 17 days (range: 0–624 days).

Corneal Morphological Features

The thinnest corneal point was predominantly displaced inferotemporally in both eyes.(Figure 1)The mean difference between the CCT and TCT was 18.68 ± 18.79 μm (median: 13 μm), and the mean difference between the ACT and TCT was 7.94 ± 11.45 μm (median: 6 μm).

Correlation Analysis of Multidimensional Parameters

AL and Disease Severity

The direct correlations between the AL and corneal thickness parameters (CCT and TCT) were weak ($r = 0.06–0.08$). However, the AL varied significantly across disease severity groups ($P < 0.001$). As shown in Table 1 and Fig. 2, the AL was significantly longer in the TCT > 490 μm group (25.41 ± 1.12 mm) than in the TCT 400–490 μm (25.14 ± 1.20 mm, $P < 0.01$) and TCT 300–400 μm groups (25.14 ± 0.93 mm, *P* = 0.01). Furthermore, the AL was significantly shorter in the Kmax > 58 D group (25.08 ± 1.13 mm) than in the Kmax < 48 D (25.51 ± 1.15 mm, $P < 0.01$) and Kmax 48–53 D groups (25.29 ± 1.16 mm, $P = 0.04$).

Table 1
Axial length (AL) in different thinnest corneal thickness (TCT) and maximum keratometry (Kmax) groups.

Group	AL(mm) Mean ± SD
TCT(μm)	
< 300	25.11 ± 1.53
300–400	25.14 ± 0.93
400–490	25.14 ± 1.20
> 490	25.41 ± 1.12
Kmax(D)	
> 58	25.08 ± 1.13
53–58	25.04 ± 1.14
48–53	25.29 ± 1.16
< 48	25.51 ± 1.15

IOP and Corneal Parameters

NCT measurements demonstrated a strong negative correlation with Kmax ($r = -0.7$, $P < 0.001$) and a strong positive correlation with the TCT ($r = 0.61$, $P < 0.001$), indicating that lower NCT values were associated with higher Kmax and thinner corneas.(Figure 3)

Corneal Epithelial Thickness Variation

The minimum epithelial thickness within the central 5-mm zone (Epi-Min) demonstrated a strong positive correlation with the CCT ($r = 0.9$) and TCT ($r = 0.95$). Notably, the min-max epithelial thickness difference demonstrated the strongest correlation with Kmax ($r = -0.83$), which was significantly higher than that of other parameters .(Figure 4)

DISCUSSION

Disease-Specific Characteristics of KC in Chinese Youth and Clinical Implications

This study is the first to identify two prominent clinical features of KC in the Chinese population: clustering in adolescence and a tendency toward unilateral initial presentation. The mean patient age was 22.32 years, with more than two-thirds of the patients aged 17–26 years. Furthermore, 90.0% of the

patients underwent unilateral surgery, which contrasts with the more frequently reported bilateral synchronous involvement in Western populations [4, 5]. This finding suggests that KC presentation in Chinese adolescents may be associated with population-specific genetic susceptibility in East Asian populations, as well as ocular developmental factors during adolescence, and behavioral influences, including eye rubbing [6–8]. The relatively low proportion of bilateral surgery (10%) suggests that simultaneous progression in both eyes may be less common, underscoring the importance of close longitudinal monitoring of the fellow eye to detect disease progression while avoiding unnecessary interventions in the fellow eye.

Correlation Between AL and KC Severity

KC is primarily driven by structural abnormalities in corneal stromal collagen, while axial elongation has been linked to reduced scleral collagen fiber strength [9]. With advancements in anterior segment imaging and biometry, increasing attention has been directed toward the relationship between the entire ocular structure, including the AL, and KC pathogenesis [10, 11].

Although previous studies focused on direct correlations between the AL and corneal thickness, our study found that this link is weak ($r = 0.06–0.08$). Notably, the AL differed significantly across disease severity strata, with shorter AL observed in patients with more severe KC (higher Kmax and thinner TCT). This finding is consistent with that of a large population-based study published in 2023, which reported shorter AL as a significant risk factor for KC prevalence [12]. Our study is the first to report a correlation between the severity of KC and AL. These results suggests that the AL may influence KC severity indirectly through alterations in the biomechanical environment of the eye rather than through direct effects on corneal thickness, thereby providing a new target for clinical intervention strategies. Patients with similar KC severity but shorter AL may signify a higher risk of progression, warranting closer monitoring.

