

ORIGINAL RESEARCH

Revisiting Keratoconus classification based on the evaluation corneal asymmetry indices, derived from Scheimpflug imaging.

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None.

Abstract

Purpose

To survey the standard keratoconus grading scale (Pentacam-derived Amsler & Krumeich stages) compared to corneal regularity indices, measured by the Pentacam and to best spectacle corrected distance visual acuity.

Patients and methods

Two hundred twelve (212) keratoconic cases were evaluated for the keratoconic grading and anterior surface indexing by Pentacam imaging, as well as for subjective refraction, measured by the best-spectacle corrected distance visual acuity (CDVA). The correlations between CDVA, keratometry, and the Scheimpflug keratoconic grading and the seven anterior – surface Pentacam-derived topometric indices (Indices of; surface variance, vertical asymmetry, keratoconus index, central keratoconus index, height asymmetry, height decentration, minimum radius of curvature) were analyzed using paired two-tailed t-tests, coefficient of determination (r^2), and trend line linearity.

Results

Average CDVA (expressed decimally) was, for all eyes: (average \pm standard deviation) 0.626 ± 0.244 , range (max-min) 1.00 to 0.10). Average flat meridian keratometry was (K1) 46.7 ± 5.89 diopters (D), and for the steep, (K2), 51.05 ± 6.59 D.

The correlations between CDVA, keratometry, the seven Scheimpflug-derived topometric indices with the Pentacam-derived keratoconus severity grading were investigated. The index of height decentration (ISV), and the Index of height decentration (IHD), had the strongest correlate for keratoconus to the value of $P < 0.001$. CDVA and keratometry were correlated poorly.

Conclusions

We report herein for the first time that the ISV and IHD, may be the most sensitive and specific criteria in the diagnosis, progression, and surgical follow-up in keratoconus. The classification proposed herein, may present a novel benchmark in clinical work and future studies.

Keywords

Keratoconus diagnosis and classification; Pentacam topometric indices; keratoconus topography diagnosis; Amsler & Krumeich keratoconus grading, index of surface variance, index of vertical asymmetry, keratoconus index, central keratoconus index, index of height asymmetry, index of height decentration, index of minimum radius of curvature.

Introduction

Keratoconus (KCN) is described as a degenerative bilateral, progressive, noninflammatory disorder characterized by ectasia, thinning, and increased curvature.^{1,2} It is associated with loss of visual acuity particularly in relation to progressive cornea irregularity^{3,4} and usually is manifested asymmetrically between the two eyes of the same patient.^{5,6}

Occasionally, the patient may present with symptoms of photophobia, glare and monocular diplopia.

The problem of specificity and sensitivity of keratoconus assessment, particularly the diagnosis of early signs of ectasia and/or subclinical keratoconus, and for monitoring the progression of the disease, has been extensively studied.⁷ The common used options for the clinician usually include optically-based anterior segment imaging modalities, such as Placido corneal topography^{8,9} and slit or Scheimpflug imaging¹⁰ that provide curvature qualitative and quantitative data.

Anterior Segment Topometric Indices

Rotating camera Scheimpflug imagery provides a multitude of corneal topometry measurements.¹¹ Data include refractive (keratometric), tomographic, and pachymetric mapping.¹² In addition, specific anterior-surface curvature regularity indices have been developed for the grading and classification of keratoconus stages, as well as the post-operative assessment¹³⁻¹⁹ which can be provided by the Pentacam software (Oculus Optikgeräte GmbH, Wetzlar, Germany).

This study aims to investigate these values, the repeatability of their measurement, the correlation of the above indices with CDVA, keratometry as well as with commonly used keratoconus classification, in a large pool of clinically-diagnosed keratoconic eyes.

Materials and methods

This study received approval by the Ethics Committee of our Institution, adherent to the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject at the time of the first clinical visit. These cases were studied over the span of at least two years.

Patient inclusion criteria

The study group consisted of two hundred twelve (212) cases presented to our institution. Subjects' ages ranged from 19–57 (average 31.9 ± 7.5 years).

Each case was subjected to a complete ocular examination, including subjective refraction, CDVA measurement with this refraction, and slit-lamp biomicroscopy for clinical signs of keratoconus.

Inclusion criteria included a minimum age of 18 years and definite findings consistent with keratoconus, such as described by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) group.²⁰ Exclusion criteria included systemic disease, previous corneal surgery, history of chemical injury or delayed epithelial healing, and pregnancy or lactation during the study (for the female patients).

Imaging, measurement and analysis

Anterior segment measurements on all subjects including anterior segment imaging measurements with the Pentacam Scheimpflug rotating camera. The device was calibrated according to manufacturer recommendations prior to undertaking the measurements. The Pentacam measurements were obtained and processed via the Examination Software (Version 1.17r47).

For each eye, four consecutive measurements were obtained and processed to test for data acquisition repeatability. The default settings of twenty-five images per single acquisition was used.

Linear regression analysis was performed to seek possible correlations. Descriptive and comparative statistics, analysis of variance between keratoconus Amsler & Krumeich stage subgroups and linear regression were performed with statistics tools provided by Minitab version 1.6.1 (MiniTab Ltd., Coventry, UK) and Origin Lab version 9 (OriginLab Corp, Northampton, MA). Paired analysis p-values less than 0.05 were considered indication of statistically significant results.

Results

Keratometric and anterior-segment topographic indices statistics

The sample population consisted of 212 cases of which 65 were female patients and 147 male patients. There is a preponderance towards male population, consistent with our clinical experience in male-female incidence in keratoconic patients,²¹ and keratoconus incidence studies.²² Of the 212 eyes, 113 were right (OD) and 99 were left (OS). Average age was, for all patients, 31.77 ± 7.23 (57-19) years of age.

Average CDVA (expressed decimally) was, for all eyes: (average \pm standard deviation) 0.626 ± 0.244 , range (max-min) 1.00 to 0.10. Average, standard deviation, maximum and minimum corneal surface keratometry, and topometric indices for all eyes in the study are reported in Table 1. Intraindividual repeatability was assessed via the standard deviation of the four consecutive measurements undertaken per each eye. Average and standard deviation of repeatability for the seven topometric indices in all 212 eyes measured is reported in Table 2.

The sample was presented with an average keratometry on the anterior surface flat axis of 46.7 ± 5.89 keratometric diopters (D), and for the steep axis of 51.05 ± 6.59 D. Our statistical analysis showed that 95% of the sample population had a steep axis keratometry > 46.025 D, consistent with the CLEK group standards.²⁰

Topographic indices correlation with CDVA

Paired statistics between CDVA and the IHD, ISV, IVA, KI, CKI, IHA, and Rmin indices (in 8 mm zone), and specifically, coefficient of determination (r^2) and Pearson linear regression data between CDVA and the IHD, ISV, IVA, KI, CKI, IHA and Rmin indices within all eyes in the study group ($n = 212$) are reported in Table 3.

The correlations between the seven keratoconic anterior – surface topometric indices with CDVA are illustrated in Figures 3a-g. Specifically, the scatter and fitted line plots of ISV (3a), IVA (3b), KI (3c), CKI (3d), IHA (3e), ISD (3f), and Rmin (3g) vs CDVA are plotted, in addition with the 95% confidence (CI) and 95% prediction interval (PI) lines. The paired data present with coefficient of determination (r^2) of linear correlation with CDVA of: ISV, 0.55; IVA, 0.34; KI, 0.424; CKI, 0.396; IHA, 0.107; IHD, 0.393, and Rmin, 0.516. Respectively, the Pearson correlation values vs CDVA were for ISV, -0.746; IVA, -0.584; KI, -0.680; CKI, -0.642; IHA, -0.344, ISD, -0.627, and Rmin, 0.718. In all cases, p-value was < 0.0001 . (Table 3).

Topographic indices correlation with Keratoconus stages grading

The 212 eyes were subjected to keratoconus Amsler & Krumeich stages grading²³ by the Pentacam software. The resulting grading designated $n_1 = 10$ eyes as KC1, $n_{12} = 11$ eyes as KC12, $n_2 = 32$ eyes as KC2, $n_{23} = 22$ eyes as KC2-3, $n_3 = 54$ eyes as KC3, $n_{34} = 45$ eyes as KC34, and $n_4 = 4$ eyes as KC4.

The correlations between CDVA, the seven Scheimpflug anterior – surface keratometric and topometric indices with the above keratoconus grading are illustrated in Figures 2a-h, showing box plots with the median level and value (also indicated by the symbol \otimes), the

average point (indicated by the symbol \oplus), the 95% median confidence range box (black line boxes), and the interquartile intervals range box (red line boxes). Descriptive statistics for the keratoconus grading subgroups for CDVA and the seven topometric indices are presented in Table 4, and two-sample T-test results (not assuming equal variances) between the keratoconus grading subgroups for CDVA and the seven topometric indices are presented in Table 5.

Discussion

The Pentacam software compares the measured values with the means and standard deviations of a normal population, and, helps provide color-coded 'flags'. For example, measured values which exceed the standard deviation by a factor of more than 2.5 are classified as abnormal and highlighted in yellow, and pathological values, i.e. values that exceed the standard deviation by a factor of more than 3, are highlighted in red.

Namely, these indices are the following:

- (a) the Index of Surface Variance (ISV), the value of deviation of individual corneal radii from the mean curvature. ISV is thus an expression of the corneal surface irregularity. It is elevated in all types of corneal surface irregularity (scars, astigmatism, deformities caused by contact lenses, pachymetric, etc). According to the manufacturer's user manual, ²⁴ an ISV larger than 37 is considered abnormal (marked with yellow), and larger than 41, pathological (red).
- (b) the Index of Vertical Asymmetry (IVA), which is a measure of the difference between superior and inferior corneal curvature (similar to the commonly used I-S ratio). ²⁵ IVA is thus the value of curvature symmetry, with respect to the horizontal meridian as axis of reflection. An IVA larger than 0.28 is considered abnormal, and larger than 0.32, pathological.

- (c) The Keratoconus Index (KI). KI increases with severity of keratoconus, and is sometimes referred to as pachymetric index. KI value larger than 1.07 is considered abnormal and/or pathological.
- (d) The Central Keratoconus Index (CKI). CKI is elevated especially in central pachymetric, and increases with the severity of central keratoconus. CKI value larger than 1.03 is considered abnormal and/or pathological.
- (e) The Index of Height Asymmetry (IHA), calculated by the height data symmetry comparison of the superior and inferior area, and provides the degree of symmetry of height data with respect to the horizontal meridian as axis of reflection. IHA is a similar to the IVA, but based on corneal elevation, and thus it is more sensitive. An IHA value larger than 19 is considered abnormal, and larger than 21, pathological.
- (f) the Index of Height Decentration (IHD). IHD is the value of the decentration of elevation data in the vertical direction, and is calculated from a Fourier analysis. This index provides the degree of decentration in the vertical direction. An IHD value larger than 0.014 is considered abnormal, and larger than 0.016, pathological.
- (g) The minimum radius of curvature (Rmin), expressed in mm. Rmin is a measurement of the smallest radius of sagittal corneal curvature (ie, the maximum steepness of the cone). Values of Rmin less than 6.71 mm are considered abnormal and/or pathological, considering that the average radius of the anterior corneal surface is 7.87 ± 0.27 mm.²⁶

Association with these indices with clinical keratoconus observations is provided by the manufacturer and are listed in Table 6.

The clinical suspicion of early-stage keratoconus may be based on refraction criteria such as a change in refractive power and the axis of astigmatism, fluctuating refraction and several clinical findings (such as conspicuous retinoscopy sings). Optical imaging, such as topometry and topography, provides valuable supplementary information, and has been long supported that the contribution of proper evaluation and analysis of anterior surface

irregularity derived from topography,²⁷ or more recently, from Pentacam topometry, like the seven topographic indices studied in this manuscript, may provide an invaluable aid in the diagnosis and progression evaluation of the disease.²⁸ We only identified two reports published in this matter of correlation of the above Pentacam-derived indices, and specifically with best spectacle corrected distance visual acuity (CDVA)²⁹ and the severity of keratoconus classification.³⁰

The correlation (Table 3, and figures 3) between the seven anterior-segment topographic indices and CDVA is not very strong. The Rmin ($r^2 = 0.516$, $P < 0.001$) and ISV ($r^2 = 0.557$, $P < 0.001$) were found to be the strongest-correlated indices with CDVA compared to the other indices. The least correlated index was IHA ($r^2 = 0.107$, $P < 0.001$). This could be a result of significantly worse intraindividual repeatability of this index, possibly as a result of the complicated nature of its algorithm. As indicated in Table 2, repeatability, measured by the standard deviation of the measured index over four consecutive acquisitions, was as low as 1.50%, on average, for Rmin, and up to 4.6% for IHD and IVA; however, the IHA index had a distinctively 43.78% average standard deviation among any four consecutive measurements. In addition, the IHA index had the worst-correlation with keratoconus severity (Figure 2f), with two stages not statistically significantly distinguished, and the remaining also borderline.

Our study is indicating that the correlation between keratoconus severity and the anterior-segment topographic indices can be better described with the ISV (with the exception of the highest stage KC4, all other P-values were < 0.001 , as seen in Table 5), followed by the IHD (with the exception of the lowest stage KC1, all other P-values were < 0.001).

Our results indicate that the visual performance in keratoconus was not clearly predictable for keratoconus severity, and thus CDVA cannot be a dependable indicator of keratoconus severity and/or progression, and thus cannot be employed in the postoperative assessment

of operations aiming to arrest the keratoconus progression such as cross-linking with riboflavin (CXL).³¹ It is customary to assess severity based on visual function and as noted above this can be deceiving. Clinicians must be cautious. For example, the data presented in this work (Figure 2a) suggest that CDVA is not very well correlated with the keratoconus severity, as the spread of CDVA measurements within the same 'severity stage', eg. KC3, KC3-4 was found to be too large. The average coefficient of determination (r^2) was in the order of 0.5, in agreement with previous studies³²

The above results are in agreement with our past clinical experience with significant number of keratoconic patients followed for over 15 years. Our observation has been that visual acuity can present with large variations, and sometimes unexpectedly good for the corresponding keratometry and overall corneal asymmetry. This may be due to a 'multifocal' and 'soft', ie adaptable cornea, in addition to possible advanced neural processing development in the individual. These 'advantages', however, are to a large degree compromised with a CXL procedure applied in young (18 to 25 years old) keratoconus patients in our long term clinical observations.

Although not specifically studied herein, our clinical assessment of this group is that CDVA is poorly correlated to keratoconus severity mainly in younger patients. As older keratoconus patients were encountered (over 30 years old and in most over 40), their CDVA started to correlate to the ISV and IHD. This observation poses an even greater reason for clinicians to employ the strongest clinical suspicion in younger patients that may be at risk for developing keratoconus and maybe labeled "normal" if a very good CDVA performance is achieved by them.

This maybe explained by the higher elasticity, of the pathologic cornea in younger keratoconus patients. This age-related difference may allow them to accomplish high CDVA

values with monocular testing by squinting and/or head tilting. ISV and IHD assessment in the younger patients with relative low keratometric values may be the crucial factor in early diagnosis of keratoconus.

Conclusions

The index of surface variance (ISV) and the index of height decentration (IHA), both derived from Scheimpflug corneal imaging, may be more sensitive and specific tools than corrected visual acuity, in evaluating early diagnosis, and possible progression in keratoconus patients and corneal ectasia. They may become a novel benchmark for future studies, and may aid in the development of new keratoconus diagnostic and follow-up criteria.

Tables

Table 1

Collective average, standard deviation (StDev), maximum (Max) and minimum (Min) anterior keratometry, and topometric indices, as measured in the 8 mm zone. Abbreviations: ISV, Index of Surface Variance; IVA, Index of Vertical Asymmetry; KI, Keratoconus Index; CKI, Central Keratoconus Index; IHA, Index of Height Asymmetry; IHD, Index of Height Decentration; Rmin, Smallest sagittal curvature; CDVA, best- spectacle corrected distance visual acuity.