Predictive Value of Corneal Epithelial Thickness Variation

This study is the first to report a very strong negative correlation between the min-max epithelial thickness difference and Kmax ($r = -0.83$), which is significantly stronger than that observed for traditional parameters (e.g., TCT vs. Kmax, $r \approx -0.7$). This finding indicates that epithelial thickness heterogeneity (degree of variation) may be a more sensitive marker of ectatic severity than absolute thickness values alone.

The outermost protective layer of the corneal epithelium plays a crucial role in maintaining corneal biomechanical stability [13]. During KC progression, the epithelium thins over the apex of the cone owing to mechanical stretching, accompanied by compensatory thickening in the periphery, resulting in an increased min–max difference. This change in the thickness variation often precedes significant alterations in the corneal stroma, serving as a "sensitive signal" for early disease progression [14]. Compared with traditional parameters, such as Kmax and TCT, the min–max difference is a noninvasive and more sensitive metric, making it a promising metric for early screening, disease monitoring, and postoperative follow-up, particularly in adolescent patients.

Bidirectional Regulatory Relationship Between IOP and Corneal Parameters

Our study confirmed a strong negative correlation between NCT and Kmax and a strong positive correlation between NCT and TCT, highlighting the complex interaction between IOP measurement corneal biomechanics in KC. Corneal thinning and biomechanical weakening in KC result in systematic underestimation of the IOP. The American Academy of Ophthalmology 2024 Clinical Practice Guidelines for Corneal Ectasia state that IOP measurements using applanation tonometers (e.g., Goldmann) are artificially low in ectatic diseases owing to tissue thinning and biomechanical weakening. The guidelines recommend using alternative devices that are less dependent on corneal regularity, such as pneumatic, thickness-compensating, dynamic contour, or rebound tonometers and emphasize the loss of corneal resistance when interpreting IOP readings. A 2023 study also found that NCT measurements increased significantly after corneal crosslinking, an effect that was attributed to increased corneal stiffness [15]. Taken together, these findings emphasize that accurate IOP assessment in patients with KC requires consideration of corneal biomechanical properties, and advanced approaches such as biomechanically corrected IOP measurements using Corvis ST may offer superior clinical utility.

CONCLUSIONS

KC in the Chinese population presents is characterized by adolescent clustering and a tendency towards initial unilateral presentation. A shorter axial length may be associated with an increased risk of disease progression. The min-max corneal epithelial thickness difference represents a highly sensitive indicator of disease severity. Future studies should further explore the influence of genetic and environmental factors on disease progression to inform optimized prevention and control strategies. Large-scale, multicenter studies incorporating genetic analyses and environmental exposure assessments are warranted to achieve a comprehensive understanding of the pathogenesis and progression of KC. Such efforts may provide a robust scientific foundation for precise diagnosis and personalized treatment, thereby supporting improved ocular health outcomes in the Chinese population.

Abbreviations

ACT
apical corneal thickness
AL
axial length
IOP
intraocular pressure
KC
keratoconus
Kmax

maximum keratometry
NCT
non-contact tonometry
TCT
thinnest corneal thickness

Declarations

Ethics Approval and Consent to Participate

This retrospective study was approved by the ethics committee of the Eye and ENT Hospital affiliated with the Fudan Institutional Review Board (ethical code 2021118-1). This study was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed explanation of the study design.

Consent for Publication

Not applicable

Competing Interests

The authors declare that they have no competing interests.

Disclosure

The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

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Author Contribution

Study concept and design (LL, LJ, CYG, XYZ,); data collection (LL, LJ, YLD, JT); data analysis and interpretation (LL, XYZ); drafting of the manuscript (LL, LJ); critical revision of the manuscript (XYZ,

CYG,); supervision (XTZ, CYG, XYZ). All authors read and approved the final manuscript.