		Average	StDev	Max	Min
Anterior Cornea	K1 – flat (D)	46.78	± 5.89	78.50	33.70
	K2 – steep (D)	51.05	± 6.59	80.70	42.10
	Km – mean (D)	48.80	± 6.05	78.80	40.60
	Astigmatism (D)	-2.10	± 6.05	+11.30	-12.40
Anterior surface topometric indices	ISV	98.99	± 47.43	262	14
	IVA	1.05	± 0.52	2.52	0.09
	KI	1.28	± 0.17	1.83	0.97
	CKI	1.06	± 0.07	1.30	0.90
	IHA	30.60	± 22.21	103.00	0.20
	IHD	0.091	± 0.054	0.256	0.005
	Rmin (mm)	6.07	± 0.88	7.73	3.30
CDVA	decimal	0.63	± 0.25	1.00	0.10

Table 2

Intraindividual repeatability measurements for the seven anterior surface topometric indices, resulting as the standard deviation (%) of the four consecutive acquisitions on each eye.

Abbreviations: ISV, Index of Surface Variance; IVA, Index of Vertical Asymmetry; KI, Keratoconus Index; CKI, Central Keratoconus Index; IHA, Index of Height Asymmetry; IHD, Index of Height Decentration; CDVA, best- spectacle corrected distance visual acuity.

	ISV	IVA	KI	CKI	IHA	IHD	Rmin
average	2.77%	4.63%	2.15%	2.02%	43.78%	4.67%	1.50%
Stdev (±)	1.32%	1.94%	1.27%	0.66%	7.18%	1.62%	0.68%

Table 3

Coefficient of determination (r^2) and Pearson correlation data between CDVA and the IHD, ISV, IVA, KI, CKI, IHA and Rmin indices within all eyes in the study group (n =212). Abbreviations: ISV, Index of Surface Variance; IVA, Index of Vertical Asymmetry; KI, Keratoconus Index; CKI, Central Keratoconus Index; IHA, Index of Height Asymmetry; IHD, Index of Height Decentration; CDVA, best- spectacle corrected distance visual acuity. In all cases, $p < 0.001$.

		CDVA	IHD	ISV	IVA	KI	CKI	IHA
Pearson correlation	IHD	-0.627						
(r^2)		0.393						
Pearson correlation	ISV	-0.746	0.91					
(r^2)		0.55						
Pearson correlation	IVA	-0.584	0.893	0.878				
(r^2)		0.340						
Pearson correlation	KI	-0.680	0.891	0.911	0.845			
(r^2)		0.424						
Pearson correlation	CKI	-0.642	0.616	0.721	0.436	0.73		
(r^2)		0.396						
Pearson correlation	IHA	-0.344	0.524	0.484	0.422	0.467	0.252	
(r^2)		0.107						
Pearson correlation	Rmin	0.718	-0.799	-0.864	-0.623	-0.790	-0.787	-0.541
(r^2)		0.516						

Table 4: Descriptive Statistics for the keratoconus grading subgroups for Age, CDVA and the seven topometric indices. Abbreviations: Stdev: standard deviation; SE mean, standard error of the mean

Keratoconus Grading	KC1	KC-12	KC2	KC-23	KC3	KC-34	KC4
Age (years)							
Mean	31.0	32.5	31.3	31.3	30.9	30.6	31.0
StDev (±)	8.4	7.6	7.8	6.0	6.7	7.3	8.4
CDVA							
Mean	0.907	0.779	0.695	0.64	0.55	0.416	0.2225
StDev (±)	0.107	0.166	0.202	0.133	0.188	0.187	0.0634
SE Mean	0.034	0.05	0.036	0.028	0.026	0.028	0.032
ISV							
Mean	40.6	50.91	72.75	93.77	114.07	157.8	218.8
StDev (±)	2.88	3.56	9.32	5.25	9.51	17.9	29
SE Mean	0.91	1.1	1.6	1.1	1.3	2.7	14
IVA							
Mean	0.422	0.5618	0.855	1.068	1.219	1.612	2.002
StDev (±)	0.0735	0.0994	0.134	0.194	0.258	0.361	0.497
SE Mean	0.023	0.03	0.024	0.041	0.035	0.054	0.25
KI							
Mean	1.10	1.12	1.1838	1.2664	1.3291	1.47	1.7475
StDev (±)	0.0163	0.0335	0.0522	0.027	0.0547	0.121	0.0929
SE Mean	0.0052	0.01	0.0092	0.0058	0.0075	0.018	0.046

CKI							
Mean	1.014	1.0145	1.0291	1.05	1.0711	1.1269	1.208
StDev (±)	0.0135	0.023	0.0352	0.0385	0.0394	0.0702	0.101
SE Mean	0.0043	0.0069	0.0062	0.0082	0.0054	0.01	0.051

IHA							
Mean	18.05	20.55	26.5	33.3	37.7	39.3	61.7
StDev (±)	9.66	7.68	15.6	17.3	19.3	28.8	14.4
SE Mean	3.1	2.3	2.7	3.7	2.6	4.3	7.2

IHD							
Mean	0.031	0.04355	0.0677	0.0878	0.1063	0.1512	0.24
StDev (±)	0.00723	0.00972	0.0183	0.0169	0.0266	0.0373	0.0185
SE Mean	0.0023	0.0029	0.0032	0.0036	0.0036	0.0056	0.0093

Rmin (mm)							
Mean	6.922	6.755	6.52	6.104	5.775	5.146	4.165
StDev (±)	0.311	0.275	0.463	0.483	0.381	0.675	0.513
SE Mean	0.098	0.083	0.082	0.1	0.052	0.1	0.26

Table 5: Two-Sample T-test results, not assuming equal variances, between successive pairs of keratoconus severity stages subgroups for CDVA and the seven topometric indices. CI: Confidence interval.

CDVA	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	-0.1279	-0.0838	-0.0558	-0.0892	-0.1344	-0.1935
95% CI for difference:	(-0.2552, -0.0006)	(-0.2115, 0.0440)	(-0.1473, 0.0357)	(-0.1657, -0.0127)	(-0.2095, -0.0593)	(-0.2890, -0.0980)
T-Value	-2.12	-1.36	-1.22	-2.34	-3.55	-4.58
P-Value	0.049	0.187	0.227	0.023	0.001	0.001

ISV	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	10.31	21.84	21.02	20.3	43.7	61
95% CI for difference:	(7.35, 13.27)	(17.87, 25.82)	(17.02, 25.03)	(16.88, 23.72)	(37.79, 49.62)	(14.1, 107.8)
T-Value	7.33	11.1	10.55	11.86	14.76	4.14
P-Value	<0.001	<0.001	<0.001	<0.001	<0.001	0.026

IVA	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	0.1398	0.2929	0.2135	0.1503	0.3939	0.39
95% CI for difference:	(0.0602, 0.2195)	(0.2139, 0.3718)	(0.1167, 0.3103)	(0.0414, 0.2592)	(0.2660, 0.5218)	(-0.419, 1.199)

T-Value	3.69	7.67	4.48	2.77	6.13	1.53
P-Value	0.002	<0.001	<0.001	0.008	<0.001	0.222

KI	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	0.02	0.0638	0.0826	0.06271	0.1414	0.2771
95% CI for difference:	(-0.0043, 0.0443)	(0.0357, 0.0918)	(0.0607, 0.1045)	(0.04394, 0.08148)	(0.1024, 0.1804)	0.1186, 0.4356)
T-Value	1.76	4.66	7.59	6.66	7.26	5.56
P-Value	0.099	<0.001	<0.001	<0.001	<0.001	0.011

CKI	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	0.00055	0.01452	0.0209	0.02111	0.0558	0.0806
95% CI for difference:	(-0.01670, 0.01779)	(-0.00459, 0.03362)	(0.0001, 0.0417)	(0.00126, 0.04096)	(0.0323, 0.0792)	(-0.0842, 0.2454)
T-Value	0.07	1.56	2.03	2.15	4.75	1.56
P-Value	0.947	0.131	0.049	0.038	<0.001	0.217