Data Availability

The data used in this study are available from the corresponding author upon request.

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Figures

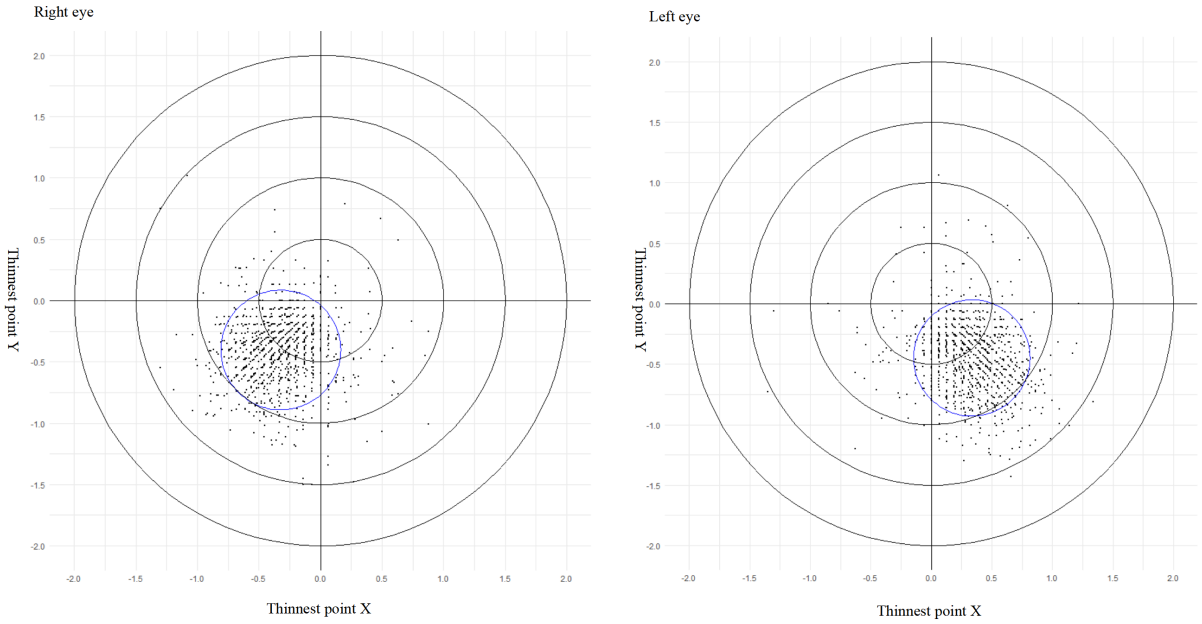


Figure 1

Distribution map of the thinnest corneal point locations.