IHA	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	2.5	5.93	6.82	4.38	1.58	22.44
95% CI for difference:	(-5.58, 10.59)	(-1.37, 13.22)	(-2.45, 16.10)	(-4.74, 13.50)	(-8.45, 11.60)	(0.90, 43.98)

T-Value	0.65	1.65	1.48	0.97	0.31	2.68
P-Value	0.522	0.108	0.145	0.338	0.755	0.044

IHD	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	0.01255	0.02411	0.02012	0.01856	0.04487	0.0888
95% CI for difference:	(0.00474, 0.02035)	(0.01522, 0.03300)	(0.01038, 0.02985)	(0.00836, 0.02876)	(0.03165, 0.05808)	(0.0610, 0.1166)
T-Value	3.38	5.52	4.16	3.64	6.76	8.21
P-Value	0.003	<0.001	<0.001	0.001	<0.001	<0.001

Rmin (mm)	K1 vs K1-2	K12 vs K2	K2 vs K2-3	K2-3 vs K3	K3 vs K3-4	K3-4 vs P4
Estimate for difference:	-0.167	-0.235	-0.416	-0.329	-0.629	-0.981
95% CI for difference:	(-0.438, 0.103)	(-0.473, 0.003)	(-0.681, -0.151)	(-0.563, -0.094)	(-0.855, -0.403)	(-1.858, -0.104)
T-Value	-1.30	-2.02	-3.16	-2.85	-5.56	-3.56
P-Value	0.209	0.053	0.003	0.008	<0.001	0.038

Table 6

Classification stages of keratoconus adapted from the classical Amsler & Krumeich standards. [30] Best spectacle corrected distance visual acuity (CDVA) correction, with topography-based graduation indices (ISV, Index of Surface Variance; KI, Keratometry Index) compared with retinoscopy signs and clinical corneal slit lamp observations. Adapted from Oculyzer User Manual. ²⁴

	CDVA	ISV	KI	Other indices	Rmin	Retinoscopy signs	Cornea Slit Lamp Observations
Pre-stage (early signs)	20/20 to 20/15	< 30	1.04 to 1.07	all 4 indices are 'normal'	7.8 to 6.7 mm	No clear light or shadow movement. Hint of 'scissors' effect	Clear cornea, unobtrusive. Horizontal, oval, or round shades central or slightly decentered, when observed under direct ophthalmoscopy.
Level 1	20/25 to 20/15	30 to 55	1.07 to 1.15	sometimes one value within the 'abnormal' range	7.5 to 6.5 mm	Distorted retinoscopic reflex. Scissors effect.	Clear cornea. Fleischer's ring at the apex base. Cone and cone base clearly visible with direct ophthalmoscopy. Decrease in apex thickness not visible, but measurable.
Level 2	20/60 to 20/20	55 to 90	1.10 to 1.25	often one value within the 'abnormal' range	6.9 to 5.3 mm	Clear scissors effect, retinoscopy difficult to perform.	Often cornea still clear, apex slightly thinner and eventually decentered. Partial or circular Fleischer' ring. Voght striae may be visible.

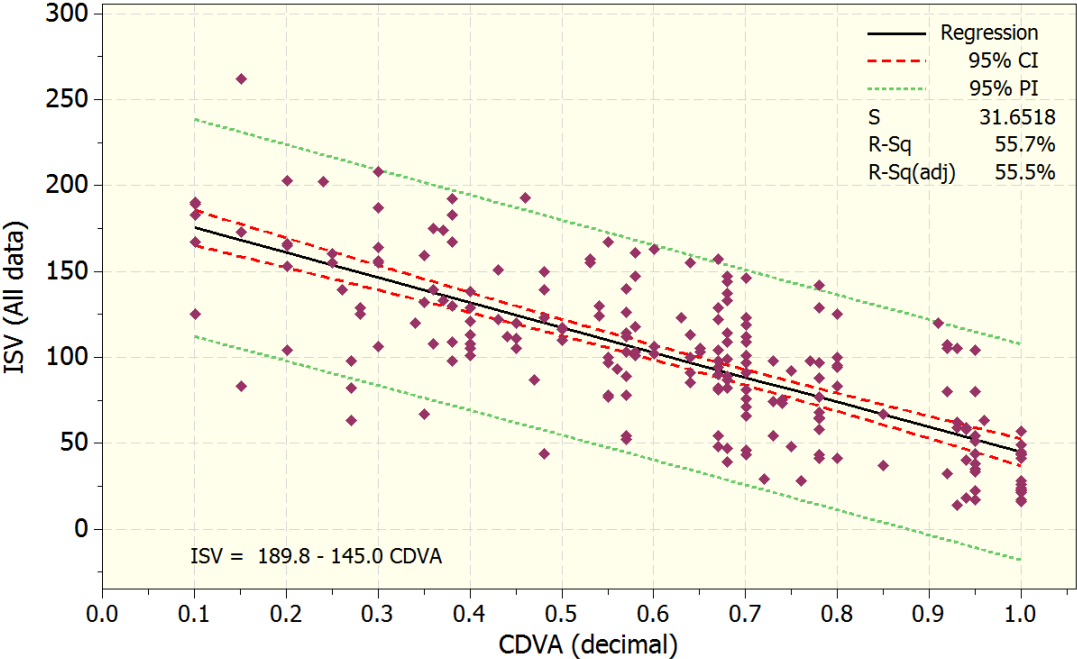
Level 3	20/125 to 20/30	90 to 150	1.15 to 1.45	at least one value within the 'abnormal' range	6.6 to 4.8 mm	Distinct scissors effect, retinoscopy nearly impossible to perform.	Apex thinner, decentered, and often slightly cloudy. Clear and mostly circular Fleischer' ring. Voght striae clearly visible. Eventually Munson-sign may appear.
Level 4	<20/400 to 20/100	> 150	> 1.50	at least one value within the 'abnormal' range	< 5.00 mm	Retinoscopy impossible to perform.	Cornea often scarred and opaque in the apex. Munson-sign evident.

Figures

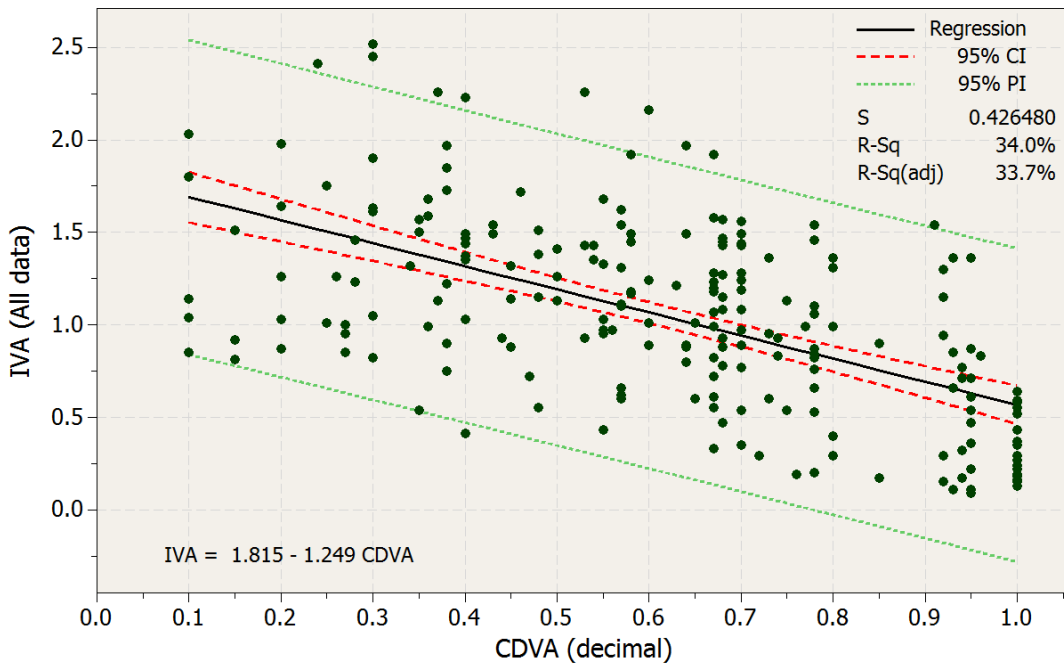
Figure 1

Scatter and Fitted Line Plot of the seven anterior-surface parameters vs CDVA (best- spectacle corrected distance visual acuity) with 95% confidence intervals (CI) and 95% prediction intervals (PI).

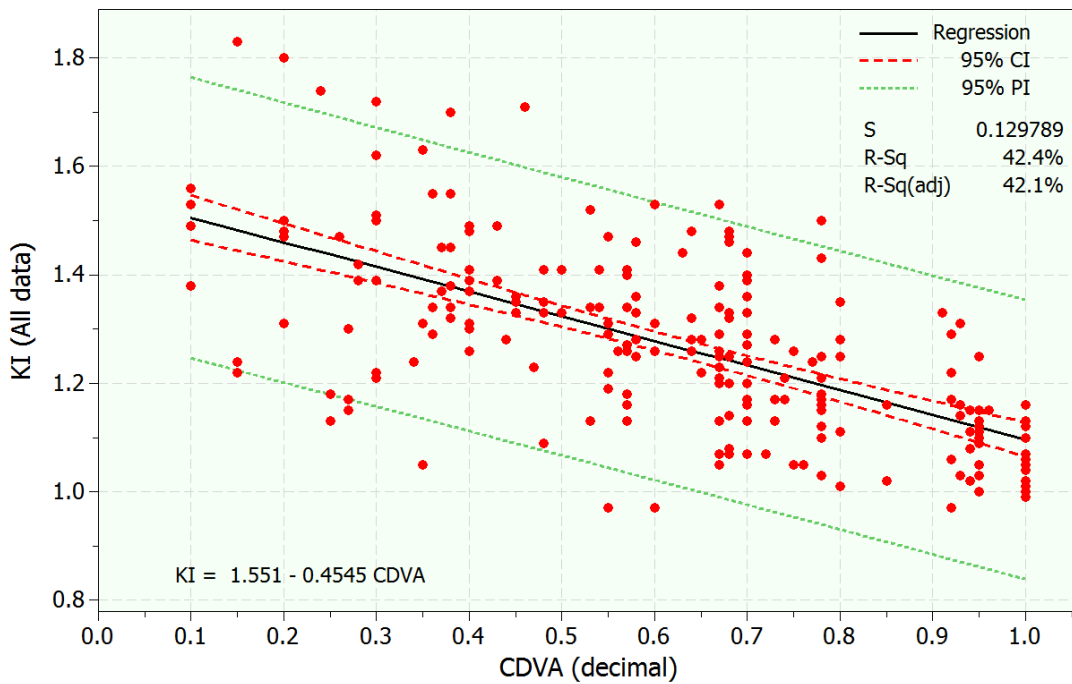
1a ISV (Index of Surface Variance) vs CDVA



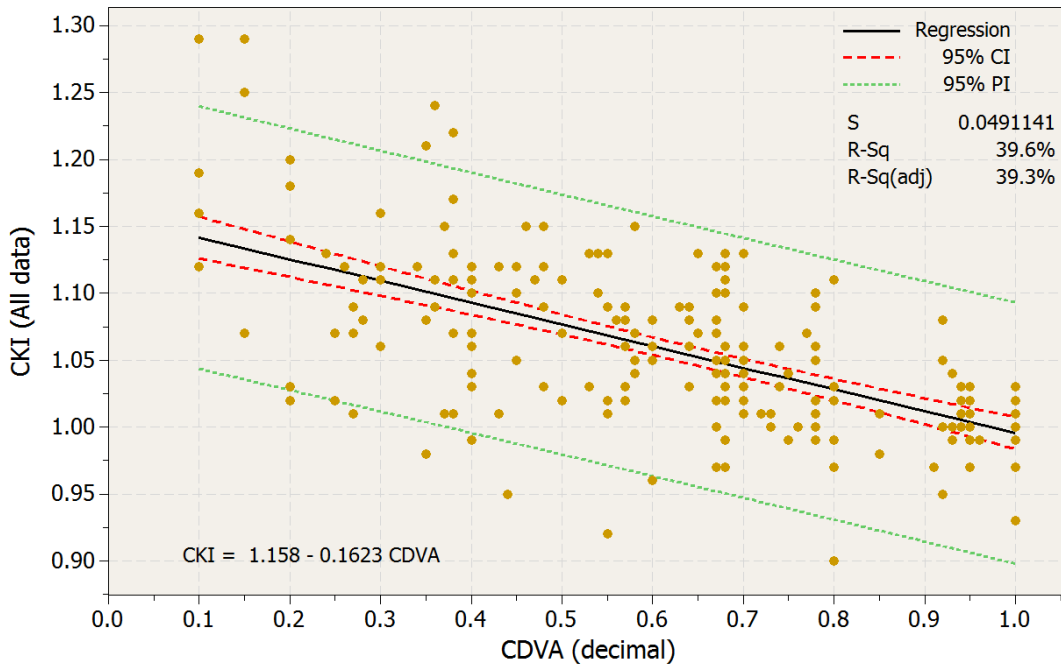
1b IVA (Index of Vertical Asymmetry) vs CDVA