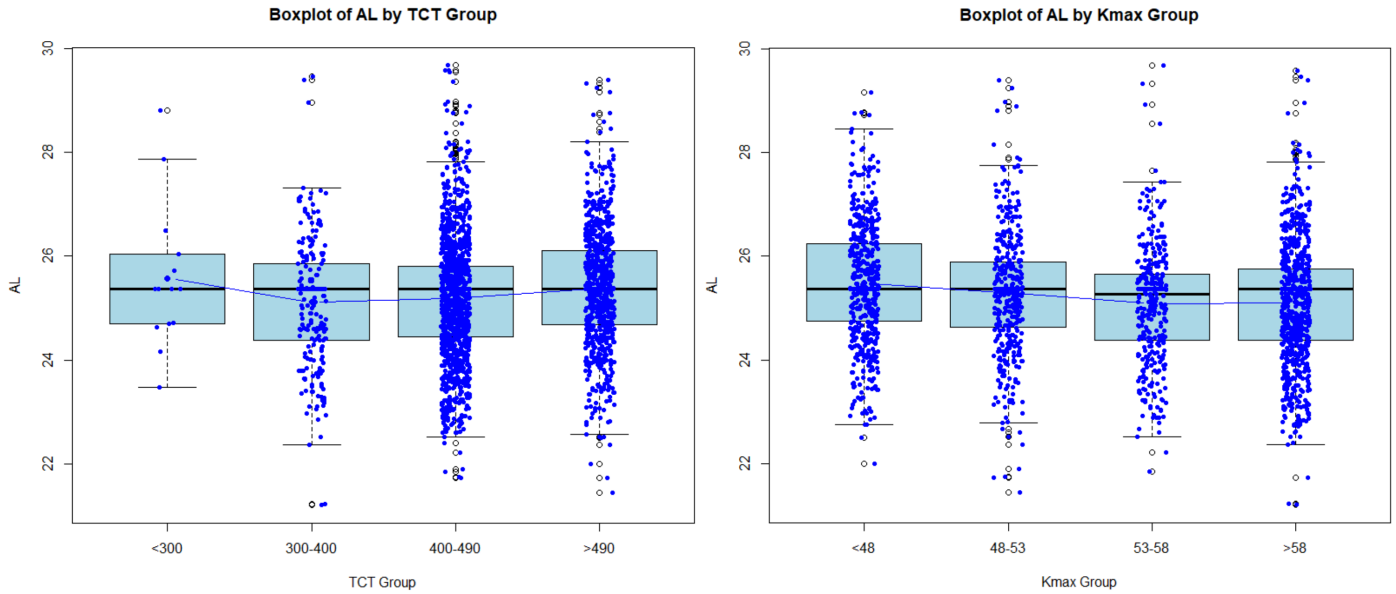


Figure 2

Correlation analysis of the axial length (AL) with different groups of thinnest corneal thickness (TCT) and maximum keratometry (Kmax)

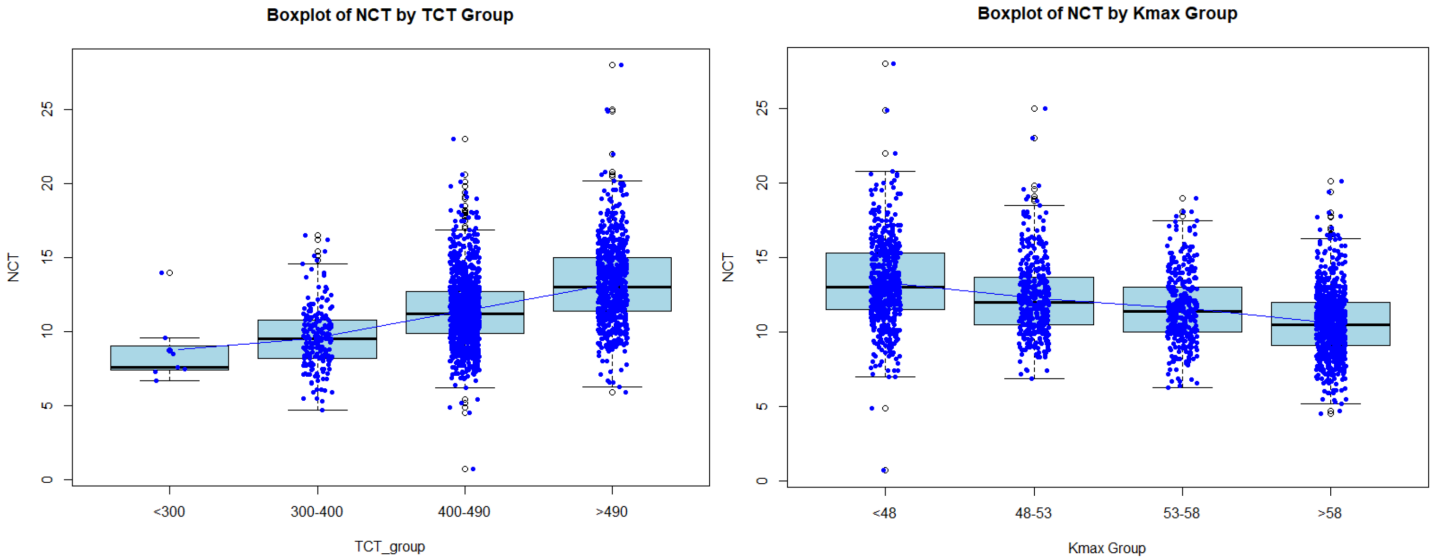


Figure 3

Non-contact tonometry (NCT) in the different thinnest corneal thickness (TCT) and maximum keratometry (Kmax) groups