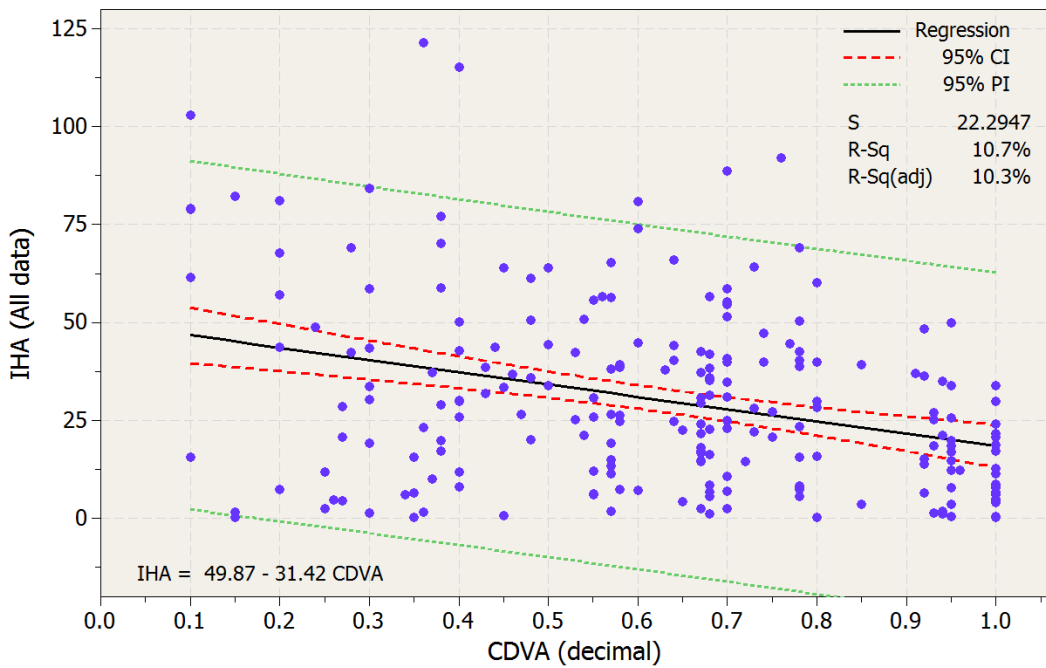
1c KI (Keratoconus Index) vs CDVA



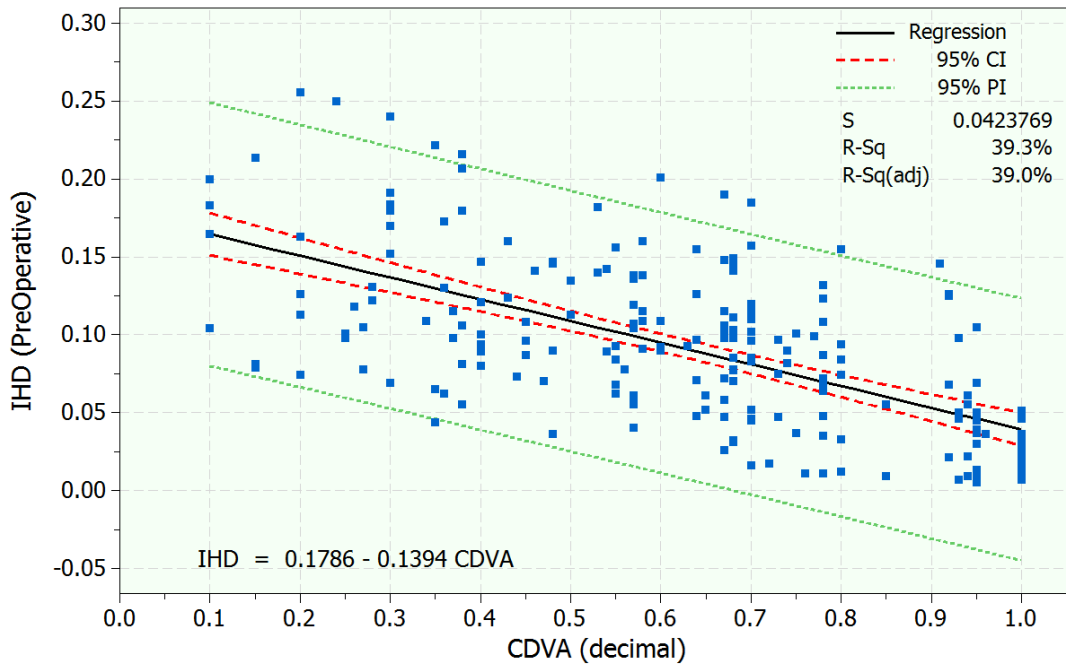
1d CKI (Central Keratoconus Index) vs CDVA



1e IHA (Index of Height Asymmetry) vs CDVA



1f IHD (Index of Height Decentration) vs CDVA



1g R min (minimum radius of curvature) vs CDVA

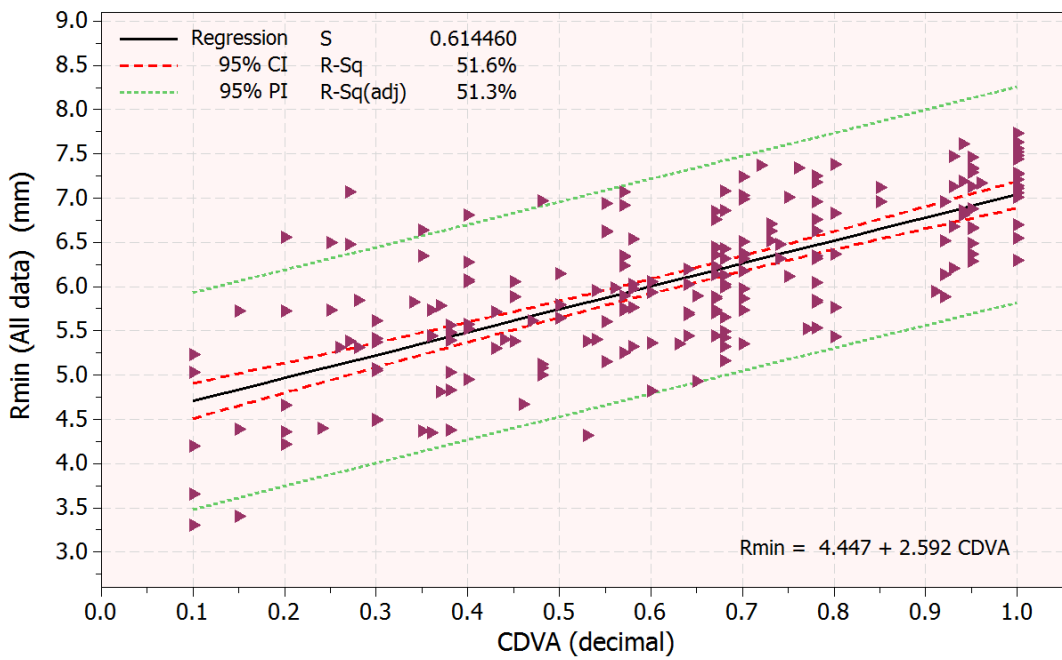
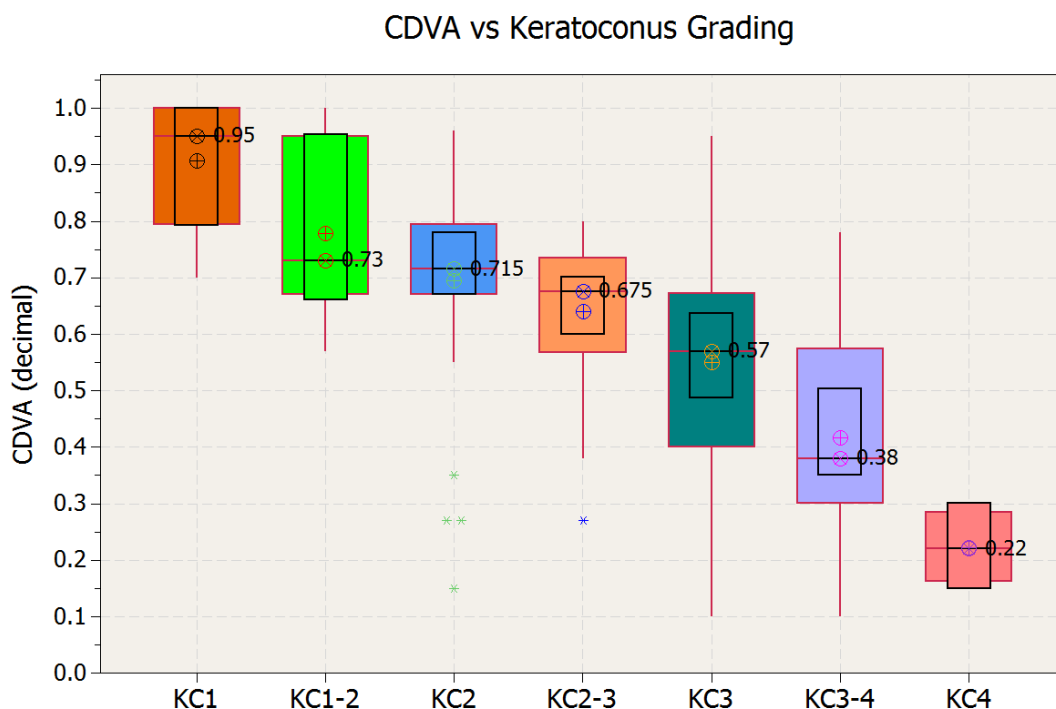


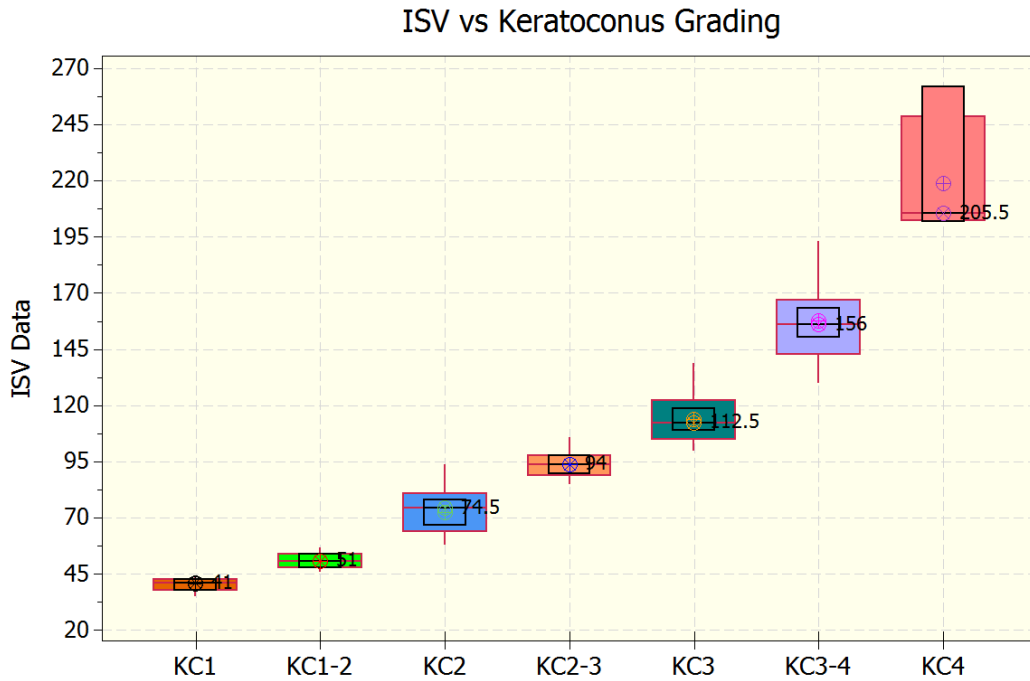
Figure 2

Box plots of measured parameters vs keratoconus grading, as produced by the Oculyzer software showing median level (indicated by \otimes), average symbol (\oplus), 95% median confidence range box (black line boxes), and interquartile intervals range box (red line boxes).

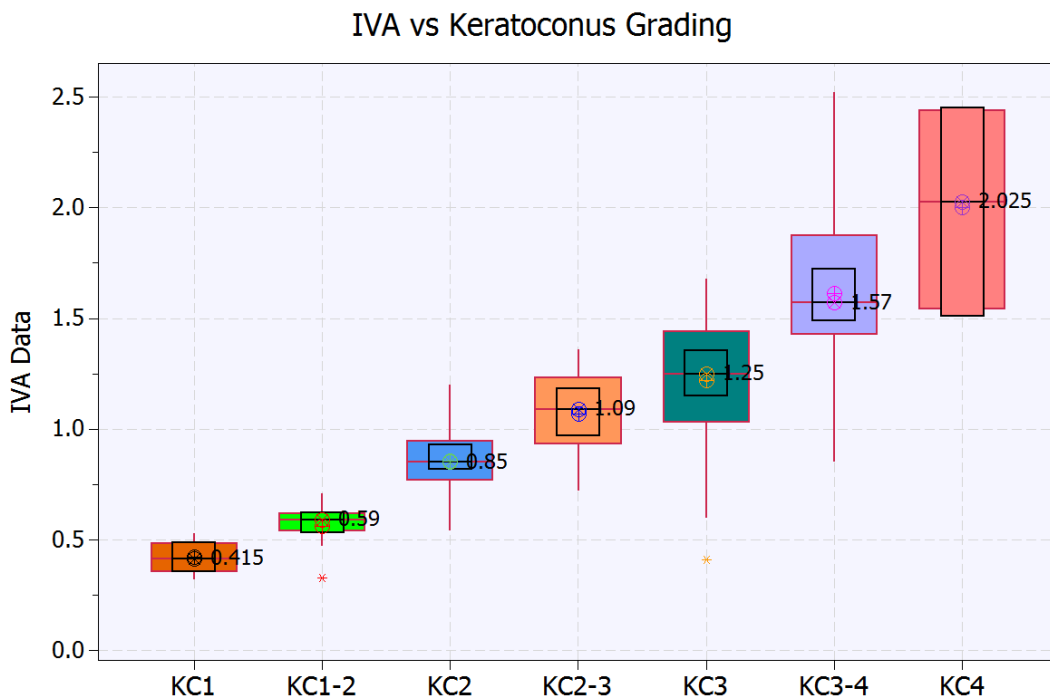
2a: best spectacle-corrected distance visual acuity (CDVA) vs keratoconus grading



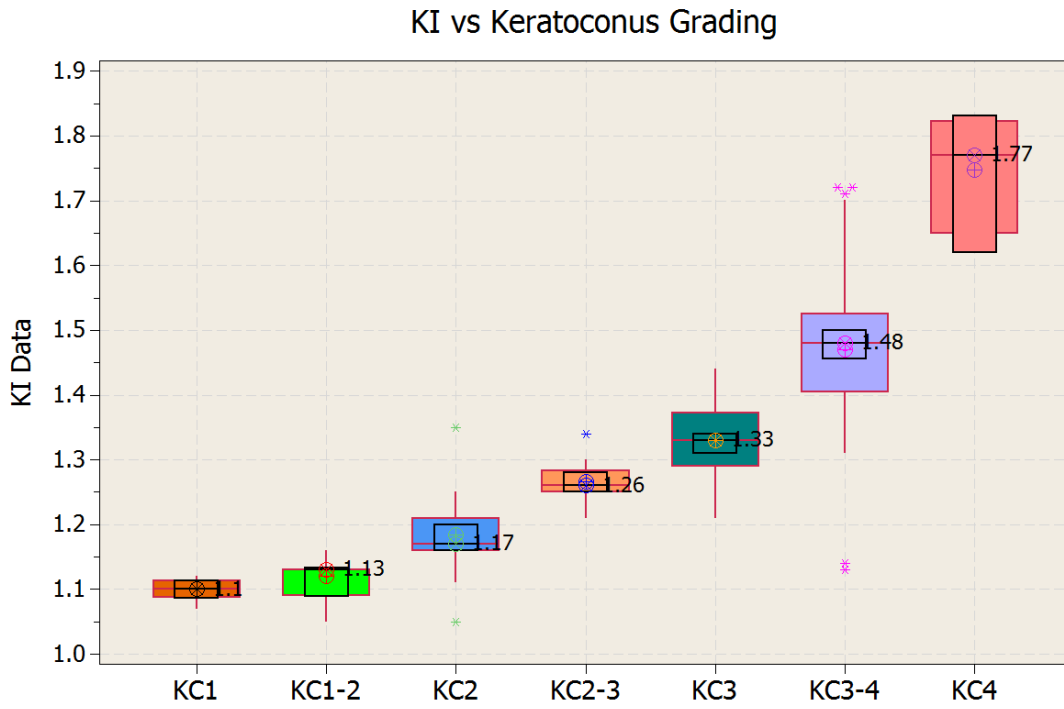
2b: ISV (Index of Surface Variance) vs keratoconus grading



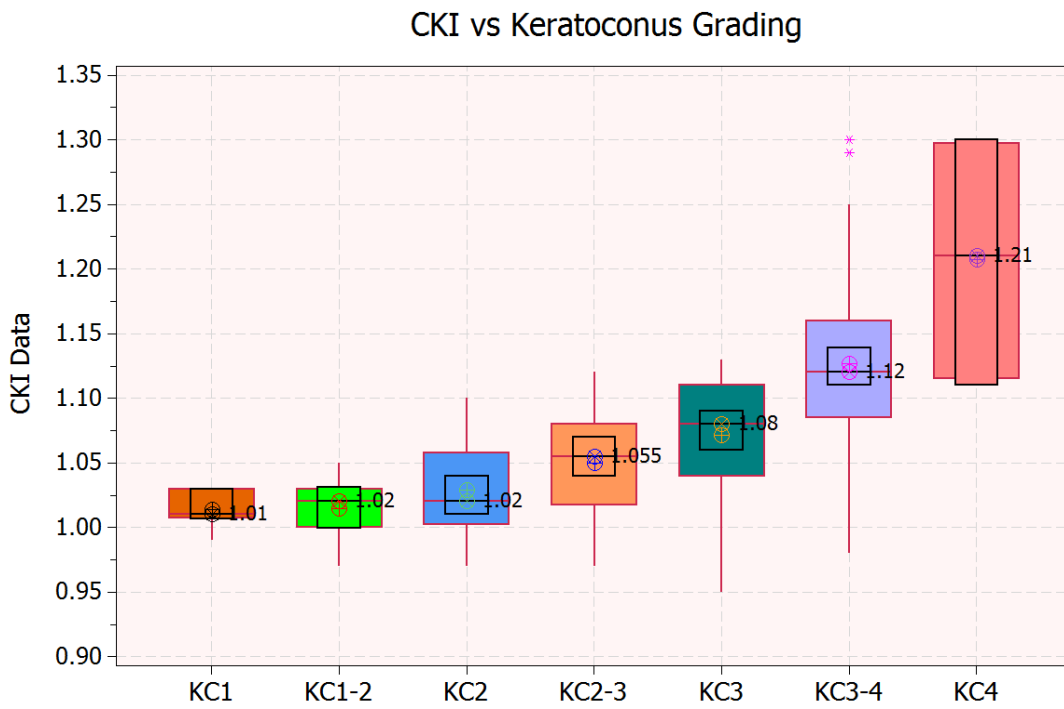
2c: IVA (Index of Vertical Asymmetry) vs keratoconus grading