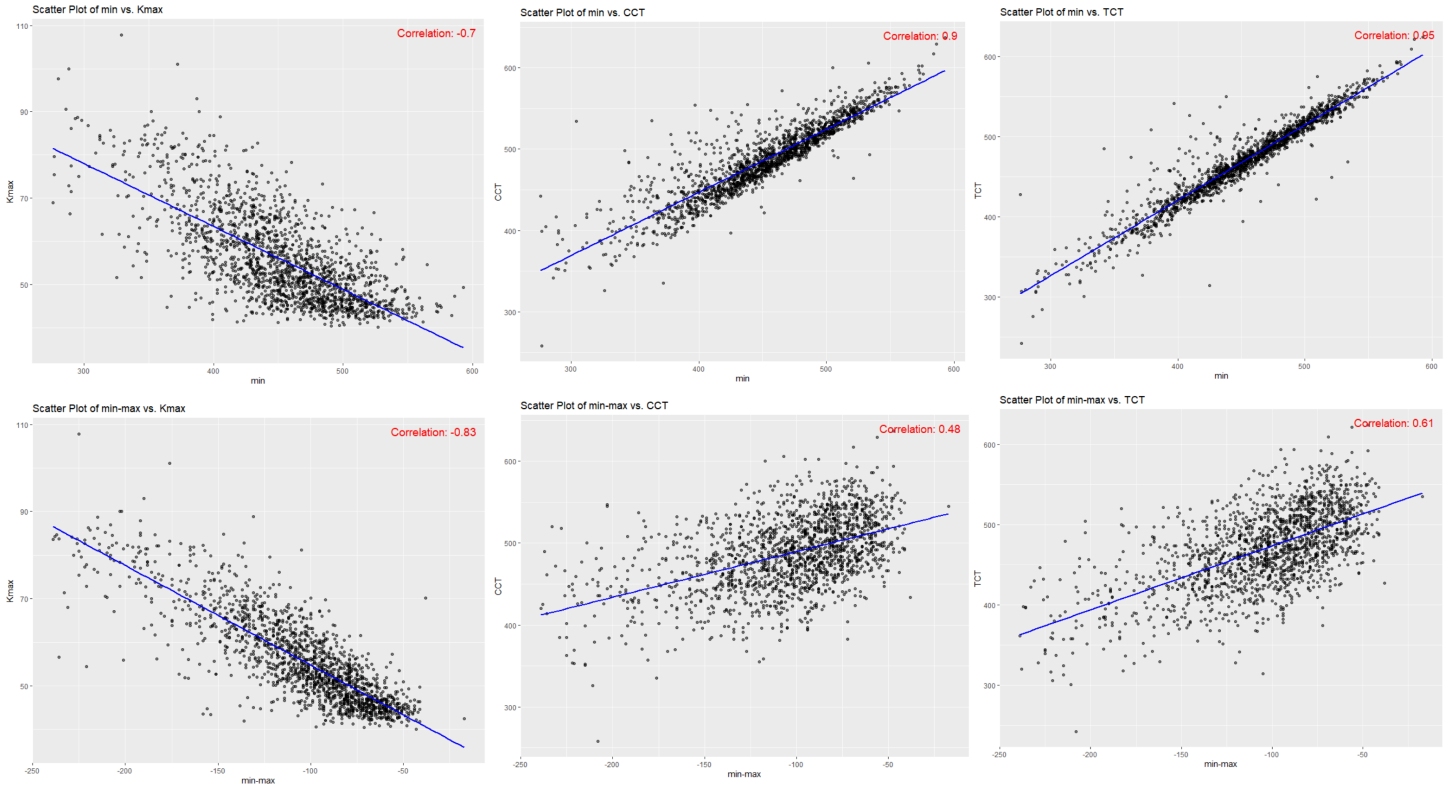


Figure 4

Correlation analysis of the minimum epithelial thickness (central 5 mm) and min–max epithelial thickness differences with the maximum keratometry (Kmax), central corneal thickness (CCT), and thinnest corneal thickness (TCT)