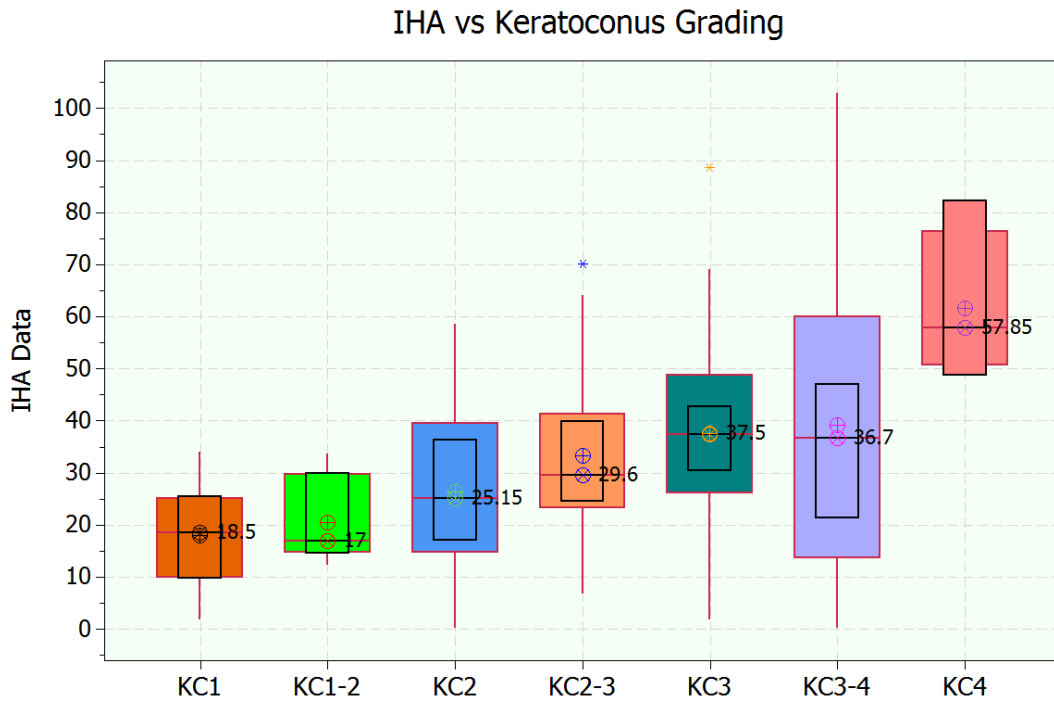
2d: KI (Keratoconus Index) vs keratoconus grading



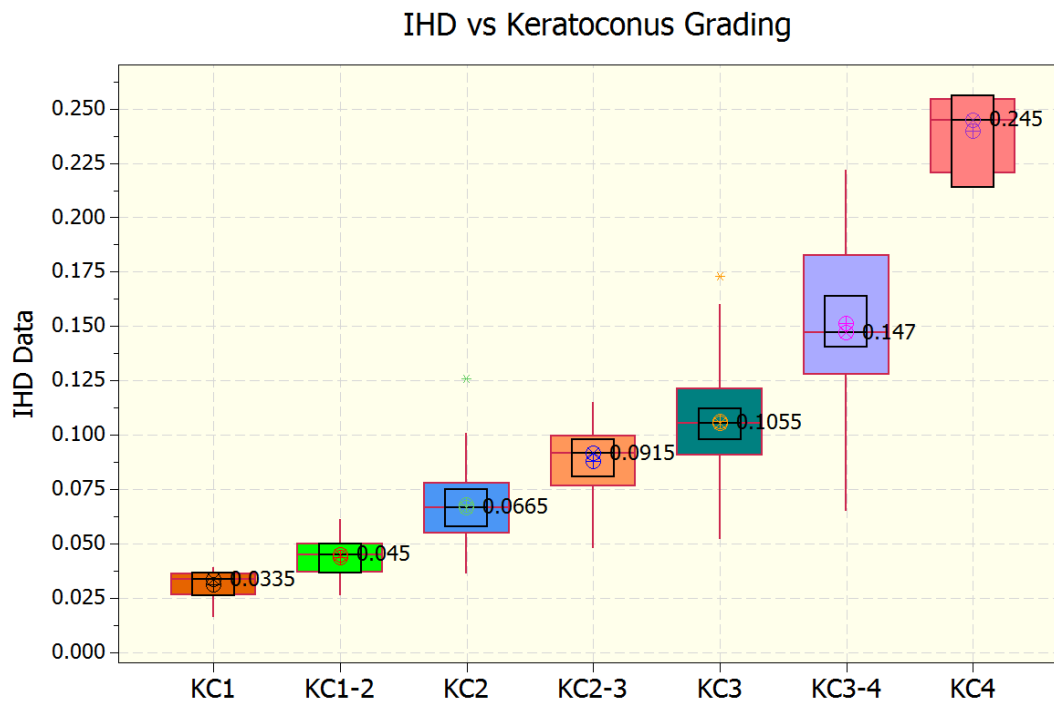
2e: CKI (Central Keratoconus Index) vs keratoconus grading.



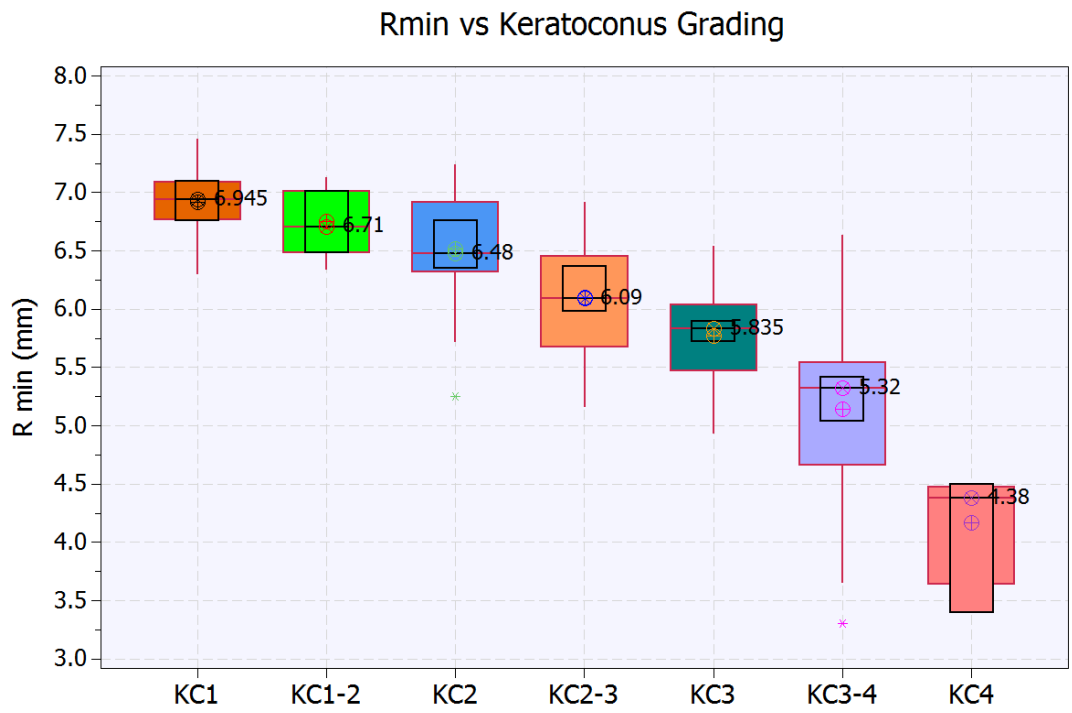
2f: IHA (Index of Height Asymmetry) vs keratoconus grading.



2g: IHD (Index of Height Decentration) vs keratoconus grading,



2h: R min (minimum radius of curvature) vs keratoconus grading,



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